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Current status of radiant whole-body hyperthermia at temperatures >41.5°C and practical guidelines for the treatment of adults. The German ‘Interdisciplinary Working Group on Hyperthermia’

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Abstract

The term ‘extreme’ whole-body hyperthermia (WBH) describes the procedure of raising a patients’ body-core temperature to 41.5–42.0°C for 60 min. WBH represents the only hyperthermia technique that enables systemic heat treatment in patients with disseminated malignancies and is, therefore, usually combined with systemic chemotherapy. Up to now, several WBH-approaches have proved to be safe and associated with acceptable toxicity rates when radiant heat devices are employed.

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Until the late 1990s, the use of radiant WBH was restricted to a few specialized treatment centres worldwide. During the last 5 years, a larger number of WBH-devices were put into operation particularly in Germany. As a result, a novel generation on phase II trials on chemotherapy and adjunctive WBH in patients with various malignancies has been completed. Based on the promising results observed herein, first multi-centric phase III-trials on chemotherapy \pm WBH have been initiated, with a considerable number of patients treated at German institutions. The authors are members of the 'Interdisciplinary Working Group for Hyperthermia' ('Interdisziplinäre Arbeitsgruppe Hyperthermie'), a sub-group of the German Cancer Society. They formulated these guidelines in order to standardize the WBH treatment procedure and supportive measures, to provide some uniformity in the selection of patients to be treated and to define criteria of a successful WBH-treatment. These recommendations may be helpful to ensure the quality of WBH performed at different institutions.

Keywords: *Hyperthermia induced, whole-body hyperthermia, practice guidelines, review, academic.*

Introduction

The aim of extreme whole body hyperthermia (WBH) is to raise the temperature of the entire body to 41.5–42.0°C over 90–150 min by using a safe power input and to maintain this temperature for at least 60 min. Methods to induce WBH in cancer patients include convective, extra-corporal and radiative techniques [1–3]. Convective procedures are based on contact with heated media, such as water, wax or hot air, or suits or mats through which hot water is pumped. They lack in efficacy with regard to heat induction up to a body-core temperature of 42°C and are associated with excess toxicity. Extra-corporal techniques have proved to be effective in attaining the targeted temperature, but similarly show a high degree of toxicity. An exception has to be made in paediatric oncology, where extra-corporal WBH is associated with a more favourable toxicity profile in children younger than 3 years of age, due to the small body size and better fluid and electrolyte control [4]. Radiative WBH proved to be safe and effective in a number of phase I/II-trials and, thus, represents the only modality that can be recommended for the induction of WBH at temperatures >41.5°C today [3, 5, 6].

Current status of radiative whole-body hyperthermia

Radiant-heat WBH-devices

Radiant WBH devices are available in the USA since the mid-1980s and in Germany since 1991 [7, 8]. Today, various applicators are commercially available that employ infrared heaters operating at different infrared light frequencies. The most commonly used devices ('closed-chamber'-type) utilize black-body radiation with a temperature of 60°C, resulting in the emission of wavelengths of $\sim 7 \mu\text{m}$ (infrared of very low frequency). When respective black-body sources are installed in an enclosed moisture-saturated chamber, they may be effectuated by electrical heating elements [9] or tubes through which hot water flows at 60°C [10]. A disadvantage of those 'closed-chamber' devices is that the radiation cannot penetrate through the patients' support, so that only $\sim 2/3$ of all possible directions can be exploited.

In other types of radiant WBH-applicators ('open-chamber'-type), the patient is placed on a net between sources emitting radiation in the temperature range of 2400°C that is subjected to additional (water-) filtering. This results in the application of infrared wavelengths close to visible light which implies a higher penetration depth of the radiation, reaching values of some mm (extending until the blood vessels in the patients' subcutis) [11]. Those 'open-chamber'-applicators appear to be advantageous with respect to the patients'

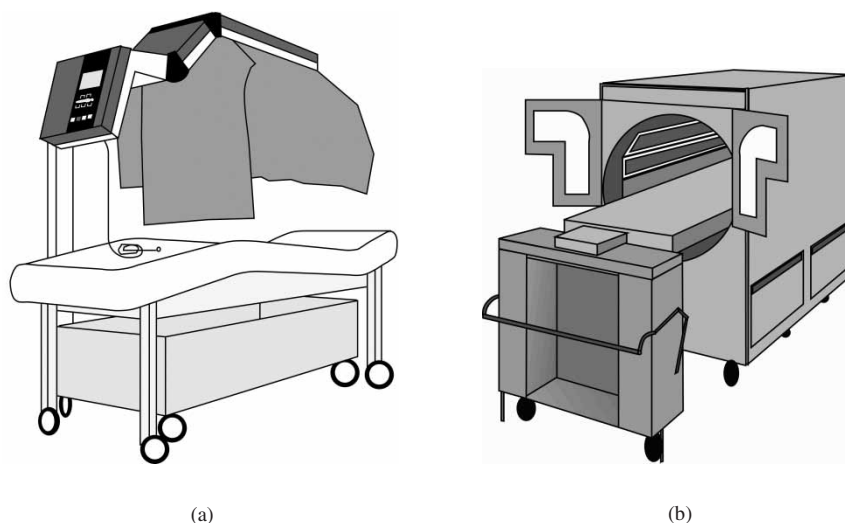


Figure 1. Commonly used radiant WBH applicators; (a) open-chamber device, (b) closed-chamber device.

observability and accessibility during treatment [2]. On the other hand, a higher thermal load of the skin in air of less humidity can provoke a major loss of heat through sweating, a process that may even be increased by the poor isolation of the treatment cabin at least in the first generation of these applicators [2, 12].

Although it is still unclear if these physical considerations are of clinical relevance, clinical data suggest that closed-chamber devices may be easier to handle and associated with lower rates of WBH-specific toxicity than open-chamber applicators.

Clinical trials

Feasibility and safety of radiant heat WBH alone or in conjunction with chemotherapy has been demonstrated in a total of eight phase I-trials [2, 7, 8, 13–17], referring to the evaluation of three different WBH-applicators. These studies have been published as original contributions between 1986–2000 and refer to either WBH alone ($n=2$), WBH plus chemotherapy ($n=5$) or WBH plus chemotherapy plus whole-body irradiation ($n=1$) (Table I).

In addition, nine phase II-trials on WBH and chemotherapy are available on patients with soft tissue sarcomas ($n=1$), colorectal cancer ($n=2$), cholangiocellular carcinoma ($n=1$), ovarian cancer ($n=3$), germ cell tumours ($n=1$), and pleural mesothelioma ($n=1$). These studies, in which four different WBH-devices have been evaluated, have been published between 2000–2004, five of them already available as full papers at the time of submission of this manuscript [12, 18–25] (Table II).

Summarizing the data of these 17 phase I-and II-trials, at least 1300 radiant WBH-treatments have been performed in 465 patients. Treatment-related deaths within the first 30 days after WBH have been reported in four (0.8%) patients. All those treatment-related deaths occurred in the neutropenic phase after chemotherapy and were due to neutropenic sepsis and consecutive multi-organ failure. Therefore, these events were more likely attributable to dose-intensive chemotherapy than to the WBH-procedure itself.

The most important side-effects of WBH are skin-burns, peripheral neuropathy, psychogenic disorders and arrhythmias. Such grade III/IV toxicities have been reported in 40 of

Table I. Phase I-trials on radiant-heat hyperthermia.

Tumour	Year	Authors	Therapy	No. of pts/treatment courses	Type of WBH-device	Type of anaesthesia
Diverse	1985	Robins et al. [7]	WBH	12/52	closed	AS
Diverse	1988	Robins et al. [13]	WBH + Lonidamine	24/93	closed	AS
Diverse	1989	Robins et al. [14]	WBH + Interferon	17/120	closed	AS
Malignant lymphoma	1990	Robins et al. [15]	WBH + Lonidamine + TBI	8/97	closed	AS
Diverse	1993	Robins et al. [16]	WBH + CBCDA	30/59	closed	AS
Diverse	1994	Steinhausen et al. [8]*	WBH	103/x	open	AS
Diverse	1997	Robins et al. [17]	WBH + L-PAM	16/49	closed	AS
Colorectal cancer*	2000	Wust et al. [2]*	WBH + FA/5-FU + MMC	10/20	open	GA

WBH, whole-body hyperthermia; TBI, total body irradiation; CBCDA, carboplatin; L-PAM, melphalan; FA, folonic acid; 5-FU, 5-flouorouracil; MMC, mitomycin C; closed, closed chamber device; open, open chamber device; AS, analgesic sedation; GA, general anaesthesia.

Table II. Phase II-trials on radiant-heat whole-body hyperthermia.

Tumour	Year	Authors	Chemotherapy	No. of pts/treatment courses	Response rates (PR/CR)	Tumour growth control (SD/PR/CR)	Type of WBH-device	Type of anaesthesia
Soft-tissue sarcoma ^a	2003	Westermann et al. [25]	IFO/CBCDA/VP-16	95/278	28%	61%	closed	AS
Colorectal carcinoma	2004	Hildebrandt et al. [23]	5-FU/FA + MMC	11/25	33%	82%	open	GA
Colorectal carcinoma	2002	Hegewisch et al. [21]	5-FU/FA + L-OHP	44/130	20%	76%	closed	GA
Cholangiocellular ca. ^b	2002	Hegewisch et al. [20]	CBCDA/VP-16	22/68	18%	64%	closed	GA
Ovarian cancer	2000	Gruber et al. [19]	CBCDA/IFO	12/38	25%	58%	closed	GA
Ovarian cancer	2000	Strobl et al. [12]	CBCDA/IFO	14/61	50%	93%	open	AS
Ovarian cancer	2001	Westermann et al. [24]	CBCDA	14/44	36%	64%	closed	AS
Mesothelioma ^c	2000	Bakshandeh et al. [18]	IFO/CBCDA/VP16	27/47	20%	76%	closed	AS
Germ-cell tumour	2000	Hildebrandt et al. [22]	IFO/CBCDA/VP16	6/16	33%	83%	open	GA

IFO, ifosfamide; CBCDA, carboplatin; VP-16, etoposide; FA, folonic acid; 5-FU, 5-fluorouracil; MMC, mitomycin C; L-OHP, oxaliplatin; closed, closed chamber device; open, open chamber device; AS, analgesic sedation; GA, general anaesthesia.

Percentage of patients who received primary treatment: ^a 33%; ^b 73%; ^c 100%.

Table III. Toxicity data of eight phase I- and nine phase II-trials on radiant-heat WBH (as given in Tables I and II).

Total number of patients treated	465	
treatment-related deaths (within 28 days)	4	(0.8%)
Total number of treatments episodes	1300	
of WBH-associated toxicity (III/IV°)	40	(3.1%)
• skin burns	16	(1.2%)
• neuropathy	7	(0.6%)
• psychological disorders	7	(0.6%)
• arrhythmias	6	(0.5%)
• others	4	(0.3%)

1300 treatments (3.1%) documented in the aforementioned clinical trials (Table III). In two of these studies, 5-FU-based chemotherapy alone and chemotherapy plus WBH was administered to the same patients sequentially [21, 23]. The toxicity analyses performed revealed no evidence that WBH actually enhances chemotherapy-related toxicity.

As a conclusion, radiative WBH can be regarded as a safe and well-established treatment modality today, but its efficacy has not been proven in the scope of a randomized trial yet. Therefore, one has to balance the potential efficacy of WBH against the expenditure of the treatment procedure (including general anaesthesia or deep analgosedation) and potential risks of severe side-effects [26–28]. However, the fact that tumour growth control rates of > 50% have been observed in all phase II-trials on adjunctive WBH seems to justify further evaluation of this modality. As a result, first randomized phase III-trials on chemotherapy \pm WBH have been initiated in Germany. As the completion of such studies can only be achieved in a multi-centric setting, the formulation of recommendations that help to harmonize the WBH-treatments at different institutions is desirable.

The authors are members of the ‘Interdisciplinary Working Group for Hyperthermia’ (‘Interdisziplinäre Arbeitsgruppe Hyperthermie’), a sub-group of the German Cancer Society. They formulated these guidelines in order to standardize the WBH treatment procedure and supportive measures at different institutions, to provide some uniformity in the selection of patients to be treated and to define criteria of a successful WBH-treatment. These recommendations may be helpful to ensure the quality of WBH performed at scientific institutions.

Practical recommendations for the treatment of adult patients with radiative whole-body hyperthermia at temperatures > 41.5°C

General requirements for radiative whole-body hyperthermia

Technical requirements. In Germany, the certification of radiant WBH-applicators is subject to the Medical Product Law (Medizinproduktegesetz, MPG) instead of the FDA (Food and Drug Administration) regulations in the USA. The MPG particularly specifies that the thermometry unit with an absolute accuracy of $\pm 0.1^\circ\text{C}$ is used in the proximity of the applicator. Before novel applicators are to be introduced into clinical practice, it is advised to review available pre-clinical data that scientifically validated the efficacy of heat-induction and treatment-related side-effects.

Before the installation of the equipment and the control unit is started, the requirements of the manufacturers have to be considered, particularly with regard to the supply of alternating current. Every WBH-unit must be equipped with appliances to perform general

anaesthesia, to administer cytostatic drugs, to continuously monitor the patients' vital functions and to gather laboratory data. There must be provisions for resuscitation and rapid transfer of the patient to an intensive care unit. An intensive care or intermediate care unit, where the patient can be observed for at least 12 h after treatment, is mandatory.

Medical staff requirements. The minimum personnel requirements include an oncologist/physician responsible for the implementation of treatment, including chemotherapy, an anaesthesiologist to perform general anaesthesia or sedation and at least one nurse/anaesthesia nurse. If analgosedation is applied, this must be carried out by a physician experienced in intensive care medicine. In addition, the supervision of the WBH-procedure has to be ensured through the team available, including continuous monitoring of the power delivery and thermometric measurements.

Patients' selection

General eligibility criteria. The date of the last tumour-specific staging results should not be more than 28 days before treatment with WBH. The documentation of both the initial findings, as well as current investigations should include computed tomographic or other radiographic imaging of a measurable reference lesion, according either WHO or 'Recist'-criteria. Other methods of follow-up, e.g. tumour markers, are admissible only in exceptional cases, for example in patients with ovarian cancer that cannot be imaged. However, the initial tumour manifestation or its recurrence must have been histologically confirmed in all patients.

The implementation of WBH requires adequate function of all vital organ systems. Consequently, patients with manifest (definition see below) heart, liver, kidney or bone marrow failure, as well as patients with partial or global respiratory failure or unstable metabolic disease should not be considered for this type of treatment. Arterial hypertension and diabetes mellitus must be treated by appropriate medications, whereas hyperthyroidism—of whatever aetiology—represents an exclusion criterion for WBH. Further ineligibility criteria include pregnancy and nursing, psychiatric diseases that compromise the ability to give informed consent, a seriously reduced perfusion in larger areas of the skin, recent treatment with beta-receptor antagonists, fracture-prone osteolytic lesions, serious neurological diseases, diseases of the central nervous system (CNS), previous irradiation of the CNS with >40 Gy at conventional fractionation (5×1.8 – 2.0 Gy) or a biologically equivalent radiation dose and the presence of bulky intra-cerebral lesions. Therefore, a pre-therapeutic cerebral CT or MRT is obligatory in patients with clinical suspicion of brain metastases or in those suffering from a disease with substantial risk of cerebral metastases.

Patients with lymphatic oedemas should be informed that these may worsen under WBH-treatment. Therefore, it can be reasonable to leave compression stockings on during treatment. As pre-irradiated areas are at increased risk of skin ulcers, particular attention must be paid to these regions during WBH.

As the induction of WBH requires a sufficient cardiopulmonary function, tests of pulmonary function and CO-diffusion capacity, a recent resting and exercise ECG, as well as a transthoracic echocardiography are obligatory. If the results of the cardiopulmonary workout are ambiguous or if the maximal ergometric load could not be reached, further evaluation is necessary in order to rule out coronary heart disease and/or heart failure > NYHA II°, respectively. This usually requires a stress echocardiography, but an additional myocardial scintigraphy or MRI may also be useful in exceptional cases. In selected patients, a coronary angiography may be required.

Table IV. General eligibility criteria for WBH.

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- ECOG (WHO)—Performance Index: 0,1,2;
 - life expectancy >12 weeks;
 - creatinine clearance >60 ml min⁻¹, if potentially nephrotoxic substances (for example carboplatin, ifosfamide) are to be applied;
 - left ventricular ejection fraction >60%, no evidence of relevant arrhythmias or other dysrhythmias, normal findings in resting and exercise ECG resp. stress echocardiography;
 - no current treatment with β -receptor antagonist
 - no hyperthyroidism
 - pulmonary vital capacity >50%, FEV1 >50%, CO-diffusion capacitance >50%;
 - no evidence of brain metastases;
 - no fracture-prone osteolysis;
 - measurable disease; and
 - possibility of a regular, long-term follow-up.
-

With regard to the maximum age at which patients can be treated by WBH, a decision should not be based on an arbitrary cut-off, but on the 'biological' age and adequate organ function. Some of the ongoing trials allow enrollment of patients up to 70 years of age.

The results of the above-mentioned investigations must be presented for an anaesthesiological consultation, which is obligatory in every patient before the 1st WBH-treatment. Furthermore, contra-indications against the medications to be used in cytostatic therapy and anaesthesia are to be considered. If the patient is anaemic, the application of transfusions or erythropoietin according current standards in oncology and intensive care medicine should be discussed.

The general inclusion criteria are summarized in Table IV.

Clinical studies. Recent clinical data demonstrate that radiant WBH, in experienced hands, is feasible and carries an acceptable risk of toxicity. In order to precisely clarify the role of WBH as an adjunct to chemotherapy, patients should be enrolled into prospective studies. An overview of current studies on whole body hyperthermia can be obtained from the authors and from www.hyperthermie.org or www.esho.info.

Treatment outside of clinical trials. The effectiveness of adjunctive WBH for any given indication has not been established yet. Therefore, no general recommendations can be given at present for the use of this treatment outside of clinical trials. Because of substantial treatment associated costs and risk of potentially life-threatening adverse effects, all WBH-treatment outside of clinical trials should only be performed in certified treatment centres. It is recommended that individual indications are to be discussed in the scope of an inter-disciplinary oncological conference, involving medical oncologists, surgeons, radio-oncologists and, where appropriate, further specialists (gynecologist, urologist, paediatric specialists, etc.). The results of this conference as well as the form of the final treatment are to be documented in an appropriate form.

Induction of WBH

Supportive measurements. Patients should be supplied with a large-calibre venous access to ensure sufficient volume replacement. Adequate hydration before treatment is imperative, especially if nephrotoxic substances are to be applied. In this practice, 2000–3000 ml of crystalloid solution is applied as continuous infusion over 12 h before the start of treatment is recommended, roughly depending on body weight.

The patient should be given a well-padded support in order to prevent pressure sores or blistering. Areas of particular exposure, such as elbows and heels, should be given additional padding (for example with fleeced shoes). The feet should give further protection with insulating shoes. In case of analgesic sedation, the patients hands should be fixed in order to avoid self-injury [21, 26, 27].

General anaesthesia/analgesic sedation. WBH may be performed in either general anaesthesia (GA) or deep analgesic sedation (AS). The application of GA during WBH generally requires an experienced anaesthesiologist and a suitably trained nurse, whereas AS can be performed by a physician experienced in anaesthesia or intensive care in the presence of a nurse. Although most of the studies available on radiant WBH (that date back to the mid-1980s) have been performed with AS, this method cannot be unequivocally recommended from a current anaesthesiological point of view today. Indeed, in five of the nine aforementioned phase II-studies on chemotherapy and WBH published since 2000, GA has been employed [19–23].

In order to more clearly define the most suitable form of anaesthesia in WBH-patients, a first randomized phase II-trial comparing analgesic sedation and general anaesthesia (both administered by the ultra-short acting opiate remifentanyl) has recently been performed, comparing oxygen-saturation, intrinsic catecholamine release and treatment-related complications between both groups [21]. Results indicate a benefit in favour of general anaesthesia, but further controlled studies will have more precisely defined the role of both methods during WBH. Until then, the choice which procedure is used is ultimately at the discretion of the anaesthesiologist concerned. From the authors' experience, the application of GA may particularly be preferable in older patients, those with impairments of general condition, with pre-existing cardiovascular or pulmonary diseases, as well as those with large or disseminated pulmonary metastases [21, 26, 27].

General anaesthesia. For WBH performed in general anaesthesia, most experiences are available for total intravenous anaesthesia (TIVA) using different combinations of narcotics and analgetics. Most experience has been gained by using schedules consisting of propofol (e.g. $1\text{--}2\text{ mg kg}^{-1}$ for anaesthesia induction) and remifentanyl ($\sim 0.1\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$) or sufentanyl (e.g. $0.4\text{ }\mu\text{g kg}^{-1}$). Prior to orotracheal intubation, a muscle relaxant is given (e.g. $0.4\text{--}0.6\text{ mg kg}^{-1}$ rocuronium), but repetition doses of relaxants are not generally required. An oesophageal temperature probe can be placed under direct laryngoscopic control.

When TIVA is applied, it may be maintained on the basis of the target controlled infusion (TCI) model. To the authors' experience, the required doses of propofol and remifentanyl in this setting range from $2\text{--}9\text{ mg kg}^{-1}\text{ h}^{-1}$ and $0.05\text{--}0.3\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$, respectively. Using the highly effective opiate remifentanyl, which has a very short half-life, may generally help to reduce the required dose of propofol and, thus, shortens the time from end of infusion to extubation [21, 27].

During GA, the patient is generally ventilated with an O_2/air mixture ($\text{FiO}_2 \sim 50\%$). Parameters for volume or pressure controlled ventilation correspond to those typically used in intensive care medicine (tidal volume $6\text{--}8\text{ ml kg}^{-1}$, frequency: of $12\text{--}16\text{ min}^{-1}$, $\text{PEEP} \geq 7\text{ cm H}_2\text{O}$, $\text{FiO}_2 \geq 0.4$). With these parameters, the target of hyperoxaemic normoventilation can be achieved in most patients [21, 23, 26, 27].

Subsequent to extubation, patients should be transferred to either an intensive or an intermediate care unit and monitored clinically, preferentially until the next morning (see below).

Sedation. If sedation under spontaneous breathing with unsecured airways is administered, a minimum requirement is performance by a physician experienced in anaesthesia or intensive care. Both a physician and a nurse must be present during the entire treatment. Should one of them have to leave the room, it has to be ensured that the person remains immediately available. Access to an intensive care unit must be guaranteed. There must be provisions for intubation and resuscitation.

For WBH under sedation, various combinations of intravenous drugs at highly individualized doses have been proposed, including thiopental, benzodiazepines and opioids [7, 8, 17]. Whereas thiopental provides sedation and theoretically elevates seizure threshold, benzodiazepines enhance the anxiolytic, amnesic and sedative components of the regimen. The additional application of opioids ensures analgesia and augments sedation. As fentanyl has been most commonly used in this setting, it has been recommended as the opiate of choice by the investigators of the 'Systemic Hyperthermia Oncologic Working Group' (SHOWG) [29]. However, fentanyl—despite its recent onset of action and short half-life—may accumulate during a longer-lasting treatment period, possibly leading to respiratory depression.

Proper implementation of general anaesthesia or sedation. It is recommended to pre-medicate every patient 1 h before WBH (e.g. with midazolam 3.75–7.5 mg per os). Further supportive measures include antiemetic prophylaxis (e.g. with dexamethasone and/or 5HT₃-antagonists), as well as a parasympatholytic agent to reduce sweating, e.g. glycopyrronium [21, 27, 29].

During therapy, the patients' vital parameters have to be monitored continuously, including (invasive) measurement of arterial and central venous pressure, pulse-oxymetry and diuresis, as well as an ECG with on-line ST-segment analysis. WBH is accompanied by a markedly hyperdynamic cardiovascular state, which can result in a drop in arterial blood pressure that is chiefly due to a substantial decrease of the peripheral vascular resistance [27, 30–32]. In order to guarantee sufficient perfusion of vital organs, the mean arterial blood pressure should be maintained above 50 mmHg during the entire treatment. This is initially accomplished by infusions of cristalloids, colloids and glucose solutions at 600–1800 ml h⁻¹. To avoid phases of severe hypotension and to preserve a diuresis of ~1 ml kg⁻¹ h⁻¹ during the plateau phase of WBH, the additional application of catecholamines may be required (e.g. continous infusion of up to 0.5 µg kg⁻¹ min⁻¹ noradrenaline). Some investigators also recommend continuous infusions of lignocaine (1–2 mg kg⁻¹ h⁻¹), dopamine (2–3 µg kg⁻¹ min⁻¹) and 20% sodium chloride (3 g h⁻¹) [2, 7, 18, 21, 23, 24].

During treatment, blood gas analyses should be performed according to clinical requirements, e.g. every 60–120 min. Serum electrolytes, haemoglobin levels and blood glucose levels should be performed at least every 2 h. The latter is kept at a level of ~250 mg dl⁻¹ by infusion of highly concentrated glucose solutions by many clinicians. A drop in haematocrite or haemoglobin values may require a substitution with packed red blood cells.

Following treatment, the patient should be transferred to an intensive care unit for clinical monitoring. During transport, facilities to monitor vital functions as well as equipment for resuscitation must be available. Alternatively, the patient may be transferred to an intermediate care unit if he/she is in a stable condition and if sufficient medical and nursing personnel is available for monitoring vital parameters over the next 12 h. Besides clinical observation, continuous monitoring of heart rate and oxygen saturation and non-invasive measurement of blood pressure should be performed. One-to-two-hourly measurements of blood glucose values are required until they have passed their nadir, in order to recognize

hypoglycaemia due to reactive hyperinsulinaemia. Hypoglycaemia should be corrected by infusion of 40% glucose.

Immediately after WBH, fluid should be infused at a rate of 200–300 ml h⁻¹ for a minimum of 4–6 h, depending on diuresis and CVP, especially if the chemotherapy schedule includes potentially nephrotoxic drugs. A drop in oxygen saturation below 95% should be treated by application of oxygen at 2–8 l min⁻¹ via a face mask. In addition, a chest X-ray should be performed. If oxygen application does not enhance O₂-saturation and radiological or clinical signs are suggesting pulmonary fluid retention, the application of loop diuretics may be valuable.

Laboratory tests, including the determination of metabolic and electrolyte status, haemoglobin and blood glucose should be carried out immediately, 4 and 12 h after treatment, even after uncomplicated treatments. The patient should stay in hospital for at least 24 h after every WBH.

For a more detailed description of anaesthesiological management during WBH see also Hildebrandt et al. [23], Hegewisch-Becker et al. [21], Kerner et al. [26,] [27,] [31] and Berry et al. [32]

Thermometry and temperature control. The temperature should be continuously monitored by using at least two central probes, employing standard thermistors with an absolute accuracy of $\pm 0.1^\circ\text{C}$. One of the obligatory sensors is placed in the rectum, the other can be inserted either into a central vein, an artery (incl. pulmonary artery) or into the oesophagus. Peripheral points of measurement include the presternal region, the axilla, the lower abdomen and the back. If the thermistors lie superficially, they must be covered in some way, both for temperature stability and to avoid direct heating through the radiation. The skin can additionally be monitored using an infrared detector (pyrometer), which allows the temperature of the skin surface to be measured without contact.

Generally, the temperature in the venous system is almost identical to that in the aorta or pulmonary artery (as measured at the tip of a Swan-Ganz catheter) and correlates well with temperature measurements from the oesophagus. A rapid input of energy into the venous system is characteristic for WBH systems that reduce the heat loss from evaporation by raising the humidity or by other measures. If the input of power into the venous system is inhibited, an increased correspondence between the temperature in the pulmonary artery and the systemic temperature (rectum or bladder) occurs. A high similarity of both temperatures may indicate a considerably lengthened warm-up phase and the necessity to replace high amounts of fluid lost by sweating [2].

It is desirable that regular measurements of the temperature is taken not only from central points, but also from particularly exposed superficial regions. One may avoid thermal skin lesions and power losses through local cooling or covering.

According to present opinion, the core temperature in extreme WBH should be maintained at 41.8°C for at least 60 min. Temperature drops to below 41.5°C are to be avoided, as are prolonged intervals of time with a core temperature exceeding 42°C. A target temperature of 41°C for 80 min is currently being evaluated in studies.

In patients treated by WBH devices with a closed chamber, the target temperature (as measured in the esophagus) can be easily maintained by taking the patient out of the chamber and covering him in blankets. As a rule, the body-core temperature, as measured rectally, can be held quite stable through these measures without any need of further heating. In case of falling temperature, the patient can be guided back a short way into the apparatus, for example up to his hips. This relies on sensitive thermometry, in order to recognize trends in temperature changes early enough. Currently, changes in the core

Table V. Recommendations for the treatment of adult patients with 'extreme' WBH.

General requirements:

- WBH applicator and thermometry unit approved by national surveillance authority (accuracy: $\pm 0.1^\circ\text{C}$); requirements of the manufacture considered; alternating current available
- Equipment is suitable to provide (1) general anaesthesia/analgesic sedation, (2) continuous monitoring of the patients vital parameters, (3) generation of laboratory data, (4) application of cytostatic drugs (5) resuscitation and rapid transfer to intensive care unit
- Intensive or intermediate care unit available for post-treatment observation
- Minimum personnel requirement: (1) Oncologist/experienced physician (implementation of WBH, chemotherapy), (2) anaesthesiologist (general anaesthesia, analgesic sedation) or physician experienced in intensive care medicine (analgesic sedation) (3) nurse

Supportive measures:

- Large-calibre venous access/central venous catheter
- Adequate (pre-) hydration
- Well-padded support to avoid pressure sores or blistering

General anesthesia (GA)/analgesic sedation (AS):

- Adequate pre-medication
- Continuous monitoring of vital parameters, including arterial (mean arterial pressure $>50\text{ mmHg}$) and central venous pressure, pulse-oxyetry, diuresis ($\sim 1\text{ ml kg}^{-1}\text{ h}^{-1}$), ECG with online ST-segment analysis
- Blood gas analyses, blood count and clinical chemistry according to clinical requirements (e.g. every 60–120 min., see text)
- GA preferred in (1) older patients (pts.), (2) pts. with impairment of general condition, (3) pts. with pre-existing cardiopulmonary disease (4) pts. with large or disseminated pulmonary metastases
- GA: intubation prior to WBH; total intravenous anaesthesia (TIVA), hyperoxaemic normoventilation ($\text{FiO}_2 \sim 50\%$); extubation at $38\text{--}39^\circ\text{C}$ (after WBH)
- AS: access to intensive care unit guaranteed
- GA/AS: Observation at intermediate care/intensive care unit after treatment

Thermometry/temperature control:

- Continuous monitoring of temperatures by using at least two central (rectum and either central vein/artery or esophagus) and peripheral probes
- Plateau of body-core temperature $>41.5^\circ\text{C}$ for 60 min
- Patients cool down passively after treatment

temperature can be registered to an accuracy of $0.01^\circ\text{C min}^{-1}$. In the hands of experienced physicians, only relatively few such manoeuvres are necessary in order to keep the core temperature stable during the plateau phase.

Following the treatment, the patients cool down passively or, if appropriate, with the help of local applications of liquid spray or ice. Even in uncomplicated cases, the patient should not be extubated (general anaesthesia) or rebuffed (sedation) before the body core temperature has dropped to $38\text{--}39^\circ\text{C}$.

The main recommendations concerning the treatment of adult patients with 'extreme' WBH are summarized in Table V.

Summary and outlook

Feasibility and safety of radiant heat WBH alone or in conjunction with chemotherapy has been demonstrated in a number of phase I-trials since the mid 1980s. In the late 1990s, radiative WBH has regained considerable interest, particularly in Germany and the Netherlands. This fact is reflected by the publication of nine phase II-trials since 2000 and the implementation of first phase III-trials comparing chemotherapy alone with chemotherapy plus radiative WBH. Up to now, 1300 radiative WBH-treatments in more than 450 patients have been documented in the scope of clinical trials. The rate of severe side-effects

was in the range of 3%. The rate of deaths within 30 days after WBH-treatment was 0.8%. All fatalities occurred in the neutropenic phase following WBH and chemotherapy and were due to neutropenic sepsis and multi-organ dysfunction. They, thus, were rather attributable to the dose-intensive chemotherapy applied to these patients than to the WBH-procedure itself. However, there may be a certain number of unreported WBH-related deaths in patients that have been treated outside of scientific institutions.

Up to now, no larger randomized trials on the effect of adjunctive WBH or comparisons of different supportive strategies (e.g. analgesic sedation vs general anaesthesia) have been completed. This is why, from a recent point of view, radiant WBH can be regarded as a practical and well-tolerated form of therapy, but its precise role in multi-modal treatment concept still needs to be defined. The major obstacle of this approach is that it consumes a vast amount of time, medical staff and financial resources. Thus, highest priority should be given to conclude the ongoing randomized studies in order to definitely proof or abandon the idea to adjuvate WBH at temperatures $>41.5^{\circ}\text{C}$ in the next few years. The here formulated recommendations are to be understood as practical guidelines for the implementation of extreme radiative WBH in adults and they may particularly help to provide some uniformity in the practice of WBH.

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References

1. Gautherie M. *Whole body hyperthermia: biological and clinical aspects*. Berlin, Heidelberg, New York: Springer Verlag, 1991.
2. Wust P, Riess H, Hildebrandt B, Loffel J, Deja M, Ahlers O, Kerner T, von Ardenne A, Felix R. Feasibility and analysis of thermal parameters for the whole-body-hyperthermia system IRATHERM-2000. *Int J Hyperthermia* 2000;16:325–39.
3. Wust P, Hildebrandt B, Sreenivasa G, Rau B, Gellermann J, Riess H, Felix R, Schlag PM. Hyperthermia in combined treatment of cancer. *Lancet Oncol* 2002;3:487–97.
4. Wessalowski R, van Heek-Romanowski R, Issels R, Jurgens HT, Gobel U. Estimated number of children with cancer eligible for hyperthermia based on population- and treatment-related criteria. *Int J Hyperthermia* 1999;15:455–66.
5. Hildebrandt B, Loffel J, Ahlers O, Wust P, Riess H. Hyperthermia: different methods, different aims, and different problems. *Onkologie* 1999; 22(5): 420–421.
6. van Der Zee J. Heating the patient: a promising approach? *Ann Oncol* 2002;13:1173–84.
7. Robins HI, Dennis WH, Neville AJ, Shecterie LM, Martin PA, Grossmann J, Davis TE, Neville SR, Gillis WK, Rusy BF. A nontoxic system for 41.8°C whole body hyperthermia: results of a phase I study using a radiant heat device. *Cancer Res* 1985;45:3937–44.
8. Steinhausen D, Mayer WK, Ardenne Mv. Evaluation of systemic tolerance of 42.0°C infrared-A whole-body hyperthermia in combination with hyperglycemia and hyperoxemia. *Strahlenther Onkol* 1994;170:322–34.
9. Robins HI, Grossman J, Davis TE, AuBuchon JP, Dennis W. Preclinical trial of a radiant heat device for whole-body hyperthermia using a porcine model. *Cancer Res* 1983; 43(5): 2018–22.
10. Robins HI, Woods JP, Schmitt CL, Cohen JD. A new technological approach to radiant heat whole body hyperthermia. *Cancer Lett* 1994;79:137–43.
11. von Ardenne M. Principles and concept 1993 of the Systemic Cancer Multistep Therapy (sCMT). *Strahlenther Onkol* 1994;170:581–9.

12. Strobl B, Janni W, Rjosk D, Rack BK, Kornya L, Bakhshandeh-Bath A, Hegewisch-Becker S, Hildebrandt B, Sommer HL. Chemotherapy with carboplatin/ifosfamide combined with whole body hyperthermia in recurrent ovarian cancer—results of a phase II study (Dolphin-1-Study). *Proc Am Soc Clin Oncol* 2002;19:A2523.
13. Robins HI, Longo WL, Lagoni RK, Neville AJ, Riggs C, Schmitt CL, Hugander A, Young C. A phase I trial of lonidamine with whole body hyperthermia in advanced cancer. *Cancer Res* 1988;43:6587–92.
14. Robins HI, Sielaff KM, Storer B, Hawkins MJ, Borden EC. A phase I trial of human lymphoblastoid interferon with whole body hyperthermia in advanced cancer. *Cancer Res* 1989;49:1609–15.
15. Robins HI, Longo WL, Steeves RA, Cohen JD, Schmitt CL, Neville AJ, O'Keefe S, Lagoni R, Riggs C. Adjunctive therapy (whole body hyperthermia versus lonidamine) to total body irradiation for the treatment of favorable B-cell neoplasms: a report on two pilot clinical trials and laboratory investigations. *Int J Radiat Oncology Biol Phys* 1990;18:909–20.
16. Robins HI, Cohen JD, Schmitt CL, Tutsch KD, Feierabend C, Arzooonian RZ, Alberti D, d'Oleire F, Longo W, Heiss C, Rushing D, Love R, Spriggs D. Phase I clinical trial of carboplatin and 41.8°C whole-Body hyperthermia in cancer patients. *J Clin Oncol* 1993;9:1787–94.
17. Robins HI, Rushing D, Kutz M, Tutsch KD, Tiggelaar CL, Paul D, Spriggs D, Kraemer C, Gillis W, Feierabend C, Arzooonian RZ, Longo W, Alberti D, d'Oleire F, Qu RP, Wilding G, Steart JA. Phase I clinical trial of melphalan and 41.8°C whole-body hyperthermia in cancer patients. *J Clin Oncol* 1997;15:158–64.
18. Bakhshandeh A, Bruns I, Traynor A, Robins HI, Eberhardt K, Demedts A, Kaukel E, Koschel G, Gatzemeier U, Kohlmann T, Dalhoff K, Ehlers EM, Gruber Y, Zumschlinge R, Hegewisch-Becker S, Peters SO, Wiedemann GJ. Ifosfamide, carboplatin and etoposide combined with 41.8°C whole body hyperthermia for malignant pleural mesothelioma. *Lung Cancer* 2003;39:339–45.
19. Gruber Y, Hegewisch-Becker S, Bakshandeh-Bath A, Sommer H, Hoffmann R, Hossfeld DK. Whole-body hyperthermia at 41.8°C combined with ifosfamide and carboplatin in relapsed ovarian carcinoma pretreated with a platin-containing regimen. *Ann Oncol* 2000;11:377P.
20. Hegewisch-Becker S, Corovic A, Jaeger E, Goeckurt J, Panse J, Nierhaus A, Hossfeld DK. Whole body hyperthermia (WBH, 41.8°C) combined with carboplatin and etoposide in advanced biliary tract cancer. *Proc Am Soc Clin Oncol* 2003;22:abstr 1247.
21. Hegewisch-Becker S, Gruber Y, Corovic A, Pichlmeier U, Atanackovic D, Nierhaus A, Hossfeld DK. Whole-body hyperthermia (41.8°C) combined with bimonthly oxaliplatin, high-dose leucovorin and 5-fluorouracil 48-hour continuous infusion in pretreated metastatic colorectal cancer: a phase II study. *Ann Oncol* 2002;13:1197–204.
22. Hildebrandt B, Wust P, Rick O, Deja M, Kerner T, Löffel J, Ahlers O, Dieing A, Weinknecht S, Bechstein WO, Siegert W, Felix R, Riess H. [Whole body hyperthermia in germ cell tumors]. *Onkologie* 2001;7:324–30, German.
23. Hildebrandt B, Dräger J, Kerner T, Deja M, Löffel J, Stroszczyński C, Ahlers O, Felix R, Riess H, Wust P. Whole-body hyperthermia in the scope of von Ardenne's 'systemic Cancer Multistep Therapy (sCMT)' combined with chemotherapy in patients with metastatic colorectal cancer—a phase I/II study. *Int J Hyperthermia* 2004;20:317–33.
24. Westermann AM, Grosen EA, Katschinski DM, Jäger D, Rietbroek R, Schink JC, Tiggelaar CL, Jäger E, Zum Vorde Sive Vording P, Neuman A, Knuth A, Van Dijk JD, Wiedemann GJ, Robins HI. A pilot study of whole body hyperthermia and carboplatin in platinum-resistant ovarian cancer. *Eur J Cancer* 2001;37:1111–7.
25. Westermann AM, Wiedemann GJ, Jäger E, Jäger D, Katschinski DM, Knuth A, Vorde Sive Vording PZ, Van Dijk JD, Finet J, Neumann A, Longo W, Bakhshandeh A, Tiggelaar CL, Gillis W, Bailey H, Peters SO, Robins HI. A systemic hyperthermia oncologic working group trial. Ifosfamide, carboplatin, and etoposide combined with 41.8°C whole-body hyperthermia for metastatic soft tissue sarcoma. *Oncology* 2003; 64:312–21.
26. Kerner T, Deja M, Gerlach H, Ahlers O, Löffel J, Wust P, Hildebrandt B, Felix R, Riess H. Whole-body hyperthermia—a secure procedure for patients with various malignancies? *Intensive Care Med* 1999;25:959–65.
27. Kerner T, Hildebrandt B, Ahlers O, Deja M, Riess H, Draeger J, Wust P, Gerlach H. Anaesthesiological experiences with whole body hyperthermia. *Int J Hyperthermia* 2003;19:1–12.
28. Pereira Arias AM, Wester JP, Blankendaal M, Schilthuis MS, Kuijper EJ, Rademaker BM, Stoutenbeek CP, Rietbroek RC. Multiple organ dysfunction syndrome induced by whole-body hyperthermia and polychemotherapy in a patient with disseminated leiomyosarcoma of the uterus. *Intensive Care Med* 1999;25:1013–6.
29. Bakhshandeh A, Bath V, Wiedemann GJ, Longo W, Lerner BM, Tiggelaar CL, Robins HI. Year 2000 guidelines for clinical practice of whole body hyperthermia combined with cytotoxic drugs from the University of Lübeck and the University of Wisconsin. *J Oncol Pharm Practice* 1999;5:131–4.

30. Faithfull NS, Reinhold HS, van der Berg AP, van Rhoon GC, van der Zee J, Wike-Hooley JL. Cardiovascular changes during whole body hyperthermia treatment of advanced malignancy. *Eur J Appl Physiol* 1984;53: 274–81.
31. Kerner T, Deja M, Ahlers O, Hildebrandt B, Dieing A, Riess H, Wust P, Gerlach H. Monitoring arterial blood pressure during whole body hyperthermia. *Acta Anaesthesiol Scand* 2002;46:561–6.
32. Berry JM, Michalsen A, Nagle V, Bull JM. The use of esmolol in whole-body hyperthermia: cardiovascular effects. *Int J Hyperthermia* 1997;13:261–8.