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● *Hyperthermia Original Contribution*

RADIOTHERAPY WITH OR WITHOUT HYPERTHERMIA IN THE TREATMENT OF SUPERFICIAL LOCALIZED BREAST CANCER: RESULTS FROM FIVE RANDOMIZED CONTROLLED TRIALS

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Purpose: Claims for the value of hyperthermia as an adjunct to radiotherapy in the treatment of cancer have mostly been based on small Phase I or II trials. To test the benefit of this form of treatment, randomized Phase III trials were needed.

Methods and Materials: Five randomized trials addressing this question were started between 1988 and 1991. In these trials, patients were eligible if they had advanced primary or recurrent breast cancer, and local radiotherapy was indicated in preference to surgery. In addition, heating of the lesions and treatment with a prescribed (re)irradiation schedule had to be feasible and informed consent was obtained. The primary endpoint of all trials was local complete response. Slow recruitment led to a decision to collaborate and combine the trial results in one analysis, and report them simultaneously in one publication. Interim analyses were carried out and the trials were closed to recruitment when a previously agreed statistically significant difference in complete response rate was observed in the two larger trials.

Results: We report on pretreatment characteristics, the treatments received, the local response observed, duration of response, time to local failure, distant progression and survival, and treatment toxicity of the 306 patients randomized. The overall CR rate for RT alone was 41% and for the combined treatment arm was 59%, giving, after stratification by trial, an odds ratio of 2.3. Not all trials demonstrated an advantage for the combined treatment, although the 95% confidence intervals of the different trials all contain the pooled odds ratio. The greatest effect was observed in patients with recurrent lesions in previously irradiated areas, where further irradiation was limited to low doses.

Conclusion: The combined result of the five trials has demonstrated the efficacy of hyperthermia as an adjunct to radiotherapy for treatment of recurrent breast cancer. The implication of these encouraging results is that hyperthermia appears to have an important role in the clinical management of this disease, and there should be no doubt that further studies of the use of hyperthermia are warranted.

Breast cancer, Hyperthermia, Radiotherapy, Randomized trial.

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INTRODUCTION

Early clinical applications of hyperthermia (HT) include those of Coley (5) and Westermark (34), whereas the origins of the use of HT as a radiosensitizing agent are to be found in the early years of the present century (20, 26). Although there was periodic interest through the intervening years, progress in the clinical application of HT was largely frustrated by a lack of adequate techniques for heating tumors. Development of a biological rationale for the use of heat began during the 1960s and, in recent years, the considerable effort applied to the physics and engineering problems associated with clinical HT has led to the development of acceptable techniques for treatment of superficial tumors (10). Sufficient knowledge has also been gained about methods of applying HT, with respect to fractionation and combination with other modalities, to result in a safe and possibly effective clinical treatment.

As a consequence, a large number of clinical Phase I and II studies (11, 15, 24, 27, 32, 33) have been carried out and their results indicate that HT may be of value in cancer treatment when given as an adjunct to either radiotherapy (RT) or chemotherapy. A few randomized clinical trials have also been performed (9, 25, 31) but, in most of these, the numbers of patients recruited were too small or the lesions were not properly heated. It became clear that properly conducted prospectively randomized trials were needed to define the role of HT in cancer management. A trial in patients with malignant melanoma reported by Overgaard *et al.* in 1995 (21) was undertaken for the same reasons.

For patients with breast cancer, previous studies have indicated that local treatment does not affect survival in patients with recurrent disease, and that distant metastases will be detected ultimately in 75–93% of patients (1, 4, 28). The median survival time for these patients ranges from 12–53 months, depending on tumor characteristics, and 21–50% will survive 5 years or longer (4). Local recurrence causes pain, bleeding, and ulceration in over 60% of patients (3), in addition to the psychological distress of watching a tumor grow. For both nonirradiated and previously irradiated recurrences, durable local control decreases with increasing size of the lesion and, for the latter group of patients, the radiation dose that can be administered safely is lower than that considered effective. Chemotherapy is also less effective in areas that have previously been irradiated. Thus, the use of a local treatment that can provide durable local tumor control for the remaining lifespan of these patients would be considered worthwhile.

The optimum HT regimen with regard to temperature or number of treatments is not known. However, a small number of HT fractions may be as effective as a larger number because of the development of thermotolerance (14). The need to select appropriate patients and tumors and the importance of compliance with appropriate quality assurance guidelines when delivering HT treatment has been highlighted by the results of previous clinical trials, especially Perez *et al.* (25).

The key question addressed by the randomized trials reported here was whether or not the addition of HT treatment to RT increased the complete response (CR) rate in patients suffering from recurrent or inoperable primary breast cancer.

METHODS AND MATERIALS

Trial design

The five randomized trials, with individual patient data combined in this analysis, were each planned independently with their own design, sample size requirements and, in some cases, stopping rules. All trials examined the effect of the addition of HT treatment to RT for treatment of breast cancer and the primary endpoint of each of the five trials was the local tumor response. The trials were performed by four collaborating groups: the Dutch Hyperthermia Group at the Academic Medical Center in Amsterdam and the Daniel den Hoed Cancer Center in Rotterdam (trial DHG), the Medical Research Council (MRC) hyperthermia group at the Hammersmith Hospital, London, UK, (trials MRC BrI and MRC BrR), the European Society of Hyperthermic Oncology (ESHO), (trial ESHO), and the hyperthermia group at the Princess Margaret Hospital/Ontario Cancer Institute, Toronto, Canada (trial PMH). The groups in Rotterdam and London coordinated multicenter trials.

At the design stage of each trial, sample sizes were calculated on the basis of the anticipated CR rate to RT alone and the anticipated increased response rates, δ, for RT + HT together with test size $\alpha = 0.05$ and power $1\text{-}\beta = 0.8$ (18). The basis of these calculations is summarised for the individual trials in Table 1 together with the corresponding recruitment targets.

The decision to combine the information from the ESHO and two MRC trials was made in October 1990, because it had become clear that the accrual rate of the separate trials was too low to reach their individual design targets. In particular, without the prospect of combining the results, the MRC trials would have been closed to recruitment, leaving, at best, considerable uncertainty about the real effect of HT. Given the similarities in design of the ESHO and MRC trials, it was possible to plan to combine prospectively the analysis of these three trials without altering the design or data management procedures of the individual trials. The MRC trials had included a third group, within the same protocol, of patients with head and neck nodes, which recruited only 9 patients and which was closed at the time of the decision to combine with the ESHO group. These patients are not included in this report. Just prior to this stage, following an interim analysis and a review of more recent literature, the required number of patients was recalculated for the MRC trials, assuming a two-tailed test size and power, but an odds ratio (OR) for obtaining a local CR equal to 2, corresponding

Table 1. Anticipated complete response (CR) rates to radiotherapy (RT), anticipated benefit by the addition of hyperthermia (HT), planned trial size, date of opening, and final patient accrual

Trial	Anticipated CR %		Anticipated benefit δ (%)	Odds ratio	Total planned	Date trial opened	Final accrual	
	RT	RT + HT					RT	RT + HT
DHG	30	60	30*	3.5	80	May '88	19	19
MRC BrI / MRC BrR	45	55	10†	1.5	800‡	Jan '89	71	108
ESHO	20–60	40–80	20*	2.25	152	Oct '89	29	27
PMH	35–50	55–75	20†	2.5	234	July '91	16	17
Total					1266		135	171

* One-sided $\alpha = 0.05$.
† Two-sided $\alpha = 0.05$.
‡ Originally planned sample size 800 for all MRC trials combined, with a 60:40 randomization in favor of the HT arm.
Recalculation in September 1990 following an interim analysis based on the first 67 patients, assuming a larger treatment effect ($\delta = 17\%$), led to a reduced target recruitment of 280.

to a difference in CR rates of $\delta = 17\%$. This gave a revised target recruitment of 280 patients. After including the ESHO trial, this target was retained for the combined analysis. Subsequently, the opportunity arose to include the DHG and PMH trials within the collaboration in 1992, retaining the combined recruitment target of 280. For purposes of this report, the trials are ordered in the sequence of the dates that the trial was opened (Table 1).

Patient eligibility criteria

The common eligibility criteria of the five trials included measurable breast cancer lesions where local therapy was indicated and surgery was not feasible. In addition, treatment with a prescribed (re)irradiation schedule and HT according to the ESHO or Radiation Therapy Oncology Group (RTOG) guidelines (8, 12) were both feasible, and informed consent was obtained. In the MRC trials, patients were included if they were already on chemotherapeutic or hormone treatment, provided that their cancers were progressing locally. In the DHG, ESHO, and PMH trials, those on systemic chemotherapy were not eligible but patients already on hormonal treatment were, if their local disease had progressed and required local intervention.

Trial specific details are:

(a) DHG
Patients with breast cancer recurrences in previously irradiated areas, patients with recurrences in nonirradiated areas, for whom shortened fractionation schedules were considered appropriate in view of poor performance status or long traveling distances, and others with inoperable recurrences in previously nonirradiated areas who were considered fit for a high dose fractionated radiation schedule. After the ESHO trial had been opened, patients with recurrences in previously irradiated areas were entered into the ESHO trial.

(b) MRC BrI
Patients with primary advanced (T3 or T4) disease that was deemed inoperable (13).

(c) MRC BrR
Patients with recurrent disease, with or without previous irradiation.

(d) ESHO
Patients with recurrent disease within a previously irradiated area.

(e) PMH
Patients with postmastectomy recurrences with or without previous irradiation.

Thus, within the combined trials, three groups of patients can be distinguished. These are patients with untreated primary inoperable breast cancer, those with recurrent tumors in sites that had no previous irradiation, and those with recurrences in previously irradiated areas.

Disease assessment

Lesions were measured at entry to the trials and were classified as single or multiple, depending on whether or not there was more than one discrete area of tumor within the intended treatment area. The area of a single tumor was calculated as the product of the maximum diameter of the lesion and its perpendicular diameter. The area of multiple disease was the product of the maximum length and width of the area of disease to be treated. The depth was defined as the maximum tumor depth in the treatment area. The majority of these and subsequent measurements were verified independently by personnel other than the clinical coordinators.

The presence or history of metastatic disease at the time of randomization was also recorded, although PMH was the only trial to conduct comprehensive staging prior to entry.

Randomization

In all trials, randomization was conducted by telephone call to a central office. In the DHG trial, stratification was

by participating center, whether or not previous RT had been given, and the preferred RT schedule. The two MRC studies were randomized, 40% to radiation only and 60% to the combined treatment, to provide more information on thermal parameters, which will be reported elsewhere. In the other trials, 50% of patients were allocated to each treatment arm. In the ESHO trial, stratification was by participating center and the diameter of the lesions ($\leq$ or $>$ 3 cm). In the PMH trial, patients were stratified according to whether or not previous RT had been administered, area of disease ($\leq$ or $>$ 25 cm^2), and tumor depth ($\leq$ or $>$ 1 cm).

In the ESHO and DHG trials, multiple lesions of one patient could be separately randomized and evaluated. However, for the purposes of this report, only one lesion per patient, the first randomized, is included.

Radiotherapy and hyperthermia schedules

Radiation was applied using either high voltage photons or electrons through one or multiple ports. Within the DHG, MRC BrR, and PMH trial protocols, radical and palliative schedules of RT were defined. Radical treatments were used where tumors occurred in areas that had not received previous radiation therapy. Palliative treatment was used for recurrences in previously treated areas. Details of radiation doses used in each trial are given in Table 2; the doses administered were the same, regardless of the outcome of randomization.

To compare the various RT treatments given by the different groups, "effective doses" have been computed for each of the treatments, based on the linear quadratic formula with α/β taken as 10 and the correction for repopulation based on 0.5 Gy per day, for a fraction size of 2 Gy. These values have been converted to equivalent RT doses as given in 30 fractions over 6 weeks. The relationship between these doses is not very sensitive to the choice of value for α/β. The topic has been thoroughly reviewed by Steel (30).

Hyperthermia treatments were given in accordance with quality assurance guidelines drawn up under the auspices of ESHO (12) or, in the case of PMH, RTOG (8). For HT treatment to be administered, patients were positioned on a couch. Thermometry probes were inserted into catheters that had been introduced into the tumorous area under local anesthesia and, also, placed on the tumor surface and on normal skin. Hyperthermia was induced using various externally applied electromagnetic applicators, most of which operated at 434 MHz. Current sheet applicators were used at Hammersmith, and water-filled waveguides in Amsterdam, Rotterdam, and Latina, Italy. In addition, dielectrically loaded waveguide applicators were used in Utrecht (custom-built), Trento[1], Warsaw[1], Graz[1], Cambridge[1], and Saarbrucken[2]. Warsaw and PMH used commercial dielectrically loaded waveguide applicators[1], operating at 915 MHz. The only HT treatment given at Sheffield involved a custom-built mechanically scanned 2450 MHz air-filled waveguide. Except for this single treatment using the air-filled waveguide applicator, all treatments involved the use of a temperature-controlled water bolus that was either contained in a flexible bag or was an integral part of the applicator.

In the DHG, MRC, and ESHO trials, the aim of each HT treatment was to achieve a minimum temperature of 43°C at all sensors located within the tumor and to maintain this for a period of 60 min. The hyperthermal treatment was considered to commence either 10 min after the electromagnetic fields were applied or from the time at which all sensors within the tumor recorded at least 43°C (if this was less than 10 min), and to finish 60 min later. In the DHG trial, the total treatment time was 60 min. In the PMH trial, the intention was to reach a minimum temperature of 42.5°C at monitored locations in the tumor within 15 min and to maintain this for 30 min.

Three measures of the actual HT treatments delivered were calculated for the MRC and PMH trials, and the treatments conducted in Rotterdam for the ESHO and DHG trials. These were the lower 90th percentile of all intratumor temperatures recorded during a treatment (T_{90}), the 50th percentile of all intratumor temperatures recorded during a treatment (T_{50}), and the maximum intratumor temperature recorded during a treatment ($Tmax_{max}$). Temperatures were recorded every 20 s at all sensors during the duration of treatment. In contrast to the other trials, in which stationary multisensor temperature probes were used, the PMH trial employed a thermal mapping technique with generally two intratumoral sensors scanning 5 mm continuously, through target volume, plus six surface sensors.

Endpoints

Local response. Local response was assessed according to the WHO criteria of objective response in measurable disease (35). Complete response of the treated area required confirmation by a second consecutive observation at least 4 weeks after the first. Following this confirmation, the date of the CR was defined as the date of the first observation without evidence of tumor within the treatment area.

Patients who either received no treatment or who died before response could be evaluated were classified as treatment failures (no CR). Death without a previously confirmed CR counted as a failure. Patients who achieved local complete regression only after the addition of a (new) systemic therapy were also classified as failures.

Progressive disease was defined as a 25% increase in the size of measured lesions, or the appearance of new lesions within the treated area. Local progression was also deemed to have occurred if additional local treatment had

[1]BSD Corporation

[2]Lund Science, Buchler

Table 2. Treatment schedules and effective radiation doses for (re)irradiation plus hyperthermia in the 5 trials

	DHG		MRC BrR	MRC BrI, MRC BrR	ESHO	PMH	
	(Palliative)	(Radical)	(Palliative)	(Radical)		(Palliative)	(Radical)
Radiotherapy							
total dose (Gy)	32	40.5–50	28.8	50	32	32	50
fraction size (Gy)	4	2–3	3.6	2	4	1.8	2
overall time (weeks)	4	3–5	2	5	4	3.5	5
boost (Gy)	–	10–20 in 5–10 fractions	–	15 in 5 fractions	–	–	10 in 5 fractions
Effective radiation dose* (Gy)	44.8	60.5–69.3	47.2	66.3	44.8	39.8	60.0
Hyperthermia							
technique (MHz)	434	434	434	434, 2450	100–1000	915	915
allowed depth (cm)	≤4	≤4	≤4	≤4	≤4	≤2.5	≤2.5
maximum number of applicators used simultaneously	1–5	1–5	1–4	1–4	1–5	1	1
margin around macroscopic tumour	≥3 cm	≥3 cm	50% SAR† at 10 mm depth	50% SAR at 10 mm depth	50% SAR at 5 mm depth	70% SAR at 10 mm depth‡	70% SAR at 10 mm depth‡
HT–HT interval (days)	≥3	≥3	7	7	≥3	14	21
Number of treatments, including boost	4–8	4–8	3	6	4–8	2	2
Duration per treatment (min)	60	60	(10) + 60	(10) + 60	(10) + 60	(15) + 30	(15) + 30
Target temperature °C	43	43	43	43	43	42.5	42.5
RT–HT interval (min)	30–60	30–60	≥90	≥90	30–60	<30	<30

* Relative to 60 Gy given in 30 fractions in 6 weeks.
† Specific absorption rate.
‡ Determined by thermographic image.

been given, whether or not a CR had previously been obtained.

Time to local failure and distant progression. For patients not reaching a CR, the time to local failure was set at zero, even if the patient initially showed a partial response or stable disease. For patients with a CR, time to local failure was the time to local progression from the date of randomization. Patients dying in local CR, or in continuing local CR at last follow-up, were censored at the date of death or last follow-up.

The time to development of distant metastatic disease was recorded.

Survival. Overall survival was calculated from the date of randomization to death or was censored at the date last known to be alive.

Side effects. Acute and late toxicities for both RT and HT treatments were documented. Tolerance and patient acceptability of the treatments were also recorded for the MRC trials by means of a self-reported questionnaire completed by the patients. A quality of life study was also conducted at PMH.

Data management. A common data set was defined for the combined interim and final analyses, although this underwent some revision toward the end of the trials. These data were abstracted from the data files of the individual trials. All data were sent to Rotterdam, the statistical center for the ESHO and DHG trials, for merging and analysis. Data management of the DHG and ESHO trials used dBase III plus. COMPACT was used for data management of the MRC trials (6). For the PMH trial, the SAS database package was used. For analysis of the data, the statistical package STATA (29) was used. In COMPACT, a module was developed to export data into STATA format.

Interim analysis and data monitoring. After the decision to combine the trials had been made, with a combined recruitment target of 280 patients, subsequent interim analyses were planned once a year, with emphasis on the monitoring of the trials, in particular, the accrual. A formal stopping rule based on the interim results of the combined data was not defined, because this could interfere with the design objectives of the individual trials. However, the following pragmatic guideline based on the intention to treat principle was adopted (17):

"At interim analyses tests of differences would be performed for each trial on an annual basis. The results would not be disclosed to participants unless both the ESHO trial and the MRC BrR trial showed a statistically significant difference (two-sided test) in the CR rate between treatments with $p < 0.05$ and the combined analysis of all trials would be statistically significant with $p < 0.001$."

On this basis, the decision to stop or continue each trial was left to the specific coordinating committee.

Statistical analysis. Logistic regression stratified by trial was used for the evaluation of the differences between treatments in CR rate and for the calculation of ORs and associated 95% confidence intervals (CI), an OR < 1 in-

dicating a benefit of the addition of HT (2, page 269). The sizes of the boxes in Fig. 1 are proportional to the standard error of log OR, and give an indication of the relative precision of the estimate of the OR for each trial. Time to local failure and survival were analysed using Kaplan–Meier curves, the logrank test and the Cox proportional hazards model. For these analyses, the relative efficacy of the two treatments was assessed by the hazard ratio (HR) and the associated 95% CIs, a HR < 1 indicating a benefit from the addition of HT (22).

RESULTS

There were 317 lesions randomized in 307 patients. Of these, one patient was excluded because she had microscopic nonmeasurable disease and, therefore, had been randomized in error. She was treated with RT only, according to randomization, and maintained local control to the time of this analysis 5 years later. Ten secondary lesions are not included in the analysis. Eight of these were from patients with multiple lesions that were separately randomized at entry to the trials, and two were MRC BrR patients who had previously been entered into MRC BrI. Of these 10 lesions, 7 were randomized to combined therapy, of which 3 achieved CR and, of these, none relapsed locally. Two patients were still alive after 3 years. Of the 3 randomized to RT only, none achieved CR.

The remainder of this report refers to the remaining 306 lesions in 306 patients.

Following interim analyses in 1991 and 1992, the third interim analysis, carried out in July 1993, fulfilled the criteria for disclosure and, at the same time, recruitment had reached 269 patients, nearing the target number of 280. At a meeting of all the participants concerned, it was decided to continue accrual until the end of 1993, and then close the trials.

The final analysis was conducted in June 1994, ensuring a minimum follow-up of 5 months for all patients.

Patient characteristics

The pretreatment characteristics including age, disease status, previous irradiation, systemic therapy prior to randomization, presence or history of distant metastases, location, size and extent of the lesions of the 306 patients recruited are summarized in Table 3. There are some clear differences between trials that reflect the different eligibility criteria within the respective protocols. For example, patients with chest wall and multiple lesions are included in all trials except MRC BrI, and nodal disease was treated in all except the MRC trials.

In 152 patients (50%), there was no evidence or history of distant disease but, as already indicated, comprehensive staging prior to randomization was only carried out for the PMH patients. Two hundred and sixteen (71%) lesions were on the chest wall and 79 (26%) in breast tissue. One hundred and fifty-nine (52%) patients had single lesions. One patient in the MRC BrR trial was male and received RT only.

In the combined treatment arm, there was a higher proportion of patients who had received chemotherapy prior to randomization and the median lesion size was greater. There appears to be no obvious explanation other than

Trial	No of CRs/No randomised RT	RT+HT	OR	95% CI
DHG	14/19	14/19	1.0	0.2 - 4.2
MRC BrI	8/12	10/18	0.6	0.1 - 2.9
MRC BrR	17/59	51/90	3.2	1.6 - 6.5
ESHO	11/29	21/27	5.7	1.8 - 19.0
PMH	5/16	5/17	0.9	0.2 - 4.0
ALL	55/135	101/171	2.3*	1.4 - 3.8

* obtained after stratification by trial

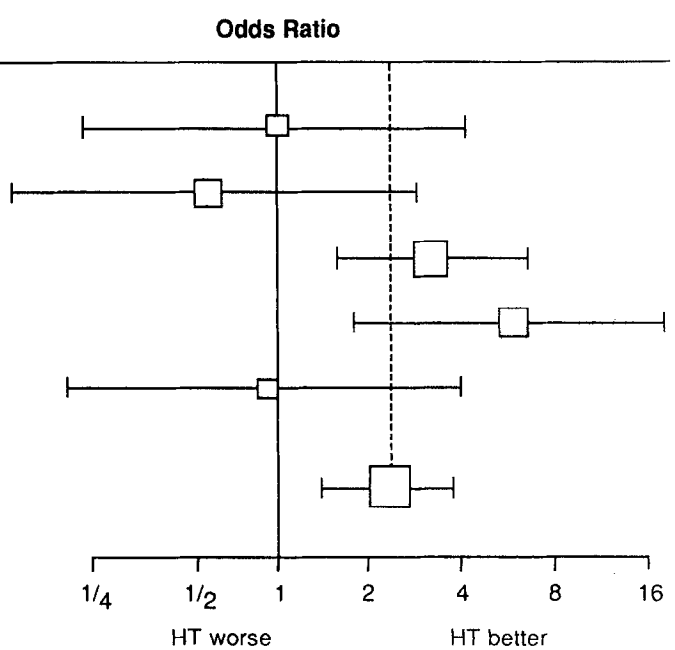

Fig. 1. The OR for a CR by trial, with associated 95% confidence intervals.

Table 3. Patient and tumor characteristics on admission to each trial

	DHG		MRC BrI		MRC BrR		ESHO		PMH		TOTAL	
	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT
Total	19	19	12	18	59	90	29	27	16	17	135	171
Age (years)												
Mean (SD)	60 (16)	58 (13)	67 (11)	70 (13)	61 (14)	60 (13)	61 (10)	59 (12)	56 (11)	59 (13)	61 (13)	61 (13)
Location of lesion												
breast	2	1	12	18	17	25	2	1	1	–	34	45
chest wall	12	15	–	–	42	65	27	24	15	16	96	120
lymph node	5	3	–	–	–	–	–	2	–	1	5	6
Number of lesions												
single	6	7	12	18	34	48	14	10	5	5	71	88
multiple	13	12	–	–	24	42	15	17	11	12	63	83
unclear	–	–	–	–	1	–	–	–	–	–	1	–
Area (cm^2)												
Median (Range)	36 (0.3–143)	39 (4–270)	20 (9–56)	33 (8–140)	40 (1.5–460)	69 (4–400)	29 (1–400)	60 (2–357)	32 (1.5–360)	69 (0.5–288)	33 (0.3–460)	56 (0.5–400)
Depth (cm)												
Median (Range)	2 (0.5–6)	2 (1–6)	3 (2–3)	3 (2–4)	2 (0.5–4)	2 (0.5–5)	1 (0.5–8)	1 (0.5–4)	1 (0.1–2)	0.4 (0.1–3)	2 (0.1–8)	2 (0.1–6)
Presence or history of metastatic disease at randomization												
no	12	11	5	10	22	41	19	15	7	10	65	87
yes	7	8	7	8	35	48	10	12	9	7	68	83
not known	–	–	–	–	2	1	–	–	–	–	2	1
Primary/recurrent disease status												
primary	–	–	12	18	–	–	–	–	–	–	12	18
rec no RT	16	15	–	–	11	11	–	–	6	7	33	33
rec with RT	3	4	–	–	48	79	29	27	10	10	90	120
Previous systemic treatment												
no	8	7	8	15	13	8	9	5	1	1	39	36
hormones	5	5	–	–	22	30	6	8	4	8	36	51
chemotherapy	2	3	3	3	3	12	3	4	–	3	10	25
both	4	4	1	–	20	39	11	10	11	5	47	58
not known	–	–	–	–	1	1	–	–	–	–	1	1
Current systemic treatment												
no	16	15	3	2	18	40	19	21	8	12	64	90
hormones	3	4	9	16	37	48	9	6	8	5	64	78
chemotherapy	–	–	–	–	3	1	1	–	–	–	4	1
not known	–	–	–	–	1	1	–	–	–	–	1	1

chance for these imbalances, but they are adjusted for in the analysis presented below.

Treatment received

Ninety-five percent of patients received the treatment to which they were randomized. Details of the treatments administered are summarized in Tables 4 and 5.

There were 11 patients (5 randomized to RT and 6 to RT + HT) who received no treatment because of disease progression. One patient allocated to RT only refused treatment and one allocated to RT only received combined treatment (five sessions of HT). The majority of patients received palliative doses of RT because they had been previously radically irradiated, although the ESHO trial was the only one in which all patients had been previously irradiated.

Although the intention in all HT treatments was to raise intratumor temperatures to a minimum of 43°C (42.5°C in the case of PMH), this target was not achieved in the majority of treatments. The results of an analysis of the actual temperatures achieved, in terms of three thermal parameters previously shown to be reasonable descriptors of HT treatment (7), are given in Table 5. In general, the duration of treatments actually delivered was similar to that intended (see Table 2).

Local response

The number of patients and CRs by trial and treatment group are given in Table 6, together with the median time to CR and details of disease progression and survival.

Fifty-five of the 135 patients randomized to RT alone (41%) and 101 of the 171 of the patients randomized to RT + HT (59%) had a CR. This difference, following logistic regression analysis stratified by trial, is statistically significant with $p < 0.001$, and translates into an $OR_{Stratified} = 2.3$ (95% CI 1.4 to 3.8). However, as is shown in Table 6, there is considerable variation in the CR rates, and the corresponding ORs, observed in the five trials. As we have already indicated, the two largest studies (ESHO and MRC BrR) both show a statistically significant (p = 0.004 and 0.001, respectively) advantage for the addition of HT, whereas the other three trials do not show a benefit (ORs < 1). Such variation in the ORs may be explained by the small patient numbers in these trials, because a formal test for interaction indicates that there is not a statistically significant difference in HT effect among the 5 trials ($p = 0.14$). Even though the individual trial results differ, they are not inconsistent with an advantage for HT, as is indicated by Fig. 1.

Univariate analysis of the effect of baseline characteristics on the CR rate showed that it depended strongly on the size of the tumor (CR rate 70% for lesions with area < 16 cm^2 compared to 45% for lesions with area ≥ 16 cm^2), the depth of the lesion (CR rate 60% for lesions with a depth < 3 cm, vs. 38% for lesions with depth ≥ 3 cm), and on a history or presence of metastatic disease outside the treatment area (CR rate 39% vs. 63%). This last effect is caused by the higher death rate of patients with a history of metastatic disease. These patients had a higher risk of dying from progression elsewhere, and the tumor in the treated area had not yet had the time to disappear completely. In the multiple logistic regression analysis, stratified by trial and adjusted for the baseline characteristics that were individually prognostic for CR (maximum diameter, area of lesions, and systemic disease), the benefit of the addition of HT to RT was con-

Table 4. Summary of radiotherapy treatment received in each trial

	DHG	MRC BrI	MRC BrR	ESHO	PMH	Total
Total	38	30	149	56	33	306
Treatment deviations						
Allocated RT						
No treatment	–	–	4	1	–	5
RT + HT	–	–	1	–	–	1
Allocated RT + HT						
No treatment	1	1	3	1	–	6
Radiotherapy, total dose (Gy) (actual)						
No RT	1	1	7	2	–	11
<28	1	1	9	2	1	14
28–32	11	–	105	52	19	187
33–40	–	2	14	–	–	16
41–50	1	3	6	–	–	10
51–60	6	9	6	–	13	34
61–70	18	14	2	–	–	34
Dose in relation to previous RT:Mean (SD)						
primary	–	58 (12)	–	–		58 (12)
recurrent no RT	59 (15)	–	47 (12)	–	58 (8)	55 (14)
recurrent RT	31 (3)	–	29 (2)	31 (3)	33 (8)	30 (4)

Table 5. Summary of hyperthermia treatment received in each trial

	DHG	MRC BrI	MRC BrR	ESHO	PMH	Total
Hyperthermia, (number of treatments)						
0	1	1	3	1	–	6
1	–	–	2	–	–	2
2	–	–	5	–	17	22
3	1	1	73	1	–	76
4	1	4	4	–	–	9
5	9	1	3*	5	–	18
6	1	11	–	1	–	13
8	6	–	–	19	–	25
Thermal parameters, median (range)	†			†		
T_{90} (°C)	39.0 (35.7–41.1)	40.4 (37.6–42.7)	40.7 (34.6–43.3)	39.5 (37.6–41.5)	40.7 (39.5–43.0)	
T_{50} (°C)	40.7 (39.3–42.2)	42.3 (39.2–44.4)	42.5 (40.2–44.7)	41.1 (38.5–42.9)	42.2 (41.0–43.6)	
$Tmax_{max}$ (°C)	43.5 (41.9–50.7)	45.1 (41.0–47.5)	45.6 (42.0–49.1)	43.3 (39.8–44.7)	44.6 (43.4–46.5)	
Duration of each treatment (min), median (range)	60 (55–61)	60 (30–60)	60 (17–65)	60 (60–60)	28 (22–36)	
No of intra-tumor sensors, median (range)	7 (4–13)	10 (4–20)	10 (3–36)	6 (0–11)	28 (7–52)‡	

* In addition, one patient allocated RT received RT plus 5 HT treatments.
† Thermal parameters for Rotterdam patients only.
‡ Thermal mapping.

firmed and enhanced, $OR_{Adjusted} = 3.0$, 95% CI 1.7 to 5.1 ($p = 0.0001$).

Primary lesions, or recurrent lesions in an area not previously irradiated, had a higher CR rate (61%) than recurrent lesions in a previously irradiated area (46%). Lesions in an area exposed to previous radiation received palliative doses of radiation around 28 Gy, and most of the lesions (80%) in areas without previous radiation received radical treatment with doses over 40 Gy.

Even though the differences in treatment effects between the studies are not inconsistent with an overall benefit of HT, as measured by a combined OR, the differences could be caused by clinically relevant differences in patient characteristics and, associated with this, in radiation

Table 6. Percentage of CR, median time to CR, disease progression, and survival, by trial and treatment

	DHG		MRC BrI		MRC BrR		ESHO		PMH		TOTAL	
	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT	RT	RT+HT
Total	19	19	12	18	59	90	29	27	16	17	135	171
CR	14	14	8	10	17	51	11	21	5	5	55	101
%	74	74	67	56	29	57	38	78	31	29	41	59
Difference	0		−11		28		40		−2		18	
OR	1.00		0.65		3.23		5.73		0.92		2.30*	
Median time to CR (days)	105	77	399	149	84	77	90	70	127	91	101	81
Local recurrence after CR	6	3	–	1	6	3	4	8	1	2	17	17
Progression elsewhere	9	11	2	3	12	42	7	18	1	1	31	75
Dead	2	6	2	4	9	36	3	6	–	–	16	52
No CR	5	5	4	8	42	39	18	8	11	12	80	70
Progression elsewhere	5	3	4	5	33	31	14	5	10	11	66	55
Dead	4	3	4	5	35	36	9	4	6	6	58	54
All Patients, % Actuarial survival at 2 year (SE)	65 (12)	62 (13)	48 (15)	44 (12)	32 (6)	21 (5)	42 (11)	68 (10)	46 (17)	59 (13)	41 (5)	36 (4)

* Estimated using logistic regression stratified by trial.

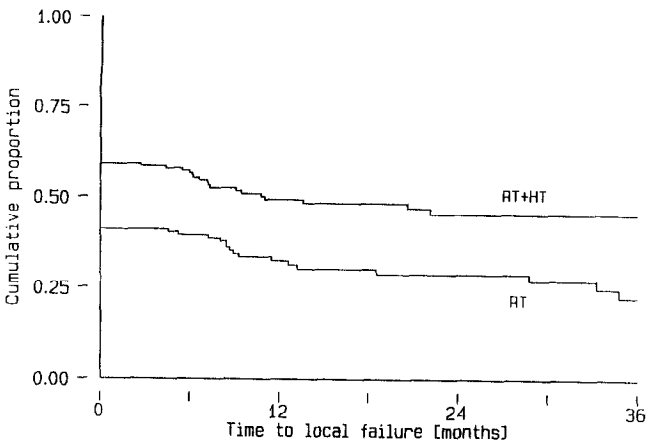

Fig. 2. Local failure-free curves by arm; pooled

treatment characteristics between the studies. Therefore, interactions between the HT treatment effect and the above-mentioned prognostic factors were studied. No significant difference in treatment effect between small lesions (<16 cm^2) and large lesions (≥16 cm^2) was found ($p = 0.41$). The HT effect was somewhat less with deeper tumors, but this was far from statistically significant ($p = 0.21$). Also, the presence or a history of metastatic disease was not related to the HT effect ($p = 0.70$). There was, however, a clear interaction between palliative and radical RT in terms of HT effect ($p < 0.01$). In the group of patients with lesions in areas not previously irradiated, generally treated with radical RT, no difference in CR rate was found between those in the RT arm ($n = 45$, CR = 60%) and those in the combined treatment arm ($n = 51$, CR = 63%), with an OR = 1.24 (95% CI 0.46, 3.32). In the group of patients with lesions in previously irradiated areas, treated with palliative RT doses, the CR rate in the combined treatment arm was much higher ($n = 120$, CR = 57%) than in the RT only arm ($n = 90$, CR = 31%). The corresponding OR in this subgroup is 4.7 (95% CI 2.4–9.5).

The median time to response was shorter by approximately 3 weeks for patients subjected to the combined treatment, as opposed to RT alone, (Table 6), although the magnitude of this difference varied from trial to trial.

Duration of response

All patients who did not reach a CR were considered to be local failures. Of the patients who achieved a CR, 17% of those receiving RT + HT, and 31% of the RT only patients had a local relapse during follow-up. Figure 2 shows the actuarial local relapse-free survival for the two treatment arms pooled over the trials. Patients who did not reach a CR were considered failures on the day of randomization. After that day, failures are patients with local relapse. Patients who did not relapse were censored either at death or at the time of last follow-up, as appropriate. These curves show that the advantage of HT is maintained during follow-up. A Cox regression analysis gave a HR, for RT + HT compared to RT alone, of 0.67 ($p = 0.007$, 95% CI 0.5–0.89).

Distant progression and survival

About 50% of the patients already had a history of metastatic disease or active disease outside the treatment area at the time of randomization (Table 3). The majority of the patients (227 of 306 or 74%) showed progression outside the treatment area during follow-up (Table 6). This had a major impact on survival and explains why the higher local CR rate with HT is not reflected in a survival advantage. Only 4 of the CR patients died without evidence of progressive disease elsewhere, 2 of them in continuous local CR and 2 after a local relapse. Of the CR patients, 64 died with distant progressive disease, 56 of them still in local CR. Of the patients who did not reach a CR, 112 have died, almost all of them (91%) with progressive disease outside the treatment area.

The survival experience is summarised in Fig. 3 and Table 6, indicating a median survival of approximately 18 months irrespective of treatment received. The 2-year actuarial survival rate for all patients was approximately 40%. Between-trial differences reflect the respective protocol eligibility requirements, as well as differing disease status at entry; for example, the MRC BrR trial contains a high proportion of patients with metastatic disease or a history of metastatic disease at randomization.

Side effects and toxicity

Overall, both treatments were well-tolerated, with no patients refusing to complete the prescribed radiation, but a small number of patients had their HT treatments terminated early because of pain. In addition, two patients had HT halted because of the discovery of pleural effusions that made it impossible for them to lie flat.

Because of the different scales used, a detailed comparative analysis of the degrees of toxicity experienced across all trials is not possible, but the common acute and

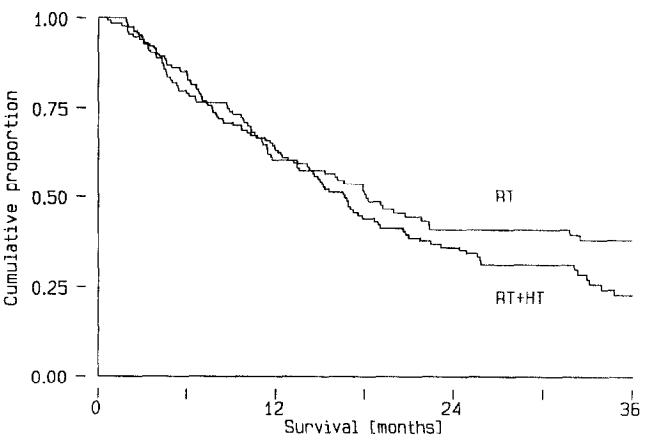

Fig. 3. Overall survival by arm; pooled

late side effects of therapy are summarized in Table 7 by treatments received, for those patients for whom this information is available.

In terms of acute reactions, there is little difference in erythema and desquamation between treatments but, as expected, more blistering occurred with the addition of HT (11%) as compared to RT alone (2%). This excess is noted in all trials except MRC BrI, where no blistering occurred in either treatment arm. Similarly, acute effects of HT were 7% ulceration and 7% necrosis in the combined arm, compared with 2% and 1%, respectively in the RT-only arm. These were greatest in the MRC BrR trial, where 10% of patients receiving HT suffered some early necrosis. In general, the acute effects of HT treatment tended to occur in areas of reduced sensitivity and healed with conservative treatment, with little impact on patient well-being.

Severe late reactions occurred: 1 each of bone necrosis, bone fracture, and brachial plexus lesion, all in the combined arm of the ESHO trial. The late effects of pigmentation, telangiectasia, and fibrosis show very little variation between treatments.

Thus, HT, as delivered in these trials, was well tolerated and did not significantly add to either the clinically relevant acute or long-term toxicity over irradiation alone, even in those patients who had received prior radical RT.

DISCUSSION

The trials presented in this paper result from a multicenter international collaboration, and the analysis has demonstrated a statistically significant benefit from the use of HT, in addition to radiation, in superficial breast cancer.

In view of the need for quality assurance for HT treatment highlighted in previous trials (23), an effort was made to ensure that only tumors that could be heated satisfactorily would be entered into the trials. For this reason, quality assurance guidelines based on general experience

Table 7. Summary of recorded treatment-related toxicity by trial and treatment

	DHG		MRC BrI		MRC BrR		ESHO		PMH		TOTAL	
	RT	RT + HT	RT	RT + HT	RT	RT + HT	RT	RT + HT	RT	RT + HT	RT	RT + HT
Erythema (mild/mod)												
No	11	9	7	11	21	46	11	10	7	5	57	81
Yes	2	7	5	6	33	42	16	15	9	12	65	82
											53%	50%
Erythema (severe/desquamation)												
No	5	8	12	15	48	77	18	17	10	9	93	126
Yes	8	8	0	2	6	11	9	8	6	8	29	37
											24%	23%
Blister												
No	13	15	12	17	53	82	27	20	15	13	120	147
Yes	0	3	0	0	1	6	0	6	1	4	2	19
											2%	11%
Ulceration												
No	13	16	12	16	52	85	27	22	16	16	119	155
Yes	0	2	0	1	2	3	0	4	0	1	3	11
											2%	7%
Necrosis												
No	13	17	12	16	53	78	27	26	16	17	121	154
Yes	0	1	0	1	1	10	0	0	0	0	1	12
											1%	7%
Fibrosis												
No	6*	5*	4	7	24*	24*	3*	9*	9	10	46	55
Yes	4	4	8	10	14	35	4	3	7	7	37	59
											45%	52%
Telangiectasia												
No	8*	9*	8	10	27*	39*	6*	10*	–	–	49	68
Yes	2	0	4	7	11	20	1	2	–	–	18	29
											27%	30%
Pigmentation												
No	4*	3*	9	14	22*	29*	1*	4*	11	12	47	62
Yes	6	6	3	3	16	30	6	8	5	5	36	52
											43%	46%

* Confined to patients with at least 1 year of follow-up.
– Not recorded.

and consensus within the HT communities in Europe and North America (8, 12) were adopted. In addition, quality assurance programs in some institutes were assessed during site visits carried out under the auspices of ESHO (16).

Superficial breast cancer was chosen for the trials because, even within the limitations of available HT equipment, it was felt by the individual trial groups that it was feasible to heat the relatively shallow lesions adequately and to obtain satisfactory measurements of the temperature distribution at several locations within the treated field.

The combined therapy was well tolerated and did not result in major toxicity. There were, however, differences in outcome between the individual trials with two, MRC BrR and ESHO, illustrating an advantage for HT. In the DHG trial, there was no apparent difference between the treatments and MRC BrI and PMH indicated a small advantage for RT alone. Note, however, that all of the 95% CIs for the odds ratios (OR) from the five trials are not inconsistent with a substantial benefit from HT (Fig. 1).

Overall survival did not differ markedly between the two treatment arms, although the pooled data suggest that the group receiving additional HT has a marginally inferior survival, as shown in Fig. 2. This may be caused by lesion size, which has been shown to be of prognostic value for overall survival (4), and was larger in the combined treatment arm.

We have shown that size and depth of lesions, distant metastatic disease, and RT dose are important factors that affect CR rate. The patients in these trials are heterogeneous in these respects and this accounts, in part, for the variable CR rates between the trials. However, following adjustment for these factors, there remains a statistically significant difference in CR rate in favor of HT. The numbers of patients in the individual trials are small and any inferences drawn from the inter-trial differences may, as a consequence, be unreliable. Nevertheless, these differences do raise some interesting questions with regard to the possible differences in efficacy of varying RT and HT regimens, which are testable hypotheses for future trials.

There are differences within the five trials that may be important. All the MRC BrI patients, approximately two thirds of the DHG patients, and a smaller proportion in the MRC BrR and PMH trials, received radical RT. The MRC BrI patients had primary breast cancer that was deemed inoperable because of disease extent, and these lesions were probably more difficult to heat adequately. The depths of these tumors were estimated clinically and it is possible that this may have been underestimated. These patients, therefore, may not have complied with the guidelines for HT. The lesion sizes of the DHG patients were smaller, and we would expect all such patients to achieve a higher CR rate. The treatments delivered also varied between trials. Estimates of the equivalent radiation doses showed considerable differences between the palliative schedules, although the radical doses were less variable. Bedwinek *et al.* (3) have defined 'adequate' RT doses for recurrent tumors of different sizes and depths. However, tumors in previously irradiated areas cannot be adequately treated by RT alone because of the effect on normal tissues, and because the hypoxia induced by previous RT renders the tumor less sensitive to the effects of radiation. We believe that it is important to give the maximum tolerated dose of radiation, even in those patients who have received previous radiation, to achieve the highest possible CR rates. There was significant variation in the prescription of heat treatments in the different trials, hence, making the establishment of a heat-response relationship difficult. It would appear, however, that the PMH trial had the lowest number and duration of heat treatments, with the lowest CR rate achieved for the combined treatment arm. A number of possibilities may account for this outcome, such as the small number of patients, variation in clinical characteristics, and low RT dose, but the possibility that this may have been influenced by the heat treatments cannot be excluded.

The combined results reported here have, we suggest, confirmed the view that the role of HT in the treatment of breast cancer is as an adjunct to a palliative dose of RT in patients with tumor recurrence following a radical course of treatment.

These trials do not establish the beneficial use of HT for patients who are able to receive a full dose of radiation, but the numbers of patients treated radically in these trials is small and the apparent lack of success with the addition of HT may be explicable by other factors, as already discussed. Biologically, there is no reason why HT should not be of benefit in the radical situation, and future trials should look at these patients in greater numbers.

The randomized trial reported by Overgaard *et al.* (21) in patients with recurrent or metastatic malignant melanoma treated by RT with or without HT, has shown CR rates of 46% for the combined arm and 28% for the radiation-only arm, which are similar to our own. This was a small trial based on only 71 patients with 134 lesions, and the form of analysis used leads to some doubt as to how reliable these estimates of CR really are (19). However, both this trial and our own, with the CR rate at 2 years of 59% for irradiation plus HT vs. 41% for irradiation alone, is in keeping with other Phase III randomized trials. Following the results of our trials, we could recommend the consideration of HT for patients with recurrent breast cancer to be retreated with irradiation. We hope that these results will encourage the use of HT in clinical practice and, also, further study into its use in other tumor types, as well as the best scheduling of HT and radiation. Further research is also required to assess the benefit of HT on those patients for whom radical radiation is planned.

We would emphasize that, without the international collaboration, each of these five trials would have been too small to contribute meaningful data on the role of HT in superficial breast cancer. This must have important implications for the planning of future trials.

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