Hyperthermia in combined treatment of cancer

P Wust, B Hildebrandt, G Sreenivasa, B Rau, J Gellermann, H Riess, R Felix, and PM Schlag

Hyperthermia, the procedure of raising the temperature of tumour-loaded tissue to 40–43°C, is applied as an adjunctive therapy with various established cancer treatments such as radiotherapy and chemotherapy. The potential to control power distributions in vivo has been significantly improved lately by the development of planning systems and other modelling tools. This increased understanding has led to the design of multiantenna applicators (including their transforming networks) and implementation of systems for monitoring of E-fields (eg, electro-optical sensors) and temperature (particularly, on-line magnetic resonance tomography). Several phase III trials comparing radiotherapy alone or with hyperthermia have shown a beneficial effect of hyperthermia (with existing standard equipment) in terms of local control (eg, recurrent breast cancer and malignant melanoma) and survival (eg, head and neck lymph-node metastases, glioblastoma, cervical carcinoma). Therefore, further development of existing technology and elucidation of molecular mechanisms are justified. In recent molecular and biological investigations there have been novel applications such as gene therapy or immunotherapy (vaccination) with temperature acting as an enhancer, to trigger or to switch mechanisms on and off. However, for every particular temperature-dependent interaction exploited for clinical purposes, sophisticated control of temperature, spatially as well as temporally, in deep body regions will further improve the potential.

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Hyperthermia is a therapeutic procedure used to raise the temperature of a region of the body affected by cancer (figure 1). It is administered together with other cancer treatment modalities (multimodal oncological strategies). The temperature increase required can be achieved by various methods.

Studies on cell cultures in vitro and on experimentally induced tumours in vivo in the early 1970s provided convincing justification for the clinical application of hyperthermia. The rationale is based on a direct cell-killing effect at temperatures above 41–42 °C.[1] However, the thermal dose–response relation varies among cell lines and depends, furthermore, on microenvironmental factors such as pH.[2] After a heat shock, all cell types show increased thermoresistance for 24–48 h (thermotolerance). The required temperatures derived from the preclinical data are not achieved under clinical conditions. Therefore, other mechanisms of heat may be relevant.

A synergistic interaction between heat and radiation dose as well as various cytostatic treatments has been validated in preclinical studies.[3,4] This thermosensitisation is

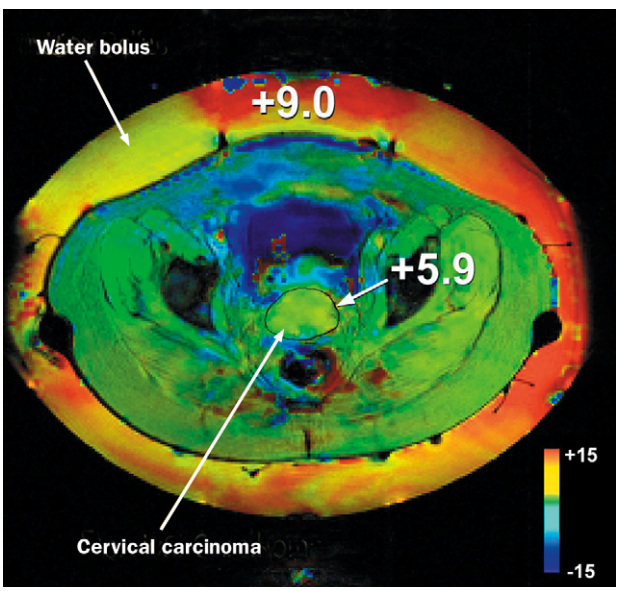

Figure 1. Non-invasive measurement of temperature distribution in the hybrid hyperthermia applicator.

effective even below 41°C. Here, as found in preclinical experiments, the time between treatments and the sequence of operation are important.[5] For the combination of radiotherapy and hyperthermia, the effect is greatest for simultaneous application, but this is not feasible in clinical practice. Several types of interaction of heat with chemotherapeutic drugs have been found,[6] such as supra-additive (alkylating agents, platinum compounds), threshold behaviour (doxorubicin), and independent or additive (fluorouracil, taxanes, vinca alkaloids). The synergistic effect in vitro can be several powers of ten even at moderate temperatures (eg, for cisplatin).

The molecular-biological mechanisms of these effects are still under investigation. Various targets in the cell affected by rises in temperature have been found, such as membranes, the cytoskeleton, synthesis of macromolecules, and DNA repair.[7,8] The expression of several genes can be upregulated or downregulated by heat, for example, the family of heat-shock proteins (HSP).[9] Expression of other genes modulated by heat is yet to be discovered (eg, the

PW, GS, JG, and RF are at the Department of Radiation Oncology and BH and HR are at the Department of Medical Oncology, Charité Medical School, Campus Virchow Klinikum, Berlin, Germany. BR and PMS are at the Department of Surgery, Charité Medical School, Campus Berlin Buch, Berlin, Germany.

Correspondence: Professor Peter Wust, Department of Radiation Oncology, Charité Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel +49 30 450 557202. Fax +49 30 450 557979. Email: peter.wust@charite.de

multiple drug resistance gene, *MDR*).[10] The HSP/peptide complex may be involved in antigen presentation together with MHC class I molecules, potentially influencing the immunogeneity of certain tumour cells.[11] Several other temperature-dependent interactions have been found, regulating molecular functions such as apoptosis, the cell cycle, and DNA repair.[12] These more specific temperature-dependent pathways in cells suggest new applications of hyperthermia such as heat-controlled gene therapy or heat-enhanced immunotherapy or vaccination.

Early clinical experience was gained with superficial easy-to-heat lesions, which were compared in the same patient (matched-pair lesions or same-patient comparison); one of the lesions was treated by a standard regimen, and a second similar lesion treated by the standard regimen plus hyperthermia. These early clinical results were very convincing, but there were difficulties with the effectiveness of heating of any unselected group of tumour diseases.[13] Some uncritical transfer of the first preclinical data to the clinical setting resulted in the 43°C dogma—the idea that a minimum temperature of 43°C had to be achieved in the target volume. This conviction has now been abandoned, because several clinical studies have clearly shown greater effectiveness with hyperthermia at lower temperatures in the clinical situation.[14]

Physiological effects may bring about this effect at lower temperatures. Our clinical data and experiments in vivo show increased perfusion in the tumour region, leading to a higher oxygen concentration (pO_2).[15,16] Higher perfusion can increase drug delivery and reoxygenation (increasing the efficacy of radiotherapy). Most human tumours have increased blood flow under hyperthermia and hours later. Only a few cases of human tumours have shown vascular breakdown.[17]

Recent studies have also shown heat-dependent immunological reactions of human leucocytes.[18] Specific effects on natural killer cells and cytokine depletion have been found.[19,20] Better understanding of this type of temperature-dependent mechanism on a cellular and physiological level will clearly open new clinical applications.

Methods to increase temperatures

To reach temperatures clearly above the systemic temperature of 37·5°C in a defined target volume is a technical challenge and still under development. The temperature increase is induced by applying a power-density specific absorption rate (SAR; measured in W/kg). Human basal metabolic rate (basal metabolism) is above 1 W/kg. Perfusion counteracts the temperature rise. Perfusion rates in human tumours are around 5–15 mL per 100 g per min, but they vary widely. To reach therapeutic temperatures of about 42°C at least in some parts of such tumours necessitates power density of about 20–40 W/kg at the target region.[21]

At present, the optimum temperature distribution for clinical purposes is unknown. Temperature distributions achieved to date have limited absolute values and homogeneity (minimum temperatures typically lie between 39·5°C and 40·5°C), mainly because of physical and physiological characteristics such as electrical tissue boundaries, local perfusion variations, and perfusion regulations. Only about 50% of deeply located tumours reach at least 42°C at one particular measurement point. Clinical studies have shown that uncritical adoption of preclinical results into clinical guidelines for tumour temperatures is not justified. Nevertheless, many phase II clinical studies have shown associations between tumour response and characteristics of temperature distribution (minimum temperature or minimum thermal dose in the tumour area).

Even though the tumour temperatures that have to be reached for clinical efficacy are still unclear, we should achieve temperature distributions as high and homogeneous as possible. Technological potential for in vivo monitoring and control of temperature distribution has not yet been intensively scrutinised, at least for the regional hyperthermia approach.

Local hyperthermia

Superficial tumours can be heated by means of antennas or applicators emitting mostly microwaves or radiowaves placed on their surfaces with a contacting medium. Several types of applicators have been used clinically, such as waveguide applicators, horn, spiral, current sheet, and compact applicators. The main components of such a hyperthermia system are shown in figure 2. The electromagnetic coupling of the applicator to the tissue is ensured by a water bolus (preceding water path). Intratumoral temperature can be controlled by the output of the power generator or by positioning the applicator. The resulting SAR distribution is subject to strong physical curtailment resulting in a therapeutic depth of only a few

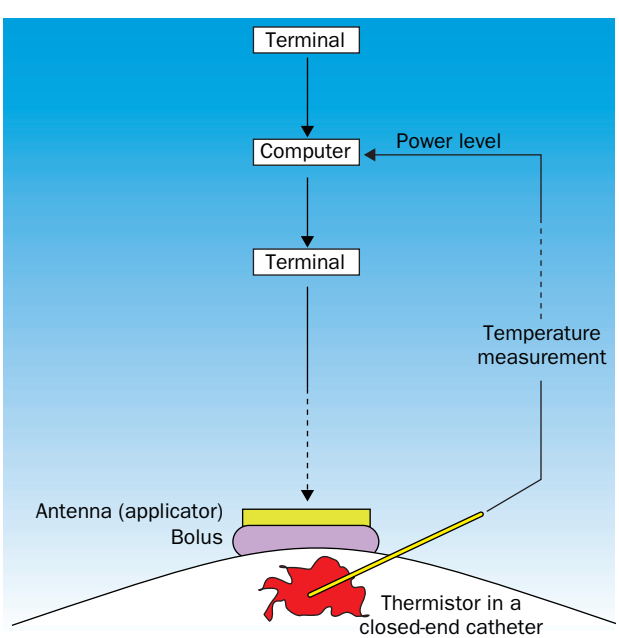

Figure 2. Scheme of a system for local hyperthermia. Applicator position and power output can be varied until a clinically satisfactory adjustment is achieved.

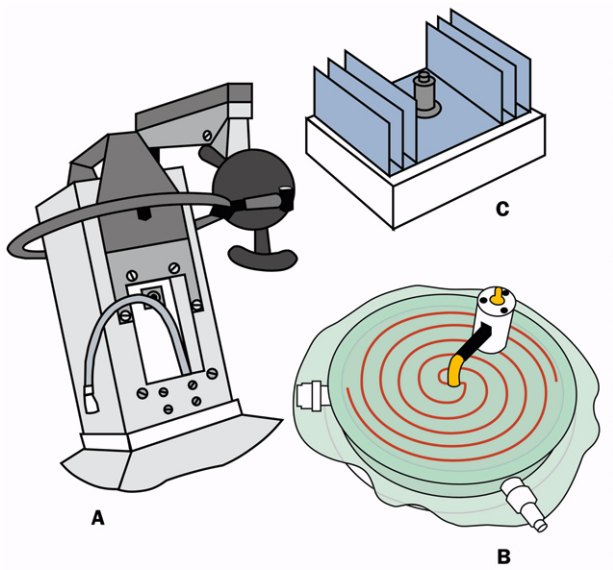

Figure 3. Applicator types for local hyperthermia, such as (a) waveguide applicator; (b) spiral applicator; and (c) current sheet applicator.

centimetres and is even further limited in regions with an irregular surface, such as the head and neck area, the supraclavicular region, or the axilla. Quality-assurance guidelines have been developed for local hyperthermia.[22]

Commercially available electromagnetic applicators (figure 3) have a typical emitting diameter of 15 cm at a frequency of 150–430 MHz with therapeutic depths not more than 3 cm. Dual or multiapplicator operation would be better, but these techniques have been developed in only a few specialised centres and are not commercially available. Ultrasound applicators offer better physical features with a wandering focus, but cause discomfort, and are thus at present of less practical importance.

Interstitial and endocavitary hyperthermia

For this procedure, antennas or applicators are implanted within the tumour, and in most cases a heat treatment is administered in combination with brachytherapy by the afterloading method in close connection to the area to be heated. This technique is suitable for tumours that are less than 5 cm in diameter, but mainly in any location feasible for implantation (eg, head and neck, prostate). Various antenna types are available, including microwave antennas, radiofrequency electrodes, ultrasound transducers, heat sources (ferromagnetic seeds, hot water tubes), and laser fibres. For physical reasons, the power-density gradient of the antenna surroundings is so high that variability in temperature is generally greater than with local hyperthermia. To ensure therapeutic temperatures at all points of the target volume requires a distance between adjacent applicators of not more than 1·0–1·5 cm. But such close positioning is very invasive. Furthermore, positioning and orientation of microwave antennas can be critical because of their sensitivity to interference. Applicators functioning according to the hot-source principle require an even smaller distance between them. The restricted axial (effective) length results in further limitations in the power-density field. Even if the number of applicators is high, the generated field cannot be adequately controlled to generate a homogeneous temperature distribution at all parts of the target area. The development of segmented RF electrodes leads to an interstitial hyperthermia system capable of three-dimensional control, ensuring improved temperature control in the target volume.[23] These systems are undergoing clinical evaluation.

Endocavitary antennas are inserted in natural openings of hollow organs such as the urethra (prostate), rectum (rectal cancer, prostate), vagina, cervix, and oesophagus. They are based on the same physical principles as interstitial antennas, with dimensions in the range of centimetres (and, therefore, larger clinical penetration depth). Counter electrodes on the body surface can be used to generate power deposition patterns.

Regional hyperthermia and part-body hyperthermia

Deep-seated tumours—eg, of the pelvis or abdomen—can be heated by arrays of antennas. The Sigma-60 applicator is a widely spread applicator (figure 4), which consists of four dipole antenna pairs arranged in a ring around the patient. Planning systems describe correctly to some extent the power-density and temperature distribution depending on various treatment variables.[24,25] Even though each antenna pair can be controlled in phase and amplitude, there are restrictions in terms of the generated SAR distribution.

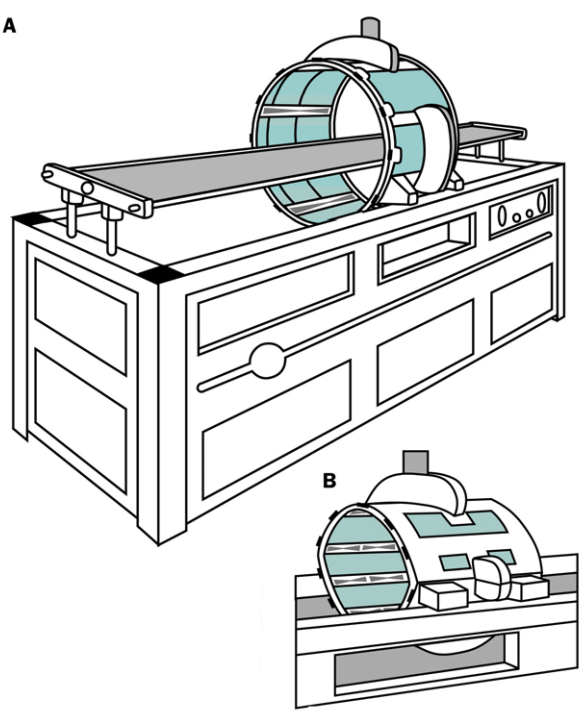

Figure 4. (a) Sigma-60 applicator (four dipole pairs) with treatment couch of the BSD-2000 system for regional hyperthermia. Dipole antennas are schematically shown. (b) A novel multiantenna applicator Sigma-Eye (12 dipole pairs) mounted on the same treatment unit as shown in (a). The elliptical form is more comfortable for the patient.

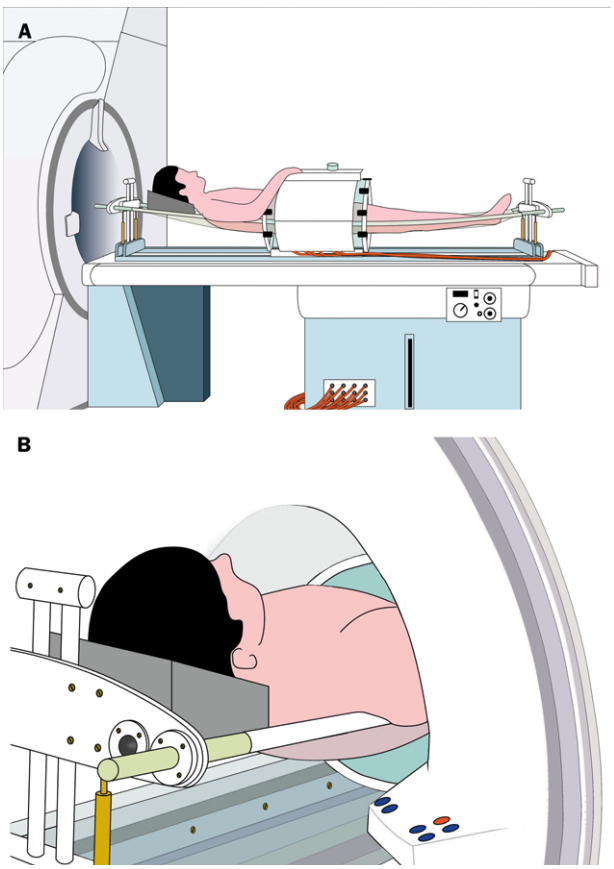

Figure 5. (a) Hybrid system (installed at the Charité Medical Center, Berlin, Germany) with positioning system for the Sigma-Eye applicator (BSD Medical, Salt Lake City, USA) located in the back (with patient) of a tunnel-like MRT (Symphony 1·5 T, Siemens, Erlangen, Germany). The elliptical applicator can be moved on guide rails into the gantry after the patient has been positioned on the sling. (b) A front view of the MRT, also used for conventional diagnostic imaging.

Model calculations show significant improvements in control of power distribution by increasing the antenna number with the assumption of optimum adjustment of phases and amplitudes.[25] The RF frequency (100–150 MHz) may be an additional variable. The three-dimensional anatomy decisively influences the power distribution. The transforming network might lead to further limitations in antenna control, since the antenna characteristics at the feed points are disturbed by coupling and imperfect symmetry.[26] Concepts to improve control are being investigated.

These theoretical studies led to hopes that use of three-dimensional multiantenna applicators with, for example, 12 channels would allow a temperature gain of more than 1°C compared with previous applicators. The Sigma-Eye applicator (figure 4) is one of the next generation of commercially available applicators, consisting of three shorter rings, each with four flat dipole-antenna pairs.

Treatment monitoring might be provided by magnetic resonance tomography (MRT) which can characterise temperature as well as perfusion. Integration of a hyperthermia system in a tunnel-like MRT is technically demanding. This problem has been solved at the Duke University Medical Center, North Carolina, USA, with a smaller applicator for the thigh region.[27] A commercially available hybrid system, a 1·5 T tunnel magnet (MR-tomograph Symphony, Siemens) is being installed at the Charité Medical Center in Berlin (figure 5). At the Grosshadern Medical Center in Munich, an open low-field MRT (0·2 T) hybrid system is already in operation in combination with a Sigma-Eye applicator.[28] Whether reasonable temperature information can be achieved with a low magnetic field is unclear, however. Problems with MR thermography have been solved with respect to phantoms.[29] But conditions in vivo cause many complexities through movement, temperature-dependent tissue changes, and perfusion, which necessitate subtle corrections.[30]

The successful implementation of a hybrid system would help to formulate clear definitions of significant and prognostically relevant thermometry characteristics (eg, minimum temperature in and around the tumour) and might lead to a better standardisation of heat treatments.

The new generation of hybrid systems has enabled a new hyperthermia technique, part-body hyperthermia. With sufficient monitoring possibilities, applicators enabling better control of the heating pattern in the longitudinal direction can cover larger anatomical regions during a heat treatment by increasing total power—eg, complete peritoneum (for peritoneal carcinosis) or upper abdomen (for liver metastases).

Whole-body hyperthermia

In carcinomas with distant metastases, a steady state of maximum temperatures of 42°C can be maintained for 1 h with acceptable adverse effects. Such a procedure can be achieved only with deep analgesia and sedation or general anaesthesia. Whether intubation is required for safe administration is still a matter of discussion. A completely different range of toxic effects arises from the systemic stress in interaction with the various anaesthesia methods applied compared with locoregional methods.[31,32]

The basal metabolic rate of a patient weighing about 70 kg is 85 W at 37°C and double that at 42°C; this in itself is enough to raise the body temperature within 180 min from 37·5°C to 42·0°C, if thermal isolation is perfect. Since the early 1980s there have been many clinical efforts to shorten the preheating time. Various methods (pyrogens, extracorporeal heating, contact heating) were abandoned because of unacceptable toxic effects and limited effectiveness. Today, only radiant systems (figures 6 and 7) are in clinical use, with typical preheating times of 60–90 min (from 37·5°C upwards).

The Aquatherm system (figure 6) is an isolated moisture-saturated chamber equipped with water-streamed tubes (50–60°C) on the inner sides, in which the patient is positioned.[33] Long-wavelength infrared waves are emitted. A substantial increase in the skin blood circulation is induced (subcutaneous venous plexus), and energy absorbed superficially is transported into the systemic circulation. Since energy release through perspiration is blocked, the heating time is quite short (60–90 min). The

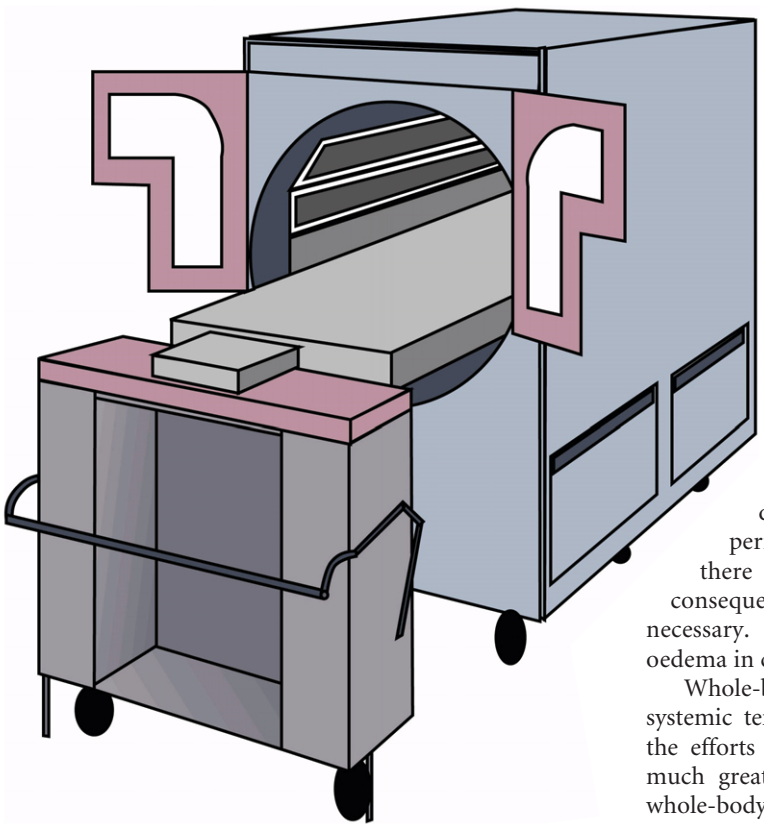

Figure 6. Schematic drawing of the Aquatherm system for whole-body hyperthermia. The patient is positioned in a moisture-saturated cabin with hot water tubes (60°C) inside. After a systemic temperature of 41·8°C has been achieved, the patient is thermally isolated with blankets.

Figure 7. Schematic drawing of the Iratherm system for whole-body hyperthermia. Water-filtered infrared radiators emit their energy from top and bottom. Thermal isolation is ensured by various transport foils. After a systemic temperature of 41·8–42·0°C has been achieved, power is reduced and a steady state is adjusted.

Iratherm-2000 system (figure 7) uses special water-filtered infrared radiators, resulting in an infrared spectrum with a maximum near to visible light. The penetration depth in this frequency range is slightly higher (about 2 mm), but every system for whole-body hyperthermia can cause superficial overheating, resulting in thermal lesions.[34] Thus, careful continuous control of skin temperatures combined with controlled power input is required to ensure that the procedure is safe.[35] With experience, systemic temperatures of up to 41·5–42·0°C can be achieved with acceptable side-effects with both systems. Systemic toxicity can include cardiac disorders, changes in the coagulation system (thrombocytopenia and disseminated intravascular coagulation), and permeability of the capillary endothelia.[32] Because there is a large fall in peripheral resistance and consequent hypovolaemia, fluid substitution is necessary. Overcompensation can lead to pulmonary oedema in connection with the capillary leak syndrome.

Whole-body hyperthermia is clinically feasible, with systemic temperatures of 41·8–42·0°C achieved. However, the efforts needed (including intensive medical care) are much greater than for locoregional methods. Therefore, whole-body hyperthermia is still in phase II evaluation.

Hyperthermic isolated limb perfusion

The isolated hyperthermic perfusion of limbs is based on bypassing a large supplying artery and a limb-draining vein—for example, the iliac artery and vein for the lower extremities. Since this surgical procedure is long established, hyperthermic perfusion with extracorporeal heat exchange is technically straightforward. Compared with whole-body hyperthermia, systemic side-effects are less, leading to early clinical application.[36,37]

Variables influencing the therapeutic ratio are, besides the temperature, the cytostatic drug concentration (higher concentrations are applied than in systemic therapy), the flow rate (30–40 mL/min), and the composition of the perfusing fluid (packed-cell volume, pO_2, pH).

Clinical trials on hyperthermia

By searches of the Medline database, we identified 18 comparative, prospective phase III trials on different hyperthermia modalities up to March 2001 (table 1). In ten of these trials, external radiotherapy alone was compared with radiotherapy plus hyperthermia[14,38–44] or interstitial radiotherapy alone was compared with interstitial radiotherapy plus interstitial hyperthermia.[45,46] Only two studies on locoregional hyperthermia included chemotherapy.[47,48] In three trials on hyperthermic perfusion, surgery alone was compared with surgery plus hyperthermic intraperitoneal perfusion[49] or hyperthermic isolated limb perfusion.[48–52] In three further trials, different schedules of local hyperthermia added to radiotherapy were compared.[53–55]

Dose–response relations

In three trials of superficial tumours (lymph-node metastases of head and neck tumours, breast cancer, cutaneous metastases or chest-wall recurrences, and melanomas), the number of applications of local hyperthermia was varied and related to local tumour control. No significant relation between the number of heat applications and outcome was observed if thermal variables

Table 1. Randomised trials on hyperthermia

Ref	Tumour site	Control	Experimental	Number of patients	Primary endpoint	Hyperthermia better (p<0·05)	Survival benefit
Local hyperthermia							
38	Head and neck (primary)	Radiotherapy	Radiotherapy and local hyperthermia	65	Response at 8 weeks	Yes	No
39	Melanoma (metastatic or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	68 (128 lesions)	Complete response (at 3 months)	Yes	No
40	Superficial (head and neck, breast, miscellaneous)	Radiotherapy	Radiotherapy and local hyperthermia	245	Initial response	possibly	No
41	Head and neck (N3 primary)	Radiotherapy	Radiotherapy and local hyperthermia (2–6 times)	44	Response (3 months)	Yes	Yes
42	Breast (advanced primary or recurrent)	Radiotherapy	Radiotherapy and local hyperthermia	307 (317 lesions)	Initial response	Yes	No
53	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	173 (240 lesions)	Best response	No	No
54	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 1x local hyperthermia	Radiotherapy and 2x local hyperthermia	41 (44 lesions)	Initial response	No	No
55	Superficial (head and neck, breast, melanoma, sarcoma)	Radiotherapy and 2x local hyperthermia	Radiotherapy and 6x local hyperthermia	70 (179 lesions)	Initial response	No	No
Interstitial and endocavitary hyperthermia							
45	Superficial (head and neck, breast, melanoma, others)	Interstitial radiotherapy	Interstitial radiotherapy and interstitial hyperthermia	184	Best response	No	No
46	Glioblastoma	Radiotherapy and interstitial radiotherapy	Radiotherapy, interstitial radiotherapy, and interstitial hyperthermia	79	2-year survival	Yes	Yes
43	Rectum (T4, locally advanced)	Radiotherapy	Radiotherapy and endocavitary hyperthermia	115	Initial response	Yes	Yes
47	Oesophagus (stages I–IV, neoadjuvant)	Radiotherapy and chemotherapy	Radiotherapy, chemotherapy, and endocavitary hyperthermia	66	Histological complete response	Yes	Yes
48	Oesophagus (stage I–IV, neoadjuvant)	Chemotherapy	Chemotherapy and endocavitary hyperthermia	40	Initial response	Yes	No
Perfusion hyperthermia							
49	Stomach (≥T3, locally advanced)	Surgery	Surgery and hyperthermic intraperitoneal perfusion	82	5-year survival	Yes	Yes
50	Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	107	Disease-free survival	Yes	Yes
52	Melanoma (stages I–III)	Surgery	Surgery and hyperthermic isolated limb perfusion	832	Disease-free survival	No	No
Regional hyperthermia							
44	Cervix uteri (primary, stage III)	Radiotherapy	Radiotherapy and regional hyperthermia	40	Initial complete response	Yes	No
14	Primary or recurrent pelvic (cervix, rectum, bladder)	Radiotherapy	Radiotherapy and regional hyperthermia	361	Complete response rate, survival	Yes	Yes
Ongoing	Rectum (uT3/4)	Radiotherapy and chemotherapy	Radiotherapy, chemotherapy, and regional hyperthermia	>150	Disease-free survival		
Ongoing	Soft-tissue sarcoma (high risk)	Chemotherapy	Chemotherapy and regional hyperthermia	>150	Disease-free survival		

were disregarded.[53–55] However, there was a clear-cut relation between the number of applications that were adequate in terms of derived thermal dose variables and response. This dose–response relation has been verified for both hyperthermic radiotherapy and hyperthermic chemotherapy, with a temperature range achieved of 39·5–41·0°C for T_{min} (or T_{90}). This finding has been confirmed by several investigations of thermal data in comparative and non-comparative trials and was even established also for endocavitary minimally invasive temperature measurements in tumour contact.[15,56–58] A clear dependency of disease-free survival on response was found in several studies.[59,60] Therefore, a positive influence of higher thermal doses on survival is expected and has been validated in our data for primary rectal cancer.[61] These dose-response relations for local and regional hyperthermia indicate the clinical efficacy of these hyperthermia approaches, in addition to the stronger verification by phase III studies.

Local and interstitial hyperthermia of superficial and intracerebral tumours

Six comparative trials on hyperthermia have been done in patients with recurrent or previously irradiated superficial tumours or metastases,[38–42,45] and one was done in patients with glioblastomas.[46]

In five of these seven trials, there was an observed benefit in the hyperthermia group in terms of local effectiveness or control; only one study on local hyperthermia and one on interstitial hyperthermia were negative. In these two trials, both carried out by the Radiation Therapy Oncology Group, lack of efficacy was ascribed to poor heating quality. In one of these trials,[40] higher response rates were found in a subgroup of tumours that are easier to heat (3 cm or less in diameter). The positive result of another interstitial trial is probably due to a rigorous quality control (stereotactically guided catheter implantation) in a homogeneous group of patients.[46] The promising results in patients with glioblastomas clearly justify further studies with interstitial hyperthermia. Nevertheless, better interstitial techniques are needed.

Thus, improvements in at least response or local control, and in some trials even in survival, can be taken in our opinion as proof of principle for local hyperthermia in conjunction with radiotherapy. Despite criticism about the design of some of these trials (low numbers of patients, statistical design, inadequate control groups), at least three well-designed studies were clearly positive for local tumour control, and two for overall survival.[39,42,46] On the basis of these data, local microwave hyperthermia in conjunction with definitive radiotherapy can be recommended as an effective palliative treatment option to be offered in non-clinical trials to patients with symptomatic recurrence of previously irradiated superficial tumours or primary locally advanced tumours not suitable for surgical resection. Additional chemotherapy might be beneficial for some indications.

Endocavitary hyperthermia in patients with rectal or oesophageal cancer

Three comparative trials have been done on intracavitary hyperthermia in patients with oesophageal cancer[47,48] or locally advanced, poorly resectable rectal cancer.[43] Endocavitary hyperthermia was an adjunct to radiotherapy in two studies and to experimental chemotherapy in the other.

A distinct improvement of local control was found with hyperthermia for rectal cancer.[43] Various criticisms (definition of resectability, small number of patients, differences in patients' characteristics between the study groups) have been made. No other group has confirmed such an impressive improvement of resectability by a preoperative treatment. In the two Japanese trials on endocavitary hyperthermia in patients with oesophageal cancer, the evidence is limited despite the positive results by shortcomings in the study design (small number of patients, with no statistical analysis, no appropriate randomisation, questionable selection of patients, and an experimental control group).[47,48]

Hyperthermic perfusion techniques

Much experience with hyperthermic chemoperfusion has been gained since 1970. In contrast to external heating methods, hyperthermic perfusion techniques carry the risk of severe and persisting adverse effects (eg, neuropathy, amputation of limbs). However, both hyperthermic isolated limb perfusion and hyperthermic intraperitoneal perfusion at different temperatures achieve high response rates in comparison with historical control groups receiving systemic chemotherapy. This success is due to both the homogeneous and well controlled heat application and the much higher (more than ten-fold) drug concentration possible.

Hyperthermic isolated limb perfusion has been mostly used as a melphalan-based induction therapy in advanced stages of non-resectable melanomas and soft-tissue sarcomas (limited to one limb). Recent trials showed further improvement in response rates with addition of high doses of tumour necrosis factor, whereas application of additional drugs (especially cisplatin) was not beneficial. Because of these high response rates in phase II studies, no prospective randomised trials on induction therapy with hyperthermic isolated limb perfusion have yet been done. We found three prospective studies with adjuvant hyperthermic isolated limb perfusion after surgery for melanomas of the limb.[50–52] Ghussen and colleagues[50] reported that compared with surgery alone the hyperthermic melphalan treatment improved both local control and survival in patients with limb melanomas of stage I–III after wide excision and regional lymph-node dissection. The design of their study was not appropriate to detect advantages in local control and survival according to stage. Koops and colleagues[52] found no benefit with regard to occurrence of distant metastases and overall survival with hyperthermic infusion of melphalan, but rates of local recurrence and regional lymph-node metastases were significantly lower.

There has been one randomised study of hyperthermic intraperitoneal perfusion (of mitomycin) in patients with gastric cancer; it found a marginally significant improvement in local recurrence with the hyperthermic procedure compared with surgery alone.[49]

None of the hyperthermic perfusion techniques can be unequivocally recommended as a standard treatment as yet, especially because these methods have not been compared systematically with normothermic perfusion. Both methods are expensive and invasive procedures and may be associated with major adverse effects. Therefore, application should be strictly restricted to experienced treatment centres, where patients are treated in clinical trials.

Regional hyperthermia

Regional heating integrated in a multimodal approach is indicated for patients with locally advanced deep-seated tumours. The application of regional hyperthermia is, however, more complex than local heating, particularly because of wide variation in physical and physiological properties. It requires more sophisticated planning, thermometry, and quality assurance. However, with the latest technology (figure 3), safe and efficient regional hyperthermia was validated in phase III studies with only minimally invasive thermometry catheters and no major side-effects.[58] In various phase II studies, high response rates have been achieved with combinations of regional hyperthermia and radiotherapy (pelvic tumours), chemotherapy (soft-tissue sarcomas, germ-cell tumours), and radiochemotherapy (cervical and rectal carcinomas).[62] Tumours of the upper abdomen are difficult to heat, mainly because of the lack of reliable measurement methods. Regional hyperthermia of other anatomical regions such as the thorax or neck presents practical difficulties and is not feasible.

Most clinical trials on regional hyperthermia have used the approach as an adjunct to radiotherapy. A multicentre European Organisation on Research and Treatment of Cancer (EORTC) trial for the assessment of regional hyperthermia in high-risk soft-tissue sarcomas has lately been initiated.[60] Chemotherapy (doxorubicin, ifosfamide, etoposide) with or without regional hyperthermia precedes surgery, and then adjuvant radiotherapy and chemotherapy (with or without regional hyperthermia) are administered. Another approach with preoperative radiotherapy plus regional hyperthermia has been investigated at the Duke Medical Center.[63] Both regimens gave encouraging clinical results. In other phase II studies, regional hyperthermia was combined with cisplatin for recurrent (preirradiated) cervical cancer, or with oxaliplatin and fluorouracil for recurrent (preirradiated) rectal cancer.[64]

Positive results have been achieved with regional hyperthermia in conjunction with radiotherapy in patients with pelvic tumours. A Dutch phase III trial showed improvement of local efficacy in a mixed cohort of patients with locally advanced cervical, bladder, or rectal carcinoma, and a major survival benefit in patients with cancer of the uterine cervix (51% *vs* 27% in a group with more than 80% of tumours of FIGO stage III or IV, which explains the poor results in the control group).[14] For patients with rectal cancer (mostly recurrences), no significant improvement was seen. As discussed elsewhere, the value of hyperthermia in these patients may have been underestimated for various reasons.[65] Based on a phase II trial,[59] another phase III trial is underway at the Charité Medical Center on patients with primary, non-metastatic, locally advanced rectal cancer (table 1). An interim analysis of this trial, with 123 patients undergoing preoperative radiochemotherapy with or without regional hyperthermia, showed a trend towards higher local efficacy in the hyperthermia group, also associated with a clear thermal dose–response relation.[15]

The favourable results of a Dutch trial have recently been confirmed by a smaller, but statistically well-designed, Japanese study of patients with cervical cancer of FIGO stage IIIb.[44] A significantly improved response was found in the hyperthermia group. Recent trials have proved that cisplatin added to radiotherapy achieves better results than radiotherapy alone,[66] so the control groups in these two trials received insufficient treatment. However, the benefit of additional chemotherapy is most relevant in patients with tumours of lower stages, whereas the benefit in locally advanced and large pelvic tumours is limited. Therefore, hyperthermic radiochemotherapy might further improve the prognosis of patients with locally advanced cervical cancer. Evaluation in a comparative trial is planned. Nevertheless, for patients with cancer of the uterine cervix who have contraindications to cisplatin-based chemotherapy, regional hyperthermia as an adjunct to radiotherapy can be recommended as an effective standard treatment.

Another important phase III trial is underway dealing with locally advanced soft-tissue sarcomas (EORTC 62961/European Society for Hyperthermic Oncology RHT-95). A neoadjuvant chemotherapy (EIA protocol) with or without regional hyperthermia is administered. This concept is based on encouraging phase II studies.[60,67]

Other hyperthermia approaches of clinical interest are under investigation for prostate cancer,[68] preirradiated rectal cancer (Hildebrandt et al, unpublished data), and particularly, use of part-body hyperthermia for peritoneal carcinosis (for ovarian cancer) in conjunction with chemotherapy (liposomal doxorubicin).

Whole-body hyperthermia

Whole-body hyperthermia in conjunction with systemic chemotherapy is the only option available for patients with advanced and metastatic malignant tumours. No randomised phase III studies have so far been completed for moderate (less than 41·0°C) or extreme whole-body hyperthermia (41·5–42·0°C), but at least four studies have started since 2000 for the extreme procedure. Reports of moderate whole-body hyperthermia induced for up to 6 h have shown that the approach is feasible. Nevertheless, its role is controversial. Therefore, we confine this discussion to extreme whole-body hyperthermia.

Promising results for whole-body hyperthermia in combination with chemotherapy have been obtained in

several phase II studies of patients with recurrent soft-tissue sarcomas, ovarian cancer, or primary pleural mesothelioma. Results are difficult to interpret because dose-intensified regimens were used, mainly with carboplatin and ifosfamide.

There is also some information about less dose-intensified chemotherapy in patients with metastatic colorectal carcinoma. A preliminary report of a phase I/II trial showed that with mitomycin and fluorouracil, 10–20% of patients could profit from additional whole-body hyperthermia through improved remission rates. Another group obtained excellent results in a phase II trial with oxaliplatin, fluorouracil, and folinic acid in pretreated patients. Phase III studies based on these results are urgently needed.

Conclusions

Recent clinical results give new insight into the mechanisms of hyperthermia in multimodal oncological treatments. Hyperthermia is thought to affect tumour sensitivity to other treatments mainly through microenvironmental factors such as pH. One hypothesis is that hypoxic and therefore resistant tumour regions are preferentially eliminated under hyperthermic conditions because associated hypovascularisation results in higher temperatures and higher sensitivity due to hypoxia. This assumption has been questioned, since chronic hypoxia also leads to an adaptation (development of tolerance), and the real temperature distribution on a cellular tissue level (hypoxic *vs* well vascularised areas) is uncertain.

By contrast, functional radiological examinations have shown that some tumours undergo a long-lasting rise in average perfusion, inducing not only an increase in the entry of cytostatic drugs, but also probably an improvement in acute oxygenation and long-term reoxygenation. This process as postulated from preclinical work occurs even at temperatures of 40–41°C and could explain the positive results of phase III studies in which lower temperatures were achieved. Such a positive effect through hyperthermia could exist below 43°C particularly in cervical carcinomas,[14] since in other clinical studies of this tumour the pO_2 was a significant prognostic indicator.[69] Recent attempts to increase the tumour pO_2 with erythropoietin supplementation in conjunction with radiotherapy are based on such results.

With whole-body hyperthermia, tumour temperatures of about 42°C can be reached for 60 min with great certainty. Thus, the method in this respect is reproducible and can be applied to some extent already without complications. Nevertheless, the method is still associated with systemic and local side-effects. The extent of the therapeutic benefit is also uncertain, since all normal cells are subjected to high temperatures like the tumour. Nevertheless, several mechanisms and hypotheses suggest synergism between the applied cytostatic drugs and hyperthermia in tumour cells. These include stronger inflow of the cytostatic drug resulting from a relative increase in perfusion at higher temperatures and vascular collapse. Another assumption is that the metabolic rate is lower in the bone marrow leading to relative protection of the haemopoietic system.[70] All these remain, nevertheless, hypotheses. Again, evidence from phase III studies is now more than overdue for this method, which is already being practised.

Locoregional hyperthermia methods may provide greater therapeutic gain than whole-body hyperthermia. Phase III studies have shown that these methods do not increase the toxicity of other associated therapies, and the hyperthermia-specific side-effects are acceptable. Furthermore, in several indications a significant increase in local effectiveness was observed by use of hyperthermia in conjunction with various schedules of radiotherapy. Three types of tumour (locally advanced cervical carcinoma, advanced neck disease of head and neck tumours, and glioblastoma) even showed a survival benefit. However, in the meantime these indications have therapeutic alternatives.

Other tumours, such as recurrent breast tumours, recurrent melanoma, and carcinoma of the bladder showed an increase in local effectiveness but no positive effect on recurrence-free or overall survival.[14] Nevertheless, these studies confirm the proof of principle for these locoregional methods. Multicentre randomised studies unfortunately showed a beneficial effect only for small lesions owing to unsatisfactory quality assurance.

Improvements are still necessary for locoregional methods. Many documented correlations of the quality of hyperthermia (thermal variables) and effectiveness (response rate) show the potential of these methods to improve clinical results by further technological improvements. Novel oncological therapies such as gene therapy, immunotherapy, or temperature-dependent liposomes could be triggered by a temperature increase or could be improved with hyperthermia.

A precondition for better reproducibility and therapy safety is non-invasive thermometry, which could permit use of the approach in such regions as the upper abdomen and lower thorax. It could lead to better selection of patients and to better definition of thermal goals and a dose-effect relation. How far the volume of a target region can be extended is still a matter of clinical research.

Improved understanding of the array applicators is also achievable, not only in the design of the single radiating element (antenna) in the near-field range (matching, symmetrisation, efficiency), but also in combining these antennas in an array. The coupling between the antennas is the most essential and critical feature, which has to be as low as possible in a well controllable array. Transforming networks are needed to link the amplifier system and antennas. A kind of feed-back control must be established between the amplifier system (ie, the single generators) and a patient-adapted power distribution.

Our present knowledge emphasises the development of feed-point control and adjustment (phases and amplitudes at the antenna feed points). Significant progress has been obtained lately in hyperthermia planning, whereby the E-field distribution in a three-dimensional patient could be calculated, and also transforming networks could be modelled.

Search strategy and selection criteria

All the completed randomised studies in this review were identified by searches of Medline. Additional continuing randomised trial are known from recent international conferences of the hyperthermia organisations (in particular the European Society of Hyperthermic Oncology). The phase II studies referenced are a collection personally weighted and known from the German Hyperthermia Organisation, where all German trials are listed, and further from international conferences of the European Society of Hyperthermic Oncology. All completed randomised studies have been published in peer-reviewed international journals in English.

Only when the physical optimum of locoregional hyperthermia is achieved will its clinical potential be apparent. New insights into molecular mechanisms will enable innovative future approaches such as heat-controlled gene therapy or heat-enhanced tumour vaccination. In every case, the best performance possible of heat treatments is desirable. Available hyperthermia technology has already shown some benefit to patients in clinical studies.

Conflict of interest

None declared.

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