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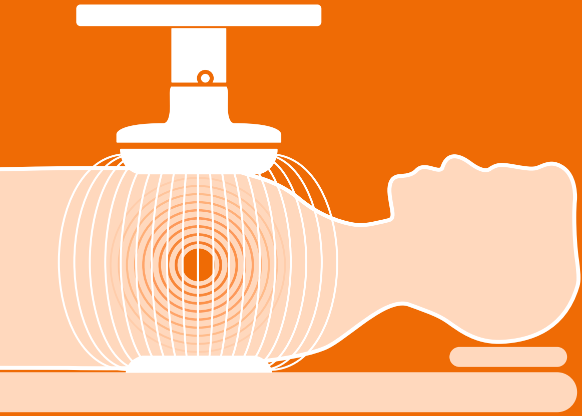


User Guide, part I

Regional hyperthermia

in relation to the technical concept of the Celsius42 device

Hyperthermia is a well-tolerated and effective method to intensify the efficacy of chemotherapy and/or radiation therapy for the treatment of cancer. Capacitive hyperthermia described in this User Guide is a widely used, practical and cost-effective method for warming up tumors in superficial and mid-depth locations. Under certain circumstances, the system is also able to reach deep-seated tumors. Evidence of the efficacy of hyperthermia for various tumors such as head-neck cancer, chest wall relapses, melanoma metastases, bone metastases and cervical cancers has been documented for capacitive and local hyperthermia systems.

Further clinical studies are needed to confirm and extend the indication range. In a parallel effort, we should also work to make capacitive hyperthermia easier to plan and to refine its technology as much as possible. The information and tips from the highly experienced Dr. Sahinbas are helpful for all users of capacitive hyperthermia in this context. This User Guide is a good start for such a standardization effort that will contribute to a better understanding and acceptance of capacitive hyperthermia. (*Prof. Wust – Charité Berlin)*

May 2018
Martin Rösch, Dr. H. Sahinbas

I

Classification of hyperthermia

1.1 What is hyperthermia?

In terms of word origin, "hyper" means 'above', 'more' and '-thermia' can be translated as temperature impact.

In the medical context, the term refers to the body temperature of a living organism and specifically to the fact that this temperature is elevated compared to the standard value or is to be increased.

A natural form of hyperthermia would be a person with a fever who sweats at 39°C. Our body responds with certain signal paths to increase the body temperature, for example when infections are detected, because our immune system is more efficient in a slightly elevated temperature environment.

Efforts to increase the body temperature, entirely or in relevant partial areas, are made for different therapeutic reasons and motivations. There are a number of associated distinctions and measures.

1.2 Forms of hyperthermia

A. Active hyperthermia

Also called fever therapy, means that the body of a patient is infected with certain pathogens, which cause fever as a natural reaction.
This idea even won a Nobel Prize in 1927, when Julius Wagner-Jauregg from Vienna found a method for treat-

ing syphilis prior to the discovery of penicillin. When he infected his patients with malaria, the resulting high fever successfully fought the syphilis, and the malaria symptoms were treated with quinine to lower the fever to a normal range.

William Coley, an American surgeon and oncologist, also had interesting successes in the late 19th century with his attempts to inject tumor patients with streptococcus bacteria to cause bouts of high fever. While this option has been greatly restricted, infusions of mistletoe extracts still play a significant role in holistic and particularly anthroposophic oncology.

B. Passive hyperthermia

This is contrasted by passive hyperthermia. In that case, the heat is introduced externally – typically with a device. In accordance with an international consensus conference in Japan *1)*, a distinction is made between whole body hyperthermia, perfusion hyperthermia, interstitial hyperthermia, and regional hyperthermia.

B1. Whole body hyperthermia

Whole body hyperthermia refers to elevating the body's core temperature in the entire body. This is typically done with water-filtered infrared lamps or a hot water bath. Depending on the scope of the desired temperature increase, whole body hyperthermia is either mild (approx. +1°C), moderate (up to approx. + 1.5 to 2.5°C) or extreme (from +3.5 to 6°C). Even mild

to moderate temperature increases must be monitored, while extreme whole body hyperthermia also requires sedation.

B2. Perfusion hyperthermia

Perfusion hyperthermia involves a circuit that is heated to approximately 42–44°C outside of the body to supply a specific body area, e.g. in a leg, the abdomen or the liver.

B3: Interstitial hyperthermia

One of the subtypes is interstitial hyperthermia. It involves placing thin applicators in natural orifices to heat the body from the inside out. Applications include tumors in the throat, esophagus or prostate and bladder cancer.

B4. Local hyperthermia

In local hyperthermia, only one local region (an organ, joint or otherwise delineated area) is heated up. In this regard, another distinction is made between invasive forms (thin needles are introduced into the body under imaging control (CT) and then heated up). The most common application is the so-called radiofrequency ablation (RFA), in which the tips of needles are heated with high frequency to reach temperatures of >70°C. This is the equivalent of minimally invasive surgical tissue destruction without the need for large open incisions. A frequent application is the removal of liver metastases.

On the other hand, there are non-invasive forms, in which the heat is applied to the patient from the outside. This is easier to accomplish with target areas located close to the surface and more demanding if the target area is deep-seated in the body. We speak of regional deep hyperthermia if the effect is also to occur within the deep tissue. The most common form of this application is the so-called dielectric heating. It involves placing the patient between two application electrodes that change their voltage polarity millions of times per second. The water molecules existing in the body tissue are dipoles and respond to these changes by rotating, which in turn increases the temperature in the body based on friction. Critics have pointed out that some dielectric heating procedures fail to reach sufficiently high temperatures in the necessary tissue depth. Commercially available equipment and the respective protocols differ in this regard; however, it has been proven with temperature verification sensors that sufficient warming is quite feasible, provided these methods are used correctly. The treatment generally lasts 60 minutes (between 45 and 90 minutes depending on the case).

1) *The Kadoto Fund International Forum 2004 – clinical group consensus. Van der Zee et al, Int.J.Hyperthermia, March 2008 (24)2:111-122*

II
Technical basics

2.1 What is dielectric heating, or: How does heat reach deep-seated locations?

Dielectric heating involves applying a voltage between a positively charged side and a negatively charged side. Since there is no conductive connection between the two poles, there is no direct current as a general rule.

How then, does the principle of heating in deep-seated locations work?

The warming effect is determined by the type of dielectric between the two charged poles. All ions (electrically charged particles) within the dielectric react to an electromagnetic field and move accordingly; this process generates heat. Ions can be found in every cell and in the intercellular space.

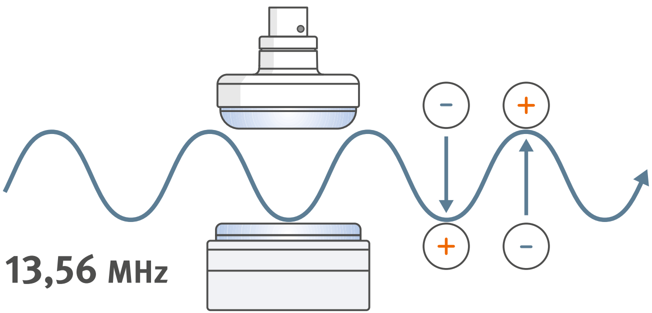


Fig. 1: Operating principle of the electromagnetic field

However, the strongest effect occurs when the dielectric includes so-called dipoles. To recap, our dielectric is the space between the lower and upper electrode and in the ideal case – in our context – represents an area that touches the human body as extensively as possible. Since human tissue is primarily water-based, we are taking advantage of a property of water molecules in this case. Water molecules are exactly such dipoles. Dipole means that an atom, namely the oxygen atom with a slightly negative electric charge is positioned on one side, and the two hydrogen molecules on the other side. From an electrical perspective, they are therefore not in balance. When an electric field is applied, the water molecules align with it (see drawing).

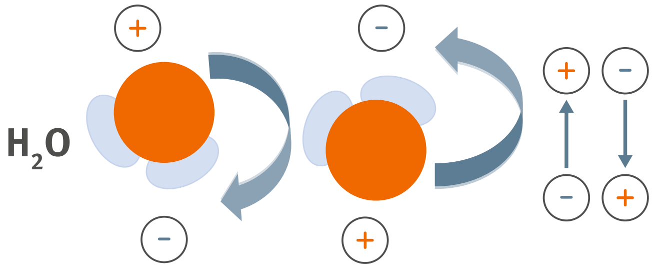


Fig. 2: Dipole structure of water

The dielectric heating mechanism of the Celsius42 device changes the polarity between the poles very quickly, namely 13.56 million times per second. These quick rotations, to which the water molecules adapt accordingly, create friction with the adjacent molecules – precisely the main effect of warming, virtually within the dielectric.

This effect increases with larger numbers of dipoles and the closer they are together. Internal organs therefore have a higher thermal coefficient than, e.g., bone structures or bone marrow structures. More details on the subject of thermal tolerance can be found below (Section V). Of course, with all other factors unchanged, the stronger the applied field, the greater this effect. In the case of operating the Celsius42 device, that is done by way of the wattage settings. The cumulative energy input is always given as a total kJ value in the documentation of a session.

2.2 Preclinical temperature experiments

In the preclinical phase, temperature experiments were performed to determine which temperature effect can be expected. This type of experiment is justified because it helps to define the technical warming parameters. In the case of applications on the body, there is always an essential factor that is not exactly tangible in experiments, in the form of the body's blood circulation that acts as a de-facto cooling system.

The preclinical temperature experiments were performed with a temperature-equivalent model that simulates the muscle tissue and consists of 4% agar agar (a polysaccharide made from algae) in a physiological saline solution (0.9% NaCl). It should also be noted that fatty tissue and the tissue of internal organs react much more sensitively to energy input than muscle tissue.

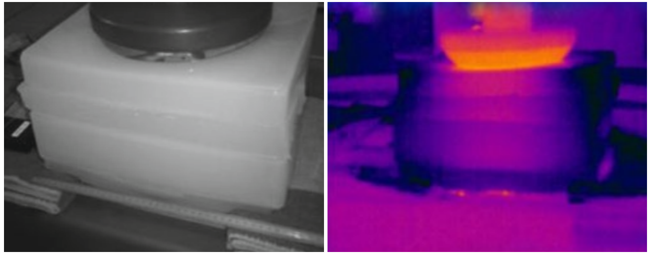


Fig. 3: Agar phantom as a muscle-equivalent temperature model

To give an example, here is one of the experiments that were conducted: In this case, only 150 W were applied (with a max. around 500 W), which resulted in an average temperature gradient of 6.6°C and a peak of +14.5°C in the upper third of the agar phantom.

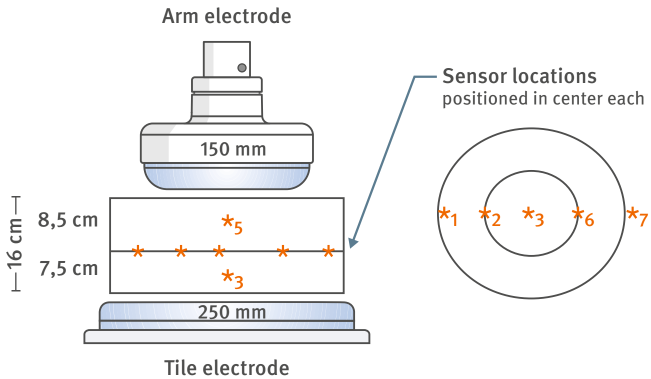


Fig. 4: Location of sensors in the agar phantom

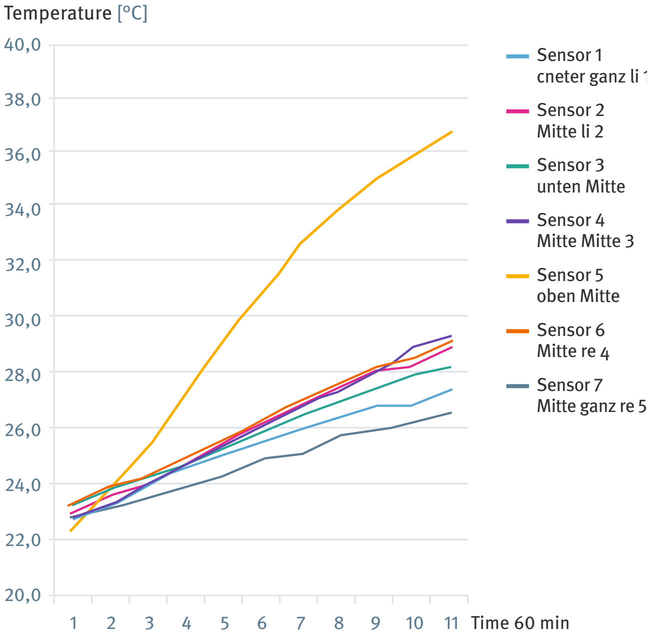


Fig. 5: Corresponding temperature measurements in agar phantom

Preclinical temperature experiments were also performed with a bio-equivalent radiation dummy. The results were comparable.

We will be pleased to share further details on request.

2.3 Active electrode selection

The Celsius42 device currently offers two electrode sizes: 250 mm diameter and 150 mm diameter, as a lower tile electrode or as an upper arm electrode, respectively. The standard application involves the use of the 250 mm electrode at the top and the 250 mm electrode at the bottom. In principle, a given energy output distributed over a large area generates a lower temperature gradient than the same energy output on a small area. The device now has the option to adjust currently two sizes on the top side and two different sizes on the bottom side. In this connection we should also mention that a third expanded size – for application on the entire chest area – will be available in the near future.

The first option consists of the nature of positioning the patient because the energy output and therefore, the effect of the upper electrode is slightly larger. The system tends to be more effective if the patient is able to lie in a prone position for the treatment of a tumor located on his or her backside. Another option consists of combining the electrode sizes at the top and bottom to achieve an exact focusing effect. This reinforces the energy output of the device in the direction of the smaller electrode.

The selective use of a 150 mm electrode on one side (top or bottom) may be advisable in the following situations:

- A relatively small area as the “region of interest” located close to the surface near the 150 mm electrode

- In confined areas of the body such as the neck region
- If a selective depth effect is to be achieved between the center of the body and the upper quarter of the body side facing the 150 mm electrode

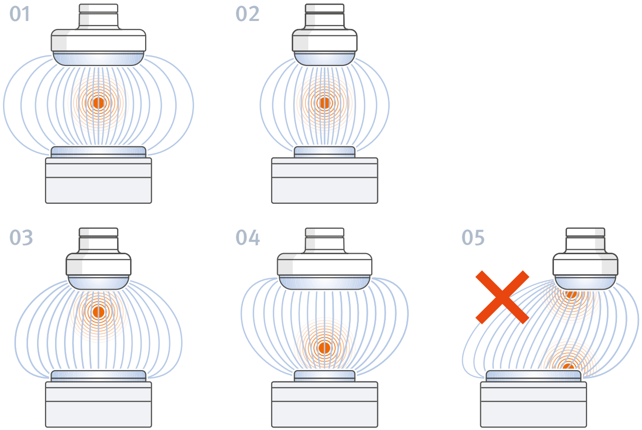


Fig. 6: Effects of various sizes and placement of the active electrodes. Please note that the image on the right shows a faulty treatment! The electrodes should always be kept perpendicular to one another.

As the experiment described below has shown, a focusing effect does exist. The temperature gradient is at its highest in the position of Sensor 8 near the smaller electrode. The temperature effect is lower very close to the electrodes because of the deliberate use of cooling. We used a so-called agar model in this case, which approximately corresponds to a muscle-equivalent temperature model – but without the blood perfusion. Eight temperature sensors were positioned in various places in the target area, which is roughly the same depth of a normal chest or abdominal cavity. The position in the yellow area of the diagram corresponds to the phantom (see illustration below). The experimental design in this case corresponds to a larger electrode on the upper side (250 mm) and the smaller tile electrode (150 mm) at the bottom on the patient bed. The treatment duration was planned for a total of 50 minutes in two stages with the first 25 minutes at 150 W, followed by 300 W.

Electrodes 2, 3, and 7 that are located at the edge or outside of the pure field effect show the least warming. We can therefore approximately conclude that the effect below the electrode surfaces is the strongest. Temperature sensors located near the surface of the electrodes (which was not tested in this experiment, but in other experiments) would also not show a very large temperature effect because they are most exposed to the influence of the water cooling system at the bolus underneath the electrodes. Otherwise, a larger temperature effect would need to be expected, which would, however, restrict the depth performance because the patient might easily experience it as painful. The temperature gradients at the greatest depth of the model (Sensors 4, 5 and 6) show a moderate effect. This is the area that is most difficult to warm up. In this arrangement, the position of Sensor 8, which has the highest temperature gradient, represents an area of high and definitely therapeutic efficacy. This demonstrates that a certain control effect can be achieved even in capacitive hyperthermia. Sensor 1 on the top side also has an adequate temperature gradient. As mentioned above, the energy output at the top side is approximately 20-25% higher.

Experiment 1: Efficacy – Capacitive/Impact Control

Experiment design

The measurement was performed with a 250-mm arm electrode and a 150-mm tile electrode. Two tests were carried out. The electrodes were not cooled.

Phase 1 of the experiment:
0 to 25 minutes at 150 W

Phase 2 of the experiment:
25 to 50 minutes at 300 W

Fig. 7: Agar-muscle phantom:
AGAR 4% + NaN3 0.9%
dim. 18 x 30 x 35 cm³

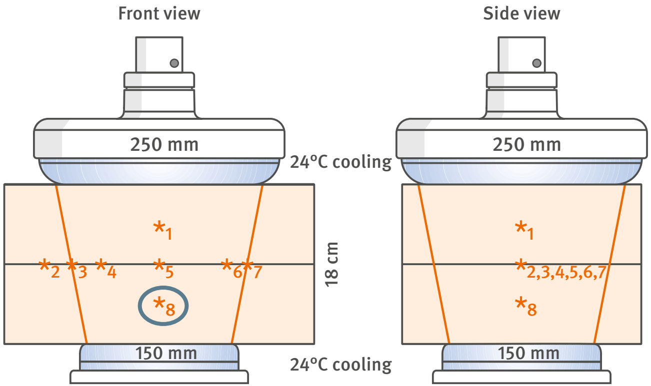


Fig. 8: Position of the temperature sensors in the agar-muscle phantom

Distributed sensor arrangement in the model

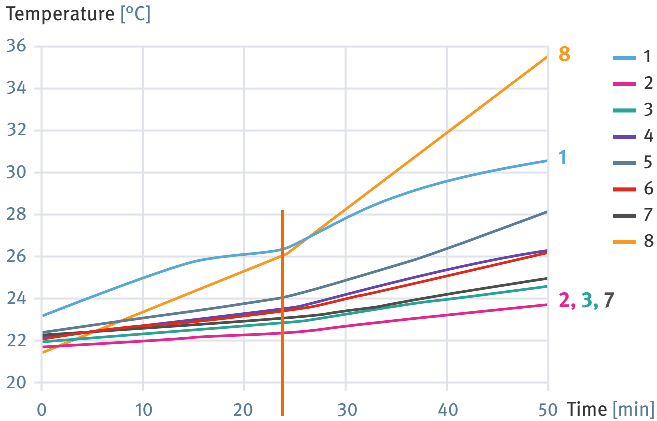


Fig. 9: Temperature measurements in the muscle phantom

Results

- Significant temperature increase
- Verifiable focusing effect
- Little effect outside the electrode cover (with little diffusion of heat by the circulating blood)

The so-called "specific absorption rate" or SAR rate is of scientific relevance. It means that a hyperthermia treatment has to achieve a temperature gradient within a certain time to be accepted as therapeutically relevant. Otherwise, one could simply provide warming for 5 hours. From a certain point in time, the temperature will increase when the normal compensation mechanisms such as perspiration can no longer achieve any adjustment. The mandated reference in this case is that a temperature increase of 1 °C is achieved in 5 minutes of hyperthermia. The paragraph below demonstrates that this requirement is met.

Illustration 2: SAR distribution 1

Experiment design

Phase 1: 25 minutes at 150 W.

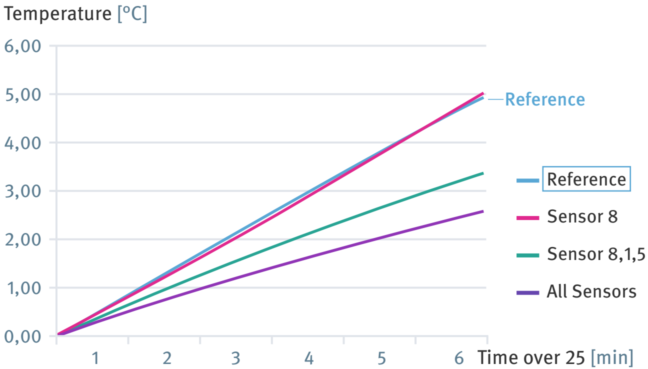


Fig. 10: Temperature measurements in the muscle phantom

Result

In phase 1, only sensor 8 reaches the reference temperature increase of 0.2°C per minute. The blue reference line is congruent with the red graph for sensor 8.

SAR distribution 2

Experiment design

Subsequent phase: 25 minutes at an energy input of 300 W.

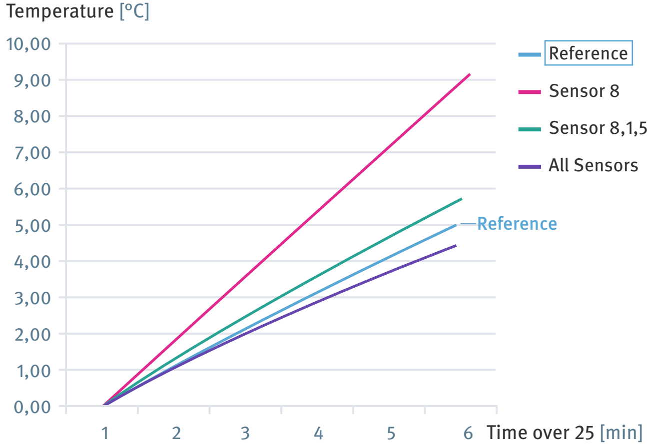


Fig. 11: Temperature measurements in the muscle phantom

Result

In this phase with an elevated power setting of 300 W, more sensors exceed the required reference (blue graph). Sensors 8 and 1 are clearly above the blue line; for all sensors between the electrodes, the line is slightly below the reference. Outside the electrode surface, the temperature rise is marginal, as expected.

2.4 Characteristics of cooling

In most clinically relevant cases, warming has to take place in deep-seated tissue locations since this is where the quantitatively most common tumors are located. It is quite a demanding undertaking to achieve a temperature increase from 40 °C to 42 °C with blood circulation in deep-seated tissue locations. Patients may also perceive the heat as an uncomfortable and ultimately, painful sensation. This point will be explained in greater detail in Section V.

As one of the valuable features of the Celsius42 device, a water buffer is installed between the electrode and the skin for easier adaptability to the skin surface. In this context, it is crucial that this water can be cooled to 8 °C during the flow. Patients may dislike the sensation that the skin surface is cold to the touch. We recommend taking some time to explain why this is acceptable. Most, but not all temperature receptors of the tissue are located in and below the skin. The application of cooling from the outside can influence these receptors, with the result that the treatment is not perceived as hot. This opens up the option to generate higher energy inputs in deeper locations.

Effective surface cooling:

- Avoid skin burns
- Reach higher thermo-tolerance in patient

Distribution of energy input

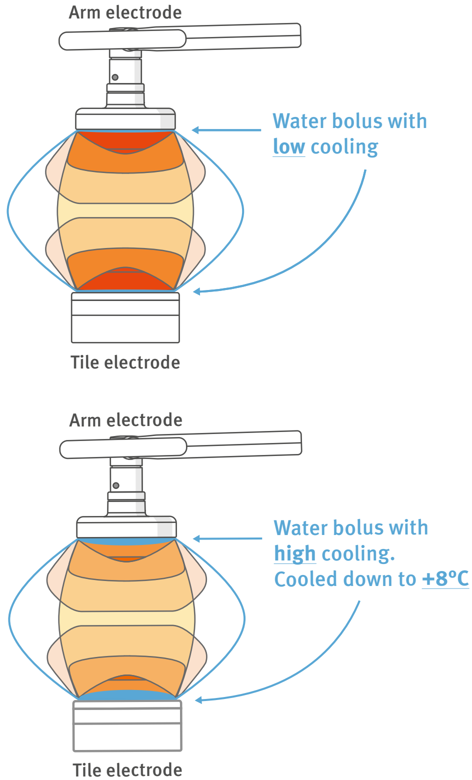


Fig. 12: Adaptable surface cooling

2.5 Safety aspects

In medical devices, safety is addressed at a very early stage, starting in the development phase. This raises questions such as: What is the risk assessment for patients, users or even uninvolved third parties, and which standards must be met?

The TCS – Tumor Cell Solution is a Class IIb medical device, which may only be operated by qualified medical professionals who have been trained in the use of the device. The installation and training is carried out exclusively by employees of Celsius42 or by contractor staff that has been trained by Celsius42 as well as physicians.

All medical devices require a so-called CE mark in accordance with DIN EN ISO 13485. Such a CE certificate stands for many years of comprehensive development and registration processes, which in detail comprise many technical dimensions such as mechanical safety, electrical safety, electromagnetic compatibility factors, but also compliance with protection regulations and standards for all sub-components of the device, with verifiable documentation and much more. The workflows and processes within the company are also reviewed and require certification according to DIN EN ISO 13485. All of these are safety aspects to protect our customers' patients.

The most important safety aspect concerns the risk of harming the patient. In the area of hyperthermia, this pertains to possible burns. This begins with minor redness of the skin and can, in the worst case, lead to third-degree burns. Again, this is closely monitored and documented within the framework of EN ISO 13485 (post-market surveillance - PMS) so that companies can correct any potential risks with appropriate measures at any time.

In the case of the TCS system, patients can interrupt the treatment with a feedback switch anytime. When higher energy inputs are applied, which are known to be potentially critical, the system requests a manual confirmation from patients once a minute to confirm that they are still feeling well. Starting from certain thresholds (for example, from 180 W with the 250 mm electrode), the device triggers a ring tone. If the patient does not press the feedback switch within eight seconds after this ring tone for confirmation, the further treatment is interrupted immediately. This ensures that the treatment doesn't simply continue in cases where a patient may have fainted. In this case, the patient arm with the upper electrode immediately moves upwards and releases the patient from the therapy position.

This approach takes many aspects and experiences into account to benefit patients and enhance user safety.

2.6 Comparison of technological alternatives to regional hyperthermia and their inherent advantages and disadvantages

In contrast to regional hyperthermia, so-called superficial hyperthermia is easier to handle. However, pure superficial hyperthermia is not frequently indicated because even tumors close to the surface such as chest wall tumors or melanomas frequently are associated with metastatic growth in depths of up to 4 cm.

Accordingly, they are also relevant for treatment with regional hyperthermia.

This section explains the following procedures in greater detail:

- Antenna method
- Capacitive method
- Inductive method

In addition to a brief explanation of the technology, we discuss the following issues:

- Efficacy with regard to temperature generation
- Patient and operator safety
- Simplicity or complexity of treatment
- Scientific evidence
- Economy, since economic criteria need to be taken into account in times where new therapy concepts, depending on the treatment, frequently cost over a hundred thousand euros.

Antenna method

This method typically involves placing several applicators in a ring around the patient. Each of these applicators can be controlled separately and radiates energy into the body, which ultimately causes warming. Depending on the location of the tumor, the closest applicators can be set to greater energy output to achieve a differentiated application Commercially available systems of this category include, e.g., Pearson 2000 or the Alba model. These devices use an operating energy in the range of 100 MHz, a technical capacity that is certainly sufficient to reach the required temperatures. The only difficulty consists of making sure that no unwanted overheating occurs in the form of so-called “hot spots”.

The fact that up to 12 applicators are used in practice, which affect one another with overlaps and cancellations and the circumstance that the target body is not a homogeneous tissue, but features a variety of densities between muscles, bones, bone marrow, fatty tissue, fluids, lumen and densifications in the organs are indications of this procedure’s high complexity. Moreover, unwanted high temperatures can occur in certain places, for example in the spinal cord or the nerves. Optimal procedures therefore utilize online temperature monitoring to prevent the occurrence of internal burns. This is not an easy undertaking because it is not sufficient to simply perform point measurements with temperature sensors. Rather, the target volume would have to be monitored in 3D quality, which can be accomplished with magnetic resonance tomographs. Since MRIs also work in the 100 MHz frequency range, these devices have to be precisely coordinated and cannot be used for another procedure than for temperature measurement. Accordingly, such antenna methods are expensive and highly complex. They are used in a few university hospitals, but the majority of hyperthermia applications both in Germany as well as worldwide does not involve antenna systems.

Even if no online temperature monitoring is used, the processes associated with preparation and implementation are quite involved (simulation based on temperature models; accurate positioning). It is of benefit that prominent studies have documented the efficacy of hyperthermia with antenna systems. However, other methods such as capacitive hyperthermia may be equally suitable to reach the required temperature gradients.

In summary, it can be noted that antenna methods are effective and achieve clinically proven results, but are complex in their application and cost-intensive in economic terms in light of their purchase price and operating costs.

Capacitive method

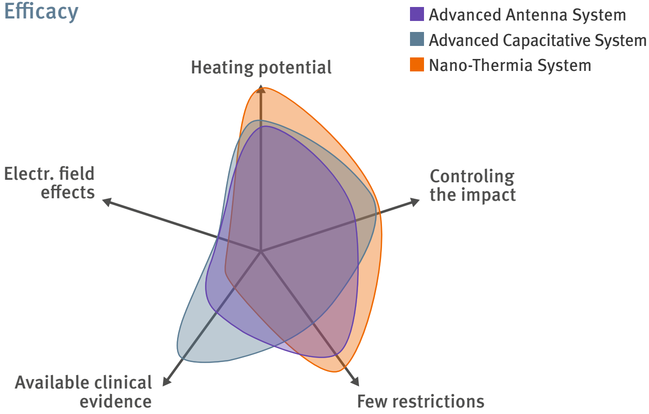
Providers of this method include Celsius42 from Germany, the Italian company Synchotherm, the Japanese Thermatron operation and the Hungarian company Oncotherm. Thanks to its simple technology, this method is relatively easy to apply. Of course, these facts also have a positive effect on profitability. Furthermore, they allow for expanded applications such as shoulder and head treatments. In addition to the field of the antenna method, an impressive number of solid studies is now available for the capacitive method.

The commonly used 13.56 MHz is based on the fact that this is a globally open frequency that does not require the installation of complex Faraday cages. Compared to devices in the 100 MHz range, the lower frequencies of 8 to 13.56 MHz have the advantage that they can penetrate water-based tissue such as the human body more deeply. Accordingly, the allegation that capacitive devices are not able to reach the required temperatures in deep-seated body locations is no longer justified, at least for the devices by Thermatron, Synchotherm and Celsius42.

Inductive method

This method, which is not completely non-invasive, is relatively new. The company "MagForce Nanotechnologies" so far is the only provider. It involves injecting magnetic iron oxide nanoparticles in a quantity of approximately 17 septillion particles per 1 ml into the tumor as a first step. The body can then be moved any number of times into a magnetic field that is activated with approximately 100,000 polarity inversions per second. The rotations of the magnetic nanoparticles generate a temperature impact that is particularly easy to control. This method successfully passed its first study in the application for brain tumors. Although the safety and application on the operator side have been proven, the local fidelity of the nanoparticles has been criticized along with potential long-term effects.

Efficacy



Summary: Factors for a successful spread and acceptance of hypertermia therapies in cancer

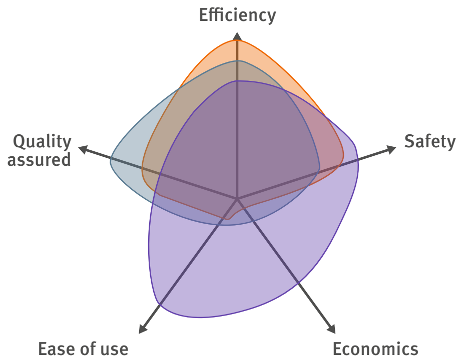


Fig. 13/14

III

Rationale of hyperthermia

3.1 Temperature as the target figure

As explained above, hyperthermia must be able to achieve verifiable warming of the target area. Accordingly, this temperature increase must primarily take place in the location of the tumor, typically in deep-seated body locations. In addition, such temperature increases must be generally detectable, which is done by measuring the temperature and the temperature increase.

In accordance with the consensus in the scientific hyperthermia community ESHO (European Society of Hyperthermia in Oncology), effective hyperthermia must meet the following conditions:

- It must cause an energy input that generates a temperature increase of 1 °C in 5 minutes of exposure time in the target tissue
- It must be able to reach a temperature of at least 40 °C to 42 °C, ideally over a period of 50% of the treatment duration
- It must be able to provide appropriate quality assurance

The literature contains evidence that suggests a correlation between the local response rate and the achieved temperature. Ohguri et al. *1)* were among the few who measured and documented the temperature attainment and then stratified it accordingly in the evaluation. Patients who reached temperatures ›=42°C were allocated to Group A, while Group B included patients with measurement results ‹ 410C (59 vs. 26 patients). The response rate was significantly better in Group A versus Group B. The median survival in Group A was 24.3 months compared to only 17.1 months in Group B (p‹0.05). As an interesting side note, the study also found that an allocation to Group A significantly correlated with major surface cooling of the skin. Other authors have reported similar results in liver *2)* and prostate tumors *3)*. Not surprisingly, the corresponding in-vitro studies also point out greater cell lethality at higher temperatures *4-6)*

1) Ohguri, T, Imada, H, Yahara, et al: Effect of 8-MHz radiofrequency-capacitive regional hyperthermia with strong superficial cooling for unresectable or recurrent colorectal cancer. Int J Hyperthermia 2004 Vol. 0(5), pp. 465-75
2) Maeta M et al: a case-matched control study of intrahepatoarterioal chemotherapy in combination with or without regional hyperthermia for treatment of primary and metastatic epatic tumors. Int J Hyperthermia 1994; 10 (1):51-58
3) Prostata CA (Tilly 2006): Strahlentherapie plus locoreg. Hyperthermie correlation between thermal dose and PSA control
4) Li 1977,
5) Hahn 1982,
6) Horseman 2007

3.2 In-vivo temperature measurements in the patient's body

Measurements are taken with a thermometer that is suitable to ensure valid function in an electromagnetic (EM) field. This device can therefore not be self-powered. The solution was to use sensors connected with fiber-optic cables that are insensitive to EM fields. The problem with this type of measurement is that it always only provides a result for a single point. For example, a sensor in the intestine may be located within an air bubble and measure hardly any temperature increase, although significant gradients could be measured just 1 cm from this place. Sensors could also be in a somewhat unfortunate location next to a blood vessel which also would lead to the display of lower values. Some practice is therefore required to obtain reproducible results. Semi-invasive measurements are easier in this context and involve placing sensors in natural orifices (vaginal, rectal as well as in the mouth and throat).

Experiment 3: Rectal Temperature Measurement

Experiment design

Patient with prostate cancer; power of initially 60 W to 170 W, total: 364 kJ.

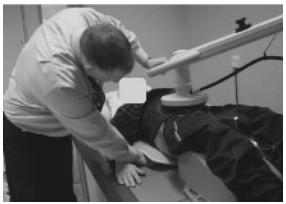


Fig. 15: Measurement: Institut für Hyperthermie & Pallativmedizin (Institute for Hyperthermia and Palliative Medicine), Bochum, Germany.

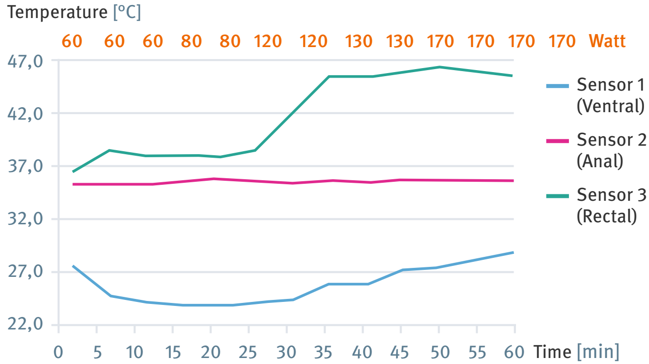


Fig. 16: Rectal (Sensor3), anal (Sensor 2) temperature profile, and between upper electrode and abdomen (Sensor 1).

Results

After 30 minutes (at 120 W) the rectal temperature reached 41.9°C and, during the following 20 minutes, increased to 45°C and even 46°C!

Sensor 1 on the skin surface indicates only an inevitable, minimal increase by 1.4°C, as expected. Sensor 2 (anal) was located slightly outside the electrode surface and did not exhibit a temperature gradient.

Experiment 4: Invasive Temperature Measurement in the Liver

Experiment design

- Male patient, 71 years old
- Liver metastases

- 2 sensors placed in the liver tumor
  1 sensor on the skin surface
- Water circuit cooled down to 8°C
- 60 minutes at 110 to 200 W; total: 590 kJ

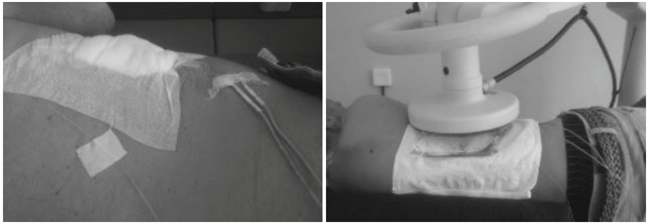


Fig. 17: Examined by Dr. H. Sahinbas. Praxis-Klinik für Hyperthermie & Supportive Care, Bochum, Germany.

Temperature profile of the first 10 minutes of the treatment at 110 W

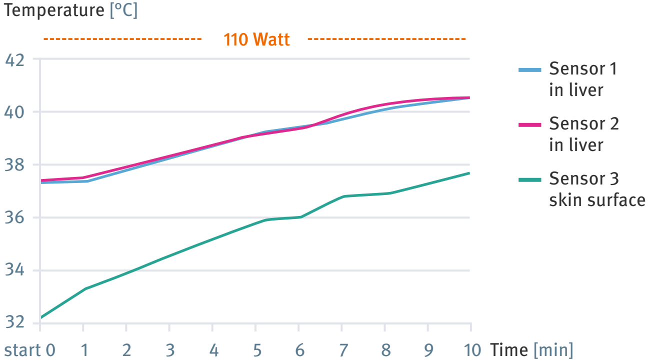


Fig. 18: Temperature profile

Temperature profile for the entire 60 minutes (110 to 200 W)

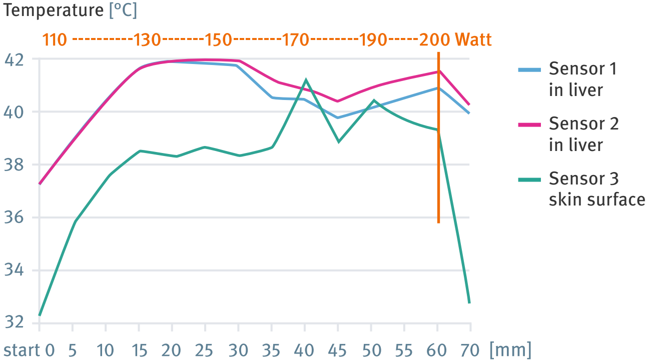


Fig. 19: Temperature profile

Result

In the first 10 minutes already, the temperature increase in the liver was 3.2 and 3.3°C, respectively, to 40.6 °C. This is a significantly higher effect than the required SAR reference of 1°C per 5 minutes. The peak temperature achieved was 42.0°C, and a plateau of ›40°C was maintained for 50 minutes!

Experiment 5: Mamma temperature measurement

Experiment design

- Low output (see table at right)
- 2 x 250 mm electrodes
- Water cooling down to 17°C

20 minutes at 40 Watt
10 minutes at 50 Watt
10 minutes at 60 Watt
10 minutes at 80 Watt
10 minutes at 100 Watt

Patient says: she can feel the heat, but no pain.

Fig. 20: Position of temperature sensors:
Sensor 1: depth of 1.5 cm
Sensor 2: subcutaneous
Sensor 3 & 4: on skin surface

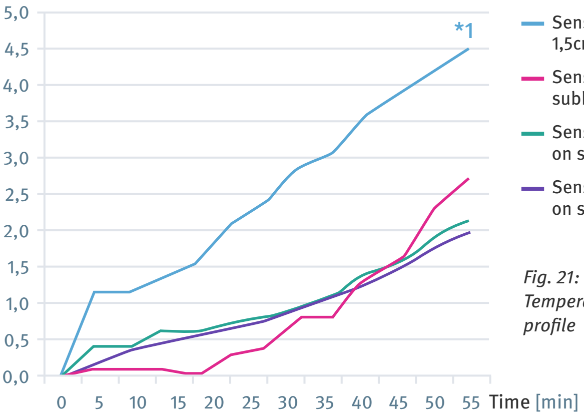


Fig. 21: Temperature profile

Result

The temperature rise in the mamma at a depth of 1.5 cm is +4.5°C; it is moderate at the skin surface with +2°C (due to cooling in the bolus and water cushion). The cooling also has a positive effect on the subcutaneous measurement point where the temperature increases moderately by only +2.5°C.
This example shows very clearly how well the surface cooling mechanism of the Celsius42 device works. The temperature gradient of the sensors near the skin is small, while the sensor at a depth of 1.5 cm, which is not affected by the skin cooling system, measures a temperature increase of up to 4.5°C.

▶ Further examples are available on request!

3.3. Recommended output protocols according to Dr. H. Sahinbas

Many measurements as well as the in-vivo temperature results in the patient's body led to the adaptation of recommended output protocols. These vary depending on the application area in the body and refer to an average patient. Accordingly, individual therapists (depending on curative or palliative intent as well as the thermal tolerance of the patient, to name just a few parameters) are responsible for adapting this recommendation in individual cases based on the patient's condition. The protocols are designed to gradually increase the energy input as the treatment progresses. Such energy output protocols provide guidance for ultimately reaching a temperature gradient of 40 °C to 42 °C (or partly even above in specific locations), especially if no temperature measurement is taking place.

Examples for treatments with the Celsius TCS – Tumor Cell Solution System

arm electrode **250 mm**			session **1**	session **2**	session **3**	session **4**	session **5**
tile electrode **250 mm**							
cooling temperature			18°C	16°C	12°C	10°C	10°C
1. level	duration	[min]	20	20	20	20	20
	power	[W]	40	60	65	80	100
2. level	duration	[min]	10	10	10	10	10
	power	[W]	60	80	85	100	120
3. level	duration	[min]	10	10	10	10	10
	power	[W]	70	100	110	125	140
4. level	duration	[min]	10	10	10	10	10
	power	[W]	90	120	130	145	160
5. level	duration	[min]	10	10	10	10	10
	power	[W]	100	≥130	Max. tolerable power (>130)	Max. tolerable power (>150)	Max. tolerable power (>160)
applied energy		[kJ]	~ 240	> 295	> 351	> 408	> 468
session time		[min]	60	60	60	60	60

Fig. 22: Example: Therapy concept by Dr. H. Sahinbas, Praxis-Klinik Hyperthermie & Support Care.

Further protocols can be found on our homepage www.celsius42.de in the Medical Blog section. Please note that user registration is required to access the Medical Blog section.

Summary

The above-listed energy output protocols are demanding, but a variety of measures are now available to increase a patient's thermal tolerance. These are needed in the context of many curative objectives and with the intention of achieving higher temperatures. For this reason, a separate section **(Section V)** is dedicated to the topic of "thermal tolerance" below.

IV
Tips and tricks for application

4.1 Positioning issues

For technical reasons, the energy output of the lower tile electrode is slightly weaker by approximately 20% for reasons associated with radiation to the metallic parts of the bed frame. In the case of anal, rectal or prostate cancer, it is therefore ideal to treat the patient in a prone position. This results in a greater thermal effect in the target area and relieves sensitive body parts such as the pubic bone. However, not every patient is in a position to remain in a prone position for the duration of the treatment. The operator therefore has to find the corresponding compromise between ideal positioning and a practically feasible solution. Part of such a compromise may also be to reposition the patient in the demanding last treatment phase with high energy input.

If the patient is positioned on his or her side, for example for brain or head/neck treatments, it may also make sense to align the tumor-relevant side toward the upper arm electrode. Depending on the position, this may also apply in the case of soft tissue sarcoma.

Important note!
It is crucial for the effective energy transfer to the target area that the electrodes are truly in perpendicular alignment. Otherwise, part of the energy that is routed around the body will be lost and a disproportional energy input may occur at the minor overlap locations, creating the risk of hot spots. Perpendicular positioning is not always as easy to achieve as it may sound because the lower electrode is covered by the patient’s body and the upper electrode can easily move out of alignment. It is therefore necessary to check the position with a bearing prior to starting the treatment.

To this end, place your fist with an outstretched thumb in the center of the outer tile that is aligned with the lower electrode, bend over slightly and aim toward the shaft of the upper arm electrode. If they are in alignment, the positioning is technically correct. Once the target area for treatment is located directly below the electrodes, you are ready to start the treatment.

This positioning information is very important! As we have observed again and again, errors frequently are made in this regard.

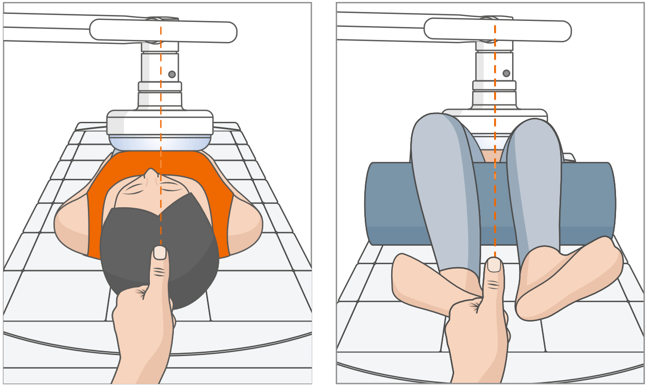


Fig. 23: Test bearing to ensure perpendicular positioning of electrodes

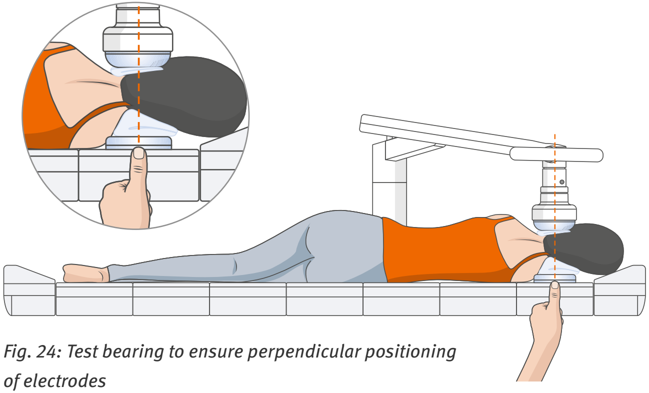


Fig. 24: Test bearing to ensure perpendicular positioning of electrodes

No metal items such as keys, belt buckles or similar items such as jewelry should be left in close vicinity of the application area. Patients should always be asked to take off necklaces or bracelets. In addition, it is recommended to position the patient on the bed largely in isolation without any connection to the wall or floor. Extended "hand-holding" by a sympathetic companion is also not recommended since it will deflect and weaken part of the field.

Placement of the upper arm electrode

It is essential to ensure good skin contact in this process. After consultation with the patient, slightly stronger pressure must be exerted at the time of setting the arm since the arm electrode will yield a few millimeters. Patients typically relax their thorax and abdomen after about 2 to 3 minutes. The resulting slight drop of the abdomen and thorax may cause an air gap to form between the arm electrode and the abdomen or the chest. Readjustment is required in those cases.

Further positioning aspects to be observed

The person in charge of patient positioning should have accurate knowledge of the exact application area. For example, a tumor located in the pancreatic head calls for a different electrode position than a tumor in the pancreas tail area. This also applies to the lungs, intestines or other organs. In the case of head/neck applications, the arm electrode in particular may not be free and come in touch with other body parts. As the image below shows, the edge of the electrode touches the patient's shoulder in a neck radiation session with the patient positioned on the side. If the shoulder is not kept at a distance and protected with multiple double-folded towels, the point of contact may even develop third-degree burns.

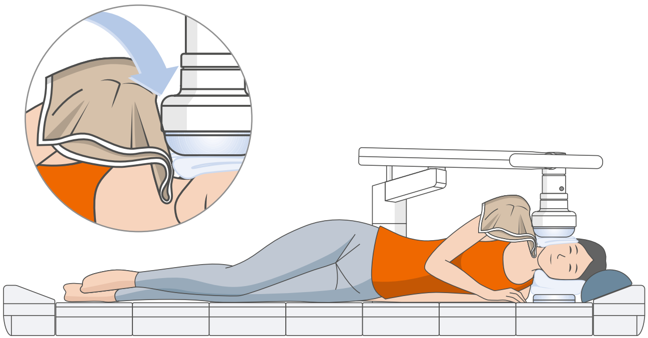


Fig. 25: Use thick insulation to protect the shoulder against unwanted contact

Water cushion as a coupling aid

Another problem consists of the unevenness of the body's physiology or is caused by body curves. The best effect is achieved if the affected body region of the patient is coupled as well as possible to the area of the electrodes between which the capacitive field is established. Strive for direct and large-surface connection of the electrode bolus with the body for direct energy coupling. In the case of a cachectic or emaciated patient, as shown in the image below, this would be difficult to achieve without additional water cushions.

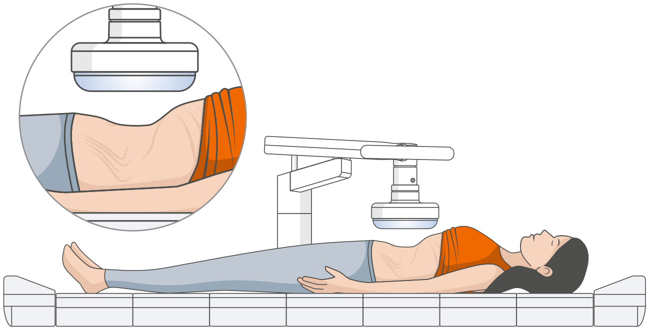


Fig. 26: Water cushion to bridge indentations and for optimal adaptation to body physiology

It is recommended to avoid situations in which only a part of the water bolus has contact while the other parts are, so to speak, hanging in the air. That would be the case with curved body surfaces, for example with liver or thigh treatments. Additional water cushions in different sizes again are the best tool in this case.

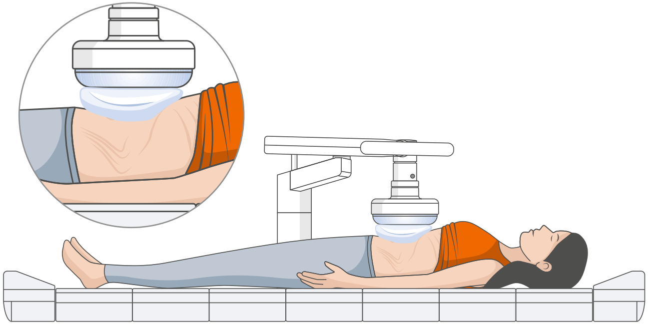


Fig. 27: Examples of using water cushions for adaptation to body curves

Water cushions should either be filled with deionized water (distilled water from a drugstore) or contain a water solution with 5% salt content. The use of regular tap water is not advisable. Distilled water has the advantage that it does not heat up or absorb energy, but may lead to scatter losses of the field. Water with 5% salt content has the disadvantage that it heats up more than deionized water. but it couples virtually without any scatter losses.

Conclusion:
Such a (deionized) water cushion not only helps to optimize the coupling, but may also make the applied electromagnetic field more homogeneous. Moreover, thanks to the associated greater distance between the electrodes, a slightly higher energy output may be applied under certain circumstances.

The images below illustrate examples of good adaptation to difficult target areas. The image on the left shows a patient in side position for treatment of a neck tumor. In spite of the pressure exerted by the upper water cushion, the patient subjectively tolerated the positioning well and the system was well coupled for the field. The field was directly in the target area. The cushion roll served to prevent slipping of the head. In the image on the right, the target area was located in the upper jaw in the area of the incisors.

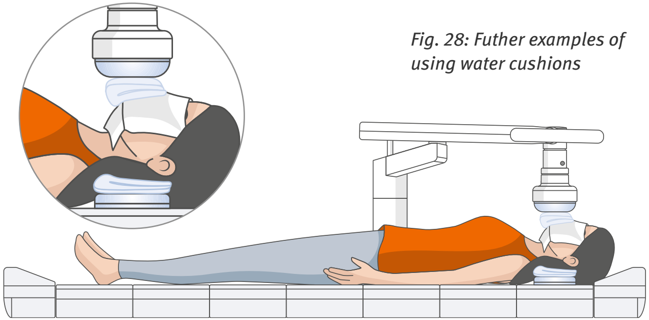


Fig. 28: Futher examples of using water cushions

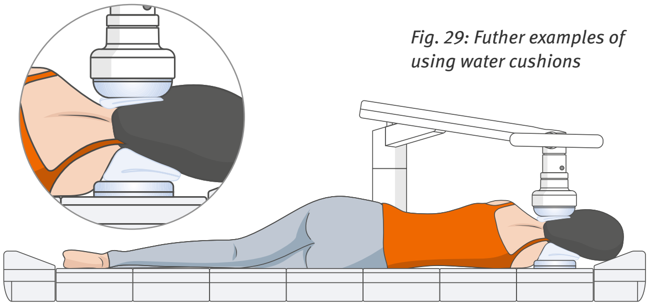


Fig. 29: Futher examples of using water cushions

Finally, an example of an impermissible positioning:
In this case, the upper electrode did not have full contact and the cushion of the lower electrode does not couple the field sufficiently to the therapeutic "region of interest".

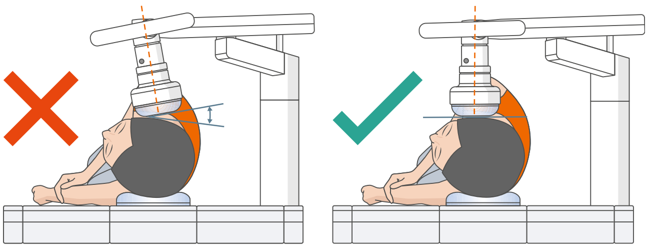


Fig. 30: Comparison of wrong and right positioning

Matchbox adjustment

Ideally, only the patient's body should be located between the electrodes, with the limitation that it makes sense to place a sweat-absorbing thin cotton cloth or paper towel between the skin and the electrode bolus for hygienic reasons and to improve thermal tolerance.

Occasionally, however, the matchbox of the Celsius 42 device cannot achieve a final adjustment. In this case, the user will hear a sliding noise and the monitor will show that the specified energy cannot be applied. The function of the matchbox is to simulate the dielectric located between the electrodes (i.e. skin, muscle, fat, bones, lumen etc.) to guarantee the quick polarity changes (13 million times a second).

Although adjustment problems in the matchbox are not common, they do happen. In most cases it is sufficient to change its position or make a small change to the dielectric to enable the matchbox to achieve the necessary adjustment for energy output

The following options are available to the user to resolve the issue. They are listed below in the order of the recommended priority:

1. Check the perpendicular position of the arm electrode to the lower tile electrode and correct it as necessary
2. Check the full placement of the electrodes on the body, including along the vertical axis, (move arm electrode a little closer if necessary); use water cushion if applicable or slightly change its position
3. Slightly reposition the patient
4. Remove any gauze, cotton towel or linen cloth or replace it with a different material; use additional cloth in rare cases
5. Change the energy output setting by +/- 5 to 10 W
6. Use an additional water cushion to create additional distance. In such a case, try to increase the energy output slightly in compensation as a next step.

Positioning aids

Supports used as positioning aids are valuable tools to make the treatment of frequently up to one hour as tolerable and pleasant as possible. Cushion rolls, blocks or wedges in various sizes are helpful for positioning the knees or lower legs as comfortably as possible. Patients in many cases like fill volumes to achieve a slightly upright position. They also appreciate blankets that can cover the body parts outside of the treatment area.

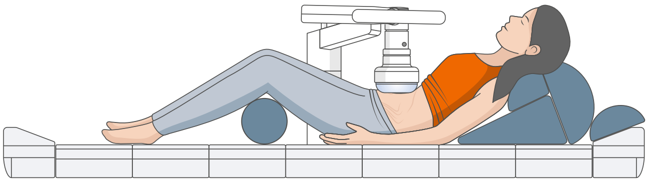


Fig. 31: Positioning aids

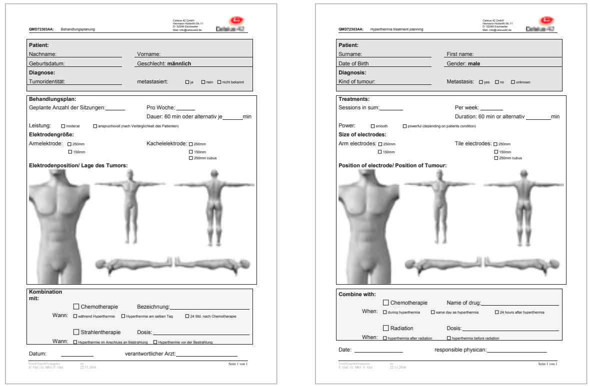
Occasionally we see patients for whom lying on a flat surface is painful. Soft anti-decubitus mats have proven useful in such cases. They must be cut out in the area of the lower tile electrode to avoid any impact on the effectiveness of the field.

4.2 Organizational questions, documentation and procedural aspects

In accordance with the quality guidelines, it is appropriate to design a special written order for hyperthermia that should explicitly include the following points:

- Time recommendations in combination with radiation therapy and/or chemotherapy
- Exact position
- Number of projected fractions
- Output protocol to be used

We also recommend the use of an information sheet, which the patient counter-signs prior to the first treatment. The following text is a suggested sample for an order sheet:



QMD72303AA: Behandlungsplanung

Celsius 42 GmbH
Hermann-Hollerith-Str.11
D- 52249 Eschweiler
Mail: info@celsius42.de

Patient:
Nachname: ______ Vorname: ______
Geburtsdatum: ______ Geschlecht: **männlich**
Diagnose:
Tumoridentität: ______ metastasiert: ☐ ja ☐ nein ☐ nicht bekannt

Behandlungsplan:
Geplante Anzahl der Sitzungen: ______ Pro Woche: ______
Dauer: 60 min oder alternativ je ______ min
Leistung: ☐ moderat ☐ anspruchsvoll (nach Verträglichkeit des Patienten)
Elektrodengröße:
Armelektrode: ☐ 250mm ☐ 150mm
Kachelelektrode: ☐ 250mm ☐ 150mm ☐ 250mm cubus
Elektrodenposition/ Lage des Tumors:

Kombination mit:
☐ Chemotherapie Bezeichnung: ______
Wann: ☐ während Hyperthermie ☐ Hyperthermie am selben Tag ☐ 24 Std. nach Chemotherapie
☐ Strahlentherapie Dosis: ______
Wann: ☐ Hyperthermie im Anschluss an Bestrahlung ☐ Hyperthermie vor der Bestrahlung

Datum: ______ verantwortlicher Arzt: ______

E: Oel | G: MO | F: Oel 22.11.2016 Seite 1 von 1

QMD72303AA: Hyperthermia treatment planning

Celsius 42 GmbH
Hermann-Hollerith-Str.11
D- 52249 Eschweiler
Mail: info@celsius42.de

Patient:
Surname: ______ First name: ______
Date of Birth ______ Gender: **male**
Diagnosis:
Kind of tumour: ______ Metastasis: ☐ yes ☐ no ☐ unknown

Treatments:
Sessions in sum: ______ Per week: ______
Duration: 60 min or alternativ ______ min
Power: ☐ smooth ☐ powerful (depending on patients condition)
Size of electrodes:
Arm electrodes: ☐ 250mm ☐ 150mm
Tile electrodes: ☐ 250mm ☐ 150mm ☐ 250mm cubus
Position of electrode/ Position of Tumour:

Combine with:
☐ Chemotherapie Name of drug: ______
When: ☐ during hyperthermia ☐ same day as hyperthermia ☐ 24 hours after hyperthermia
☐ Radiation Dosis: ______
When: ☐ hyperthermia after radiation ☐ hyperthermia before radiation

Date: ______ responsible physican: ______

E: Oel | G: MO | F: Oel 22.11.2016 Seite 1 von 1

Fig. 32: Sample for an order sheet

It is astonishing how frequently relevant treatment information is not communicated adequately to the hyperthermia operating staff. That begins with the exact (!) designation of the target area (for instance, the terms “abdomen” and “neck” are too vague), continues with the failure to communicate comorbidities, and ends with imprecise specifications of what is to be achieved in a hyperthermia session. A structural specification and some organizational clarification must be available for these points.

Supervision

As stated above, continuous supervision of the patient is essential, especially in a more demanding setting for a curative objective. Starting from certain energy input levels, the Celsius TCS system calls for patient feedback via the safety switch once a minute. However, the well-being and possible perspiration of the patient should also be continuously monitored below these thresholds and controlled very frequently. Such procedures are highly labor-intensive, but bottlenecks and shortage of operating staff are the main causes for loss of quality and not achieving the otherwise attainable therapeutic result.

Documentation

The CELSIUS42 system software allows for easy documentation of observations and incidents during the treatment. There are two fields: one field with comments that are automatically transferred to the optional treatment/medical report and an internal field that only documents records in the database. Such notes help to build systematic experiences in hyperthermia.

In this context, recording various classifications and tumor stagings is important as well. Across all clients, such data can provide guidance for best practice experiences, differentiated by tumor type. Hyperthermia is still criticized these days for its lack of consensus for application. Such documentation could generate valuable suggestions over the course of time. Thanks to the option to connect a second parallel monitor, the documentation can also be recorded during the ongoing patient treatment.

Of course, non-university clinics or medical practices will find it difficult to carry out studies. On the other hand, the relative absence of specific studies has led to the fact that hyperthermia still does not play the role it deserves in clinical oncological practice. There has been discussion of new epidemiological approaches that can also take into account results from past treatments; however, this requires at least a minimal level of documentation. The system at least saves all technical energy input parameters of a session in its own database, but evaluations only make sense if tumor characteristics and patient information are recorded as well.

V

The complex aspects of thermal tolerance

It takes demanding energy input protocols to achieve temperature increases to 40 °C or even above 42 °C. It must also be noted in this context that such energy protocols in the last third or fourth of the application easily reach the thermal tolerance of the patient. At that time, the output of the 250 mm electrode ranges from 150 W to 200 W, and the total energy input of the session can reach 550 kJ. As a consequence, treatments are frequently aborted because the patient is in pain. Over the course of the years, operators compile a body of knowledge about effective ways to increase a patient's thermal tolerance that enable the affected individual to undergo the demanding hyperthermia treatment without pain.

Accordingly, the **definition of thermal tolerance in this context** is the ability of a patient to endure hyperthermia treatment without pain and therefore, without aborting the procedure. This is contrary to a definition that would see thermal tolerance as a patient’s fundamental ability to react to the energy impact with an elevated temperature. It is also contrary to the definition that tumor cells protect themselves against the impact of heat with heat shock proteins.

Let’s begin with an overview of the main factors that impact the energy input and the associated achievable temperature gradient:

In case of overly high energy input (W/kJ):

- Skin burns
- Subcutaneous fat burns
- General pain sensations

In case of overly low energy input (W/kJ):

- The fat absorbs the energy so that the target region is located below layers of fat
- In heavy patients, the target region is deep-seated in the body. This causes a loss of energy input in the amount of the squared distance of the electrodes to each other
- The target volume is located closely to large blood vessels. (Cooling effect of vascularization or insulating air-filled lumina).

Suitable measures

Based on our experience of several years we can say that the total effect of measures can significantly impact the thermal tolerance of a patient and allow for using higher energy inputs, which generate higher temperature gradients in the target area. It is obvious that such a process must be associated with continuous personal presence and support along with ongoing observation during the second half of a treatment session. This must be guaranteed from an organizational point of view.

The following actions are available:

1. Energy inputs in a “step-up heating” structure
2. Psychological aspects
3. Manual adaptations such as protection of sensitive areas, repositioning, minor distance changes/adaptations with water cushions
4. Energy adjustments, small breaks
5. Skin cooling
6. Keeping the skin dry - no perspiration!
7. In special situations: Minor sedation with continuous, attentive supervision

To Point 1: Step-up heating

The energy protocols recommended in Section 3.3 represent a step-up heating structure that comprises two dimensions: First, a step-by-step energy increase during a session (applies generally to all sessions).

Second, an increase of energy inputs from the initial session to the next to ensure that sufficient sensitization has been achieved after 5 treatment sessions. No scientific evidence is available to justify this recommendation, which is based on plausibility considerations. However, the empirical observation that patients are able to tolerate a higher energy input when a step-up heating structure was used as opposed to an aggressive direct approach is very convincing. It appears important in this context that there is a physiological habituation effect, which in our experience makes higher energy inputs easier to tolerate in subsequent sessions.

Since new treatments will naturally cause patients to feel uncertain, it is certainly beneficial not to push the pain threshold in the first three treatments.

To Point 2: Psychological aspects

It has been repeatedly observed that patients appear to perceive small uncertainties, such as, e.g., an unfamiliar feeling of warmth or minor pain sensation as more harmless in the presence of a competent operator compared to situations in which no professional staff person is present. Of course, a conversation in a relaxed atmosphere is ideal. With a little experience, the user can anticipate which sensation is likely to occur in each treatment phase. Proactively addressing such an experience before the effect occurs builds patient trust, and trust is a valuable, powerful ally for increasing thermal tolerance. All aspects that promote confidence are useful; this may include the fact that the same operator always supervises patient sessions to build up a gradual sense of familiarity.

Distraction or focusing on something else is the next step in this direction and can easily reach the nature of trance. We like to ask our patients about their past sports interests. When treatment becomes somewhat strenuous in the last phases of a session, a description of the relevant sports activities can capture the attention to effectively distract the patient from moderately distressing or frightening side effects. (One example from swimming: how you get changed, set up your towel etc. for later, cool off, get into the water, the first strokes… Change of swim style… how the body feels as it moves through the water, what the breath is doing… movements in their own rhythm… the absence of thought… attention to individual movements or body parts… turning point… sprint…and reach the mark…) A valuable interval of 10 minutes can easily be bridged in this way.

To Point 3: Manual adaptations

Scars in the target area are among the sensitive sites that need to be protected. The bellybutton is such a sensitive region as well. And finally, ribs and pubic bone are among the most frequently cited local pain lines. One pragmatic solution is to protect these areas with a doubly or triply folded cotton cloth or gauze as shown in the images below.

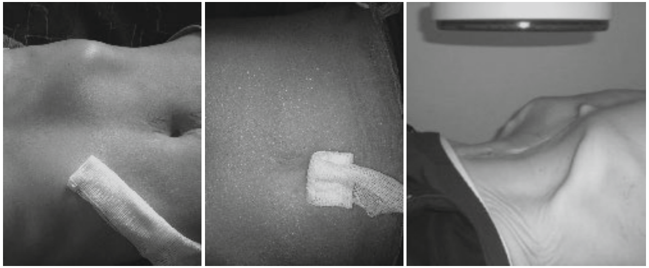


Fig. 33: Sensitive body locations

Repositioning

Pain is sometimes felt on a highly localized basis. Shifting the electrode by approximately 1 cm, slight repositioning of the patient body or changing the angle of the arm electrode (within the available small range of 5 degrees) can achieve positive results. You can also consider a slightly different tilt or position of the patient. Particular care should be taken to ensure that the electrodes are perpendicular to one another since a shift can cause higher selective energy peaks (see section above).

Small distance changes/adaptations with water cushions

Especially needle-like, piercing pain can be caused by the fact that the field is not uniformly distributed over the area below the electrodes. Depending on the dielectric, there may be small voltage peaks, which are often described as needle-like. Bone marrow seems to be particularly sensitive to them.

One method to counter them is to slightly increase the distance to the upper electrode. Even a water cushion (see section above) with a height of only 1 cm can help to minimize or even eliminate this effect. Strictly speaking, the energy input should be slightly increased after spacing the electrodes further apart but in practical terms, the operator will be simply glad to have found a solution and a mere centimeter will not make a major difference.

In the last phases of treatment, additional water cushions can also be brought in. Patients usually welcome their use, particularly if they have been cooled in the refrigerator.

To Point 4: Energy adjustments

In this context it should also be noted that various physiological dispositions of a patient can change from session to session. Thus, the (cooling) blood circulation in the micro-range of the tumor is highly irregular and cannot be predicted (P. Vaupel). As a consequence, a patient may tolerate an identical energy protocol well on one day and find it almost unbearable in the next session. That means if a patient has “a good day”, the energy protocol may need to be adjusted upwards with more energy applied than planned. If the energy input appears too high, it can and should be adjusted to the lower range accordingly. The Celsius42 device offers the option to briefly interrupt the treatment at any time and to step the energy level up or down in steps of 5 W. For this reason, the protocol recommendations for the last phases of a treatment feature a free scale. Short breaks in the last periods also significantly contribute to completing the necessary treatment. Even taking 10 seconds off can be helpful.

To Point 5: Skin cooling

The Celsius42 device features an active cooling system in the form of a water circuit located below the electrodes, which can be cooled down to 8 °C and causes a subjectively felt cold sensation on the skin. However, influencing the thermal receptors allows for a higher energy input to ensure that a higher temperature development can occur deep in the body.

Thermal receptors for heat and cold are physiologically complex. The cutis contains direct heat receptors as well as a paradoxical discharge of cold receptors. In addition, there are polymodal heat pain receptors with neuronal and molecular mechanisms deep in the body. The heat receptors located directly in the epidermis are mainly found in a depth ranging from 0.6 mm to 2.5 mm. They are within easy reach of externally applied coolin.

Thermal receptors respond primarily, but not exclusively, to changes in temperature with the following parameters:

- Extent of temperature change
- Speed of temperature change
- Area of exposure

Static discharge frequency

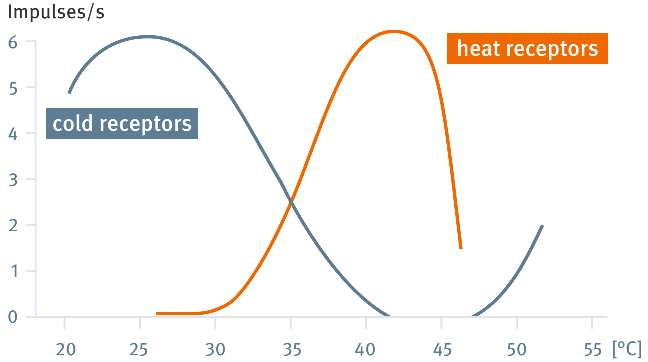


Fig. 34: Activated temperature receptors as a function of temperature
In: Thews et al Physiologie, 1999, p.706.

The actual heat pain is therefore only perceived as superficial pain3). Nociception in deeper tissue seems to mainly respond to temperatures above 43°C 4), i.e. outside the temperature thresholds that are of interest for us. When individual hot spots occur, which – as explained in Section 2 – are more common with antenna procedures than with capacitive hyperthermia, they are described as pressure or a dull ache. Authors reporting on experiences with antenna systems have also described them as follows: "In practice, deep-seated hot spots are often indicated as a sensation of pressure inside, diffuse pain, pain in the back, nausea, urinary urgency, or mistakenly identified as pressure by the water bolus."5)

Perceived pain, which is not associated with avoidable causes such as perspiration, appears to be caused by electrical peaks rather than the actual heat and is frequently described as a sharp, needle-like unpleasant sensation. Cooling with a continuous cooling circuit that is not just used for the water bolus for coupling purposes can therefore have a favorable influence on a patient's thermal tolerance. This explanation is also helpful when patients initially complain about the cold sensation of the electrodes.

To Point 6: Continuously dry skin: No sweat

It is enormously important to remove any perspiration forming on the skin as soon as possible. Drops of sweat are salty and therefore highly ionized, which means that they draw a lot of energy. In that way, they act like a magnifying glass for the region and severe skin burns may occur easily if this perspiration is not addressed. It is therefore required and expedient to place a thin cotton or paper towel between the skin and the water bolus to absorb any perspiration at an early stage. The theoretically insulating effect is negligible and so marginal that we could not measure it. As soon as such a cloth has absorbed significant moisture, the operator must interrupt the treatment, as one of the most effective measures to prevent pain sensation, and change the cloths to avoid the side effect of a possible burn.

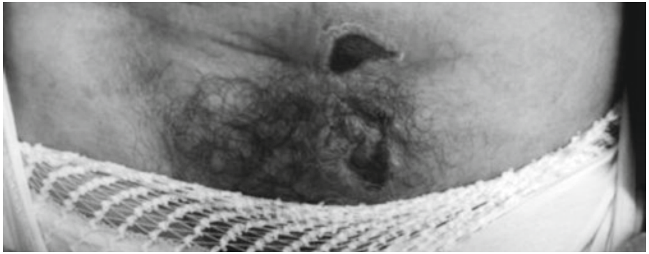


Fig. 35: Example of a burn caused by failure to absorb perspiration during a treatment

To Point 7: In special situations

In special cases involving highly sensitive patients, minor sedation under attentive and continuous care can be justified. This applies especially in the case of certain tumor entities and/or clinical therapy rationales, in which hyperthermia represents an important therapeutic element.

VI Contraindications, side effects and cave situations

6.1 Contraindications to capacitive hyperthermia

Contraindications result from technical reasons, the individual condition of a patient, and the accompanying circumstances of a treatment.

Technically induced contraindications include:

- Cardiac pacemakers or other implanted electrical devices worn on the body or devices with circuits made of metal.
- Stents or metallic implants in the target area. If metallic implants are MRI-compatible, a different assessment may result
- Non-removable devices worn on the body or devices with circuits made of metal, metallic lengths and coils

Patient-induced contraindications include:

- Sedated patient, unless under the absolutely permanent supervision of an experienced medical professional. This also applies to patients with epilepsy.
- Patients with recent surgeries if the surgical wound is in or near the target area (wait 7-10 days or use extremely reduced energy output with continuous monitoring)
- Patients who recently received a bone marrow transplant
- Insufficient organ functions
- Pregnancy or lactation
- Active alcohol or drug abuse
- Active, severe infection (e.g. sepsis)

- Karnofsky performance scale index ‹ 50 or serious internal or neurological comorbidity with poor prognosis or extremely fragile cardiac/circulatory situation or general condition according to the WHO (ECOG) performance status 2 (=KI ‹50%)

Procedure-induced contraindications include:

- Demanding energy input protocols <u>without</u> continuous presence of a qualified professional, at least in the last half of a treatment.
- Caution should also be exercised by pregnant medical staff! A pregnant medical professional should no longer work directly with hyperthermia patients.

6.2 Side effects of capacitive hyperthermia

Many of the side effects listed below can be prevented with appropriate precautions. These are explicitly addressed in the sections above, but are summarized here again in the form of a list.

Main adverse side effects include:

- Burns (1st to 3rd degree)
- Pain sensations
- Enhanced effects in combination with radiation therapy and some chemotherapies (e.g. mitomycin; thermosensitive doxorubincin and others (in part intentional)). Side effects of radiation therapy such as

skin redness or cerebral edema can be reinforced by hyperthermia. Local infections may also be activated under radiation and reinforced by hyperthermia.

Part II of this User Guide addresses **special side effects** related to organs and target areas. As a preview, we would like to draw particular attention to the risk of cephalagia and epileptic seizures associated with the treatment of brain tumors.

Further side effects may include:

- Short-term (up to two hours) asthenia after treatment
- Skin redness
- Diffuse abdominal pain (rare)
- Sub-febrile temperatures up to 39°C rectal
- Neurological sensations (hypersensitivity of the hands, feet and legs); "electrifying" effects can occur up to approx. 1 hour after the treatment. **Tip: Massage is helpful**

6.3 Cave situations

There are a number of applications that are contraindicated for an inexperienced user, such as brain treatment. Experienced hyperthermia therapists will know how to handle them.

Such situations pertain to*:

- Applications in the brain region
- Patients with a history of epileptic seizures
- Patients with cardiovascular disorders
- Patients with metallic implants
- Multi-morbid patients

As with many other therapies, a personal experience factor is very valuable for the application of hyperthermia, and hyperthermia therapists develop a learning curve over the years. Overall, hyperthermia, if used properly, represents a great potential that has not yet been given the widespread recognition it deserves.

* *We will discuss the potential entities in detail in Part 2 and will also describe the CAVE situation accordingly.*

Postface

The authors would like to thank Christian Hartmann, the new CEO of Celsius42 GmbH, who initiated and consistently encouraged the creation of this short Hyperthermia User Guide. We are confident that users will find the information of this booklet useful and beneficial and are grateful to Mr. Hartmann for suggesting and supporting the concept. We hope it will contribute to the further recognition of hyperthermia as a relevant treatment to help it gain the place it deserves among the many available therapy options.

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Please find a complete list of literature sources at www.celsius42.de

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