EUROPEAN JOURNAL OF CANCER 44 (2008) 2546–2554

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Current Perspective

Hyperthermia adds to chemotherapy ☆

Rolf D. Issels[*]

University of Munich – Campus Grosshadern, Medical Clinic III, 81377 Munich, Germany
HelmholtzZentrum München, Institute for Molecular Immunology, 81377 Munich, Germany

ARTICLE INFO

Article history:
Received 29 May 2008
Received in revised form 17 July 2008
Accepted 24 July 2008
Available online 11 September 2008

Keywords:
Hyperthermia
Chemotherapy
HSP
Immunology
Liposomes
HIPEC
ILP

ABSTRACT

The hallmarks of hyperthermia and its pleotropic effects are in favour of its combined use with chemotherapy. Preclinical research reveals that for heat killing and synergistic effects the thermal dose is most critical. Thermal enhancement of drug cytotoxicity is accompanied by cellular death and necrosis without increasing its oncogenic potential. The induction of genetically defined stress responses can deliver danger signals to activate the host's immune system. The positive results of randomised trials have definitely established hyperthermia in combination with chemotherapy as a novel clinical modality for the treatment of cancer. Hyperthermia targets the action of chemotherapy within the heated tumour region without affecting systemic toxicity. In specific clinical settings regional hyperthermia (RHT) or hyperthermic perfusion has proved its value and deserve a greater focus and investigation in other malignancies. In Europe, more specialised centres should be created and maintained as network of excellence for hyperthermia in the field of oncology.

© 2008 Elsevier Ltd. All rights reserved.

1. Hyperthermia or heat shock exposure: Arrhenius relationships from the molecule and cell to the clinic

Hyperthermia can be defined as controlled temperature elevation by targeting the heating field to the malignant tumour as well as the surrounding tissue, organ, part of body or even to the whole body. Following the results of profound research starting in the early 1970s for exponentially growing cells when exposed to heat shock above a threshold temperature – in general – a strict temperature–time relationship was noted. This is specific for the individual cell line, and different in the various phases of the cell cycle using clonogenic cell death as an end-point.[1] The thermal energy dose for induction of cell death was found to be closely related to the amount of energy required for cellular protein denaturation. This led to the conclusion that the direct cytotoxic effect of hyperthermia itself is mainly based on denaturation of nucleolic, cytoplasmatic or membrane proteins. Based upon complete sets of survival data testing different cell lines, Arrhenius blot relationships were performed to allow the numerical description and calculation of the thermal dose achieved during a certain exposure time at a given temperature.[2]

Calculation of the thermal dose applied in hyperthermia has been successfully integrated into the concept of a 'thermal isoeffect dose' (TID).[3] By the TID concept, heating time periods at different temperatures are converted into equiva-

☆ *Source of support*: Helmholtz Gemeinschaft Deutscher Forschungszentren – VH-VI-140 Clinical Hyperthermia and Related Technology SFB455 – Virale Funktionen und Immunmodulation Deutsche Krebshilfe e.V.

* Tel.: +49 89 70954768; fax: +49 89 70954776.
E-mail address: rolf.issels@med.uni-muenchen.de.

0959-8049/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2008.07.038

lent heating minutes at 43 °C. For consecutively applied heat treatments, the TID for each single treatment can be added to give the cumulative equivalent minutes at 43 °C (CEM_{43}). When treated with heat shock, mammalian cells develop a transient resistance to subsequent heat exposure. This phenomenon has been called 'thermotolerance' and is at least partially due to the induction of heat shock proteins (HSPs) and other post-transitional adaptation processes (e.g. cell cycle arrest in the G2-phase). The TID calculation is complex and is influenced by a number of environmental factors as well as by the transient development of thermotolerance. However, it at least allows to predict the outcome *in vitro* for a given heat dose.

There is no intrinsic difference between heat sensitivity of normal and tumour cells *in vitro*. There is, however, a tumour-selective effect of hyperthermia at temperatures between 40 °C and 43 °C *in vivo*. The architecture of the vasculature in solid tumours is chaotic, resulting in regions with hypoxia and low pH levels, which is not found in normal tissues under undisturbed conditions. These factors turn cells more sensitive to hyperthermia especially in low perfused areas. Therefore, in addition to direct cytotoxicity, hyperthermia leads *in vivo* to an almost selective destruction of tumour cells in hypoxic and, consequently, acidic environment within parts of solid tumours.[4,5] Despite complexity and limitations of thermal dose dosimetry, the notion is that thermal dose, quantified by the TID concept as CEM 43 °C, is related to outcome in randomised studies, both in canine[6] and in human[7] tumours.

2. Enhancement of drug cytotoxicity by hyperthermia: its reality at clinically relevant temperatures

Heat modifies the cytotoxicity of many chemotherapeutic agents (see Table 1).[8–13] The extent of 'thermal chemosensitisation' both *in vitro* and *in vivo* can be quantified by the quotient of the clonogenic cell growth or tumour cell growth or tumours treated either with the drug alone or with the same drug at elevated temperature. The thermal enhancement ratios (TER) for certain antineoplastic agents at two different temperatures (41.5 °C *versus* 43.5 °C, respectively) are given in Table 2. The TER mainly represents the pharmacodynamic features of the drug-heat-interaction. More recent *in vivo* studies have demonstrated that the thermal enhancement of cytotoxicity of many chemotherapeutic agents is maximised at temperatures between 40.5 °C and 43.0 °C.[14] The mechanisms of interaction *in vitro* are tested on the basis of an isobologram analysis.[15,16] Synergism is observed as a continuous change with increasing temperatures of the rate at which cells are killed by the drug. It is generally accepted that most alkylating agents (e.g. cyclophosphamide and ifosfamide) and platinum compounds as well as the nitrosoureas

Table 2 – Thermal enhancement ratio (TER) of selected chemotherapeutic agents

Drug	Treatment time (min)	TER	
		41.5 °C	43.5 °C
Cisplatin	30	1.48	1.59
Cyclophosphamide	30	2.28	2.74
Ifosfamide	30	1.52	–
Ifosfamide	90	3.60	–
Melphalan	30	3.60	–
BCNU	30	2.27	2.71
Bleomycin	30	1.24	1.65
Mityomycin C	30	1.05	–
5-Fluorouracil	30	1.0	1.0
Doxorubicin	30	1.0	1.0

Data taken from Urano et al.[103]

Table 1 – Overview of the interactions between some chemotherapeutic agents and heat

Class of agent		Interaction	Remarks
Platinum drug	Cisplatin	More than additive	Gradual increase with increasing temperature; highest when simultaneous
	Carboplatin		
Alkylating agents	Cyclophosphamide	More than additive	Gradual increase with increasing temperature; highest when simultaneous
	Ifosfamide		
	Melphalan		
	Mitomycin		
Nitrosources	Carmustine (BCNU)	More than additive	Highest when simultaneous
	Lomustine (CCNU)		
Antibiotics	Bleomycin	More than additive	Only >42 °C; largest when simultaneous
	Doxorubicin	Complex	Less than additive when heat precedes drug
	Actinomycin D		
Pyrimidine antagonists	5-Fluorouracil (5-FU)	Independent	No interaction
	Cytarabine (Ara C)		
Vinca alkaloids	Vincristin	Independent	
	Vinblastin		
Taxanes	Paclitaxel	Complex	Cell type dependent; temperature 41.5–43.0 °C
Nucleosidanalog	Gemcitabine	Additive	Only if applied 24 h before or after heat

Derived and adapted from Kampinga.[102]

(BCNU and CCNU) are linearly enhanced in their cytotoxic effect if temperatures are raised from 37 °C to over 40 °C. In contrast, for example, doxorubicin or bleomycin, there are threshold temperatures for the interaction with heat at or near 42.5 °C, whereas most antimetabolites (e.g. 5-fluorodeoxyuridin and methotrexate) as well as vinca-alcaloids or taxanes show independent action. However, lack of interaction would not rule out an improved therapeutic result *in vivo* because spatial cooperation and/or toxicity independency could exist. Mechanisms for the thermal enhancement include increased rate constants of alkylation, increased drug uptake and inhibition of repair of drug-induced lethal or sublethal damage. Studies on drug-heat sequence show, in general, that drugs administered immediately before hyperthermia is most effective. However, there are exceptions like the antimetabolite gemcitabine, where a time interval of 24 h between drug application and heat is necessary to achieve a synergistic effect *in vitro* and *in vivo*.[17,18] Clinical trial design of heat and drug combinations should also take into account the complex changes in drug pharmacokinetics under hyperthermic conditions.

3. Cell lethality and oncogenic potential: what do we pay for the enhancement?

Heat could theoretically enhance both the cytotoxic and oncogenic potential of the drugs. Examination of transformation incidences expressed as a function of surviving fraction showed that for a given level of cell killing the combination of heat and, e.g. cisplatinum resulted in fewer transformants per surviving cell than for cisplatinum alone.[19] Chemotherapy behaves in a manner similar to X-rays combined with heat, i.e. heat appears to convert sublethal damage to lethal damage, thus reducing the expression of transformation.[20] Several studies have shown S-phase specific cell lethality and/or oncogenic transformation of cells exposed to a variety of chemotherapeutic agents.[21,22] Since a substantial proportion of transformation occurs when cells are in S-phase, it is not surprising that hyperthermia (which preferentially kills cells in S-phase) could reduce the incidence of transformation. These observations are consistent with the dogma that moderate heat treatment itself does not induce directly chromosomal DNA strand breaks but can alter chromatin structure influencing DNA repair.[23–25] A broader conclusion with practical implications may be inferred from these data. The treatment strategy combining chemotherapy with hyperthermia may not only be advantageous to the treatment of primary cancers, but also may result in a lower risk of treatment-induced secondary cancers. Addressing the concern for oncogenic potential of common anticancer treatment technologies, hyperthermia seems to be one of the few modalities not increasing oncogenic transformation.

4. Hyperthermia as targeted therapy: perspective for delivery of anticancer agents

For those drugs which show temperature-dependent enhancement, the rationale for their combined application is that hyperthermia 'targets' the action of the chemotherapeutic agent within the tumour region with elevated temperatures without affecting systemic toxicity. There are new biological aspects that have to be transferred into clinical research.[26] Hyperthermia can be used to enhance the delivery of drugs to the volume targeted by heat. However, microvascular damage that is caused by hyperthermia might counteract any advantage that could be gained from the initial improvement in blood flow. In general, impaired blood supply and increased interstitial pressure interfere with the delivery of therapeutics to solid tumours.[27] The recent findings that clinical temperatures are rarely high enough (>43 °C) to cause vascular damage, along with the recognition that regional hyperthermia at 40–43 °C causes increasing tumour blood supply,[28,29] led to resumption of interest in this approach. Blood flow and vascular permeability are both the critical factors for drug uptake[27] that are increased by hyperthermia. Hyperthermia has been shown in general to enhance the uptake of mAbs into tumour tissue but – unfortunately – data on the uptake of currently approved antibodies in cancer therapy targeting EGFR (cetuximab, panitumumab) and HER2 epitopes (trastuzumab) or blocking VEGF (bevacizumab) are not available so far.

The most exciting and potentially useful delivery systems are based on recent developments in the field of liposomes, proteins or polymers. These microcarriers are used to transport a variety of agents to tumours, including traditional anticancer agents but also siRNAs to switch off genes or gene products by RNA interference. The first paper on the concept of using temperature-sensitive liposomes to achieve enhanced delivery of anticancer agents to malignant tumours by heat was published as early as 1978.[30] After decades of intensive research activities, several types of thermosensitive liposomes have been constructed so far[31,32] and doxorubicin containing thermosensitive liposomes (e.g. Thermodox®) have entered clinical trials.[33] Thermosensitive liposomes are designed to release their payload at elevated temperatures by choosing lipid compositions with appropriate phase transition temperatures. In the case of thermosensitive proteins or polymers, the molecules are in hydrophilic state at 37 °C, whereas above the phase transition temperature (usually >40 °C) they become hydrophobic and aggregate within the hyperthermia exposed tissue.[34] Thereby the localised expression of therapeutically relevant genes or localised uptake of nanoparticle in heated tumour tissue to increase efficacy in the tumour itself and to minimise side-effects in healthy tissue is another important field for 'new drug' delivery by hyperthermia.[35]

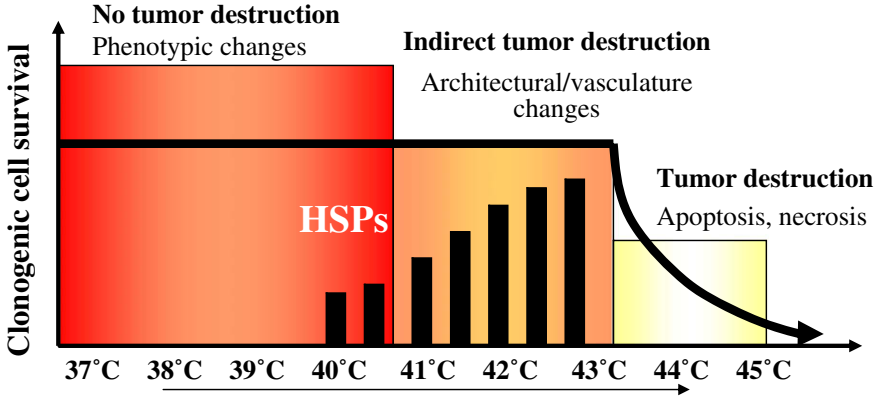
5. Hyperthermia combined chemotherapy-induced necrosis: the role of released HSP and the immune response

The antineoplastic properties of chemotherapeutic agents are mainly based upon their ability to induce either a necrotic or apoptotic programmed cell death. Whereas necrosis is marked by a passive pathological cell damage followed by an inflammatory response, apoptosis represents a genetically controlled, active death programme.[36,37] Heat treatment induces both, apoptosis and necrosis, and the form of death changes from apoptosis to necrosis above a certain threshold temperature.[38,39] The pleotropic effects of the temperature-

dependent cellular and molecular events are illustrated in Fig. 1. Enhanced drug cytotoxicity by simultaneous heating *in vivo* has been shown to increase the fraction of necrotic areas within the tumour tissue as a surrogate marker of tumour response to the combined treatment.[40,41] At high temperatures, proteins become structurally unstable and may even unfold leading to loss of function of the affected proteins and to intracellular accumulation of aggregates.[42] The cells respond by producing increasing amounts of molecular chaperones (HSPs), a phenomenon referred to as 'heat shock' or 'heat response'.[43,44] An immediate adaptive mechanism is provided by activation of heat shock factors (HSFs) which activate the promoter regions of various heat shock genes.[45,46] Some HSPs, in particular HSP70, are heat-inducible and can be released by necrosis, where – once extracellular – they gain potent immunostimulatory functions.[47–49] After a non-lethal heat shock, HSP70 was found to be expressed on the surface of malignant cells that became more susceptible to lysis by NK cells.[50,51] Recently HSP70 activated NK cells have been shown to control HSP70-positive primary or metastatic cancer *in vivo*[52] or to generate immune responses in patients.[53] HSP peptide complexes released from dying tumour cells or extracted of tumour cells are also able to generate an adaptive T-cell response by targeting tumour-derived antigenic peptides to the professional antigen presenting cells (e.g. dendritic cells).[54,55] As proof of principle, in situ autovaccination has been achieved by localised hyperthermia combined with intratumoural injection of dendritic cells to induce systemic antitumour immunity.[56] Therefore there is a strong rationale that hyperthermia combined chemotherapy might also have a positive impact on the hosts' immune system by the potential to induce innate and adaptive immunity (see Fig. 2).[57]

6. Combination trials: clinical application and results

The current interest in hyperthermia came into the limelight again in the beginning of 2000, where the medical community started re-addressing both the biological and clinical usefulness of this modality.[58–61] For many years, it has been an unproven dogma in hyperthermia research that antineoplastic heat action requires temperatures >43 °C in the clinic. The thermal isoeffect dose (TID) concept based upon pre-clinical *in vitro* results was – in simple analogy – transferred into the clinic in order to estimate the required temperature dose parameters for clinical efficacy. Even for combined treatment, the dose relevant effect was considered to be heat cytotoxicity only. Addressing thermotolerance in the clinical setting, the magnitude and duration of thermotolerance are reduced greatly as the amount of heat delivered during the initial heating is decreased. Therefore, for heat killing and heat chemosensitisation, thermotolerance is most likely not clinically relevant. In conclusion the clinically relevant temperature range between 40.5 °C and 43 °C, the 'old' concept,



Molecular response	Cell cycle; DNA repair Apoptosis/Necrosis Induction of heat shock proteins/HSP-70 membrane expression
Clinical setting	Thermosensitisation for chemotherapy and/or radiation

Fig. 1 – During deep regional hyperthermia intratumoural temperatures between 40 °C and 44 °C are achieved. Heat at thermal doses below the breakpoint temperature (i.e. 43 °C/60 min) does not exert direct cytotoxicity (sub-lethal temperature). The antitumoural effect of heat is the consequence of sensitisation to chemotherapy and radiation. Architectural and vascular changes at these thermal doses lead to an increased blood flow, enhanced drug delivery and drug extravasation (chemosensitisation) and higher oxygenation of the tissue (radiosensitisation). At molecular level the mechanisms of thermosensitisation are based on protein denaturation and aggregation that lead to inhibition of the DNA repair machinery and proteins involved in cell cycle regulation. Sub-lethal temperatures induce overexpression of inducible heat shock proteins, ie. HSP70 and turn tumour cells transiently thermoresistant. Thermal doses above the breakpoint temperature exert direct cytotoxicity and tumour cells die exponentially by induction of apoptosis and necrosis. Heat-induced tumour death is immunogenic by release of HSPs and HSP-PC in the extracellular milieu (by courtesy of V. Milani).

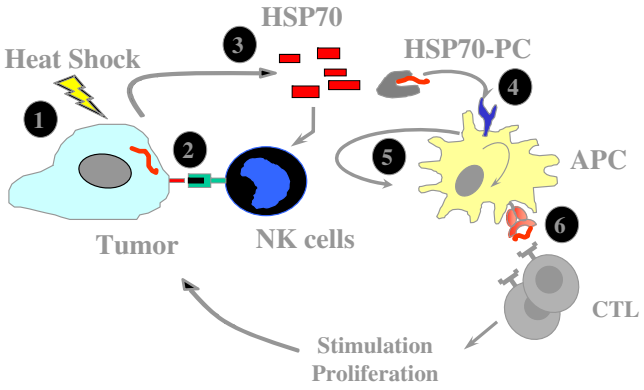


Fig. 2 – Working hypothesis for hyperthermia as targeted immunotherapy. (1) Clinical hyperthermia (heat shock) upregulates HSP70 expression in tumour tissues. (2) HSP surface expression occur in some tumour cells activating NK cells. (3) Due to induction of local necrosis, HSP70 and HSP70-PC can be released. (4) HSP70-PC bind to APC and induce cytokine secretion, APC activation, and in parallel deliver the peptide cargo into the cross-presentation pathway for MHC class I restricted presentation and antigen specific T-cell activation. Taken from Milani et al.[57]

leads to an underestimation of the cytotoxic potential of heat in combination with chemotherapy and, *vice versa*, to an overestimation of the thermal dose (e.g. CEM_{43}) necessary to achieve a clinical benefit.

In contrast to the number of multicentre clinical trials addressing the role of hyperthermia in conjunction with radiation or radiochemotherapy, only few comparative studies have been completed, where hyperthermia was tested combined with chemotherapy alone. Using cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (=HIPEC) in gastric cancer,[62] malignant mesothelioma,[63] ovarian carcinoma,[64] or pseudomyxoma,[65] it is important to note that these phase II studies as well as the only completed phase III study in patients with peritoneal spread of colorectal carcinoma[66] were not designed to evaluate the relative contributions of the extended surgery separated from HIPEC to the significant improvements in the outcome as seen in some of these trials.

There is one randomised trial for the prevention of peritoneal recurrence of gastric cancer showing marginally significant improvement in terms of local recurrence when HIPEC (using mitomycin C) was compared with surgery alone.[67] Improvement in recurrence-free survival was also seen in a multicentre clinical trial comparing intravesical chemotherapy (with mitomycin C) alone, with local microwave hyperthermia for prevention of recurrence in STCC of the bladder.[68] None of the HIPEC techniques can be unequivocally recommended as a standard treatment today. Prophylactic hyperthermic isolated limb perfusion (ILP) with melphalan alone tested in malignant melanoma, a well-designed large multicentre randomised trial, has clearly been shown to be of no significant value.[69] However, the situation has changed completely by the utilisation of TNF (tumour necrosis factor) in the ILP setting. TNF plus melphalan-based hyperthermic ILP has been proven to be highly effective in multicentre non-randomised trial settings demonstrating response rates above 70% and limb salvage rates above 80% especially in locally advanced soft tissue sarcomas of the extremities. This resulted in the approval of TNF in Europe for the ILP setting.[70] Still, no firm conclusion can be drawn for ILP to the relative effect of hyperthermia in the combined action with TNF or melphalan.

Substantial improvements in the technology have allowed heating of deep-seated tumours, especially in the pelvis and abdomen. Regional hyperthermia (RHT) can be performed using an electromagnetic deep heating device consisting of multi-antenna applicators (BSD systems, BSD Medical Corporation, Salt Lake City, USA). RHT combined with standard radiotherapy *versus* radiotherapy alone clearly showed not only substantial improvement in locoregional control, but also better long-term survival for patients with locoregional advanced cervix carcinoma.[71,72] For recurrences following radiotherapy, the use of simultaneous application of weekly cisplatin (CDDP) and RHT resulted in a 50% response rate,[73,74] whilst the response rate was expected to be about 15% without RHT.

Using the same deep heating methodology, most recently, the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society for Hyperthermic Oncology (ESHO) completed a multicentric, large Intergroup phase III trial (EORTC 62961/ESHO RHT-95) in order to define the impact of RHT within the treatment strategy for patients with primary or recurrent high-risk soft tissue sarcoma (STS) ($\geqslant$5 cm + grade II or III + deep + extracompartmental extension) or for the same group of patients after inadequate surgery. In this trial all patients with high-risk STS stratified to extremity (E) and to non-extremity (Non-E) received systemic EIA chemotherapy (four cycles etoposide, ifosfamide, doxorubicin (adriamycin)) and were randomised in two arms (chemotherapy alone *versus* chemotherapy and RHT) followed by definitive surgery and radiotherapy. Thereafter, additional four cycles of the EIA regimen were administered with or without RHT according to the initial randomisation. The preliminary results have been presented recently.[75] After median follow-up for all patients of 24.9 months (range: 0–106.9 months), an intention-to-treat analysis of 341 randomised patients showed a significantly superior disease-free survival (median 31.7 months (CI-95: 27.2–55.3 months) *versus* 16.2 months (CI-95: 12.8–20.7 months), $p < 0.01$ (Log-Rank-Test)) for the patients who received EIA and RHT ($n = 169$) as compared to those treated with EIA chemotherapy alone ($n = 172$). The objective response rate and the median local progression-free survival were also significantly improved for the combined treatment arm. In a separate trial including patients with progressive disease after first-line chemotherapy combinations, patients who received systemic ICE chemotherapy (ifosfamide, carboplatin, etoposide) with RHT showed an objective response rate of 20%.[76] The results are in the same range as previously reported by the SHOWG-phase II trial in a larger series of patients with metastatic STS using a closed radiant heat device (Aquatherm) for whole-body hyperthermia (WBH) to raise the patients' core temperature to 41.8 °C for 60 min. In pretreated patients, the response rate to ICE chemotherapy simultaneously with WBH was 24%.[77]

Several phase II studies have been completed with some promising results,[78] but the efficacy of radiative WBH combined with chemotherapy has not yet been proven in the scope of a randomised trial. At the borderline of WBH, there is interest to define fever-range (39–40 °C) whole body hyperthermia (FR-WBH) combined with systemic chemotherapy. This approach is based on preclinical results in animal models showing stimulation of the immune system[79,80] and an equal anti-tumour efficacy for long durations (4–6 h, 39–40 °C) of FR-WBH as compared to conventional WBH (1 h, >41.5 °C).[81,82]

Partial-body hyperthermia (PBH) is based upon three-dimensional multi-antenna applicators (Sigma-Eye applicator) integrated in an open low field (0.2 Tesla) or tunnel high field (1.5 Tesla) magnetic resonance tomograph.[83–85] Non-invasive treatment monitoring is provided by such hybrid systems to characterise temperature as well perfusion during hyperthermia.[86] The heating pattern can cover larger anatomical regions, e.g. full peritoneum (for peritoneal carcinosis) or upper abdomen (for liver metastases). First phase II results of gemcitabine + cisplatin combined with RHT or PBH as second-line treatment of gemcitabine-refractory patients with local advanced or metastatic disease are promising.[87] The experience with RHT in children and adolescents is limited to a few specialised treatment centres, particularly in Germany.[88,89] The more recent results (matched pair analysis) of RHT combined with PEI chemotherapy (cisplatin, etoposide and ifosfamide) in chemo-refractory or recurrent germ cell tumours with long-term follow-up are impressive.[90,91]

7. Clinical aspects for future directions

In the past decade, combined use of local hyperthermia and radiation compared to radiation alone has clearly been shown to have clinical potential for relatively '*superficial*' malignant tumours[92,93] in the appropriate situation, especially in recurrent breast cancer,[94] both in terms of response rate and local control. At present, we are witnessing the coming of age for regional 'deep' hyperthermia (RHT, PBH and HIPEC) as a new treatment component for malignancies in general and if combined with chemotherapy, in particular. In Europe, primarily initiated by the ESHO, both the Dutch trial[71] and the EORTC-ESHO Intergroup trial[74] can be considered in a time of evidence-based oncology as proof of concept not only for the clinical benefit by adding hyperthermia to enhance outcome of mainline therapies, but also for adequate achievement of deep heating in locally advanced tumours.

The positive results of the intergroup trial in high-risk STS are of great importance in several aspects. This is the first completed, large randomised study where RHT combined with systemic chemotherapy has been applied as first-line treatment of a potentially curable disease with significant impact on outcome.[75] Secondly, the design of the phase III study was based on the results of two prior consecutive phase II studies. Besides safety, achievement of measured tumour temperature ($T_{max} \geqslant 42$ °C), and efficacy in terms of impressive progression-free survival rates, the results suggested that post-surgical hyperthermia may be crucial for local control.[95]

By comparison, neither the only randomised trial on neo-adjuvant chemotherapy[96] nor the recently completed randomised trial on adjuvant chemotherapy,[97] both initiated by the EORTC, could demonstrate clinical benefit compared to local treatment alone in terms of progression-free or overall survival. So far, based on the preliminary data as presented, no firm conclusions are possible. However, RHT seems to offer at least an appropriate treatment option for high-risk STS where local control is difficult to achieve and death may result for inoperable local disease progression.[95] Targeting other high-risk cancer entities, the role of RHT or PBH combined with gemcitabine-based chemotherapy should be more investigated in pancreatic cancer in the scope of an ESHO phase III trial as planned.

The clinical potential for HIPEC after debulking surgery for patients with peritoneal spread of different malignancies is shown in several trials.[98] Deep heating within the peritoneal cavity (41–43 °C) is feasible and, for example, the HIPEC approval with taxanes in ovarian cancer needs further clinical investigations.[99] The addition of intraperitoneal normotherm instillation-chemotherapy to systemic chemotherapy following surgery showed survival benefit in two randomised trials.[100,101] An alternative approach for further enhancement of drug efficacy – beside HIPEC – could be achieved by the use of RHT or PBH within this setting. Based on the thermal dose concept, such combined strategy should greatly enhance its potential effect since – in contrast to HIPEC – the clinical application of RHT or PBH can be repeated in consecutive cycles. By comparing the same strategy without hyperthermia at normothermic conditions, the design of such trials would allow to assess the impact of hyperthermia on clinical outcome.

Available data on WHB in conjunction with chemotherapy merely demonstrate feasibility and some efficacy in chemo-refractory patients with advanced disease. Its application to induce core temperatures up to 42 °C is relatively invasive and accompanied with a broader spectrum of toxicity than RHT. Nevertheless, given that the addition of RHT to chemotherapy recently has been shown to have significant impact on locally advanced tumours – such as high-risk STS – one can reasonably conclude that WBH should be administered early in the management of metastatic cancer patients and should be tested in a randomised study with an appropriate design.

In summary, supported by a wealth of new biological data, the results of clinical trials strengthen the current evidence that hyperthermia combined with chemotherapy is an effective and useful modality which should be integrated in the present cancer treatment armamentarium.

However, there is need to encourage more widespread interest in hyperthermia by oncologists and funding agencies. Taking into consideration the enormous resources and activity which are placed in various technologically advanced and difficult treatment modalities, it is evident that there should also be a platform for hyperthermia. A number of dedicated centres, which are working in collaboration with the ESHO and EORTC, should be identified and maintained within the European community, and, most importantly, their necessary support should be secured.

Conflict of interest statement

None declared.

Acknowledgements

Thanks to Lars Lindner, Katharina Tschoep, Valeria Milani and Elfriede Noessner for their suggestions and critical and insightful comments on the manuscript and to Martina Lahm for her writing assistance.

REFERENCES

1. Sapareto A, Hopwood LE, Dewey WC, Ragu MR, Gray JW. Hyperthermic effects on survival and progression of CHO cells. *Cancer Res* 1978;**38**:393–400.
2. Bauer KD, Henle KJ. Arrhenius analysis of heat survival curves from normal and thermotolerant CHO cells. *Radiat Res* 1979;**78**:251–63.
3. Dewey WC. Arrhenius relationships from the molecule and cell to clinic. *Int J Hyperthermia* 1994;**10**:457–83.
4. Vaupel P, Kallinowski FK, Okunieff P. Blood flow, oxygen and nutrient supply, and metabolic micro-environment of human tumors: a review. *Cancer Res* 1989;**49**:6449–65.
5. Vaupel P. Tumor microenvironmental physiology and its implications for radiation oncology. *Semin Radiat Oncol* 2004;**14**:198–206.
6. Thrall DE, LaRue SM, Yu D, et al. Thermal dose is related to duration of local control in canine sarcomas treated with thermoaradiotherapy. *Clin Cancer Res* 2005;**11**:5206–14.
7. Jones EL, Oleson JR, Prosnitz JR, et al. Randomized trial of hyperthermia and radiation for superficial tumors. *J Clin Oncol* 2005;**23**:3079–85.
8. Hahn GM. Potential for therapy of drugs and hyperthermia. *Cancer Res* 1979;**39**:2264–8.
9. Marmor JB. Interactions of hyperthermia and chemotherapy in animals. *Cancer Res* 1979;**39**:2269–76.
10. Engelhardt R. Hyperthermia and drugs. *Recent Res Cancer Res* 1987;**104**:136–203.
11. Dahl O. Interaction of hyperthermia and chemotherapy. *Recent Res Cancer Res* 1988;**107**:157–69.
12. Bull JMC. An update on the anticancer effects of a combination of chemotherapy and hyperthermia. *Cancer Res* 1984;**44**(Suppl.):4853–6.
13. Hildebrandt B, Wust P, Ahlers O, et al. The cellular and molecular basis of hyperthermia. *Crit Rev Hematol Oncol* 2002;**43**:33–56.
14. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. *Int J Hyperthermia* 1999;**15**:79–107.
15. Deen DF, Williams ME. Isobologram analysis of X-ray–BCNU interactions in vivo. *Radiat Res* 1979;**79**:483–91.
16. Valeriote F, Lin H. Synergistic interaction of anticancer agents: a cellular perspective. *Cancer Chemother Rep* 1975;**59**:895–900.
17. Haveman J, Rietbroek RC, Geerdink A, van Rijn J, Bakker PJM. Effect of hyperthermia on the cytotoxicity of 2′,2′-difluorodeoxycytidine (gemcitabine) in cultured SW1573 cells. *Int J Cancer* 1995;**62**:627–30.
18. van Bree C, Beumer C, Rodermond HM, Haveman J, Bakker PJ. Effectiveness of 2′,2′-difluorodeoxycytidine (gemcitabine) combined with hyperthermia in rat R-1 rhabdomyosarcoma in vitro and in vivo. *Int J Hyperthermia* 1999;**15**:549–56.
19. Miller RC, Richards M, Baird C, Martin S, Hall EJ. Interaction of hyperthermia and chemotherapy agents; cell lethality and oncogenic potential. *Int J Hyperthermia* 1994;**10**:89–99.
20. Miller RC, Roizin-Towle L, Komatsu K, Richard M, Hall EJ. Interaction of heat with X-rays and cis-platinum; cell lethality and oncogenic transformation. *Int J Hyperthermia* 1989;**5**:697–705.
21. Grisham JW, Greenberg DS, Kaufman DG, Smith GJ. Cycle-related toxicity and transformation in 10T1/2 cells treated with *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine. *PNAS* 1980;**77**:4413–7.
22. McCormick PJ, Bertram JS. Differential cell cycle phase specifity for neoplastic transformation and mutation to ouabain resistance induced by *N*-methyl-*N*′-nitro-*N*-nitroguanidine in synchronized C3H 10T1/2 cells. *PNAS* 1982;**79**:4342–6.
23. Kampinga HH, Dikomey E. Hyperthermic radiosensitization: mode of action and clinical relevance. *Int J Radiat Biol* 2001;**77**:399–408.
24. Hurt CR, Dix DJ, Sharma GG, et al. Genomic instability and enhanced radiosensitivity in Hsp70.1- and Hsp70.3-deficient mice. *Mol Cell Biol* 2004;**24**:899–911.
25. Hunt CR, Pandita RK, Laszol A, et al. Hyperthermia activates a subset of Ataxia-Telangiectasia mutated effectors independent of DNA strand breaks and heat shock protein 70 status. *Cancer Res* 2007;**67**:3010–7.
26. Dewhirst MW. Future directions in hyperthermia biology. *Int J Hyperthermia* 1994;**10**:339–45.
27. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005;**307**:58–62.
28. Song CW, Park JH, Lee CK, Griffin R. Implications of increased tumor blood flow and oxygenation caused by mild temperature hyperthermia in tumor treatment. *Int J Hyperthermia* 2005;**21**:761–7.
29. Gellermann J, Hildebrandt B, Issels R, et al. Non-invasive MR-thermography of soft tissue sarcomas during regional hyperthermia: correlation with response and direct thermometry. *Cancer* 2006;**107**:1373–82.
30. Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R. Design of liposomes for enhanced local release of drugs of hyperthermia. *Science* 1978;**303**:1290–3.
31. Needham D, Anyarambhatla G, Kong G, Dewhirst MW. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. *Cancer Res* 2000;**60**:1197–201.
32. Lindner LH, Eichhorn ME, Eibl H, et al. Novel temperature sensitive liposomes with prolonged circulating time. *Clin Cancer Res* 2004;**10**:2168–78.
33. Jones E, Vujaskovic Z, Dewhirst M, et al. An update of the duke experience for thermally sensitive liposomes containing doxorubicin in combination with hyperthermia in breast cancer patients with chest wall recurrence (Abstract). In: 10th international congress of hyperthermic oncology, Munich, Germany; April 2008.
34. Zintchenko A, Ogris M, Wagner E. Temperature dependent gene expression induced by PNIPAM-based copolymers: potential of hyperthermia in gene transfer. *Bioconjug Chem* 2006;**17**:766–72.
35. Wagner E. Programmed drug delivery: nanosystems for tumor targeting. *Expert Opin Biol Ther* 2007;**7**:587–93.
36. White E. Life, death, and the pursuit of apoptosis. *Genes Dev* 1996;**10**:1–15.
37. Kaufmann SH, Earnshaw WC. Induction of apoptosis by cancer chemotherapy. *Exp Cell Res* 2000;**256**:42–9.
38. Harmon BC, Corder AM, Collins JR, et al. Cell death induced in murine mastocytoma by 42–47 °C heating in vitro: Evidence that the form of death changes from apoptosis to

necrosis above a critical heat load. *Int J Radiat Oncol Biol* 1990;**58**:845–58.
39. Yonezawa M, Otsuka T, Matsui N, et al. Hyperthermia induces apoptosis in malignant fibrous histiocytoma cell *in vitro*. *Int J Cancer* 1996;**66**:347–51.
40. Leopold KA, Dewhirst M, Samulski T, et al. Relationships among tumor temperature, treatment time, and histopathological outcome using preoperative hyperthermia with radiation in soft tissue sarcomas. *Int J Radiat Oncol Biol* 1992;**22**:989–98.
41. Baur A, Stäbler A, Wendtner CM, et al. MR-imaging changes of musculoskeletal soft-tissue sarcomas associated with neoadjuvant chemotherapy and hyperthermia. *Int J Hyperthermia* 2003;**19**:391–401.
42. Walter S, Buchner J. Molecular chaperones – cellular machines for protein folding. *Angew Chem Int Ed* 2002;**41**:1098–113.
43. Ellis J. Proteins as molecular chaperones. *Nature* 1987;**328**:378–9.
44. Fuller KJ, Issels RD, Slosman DO, Guillet JG, Soussi T, Polla BS. Cancer and the heat shock response. *Eur J Cancer* 1994;**30A**:1884–91.
45. Morimoto RI. Cells in stress: transcriptional activation of heat shock genes. *Science* 1993;**259**:1409–10.
46. Yao J, Munson KM, Webb WW. Lis JT: Dynamics of heat shock factor association with native gene loci in living cells. *Nature* 2006;**442**:1050–3.
47. Srivastava P. Interaction of heat shock proteins with peptides and antigen presenting cells: chaperoning of the innate and adaptive immune responses. *Annu Rev Immunol* 2002;**20**:3425–956.
48. Melcher A, Todryk S, Hardwick N, Ford M, Jacobsen M, Vile RG. Tumor immunogenicity is determined y the mechanism of cell death via induction of heat shock protein expression. *Nat Med* 1998;**4**:581–7.
49. Basu S, Binder RJ, Suto R, Anderson KM, Srivastava PK. Necrotic but not apoptopic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-k B pathway. *Int Immunol* 2000;**12**:1539–46.
50. Multhoff G, Botzler C, Wiesnet M, et al. A stress-inducible 72 kDa heat shock protein (HSP72) is expressed on the surface of human tumor cells, but not on normal cells. *Int J Cancer* 1995;**61**:272–9.
51. Multhoff G, Botzler C, Jennen L, Schmidt J, Ellwart J, Issels RD. Heat shock protein 72 on tumor cells: a recognition structure for natural killer cells. *J Immunol* 1997;**158**:4341–50.
52. Stangl S, Wortmann A, Guertler U, Multhoff G. Control of metastasized pancreatic carcinomas in SCID/Beige mice with human IL-2/TKD-activated NK cells. *J Immunol* 2006;**176**:6270–6.
53. Krause SW, Gastpar R, Andreesen C, et al. Treatment of colon and lung cancer patients with ex vivo heat shock protein k70-peptide-activated, autologous natural killer cells: a clinical phase I trial. *Clin Cancer Res* 2004;**10**:3699–707.
54. Sauter B, Albert ML, Francisco L, Larsson M, Somersan S, Bhardwaj N. Consequences of cell death: exposure to necrotic tumor cells, but not primary tissue cells or apoptopic cells, induces the maturation of immunostimulatory dendritic cells. *J Exp Med* 2000;**191**:423–34.
55. Noessner E, Gastpar R, Milani V, et al. Tumor-derived heat shock protein 70-peptide complexes are cross-presented by human dendritic cells. *J Immunol* 2002;**169**:5425–32.
56. Mukhopadhaya A, Mendecki A, Dong X, et al. Localized hyperthermia combined with intratumoral dendritic cells induces systemic antitumor immunity. *Cancer Res* 2007;**67**:7798–806.
57. Milani V, Noessner E, Ghose S, et al. Heat shock protein 70: role in antigen presentation and immune stimulation. *Int J Hyperthermia* 2002;**18**:563–75.
58. Falk MH, Issels RD. Hyperthermia in oncology. *Int J Hyperthermia* 2001;**17**:1–18.
59. Nielson OS, Horsman M, Overgaard J. A future for hyperthermia in cancer treatment? *Eur J Cancer* 2001;**37**:1587–9.
60. van der Zee J. Heating the patient: a promising approach? *Ann Oncol* 2002;**13**:1173–84.
61. Wust P, Hildebrandt B, Sreenivasa G, et al. Hyperthermia in combined treatment of cancer. *Lancet Oncol* 2002;**3**:487–97.
62. Fujimoto S, Takahashi M, Muto T, et al. Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined with surgery. *Cancer* 1997;**79**:884–91.
63. Loggie BW, Fleming RA, McQuellon RP, Russell GB, Geisinger KR, Levine EA. Prospective trial for the treatment of malignant peritoneal mesothelioma. *Am Surg* 2001;**67**:999–1003.
64. Helm CW, Randall-Whitis L, Martin RS, et al. Hyperthermic peritoneal chemotherapy in conjunction with surgery for the treatment of recurrent ovarian carcinoma. *Gyn Oncol* 2007;**105**:90–6.
65. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. *Ann Surg Oncol* 1999;**6**:727–31.
66. Verwaal VC, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003;**20**:3737–43.
67. Hamazoe R, Maeta M, Kaibara N. Intraperitoneal thermochemotherapy for prevention of peritoneal recurrence of gastric cancer. Final results of a randomized controlled study. *Cancer* 1994;**73**:2048–52.
68. Colombo R, da Pozzo LF, Salonia A, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J Clin Oncol* 2003;**21**:4270–6.
69. Koops HS, Vaglini M, Suciu S, et al. Prophylactic isolated limb perfusion for localized, high-risk limb melanoma: results of a multicenter randomized phase III trial. *J Clin Oncol* 1998;**16**:2906–12.
70. Eggermont AM, de Wil JH, ten Hagen TL. Current uses of isolated limb perfusion in the clinic and a model system for new strategies. *Lancet Oncol* 2003;**4**:429–37.
71. van der Zee J, Gonzalez Gonzalez D, van Rhoon G, et al. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospective randomized, multicenter trial. *Lancet* 2000;**355**:1119–25.
72. Franckena M, Stalpers LJA, Koper PC, et al. Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch deep hyperthermia trial. *Int J Radiat Oncol Biol Phys* 2008;**70**:1176–82.
73. Rietbroek RC, Schilthuis MS, Bakker PJM, et al. Phase II trial of weekly locoregional hyperthermia and cisplatin in patients with a previously irradiated recurrent carcinoma of the uterine cervix. *Cancer* 1997;**79**:935–43.
74. de Wit R, van der Zee J, van der Burg MEL, et al. A phase I/II study of combined weekly systemic cisplatin and locoregional hyperthermia in patients with previously irradiated recurrent carcinoma of the uterine cervix. *Br J Cancer* 1999;**80**:1387–91.

75. Issels RD, Lindner LH, Wust P, et al. Regional hyperthermia (RHT) improves response and survival when combined with systemic chemotherapy in the management of locally advanced, high grade soft tissue sarcomas (STS) of the extremities, the body wall and the abdomen: a phase III randomized prospective trial (EORTC-ESHO Intergroup trial) (ASCO abstract 10009). *J Clin Oncol* 2007;**25**:547s.
76. Fiegl M, Schlemmer M, Wendtner CM, Abdel-Rahman S, Fahn W, Issels RD. Ifosfamide, carboplatin and etoposide (ICE) as second-line regimen alone and in combination with regional hyperthermia is active in chemo-pre-treated advanced soft tissue sarcoma of adults. *Int J Hyperthermia* 2004;**20**:661–70.
77. Westermann AM, Wiedemann GJ, Jager E, et al. A systemic hyperthermia oncologic working grout trial. *Oncology* 2003;**64**:312–21.
78. Hildebrandt B, Hegewisch-Becker S, Kerner T, et al. Current status of radiant whole-body hyperthermia at temperatures >41.5 °C and practical guidelines fort he treatment of adults. The German "Interdisciplinary Working Group of Hyperthermia". *Int J Hyperthermia* 2005;**21**:169–83.
79. Burd R, Dziedzic TS, Xu Y, Caligiuri MA, Subjeck JR, Repasky EA. Tumor cell apoptosis, lymphocyte recruitment and tumor vascular changes are induced by low temperature, long duration whole body hyperthermia. *J Cell Physiol* 1998;**177**:137–47.
80. Chen Q, Fisher DT, Clancy KA, et al. Fever-range thermal stress promotes lymphocyte trafficking across high endothelial venules via an interleukin 6 *trans*-signaling mechanism. *Nature Immunol* 2006;**7**:1299–308.
81. Bull JMC, Scott GL, Strebel FR, Nagle V, Koch SM. A phase I trial for fever-range whole-body hyperthermia (LL-WBH) optimally timed with cisplatin (CIS), gemcitabine (GEM) and interferon-a (IFN-a). In: Proceedings for the 93rd Annual Meeting of the American Association of Cancer Research, 6–10 April, San Francisco, CA; 2002. p. 556.
82. Kraybill WG, Olenki T, Evans SS, et al. A phase I study of fever-range whole body hyperthermia (FR-WBH) in patients with advanced solid tumours: correlation with mouse models. *Int J Hyperthermia* 2002;**18**:253–66.
83. Carter DL, MacFall JR, Clegg ST, et al. Magnetic resonance thermometry during hyperthermia for human high-grade sarcoma. *Int J Radiat Oncol Biol Phys* 1998;**40**:815–22.
84. Bertsch F, Mattner J, Stehling MK, et al. Non-invasive temperature mapping using MRI: comparison of two methods based on chemical shift and T1-relaxation. *Magn Res Imag* 1998;**16**:393–404.
85. Peller M, Löffler R, Baur A, et al. MRT-gesteuerte regionale Tiefenhyperthermie. *Radiologe* 1999;**39**:756–63.
86. Gellermann J, Wlodarczyk W, Hildebrandt B, et al. Noninvasive magnetic resonance thermography of recurrent rectal carcinoma in a 1.5 Tesla hybrid system. *Cancer Res* 2005;**65**:5872–80.
87. Tschoep KE, Boeck S, Berger F, et al. Regional hyperthermia (RHT) combined with gemcitabine (GEM) + cisplatin (CIS) in patients with GEM-refractory advanced pancreatic cancer: results of the ESHO phase II trial (ASCO abstr 4635). *J Clin Oncol* 2008;**26**(Suppl.).
88. Romanowski R, Schött C, Issels R, et al. Regionale Hyperthermie mit systemischer Chemotherapie bei Kindern und Jugendlichen: Durchführbarkeit udn klinische Verläufe bei 34 intensiv vorbehandelten Patienten mit prognostisch ungünstigen Tumorerkrankungen. *Klin Pädiatr* 1993;**205**:249–56.
89. Wessalowski R, van Heek-Romanowski R, Issels RD, Jürgens HT, Göbel U. Estimated number of children with cancer eligible for hyperthermia based on population- and treatment-related criteria. *Int J Hyperthermia* 1999;**15**:455–66.
90. Wessalowski R, Blohm M, Calaminus G, et al. Treatment results in children and adolescents with loco-regional recurrences of abdominal germ cell tumors (GCTs): a pilot-study with PEI chemotherapy and regional deep hyperthermia (RHT) in comparison to a matched cohort. *Klin Pädiatr* 1997;**209**:250–6.
91. Wessalowski R, Schneider DT, Mils O, et al. An approach for cure: PEI-chemotherapy and regional deep hyperthermia in children and adolescents with unresectable malignant tumors. *Klin Pädiatr* 2003;**215**:303–9.
92. Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrent or metastatic malignant melanoma. European Society for Hyperthermic Oncology. *Lancet* 1995;**345**:540–3.
93. Valdagni R, Amichetti M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymphnodes in stage IV head and neck patients. *Int J Radiat Oncol Biol Phys* 1994;**28**:163–9.
94. Vernon CC, Hand JW, Field SB, et alInternational Collaborative Hyperthermia Group. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials. *Int J Radiat Oncol Biol Phys* 1996;**35**:31–44.
95. Issels RD. Regional hyperthermia in high-risk soft tissue sarcomas. *Curr Opin Oncol* 2008;**20**:438–43.
96. Gortzak E, Azzarelli A, Buesa J, et al. A randomised phase II study on neo-adjuvant chemotherapy for "high-risk" adult soft-tissue sarcoma. *Eur J Cancer* 2001;**37**:1096–103.
97. Woll PJ, van Glabbeke M, Hohenberger P, et al. Adjuvant chemotherapy (CT) with doxorubicine and ifosfamide in resected soft tissue sarcoma (STS): Interim analysis of a randomised phase III trial. *J Clin Oncol* 2007;**25**(18S):10008.
98. Glehen O, Mohamed F, Gilly FN. Peritoneal carcinomatosis from digestive tract cancer: new management by cyroreductive surgery and intraperitoneal chemohyperthermia. *Lancet Oncol* 2004;**5**:219–28.
99. de Bree E, Rosing H, Michalakis J, et al. Intraperitoneal chemotherapy with taxanes for ovarian cancer with peritoneal dissemination. *Eur J Surg Oncol* 2006;**32**:666–70.
100. Alberts DS, Liu PY, Hannigan EV, Rothenberg ML, Muggia F, Howell SB. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *New Engl J Med* 1996;**335**:150–5.
101. Markman M, Bundy B, Alberts DS, et al. Phase III study of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an Intergroup Study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;**19**:1001–7.
102. Kampinga HH. Cell biological effects of hyperthermia alone or combined with radiation or drugs: a short introduction to newcomers in the field. *Int J Hyperthermia* 2006;**22**:191–6.
103. Urano M, Kuroda M, Nishimura Y. For the clinical application of thermochemotherapy given at mild temperatures. *Int J Hyperhtermia* 1999;**15**:79–107.