

## Heating the patient: a promising approach?

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There is a clear rationale for using hyperthermia in cancer treatment. Treatment at temperatures between 40 and 44°C is cytotoxic for cells in an environment with a low pO<sub>2</sub> and low pH, conditions that are found specifically within tumour tissue, due to insufficient blood perfusion. Under such conditions radiotherapy is less effective, and systemically applied cytotoxic agents will reach such areas in lower concentrations than in well perfused areas. Therefore, the addition of hyperthermia to radiotherapy or chemotherapy will result in at least an additive effect. Furthermore, the effects of both radiotherapy and many drugs are enhanced at an increased temperature. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources, regional hyperthermia by perfusion of organs or limbs, or by irrigation of body cavities, and whole body hyperthermia.

The use of hyperthermia alone has resulted in complete overall response rates of 13%. The clinical value of hyperthermia in addition to other treatment modalities has been shown in randomised trials. Significant improvement in clinical outcome has been demonstrated for tumours of the head and neck, breast, brain, bladder, cervix, rectum, lung, oesophagus, vulva and vagina, and also for melanoma. Additional hyperthermia resulted in remarkably higher (complete) response rates, accompanied by improved local tumour control rates, better palliative effects and/or better overall survival rates. Generally, when combined with radiotherapy, no increase in radiation toxicity could be demonstrated. Whether toxicity from chemotherapy is enhanced depends on sequence of the two modalities, and on which tissues are heated. Toxicity from hyperthermia cannot always be avoided, but is usually of limited clinical relevance.

Recent developments include improvements in heating techniques and thermometry, development of hyperthermia treatment planning models, studies on heat shock proteins and an effect on anti-cancer immune responses, drug targeting to tumours, bone marrow purging, combination with drugs targeting tumour vasculature, and the role of hyperthermia in gene therapy.

The clinical results achieved to date have confirmed the expectations raised by results from experimental studies. These findings justify using hyperthermia as part of standard treatment in tumour sites for which its efficacy has been proven and, furthermore, to initiate new studies with other tumours. Hyperthermia is certainly a promising approach and deserves more attention than it has received until now.

**Key words:** chemosensitisation, heating techniques, hyperthermia, improved clinical results, radiosensitisation

### Introduction

Written reports concerning the use of increased temperatures in cancer treatment have existed for many centuries. Probably the oldest report was found in the Egyptian Edwin Smith surgical papyrus, dated around 3000 BC. Hyperthermia

researchers like to cite Hippocrates (460–370 BC) in particular, although the method he describes in one of his aphorisms, i.e. hot irons, concerns higher temperatures, such as those used in cauterisation. In the 19th and 20th centuries, fever therapy has been used as a method to increase temperatures, while other investigators started to apply radiofrequency techniques [1].

A worldwide interest in hyperthermia was initiated by the first international congress on hyperthermic oncology in Washington in 1975. This interest has followed a course that is usual for a new type of treatment. In the first decade there was

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a growing enthusiasm, reflected by an exponential increase in the number of papers and participants at meetings. Thereafter the interest waned, due to disappointing clinical results from some of the first randomised studies, accompanied by a reluctance among sponsoring authorities and hospital boards to support further research. Nowadays there appears to be a renewed interest, thanks to several randomised studies demonstrating that the improvements in treatment outcome by additional hyperthermia can be very substantial, provided that adequate heating procedures are used.

This report summarises the rationale for the use of hyperthermia in cancer treatment, the methods available to apply and monitor hyperthermia treatments, the first clinical results and the results of randomised trials, and new developments.

## Rationale for hyperthermia in cancer treatment

### The tumour-selective effect of hyperthermia

Generally, there is no intrinsic difference between hyperthermia sensitivity of normal and tumour cells, except for haematological malignancies. Nevertheless, *in vivo* a selective tumour cell killing effect is achieved at temperatures between 40 and 44°C, which is related to a characteristic difference between normal and tumour physiology. The architecture of the vasculature in solid tumours is chaotic, resulting in regions with hypoxia and low pH [2–4], which is not found in normal tissues in undisturbed conditions. These environmental factors make cells more sensitive to hyperthermia. The effect of hyperthermia depends on the temperature and the exposure time. At temperatures above 42.5–43°C, the exposure time can be halved with each 1°C temperature increase to give an equivalent cell kill [5]. Most normal tissues are undamaged by treatment for 1 h at a temperature of up to 44°C [6]. Only nervous tissues appear more sensitive. For the central nervous tissue, irreversible damage was found after treatment at 42–42.5°C for longer than 40–60 min [7]. Treatment of peripheral nervous tissue for >30 min at 44°C, or an equivalent ‘dose’, results in temporary functional loss, which recovers within 4 weeks [8]. The main mechanism for cell death is probably protein denaturation, observed at temperatures >40°C, which leads to, among other things, alterations in multimolecular structures like cytoskeleton and membranes, and changes in enzyme complexes for DNA synthesis and repair [9].

### Radiotherapy plus hyperthermia

Several mechanisms are responsible for the supra-additive effect of the combination of radiotherapy and hyperthermia. The additive complementary effect comes from the sensitivity of cells in the hypoxic, low pH areas, and the cells in S-phase, which are both relatively radioresistant [5]. Hyperthermia may cause an increased blood flow, which may result in an

improvement in tissue oxygenation, which then results in a temporally increased radiosensitivity [10]. Experimental studies have also shown for almost all cell lines studied that hyperthermia also potentiates radiation effects. The most important mechanism for this interactive effect is that the effect of hyperthermia interferes with the cellular repair of radiation-induced DNA damage, probably by an effect on cellular proteins [11]. The thermal enhancement ratio for radiation-induced cell kill is greater under hypoxic conditions, increases with higher temperatures and longer exposure times, and decreases with longer time-intervals between the two modalities. Maximum thermal enhancement ratios are obtained when radiation and hyperthermia are applied simultaneously, but this has been found for both tumour and normal tissues. *In vivo* studies have demonstrated that the effect of radiotherapy can be enhanced by a factor of between 1.2 and 5 [12, 13]. When tumour and normal tissue are heated to the same degree, maximum therapeutic gain will be obtained with a time interval between the two treatments [14]. Overall, hyperthermia is probably the most potent radiosensitiser known to date.

### Chemotherapy plus hyperthermia

An extensive review on the combination of hyperthermia with chemotherapy was published in 1995 [15]. For the combination of hyperthermia and chemotherapy, spatial cooperation can again explain the additive effects. Drug concentration will be less in the insufficiently perfused tumour regions. In addition, many drugs are potentiated by heat. Furthermore it has been shown for mitomycin C, nitrosureas, cisplatin, doxorubicin and mitoxantrone that the addition of hyperthermia to chemotherapy can counteract drug resistance. Generally, interaction is only seen when the two treatments are given in close sequence. The most important mechanisms for an interactive effect are an increased intracellular drug uptake, enhanced DNA damage and higher intratumour drug concentrations, resulting from an increase in blood flow. Pharmacodynamics may also play a role, e.g. when doxorubicin, cyclophosphamide and melphalan pharmacokinetics are altered, an increased area under the curve and/or decreased excretion occur. This can be explained by a decrease in biliary excretion, as observed with liver perfusion, or a change in perfusion distribution, as found during whole body hyperthermia [16–18].

An interactive effect was observed for virtually all cell lines treated at temperatures above 40°C for alkylating agents, nitrosureas and platin analogues, with enhancement ratios depending on temperature and exposure time. The effect of these drugs can be enhanced by a factor of between 1.2 to 10, and an extremely high thermal enhancement ratio of 23 was even observed for *in vitro* application of melphalan to drug-resistant cells at 44°C [16]. In combination with bleomycin, an interactive effect was seen at temperatures >42°C. In the combination with anthracyclins, the results show discrepancies and appear to vary with cell type, growth conditions and

drug scheduling. *In vivo* experiments showed improved results when hyperthermia was combined with doxorubicin and mitoxantrone. With antimetabolites vinblastine, vincristine and etoposide, most experiments did not show an interactive effect. In the case of etoposide, cytotoxicity was even reduced, which was explained by instability of the drug at an increased temperature. Whether the clinical combination of hyperthermia and chemotherapy leads to therapeutic gain will depend on the temperature increase in the organs for which the used drug is toxic, which depends on the heating method (see below). In animal studies, increased toxicities were seen in skin (cyclophosphamide, bleomycin), heart (doxorubicin), kidney (cisplatin, with a core temperature  $>41^{\circ}\text{C}$ ), urinary tract (carmustine, with a core temperature  $>41^{\circ}\text{C}$ ) and bone marrow (alkylating agents and nitrosureas). Lethal toxicity was enhanced when systemic hyperthermia was applied in combination with cyclophosphamide, methyl-CCNU and carmustine.

### Methods to increase tumour temperatures

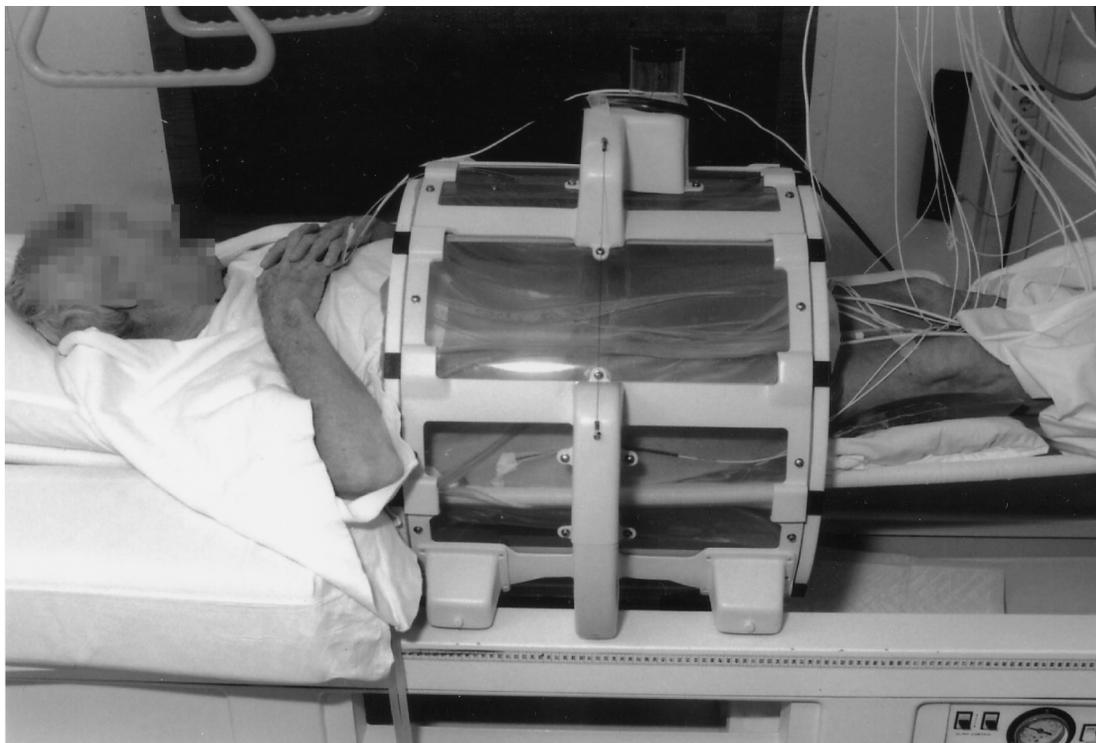
In the clinical application of hyperthermia, three methods can be distinguished: local, regional and whole-body hyperthermia.

### Local hyperthermia

With local hyperthermia, the aim is to increase mainly the tumour temperature. Local hyperthermia can be applied by external, intraluminal or interstitial methods. Electromagnetic or ultrasound energy is directed at the treatment volume. The volume that can be heated depends on the physical characteristics of the energy source and on the type of applicator (array) [20]. Methods for applying hyperthermia externally can be divided into superficial techniques (the energy coming from one direction) and deep, also termed regional hyperthermia (energy directed from around the part of the body in which the target volume is located). Examples of external hyperthermia application are given in Figures 1 and 2. The energy distribution in the tissues strongly depends on tissue characteristics and is thereby inhomogeneous. The temperature distribution is not simply a result of the energy distribution, but also depends on thermal tissue characteristics and blood flow. The reduced blood flow in tumour tissue compared with that in normal tissues is advantageous, since tumour tissue will heat more easily. During local hyperthermia the systemic temperature may also increase; the absolute temperature increase will depend on both the treatment volume to which energy is applied and the measures taken to help the patient lose energy. During local hyperthermia, the tumour temperatures are



**Figure 1.** Example of a clinical hyperthermia treatment set-up for a patient with recurrent breast cancer on the chest wall. Hyperthermia is applied using 433 MHz through four (custom-built) Lucite Cone waveguide applicators. The power output can be adjusted for each applicator separately. Optical fibre thermometry probes, which are not disturbed by electromagnetic radiation, are placed interstitially within catheters and on the skin. A perfused water bolus bag is placed between applicators and skin.



**Figure 2.** Example of a patient during deep hyperthermia treatment in the BSD-2000 system (BSD Medical Corporation, Salt Lake City, UT). Eight radiating antennae are built-in in the wall of the cylinder-shaped applicator surrounding the pelvic area of the patient. The space between applicator and skin is filled with water in a bolus bag. Thermometry probes are placed interstitially and intraluminally within catheters, and on the skin. This system is placed in a room shielded from electromagnetic radiation.

increased to levels that are as high as possible, as long as the tolerance limits of the surrounding normal tissues are not exceeded.

### Regional hyperthermia

Regional hyperthermia is applied by perfusion of a limb, organ or body cavity with heated fluids [21, 22]. When regional hyperthermia is applied to limbs, and without a cytotoxic agent, the temperature can be increased to  $\sim 43^{\circ}\text{C}$  for a duration of 2 h. The temperature must be lower in combination with cytostatic drugs to avoid unacceptable toxicity.

### Whole-body hyperthermia

For whole-body hyperthermia, several methods have been used. A common characteristic is that energy is introduced into the body, while at the same time energy losses are minimised. The temperature increase is usually limited to  $41.8\text{--}42^{\circ}\text{C}$ . The toxicity of the treatment depends on the procedure used. Recent experience with radiant heat methods, for which the patients need only sedation during the treatment, has shown that this procedure is tolerated very well [23, 24]. A newer approach is to increase the temperature to  $\sim 40^{\circ}\text{C}$  for a longer period, which, in combination with cytokines and cytotoxic drugs, is expected to lead to a greater therapeutic

index than whole-body hyperthermia at the maximum tolerated level [25].

### First clinical results

The first reports on the clinical use of hyperthermia generated great enthusiasm. The results appeared considerably better than without hyperthermia, for example when studying hyperthermic regional isolated perfusion [26], whole-body hyperthermia in patients for whom no standard treatments were available [27] or hyperthermia combined with low doses of radiotherapy [28, 29]. Many reports are anecdotal, or compare results of a combined treatment with historic control groups. However, among the many non-randomised studies one can find rather convincing results.

Several groups used hyperthermia alone. A review of 14 such studies including a total of 343 patients reported complete response rates varying from 0% to 40% (overall 13%) and partial response rates from 0% to 56%, with an overall objective response rate of 51% [30]. Three additional studies report complete response rates of 11%, 16% and 18% [31–33]. A drawback of the use of hyperthermia alone is that in general the duration of response is short, with a median of only 6 weeks.

Many studies concerned the combination of hyperthermia with radiotherapy. Several investigators studied the effect of additional hyperthermia in 'matched lesions': in patients with more than one tumour lesion, some of the lesions were treated with hyperthermia, while the other(s) received the same radiotherapy without hyperthermia. Such studies consistently show a higher complete response rate for combined treated lesions. A summation of the data from these studies (total 713 lesions) shows an increase in complete response rate from 31% to 67% [34]. Literature reviews concerning complete response rates following the addition of hyperthermia to radiotherapy in breast cancer, malignant melanoma and neck nodes suggest a clinical thermal enhancement ratio of 1.5 to 1.7 [35, 36]. Comparison of results over a longer period revealed that the clinical outcome very much depends on the heating technique used. With recurrences of breast cancer, for example, reirradiation plus hyperthermia resulted in 31% complete response in the initial experience, while the complete response was 67% with a better heating technique [37].

Experience with a combination of hyperthermia and chemotherapy is more scarce, but again the results are promising. Use of a simultaneous combination of cisplatin and hyperthermia in cervical cancer, recurring following irradiation, resulted in a 50% response rate [38, 39], while without hyperthermia the response rate was expected to be ~15%. Recently, two phase II studies on hyperthermia in combination with pre- and/or postoperative chemotherapy in high-risk sarcomas have demonstrated quite impressive 5-year overall survival rates. A phase III trial has been started to confirm the value of hyperthermia in the treatment schedule [40, 41]. Another study [42] evaluated the safety and effectiveness of whole-body hyperthermia at 41.8°C plus carboplatin in 16 patients with platinum-resistant ovarian cancer. Of 12 patients evaluable for response, one had a complete response and four had a partial response. In these studies, the toxicity was not in excess of that expected. Earlier experience with ifosfamide, carboplatin and etoposide and whole-body hyperthermia in patients with sarcomas also suggests that drug resistance can be overcome by hyperthermia at 41.8°C [43].

The experience with hyperthermia in children is limited, although both regional and whole-body hyperthermia appear feasible [44]. In 10 patients with recurrent or refractory germ cell tumours, regional hyperthermia combined with cisplatin, etoposide and ifosfamide resulted in five complete and two partial responses, again suggesting that hyperthermia counteracts drug resistance [45].

## Results of randomised studies

The results of the first two randomised studies performed in the United States were disappointing, as these failed to show a beneficial effect of adding hyperthermia to radiotherapy. Retrospectively, these negative results have been explained by the use of hyperthermia treatment techniques that were inade-

quate for the patients included in these studies [46–48]. Besides these two studies, at least 24 other randomised trials studying the addition of hyperthermia to radiotherapy and/or chemotherapy have been performed, of which 18 showed significantly better results with the hyperthermia group (Table 1). The best-known randomised trials are those on metastatic lymph nodes of head and neck tumours [49, 50], and on malignant melanoma [51], breast cancer [52], glioblastoma multiforme [53] and pelvic tumours [54], which were performed in Europe and North America. Patients with cervical lymph nodes were randomised to radiotherapy to a total dose of 64–70 Gy, or the same radiotherapy with twice weekly hyperthermia. The complete response rate improved from 41% to 83%, with 5-year local control increasing from 24% to 69%, and 5-year overall survival increasing from 0% to 53% [49, 50]. In malignant melanoma, the addition of hyperthermia to radiotherapy (three fractions of 8–9 Gy) increased the complete response rate from 35% to 62%, and 2-year local control from 28% to 46% [51]. A combined analysis of the results of five randomised trials in recurrent or advanced breast cancer showed an improvement in complete response rate from 41% to 59% following the addition of hyperthermia to either conventional high-dose radiotherapy or low-dose re-irradiation. The difference in local control was maintained over the 3 years of follow-up. The best results from additional hyperthermia were seen in the two trials where 90–100% of the patients were treated with re-irradiation. These two trials both showed a significant improvement in complete response rate, from 38% to 78% and from 29% to 57% [52]. Patients with glioblastoma multiforme were randomised to receive either interstitial hyperthermia or not in addition to a complex treatment schedule including surgery, external radiotherapy and brachytherapy. With hyperthermia, the median survival time was 85 weeks and the 2-year survival rate 31%, compared with 76 weeks and 15% in the control group [53]. Hyperthermia added to standard radiotherapy in irresectable tumours of bladder, cervix and rectum resulted in overall significantly better local control and survival rates. The effect of hyperthermia appeared especially worthwhile for patients with advanced cervix cancer, where the 3-year local control rate improved from 41% to 61%, and 3-year overall survival from 27% to 51% [54].

Besides the studies listed above, there are less well-known randomised trials, all showing an improvement in one or more end point (Tables 1 and 2) [55–72]. In 13 studies the improvement with hyperthermia of either response, complete response, palliative effect or overall survival was significant, while in six studies the differences were not significant. Significant improvements were seen for tumours of the rectum (three studies), bladder (two), cervix (two), lung (small cell cancer, one), vulva and vagina (one) and oesophagus (three). Significant improvements were seen when adding hyperthermia to radiotherapy in 13 out of 20 studies, to chemotherapy in three out of four studies, and to radiotherapy plus chemotherapy in two out of two studies.

**Table 1.** Summary of randomised trials showing significantly better results following a combination of radiotherapy (RT), chemotherapy (CT) or RT plus CT with hyperthermia (HT), compared with the same treatment without HT

Ref no.	Tumour	Treatment	Patients (lesions)	End point	Effect with HT	Effect without HT
[49, 50]	Lymphnodes of head and neck tumours	RT	41 [44]	CR rate	83%	41%
				5-year local control	69%	24%
				5-year survival	53%	0%
[51]	Melanoma	RT	70 (138)	CR rate	62%	35%
				2-year local control	46%	28%
[52]	Breast	RT	306	CR rate	59%	41%
[53]	Glioblastoma multiforme	Surgery, RT	68	Median survival	85 weeks	76 weeks
				2-year survival	31%	15%
[54]	Bladder, cervix and rectum	RT	298	CR rate	55%	39%
				3-year survival	30%	24%
[55]	Rectum	RT, surgery	115	5-year survival	36%	7%
[56]	Bladder	CT	52	pCR	66%	22%
[57]	Cervix	RT	64	CR	55%	31%
[58]	Various	RT	92	Response	82%	63%
[59]	Lung	CT	44	Response	68%	36%
[60]	Cervix	RT	40	CR	85%	50%
[61]	Rectum	RT	14	Response	100%	20%
[62]	Oesophagus	RT, CT	66	CR	25%	6%
[63]	Vulva/vagina	CT	65	Response	59%	19%
[64]	Bladder	RT, surgery	102	3-year survival	94%	67%
[65]	Oesophagus	RT, CT, surgery	53	Palliation	70%	8%
[66]	Oesophagus	RT	125	3-year survival	42%	24%
[67]	Rectum	RT, surgery	122	pCR	23%	5%

**Table 2.** Summary of randomised trials showing no significant differences between results from treatment with the combination of radiotherapy (RT), chemotherapy (CT), or RT plus CT with hyperthermia (HT), and those of the same treatment without HT

Ref no.	Tumour	Treatment	Patients (lesions)	End point	Effect with HT (%)	Effect without HT (%)
[46, 47]	Various	RT	145	CR	32	30
[48]	Various	RT	173	2-year survival	36	29
[68]	Head and neck	RT	65	CR	74	58
[69]	Various	RT	15 (30 matched lesions)	Better response	47	7
[35]	Breast	RT, surgery	507	5-year survival	73	67
[70]	Cervix	RT	50	18 months local control	70	50
[71]	Stomach	RT, surgery	193	5-year survival	51	45
[72]	Oesophagus	CT	40	pCR	41	19

## Toxicity

Normal tissue toxicity will result directly from hyperthermia when the tolerance limits are exceeded. Experimental studies have shown that most normal tissues are not damaged when the temperature over 1 h of treatment does not exceed 44°C

[6]. During local hyperthermia, it is not always possible to avoid higher temperatures due to the heterogeneity of the temperature distribution and the limited thermometry. The patient is not always able to feel painful hot spots, e.g. when the target area has been subject to surgery in the past and sensitivity is disturbed. The toxicity from superficial hyperthermia is

usually a skin burn (in ~25% of the patients with recurrent breast cancer [37, 52, 73], healing with conservative treatment). During hyperthermia for deep-seated tumours the skin is extensively cooled, through which the hot spots will develop in deeper tissues. A temperature that is too high in subcutaneous fat or muscle tissue results in a feeling of pressure, which is not always recognised by the patient. As a result of this patients may be reluctant to mention unpleasant sensations. Subcutaneous fat or muscle tissue burns do not usually cause much discomfort: the patient feels a subcutaneous lump, which is tender for a few days to a maximum of a few weeks and then disappears spontaneously. Subcutaneous fat burns were seen in 3–12% of the patients treated with deep hyperthermia. The risk of developing skin burns appears to be higher following treatment with a radiofrequency capacitive heating technique (5–16%) than with a radiative heating technique (0–3%) [54, 74–76]. The randomised studies did not show an increase in acute or late toxicity of radiotherapy. Whether the toxicity of chemotherapy is enhanced will depend on the temperature in the drug-sensitive tissues.

Toxicity from whole-body hyperthermia depends on, besides temperature, the patient's general condition, condition of organ systems and the physiological conditions during the treatment [25]. Serious toxicity from regional hyperthermic perfusion with modern technology and proper choice of perfusate composition, flow rate and pressure, blood gas values, drug doses, temperature dose and scheduling, is limited [77]. During any application of hyperthermia it is important to avoid pressure sites, since hypoxic normal tissues will be more sensitive to hyperthermia.

## Economic aspects

The application of hyperthermia is relatively labour intensive. Usually the duration of a treatment is 60 min or longer. With local hyperthermia, the energy distribution and the resulting temperature distribution can only partially be monitored with temperature sensors placed interstitially. During treatment the information given by the patient, especially on (painful) hot spots, is crucial in preventing the development of thermal burns. Clinical staff must remain continuously alert in interpreting both the measured temperature distribution and the symptoms mentioned by the patient, in order to adjust the applied energy distribution appropriately. Both whole-body and regional hyperthermia are also time-consuming procedures, requiring appropriate equipment and skilled personal. Nevertheless, thanks to the large therapeutic gain achieved the cost-effectiveness of hyperthermia appears acceptable. Within, for example, the Dutch randomised trial on intrapelvic tumours, the cost per life-year gained for cervical cancer was less than •4000 [78].

## Further developments

### Heating technique and thermometry

Research areas in the delivery of local hyperthermia include development of additional techniques for heating, to expand the tumour locations that can be treated adequately, and improvement of existing systems [79–81]. A new method for interstitial hyperthermia is to inject a fluid containing magnetic nanoparticles intratumourally, and then to apply alternating current magnetic fields [82]. Hyperthermia treatment planning systems have been developed [83, 84] and are now clinically verified [85]. Another important development is that of non-invasive thermometry, requiring large technical efforts in combining MRI systems with heating equipment, and programming for data analysis [86, 87]. These tools will contribute to an easier and better controlled application of hyperthermia, and will expand the tumour locations that can be treated adequately.

### Targeting drugs to tumours

The old idea of using temperature-sensitive liposomes containing cytotoxic drugs [88] recently regained interest. In pet animals with soft tissue sarcomas, intratumour liposome accumulation was two to 13 times higher with local hyperthermia than without hyperthermia [89]. In a mouse model, treatment with temperature-sensitive liposomes containing doxorubicin and local hyperthermia resulted in higher intratumour drug concentrations and an improved therapeutic efficacy compared with treatment with either free doxorubicin, or doxorubicin containing liposomes without hyperthermia. None of the treatment regimens caused any obvious signs of morbidity [90].

### Heat shock proteins

Heat shock proteins (HSPs) are synthesised in response to stress such as a hyperthermic treatment. After a non-lethal heat shock, HSPs were found to be expressed on the surface of malignant cells but not on normal cells. HSP-expressing cells are more susceptible to lysis by natural killer effector cells [91, 92]. HSPs are released following necrotic cell death, and released HSPs stimulate macrophages and dendritic cells to secrete cytokines, and activate antigen-presenting cells [93]. Tumour growth in a rat model was significantly inhibited following a pre-implantation heat treatment, while splenic lymphocytes displayed specific cytotoxicity against the implanted cells [94]. In a study comparing radiotherapy with radiotherapy plus hyperthermia in cervical cancer, the percentage of patients with continuing pelvic control developing metastatic disease was significantly lower in the combined treated group than in the radiotherapy-alone group, which may be explained by an effect of HSPs on tumour immunogenicity [78].

## Hyperthermia and gene therapy

Gene expression with a heat shock promoter can be elevated to adequate levels by hyperthermia treatment. The enhancement can be as great as many thousand-fold over background. Otherwise, gene-infected cells were found to be more sensitive to hyperthermia [95–97]. In a murine system, intratumourally injected viral gene therapy encoding for interleukin-12, controlled with a heat shock promoter and followed by hyperthermia was shown to be feasible and therapeutically effective, with no apparent systemic toxicity [98].

## Bone marrow purging

The clinical trial data concerning bone marrow purging for patients undergoing autologous bone marrow transplantation have as yet failed to show a survival benefit, which may be explained by the fact that purging techniques are still not good enough [99]. Murine and human leukemic bone marrow-derived stem cells have been shown to be much more sensitive than their normal counterparts [100–102]. The addition of drugs that protect the normal cells can enhance further the therapeutic index to values of  $>5000$  [103]. To date, purging by hyperthermia has not been tested clinically.

## Targeting tumour vasculature

Several drugs decrease tumour blood perfusion and thereby may secondarily induce tumour cell kill. Drugs like KB-R8498, flavone acetic acid, vinblastin and combretastatin have been studied in combination with hyperthermia. In the animal models investigated, all drugs induced a temporary reduction in tumour blood flow but generally, following a single application, had no effect on tumour growth. In combination with hyperthermia at 41.5–44°C, significant tumour responses were observed [104–107].

## Trimodality treatment

There is an increasing interest in the clinical application of trimodality treatment, in which radiotherapy, chemotherapy and hyperthermia are combined. Japanese colleagues were probably the first to test trimodality treatment in patients [108], and in the meantime have demonstrated the value of additional hyperthermia in patients with oesophageal cancer [62, 65]. More recent studies on preoperative treatment in rectal cancer, on head and neck tumours and recurrent breast cancer have made it clear that trimodality treatment is feasible and appears effective [109–113].

## Discussion and conclusions

The results from experimental studies indicate that hyperthermia is both the ideal complementary treatment to, and a strong sensitiser of, radiotherapy and many cytotoxic drugs. Results from clinical studies have confirmed the expectations

raised by the laboratory studies. In spite of the remarkable therapeutic gain that has now been demonstrated in patients, hyperthermia still is not widely recognised as a useful treatment. There are several reasons for this lack of acceptance.

First, many years have passed since the first anecdotal reports of results that were better than expected in patients, and the publication of positive results from randomised clinical trials. This can be explained by the limited availability of treatment techniques, which were being developed during the first clinical studies. The first randomised studies performed in the United States failed to show evidence of a beneficial effect from hyperthermia due to the use of inadequate treatment techniques. This initial result has had a strong negative impact on further interest for this treatment. Over the years, it has become clearer how important it is to use adequate heating equipment. In the study by Perez et al. [46, 47], for example, the more easily heated lesions ( $<3$  cm in diameter) did show a difference in complete response rate (52% compared with 39%), while the larger lesions did not (25% compared with 27%). A study on recurrent breast cancer showed that the complete response rate in tumours  $>3$  cm increased from 31% to 65% by using a better heating technique [37]. A further study [73] has shown that the energy distribution in the target area is an important prognostic factor for complete response.

Secondly, most of the positive randomised trials have been relatively small and/or were performed in Asia and Russia and have therefore received less attention than the North American studies. Altogether, however, both non-randomised and randomised clinical studies have shown how remarkable the improvement can be by adding hyperthermia to other treatment modalities. It is therefore peculiar that, in general, the oncology community still appears hesitant to start using it. The application of hyperthermia is mainly performed by a small group of dedicated institutes. What can the further obstacles be?

While hyperthermia requires investments in equipment and personnel training, the same is true for other types of cancer treatment, such as radiotherapy or bone marrow transplantation. In spite of the required investments, the economic evaluation of hyperthermia in cervical cancer has made clear that the cost-effectiveness can be within an acceptable range. Another obstacle for the acceptance of hyperthermia may be that it lacks public awareness [114]. Hyperthermia used as single modality resulted in an overall complete response of 13%. Hyperthermia added to radiotherapy or chemotherapy results in up to a doubling of complete response rate. In selected patient groups, a substantial gain in overall survival was found. If a drug were to achieve similar successes, its corporate sponsor would have announced it as a new breakthrough in cancer treatment, and it would have received extensive attention from the media. Hyperthermia equipment is manufactured by a few relatively small organisations that lack the finances for mass media promotion and support of clinical trials.

Hyperthermia is not yet a fully developed modality; there are still problems with its routine clinical application, and there is still room for further technological improvements. Most of the clinical studies are on its combination with radiotherapy. However, the experimental and the few clinical results with combined chemotherapy and hyperthermia make clear that this combination is also worth testing further. With the presently available equipment for local hyperthermia, only a limited number of tumour sites can be treated adequately. It may not seem a sensible approach to combine systemic chemotherapy with local hyperthermia, but for patients who are palliatively treated for a tumour in an accessible location, the addition of hyperthermia can be valuable. Whole-body hyperthermia can be applied only to patients in a good general condition, and when combined with drugs the first step must evidently be to demonstrate its safety, but patients in a good general condition do exist and there is room for improvement of the efficacy of chemotherapy. The more recent findings on hyperthermia used in drug targeting, gene therapy and stem cell purging, and on its effect on tumour immunogenicity or in combination with drugs targeting tumour vasculature, make it an even more interesting treatment modality. It would be to the benefit of present and future patients if more institutes would invest in hyperthermia equipment and personnel. All patients with a tumour for which a beneficial effect of hyperthermia has been clearly shown should have access to the treatment. Only when hyperthermia is available more widely can larger studies be performed to learn how to fully exploit its therapeutic effect.

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