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Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements

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ABSTRACT

Quality assurance guidelines are essential to provide uniform execution of clinical trials and treatment in the application of hyperthermia. This document provides definitions for a good hyperthermia treatment and identifies the clinical conditions where a certain hyperthermia system can or cannot adequately heat the tumour volume. It also provides brief description of the characteristics and performance of the current electromagnetic (radiative and capacitive), ultrasound and infra-red heating techniques. This information helps to select the appropriate heating technique for the specific tumour location and size, and appropriate settings of the water bolus and thermometry. Finally, requirements of staff training and documentation are provided. The guidelines in this document focus on the clinical application and are complemented with a second, more technical quality assurance document providing instructions and procedure to determine essential parameters that describe heating properties of the applicator for superficial hyperthermia. Both sets of guidelines were developed by the ESHO Technical Committee with participation of senior STM members and members of the Atzelsberg Circle.

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Introduction

These quality assurance (QA) guidelines were developed in response to a request from the Atzelsberg Circle for Clinical Hyperthermia of the Interdisciplinary working group of hyperthermia "Interdisziplinäre Arbeitsgruppe Hyperthermie" (IAH) [1] of the German Cancer Society ("Deutsche Krebsgesellschaft") to the European Society for Hyperthermic Oncology (ESHO) [2]. ESHO delegated this task to the ESHO technical committee (TC), who formulated the guidelines with participation of experienced members of the Society for Thermal Medicine (STM) [3]. In addition the manufacturers providing equipment for superficial hyperthermia have been invited to provide their feedback on the QA guidelines during public sessions during the 2014 and 2015 annual meetings of ESHO or alternatively by personal communication.

The guidelines seek to establish a single uniform level of quality in hyperthermia treatments delivered in all multi--institutional studies initiated by the Atzelsberg Circle or under the auspices of the ESHO, but may also be applied for guidance to clinical studies initiated by other groups as well. The goal of this effort is to establish QA guidelines for the application of superficial hyperthermia, similar to the QA guidelines for administration of deep hyperthermia defined earlier [4,5] and as a long-awaited follow-up to the earlier QA guidelines for superficial hyperthermia provided by Radiation Therapy Oncology Group and ESHO [6–8].

The QA guidelines for the application of superficial hyperthermia are described in two documents; one describing the clinical requirements and the other describing in detail the technical requirements [9]. "Together, they provide the essential QA standards based upon current knowledge and experience of both technological and clinical considerations to properly guide the application and registration of superficial hyperthermia treatments within clinical trials."

A fundamental premise of these QA guidelines is that the proven effectiveness of hyperthermia in clinical studies relies exclusively on its thermal effect on tumours which is dependent on temperature and time [10–16]. For this reason superficial hyperthermia treatments must be conducted using hyperthermia devices that are technically capable of controlled heating of the specific target volume to the required temperature and thermal dose range (as defined in section

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2) while minimising dose to surrounding critical normal tissues. The target volume and organs/areas at risk are to be defined by the responsible oncologist using physical examination and/or imaging studies.

Prior to developing these QA guidelines, ESHO recognised that there is a wide variation of technologies available to apply hyperthermia treatment. Therefore, ESHO assigned the ESHO-TC with the responsibility to design QA guidelines that are applicable to all currently used superficial hyperthermia systems, i.e. electromagnetic (EM), ultrasound (US), and infrared (IR) heating systems. This does not mean that these systems have equal heating abilities. On the contrary, ESHO recognises that while all systems can be used for heating some superficial tumours, each device has specific benefits and limitations for tumours that it can heat adequately. Differences in performance concern the lateral extent and depth of heating, feasibility of spatial control, location, contact or coupling requirements, etc. The intention of these QA guidelines is to identify clinical conditions where a certain hyperthermia system can or cannot adequately heat the tumour volume. In this way, participation in clinical trials is open for all participants providing they have both implemented the QA guidelines and strictly follow the specific requirements of the clinical study protocol to apply hyperthermia to the defined clinical target. Hence it is the responsibility of every institute to characterise its hyperthermia equipment and make the data available to the ESHO-TC. As a follow-up of the development of these QA guidelines and using the experimental and clinical information obtained via the implementation of the QA guidelines, the ESHO-TC will investigate the possibility to formulate a public list of device types with a description of the potential tumour size, depth and location that can be heated.

There are two important reasons to follow strict QA guidelines during hyperthermia treatments:

a. Treatment outcome and toxicity has been shown to be correlated with temperature parameters.
   Over many years dose effect relationships have been found in retrospective studies for penetration depth [17], coverage by the 25% iso-SAR contour [18] and thermal dose expressed as T90[1], T50 and Tmax for a specified duration [19–21], temperature homogeneity [22], CEM43 and CEM43T90 and more recently Trise [23,24]. In addition, thermal dose effect thresholds vary for tumour pathology [25,26]. The study of Jones *et al.* [27] in superficial tumours is unique, as it is the only human study showing a thermal dose effect relationship in a prospective study design. Most recently, Linthorst *et al.* [28] reported that the incidence of skin toxicity increases with higher superficial temperature. The potential value of CEM43 as thermal dose parameter in hyperthermia has recently been summarised [29].
b. High quality superficial hyperthermia treatment is a demanding and complex task.
   Patients referred for superficial hyperthermia comprise a wide variety of tumour pathologies, spatial extent and location in the body. Tumours may appear on smooth or highly irregular surfaces with variable depth below and/or protruding from the skin. As excellently summarised by de Bruijne *et al.* [30], heating superficial tumours involves complex technology and the operator of hyperthermia equipment needs to manage a multiple-input multiple-output system where the tissue dynamics are time-varying and non-linear. In addition, the temperature data is often recorded by a limited number of sensors that sample temperatures from a relatively small percentage of the target volume. Furthermore, the technician must combine measured temperatures with patient feedback in the form of subjective pain complaints and signs of discomfort.
   Many different systems are used to apply superficial hyperthermia, as built commercially or in academic medical centres [31,42]. Each system has unique and differing characteristics and benefits. Further, with the variation in clinical protocols, prescribed number of hyperthermia treatments, temperature and thermal dose goals, defined and uniform methods to how to respond to patient feedback, it is not surprising that a large heterogeneity may exist in the quality of applied hyperthermia treatments between various hyperthermia institutions. For participation in multi-institutional clinical studies, the protocol variations must be minimised. The objective of the QA guidelines presented in this document is to reduce differences in hyperthermia treatment quality achieved using the existing range of heating technology. Towards that end, this guideline provides clear instructions how to characterise the clinical performance of each hyperthermia device, and what to document. These measurement results should provide quantitative support for determination of which tumours can or cannot be heated with each device and whether or not a patient is appropriate for a clinical study.

Definition of a minimum thermal dose requirement for a hyperthermia treatment

In general, a good superficial hyperthermia treatment is defined as heating the target volume above the minimum prescribed thermal dose while maintaining critical normal tissues below the maximum prescribed normal tissue dose. The target volume is always defined by the responsible clinician.

Clinical evidence of a benefit of hyperthermia exists only for application of hyperthermia in combination with chemotherapy and/or radiotherapy [32,33]. Different protocols specify different thermal dose goals depending on combinations with other therapeutic agents like radiation or chemotherapy and location in the body. The clinical protocol also defines the time interval between the chemotherapy/radiotherapy and

[1]T90, T50 or Tx being the temperature at which 90%, 50% or x% of the tumor temperature measurements exceed. Tmax is the maximum temperature measured during treatment. CEM43T90 is the cumulative equivalent minutes at 43 °C thermal dose calculated for the T90-temperature over the course of treatment. Trise is defined as the average temperature increase above 37 °C, multiplied by the ratio of the prescribed duration to the actual treatment duration.

Table 1. Applicator feasibility guidance table indicating general performance of EM, US and IR heating systems.

	Thermal or temperature effective penetration depth*	Spatial power control		Thermal or temperature effective field size**
		Single applicator	Array applicator	
EM (radiative)	+	− −	+ +	− to ++□
EM (capacitive)	+	− −		+
US	++	− −	+ +	−
IR	− −	+		+ +

This table provides a fast, subjective and qualitative impression of the strength and weaknesses of each superficial hyperthermia system. It is intended to provide the clinician with an indication of the feasibility of each system to heat a specific superficial tumour taking into account for tumour size, depth and distribution over the treatment volume. The performance is indicated by following grades: ++ very good, + good, o fair, − poor, − − very poor).
*Thermal Effective Penetration Depth (TEPD) is defined as the depth at which the maximum TR is 50% of the maximum TR at 1 cm depth.
**The Thermal Effective Field Size (TEFS) is defined as the area within the 50% of maximum TR contour in the 1 cm deep plane under the aperture [9].
□Applicator or array dependent.

hyperthermia treatment session, aiming for optimal sensitisation of chemo- and radiotherapy. In current practice, chemotherapy is applied just before or simultaneously with hyperthermia, while radiotherapy is mostly applied close to hyperthermia with a time interval around 1 h and less than 4 h. In rare cases when technically feasible, radiotherapy and hyperthermia can be applied simultaneously [34–36].

For superficial hyperthermia of tumours extending from skin to cutaneous tissue layers, the minimum goal is to reach a T90 of 40 °C for 60 min and a T50 exceeding 41 °C throughout the target volume, with maximal normal tissue temperature of 43–45 °C as considered acceptable by the responsible clinician. This represents a thermal dose expressed by cumulative equivalent minutes at 43 °C (CEM43T90) close to 1 and a Trise >3 °C per hyperthermia session. In the study of Jones *et al.* [27] patients were selected on the basis of heatability with a threshold of 1 CEM43T90.

To ensure high-quality hyperthermia treatment, it has been common practice to push for "uniformly[2]" high temperatures from the tissue surface to the entire target volume. Besides enhancing treatment outcome, the aggressive "pushing" strategy may also increase acute side effects such as blisters and burns. Clinical studies reported in the literature mention various percentages of patients with grade 1, 2 or 3 toxicity. The pre-treatment status (e.g. scars and skin flaps) and treatment set up are important factors determining the maximum tolerable skin temperature. Literature shows that the risk of inducing skin or subcutaneous tissue toxicity increases when skin temperature exceeds 43–44 °C for 60 min [28,37–39]. Published data indicate that skin flaps are not a contraindication for superficial hyperthermia. However, as thermal physiology is disturbed in skin flaps and scars, temperatures at these locations should be carefully monitored to avoid excessive temperatures and ensuing enhanced toxicity [28,37–40]. Therefore, accurate characterisation of surface temperature distributions is important for treatment quality.

Clinical requirements for heating devices

A heating system should be able to increase target temperature at a rate of 1 °C per minute, which corresponds to a SAR of 60 W/kg in muscle [41] and should allow full adjustment of output power from 0 to 100%. An EM or US heating system consists of one or more power amplifiers, an applicator(s) to transfer EM or US energy into tissue and a temperature controlled water bolus to maintain skin temperature at the prescribed level and to provide coupling between the body and applicator [42]. An IR system uses lamps to irradiate the skin surface without water bolus [43]. All systems must have a temperature measuring unit and a computer controller with graphical user interface to record and display temporal temperature data and control power. For superficial heating, a large variety of applicators may be employed as long as the device meets the above stated requirements to guarantee high quality heating.

In addition, all documentation must be according to Appendix and fulfil the conditions defined in the study protocol.

Systems available for superficial heating

In this section a brief summary is given of the operating principles of various systems for heating superficial tissue, including a "feasibility guidance table" (Table 1) for selection of an appropriate device for specific clinical situations. The device used must obey the national regulations regarding frequency and screening for EM compatibility. Details and specifications are provided in part II: "Technical requirements for heating devices" of the superficial hyperthermia QA guidelines [9].

EM radiative heating systems

At frequencies above 400 MHz, heating results predominantly from displacement currents, i.e. friction between adjacent polar water molecules which oscillate in response to the time varying field [44]. Numerous applicators are used for hyperthermia treatment and each has unique power deposition characteristics. In order to localise heat into practical tumour size volumes, frequencies are usually in the range 400 MHz to 2.45 GHz. Power deposition decreases exponentially at increasing depth into tissue and the penetration of EM energy is strongly dependent on frequency and on applicator size. Most applicators operate at ISM band frequencies of 915 MHz or 400–434 MHz, which give therapeutic depths of up to 3 or 4 cm. Small applicators achieve less penetration than large applicators. Two classes of EM applicators can be distinguished, waveguide [45,46] and microstrip applicators

[2]Due to the heterogeneous tumor perfusion a uniform temperature will never be reached, though we strive for a temperature distribution which is as homogeneous as possible.

[36,47–51]. In order to produce effective heating of large area tumours, EM applicators can be combined into large multi-element arrays with separate power control of each element that enables 2-D power steering by adjusting power of individual elements [52–54].

EM capacitive systems

For EM frequencies below 400 MHz heating is mostly determined by energy loss via conduction currents, i.e. friction between ions and free electrons, which move over short distances in response to the time varying field [44]. EM capacitive heating utilises two electrodes placed on either side of the body and has been used for superficial hyperthermia [55–57]. In order to heat superficial locations, a small size electrode must be placed on the target lesion while a larger electrode is situated on the opposite side of the body. The electrodes are connected to a radiofrequency (RF) power source (8–27 MHz) and the resulting power absorption pattern is mainly determined by the size and location of the smaller electrode. Descriptions on the use of EM capacitive heating are given in [58,59]. An important factor to consider when applying EM capacitive heating is to be careful of unintended preferential heating of the fat tissue layer [60].

US heating

Ultrasound energy propagates through tissue as a travelling pressure wave that generates periodic motion or displacements within the tissue, and produces heat from viscous friction losses [61–63]. Similar to EM radiation, US intensity or energy deposition (proportional to acoustic pressure squared) decreases exponentially with depth in tissue and penetrates deeper for lower frequencies. Because the speed of sound is orders of magnitude less than the speed of light, the wavelength in soft tissue is only $\lambda = 0.1–3$ mm for typically used frequencies ($f = 0.5–10$ MHz). Dispersion of the beam is minimal, and may be focussed into very small tissue volumes as the wavelength at these frequencies is much shorter than the dimensions of both tumours and applicators. Because of the low attenuation in soft tissue, US sources at low frequency can penetrate deep into the body; similarly, higher frequency transducers can be utilised for reduced penetration for more shallow superficial tumours. Additionally, due to the short wavelength, practical size phased array applicators with multiple transducers can be electronically or mechanically scanned to produce an intense focal hot spot or produce complex beam distributions at depth. Alternatively, non-focussed transducer arrays are possible for superficial heating of large surface areas [64,65].

IR heating

For heating tissue with infra-red, only the IR-A radiation associated with wavelengths between 760 and 1400 nm can be utilised [43,66,67]. The penetration depth of such a system is in the range of 1 mm to 3 mm and increases due to the heat transport through blood vessels. In order to reduce thermal exposure of skin surface, a water filter system must be integrated with the IR radiation source (wIRA) [43,68]. Recently an effective penetration depth of 15 mm has been reported for such a system [69,70]. Temperatures of $T >= 42\,^{\circ}C$ and a surface homogeneity can be achieved over large surface areas with this setup within five to ten minutes. The heating pattern can be shaped using an opaque mask to block IR radiation at locations where it is not needed.

Requirements and guidelines for proper clinical use of the applicator:

1. Each radiating aperture should be capable of accomplishing superficial hyperthermia (as given in part II of the guidelines).
2. The effective portion of the aperture footprint of a single applicator or an array applicator should be chosen such that the therapeutic region covers the whole target volume. If the complete target volume is not covered by the effective portion of the applicator, multiple sequential treatment sessions must be administered together with abutting fields for covering the entire target area (patch work).
3. The therapeutic or effective region of a multielement array applicator is defined analogous to the definition of therapeutic region for a single aperture applicator.
4. It is strongly advised to have thermometry measurement points underneath each independently controlled heat aperture, either on the surface of the tumour or preferably within.

Water bolus

The function of the temperature-controlled circulating water bolus is to match the rigid, flat surface of an applicator to the irregular contours of the patient's tissue surface, to efficiently couple EM or US energy into the patient, and to control the skin surface temperature. The temperature of the water in the bolus provides an additional control parameter to modulate to some extent the depth of heating. Lowering the bolus temperature is recommended to maintain a lower surface temperature for protecting skin, and for higher applied power levels to improve heating at deeper locations. IR systems generally operate without a water bolus and can achieve control of skin surface temperatures through forced convection of air.

For EM radiative hyperthermia systems, the water bolus must be filled with deionised or distilled water with (minimal) temperature adjustment in a range of 30–45 °C. US systems require deionised and degassed water, with the degree of degassing required inversely proportional to frequency and critical for operation in the 0.5–1.0 MHz range. In capacitive heating systems, the use of saline water (0.1–1.5%) has been suggested [71,72] to improve impedance matching between electrodes and muscle tissue, as well as to spread RF-currents over the contact area and thereby reduce the risk of skin burns under the edges of an electrode. Since the dimensions and temperature of the water bolus significantly affect performance of an applicator, an adequate design procedure and testing is required. More detailed concerns of the bolus

design are given in part II of the guidelines [9], while the clinical recommendations are given below.

Guidelines for proper clinical use of the water bolus:

- Impact of water temperature
  The water temperature has a clinically significant impact on the effective penetration depth. For target volumes including skin, the water bolus temperature should be between 39 and 42 °C. The use of cold water, i.e. <39 °C, will decrease the most superficial temperatures and increase the effective penetration depth [73,74]. It must be noted that the temperature measurements at the skin surface will overestimate or underestimate the true skin temperature for a high or low water bolus temperature, respectively. In both cases the skin temperature measurements do not provide accurate measurement of tumour temperatures at depth [75,76]. The use of a Pennes Bioheat Transfer Equation (PBHTE) based model [77] or similar (which include blood flow effects) to estimate the actual tumour temperature is recommended to understand these temperature dynamics. The PBHTE model can be also applied for estimating the impact of water bolus dimensions and flow. Good contact between bolus and skin must be guaranteed by taking proper care of ensuring that no air gaps occur at the bolus-skin interface. For EM radiative systems a wet gauze can be used to improve heat transfer at the bolus/skin interface [73]. For EM capacitive systems, the use of saline soaked gauze is recommended to avoid hot spots at the edges of electrodes and also to minimise the effect of small hot spots induced at pockets of (saline) sweat.
- Impact of water bolus size on applicator performance.
  For EM radiative systems the effective field size has been shown to be affected by the water bolus dimensions [71,72]. In general it is recommended that the water bolus should extend at least 1 cm beyond the perimeter of the applicator aperture and ideally at least 2–5 cm outside the perimeter.
  For EM capacitive systems the effective field size is directly proportional to the size of the contact area of the water bolus [56].
- Impact of water bolus thickness
  The optimal water bolus thickness depends on type of applicator, its dimensions as well as target depth [73,78–80]. Small variations in bolus thickness (±50%) are inevitable due to irregular skin surface and this has been shown to affect heating patterns [81].
  For EM-radiative systems the impact of these variations on field homogeneity and effective field size should be assessed experimentally or by simulations to assure that users know how to respond effectively to patient complaints and to unexpected temperature heterogeneity.
  EM capacitive systems, utilising a frequency below 100 MHz, are insensitive to waterbolus thickness.
  For US, bolus thickness has negligible effect on energy propagation but possible changes to beam pattern shape within the near-field or positioning of a focal zone should be considered, depending upon the device. Phantom experiments or direct SAR or intensity measurements of the applicator with various bolus thicknesses in the clinically relevant range are recommended.
- Suppression of local hot spots
  For instance in scar tissue having reduced heat removal by blood flow, energy absorption can be reduced by using small sections of dry gauze between bolus and skin to create a local air bubble at that location. This works for US, EM-radiative and EM-capacitive systems. Further, thin patches of 1–2 mm thick closed cell-packing foam can be used to block US. While this may reduce power deposited in tissue under the air inclusion, care should be taken when separating skin from the cooling effect of the water bolus.

Thermometry: clinical monitoring

Monitoring thermal dose delivered to the tumour is crucial to control and evaluate treatment quality. Thermometry sensors should be placed on the skin and interstitially at as many sites as possible to sample representative locations across the entire target. Locations with a high risk of hot or cold spots should be monitored by temperature sensors (e.g. scars and over shallow depth bone like clavicles). With a multi-aperture array, thermometry sensors are ideally located under each individual heat source to provide proper feedback control. Extensive thermometry can be achieved by placing multiple sensors to sample temperatures across the surface, or by cyclically pulling probes through catheters and mapping temperatures across the skin surface or invasive catheter [53]. The minimum number of temperature measurement locations is five, with a reading cycle of at least once per minute. For tumours extending >1 cm deep, placement of one or more interstitial sensors is highly recommended. If placement of catheters for invasive thermometry is contraindicated or judged impossible by the responsible clinician, then the temperature at depth should be estimated using the applicator power, bolus water temperature, and skin temperature. This estimate can be obtained using treatment planning or with generic guidelines from the literature [73,74,76]. Finally, hyperthermia staff members should understand in all their actions and decisions, that it is our objective to heat the entire target volume to a sufficiently high thermal dose by the end of treatment, and not focus only on instantaneous temperatures at the specific sites where temperature is measured.

Temperature measurement during EM-radiative and EM-capacitive hyperthermia

Temperature sensors are preferably minimally perturbing and appropriate for the heating technique used. For EM heating this means sensors should have minimal interaction with the EM field as in fibre optic probes or high resistance lead thermistors, though even these have minor errors in reading temperature especially when used in air filled catheters [82]. With care, thermocouple sensors [79,82] can be used if appropriately protected from EM field interactions with shielded electronics and oriented perpendicular to the field

to minimise coupling [83–87]. If thermocouple or other metallic thermometry sensors are used, applicator power should be interrupted briefly (∼5s) before reading to further reduce field-induced errors in the temperature measurements. To minimise perturbation of the electric field due to the presence of air or plastic, the catheter diameter should be as small as possible relative to the frequency and directed perpendicular to the E-Field [75,82]. For clinical monitoring, the resolution of temperature sensor readings should be 0.1 °C with an accuracy of ±0.2 °C.

Temperature measurement during US hyperthermia

Monitoring of tissue temperature during US treatments has unique restrictions, required to minimise absorption and viscous heating artefacts [88,89], as well as thermal conduction errors along multi-sensor thermocouple probes [90]. Plastic absorbs US energy, so the catheter thickness and dimensions should be minimised to reduce artificially high-temperature readings. Where interstitial thermometry is required, tissue temperatures are best measured with either thermocouples, thermistors, or fibre optic sensors placed inside small metal needles in the 18–20 gauge range, that are small in diameter relative to the US wavelength ($\leq 0.3\ \lambda$). The wavelength in soft tissue at 1 MHz is 1.5 mm, at 3 MHz ∼0.5 mm. Small diameter Teflon, polyimide, or polyethylene encased thermocouples, or preferably bare wire thermocouples that are electrically isolated, may be used on the skin surface but these may show artefactually high temperatures due to US power absorption in the plastic. Methods have been devised to estimate and correct for these artefacts during US hyperthermia by applying periodic 5–10 s intervals of power off immediately before taking the readings. The tissue temperatures can be approximated with these readings, or by estimating using more complex curve fitting approaches [91–93]. Multi-junction thermocouple probes are often used with US systems, though small diameter low thermal conductivity constantan-manganin or chromel-alumel probes are recommended to minimise errors from thermal conduction spatial smearing of the temperature profile obtained with copper-constantan probes [88,90,94–96]. Care must be taken that good coupling between the ultrasonic field and underlying skin is maintained, with no air trapped at the skin interface.

Temperature measurement during IR hyperthermia

The absence of a water bolus during IR hyperthermia offers a unique possibility of real time thermography measurement and control of the superficial temperature distribution. An IR thermography camera mounted to the wIRA radiator and remotely controlled by a computer allows for dynamic adaptation of the skin and tumour temperatures. Furthermore, visual inspection of the temperature colour-coded images can also be used for guidance of applicator positioning. The precision and relative accuracy of the thermographic camera should be 0.1 °C and 0.4 °C or better, respectively. The resolution of readings and relative accuracy of the thermographic camera should be 0.1 °C and 0.05 °C or better, respectively. The spatial resolution should be 1–2 mm. The camera should be placed at a proper height to cover the entire treated area. Since current IR thermography cannot provide the accuracy of ± 0.2 °C, it must be applied in combination with thermometry sensors placed on the surface of the treated area. The unknown and variable emissivity of skin and tumour is prone to compromise the accuracy of IR thermometry. The temperature can be recorded by any standard technology, i.e. by thermocouples, thermistors or fibre optic sensors but the latter should be tested for possible self-heating when irradiated with IR. Where interstitial thermometry is required, tissue temperatures are best measured with non-perturbing sensors placed inside small diameter catheters.

Documentation of the hyperthermia treatment

Thorough and standardised documentation of the hyperthermia treatment is mandatory for analysing the effectiveness of the treatment protocol. In hyperthermia, documentation consists of clinical, dosimetry and technical parts. Clearly, the documentation procedures have to follow both national and international standards for using and processing patient data. Also patient-related medical data protection regulations and doctor–patient confidentiality apply. The clinical documentation will commonly be recorded in the electronic medical record of the patient. Clinical documentation involves broad based data collection including prognostic parameters obtained before, during and after treatment with an aim to facilitate assessment of clinical effectiveness of the treatment. Documentation of the recorded temperatures and technical treatment parameters has a shorter time line. In general it focuses on collection of all treatment-related system control parameters (e.g. forward and reflected power, etc.) as well as all temperature measurement values during each treatment. Changes to the treatment parameters should have accurate temporal reference. Temperatures must be documented in a manner that they can be clearly related to both treatment time and measurement location.

A detailed description of what must be documented is provided in Appendix. Further, de Bruijne [30] provides a good overview and example of appropriate treatment documentation.

Demands on personnel

Hyperthermia is a multi-disciplinary treatment involving complex interrelated clinical and technical aspects. It requires input and close cooperation of radiation oncologists, medical oncologists, medical physicists, engineers, technicians and nurses. Recommendations and responsibilities for all hyperthermia treatment staff are summarised in Bruggmoser et.al. [5] and Myerson et al. [97]. Local and country-specific regulations must be respected.

Hyperthermia training

For all below-mentioned staff members, in addition to their main qualification, practical training in the form of active

participation at an established hyperthermia centre is required. The recommendation for practical training is that at least 25 treatment sessions be performed with the heating system in 7–10 different patients, under the guidance of an experienced user.

Physicians

Hyperthermia treatments are performed under the supervision of a radiation oncologist or medical oncologist who has been adequately trained in the theory and clinical practice of hyperthermia therapy. The physician is responsible for all clinical aspects of the hyperthermia treatment (e.g. diagnosis, imaging, patient selection, treatment prescription, fractionation, documentation).

Physicists/engineers

A qualified medical physicist or engineer with sufficient training (according to 6a) is responsible for the physical and technical aspects of the hyperthermia system (e.g. quality assurance and consistency cheques, specifying the technical treatment parameters, intervention in case of technical failures, phantom measurements, physical-technical part of the treatment planning) as described in this document. A physicist/engineer must always advise the initial set up. If the hyperthermia equipment is operated by a technician, the responsible physicist must be on-call in order to take direct action (maximum acceptable response time 5 min).

Technicians

The hyperthermia treatment can be assigned to a hyperthermia-trained assistant, for example, a Radiation Therapist or Radiographer under the direct supervision of a physician and/or physicist. The technical assistant should be specifically trained in the application of hyperthermia, with minimum training defined in "Hyperthermia training" section above.

Nurses

Nurses can support a medical technician to perform hyperthermia treatments after completing a training programme. In most institutes, nurses are involved in the preparation of patients for the hyperthermia treatment and are responsible for the well-being of the patient (e.g. assist with placement of interstitial thermometry catheters, minimally invasive catheters, additional water bags, monitoring of patient vital signs during therapy, wound and pain management, etc.). When properly trained, the nurse may also replace the hyperthermia technician with regard to the application of the hyperthermia treatment.

Arranging substitutes

As in many other clinical treatments, two of the previously described responsible professionals must be present at the beginning of each treatment session in order to take care of the patient, to control the hyperthermia device, and to guarantee correct implementation and verification of all aspects of the standard operational procedure (SOP). During treatment, one person might be sufficient if the other is available on call. An adequate number of qualified and trained staff must be available to act as substitute in case of illness or vacation. When superficial hyperthermia is applied in combination with chemotherapy, a second person is responsible for the chemotherapy application as described in the SOP for chemotherapy.

Treatment planning

Hyperthermia treatment planning can be helpful in situations that deviate from typical treatment situations, in particular when dealing with metallic or breast implants or other situations that could give rise to unwanted treatment limiting local hot spots. An important aspect for treatment planning in superficial hyperthermia is accurate positioning of the applicator relative to the target tissue volume. A perfect match must exist between the modelled anatomy and applicator with the actual clinical set-up in order to obtain reliable guidance on the SAR distribution in the patient. Therefore at this time, treatment planning for superficial hyperthermia is limited to a few academic centres that study specific patient cases with, whenever possible, validation of the predicted SAR/temperature distribution with measurements made during the patient treatment. From these experiences, recommendations for treatment have been formulated in the literature for some general cases (e.g. metallic or silicone implants, shallow depth bone, etc.) that can be applied by the hyperthermia community [58,98–102].

Disclosure statement

This publication is based on literature and other sources of information judged to be reliable by the authors representing the ESHO-TC. However, the authors, ESHO-TC and editors disclaim any warranty or liability based on or relating to the contents of this publication. The authors and ESHO-TC does not endorse any products, manufacturers, or suppliers. Nothing in this publication should be interpreted as implying such endorsement. Several companies were invited to provide feedback on the document but have not participated actively either at ESHO-TC meetings or in the writing of this document. Some companies were invited to provide feedback on the document but have not participated actively either at ESHO-TC meetings or in the writing of this document. The authors and ESHO-TC alone are responsible for the content and writing of this paper.

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Appendix

Analysis and documentation of treatments mandatory for institutes participating in clinical trials and recommended in general

Temperature data are preferably reported using the temperature parameters T10, T50, and T90, the temperatures achieved in 10%, 50% and 90% of measured points, respectively. These three parameters give a fair representation of the temperature distribution during treatment when a sufficient number of temperatures are monitored with appropriate spatial sampling as described in the clinical study protocol. Thus the number of sensors (interstitial & superficial) and the area enclosed by the sensors in relation to the target area should be recorded to reflect the quality of the temperature measurements. Thermal dose accumulates as a function of temperature and time and is preferably reported with the Cumulative Equivalent Minutes at 43 °C for T10 (CEM43T10), T50 (CEM43T50) and T90 (CEM43T90) temperatures [4,5,26].

The exact evaluation procedure to be followed is prescribed by the particular study protocols, but in general good documentation encompasses the following items:

- Treatment efficacy:
  - Tumour response: local control (LC), complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) following the international definitions for these evaluation criteria.
  - Survival analysis following the international practice and definitions
- Toxicity using the latest version of the standard CTCAE scoring list:
  - Acute Toxicity (treatment related toxicity occurring during treatment/treatment period and/or 3 months after completing the treatment)
  - Late toxicity (treatment related toxicity after 4 months after completing the treatment)

Further, each clinical study protocol under the oversight of ESHO will be executed in accordance to the latest ESHO quality assurance guidelines and will include the following statements:

a. Audit of the participating institutes to validate documentation after ¼ of the proposed study period. Site visit of the institution, if required after examination of the documents
b. The site visit will be performed by a member of the ESHO-TC. Selection of this person will be in close cooperation with the principal investigator of the study, the institutes local coordinator of the study, the chair of the Medical Committee of ESHO and the chair of the ESHO-TC
c. The institution that will be visited is responsible for the support (travelling, lodging and time) of the auditor

The following points should be considered for evaluating clinically relevant hyperthermia studies:

1. Patient selection for trial participation
   Before starting the therapy, a qualified physician must define the indications for the hyperthermia treatment, regarding the inclusion and exclusion criteria. When the patient agrees to participate in the clinical study a hard copy of the informed consent signed by patient and MD must be stored. Duration of storage is prescribed in the study protocol, but should also be in accordance with local regulation. Qualified staff should be present during the whole treatment, complaints (for e.g. pain) should be recorded.
2. Documentation
   The documentation includes a clinical part, as well as a physical-technical part. The local situation of the designated treatment field should be documented with pictures.
   For patient-related medical data, protection regulations and doctor-patient confidentiality apply. Availability and readability of the treatment-relevant data must be ensured for the period as required by the clinical protocol and (inter)national law.

2.1 Physical-technical documentation

All treatment relevant system control parameters (e.g. power, reflection etc.) as well as all temperature measurement values must be stored. Changes to the treatment parameters must be documented with chronological reference. Temperatures must be documented in a manner that they can be related chronologically to the corresponding measurement location.

a. Data log of the course of treatment
Logging must be performed of: all temperatures, power or water temperature related pain, pain caused by the position of the applicator or the applicator itself, treatment interruptions or treatment stops.

b. Data log of the hyperthermia system
All hyperthermia device-related quality assurance data must be documented in the device logbook. The recordings must be according to the existing national law (e.g. the German Medizinprodukte Gesetz (MPG)

2.2. Clinical documentation

a. Clinical Setup - Clinical documentation should describe the positions of patient, applicator, and temperature probes. Photo documentation or drawing of superficial sensor locations should show a general overview and close-up of applicator and thermometry placement on patient, sufficient to reproduce treatment setup. For interstitial sensors, additional CT or US imaging is recommended.

b. Medications (including cytotoxic drugs), concurrent radiotherapy, and any other concurrent medical treatment.

c. Informed consent with a list of potential side effects of adjuvant hyperthermia is mandatory (according to national law).

d. Side effects caused by the therapy must be documented with a chronological reference to the hyperthermia treatment. Side effects that are specifically caused by hyperthermia are primarily unwanted high temperatures in the skin or non-target tissues, especially in patients with compromised temperature sensitivity, for example in polyneuropathy or near surgical scars. Moderate temperatures may be accompanied by false sensations or skin irritation, pain, and/or local oedema. In case of sustained overheating of tissue, tissue damage and necrosis may result. The temperature threshold for such irreversible damage is 44–46 °C depending on the tissue type. Specific side effects are given in Table A-1. Hyperthermia treatment (in terms of these guidelines) is not a single therapy mode, but supplements systemic chemotherapy or radiation therapy. Side effects of the combined treatment therefore correspond primarily with intensification of the spectrum of side effects of chemotherapy or radiation therapy alone. Classifying the side effects should follow the latest version of the internationally established scoring systems (CTCAE, RTOG), as applicable.

2.3. Standardisation of the analysis of physical/technical treatment data

In order to create comparable analysis for all study participants, the relevant data are extracted and, as far as possible, analysed using standard software.

Table A-1. Classification of hyperthermia specific side effects according to Common Toxicity Criteria Adverse Events (CTCAE) v4.03 and Quality Management in Hyperthermia (QMHT).

Degree	I	II	III	IV	V	
a. Treatment associated complaints						
Skin/subcutaneous pain	Mild pain	Moderate pain, limits every day activities	Severe pain, that limits necessary activity of self-sufficiency of every day life	–	–	CTCAE v4.03
Hot spot/heat build ups	Simple reverseable, therapy can be completed as planned	Power reduction necessary, continuation of therapy is possible	Early termination of therapy, limitation of therapy time and temperature is reached	Refusal/Impossibility of continuing the therapy	Death	QMHT
Bolus pressure	Simple reverseable, therapy can be completed as planned	Power reduction necessary, continuation of therapy is possible	Early termination of therapy, limitation of therapy time and temperature is reached	Refusal/Impossibility of continuing the therapy	Death	QMHT
b. Acute side effects (up to 3 month)						
Skin/subcutaneous pain	Slight pain	Moderate pain, limits every day activities	Severe pain, that limits necessary activity of self-sufficiency of every day life	–	–	CTCAE v4.03
Oedema	Swelling, identified upon close inspection	Immediately recognisable and deviation from normal anatomical contour; limitation of activities of every day life	Distinct deviation from the normal anatomical contour; the activities necessary for self-sufficiency of every day life are limited	–	–	CTCAE v4.03
Burn	Minimum symptoms, no intervention indicated	Medical intervention necessary, minimum debridement indicated	Moderate, up to significant debridement necessary or reconstruction required	Life threatening consequences	Death	CTCAE v4.03
Soft tissue necrosis		Local wound care; medical intervention indicated (e.g. dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; Urgent intervention indicated	Death	CTCAE v4.03

(*continued*)

Table A-1. Continued

Degree	I	II	III	IV	V	
c. Late side effects						
Skin pain	Slight pain	Moderate pain, limits every day activities	Severe pain that limits necessary activity of self-sufficiency of every day life	–	–	CTCAE v4.03
Oedema	Swelling, identified upon close inspection	Immediately recognisable and deviation from normal anatomical contour; limitation of activities of every day life	Distinct deviation from the normal anatomical contour; the activities necessary for self-sufficiency of every day life are limited	–	–	CTCAE v4.03
Burn consequences	Minimum symptoms, no intervention indicated	Medical intervention necessary, minimum debridement indicated	Moderate, up to significant debridement necessary or reconstruction required	Life threatening consequences	Death	CTCAE v4.03
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting join or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death	CTCAE v4.03
Soft tissue necrosis		Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; Urgent intervention indicated	Death	CTCAE v4.03