Guideline for local capacitive radiofrequency (RF) hyperthermia

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Guideline for local capacitive radiofrequency hyperthermia

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1. Definition and efficacy of local capacitive radiofrequency (RF) hyperthermia

Hyperthermia is an easily understood natural phenomenon associated with fever that was even mentioned as a treatment three thousand years ago. In the 1970s, the fundamental principles and rationale of hyperthermia for modern multimodal therapy concepts in conjunction with radiotherapy and chemotherapy were established. In modern medicine, this concerns the targeted heating of the body or individual regions of the body. In contrast to fever or endogenous whole-body hyperthermia (WBH) using pyrogenic drugs, heat is supplied to the patient externally which heats up the body or the organs and tissue affected by a tumor.

Hyperthermia, but also other cellular stress conditions, such as external noxious substances, ionizing radiation, tumor-toxic substances, hypoxia and hypoglycemia, can cause what is termed a heat shock response. What all these different types of stress have in common is that they generally inhibit translation (= the forming of cells using the information contained in the cell nucleus, more specifically the genetic information) and result in the increased expression of heat shock proteins (HSP) instead. Most members of the HSP family are molecular chaperones that play a role in the folding of proteins, the transport of proteins and the assembling of multi-protein complexes. Functions of individual heat shock proteins (e.g. HSP-70) for the immune response (e.g. antigen presentation) has become indisputable. These proteins are signals for autologous killer cells of the immune system to break down “weakened” cells.

The efficacy of hyperthermia depends, among other things, on the temperature reached. At 42.5 °C, a direct cytotoxic effect begins. In the case of tumors that are poorly supplied with blood and nutrients, even slightly elevated temperatures are reported to be cytocidal, although tumors – and tumors with larger necrotic zones even more so – can be heated up or overheated better.

Even at temperatures from 39°C, experiments have demonstrated a radiosensitizing effect, i.e. the cell’s own repair of the tumor DNA single-strand and double-strand breaks generated by the ionizing radiation of the radiotherapy is inhibited in the heated cells. Similarly, a sensitizing effect occurs in certain chemotherapeutics at these temperatures, in particular in alkylating agents, such as cytostatics which interact particularly directly with the DNA. Further physiological effects of hyperthermia are also known, such as the increase in the supply of blood and/or vascular permeability, which can potentially cause an increased substrate supply of tumor-toxic substances in the overheated area of the tumor.

Experiments repeated multiple times in scientific laboratories demonstrated that approx. 10–15% of the tumor stem cells, thus the cells crucial for therapy success, are already killed at 45–60 minutes of constant heating from 38.5–40.5°C.The number of eliminated clonogenic cells increases with increasing temperature.

An essential problem associated with increasing the tissue temperature in the target area is the downregulation of the immune system. [21] Basic research has shown that direct damage to tumor cells can only be expected by applying heat above a temperature of 42–42.5°C for an application time of at least 30–45 min.

Below this temperature limit, enhancing effects for chemotherapy or radiotherapy are crucial, including influencing the immune system (as even in fever therapy), among other things, in terms of stimulating the NK cells (natural killer cells). A few years ago it was possible to demonstrate that a temperature increase exceeding 40.5°C reduced the immune defense system by decreasing the number of NC cells significantly. Using this data, the targeted temperature for the complementary therapy ranges between 38.5–40.5°C. [21]

An important application of hyperthermia is the treatment of local advanced tumors which are not operable or only operable using extremely radical (mutilating) modalities, or tumors that cannot be treated sufficiently therapeutically either by radiotherapies or chemotherapies, for example, glioblastoma multiforme WHO IV, head and neck tumors, locally advanced breast cancers, bronchial carcinomas, pancreatic carcinomas and tumors of the pelvic organs, in particular capacitive hyperthermia for cervical carcinomas, which has provided the best study results to date.

However, this does not mean that the treatment outcomes have to be worse in other types of tumor, such as pleural mesotheliomas, very large lymph node metastases, liver and bile-duct carcinomas, as so far the sensitivity for particular histopathologies is not known to be considerably worse. Positive data on capacitive hyperthermia is not only available from randomized trials on ENT tumors, cervical carcinomas and esophageal carcinomas, but according to Gadjar [79], capacitive hyperthermia is also apparently a useful simultaneous adjuvant therapy to the radiotherapy of bone metastases, as he demonstrates in his article summarizing his Taiwanese trial [78].

Expanding the application of capacitive hyperthermia systems to other body sites, such as the brain, lungs and mediastinum, appears to be also favorable. Combined with hyperthermia, even low doses of classic therapeutic modalities, such as radiotherapy and chemotherapy, can achieve greater efficacy as standard doses - while maintaining the patient’s quality of life as there are fewer side effects (important in highly palliative situations).

However, applying hyperthermia in the indications listed totally depends on effective and practical workability. Heat can be generated in the human body using various technical procedures and depending on the heated region is termed local, regional or whole-body hyperthermia. Capacitive heating requires two electrodes. A high-frequency alternating field is generated between the electrodes resulting in the effective overheating of the body in this region.

The major challenge in applying heat within the framework of a hyperthermia therapy is the physical problem of increasing the temperature in the target area homogeneously and reproducibly. The advantage of regional radiofrequency hyperthermia (RF) hyperthermia is that the therapy is tolerated extremely well. Patients find the therapy less wearing and it has hardly any noticeable additional side effects. Possible minor side effects occur directly during therapy and result from circulatory strain due to heat stress, from local overheating and pain resulting from this or minor burns (e.g. in adipose tissue), or manifest as persistent paresthesia (rare) which can usually be prevented by following all necessary precautions.

RF hyperthermia is regarded by oncologists in the treatment of locally advanced and recurrent deeply-seated carcinomas of the pelvis and abdomen – in particular if these spread regionally (for example in the form of locally advanced pancreatic carcinomas, liver metastases or a peritoneal carcinosis).

Presacral relapses of rectal or sigma carcinomas that are mainly inoperable are a major problem in palliative therapy. Their cardinal symptom is sacral or deep pelvic pain. In most cases, this pain can

be only stopped unsatisfactorily using analgesics. In the case of a local relapse, many patients previously radiated can only be treated with reduced further doses as doses of ionizing radiation have already been partly used. If the maximum dose has not already been reached, the limited amount available only brings about short-term results.

In more than 80% of patients, pain is significantly attenuated or mostly absent over a longer period by combining a chemotherapy and/or radiotherapy with regional hyperthermia. [85] This data is an example that proves the increase in effect by combining chemoradiotherapy and hyperthermia. Compared to normofractionated radiotherapy, hyperfractionated accelerated radiation therapy reduces single doses, but increases the number of doses each day (radiation intervals > 6 hrs.) and can increase the benefits of RF hyperthermia in non-conventional therapies further and simultaneously reduce the rate of long-term side effects dramatically. To this end, it seems advisable to apply RF hyperthermia as early as possible after the first radiation fraction or as close as possible before the second fraction (see Fig. 1). Moreover, there is data of phase II and phase III trials for the combination of regional hyperthermia with standard therapies in advanced rectal carcinomas in a pre-operative chemoradiotherapy plan. [76]

2. Rationale of capacitive RF hyperthermia

Capacitive RF hyperthermia is a well-studied and promising oncological therapy. Findings of experimental and clinical trials indicate that hyperthermia is an ideal complementary therapy and can be a strong sensitizer for radiotherapy and chemotherapy. New technological methods and extensive experimental and clinical trials have confirmed the efficacy of its options and substantiate its application in cancer therapy as a benefit to the patient.

The effects of capacitive RF hyperthermia on biological structures are pleiotropic and complex. [18] In addition to the technology used, its effects depend on the temperature, application time, heating-up time as well as the shape, type and size of the tissue, the perfusion and the homogeneity of the temperature distribution. Its effects range from the denaturation of cellular and sub-cellular elements to impacting the entire tumor tissue and the tumor's surroundings – among other things, also due to the obligatory electromagnetic fields that facilitate the temperature increase in the tissue in the first place (see Wust P et al.: Non-thermal effects of radiofrequency electromagnetic fields. Sci Rep. 2020 [83]).

Numerous publications report on the positive effects of combined hyperthermia and radiotherapy. Nevertheless, this combination treatment has still not been used sufficiently in clinical oncology. In their reviews, Horsman and Datta [1, 22] are convinced that hyperthermia could be one of the most effective modalities to support radiotherapy.

Even randomized phase III trials prove its effectiveness (**see 13.3.2.**). Thus, the National Comprehensive Cancer Network (NCCN) updated and revalued the 2019 German Society for Oncology [DGO] guidelines and in doing so included the combination therapy comprising radiotherapy (RT) and hyperthermia (HT) in its guideline for the treatment of breast cancer recurrences.

Depending on the location, size and type of the tumor, different technical methods of heat induction are applied.

2.1. Hyperthermia as an adjuvant therapy to (chemo)radiotherapy

In vivo trials have shown that the efficacy of radiotherapy can be increased by hyperthermia by a factor of 1.2 to 5. [80]

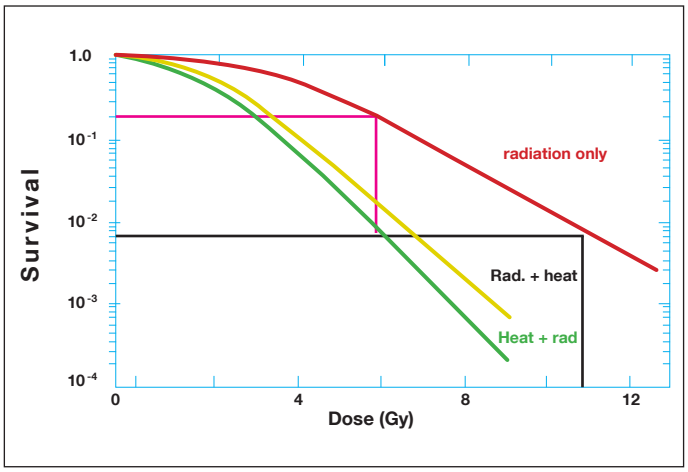


Fig. 1: 60 min. of treatment at 43°C [81]

The enhancement of the radiosensitizing effect by up to 2.3 times is based on, among other things, initially increasing tumor perfusion using an increased supply of O_2, thereby starting the formation of radicals and the effect of radiotherapy. After the O_2 radicals damage the cells, the locally elevated temperature blocks the subsequent repair process of the damaged tumor cells.

2.2. Potentiating the efficacy of a sole chemotherapy by means of hyperthermia

The most important mechanisms that lead to an interactive effect with cytostatic drugs are, among other things, an increased intratumoral drug concentration as well as increased intracellular drug metabolism. Similarly, the loosening of the cell structure and a related "lymphatic trafficking" play role. Nordenström [86] already reported in 1983, which was subsequently confirmed by other authors, that good treatment outcomes of deep hyperthermia in combination with cytostatics can be reached by damaging the ion channels in the cell membrane under the effect of electromagnetic fields as a result of the potential difference between the extracellular fluid (ECF) and the intracellular fluid (ICF).

Similar potentiation is also found when combining radiotherapy with cytostatics. Ionizing radiation also attacks the ion channels so well that simultaneously applied cytostatics become devastatingly effective in tumor cells, which would be considerably less effective without being combined with radiotherapy (radiosensitization), i.e. they would not have found their way into the cell at all (e.g. carboplatin instead of cisplatin in carcinomas, e.g. head/neck tumors, cervical carcinomas and esophageal carcinomas).

2.3. Qualitative interactions between RF hyperthermia and chemotherapeutics

According to various authors (mostly unanimous), combining RF hyperthermia and chemotherapeutics enhances treatment qualitatively.

2.3.1. Several CTx therapeutical potentials in combination with hyperthermia according to Hager

Interaction between HT and chemotherapy		
Independant	**Additive**	**Potentiating**
Actinomycin D (Act-D)	Carmustin (BCNU) +	Bleomycin (BLM)
Cytarabine (ARA-C)	Cyclophosphamide (CPM)	Carboplatin (CBP) +
Etoposide (VP-16)	Dacarbacine (DTIC)	Cisplatin (DDP) +
5-Fluorouracil (5-FU)	Doxorubicin (ADM)	Mitomycin C (MIM) +
Floxuridine (FUdR)	Epirubicin (EPI)	
Methotrexate (MTX)	Gemcitabine (GEM)	
Taxanes	Ifosfamide (IFS) +	
Vincristin (VCR)	Lomustine (CCNU)	
Vindesin (VDS)	Melphalan (MLP) +	
	Mitoxantrone (MOX)	
	Nimustine (ACNU)	Irinotecan (CPT-11)

* Preclinical results from human cancer cell lines or xenograft models
+ In clinical studies verified: # Time delay for hyperthermia of 20–24h

Fig. 2: CTx therapeutical potentials in combination with hyperthermia according to Hager (selection)

2.3.2. Therapeutical potentials of chemotherapeutics in combination with hyperthermia according to Wust and Issels (1981–1983)

Effect	Potentiated by heat	Unaffected by heat
Linear increase	Etoposid (→ 24 h HT)	
Linear increase	Cisplatin *	Hydroxyurea
	Carboplatin *	Methotrexate
Linear increase	Mitomycin C *	Vinblastin
> Linear increase	BCNU */ACNU	Cytarabin
Linear increase	Cyclophosphamide	Floxuridin
	Bleomycin *	Actinomycin
> Linear increase	Melphalan *	Etoposid
Expotential	Adriamycin	PALA
	Epirubicin *	Taxane
	Dacarbacin	
Linear increase	Ifosfamid *	
	Lomustin/Nimustin	
	Temozolomide	
> Linear increase	Mitoxantron/Vepesid	
Linear increase	5-FU/Bendamustin	
> Linear increase	Doxorubicin/Gemcitabine (<== 24 h HT)	

* Verified in clinical studies

3. Forms and impact of hyperthermia – general consensus

3.1. Forms of RF hyperthermia in the general consensus of its users

In the Kadota Fund International Forum 2004 – clinical group consensus – in Japan, the following forms of hyperthermia were fundamentally recognized and agreed upon by consensus. [82]

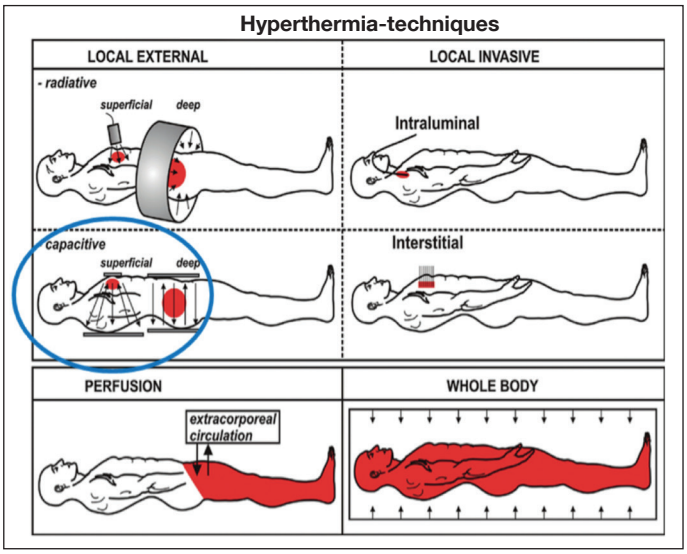


Fig. 3: Different hyperthermia techniques

3.1.1. Forms of hyperthermia

For regional applications of hyperthermia, there are non-invasive forms using a. antenna systems and b. capacitive systems, in addition to interstitial methods (including a hybrid form using injected ferro-nanoparticles). Local hyperthermia can be applied using external, intraluminal or interstitial applicators or application systems. The external application of heat is used for superficial hyperthermia and local deep hyperthermia. Devices with capacitively coupled electrodes or radiative high-frequency equipment can be applied in local hyperthermia. A special form is intraluminal capacitive prostate hyperthermia which is not covered by this guideline.

Capacitively coupled technology has, however, gained acceptance in the widespread clinical practice of local hyperthermia.

In this regard, the latter form is used most frequently in Germany and worldwide. Thus, only capacitive RF hyperthermia technologies applied externally are described in this guideline.

3.2. Effect of RF hyperthermia and its interactions

To what extent radiosensitizing/chemosensitizing or even cytotoxic effects are triggered by RF hyperthermia in terms of additivity, supra-additivity and potentiation depends on the temperature in the region of the tumor and the tissues surrounding it; also on whether the tumor and surrounding tissues react to electromagnetic fields and/or frequencies/frequency modulations in a different way; and whether the RF hyperthermia is applied alone with radiotherapeutic, oncology drug treatments or combinations thereof.

It is still not known to what extent electromagnetic fields play a tumoricidal role in capacitive hyperthermia and if these fields and the tissue heating, which these fields cause, enhance each other in their antitumoral efficacy. To obtain this essential information, further scientific work is required, preferably in the short term. Several clinical observations as well as animal and oncocytologic laboratory test result appear to support this. [50,51,84]

4. Features of local hyperthermia

There are currently no tumor-related or organ-related therapy standards with resultant comparability of the clinical potentials of different local RF-capacitive deep hyperthermia as well as objective, generally applicable results of its energy input and its quantifiable or qualifiable effects as attributes of individual capacitive hyperthermia variants.

4.1. Features in capacitive therapy procedures and resulting issues

4.1.1. Proof of temperature as the sole characteristic of hyperthermia?

Quality assurance in the form of validating attained temperatures in the tumor tissue is the major methodical problem of hyperthermia. On the one hand, there is the question when measuring temperature as to whether spot, area or volume measurements are to be carried out. The latter is certainly desirable; however, this is extremely time-consuming and laborious. On the other hand, the (patho)physiological characteristics are different depending on the individual patient; intra-individual differences can even exist in one individual patient at different treatment times and sites.

Pathophysiologically, perfusion is extremely irregular in the tumor tissue [2, 4] and the generation of heat is dependent to a large extent on the position and size of the blood vessels in the ROI (region of interest), as well as on the extent of the blood perfusion which causes a cooling effect. [3] Finally, there is a fundamental problem in defining a dose of heat. Is a high temperature with a shorter application time equivalent to a slightly lower temperature with a (correspondingly) longer application time? How do temperature and application time relate to body temperature and ambient room temperature, and which limits should be used? Are strong electromagnetic fields more cytotoxic or potentially even less strong at lower energy inputs?

4.2. Principle of RF hyperthermia in deep-seated body tissue

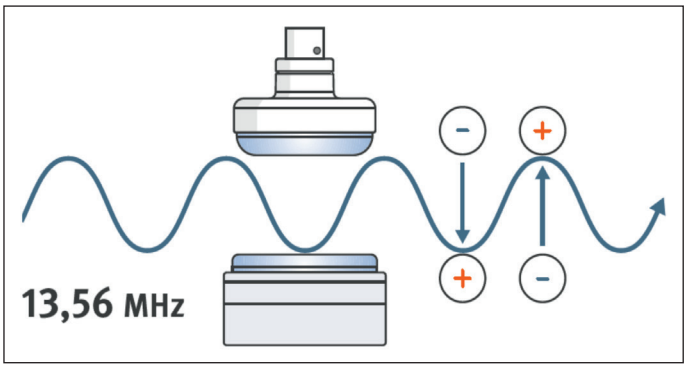


Fig. 4: Dielectric between charged poles

The type of dielectric between both charged poles is crucial for the heating effect. All ions (electrically charged particles) within the dielectric react to the electromagnetic field and move accordingly, thus generating heat. Ions are present in every cell and in every intercellular space.

However, the strongest effect occurs when dipoles are present in the dielectric. To reiterate, our dielectric is the space between the upper and lower electrode and it is ideally – in this present context – a contact surface touching the human body as extensively as possible. Human tissue is primarily water-based, and we can utilize the characteristics of the water molecule here because water molecules are such dipoles. Dipole means that one atom with slight negative charge, namely the oxygen atom, is positioned on one side and both hydrogen atoms on the other side. Therefore, they are not in balance electrically. If an electrical field is applied, the water molecules align themselves in the field direction (see Fig. 5).

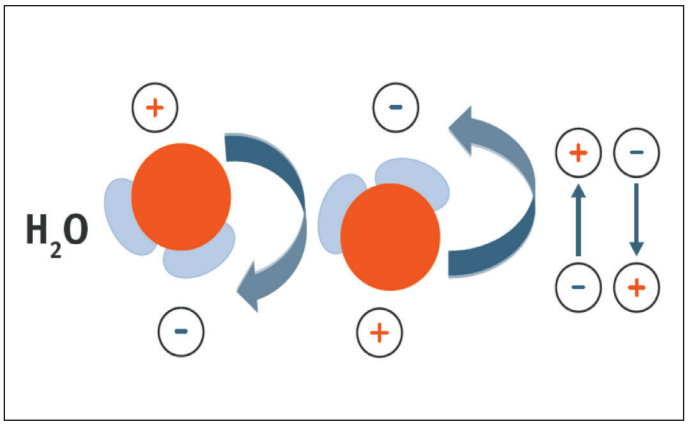


Fig. 5: Dipole structure of water

In the case of energy transmission by means of an electrical field (capacitive coupling), the electrodes are active as capacitors. The patient's body basically becomes the "insulating material" (dielectric) in the capacitor. An electrical field is formed between the (two to four) electrodes.

In capacitive coupling, there is a carrier frequency between 8 MHz, 13.56 MHz and a maximum of 27 MHz; above this emission frequency, a given amount of energy (unit: watt) can now be introduced into the tissue. The higher the applied energy over a unit of time (= (energy) output in joules), the greater the temperature impact in principle (Fig. 6).

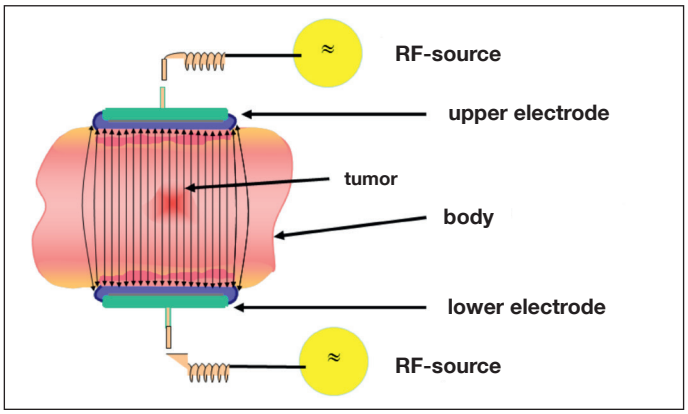


Fig. 6: The higher the applied energy over a unit of time, the greater the temperature impact

The limiting factor for this is the (subcutaneous) adipose tissue that potentially may absorb too much energy in obese patients and then, as a result, does not allow sufficient temperature impact more deeply, but rather reacts to internally stored heat by forming painful scarring “burn nodules”. In this regard, further physical factors described in the following influence the generation of heat, creating great differences between individual device types:

a. the size of the electrodes (individually and in relation to each other)

b. the underlying carrier frequency (in marketed devices 8 MHz, 13.56 MHz or 27 MHz)

c. the applied power (devices with up to 150, 400, 600, 800 or 1,600 W – Thermotron, Japan)

d. conditions dependent on design (e.g. number of active therapy electrodes, round cooling water electrodes of varying size and shape, and an electrode application with or without the circulation of cooling water)

e. the size of the electrodes

f. active cooling of the therapy electrodes at the therapy surfaceif necessary – among other things, adjusted to device-related requirements

4.3. Preclinical results and trials

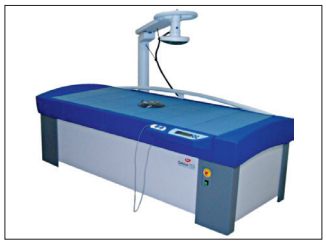
Even in previous attempts with capacitive coupling energy transfer, it could be shown that the technology of this device principally enabled temperature increases to be triggered deep in biological tissue. For this purpose, criteria were discussed and performance characteristics were defined. Such temperature measurements were performed on capacitive coupled systems with frequencies of 8 MHz and 13.56 MHz. [19, 20] Different therapy frequencies ranging between 8 MHz (Japan) and 13.56 MHz (Europe) have both got closer to what has been discovered in the meantime as the therapeutically optimal frequency of 10 MHz, which is why Asian and European therapeutic results/successes are analogous with each other. [86]

However, different frequencies require different energy outputs in watts in order to achieve the same tissue temperatures, so that it is not meaningful to compare devices alone on applicable/applied energy input by power rating per time unit, and this alone tells us nothing about the qualities of the devices used.

4.4. Types of capacitive devices used primarily and their properties

Irrespective of the manufacturer and the forms of electrode, the energy applied over a certain period is stated in kilojoules (energy level in watts × time = kilojoules). It thus also only be converted into temperature equivalents (degrees Celsius) by greatly lowering accuracy, thereby the attainable temperature in the treatment target areas of the individual patients is seldom exactly calculable. These kilojoule inputs can be measured again later on a phantom dummy (phantom) and also indicated in degrees Celsius after being converted very carefully. With regards to the phantom, it must be taken into consideration that there is no heat convection resulting from blood circulation, what as an “aid to calculating temperature” also needs to be evaluated critically.

(pre-clinical phantom measurments) (in vivo measurments) differentiated accoring to device **Celsius42+ | Thermothoron (Japan) | Oncotherm EHY-2000 u. EHY-3010/2030 | Synchrotherm (Italy)**

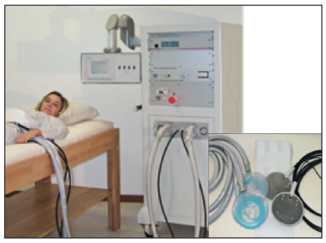


Celsius42+

- ✓ capacitive coupling
- ✓ 13.56 MHz frequency
- ✓ symmetrical configuration
- ✓ 600 W output power
- ✓ high-performance cooling
- ✓ treatment space not screened
- ✓ (no) invasive thermometry

Oncotherm EHY-2000 und EHY-3010/2030

- ✓ capacitive coupling
- ✓ 13.56 MHz frequency
- ✓ asymmetrical configuration
- ✓ 150–400 W output power
- ✓ no active cooling
- ✓ treatment space not screened
- ✓ (no) (invasive) thermometry



Synchrotherm (Italy)

- ✓ capacitive coupling
- ✓ 13.56 MHz frequency
- ✓ symmetrical configuration
- ✓ 800 W output power
- ✓ high-performance cooling
- ✓ treatment space not screened
- ✓ (no) invasive thermometry

Thermotron (Japan)

- ✓ capacitive coupling
- ✓ 8 MHz frequency
- ✓ asymmetrical configuration
- ✓ 1,800 W output power
- ✓ high-performance cooling
- ✓ treatment space not screened
- ✓ no (invasive) thermometry

Fig. 7: Types of widely used capacitive devices

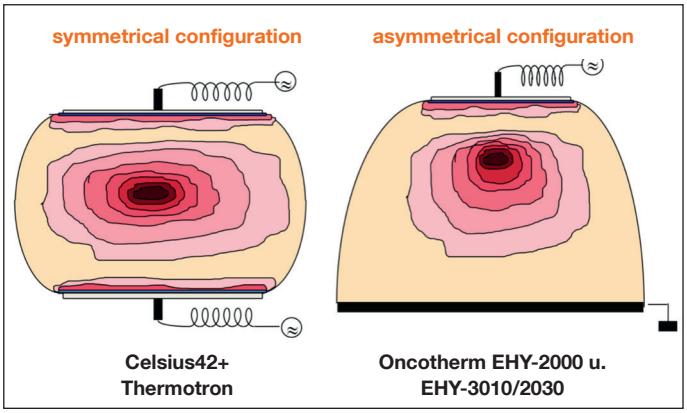


Fig. 8: Two of the types of devices described above (Fig. 7) with capacitive coupling, but with a differing arrangement of electrodes as well as temperature distribution - resulting in different performance characteristics.

5. Quality assurance in capacitive RF hyperthermia of malignant tumors (primary or metastatic)

5.1. Minimum qualitative requirements for hyperthermia therapy

Local RF hyperthermia should not be applied as the only anti-tumor measure. There are no studies proving the clinical benefit of hyperthermia administered on its own. The rationale behind this justification could refer to the immunostimulating effect of higher temperature environments [20, 21] and to an impact of electromagnetic fields that is also postulated for cancer. [50] There are isolated cases of patients (e.g. with glioblastomas) who refused other therapies or had exhausted such therapies but experienced temporary positive clinical outcomes using capacitive hyperthermia alone. However, no recommendations can be derived from such extremely rare individual cases.

In contrast, there is extremely broad consensus for **guideline recommendations** that **local hyperthermia should not be applied as the only anti-tumor modality**, but rather combined simultaneously with a whole series of oncological causal therapies. In a unanimous vote in the expert panel, in the executive board and in the scientific advisory board of the DGHT, the validation of the modalities thus depends on the necessity of the following combination options, as well as on the scientific review of the therapy results in trials and everyday clinical practice.

5.2. Combination options of capacitive RF hyperthermia

Capacitive hyperthermia can be combined, in principle, with various therapeutic methods, including:

- radiotherapy
- chemoradiotherapy
- “targeted” therapeutics (antibody and inhibitor therapies)
- whole-body hyperthermia
- • superficial hyperthermia (infrared HT)
- further tumor-toxic and tumor-static or supportive therapies (e.g. biologicals)
- cellular immunotherapies, e.g. with dendritic cells

5.3. Number of capacitive RF hyperthermia sessions per week (recommendations)

As defining the exact number of weekly capacitive RF hyperthermia sessions is not as much in the focus as the need to combine the modalities with other oncological treatments, and as the number of sessions depends on different accompanying clinical and therapeutic situations that cannot be so easily transferred from one patient to another, this guideline only provides recommendations.

5.3.1. n = 2

n = 2 is potentially already sufficient given the fact that **many** study protocols have been conducted with n = 2.

5.3.2. n = 3

n = 3 is desirable, usually with an interval of one day without a hyperthermia therapy session.

5.3.3. n = 4

n = 4 is indicated, among other things, potentially in the first week of therapy, e.g. under radiation therapy and/or perfusion chemotherapy, or chemoembolization on a tumor or organ (e.g. liver)

5.3.4. n = 5

n = 5 is possible under daily radiation. In the case of longer continuous application (for more than 1–2 weeks), the daily application of capacitive RF hyperthermia without simultaneous (chemo) radiotherapy could cause the cancer cells to become accustomed to the method and reduce the efficacy of the treatment (among other things, due to a worrying HSP (heat shock protein) formation with consecutive resistance development). Daily applications should therefore not last longer than 2 × 5 days (with session-free periods on weekends). Daily application of capacitive hyperthermia may also be regarded as appropriate in the event of simultaneous chemoperfusions or chemoembolizations during a treatment block of 4–5 days.

5.4. Therapy protocols of capacitive hyperthermia

First and foremost, the overall number of therapy sessions depends on being embedded meaningfully in therapy combinations, and this must take into account logistical planning as well as the compliance of all parties concerned (patients as well as physicians from differing oncological specialisms). Moreover, the overall number of sessions depends on whether it is an adjuvant therapy situation or a highly palliative situation (dependent on prognosis).

In comparison with recommendations regarding the overall number of therapy sessions, the following protocols have proven effective: During the regular period of radiotherapy continuously approx. 3–5 times a week, and after completing radiotherapy for approx. 1–2 further weeks 3 times a week. 12–15 sessions (1 cycle) are the minimum number of sessions. Afterwards, there can be a session-free period of 1–2 weeks, if necessary, repeating or continuing therapy with 1–3 sessions a week during a subsequent chemotherapy (2nd cycle). Accompanying staging examinations to specifically check, for example, increased tumor markers are mandatory in order to determine the direction of the therapeutic response to treatment.

Otherwise, the therapy protocols for the individual sessions could also vary depending on the device and the recommendations of the device manufacturer as well as according to the differing diameter size of the electrodes used. It has become evident that the “step-up” method results in more medical benefits and simultaneously makes starting a series of hyperthermia therapy more tolerable for patients, what ultimately allows the input of more energy. Generally, slowly increasing the energy input results in better patient compliance than if the energy input is repeatedly reduced due to heat sensations being too strong for the patient.

For this purpose, examples on how to carry out local hyperthermia treatment that has proved to be effective and feasible during the last two decades (GCP - “good clinical practice”) are given in Section 6.9.

5.5. Contraindications for capacitive RF hyperthermia

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

5.5.1. Contraindications caused by technology and relative* contraindications

- Pacemakers or other implanted devices or electrical devices worn on the body or devices with metal circuits
- Stents* or other metal implants (long shaft hip prostheses in contrast to short shaft hip prostheses*) in the target area
- If metal implants are considered to be compatible with an MRI, this assessment may possibly be different.

5.5.2. Patient contraindications

- Sedated patient – unless under the completely continuous supervision of an experienced physician; this also applies analogously to patients with a diagnosis of epilepsy for treatments in the head region
- Recently operated patient, if surgical wounds are in or close to the target area (wait 7–10 days or strongly reduce power output under constant monitoring); patients who have recently undergone a bone marrow transplant
- Pleural effusions*, ascites* and fresh thromboses/embolisms are to be regarded as relative contraindications, among other things, dependent on fluid volumes*, the spread and possibility reducing the energy input consecutively
- Insufficient organ function
- Pregnancy or breastfeeding
- Active alcohol and drug abuse
- Active, life-threatening infection (e.g. sepsis)
- Karnofsky Performance Status < 50 or severe internal or neurological co-morbidity with poor prognosis, but also extremely fragile cardiovascular situation or very poor general health as per the WHO (ECOG) performance status 2 (= KPS < 50%).

5.5.3. Contraindications associated with procedures

- Demanding therapy protocols using high energy outputs without the continued presence of a qualified specialist, at least in the last half of a therapy session.
- Caution is also needed in the case of pregnant care staff; pregnant employees should not care for patients during therapy at the treatment bed.

5.6. Side effects of capacitive hyperthermia

Many of the following side effects can be prevented using necessary precautions and appropriate caution. These were explicitly dealt with in the previous chapters. Nevertheless, they are listed again here.

5.6.1. Significant adverse side effects

- Pain sensations and burns (first to third degree) due to a lack of pain sensation (e.g. postoperatively)
- Increased effect (which is partly wanted) in combination with radiotherapy and some chemotherapies (e.g. mitomycin, thermosensitive doxorubicin and others)
- Acute side effects of radiotherapy (such as erythema or cerebral edema) can be intensified by the high energy input in an individual session
- Local infections can be activated under radiation therapy and intensified more with high single energy inputs under hyperthermia

5.6.2. Special side effects depending on the organ or target area

- Risk of cephalalgia and epileptic seizures when treating brain tumors, in particular under simultaneous radiation therapy and a lack of or insufficient anti-edematous prophylactic measures

5.6.3. Further potential side effects

- Short-term (lasting up to 2 hours) asthenia after a treatment session
- Redness of the skin
- Diffuse abdominal pain (rare) in abdominal treatment
- Temperatures up to 39°C rectally (but also caused and wanted therapeutically as fever to destroy tumor cells)
- Temporary occasional tiredness (among other things as a result of the tumor cells being metabolized)
- Neurological sensations (hypersensitive hands, feet and legs); “electrifying” sensations may occur temporarily after treatment and last approx. 1 hour
- Micronodular, such as subcutaneous metastasis, clinically palpable adipose tissue necrosis in obese patients
- First to second degree burns in patients who are very hairy on the side of the counter electrode (e.g. back of patient in a supine position in the event of using textile electrodes in the Oncotherm EHY-3010 device, avoidable by shaving prior to treatment).

5.7. Obligation to provide information on capacitive RF hyperthermia

There is a reviewed and approved information sheet for the different forms of capacitive hyperthermia applied by us (see Appendix). This is the Diomed Information Sheet published by Thieme Compliance GmbH, Erlangen, and recommended by the Deutsche Gesundheitshilfe e.V., a German non-profit and independent organization providing health information.

6. Planning/clinical application of local hyperthermia

This section deals with the planning and clinical application of local hyperthermia including therapy recommendations and instructions for local capacitive deep hyperthermia.

A treatment concept depends on various different factors. In determining when to apply hyperthermia, the times in which patients are administered parallel therapies (chemotherapy and radiotherapy) is crucial. The most important prerequisites for administering local capacitive hyperthermia are mentioned in the following, wherein we specifically address individual important aspects in its operation and handling in accordance with guidelines.

6.1. Medical interview regarding the current diagnosis

6.2. Information on further therapy options

6.3. Information on hyperthermia and side effects

6.4. Information on organization and costs

6.5. Obtaining written consent

6.6. Preparing the patient

6.7. Choice of device, electrodes/applicators and their positioning

6.8. Positioning of the patient

6.9. Therapy scheme (performance profile)

6.10. Cooling circuit (yes/no)

6.11. Supervision and documentation

6.1. Medical interview regarding the current diagnosis

The patient must/should be informed about current results with empathy, but without glossing over these, and also without establishing worse-case scenarios. Taking into consideration the patient's wishes and needs, possible medical alternatives should also be explained and time should be given to consider these (at least 24 hours).

6.2. Information on therapy options and alternatives

The patient is always to be informed about the current diagnosis, intended or recommended conventional therapies as well as individual alternatives to other indicated/planned therapies (surgical measures, options of further chemotherapies, immunotherapies or radiotherapies or combinations thereof). If necessary, the case needs to be presented to a tumor board review.

6.3. Information on hyperthermia and side effects

See chapter 5.7. Obligation to provide information on capacitive RF hyperthermia as well as the information sheet in the Appendix.

6.4. Information on organization and costs

6.4.1. Planning

Within the scope of the overall therapy, the patient concerned is not allowed to be caught in a conflict between conventional therapies and complementary treatments. Planning and the course of therapy must be arranged primarily around the appointments of the conventional therapies in the event of therapy combinations. Similarly, timing between chemotherapy and radiotherapy and hyperthermia must be carried out considerately, also between all colleagues, in which the patient's needs are to be discussed in depth – provided this is possible.

6.4.2. Cost

The costs of hyperthermia therapy are not normally covered by (statutory) insurance providers. Thus, information about the additional costs that the patient must pay himself/herself is even more important. The patient must be informed about both the costs of the individual hyperthermia therapy as well as any overall costs of an (additional) series of hyperthermia – provided this is foreseeable. If necessary, the patient must also know about the costs for additional consultations, supplementary tests or any additional services within the scope of complementary oncological therapies (mistletoe therapy, immunotherapeutics, vitamins etc.). The patient must also be made aware that hyperthermia treatments in palliative situations must be continued (with session-free periods), e.g. as long as this is indicated, e.g., for chemotherapy (i.e. probably lifelong including all the costs this entails). The possible mandatory inclusion of legal authorities regarding the reimbursement of costs by statutory health insurance companies including the prerequisites for this must also be discussed in the medical interview.

The invoicing of costs is based on the currently applicable "Gebührenordnung für Ärzte" - GOÄ [German medical fee schedule] codes that have been legally adopted according to the recommendations of Hufelandgesellschaft e.V. [Hufeland Association, German umbrella organization of integrative medicine] in collaboration with DGHT e.V. and previously recognized by Verband der Privaten Krankenversicherung e.V. [Association of Private Insurance Companies].

6.5. Obtaining written consent

As with any therapy or procedure, written consent is to be obtained after providing the information and following a period to allow the patient to consider the options. This written consent is to be archived as a document (in the original with the physician). The patient is to receive a copy. As is customary in medical practice, the patient must be granted the right to stop or end the therapy, even prematurely, at any time without providing any reasons. This process must also be documented.

6.6. Preparing the patient

The patient should only undress or uncover himself/herself in the area in which treatment is provided. All metallic objects must be removed from the are to be treated.

6.7. Choice and position of the electrodes

This depends on the size and intensity of the region to be treated as well as the manufacturer's technological requirements for the device, which must correspond to clinical requirements.

The standard application, e.g. in the **Celsius42 TCS device** or **Synchrotherm RF 800**, is the use of a 250-mm electrode above and a 250-mm electrode below. In the **Oncotherm EHY-2000**, the arm electrode is usually used with a diameter of 300 mm in the torso area and regularly used with a diameter of 200 mm in the head and neck area. In the **Oncotherm EHY-3010**, the size of the textile electrode depends on whether the thorax, the abdomen/pelvis or both are being treated. In the case of diffuse bone metastases, an individual special-purpose electrode is to be manufactured according to the patient's measurements.

In the following situations, the selective application of a 150 mm electrode is recommended in the **Celsius42 TCS device on one side** (above or below) if:

a. a relatively small area as "region of interest" is near the surface to the 150 mm electrode (see Fig. 9) and/or

b. it is a smaller region of the body that can be delimitated, such as the neck region.

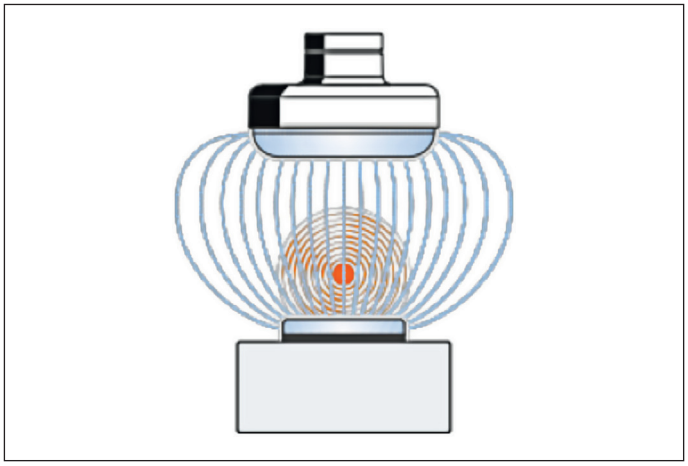


Fig. 9: Example representation of electrode positioning in the Celsius42 TCS

Fig. 10: Oncotherm EHY-3010 with a textile electrode that allows the whole lung or the whole liver to be treated for one hour.

In the case of the **Oncotherm devices (EHY-2000 and EHY-3010)**, the patient's position does not have to be adjusted to the position of equally-sized or differently-sized electrodes as the counter electrode which is the size of a mattress is part of a metal plate or a metallic sheet electrode of the same size. The largest electrode in the EHY-2000 (approx. 30 cm in diameter) is used to treat the mediastinum, one side of the lung, a large part of the liver or large parts of the abdomen/pelvis, while the medium electrode (approx. 20 cm in size) is used in the head and neck region and the 8 cm electrode (very rarely used) is available for even smaller lesions. The textile electrode of the EHY-3010 device can even be (individually) adapted or tailored to the size of whole organs (lung, liver) or also the whole axial skeleton plus pelvic skeleton and femur.

6.8. Positioning of the patient

The treatment is most effective – irrespective of the manufacturer – if the patient's region of interest is coupled to the areas of the electrodes as well as possible, between which the capacitive field is activated. The aim is a connection as direct as possible as then the energy is also directly coupled. Air cavities between the electrode and the patient's skin must be avoided.

Due to the design, water boluses are installed under the upper electrode or above the lower electrode in the capacitive devices used (Celsius42 TCS, Synchrotherm RF 800, EHY-2000); these water boluses are for cooling and used as a spacer. This water is not heated by the capacitive field due to its high pump flow rate. Here, the energy field is coupled well to the patient's body located between the boluses. Ideally, nothing else should be located in between – in particular, no insulating (air-containing) cushions or blankets. Care should be taken to ensure that the water bolus rests on the body flatly. In addition, situations should be avoided where one part of the water bolus rests on the body but the other part is almost in the air. This would be the case in bulging body surfaces (see Section 6.8.1.1.).

Entrapped air must be avoided when filling the water boluses. The filling of the water boluses must be sufficiently full so that, for example, a protruding body part (front of the ribcage) does not push against the electrode surface which would increase the risk of burns in the cartilage and the skin above. In contrast, if the water bolus is filled too much, it would only rest flush against a small surface as it would be curved too convexly and parts of the target area would no longer be included in the treatment. Moreover, there would be a danger of an excessive energy input over the reduced contact area, which could lead to burns.

The same applies to the textile electrode of EHY-3010. To make it rest as flushly as possible, large flat water cushions can be placed on it. Textile electrodes that are so wide that they hang down the side of the patient and potentially come into contact with the counter-electrode must be avoided as this could cause the dissipation of energy past the patient and would impede the efficacy of the therapy.

A thin layer of paper between the skin and the applicator does not cause any coupling problems between the electrodes but is used to adhere to hygiene requirements. A thin layer of pure cotton can also rest under the paper, for example, in thorax treatments as a shirt. However, even small amounts of synthetic fibers in such shirts or long underwear could severely disrupt the fine tuning of the device and cause it to shut down.

6.8.1. Special positioning requirements

Special positioning requirements (see also treatment protocols on individual device-specific positioning aids).

6.8.1.1. Very convex body surfaces

The best way to adapt to a body's curves and any unevenness is to use additional water cushions in the case of very convex body surfaces (a round abdomen or thigh) as well as very concave body surfaces (e.g. caused by cachexia or a funnel chest).

6.8.1.2. The head and neck

Usually, head tumors need to be treated in a lateral position, i.e. the distance between where the shoulder rests and the head needs to be bridged. This is best achieved using water cushions. Similarly, on the upper side of the electrode, the coupling should occur preferably directly or via water cushions. If a water cushion seems appropriate for optimal coupling, a small water cushion should be used which is not full to bursting. This can also be slightly cooled as required in advance or must be changed multiple times during the therapy if needed.

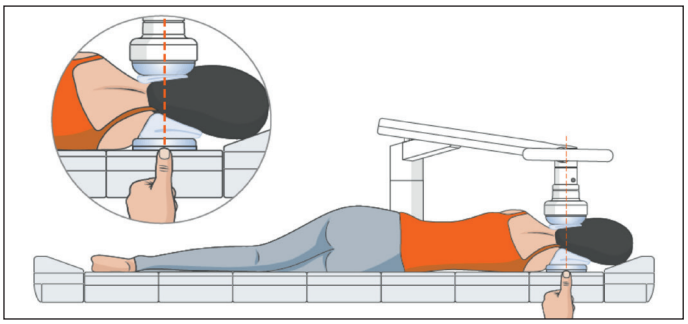


Fig. 11: Examples of positioning aids

Textile electrodes are only rarely capable of being used in the head region as (in particular damp) hair can act as high-frequency radio wave antennas, potentially causing pain/burns. Formation of perspiration on the patient's skin touching the (counter) electrode can develop into a painful "boiling film of liquid" that potentially must be dried multiple times during a treatment session.

Occasionally, the matchbox cannot be tuned properly and thus the pre-set power cannot be released. This is recognizable by the yellow curve that sinks under the blue normal range directly on the screen in Celsius42 devices, and in the EHY-2000 and EHY-3010 devices by the fact that a "black synchronous line" no longer is present and/or the readable reflectance values remain too high (> 5–10 W).

(Partly) irrespective of the device used, one or more of the following listed measures contribute to tuning successfully:

1. Remove textiles or items of clothing containing synthetic fibers that are between the electrodes
2. Adapt power plus or minus 5 W
3. Apply the upper electrode slightly more tightly (carefully increase contact pressure)
4. Change the patient's position (potentially push slightly backwards or forwards)
5. Check the position of the electrodes and, if necessary, correct them
6. Change the distance of the electrodes to each other (water cushions)

6.9. Therapy scheme (performance profile)

As described in the instruction manuals, once the treatment request is defined, then it is to be worked up into different individual treatment sessions (fractions). The systems have the option to work with high energy.

6.9.1. Step-Up heating

Experience has resulted in the recommendation to implement what is called "step-up heating", i.e. increasing the power step-by-step over the course of the treatment cycle. Another dimension of "step-up heating" can also be discussed, namely concerning an increase in power between the first three to four fractions. Experience has shown that patients are more sensitive to hyperthermia in the first session than after several further sessions.

The first two to three sessions serve to test these tolerances if needed. Even in step-up heating, treatment always lasts for 60 minutes and the treatment time of the first therapy application must not be reduced.

In the following, a plan of such a therapy scheme is depicted. However, it should not be regarded as fixed, but an individual process is to be determined mutually with the patient taking their tolerance values into account. This step-up heating applies in principle not only for the Celsius42 TCS device but based on this also for the Oncotherm EHY-2000 and EHY-3010 devices.

In the Oncotherm EHY-3010 device, the treating physician can apply energy levels from 350–400 W (depending on the size of the textile electrodes used). Such high energy levels (> 200–250 W) are however barely applicable without causing pain and harming the patient. For the user, they appear like an admission of the required invoicing prerequisites on the part of the health insurance companies and their medical services.

250 mm upper electrode 250 mm bottom electrode	treatment fraction 1	treatment fraction 2	treatment fraction 3	treatment fraction 4	treatment fraction 5+
Duration of fraction (suggested timing)	60 min.	60 min.	60 min.	60 min.	60 min.
LEVEL 1					
Duration	20 min.	20 min.	20 min.	20 min.	20 min.
Power	60 W	60 W	60 W	80 W	90 W
LEVEL 2					
Duration	10 min.	10 min.	10 min.	10 min.	10 min.
Power	70 W	70 W	80 W	100 W	110 W
LEVEL 3					
Duration	10 min.	10 min.	10 min.	10 min.	10 min.
Power	80 W	90 W	100 W	120 W	135 W
LEVEL 4					
Duration	10 min.	10 min.	10 min.	10 min.	10 min.
Power	90 W	100 W	120 W	140 W	160 W
LEVEL 5					
Duration	10 min.	10 min.	10 min.	10 min.	10 min.
Power	100 W	110 W	max. tolerable power (135 W)	max. tolerable power (170 W)	max. tolerable power (200 W)
cumulative applied energy in kJoule	276 kJoule	294 kJoule	~330 kJoule	~447 kJoule	~471 kJoule

Fig. 12: Example for a therapy using step-up heating. Example for a therapy with the Celsius42 TCS device.

The indicated values are reference values and do not represent a binding therapy concept. Ultimately, the treating physician always decides about how much power is to be outputted. Furthermore, the parameter "cooling temperature" and the therapy setup (use of water cushions, size and position of electrodes) influences the power (still) tolerated by the patient. Wipe off any sweat at all times! Monitor the patient carefully, particularly in the 5th step and from the 4th session. Moderate cooling until the 3rd session (16–12°C); after level 4, patients must be particularly monitored; from the 5th, more efficient cooling should be set (11–8°C). If needed, adjust the cooling and the power according to the patient's tolerance.

Note: If higher power should not be applied in a patient due to their sensitivity to temperature, the treatment time should be increased at lower power so that the energy target in kilojoules is reached. In individual cases, a patient may also tolerate a high-power output without having any complaints. As already outlined, a process is to be determined here together with the patient regarding which power inputs are possible in their case.

Obere Elektrode/upper electrode **250 mm** Untere Elektrode/lower electrode **250 mm**		Sitzung / session 1	Sitzung / session 2	Sitzung / session 3	Sitzung / session 4	Sitzung / session 5
Kühltemperatur/ cooling temperature		**8 °C**	**8 °C**	**8 °C**	**8 °C**	**8 °C**
1. Stufe/Step	Dauer/duration Leistung/power	20 min. 60 W	20 min. 60 W	10 min. 100 W	10 min. 100 W	20 min. 100 W
2. Stufe/Step	Dauer/duration Leistung/power	10 min. 100 W	10 min. 100 W	10 min. 150 W	10 min. 180 W	10 min. 180 W
3. Stufe/Step	Dauer/duration Leistung/power	10 min. 150 W	10 min. 150 W	10 min. 180 W	10 min. 220 W	10 min. 260 W
4. Stufe/Step	Dauer/duration Leistung/power	10 min. 200 W	10 min. 200 W	10 min. 220 W	10 min. 260 W	10 min. 320 W
5. Stufe/Step	Dauer/duration Leistung/power		10 min. 250 W	10 min. 260 W	10 min. 300 W	10 min. 400 W
6. Stufe/Step	Dauer/duration Leistung/power			10 min. 300 W	10 min. 350 W	10 min. 450 W
Abgegebene Energie / applied energy						
Sitzungsdauer/session time		60 min.	60 min.	60 min.	60 min.	60 min.

Fig. 13: Example for therapy with the Synchrotherm RF 800 device.

Furthermore, what appears to be very important in the EHY-3010 is that the pleura or the peritoneum must not be stimulated to develop even more fluid output by using high-power inputs in patients with large volumes of free fluid, such as pleural effusions and ascites, but only wattages are to be used that amount in part to less than half of the energy input that would have been selected without any fluid increase.

As it does not make sense to cool skin metastases, the device's cooling system (e.g. of EHY-2000) must be switched off before treatment, which means the patient must be monitored more closely during treatment.

6.10. Cooling circuit

Everyday experience has shown that thermosensors act as differential receptors. Thus, patients perceive temperature changes more distinctly than constant temperatures. This means for the application of **capacitive hyperthermia** that in order to achieve optimum thermotolerance in the patient, the power increases and the related increase in heat should be done in steps (step-up heating) and the cooling of the water boluses, if adjustable, should ideally be carried out gradually to low temperatures irrespective of device.

Moreover, as already mentioned, it is important to ensure that there is no perspiration or condensation on the skin as this would more likely cause burns. Saline moisture, such as perspiration, acts as a magnifying glass that focuses the power output over these water droplets and may result in undesirable heat sensations and lead to burns. For this reason, we also cool the water bolus with a flowing exchange of water at a predefined temperature. We keep the surface of the skin dry and regularly monitor the patient for any moisture during the treatment.

6.10.1. Cooling in the Oncotherm EHY-2000 device

In the Oncotherm EHY-2000 device, the cooling in the arm electrode depends on the room temperature and usually amounts to 22–26°C. If higher temperatures are required, or if cooling of the skin is undesirable, the circulation of cooling water can be interrupted by shorting the cooling water connectors.

session 1	session 2	session 3	session 4	session 5	session 6	session 7	session 8	session 9	session 10	session 11	session 12	session 12+
20 min.	**30 min.**	**40 min.**	**50 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**	**60 min.**
10 min. 40 W	10 min. 50 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W	20 min. 60 W
10 min. 50 W	10 min. 60 W	10 min. 80 W	20 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W	10 min. 80 W
	10 min. 70 W	10 min. 90 W	10 min. 100 W	20 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W	10 min. 100 W
				10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W	10 min. 120 W
					10 min. 140 W	10 min. 140 W	10 min. 140 W	10 min. 140 W	10 min. 140 W	10 min. 140 W	10 min. 140 W	10 min. 140 W
EHY-2000						10 min. Rife	20 min. Rife	30 min. Rife	40 min. Rife	50 min. Rife	60 min. Rife	60 min. Rife

Fig. 14: Example of a head therapy using the Oncotherm EHY-2000 device, in particular for treating the brain

6.10.2. Cooling in the Celsius42 TCS and the Synchrotherm RF 800 devices

The cooling in the Celsius42 TCS device and the Synchrotherm RF 800 device can be actively selected between 8°C and 40°C according to performance and sensitivity of the patient.

6.10.3. Cooling in the Oncotherm EHY-3010 device

In the Oncotherm EHY-3010 device, extra cooling of the skin is not intended and it is not necessary as the textile electrodes are used.

6.11. Supervision and documentation

6.11.1. Supervision of the patient during capacitive hyperthermia sessions

Continuous supervision of the patient remains indispensable. Treatment using this form of overheating is to be performed solely by specially trained/instructed skilled personnel who care for the patient constantly. Accordingly, it must be possible for the patient to talk to medical staff at any time and have enough time for a face-to-face interview. Local hyperthermia is carried out under medical direction and supervision, during which the patient's state of health and any potential perspiration is controlled continuously or at least regularly at brief intervals.

6.11.2. Documentation

The software of the systems facilitates very simple documentation of observations and events during the therapy. An internal field that merely documents recordings in the database permits taking such notes. These help to gather the experiences gained in hyperthermia systematically.

In this context, it is also important to compile information on combination therapies (chemo- and radiotherapies), the histopathology as well as the stage and grade of the tumor. Collecting such data about all patients can provide reference points for good clinical practice (GCP) guidelines. Hyperthermia is still criticized for not having any consensus regarding its application. This guideline is intended to provide a long overdue counterpoint to the absence of such standardization.

7. Clinical Trials and Literature

7.1. Clinical outcomes

Numerous trials consistently show significantly higher rates of complete remission when radiotherapy/chemotherapy is combined with hyperthermia as compared to radiotherapy/chemotherapy alone. In more than 28 randomized controlled clinical trials, the addition of hyperthermia to radio- or chemotherapy has been investigated independent of the device used: In 21 trials, significantly better outcomes were proven when hyperthermia was combined. [1,19, 22]

8. History and current perspectives of local RF hyperthermia

8.1. History

RF hyperthermia has been used to successfully combat cancer since the 1990s. The fact that it was generally accepted more in Asia and could therefore develop more rapidly there than in Europe, in particular in German-speaking countries, is very likely due to the fact that RF hyperthermia does not constitute a separate specialist field or one in which a specialist group of physicians has been clearly classified, but rather could be applied for years by any physician without requiring an examined qualification or certification, provided that the physician deemed himself/herself as being sufficiently capable.

How often RF hyperthermia has been applied and how much could be invoiced has been curbed by pharmaceutical products and competing local hyperthermia modalities (e.g. microwave-induced hyperthermia) as well as related professional quarreling and general fears by oncologists – excluding radiation oncologists – which in turn has greatly limited the acceptance and spread of RF hyperthermia in Europe and the USA.

Due to this in part, the number of studies on RF hyperthermia in German-speaking countries was also unacceptably small even into the turn of the millennium, and studies from non-European countries have been largely ignored. It is therefore not surprising that in 2005 the Federal Joint Committee (G-BA) subsequently refused that statutory health insurers assume the cost of this treatment due to the lack of consensus among its users. Offering a summary of the present state of local capacitive hyperthermia within this current scientific guideline could, however, **lead to a change in opinion as its content substantially answers the questions that were still regarded as unanswered by the G-BA in 2005**.

8.2. Perspectives

It can be expected that the outlook for the future of RF hyperthermia may include the following scenarios:

A. The application of local RF hyperthermia will be increasingly in demand due to its success in the treatment of cancer patients, but without compliance to relevant therapeutical guidelines will only continue to be available to patients with statutory health insurance for off label use if these patients (can) pay for the treatment themselves, in accordance with the assessment of decision-making bodies.

B. In countries in which the high costs of drugs, such as ATMPs (**A**dvanced **T**herapy **M**edical **P**roducts), are not (or cannot be) paid by the general public, competing therapies using medical devices, such as RF hyperthermia and the like, are increasingly being used and have already been regularly used for some time now (in Asia).

C. Unfortunately with a delay of approx. 10–15 years, even European oncologists will not be able to continue ignoring the non-European results and the scientific publications and Phase II to Phase III trials published at universities.

D. Globalization will become at least a blessing for cancer patients, even in Germany. Chinese papers will soon be translated or published in full in English and will be given the recognition they deserve.

E. Of course, capacitive RF hyperthermia must continue more than ever to be integrated into other therapies as an oncological local treatment modality that is practically without side effects. This is particularly true for modalities that use the patient's entire immune system and undoubtedly for therapy combinations comprising a comprehensive range of therapies across several specialist fields, wherein this range of therapies is to be optimally tailored to the individual patient on a case-by-case basis.

Two examples of such combination therapies, e.g. in patients for whom the systematic full-dose chemotherapy is out of the question, where only textile electrodes of the Oncotherm EHY-3010 device can therapeutically cover the whole lung or liver for 1-hour sessions:

1. In multiple lung metastases (preferably less than 1.5 cm), combination from:

   a. Hyperfractionated accelerated radiotherapy (single dos1.1 Gy, 2 times a day in 7-hr intervals, up to a cumulative dose of 14.3 Gy)

   b. Local RF hyperthermia four times before the first radiotherapy, during each day of radiotherapy shortly after the first or just before the second daily radiotherapy fraction, and three times after the last day of radiotherapy

   c. Low-dose chemotherapies, preferably according to the result of a current liquid biopsy, e.g. defined molecular-genetically/molecular-biologically after detecting tumor cells in the peripheral venous blood, possibly insulin-potentiated: 1 dose before commencing radiotherapy, 2 doses during radiotherapy and 1 dose after completing radiotherapy.

2. In multiple lung metastases (preferably less than 1.5 cm), combination from:

   d. Hyperfractionated accelerated radiotherapy (single dose 1.2 Gy, 2 times a day in 7-hr intervals, up to a cumulative dose of 19.2 Gy)

   e. Local RF hyperthermia four times before the first radiotherapy, during each day of radiotherapy shortly after the first or just before the second radiotherapy daily fraction and three times after the last day of radiotherapy

   f. Low-dose chemotherapies, preferably according to the result of a current liquid biopsy, e.g. defined molecular-genetically/molecular-biologically after detecting tumor cells in the peripheral venous blood, possibly insulin-potentiated: 1 dose before commencing radiotherapy, 2 doses during radiotherapy and 1 dose after completing radiotherapy.

9. Bibliography: Sources, studies and articles, in particular on local capacitive hyperthermia

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In randomized studies, significantly better results are found in study arms involving hyperthermia with regard to survival, interval time as well as occurrence of progression and remission rates (with complete or partial remission). There were significantly better results if a radiotherapy (RT), a chemotherapy (CT) or a chemoradiotherapy was combined with hyperthermia (HT) in comparison to the same treatment without hyperthermia.

Ref no.	tumor	Treatment	Patients (lesions)	endpoint	Effect with HT	Effect without HT
14	Lymphnodes of head & neck tumours	RT +/– LHT	41 (44)	CR rate	83 %	41 %
				5-yr local control	69 %	24 %
				5-yr survival	53 %	0 %
15	Melanoma	RT +/– LHT	70 (138)	CR rate	62 %	35 %
				2-yr local control	46 %	28 %
16	Breast	RT +/– LHT	306	CR rate	59 %	41 %
17	Glioblastoma multiforme	RT +/– LHT postoperative	68	Median survival	85 weeks	76 weeks
				2-yr survival	31 %	15 %
18	Bladder, cervix and rectum	RT +/– LHT	298	CR rate	55 %	39 %
				3-yr survival	30 %	24 %
	Cervix	RT +/– LHT	114	CR rate	83 %	57 %
				3-yr survival	51 %	27 %
19	Rectum	RT +/– LHT preoperative	115	5-yr survival	36 %	7 %
20	Cervix	RT +/– LHT	64	CR	55 %	31 %
21	various malign cell population	RT +/– LHT	92	Response	82 %	63 %
22	Cervix	RT +/– LHT	40	CR	85 %	50 %
23	Rectum	RT +/– LHT	14	Response	100 %	20 %
24	Bladder	RT +/– LHT preoperative	102	3-yr survival	94 %	67 %
25	Oesophagus	RT +/– LHT	125	3-yr survival	42 %	24 %
26	Rectum	RT +/– LHT preoperative	122	pCR	23 %	5 %
27	Bladder	CT +/– RHT preoperative	52	pCR	66 %	22 %
28	Bladder	CT +/– RHT postoperative		2-yr relapse free survival	~82 %	~38 %
29	Lung	CT +/– WBHT	44	Response	68 %	36 %
30	Soft tissue sarcoma	CT +/– LHT	341	Response	28.7 %	12.6 %
				Local relapse free survival	45,3 months	23,7 months
				Disease free survival	31,7 months	16,2 months
31	Oesophagus	RT + CT +/– LHT	66	CR	25 %	6 %
32	Oesophagus	RT + CT +/– LHT preoperative	53	Palliation	70 %	8 %

Fig. 15: Organ-related hyperthermia studies

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10. Appendix

10.1. Training programs for local RF hyperthermia

Objective of the training: Two days of lessons are scheduled comprising both theoretical and practical sections. After 2 months, a repeat training session lasting 1–2 days including a final discussion and the subsequent certification.

In the theoretical section, the following information is provided: basic knowledge about the forms of hyperthermia, application areas of the different forms of hyperthermia, mode of operation of local hyperthermia, indications and contraindications, billing codes, therapy planning (number of cycles), literature on the subject/info folder, informed consent form, interactions between hyperthermia and chemotherapy/radiotherapy, documentation forms, work protocols, and therapy settings etc.

The practical aspects of the training program comprise providing information on treatment to the patient, maintenance of the hyperthermia unit (not technical), remedying sources of error (not major technical errors), patient positioning according to different indications, changing electrodes, recording patient data (using the software), independent work on capacitive RF (complete therapies).

10.2. Informed Consent Form for Patients

The “Hyperthermia Treatment” informed consent form published by Thieme Compliance GmbH, Am Weichselgarten 30a, 91058 Erlangen, Germany, can be found on the following pages. We would like to thank Thieme Compliance GmbH for its warm support.

More information can be found under:
www.thieme-compliance.de

Hospital / Medical Practice

Thieme Compliance

Kom 3

Diomed

Hyperthermia Treatment

Patient's name and address

Dear patient, dear parents,

This informed consent form contains all information your physician will explain to you about the treatment. Please read it carefully before your appointment and answer the questions accurately.

Hyperthermia

Hyperthermia (overheating of the body) is a long-established treatment for curing disease and for strengthening a person's general state of health. Presumably, it was observed thousands of years ago that surviving a high fever often marked the turning point in the progression of long-term and severe diseases and this stage led to a "breakthrough" in terms of being healthy again.

The oldest examples of hyperthermia date back to Egypt 5,000 years ago. Later, similar examples were documented by the ancient Greeks, e.g. by the famous physician Hippocrates. Another Greek physician and philosopher (Fig. 1) is supposed to have said the following sentence:

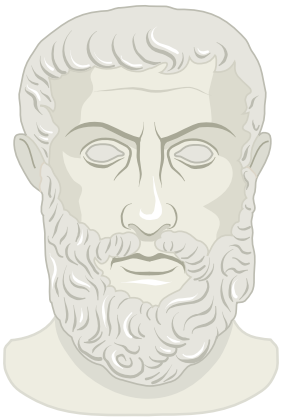

Fig. 1: Parmenides (Greek physician/philosopher)

"Give me the power to produce fever and I will cure all disease!"

It is known that the body of a chronically ill person is often not capable of producing such "purifying" fever due to their weakened immune system. This is where hyperthermia comes in. On the one hand, it can specifically weaken pathogens that cause disease (cancer cells, bacteria), thus enabling them to be combated. On the other hand, it can mobilize the immune system into fighting the disease.

Hyperthermia can be applied in:

- **Tumors**

  to support a weakened immune system and to specifically weaken/kill cancer cells,

- **Weakness/insufficiencies of the immune system:**

  allergies, asthma, atopic dermatitis, rheumatic diseases, soft tissue rheumatism, chronic inflammations, chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) etc.

- **Chronic medical conditions and conditions of chronic pain:**

  Arthrosis, sciatica, neuralgia, chronic inflammations, migraine, hypertension, respiratory diseases etc.

The cost of hyperthermia therapy and eventual complications needing treatment may not be covered by your health insurer. Therefore please clarify any issues regarding costs in advance.

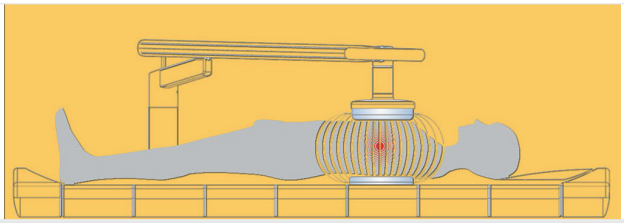

Fig. 2: Regional deep hyperthermia

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Performing hyperthermia

Depending on the disease, hyperthermia can be carried out using different modalities. The choice of modality depends on your clinical picture, but also on personal features. Therefore we will need to ask you various questions about yourself and your medical history. Relevant medical diagnostic investigations should always be carried out in advance so that we can select the right treatment method for you at the right time and that we can exclude any diseases that require orthodox medical treatment first.

Hyperthermia can be used alone or combined with other modalities. The hyperthermia therapy planned for you is checked on the last page of this informed consent form. In principle, various options are possible:

- **Active hyperthermia** (fever therapy, "artificial therapeutic fever")

  You will be under constant observation while your body generates an "artificial" fever after being administered drugs to cause fever.

  This method is more difficult to control and involves more risks than the other procedures listed.

- **Passive hyperthermia**
  - **Local:** hyperthermia in regions of the body
    - Superficial hyperthermia

      Specially filtered infrared radiation (thermal radiation) is applied externally to treat superficial neoplasms (skin cancer, melanomas, skin metastases etc.).

    - Hyperthermia of hollow viscus organs/body cavities (e.g. stomach, bladder, abdominal cavity)

      Lavage of the cavities with a fluid that contains mainly cytostatics (drugs to destroy the tumor) and is up to 45°C warm by means of a supply and drainage tube of a heat exchanger. The relevant heat is however also possible using a probe introduced into the body (intraluminally).

    - Prostate hyperthermia

      Under moderate pain medication, a special probe that emits microwaves or radio waves is introduced through the urethra up to the prostate and it then overheats the surrounding prostate tissue to a local fever temperature of up to 48°C. Usually, cytostatics are administered simultaneously.

    - Hyperthermia of the extremities (arm, leg)

      Two access ports are placed on the blood vessels of an arm/leg so that blood can initially be taken via a vein, heated externally in a heat exchanger to the hyperthermia temperature and then returned to the relevant body part via an artery. If necessary, relevant drugs are added.

  - **regional:** Hyperthermia of whole-body regions:
    - **Deep hyperthermia**

      The body region to be treated is heated to the core to the intended tissue temperature by a corresponding hyperthermia device (see Fig. 2). This occurs, depending on the type of device, e.g. using microwaves, via radio frequencies, via ultrasound or via laser technology.

  - **whole body:**
    - **Whole-body hyperthermia (WBH)**

      In a heating device (see Figs. 3–5), your whole body is warmed to a corresponding core temperature over the physiological (i.e. normal) body temperature of approx. 37°C. The following hyperthermia temperatures will be attained in your body for a given period (up to several hours) depending on your clinical picture, your tolerance and the intended effect: lower than 38.5°C (mild WBH), 38.5–40.5°C (moderate WBH), higher than 40.5°C (extreme WBH) body-core temperature.

      If moderate to extreme temperatures are planned, you will receive what is termed an analgosedation – a combination of sedatives and painkillers. Information on their risks will be provided separately.

      Whole-body hyperthermia is tolerated quite well. The body's own immune response is activated by this modality of hyperthermia and the tumor cells are made sensitive to radiation and cytostatic drugs (sensitization). This can increase the efficacy of drugs used and reduce side effects. There are now numerous clinical experiences on all of these findings.

In your medical interview, we will not only inform you about the hyperthermia therapy, but also the pros and cons of corresponding conventional methods, how well they are tolerated, their risks and the chances of recovery for your disease.

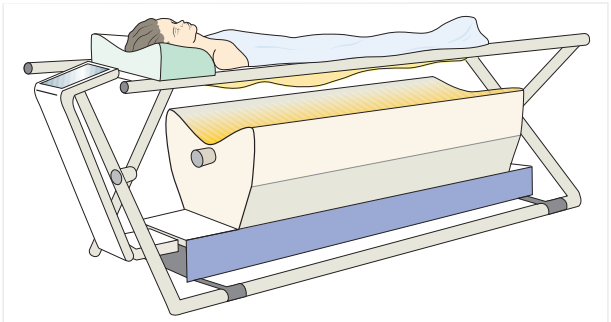

Fig. 3: Mild/moderate/extreme whole-body hyperthermia

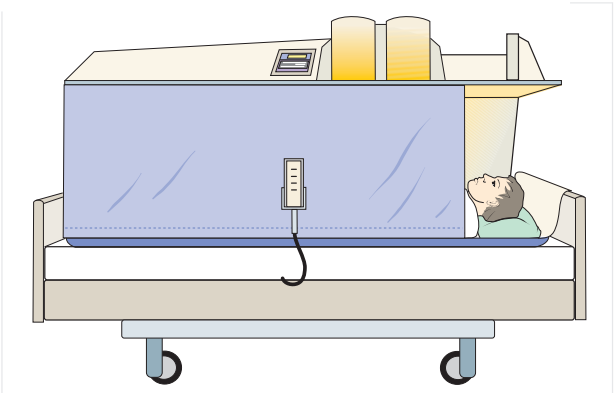

Fig. 4: Mild/moderate/extreme whole-body hyperthermia

These methods could also be considered in your case as a supplement to or instead of hyperthermia.

Contraindications

For WBH

- Active or extreme hyperthermia may not be carried out if you have an acute and/or feverish microbial infection or if you are known to have cardiovascular conditions (heart failure, high blood pressure, angina, stenosis) or acute organ problems (e.g. peptic ulcers, hepatitis/hepatic cirrhosis, renal failure).

- WBH is also contraindicated if you tend to bleed easily, tend to have febrile convulsions/epilepsy or have cerebrovascular aneurysms, brain tumor/brain metastases, hyperthyroidism or thromboses as well as if you are suffering from wasting syndrome (cachexia).

For regional hyperthermia

- If you have a pacemaker or metal implants in the region to be treated or if you have metastases in other organs, the use of local/regional deep hyperthermia is prohibited.

In early pregnancy (until the 4th month)

- Just like in many therapeutic modalities – hyperthermia may not be applied or only applied if there is a compelling indication for its use.

Risks and possible complications

Despite all due care, complications may develop which may be life-threatening in some cases and require further treatment/operations. Information on the frequency of such complications is based on general assessment and are to help you weigh the risks against each other. They do not correspond to the definitions for side effects in the package insert of medications. Existing conditions and individual circumstances can have a considerable impact on the frequency of complications.

- General side effects can occur such as headaches and joint pain, muscle spasms, stomachache with nausea/vomiting, increase/decrease in blood pressure, increased pulse rate as well as an irregular heartbeat.

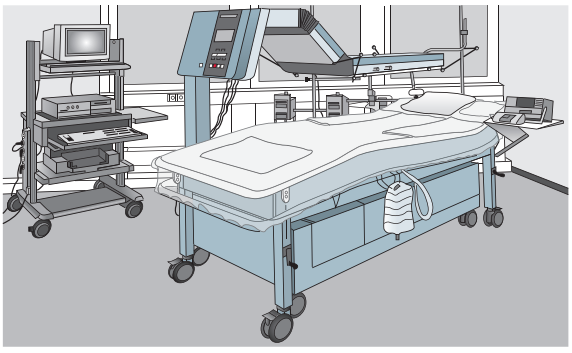

Fig. 5: Extreme whole-body hyperthermia

- Swelling, itching, sneezing, skin rashes, dizziness or vomiting and other similar mild reactions can temporarily occur if you have allergies or hypersensitivity (e.g. to drugs, anesthetic, disinfectants, latex) Stronger reactions can lead to an acute shock that requires intensive care treatment. Very rarely, there is serious or even lasting damage (e.g. organ failure, brain damage, paralysis).

- Particularly in the case of prostate hyperthermia, you may experience temporary burning when urinating, blood may appear in the urine for a short period and very rarely, you may have acute urinary retention which requires immediate medical attention. In adverse cases, hyperthermia may even lead to a urinary tract infection, potentially even epididymis/epididymo-orchitis and can even result in urethral injury/stenosis.

- You may experience pain in the overheated region, which is something you must inform us about immediately. Also, severe reddening of the skin and the possibly moderate burns that usually heal on their own – without needing follow-up treatment (e.g. ointment, drugs).

- Skin, tissue and nerve damage as a result of your positioning during treatment and measures taken during the procedure (e.g. injections, disinfection, laser, electricity) are rare. Potential, possibly long-term consequences: Pain, inflammation, tissue death (necrosis), scarring as well as sensory disturbances, dysfunction, paralysis (e.g. of the limbs).

- During or after treatment, the signs and symptoms of the disease may initially worsen for a brief period. This should not unsettle you as it shows that you are responding to treatment.

Prognosis for positive outcomes

Regular follow-up examinations will be necessary in the first weeks after treatment in order to assess the success of the treatment. Success can vary strongly or potentially even never happen at all depending on the modality applied and, in particular, how well your disease responds to the treatment. It can also not be excluded that your disease will worsen. Further actions (e.g. repeat treatment, change of modality) will be determined based on examination results obtained.

Instructions on what to do

Before treatment

Please present all relevant documents, such as identity card/passports (allergies, diabetes, ante-natal records, x-rays, implants etc.), results and images – where available.

Before treatment, you should be well rested and have emptied your bladder and bowels.

On the day, please avoid before treatment as much as possible:

- situations that could trigger strong mood swings (e.g. anger, grief, shock or excitement)

- large appetite, thirst, a large loss in body fluid, rich meals

- excessive physical and nervous activity (e.g. getting chilled, sauna, competitive sport, rushing around)

- stimulating/calming and other substances (e.g. alcohol, coffee, strong tea, nicotine, painkillers and sleeping drugs)

Please indicate in the questionnaire all medication that you are currently taking (even herbal remedies and over-the-counter products). In agreement with your treating physician, it will then be decided as to whether a medication must be stopped or replaced by another. This relates in particular to anticoagulants (e.g. Marcumar®, Aspirin®, Plavix®, Iscover®, Pradaxa®, Xarelto®, Eliquis® etc.) and in the case of diabetics, to medication containing metformin, but also other anti-inflammatory substances, such as ibuprofen or even ascorbic acid (vitamin C).

During treatment

Please inform us immediately if you feel unwell during treatment or afterwards.

After treatment

- Please rest according to our instructions. After treatment, inform us immediately if you notice anything unusual or feel unwell before leaving our medical practice.

- Drink amply (e.g. boiled warm water, weak tea).

- Go to bed early. Further instructions for before treatment.

You are only allowed to drive 30 minutes after treatment; until then you must remain in our medical practice. We will inform you if in rare cases your ability to drive is impaired for a longer period due to this treatment. In this case, you must be picked up by an adult. At the same time, we will tell you, if applicable, if and for how long support at home will be necessary. You should not drink any alcohol during this period. Do not operate any heavy machinery and do not make any important decisions.

Please inform us immediately if after the treatment you have discomfort, a prolonged worsening of your symptoms, difficulty breathing, fever (over 38°C) or severe pain!

Place, date, time

Physician

Patient's name and address

Hyperthermia Treatment **Kom 3**

Diomed

Questionnaire (Medical History)

Please answer the following questions carefully so that we can prevent any risks more effectively. Please tick the box and underline or supplement as applicable. If needed, we are happy to support you in filling out this questionnaire.

Age: ____ years | Height: _____ cm | Weight: _____ kg | Sex: ____

1. Do you take any medication (e.g. blood thinning medication (anticoagulants) [e.g. Marcumar®, aspirin], painkillers, anti-diabetic drugs [in particular containing metformin], cardiovascular drugs, hormone preparations, sleeping pills or sedatives, drugs for high blood pressure [hypertension])? ☐ n ☐ y

   If yes, which one(s)?_____

2. Do you have an allergy (e.g. medication [e.g. antibiotics, metamizole, paracetamol], anesthetic, contrast agents, latex, disinfectants, iodine, plasters, plastic)? ☐ n ☐ y

   If yes, which one(s)?_____

3. Do you tend to bleed easily e.g. frequent nosebleeds/bleeding of the gums, bruises, a tendency to bleed a lot after an injury? ☐ n ☐ y

4. Do you have/have you had an infectious disease (e.g. hepatitis, HIV/AIDS, meningitis, tuberculosis)? ☐ n ☐ y

   If yes, which one(s)?_____

5. Do you have/have you had (other) cardiovascular disease (e.g. coronary heart disease, high blood pressure [hypertension], heart rhythm problems [arrhythmia], stroke, heart attack, angina, inflammation of the heart muscle [myocarditis], heart valve disease)? ☐ n ☐ y

   If yes, which one(s)?_____

6. Do you have/have you had any (additional) cardiovascular diseases (e.g. arteriosclerosis, varicose veins, coronary heart disease, circulatory disorders, aneurysm, narrowing of a carotid artery)? ☐ n ☐ y

   If yes, which one(s)?_____

7. Did you have a disease of the upper abdominal organs (e.g. hepatitis, fatty liver, cirrhosis, biliary colic/gallstones, jaundice, pancreatitis)? ☐ n ☐ y

   If yes, which one(s)?_____

8. Do you have a metabolic disorder (e.g. diabetes, gout)? ☐ n ☐ y

   If yes, which one(s)?_____

9. Do you have/have you had any thyroid diseases (e.g. underactive/overactive thyroid, goiter, Hashimoto's disease)? ☐ n ☐ y

   If yes, which one(s)?_____

10. Do you have a brain disease (e.g. brain tumor, brain metastases, aneurysm) ☐ n ☐ y

    If yes, which one(s)?_____

11. Do you have/have you had any diseases of the nervous system (e.g. difficulty in walking/ paralysis, epilepsy, Parkinson's disease, sensory impairments, polyneuropathy , pain)? ☐ n ☐ y

    If yes, which one(s)?_____

12. Do you have a mental health condition (e.g. depression, burnout, schizophrenia, borderline personality disorder, anxiety disorders)? ☐ n ☐ y

    If yes, which one(s)?_____

13. Do you have a skin disease (e.g. rash psoriasis, tumor)? ☐ n ☐ y

    If yes, which one(s)?_____

14. Do you have disease of the immune system (e.g. ulcerative colitis, Crohn's disease, multiple sclerosis, rheumatism, scleroderma, immune deficiency)? ☐ n ☐ y

    If yes, which one(s)?_____

15. Do you have any other diseases? ☐ n ☐ y

    If yes, which one(s)?_____

16. Do you have any implants in your body (e.g. pacemaker, ICD, artificial heart valve, stent, artificial joint, silicon, hydrogel, teeth, metal)? ☐ n ☐ y

    If yes, which one(s)?_____

17. You do get infections frequently? ☐ n ☐ y

    If yes, which one(s)?_____

18. Have you ever had surgery in the abdominal cavity? ☐ n ☐ y

    If yes, which one(s)?_____

19. Do you smoke? ☐ n ☐ y

20. Do you drink alcohol every week regularly (e.g. beer, wine, spirits)? ☐ n ☐ y

    If yes, what?_____

Additional question for women

1. Could you be pregnant? ☐ n ☐ y

Physician's comments on this medical interview

The following was discussed: e.g. terms, history and possible applications of hyperthermia, questions regarding who will pay for treatment, choice of modality and how it is performed, pros and cons compared to other (conventional) methods, contraindications, features that pose an increased risk, risks and possible complications, possible secondary and subsequent procedures, potential pain relief, potential initial worsening of symptoms, prognosis for positive outcomes, what the patient should do before, during and after treatment (in particular, please document anything that specific to the individual, e.g. rejection of particular measures, determining whether a minor is able to understand the procedures, legal representatives, need for care, authorized representative and, if applicable, special notes and the length of the interview):

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

You are scheduled for the following treatments:

Active hyperthermia

- ☐ Fever therapy/artificial therapeutic fever

Passive hyperthermia

- Local
  - ☐ superficial hyperthermia
  - ☐ hyperthermia of hollow viscus organs/body cavities
  - ☐ prostate hyperthermia
  - ☐ hyperthermia of the extremities
- Regional
  - ☐ deep hyperthermia
- Whole body
  - ☐ whole-body hyperthermia (WBH)
  - ☐ 38.5 (mild)
  - ☐ 39–40°C (moderate)
  - ☐ 41.5–42.5°C (extreme)
  - ☐ _____
    Other temperature

☐ Within the scope the selected procedure, if applicable, the following drugs will be administered:

_____
Please name drug(s)

Scheduled appointment for the therapy: _____
Date

Only in the case of rejection

I do not consent to the proposed treatment. I have read the informed consent form, understood it and have been explicitly informed that a recognized orthodox medical treatment method should be applied however to prevent adverse health effects.

_____
Place, date, time

_____
Patient

_____
Legal guardian*

_____
If applicable, witness

_____
Physician

Consent

I have read and understood the informed consent form. During a medical interview to provide information for my informed consent, I have been informed in detail about the scheduled procedure, treatment alternatives, the nature and importance of the procedures, risks and possible complications, prognosis of positive treatment outcomes, medically required secondary and subsequent procedures as well as possible required changes and expansion of the procedures by the physician.

Any questions that seemed important to me were answer in full and in a way that was understandable.

I do not have any further questions, I feel that I have been informed sufficiently, I do not require any more time to consider the treatment, and I consent to the scheduled procedure.

I also agree to any unforeseeable, medically necessary changes or expansions to the procedure as well as secondary and subsequent procedures.

I will comply with any medical instructions and recommendations regarding aftercare.

I will pay the costs of the hyperthermia treatment and the costs of any complications that may arise if these are not covered by my health insurance company.

_____
Place, date, time

_____
Patient

_____
Legal guardian*

_____
Physician

* Only in the case of patients who are minors: If only one legal guardian signs, in doing so, this legal guardian declares that he/she has sole custody or is acting in agreement with the other legal guardian. Both legal guardians must sign in the case of complicated procedures. Patients who are able to understand the treatment should always sign.

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