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INVITED REVIEW

Hyperthermia in oncology

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The purpose of this article is to provide an overview on the current clinical application of hyperthermia combined with conventional treatment modalities (e.g, ionizing radiation, chemotherapy) in the treatment of malignant disease. The clinical application of hyperthermia with increase of tissue temperatures (range 40-44°q has been integrated in multimodal anti-cancer strategies. This review describes selected phase I or II ($n = 17$) and phase III trials ($n = 16$) investigating the effect of hyperthermia combined with radiotherapy ($n = 10$ trials), chemotherapy ($n = 15$ trials), or both ($n = 8$ trials) in a total of more than 2200 patients. The trials were performed in a variety of solid turn ours (e.g. melanoma, head and neck cancer, breast cancer, cancer of the gastrointestinal or urogenital tract, glioblastoma, sarcoma) in paediatric or adult patients. Profound research has produced a scien tific basis for the simultaneous application of hyperthermia in combination with ionizing radiation and/or systemic chemotherapy. Hyperthermia is becoming more accepted clinically, due to the substantial technical improvements made in achieving selected increase of temperatures in superficial and deep-seated tumours. At present, the combination of hyperthermia and chemotherapy or radiochemotherapy is further tested within clinical protocols (phase II/III) in order to improve local tumour control and relapse-free survival in patients with high-risk or advanced tumours of different entities.

Key words: Hyperthermia, thermo biology, clinical trials, combined treatment modalities.

1. Clinical application of hyperthermia

First, clinical hyperthermia can be divided into three almost separate domains: whole body hyperthermia (WBH), regional hyperthermia (RHT), and local hyperthermia (including superficial local and interstitial local hyperthermia) (LHT). The clinical application of heat can be induced by electromagnetic field technique, ultrasound, or perfusion methods. Lately, non-invasive WBH can be administered with an Aquatherm radiant heat device (Cancer Research Institute, New York) achieving systemic temperatures of 41.8°C (Robins *et al.* 1994). At the present time, LHT is most commonly performed using single microwave or ultrasound applicators, whereas deep RHT is performed using arrays of multiple applicators for deep heating (Hand and Hind 1986). In the annular phased array system (e.g. BSD 2000), microwave antennae are arranged cylindrically around the axis of the body to focus

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the electromagnetic field in the centre of the antenna by microwave interference. Wi thin the range of frequency used (,,-,60-110 MHz), the focus diameter can be switched from rv 15 em at 60 MHz to rv8 em at 100 MHz. Preferential heating of different tumour regions is achieved by the lower convection of heat from relatively poor vasculated areas of tumours compared to their surrounding tissues. The use of isolated limb perfusion and other perfusion techniques has recently been reviewed by Urano *et al.* (1999), and an excellent review on local interstitial hyperthermia has been published by Seegenschmiedt *et al. (1995).*

During hyperthermia treatments, the measurement of the actual temperature distribution in the tumour or immediately adjacent tissue is crucially important to the clinical evaluation of the quality of hyperthermia (Feldmann *et al.* 1993). So far, non-invasive methods for temperature measurements in deep-seated tissues are under current investigation (Carter *et al.* 1998). For invasive thermometry, thin plastic catheters must be implanted either under CT guidance percutaneously or intraoperatively at the time of explorative surgery (e.g. incisional biopsy). In order to obtain as much information as possible about the temperature distribution, a step-by-step movement of thermal probes (e.g. thermocouples, fibre-optic probes) within the catheter tracks allows the acquisition of data which map a temperature profile through the treatment region. From all the temperature measurements acquired as temperature vs. time and temperature vs. depth plots, time-averaged temperatures can be calculated at each monitored site. In addition, the time-averaged temperatures above 20, 50 and 90 of the monitored points (reported in terms of *T20, T_{so}* and *T_{90})* allow comparison of different hyperthermia treatments in clinical protocols in regard to the quality of heating (Oleson *et al.* 1993, Wust *et al.* 1998). More recently, the clinical application of the thermal isoeffect dose (TID) concept has been applied in retrospective analyses of clinical data to guide future clinical studies in which different treating protocols for different times at different temperatures are converted into equivalent minutes at 43°C (Dewey 1994).

Toxicity of hyperthermia in general is low. In no recently published report was hyperthermia-related toxicity treatment-limiting. The incidence of (reversible) pain at the treated region varies between 0--60. Burns are a typical hyperthermia-associated toxicity with low incidence (Vernon *et al.* 1996), that are dependent on correct heating techniques. The combination of local or interstitial hyperthermia with radiotherapy resulted in tissue damage that was not significantly greater than that in radiotherapy-sites alone (Meyer *et al.* 1989). Regional deep hyperthermia led to moderate local complications when combined with radiotherapy (Leopold *et al.* 1989). The combination of RHT with chemotherapy produced mainly systemic toxicity which was fully reversible (IsseIs *et al.* 1990). The first trials on whole body hyperthermia using techniques that were far from ideal revealed severe toxicity and lethality. The introduction of newer heating devices for whole body led to a drastic reduction of toxicity. Likewise, hyperthermia with the Aquatherm system was well tolerated, with minor signs of systemic toxicity (Robins *et al. 1997).*

2. Clinical results of hyperthermia combined with different treatment modalities

2.1. Hyperthermia and radiation

Within the past, the most often performed treatment modality involving hyperthermia was its local or regional application with radiation. Substantial clinical data exist demonstrating the improved efficacy and relative lack of normal tissue toxicity of combined radiation and hyperthermia treatments as compared to radiation ther-

apy alone for the treatment of locally advanced superficial tumours of different entities (Overgaard 1989). Complete response rates with hyperthermia alone are .....,15, with radiotherapy "-'35, and with combined radiotherapy and hyperthermia .....,70. Toxicity, principally thermal bums and blisters, is usually "-'10-15. No evidence exists for enhanced late effects of radiotherapy in these studies. These trials have established safety and efficacy for combined treatment in superficial lesions, particularly when prior radiotherapy limits additional doses to suboptimal levels. The encouraging nature of reports obtained from these studies triggered the initiation of randomized multiinstitutional phase III trials (table 1) (Valdagni *et al.* 1988, Datta *et al.* 1990, Perez *et al.* 1991, Valdagni and Amichetti 1994, Overgaard *et al.* 1995, Emami *et al.* 1996, Vernon *et al.* 1996, Sneed *et al.* 1998, van der Zee *et al.* 2000). In addition to the results of randomized studies completed in the US, the results of phase III randomized European multicentre trials initiated under the auspices of the ESHO recently also became available. For example, in superficial tumours, an advantage for the combined treatment was shown for recurrent or metastatic melanoma (Overgaard *et al. 1995).*

2.2. Hyperthermia and chemotherapy

Completed clinical protocols on the combination of hyperthermia and chemotherapy are rather limited, but this approach has now gained much more interest within the field of medical oncology. One of the main reasons are the substantial technical improvements made in available commercial equipment for local or regional heating, especially for deep-seated lesions and systemic heating. Another reason is related to the more general acceptance using multimodal strategies in the neoadjuvant treatment of locally advanced cancers in order to obtain optimal local control and to prevent distant metastases. The advanced stage (e.g. T3/4 N1I2) or tumours in unfavourable anatomic locations often prevents primary resection with adequate margins, and the toxicity of radiotherapy limits the use of potentially therapeutic doses. Therefore, based on the benefits of heat-induced enhancement of drug-efficacy, the integration of hyperthermia as an additional treatment modality given simultaneously with systemic chemotherapy is currently used in the clinic.

RHT given as an adjunct to systemic chemotherapy has been proven feasible with promising results in phase II trials. In table 2, results are given of several selected studies which have been, in part, extended to well designed phase III trials already started, mainly in Europe (Falk *et al.* 1986, Li and Hou 1987, Kakehi *et al. 1990,* Issels *et al.* 1990, 1991, 1993, 1998, Romanowski *et al.* 1993, Sugimachi *et al. 1994,* Takahashi *et al.* 1994, Wiedemann *et al.* 1994, 1996, IsseIs 1995, Eggermont *et al.* 1996, Rietbroek *et al.* 1997, Robins *et al.* 1997, Wessalowski *et al. 1998).*

2.3. Hyperthermia and radiochemotherapy

An extension of multimodal therapy concepts incorporating hyperthermia is its combination with radiation and chemotherapy ('triple modality'), which seems to be feasible and effective, as tested in several phase VII trials. A few examples of trimodality studies are given in table 3 (Hou *et al.* 1989, Ueo and Sugimachi 1990, Bornstein *et al.* 1992, Sugimachi *et al.* 1992, Amichetti *et al.* 1993, Ohno *et al.* 1997, Rau *et al.* 1998).

In the following part of this review, specific examples of tumour entities will be used to illustrate recent results of hyperthermia combined with different treatment modalities based on phase II/III protocols without the attempt to be all-inclusive.

Table 1. Hyperthermia in combination with radiotherapy: phase III studies.

Reference! name of trial	Tumour entity (stage)	Type of trial	No. of patients	Type of hyperthermia	Results of control arm (RT only)	Results of hyperthermia arm (RT + HT)	Significance of results ($p < 0.05$)
Pererez *et al.* (1989, 1991) RTOG 81-04	Head and neck (superficial measurable tumour)	prospective randomized multicentre	106	superficial (915 MHz microwave)	34'Yo CR	34 CR	
Datta *et al. (1990)*	Head and neck (untreated locoregional tumour)	prospective randomized	65	superficial (27-12 MHz microwave)	*32'Y.*, DR 19 DFS at 1.5 years	55 CR 33 DFS at 1.5 years	+ +
Valdagni *el al.* (1988, 1994)	Head and neck (N3 locoregional tumour)	prospective randomized	41	superficial (280M Hz microwave)	41 CR 24 LRFS 0 OS at 5 years	83 CR 68 LRFS 53 OS at 5 years	+ + +
Overgaard *e I al.* (1995) ESHO-3	Melanoma (skin metastases or recurrent skin lesions)	prospective randomized multicenter	70	superficial (various techniques)	35 CR 28°;', LRFS at 5 years	62 CR 46 LRFS at 5 years	+ +
Vernon *et al. (1996)* *MRC/ESHO-5*	Breast cancer (local recurrences or inoperable primary lesions)	randomized multicentre	306	superficial (various techniques)	41 CR ca. 30 LRFS ca. 40 AS at 2 years	59 CR ca. 50 LRFS ca. 40 AS at 2 years	+ + −
van der Zee *et a/.* (2000)	Rectal cancer	prospective randomized multicentre	143	deep regional HT (various techniq ues)	15 CR 22 OS at 3 years	21 CR 13 OS at 3 years	– –
	Bladder cancer		101		51 CR 22 OS at 3 years	73 CR 28 OS at 3 years	+
	Cervical cancer		114		57 CR 27 OS at 3 years	83 CR 51 OS at 3 years	+ +
Emami *et al.* (1996)	Various (recurrent or progressive lesions)	prospective randomized multicentre	174	interstitial HT (300-2450 MHz microwave or RF)	54 CR 34 OS at 2 years	57 CR 35 OS at 2 years	
Sneed *et al. (1998)*	Glioblastoma (postoperative)	prospective randomized	79	interstitial HT	15 OS at 2 years	31 OS at 2 years	+

AS = actuarial survival; CR = complete remission; DFS = disease free survival; HT = hyperthermia; LRFS = local relapse free survival; OS = overall survival; R F = radiofrequency electric currents; RT = radiotherapy.

Table 2. Hyperthermia combined with chemotherapy.

Reference	Tumour entity (stage)	Type of trial	No. of patients	Type of hyperthermia	Type of chemotherapy	Results
Li and Hou (1987)	Oesophagus cancer (preoperative)	Phase II	32	Local *HTI* Endoluminal MW	CDDP+ Bleo+ Cyc	8 CRII3 PR (65 RR)
Sugimachi *et al.* (1994)	Oesophagus cancer (preopera ti ve)	Phase III	20	Local *HTI* Endoradiotherm	CDDP+ Bleo	I *CR/5 PR/4* MR (50 RR); FHR (41.2)
			20	Control	CDDP+ Bleo	0 *CR/5 PR/O* MR (25 RR); FHR (18.8)
Kakehi *et al.* (1990)	Stomach cancer	Phase II	33	RHT/Thermotron	Mitomycin+ 5FU	3CR+ 10 PR (39 RR)
	Pancreatic cancer		22	8MHz	Mitomycin+ 5FU	3 CR+ 5 PR (36 RR)
Falk *et al. (1986)*	Pancreatic cancer	Phase II	77	RHT 13.5MHz	Mitomycin+ 5FU ± immunostimulation	27.3'),(. survival at I year
Isseis *et al.* (1990, 1991)	Sarcomas (pretreated with chemotherapy)	Phase II (RHT 86)	38	RHT/BSD 1000 60-110MHz	VPI6+ IFO	6 pCR+ 4PR+ 4FHR (37 RR)
		Follow-up	65		VPI6+ IFO	9pCR+ 4PR+ 8FHR (32 RR)
IsseIs *et al.* (1993, 1998)	High-risk soft tissue sarcomas	Phase **II** (RHT 91)	59	RHT/BSD 2000 80-110MHz	VPI6+ IFO+ ADR	ICR/6pCR+ 8PR+ 13MR (47) OS: *46'Y.*, at 5 yea rs
IsseIs (1995)	High-risk soft tissue sarcomas	Phase **III** (EORTC 62961)	112	RHT/BSD 2000 80-110 MHz (randomized)	VPI6+ IFO+ ADR	(08/00)
Eggennont *et al.* (1996)	Soft tissue sarcomas	Phase II	55	ILP with HT	TNF+ IFN+ L-PAM	IOCR/35PR (82'Yo RR)
Wiedemann *et al. (1994)*	Sarcomas/teratomas (metastatic)	Phase IIIl	19	WBH	IFO+ CBDCA	6PR (32 RR)
Wiedemann *et al. (1996)*	Sarcomas (metastatic)	Phse II	12	WBH	IFO+ CBDCA+ VPI6	7PR (58 RR)
Robins *et al. (1997)*	Refractory cancers (advanced or metastatic)	Phase I	16	WBH (Aquatherm)	L-PAM (dose-escalation)	ICR/2PR (19 PR)
Romanowski *et al. (1993)*	Paediatric sarcomas	Phase II	34	RHT/BSD 2000 80-110MHz	VPI6+ IFO+ CBDCA	12NED ('best response')/7CR Duration: 7--64 months
Wessalowski *et al. (1998)*	Paediatric non-testicular genn cell tumours	Phase II	10	RHT/BSD 2000 80-110 MHz	CDDP+ VPI6+ IFO (= PEl)	5CR+ 2PR (70 RR) Six patients alive without evidence of tumour (10-33 months)
Rietbroek *et al. (1997)*	Cervical cancer (recurrences)	Phase II	23	RH T / arra y-system 70MHz	CDDP (weekly)	2pCRIICR+ 9PR (52 RR)
Takahashi *et al. (1994)*	Rectal cancer (Dukes C preoperative)	Phase II	27	Intraoperati ve I HP	Mitomycin C	3 LR
			35	Control	Mitomycin C	13 LR

P = intraperitoneal hyperthermic perfusion; WBH = whole body hyperthermia; 5FU = 5-fluorouracil; VP 16 = etoposide; IFO = ifosfamide; ADR = Adriamycin = Doxorubicin; COOP = Cisplatin; CLDCA = Carboplatin; Bleo = Bleomycin; L-PAM = Melphalan; TNF = tumour necrosis factor-a; IFN = interferon-y; p = pathohistological; RR = response rate; CR = complete remission; PR = partial remission; MR = minor response; FHR = favourable histological response > 75; LR = local recurrence; NED = no evidence of disease.

Table 3. Hyperthermia combined with radiochemotherapy.

Reference	Tumour entity (stage)	Type of trial	No. of patients	Type of hyperthermia	Type of radio-chemotherapy	Results
Hou *et al. (1989)*	Oesophagus Ca	Phase III	23	LHTI Endoluminal MW	40Gy + Bleo + COOP (4 weeks)	CR + PR (94 RR) 2 year survival: 48
Ueo and Sugimachi (1990)	Oesophagus Ca (resectable)	Phase III III	62	LHTI Endoradiotherm	30Gy + Bleo (3 weeks)	14 pCR (23) 2 year survival: 50.4
			121	Control	30 Gy+ Bleo (3 weeks)	14 pCR (12) 2 year survival: 26.9
Ueo and Sugimachi (1990)	Oesophagus Ca (not-resectable)	Ph ase III III	31	LHTI Endoradiotherm	46.9 Gy + Bleo (5 weeks)	2 year survival: 15.5
			83	Control	48.5 Gy+ Bleo (5 weeks)	2 year survival: 1.2
Sugimachi *et al.* (1992)	Oesophagus Ca (preoperative)	Phase III	53	LHTI Endoradiotherm 13-56 MHz	32 Gy + Bleo (3 weeks)	7pCR (26) with RHT (n = 27) 2pCR (8) without RHT (n = 26)
Ohno *et al.* (1997)	Rectal cancer	Phase J[	36	LHTI Endoradiotherm	30 Gy + 5FU (3 weeks)	5 year survival: 91
			52	Control	30 Gy+ 5FU (3 weeks)	5 year survival: 64
Rau *et al. (1998)*	Rectal cancer (preoperative)	Phase II	37	RHTIBSO 2000 90 MHz	45Gy + 5FU/Lv (4 weeks)	5pCR (14) + 17PR (46) 3 year survival: 86
Bornstein *et al.* (J 992)	Breast cancer (recurrences)	Phase IIII	29	LHT/Clinitherm Sonotherm	30-60Gy + COOP (3-6 weeks)	15 CR (53°;\, RR)
Amichetti *et al. (1993)*	Head and Neck *(N2/N3)*	Phase IIII	18	LHT/BSO-MA 150 280-300 MHz	70Gy + COOP (7 weeks)	13 CR + 3PR (89)

LHT= local hyperthermia; RHT = regional hyperthermia; Bleo = Bleomycin; COOP = Cisplatin; 5FU = 5-fluorouracil; Lv = Leucovorine; p = pathohistological; CR = complete remission; PR = partial remission; RR = response rate

2.4. Esophageal, stomach and pancreatic cancer

Despite the encouraging results with combinations of chemotherapy and radiation in the neoadjuvant treatment of esophageal cancer, local persistence and progression of disease still present major problems. Depending on the disease status, 2-year survival rates in the range of 20-30 have been observed (Roth *et al. 1997).* Reports on treatment of esophageal carcinoma by use of hyperthermia come mainly from the far East. There, application of hyperthermia by using intracavitary microwave or radiofrequency (RF) heating devices in combination with chemotherapy and/or radiation therapy has been investigated for a long time, and current phase II/III trials are ongoing. In an early report from a cooperative group from Henan in China, Hou *et al.* (1989) reported on pre-operative treatment of 23 cases of esophageal cancer by triple therapy (table 3). Their previous results (Li and Hou 1987) using intraluminal microwave hyperthermia and chemotherapy alone showed an overall response rate of 65 (8 CR/13 PR) in 32 cases (table 2). But, only two patients with CR survived more than 2 years without any evidence of disease. By the addition of radiation to thermochemotherapy ('triple modality'), total response rate was 94 and 2-year survival 48 (Hou *et al. 1989).*

Another report by Ueo and Sugimachi (1990) describes a similar approach in 183 Japanese patients with resectable esophageal carcinoma (table 3). Sixty-two of these patients (group A) received pre-operative hyperthermia combined with radiochemotherapy, whereas the remaining 121 patients (group B) received only radiochemotherapy before surgery. The authors did not specify how the patients were selected. Besides an increase in histopathological complete responses (23 vs. 12), a marked improvement of 2-year survival from 26.9-50.4 was observed by addition of hyperthermia to radiochemotherapy. In a further series of 114 patients (group C) with unresectable esophageal carcinoma, patients receiving radiochemotherapy had a 2-year survival rate of 1.2, compared to 15.5 when applying radiochemotherapy with hyperthermia.

In a later report from the same group (Sugimachi *et al.* 1992; see table 3), 53 patients with resectable esophageal carcinoma were prospectively randomized to receive either radiochemotherapy ($n = 26$) or triple therapy ($n = 27$). Histopathological effectiveness was substantially better in the triple therapy group (7 pCR vs. 2 pCR). In a prospective trial comparing pre-operative chemotherapy with ($n = 20$ patients) or without ($n = 20$ patients) hyperthermia, improvement of objective tumour regression and improvement of histopathological effectiveness had been documented (Sugimachi *et al.* 1994). In a later study on 119 patients with esophageal cancer, Kitamura *et al.* (1997) noted that pre-operative triple therapy had the greatest effect on well differentiated squamous cell carcinoma.

In stomach and pancreatic cancer, treatment of patients with hyperthermia in combination with mitomycin C and 5-fluorouracil has been performed (Kakehi *et al.* 1990). In 33 patients with stomach cancer (29 of them stage IV), three CR and 10 PR were achieved (table 2). Improvement of objective complaints (loss of appetite, abdominal pain, ascites, GI bleeding, nausea, vomiting etc.) was observed in 66 of the cases. In the same report, therapy of 22 patients with pancreatic cancer (stage III/IV) by hyperthermia with the same drugs is described. Three CR and five PR were observed. Although follow-up was limited, two patients survived longer than 30 months disease-free and four patients were still alive with no regrowth of tumour.

Already in a report from 1986, Falk *et al.* (1986) achieved a 1 year survival rate of 27.3 in 77 patients with unresectable pancreatic cancer by combining hyperthermia

with chemotherapy and immunostimulation (table 2). However, these authors used suboptimal heating techniques and did not report on temperatures. The combined use of hyperthermia with either external beam irradiation or intraoperative radiotherapy (lOR T) in pancreatic cancer patients has been described by Shibamoto *et al.* (1996). From 15 patients with unresectable tumour that had received thermo radiotherapy, two remained free of disease, for 1 and 9 years, respectively. Certainly, these results warrant further clinical investigation.

2.5. Soft tissue sarcomas and bone tumours

Prognosis of patients with soft tissue sarcomas is limited, depending on tumour grade, size and localization, e.g. in patients with deep and high grade sarcoma (size > 5 em) of the extremities, lO-year freedom of metastasis is ,,-,25 (Gaynor *et al.* 1992). Adjuvant radiotherapy has allowed limb-sparing surgery, but the role of adjuvant or neoadjuvant chemotherapy or neoadjuvant radiotherapy is still subject of investigation. The sarcoma study group in Munich has focused their interest in hyperthermia on local advanced sarcomas as a clinical model to evaluate the efficacy of combined thermochemotherapy in such tumours. First results were obtained from a phase II study in 38 adult patients mainly with soft tissue sarcomas (Isseis *et al.* 1990). These patients had relapsed after prior surgery and radiation and had not responded to previously given chemotherapy alone (table 2). Local response rate was 37. A drug combination of ifosfamide and etoposide (VP 16) has been used, combined with RHT as a second line treatment. Beside long-term tumour control in some of the patients, their analysis of tumour temperatures (e.g. *T20, Tso, T_{90})* achieved with the BSD system showed significantly higher temperature parameters in responders vs. non-responders. These results were confirmed in an extended trial recruiting 65 patients with chemo-pre-treated sarcomas (Issels *et al.* 1991). The consecutive phase II protocol (RHT -91) was designed as a neoadjuvant study where the EIA regimen (etoposide, ifosfamide, adriamycin) was given to 59 patients with high-risk soft tissue sarcomas (size > 8 em, grade II/III, extracompartimental) for four cycles prior to surgical resection. After a first initial analysis, showing no severe toxicity or unexpected treatment side effects (Issels *et al.* 1993), the evaluation of clinical and pathohistological response was 47. At present, 29 patients are alive and the median follow-up of all patients is now more than 3.5 years. The estimated rate of 5 year overall survival is 46 (Isseis *et al.* 1998). The EOR TC Soft Tissue And Bone Sarcoma Group (STBSG) is further testing this multimodal concept as a first line treatment of high-risk soft tissue sarcomas in adults in a multicentre prospective phase III trial (EORTC 62961/ESHO RHT -95), as an Intergroup study with the European Society of Hyperthermic Oncology (ESHO) (Issels 1995). Patients meeting all of the eligibility criteria at first presentation (tumour size ~5 em, grade II or grade III, extracompartmental) or after inadequate surgery (resections with microscopic/macroscopic residual tumour) should be entered in this protocol with the intention to improve local tumour control and early prevention of systemic metastasis.

A similar concept using pre-operative hyperthermia but combined with radiation therapy has been performed at the Duke University Radiation Oncology Department. Ninety-seven patients with high grade sarcomas received two hyperthermia treatments per week, in addition to concurrent radiotherapy. For 78 patients with extremity tumours, locoregional control (94 actuarial lO-year local control)

was excellent and, for 63 of these, limb sparing surgery was possible without local failure (Prosnitz *et al. 1999).*

In addition to RHT combined with systemic chemotherapy, the hyperthermic isolated limb perfusion (ILP) technique has gained interest in which the arterial supply and venous outflow are connected to an extracorporal circulation system including an heat exchanger (Parks and Smith 1983). Isolated limb perfusion at moderate temperatures ($T_{max} = 40°C$) with tumour necrosis factor *a (TNFa)* and melphalan (L-PAM) in patients with large primary or recurrent sarcomas showed impressive responses (CR, 18; PR, 64 in 55 patients) and local tumour control (18 local failures), but no impact on the incidence of distant metastases (Eggermont *et al.* 1996, see table 2). For theoretical reasons, these results might be explained by the fact that occult distant micrometastases already present at the time of starting the isolated perfusion will be spared from the initial thermochemotherapy.

Whole body hyperthermia (WBH) achieved by rein fusion of extracorporal heated blood combined with ifosfamide and carboplatin (CBDCA) was applied in 19 patients with refractory sarcomas and teratomas, and six partial responses were observed (Wiedemann *et al.* 1994; table 2). In a consecutive phase II study using the same method, the ICE regimen (ifosfamide, carboplatin, etoposide) was given. In 12 sarcoma patients with distant disease, seven partial responses were seen (Wiedemann *et al.* 1996). Six patients remained free of relapse at a median of 201 days of observation.

Non-invasive WBH achieved with an Aquatherm radiant-heat device has been combined with carboplatin in patients with refractory sarcomas and cancers (Robins *et al.* 1993). It is noteworthy that WBH did not affect the pharmacokinetics of carboplatin in that trial. Also, there was no significant difference in the myelosuppression caused by carboplatin with or without WBH in repeated paired courses. More recently, the application of melphalan and WBH at 41.8°C for 60 min was well tolerated and the clinical results served as a basis to elucidate further the potential role of WBH as an adjunct to systemic chemotherapy in advanced cancer patients (Robins *et al. 1997).*

2.6. Melanoma

The easy access of superficial melanoma lesions to heating, together with the bad prognosis, made this disease one of the first clinical entities to be evaluated for response to treatment with hyperthermia. Kim *et al.* (1982) described an improvement in local response rate by application of hyperthermia as an adjunct to radiotherapy in malignant melanoma. Further evidence for effectiveness of hyperthermia in melanoma came from a study of Gonzalez Gonzalez *et al.* (1986), who found an 83 CR rate in 24 patients with metastatic melanoma treated by thermoradiotherapy, compared to 38 CR in a radiotherapy control group. Results of an European prospective randomized multi centre trial initiated under the auspices of the ESHO recently became available. These authors randomized 134 metastatic or recurrent lesions in 70 patients, to receive either radiotherapy alone or radiotherapy followed by hyperthermia (Overgaard *et al.* 1995). There was an increase in complete responses of 35-62 , with a 2-year local control rate of 28 versus 46. The overall 5-year survival rate was 19, but 38 of the patients for whom all known disease was controlled survived 5 years.

In localized melanoma of the extremities, several trials have investigated the effect of hyperthermic isolated limb perfusion (HILP) with melphalan. According to the report of Ghussen *et al.* (1989), 97 patients with primary high risk melanoma were prospectively randomized to receive either surgery or surgery plus HILP. The study was closed prematurely because of the significant advantage for the HILP group with respect to local failure (21 vs. 4 recurrences). The same trial design was used in a study by Hafstrorn *et al.* (1991). They randomized 69 patients with recurrent melanoma and observed a median survival of 57 vs. 35 months in favour of the HILP group, which was statistically not significant. More recently, a large phase III trial with 832 patients was published (Koops *et al.* 1998). In this trial, patients were randomized to receive either surgery or HILP followed by surgery. No statistically significant benefit for the HILP group patients was observed. Thus, the role of HILP in treatment of melanoma remains to be defined. From all these studies, the value of hyperthermia in HILP remains uncertain, since all trials investigated the effect of hyperthermia in combination with HILP.

2.7. Paediatric cancers

The application of hyperthermia as part of a combined modality therapy in paediatric patients, especially in tumours that failed to respond to standard regimen, has been proven feasible with several drug combinations. A multi centre study of the German Society of Paediatric Oncology and Hematology (GPOH) recruited 34 patients (mean age 11 years), mainly with deep seated advanced soft tissue sarcomas and Ewing tumours, who received chemotherapy combined with regional deep hyperthermia applied by external RF electromagnetic induction (BSD system), as described previously (table 2). Among 25 patients with local advanced tumours, 12 patients achieved no evidence of disease (NED), including seven patients with complete response (Romanowski *et al.* 1993). Follow-up of these patients showed long-term tumour control ranging from 7-64 months, **RBI** in combination with cisplatin-based systemic chemotherapy in recurrent or refractory extracranial non-testicular germ cell tumours of children and adolescents was found to induce objective tumour response in 70 (table 2). In comparison to a matched cohort, probability of event-free survival was shown to be superior for these patients (Wessalowski *et al.* 1998). The results so far are encouraging and the study has been extended to patients with a poor response to first-line treatment.

2.8. Cervix cancer

The disappointing results for inoperable advanced tumours of uterine cervix after conventional therapy remain a challenge for improvements. Although the majority of these recurrences occur in the pelvis without distant metastases, therapeutic options are usually limited in this situation. In patients who have previously been treated with pelvic irradiation, the response rate of chemotherapy is generally below 15, with a median survival of only 7 months (Rietbroek *et al.* 1997). More recently, results of radiochemotherapy with 3-year survival rates of 60-80 in advanced cervical carcinoma patients (stages IB to IV A) have been reviewed (Thomas 1999).

In the early 1990s, a large prospective randomized phase III trial, investigating the role of regional deep hyperthermia as an adjunct to radiotherapy in patients with locally advanced tumours of the cervix as well as rectal or bladder cancers, was started in the Netherlands. A total of 358 patients were randomized (table 1). In

114 patients with cervical cancer, a significantly higher response rate (83 versus 57 CR) and prolonged 3 year overall survival (51 versus 27) was obtained in the hyperthermia group (van der Zee *et al.* 2000). In parallel, a phase II trial combining hyperthermia with cisplatin was initiated in Amsterdam (Rietbroek *et al.* 1997). Twenty-three patients with previously irradiated and recurrent cervical carcinoma received weekly regional deep hyperthermia (RHT) with cisplatin (table 2). The response rate was 52 , with a median duration of response of 9.5 months and a I-year survival of 42 . A further report on 18 patients with advanced cervix carcinoma comes from Germany (Dinges *et al.* 1998). They performed a phase II study investigating thermoradiotherapy. In 16118 patients, a rapid tumour regression was observed with 13 complete and four partial remissions. In summary, hyperthermia combined both with chemotherapy or radiotherapy is efficient in the treatment of cervix carcinoma. In the Netherlands, thermo radiotherapy is already considered as standard treatment for recurrences of cervical carcinomas.

2.9. Rectal cancer

Local recurrences after curative surgery of rectal cancer occur in the range of 35 with conventional surgical techniques and are reduced to below 10 after the introduction of total mesorectal excision (Havenga *et al.* 1999). In a report from Japan (Takahashi *et al.* 1994), regional hyperthermia combined with intraoperative peritoneal perfusion with mitomycin C was applied to 27 patients with Dukes C rectal cancer. A group of 35 untreated patients served as a control. The local recurrence rate in the hyperthermia group was 11.1 , compared to 37.1 in the control group. More recently, neoadjuvant approaches combining hyperthermia with radiotherapy and! or chemotherapy have been investigated in patients with locally advanced rectal carcinomas. In the large Dutch prospective randomized phase III trial on the role of hyperthermia in patients with pelvic turnours (table 1), 143 patients with advanced rectal cancer (including 119 patients with irresectable disease or residual disease after surgery) were randomized to receive either radiotherapy or radiotherapy plus regional deep hyperthermia (RHT). Although not significant, an improved response rate in the hyperthermia group was observed (van der Zee *et al.* 2000). Ohno *et al.* (1997) have treated 36 patients with primary carcinoma of the rectum (11, 9, and 16 with Dukes' stage A, Band C, respectively; selection criteria not specified). Patients received a triple modality therapy before surgery and reached 5 year survival rates of 91 compared to 64 in 52 control patients. Particularly, for patients with tumours invading beyond the muscularis propria and/or with positive lymph node metastases, a significantly better survival was obtained with thermochemoradiotherapy plus surgery than in surgery alone. A similar approach was used by a German group (Rau *et al.* 1998). Thirty-seven patients with *T3! T4* rectal cancer were treated with pre-operative regional hyperthermia combined with radiochemotherapy (table 3). Overall resectability was 98. The histopathological report confirmed no evidence of residual tumour in five resected tumours and downsizing in more than 50 of the tumours, as documented by CT in another 17 patients (five pCR, 17 PR). The survival rate after 38 months was 86. The contribution of regional hyperthermia to locoregional tumour control and overall survival within this pre-operative setting is now being investigated in an ongoing phase III trial initiated by the same study group.

2.10. Breast cancer

For patients with a local recurrence of breast cancer, major complaints consist of pain, bleeding, and ulceration in over 60 of the cases (Bedwinek *et al.* 1981). With increasing size of the lesion for both non-irradiated and previously irradiated recurrences, durable local control decreases with increasing size of the lesion. Frequently, the radiation dose that can be administered safely is lower than that considered effective. Therefore, superficial hyperthermia has been added to radiotherapy in order to increase therapeutic efficacy. Results from five randomized controlled trials on the value of hyperthermia as an adjunct to radiotherapy have been reported (Vernon *et al.* 1996). In 306 randomized patients, the cooperative study of the Medical Research Council (MRC, UK) and the Princess Margaret Hospital (Ontario, Canada) demonstrated an increase in complete response of 41 for radiotherapy to 59 for the combined treatment arm (table 1) in recurrent breast cancer. This improvement in response rate converted into statistically significantly prolonged relapse-free survival ($p = 0.007$) with a 2-year control rate from 20-50, but no statistical difference in overall survival. The greatest effect of hyperthermia was observed in patients with recurrent lesions in previously irradiated areas, where further irradiation was limited to low doses. Based upon 148 patients with breast cancer recurrences treated within this phase III trial, the relationship between thermal dose and treatment outcome was analysed by Sherar *et al.* (1997). Higher tumour temperature or higher thermal dose was statistically significantly correlated with complete response rate. Furthermore, a higher thermal dose was associated with longer local disease-free survival, time to local failure, and overall survival.

An earlier report on treatment of 29 patients with locally or regionally recurrent or advanced breast cancer by trimodal therapy using hyperthermia, radiation therapy and chemotherapy comes from Boston (Bornstein *et al.* 1992; table 3). Cisplatin alone or cisplatin combination chemotherapy was delivered just prior to hyperthermia once weekly. Following hyperthermia, a 400 cOy fraction of radiation was given. An overall complete response rate of 53 was observed. Thus, the results of a combination of radiation therapy, hyperthermia and chemotherapy appear promising and are being investigated in prospective randomized trials.

2.11. Head and neck tumours

As early as 1981, a randomized multicentre phase III trial was started in the US, comparing radiotherapy vs. radiotherapy plus hyperthermia in 307 patients with superficial tumours. This study revealed no significant difference in outcome of a subgroup of 106 patients with head and neck tumours (table 1). However, detailed analysis of the data showed that temperature control and heat application techniques were insufficient, especially in larger tumours (>3cm) (Perez *et al.* 1989,1991). A later prospective randomized phase III trial (Datta *et al.* 1990) demonstrated, in 65 patients with locoregional (cheek, tongue, hard palate, tonsil, alveolus, floor of the mouth) limited disease and all stages (5, 8, 22 and 30 patients in stage I, II, III and IV, respectively), a statistically significant advantage for patients receiving hyperthermia in addition to radiotherapy with respect to CR (55 vs. 32) and disease-free survival (33 vs. 19 ; table 1). A third randomized study (Valdagni and Arnichetti 1994; table 1) investigating the value of hyperthermia as an adjunct to radiotherapy in patients with *N2IN3* positive head and neck cancers (41 patients) revealed a significantly improved outcome in the hyperthermia group with respect to complete

remission (83 vs. 41), local relapse free survival (68 vs. 24) and 5-year overall survival (53 vs. 0).

In order to further increase therapeutic efficacy, a triple modality therapy combining heat, radiation and chemotherapy was investigated by Amichetti *et al. (1993).* They treated 18 patients with a combination of cisplatin and thermoradiotherapy. Thirteen CR and three PR were achieved, yielding a response rate of 89 (table 3). A combination of radiotherapy with interstitial hyperthermia was investigated in 75 patients with head and neck tumours, a subgroup of the 174 patients with various tumours reported by Emami *et al.* (1996; table 1). No significant advantage for the hyperthermia group in this randomized trial was observed. However, using the same technique applied in 79 patients with glioblastoma, Sneed *et al.* (1998) demonstrated a significant advantage in local relapse-free survival for the patients receiving interstitial hyperthermia (31 vs. 15; table 1). The value of interstitial hyperthermia combined with radiotherapy in the treatment of head and neck tumours has also been investigated by a German group (Seegenschmiedt *et al.* 1994). They treated a total of 90 patients, including 62 patients with tumours of the head and neck. In 66 of the patients, a CR was observed. Median relapse-free survival for all patients was 17 months. Multivariate analysis revealed high tumour temperatures during therapy as an independent predictor of CR.

3. Conclusion

In general, the technical application of local-regional hyperthermia or whole body hyperthermia is feasible and effective if combined with chemotherapy as shown in numerous phase IIII studies. Clinical studies (phase II/III) on regional hyperthermia combined with radiation, chemotherapy or radiochemotherapy have shown impressive results at clinical relevant temperatures in local advanced turn ours of different entities in terms of objective response rate, local tumour control and relapse free survival. Especially in well defined clinical situations in breast cancer, melanoma, head and neck tumours, cervix cancer and glioblastoma, the addition of hyperthermia to radiotherapy significantly improves response and survival and, thus, should be considered as a presently proven therapy to improve patients outcome. In other clinical situations, hyperthermia as an adjunct to conventional treatment strategies should be recommended in the setting of clinical protocols only. Therefore, further testing of the potential of hyperthermia combined with radiotherapy and/or chemotherapy in prospective randomized trials is warranted. The results of prospective trials will answer the question of which types of high-risk patients with local advanced or metastastic tumours will benefit from hyperthermia as part of a multimodal therapy strategy.

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