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RELATIONSHIP BETWEEN THERMAL DOSE AND OUTCOME IN THERMORADIOTHERAPY TREATMENTS FOR SUPERFICIAL RECURRENCES OF BREAST CANCER: DATA FROM A PHASE III TRIAL

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Purpose: The objective of this study was to determine whether the thermal dose delivered during hyperthermia treatments and other thermal factors correlate with outcome after combined radiation and hyperthermia of breast carcinoma recurrences. Data were from the combined hyperthermia and radiation treatment arms of four Phase III trials, which when pooled together, demonstrated a positive effect of hyperthermia.

Methods and Materials: Four Phase III trials addressing the question of whether hyperthermia could improve the local response of superficial recurrent breast cancer to radiation therapy were combined into a single analysis. Thermal dosimetry data were collected from 120 of the 148 breast cancer recurrence patients who received hyperthermia. The data were analyzed for correlations between thermal parameters as well as important clinical parameters and outcome (complete response rate, local disease free survival, time to local failure, and overall survival).

Results: Five thermal parameters were tested, all associated with the low regions of the measured temperature distributions. Max(TDmin) and Sum(TDmin) were associated with complete response where TDmin is the minimum thermal dose measured by any of the tumor temperature sensors during a treatment: Max(TDmin) is the maximum of TDmin over a series of treatments. Using a categorical relationship with a cutoff of 10 min for Sum(TDmin), the complete response rate was 77% for Sum(TDmin) >10 min and 43% for Sum(TDmin) ≤10 min ($p = 0.022$, adjusted for study center and significant clinical factors). The overall complete response rate for hyperthermia and radiation was 61% compared to 41% for radiation alone. Either Max(TDmin) or Sum(TDmin) were also associated with local disease free survival, time to local failure and overall survival.

Conclusions: An earlier report of this trial demonstrated a significant benefit when hyperthermia was added to radiation in the treatment of breast cancer recurrences. The analysis of thermal factors demonstrates that parameters representative of the low end of the measured temperature distributions are associated with initial complete response rate, local disease-free survival, time to local failure and overall survival. © 1997 Elsevier Science Inc.

Hyperthermia, Randomized trial, Thermal dose, Outcome, Breast cancer, Recurrence.

INTRODUCTION

We recently reported that hyperthermia is an effective adjunct to radiation in the treatment of chest wall recurrences of breast carcinoma (11). This result is consistent with that of a recent trial of the effect of hyperthermia on the response of malignant melanoma (19) and neck node metastases from head and neck cancer (27). However, other studies have shown no benefit in the addition of hyperthermia to radiation either for the treatment of chest wall recurrences of breast cancer using external heating (22,23), or for interstitial heating of miscellaneous tumors (9).

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Perez *et al.* (22) reported that the negative result of the RTOG trial was influenced by the inability to heat deep tumors. When the analysis was restricted to tumors less than 2.5 cm an improvement with the addition of hyperthermia was detected, although this was not statistically significant. Similarly, Emami *et al.* (9) reported that very poor heating was achieved in the majority of patients treated with interstitial applicators and that a nonsignificant improvement in complete response rate was detected for tumors less than 4 cm in depth.

The hypothesis that negative results in previous Phase III randomized trials were due to inadequate heating, particularly in large tumors, is supported by Phase II human trial data (2, 7, 17, 25, 29). These data indicated that higher minimum temperatures measured during hyperthermia treatments correlated with improved complete response. However, thermal parameters did not correlate with response in a Phase III trial of hyperthermia and radiation for metastatic lymph nodes from head/neck cancers (28). Data from the ESHO Phase III trial of hyperthermia and radiation for malignant melanoma indicated that measures of the maximum temperatures achieved correlated with response while measures of minimum temperature were not significant in a multivariate analysis (20). The purpose of this report is to present results of an analysis of thermal parameters and their correlation with clinical outcome in a Phase III randomized trial that had demonstrated a benefit in the addition of hyperthermia to radiation (11).

METHODS AND MATERIALS

Results from four independent randomized trials were pooled. The groups participating were the Dutch Hyperthermia group (trial DHG), the European Society for Hyperthermic Oncology (trial ESHO), the Medical Research Council at the Hammersmith Hospital, UK (trial MRC), and the Ontario Cancer Institute/Princess Margaret Hospital, Toronto, Canada (trial OCI/PMH). A total of 317 patients were randomized to either radiation alone or radiation plus hyperthermia for the treatment of superficial localized breast cancer, of which 306 had single measurable lesions. Of these patients, 276 were diagnosed with chest wall recurrences. The remaining 30 patients who had primary inoperable carcinomas in an intact breast represent a distinct group, but are too few for modeling the hyperthermia parameters. Therefore, for this analysis, only the patients with recurrent tumors (276 patients) were considered). One hundred and fifty-three of these patients were randomized to the hyperthermia arm, with 148 receiving hyperthermia treatment. The difference between these two numbers is accounted for by the fact that five of those randomized to radiation plus hyperthermia were not treated at all due to disease progression, one received radiation only, and one patient randomized to radiation alone received hyperthermia treatment. Thermal dosimetry data were collected for 120 of the 148 patients who received hyperthermia. It is the data from this group of 120 patients that were analyzed for this report. Data for the other 28 patients were not available either because it was not collected or because the thermometry equipment malfunctioned. The patients for which thermometry data were not available did not have significantly different outcomes from those for whom data was available (data not shown).

The details of the hyperthermia and radiation treatments have been provided in the previous article (11), but in brief, radiation doses for the majority of the breast cancer recurrence patients were in the range 28–32 Gy for those with previous irradiation and up to 74 Gy for patients not previously irradiated. Hyperthermia prescriptions varied from two 30-min sessions with a target temperature of 42.5°C for the OCI/PMH trial, to as high as eight 60-min treatments, with a target temperature of 43°C for the DHG and ESHO trials. Thermal dosimetry was achieved with stationary temperature probes for all centers except OCI/PMH where a thermal mapping technique with two scanning intratumor sensors plus six surface sensors were used. Consequently, the median number of measurement points was 28 for OCI/PMH and from 6 to 10 for the other centers.

Five thermal parameters were calculated from the recorded temperature data, all associated with the low end of the measured temperature distributions. 1) Max(T90): T90 is the 90th percentile (90% of recorded temperatures are above T90) of all temperatures recorded over the treatment duration. Max(T90) is the maximum of these T90 values over a series of treatments to a particular patient. 2) Max(t42min): t42min is the lowest cumulative time above 42°C recorded at any measurement point during a particular treatment session. Max(t42min) is the maximum of these t42min values over a series of treatments to a particular patient. 3) Sum(t42min): t42min is as described above. Sum(t42min) is the t42min values summed over a series of treatments for a particular patient. 4) Max(TDmin): TDmin is the lowest thermal dose recorded at any measurement point during a treatment. [TDmin is equivalent to the parameter EQMIN $T_{100}43$ introduced by Oleson *et al.* (18) and termed T_{min} in the analysis by Overgaard *et al.* (20)]. Max(TDmin) is the maximum of these TDmin values over a series of treatments for a particular patient and is equivalent to $T_{min/any}$ in (20). 5) Sum(TDmin): TDmin is as described above. Sum(TDmin) is TDmin values summed over a series of treatments for a particular patient.

Thermal doses (equivalent minutes at 43°C) were calculated according to the formula of Sapareto and Dewey (24):

$$TD = \int_0^{t_f} R^{(43-T(t))} dt$$

where R = 1/2 or T > 43°C, and R = 1/4 or T ≤ 43°C.

$T(t)$ is the recorded temperature as a function of time between the start of treatment (time = 0) and the end of

treatment (time = t_f). In practice, the integral is calculated as a sum of thermal doses based on individual temperature measurements made at regular intervals during the treatment where the temperature is assumed constant during the interval. The interval between temperature measurements varied between 20 s at MRC to as high as 2 min at OCI/PMH where a thermal mapping technique was used.

Parameters associated with the low end of the temperature distribution were investigated in this study based on previous studies that have pointed to these as being significantly associated with outcome in this group of patients (15, 26). The particular parameters analyzed here were designed as representative parameters of the best treatment and also of the cumulative effect of a series of treatments in the same patient. Max(t42min) and Max(TDmin) are representative of the quality of the best treatment, whereas Sum(t42min) and Sum(TDmin) are cumulative measures over a series of treatments in a particular patient and so are representative of the quantity of hyperthermia given. The value of 42°C was chosen for the cumulative time above a threshold temperature calculations because it represents the low end of the temperature range through which cytotoxicity is expected to change rapidly. The number of hyperthermia sessions was also tested for a possible association with outcome.

Several clinical parameters were also tested for correlations with patient outcomes as summarized in Table 1. Tumor depth and area were included based on previous studies indicating the probable importance of tumor size on the success of hyperthermia as an adjunct to radiation therapy in this patient group (11, 23). Similarly, we reported that previous radiation treatment was a significant clinical parameter in the overall study (11). Systemic disease at entry was included as an indicator of disease advancement and was an important factor in determining disease-free survival and overall survival in the overall study (11). The effects of individual trials were also included in the analysis to control for differences in outcome between study centers that may not be attributable to treatment factors.

The clinical outcomes considered were: 1) local response: complete response (CR, the disappearance of tumor) was assessed according to WHO criteria of objective response in measurable disease including a second observation at least 4 weeks after the first (31). Further details on the classification of patient response are given in our previous article (11); 2) local disease-free survival (event = no CR, local relapse or death); 3) time to local failure (event = no CR, local relapse). Time to local failure and local disease-free survival differ only in that deaths are censored from the former; and 4) overall survival (event = death).

Associations between thermal and clinical parameters with outcome were analysed using multiple regression models. Logistic regression was used when analyzing local response rate while a proportional hazard model was used for the analysis of local disease-free survival, time to local failure, and overall survival. Dummy variables describing the four study centers were kept in the model at all times to control for the differences between centers. The model was built by first determining the significant clinical parameters using a step-wise selection technique (forward and backward). The thermal parameters were then added to the model using the same technique keeping the study centers and the clinical parameters from the first step in the model regardless of changes to their significance level. The model is, therefore, conservative because greater weight is given to the study centers and the clinical parameters than to the thermal parameters. The steps described were used in building models for both logistic regression (CR vs. no CR) as well as for the Cox proportional hazard (local disease-free survival, time to local failure, and overall survival). Details of the Cox modeling procedures are described by Parmar and Machin (21), and those for logistic regression by Collett (3).

Models were built assuming the continuous parameters such as Max(TDmin) could be both continuously and categorically classified. In the case of continuous parameters, transformations were applied if suggested by a graph of log [probabilty of CR/(1 − probability of CR)] vs. the variable in question. For example, if the graph were nonlinear and a logarithmic transformation of the variable in question resulted in a linear graph, then this transformation was applied to the variable before the model was built. For the analysis of categories, patients were divided into "low" and "high" groups for each of the five thermal parameters. The median value of each parameter was used as the threshold between categories so that approximately equal numbers of patients fell in each group. This position was taken because we assumed no prior knowledge of threshold values for the thermal parameters above which hyperthermia might be effective.

Table 1. Parameters used in statistical model analysis

Model parameters			
Thermal	Clinical	Study	Outcome
Max(T90)	Age	MRC	Initial local complete response rate (CR rate)
Max(t42min)	Tumor depth	DHG	Local disease-free survival
Sum(t42min)	Tumor area	ESHO	Time to local failure
Max(TDmin)	Systemic disease at entry	OCI/PMH	Overall survival
Sum(TDmin)	Previous radiation treatment		
Number of HT sessions			

RESULTS

The measurements of thermal parameters are summarized in Table 2 showing the breakdown by study center. In general, the quality and quantity of hyperthermia was greater at MRC and ESHO than at DHG or OCI/PMH. This is presumably related to the median numbers of hyperthermia sessions delivered [3 at MRC, 8 at ESHO, 5 at DHG and 2 at OCI, see Table 5, ICHG (11)] and to the median time of treatment (28 min at OCI/PMH and 60 min at all other centers).

The distributions of the five thermal parameters for all patients are shown graphically in Fig. 1. The groupings shown were arrived at by splitting the ranges into quartiles by number of patients. Deviations from quartiles were caused by rounding the ranges to integer values. These plots indicate that in general, for all parameters, the proportion of complete responders increased as the value of the thermal parameter increased. For example, for Max(TDmin), the proportion of complete responders is 36% for Max(TDmin) $\leq$ 1 min rising to 79% for Max(TDmin) $>$ 20 min.

Results of the statistical modeling are given in Table 3. For the analysis of continuous variables, a plot of log [probability of CR/(1 − probability of CR)] vs. Max(TDmin) shown in Fig. 2 suggests that a logarithmic transformation of Max(TDmin) is a more suitable continuous variable to analyze (see Fig. 2b). In a similar way, the other continuous variables were transformed if suggested by equivalent plots and are indicated as such in Table 3. Initial CR rate is significantly correlated with thermal dose; Max(TDmin) when continuous variables are analyzed (p = 0.009) and Sum(TDmin) when categorical variables are analyzed (p = 0.022). Complete response rate is also significantly correlated with tumor depth for either continuous or categorical classification. It is important to note that tumor depth and Max(TDmin) are independently correlated with response in this data set. A scatter plot of tumor depth vs. Max(TDmin) shows that these two variables are very weakly associated with one another (correlation coefficient = 0.15, Fig. 3).

Kaplan Meier curves for local disease free survival and overall survival are shown in Fig. 4a and b, respectively. The significant thermal parameters are shown in each case using a univariate log rank test for Fig. 4a (p = 0.0003) and b (p = 0.0001), respectively. Local CR rate was 74% for Max(TDmin) $>$6 min and 47% for Max(TDmin) $\leq$6 min. Similarly, CR rate was 77% for Sum(TDmin) $>$10 min and 43% for Sum(TDmin) $\leq$10 min. These differences in response rates remain approximately constant with time after treatment such that local disease-free survival and time to local failure curves for "good" and "poor" hyperthermia are near parallel. Although several clinical parameters were associated with disease-free survival, systemic disease at entry was the only significant clinical parameter associated with time to local failure. Overall survival at 18 months after treatment is 22% for Sum(TDmin) $\leq$6 min and 57% for Sum(TDmin) $>$6 min (Fig. 4b). The clinical parameters associated with overall survival were systemic disease, tumor depth and area, and age.

The logistic regression model for complete response can be used to generate a dose–response curve for hyperthermia when added to radiation for treatment of breast cancer recurrences. A model was built using the thermal parameters significantly associated with complete response as shown in Fig. 5. Plots of the probability of CR vs. Max(TDmin) are shown in Fig. 5 for two tumor depth categories ($\leq$2 cm and $>$2 cm) based on a model including these two parameters only. The results demonstrate the thermal dose–response relationship for complete response in this set of patients and are in good agreement with the model derived by Oleson *et al.* (18) for the treatment of superficial adenocarcinoma of the breast.

DISCUSSION

The results presented here demonstrate a strong relationship between thermal parameters representative of the low end of measured temperature distributions and clinical outcomes in combined hyperthermia and radiation treatment of superficial breast cancer recurrences. In particular, either Max(TDmin) or Sum(TDmin) are significantly correlated with initial local CR rate whether continuous or categorical variables are considered. The association of sum of minimum thermal doses with outcome is consistent with data from a nonrandomized trial of hyperthermia in this patient group where the sum of the 90th percentile of the thermal doses was shown to be the significant thermal parameter in multivariate analyses (15). An association between thermal parameters and outcome was also shown in data from a Phase III trial investigating hyperthermia as an adjuvant to radiation in the treatment of malignant melanoma (20). However, a measure of the maximum rather than the minimum thermal dose was significant in that analysis. Av-T_{max} (the maximum thermal dose mea-

Table 2. Summary of thermal parameters (median and range) by center

	Max(T90)	Max(t42min)	Sum(t42min)	Max(TDmin)	Sum(TDmin)
MRC	41.4 (38.4–43.3)	9 (0–60)	11 (0–220)	7.5 (0.1–87.7)	12.2 (0.1–204.7)
DHG	40.5 (37.7–42.4)	0 (0–69.5)	0 (0–290.6)	3.95 (0–122)	9.9 (0–328.5)
ESHO	40.6 (38.9–41.5)	5 (0–59)	10 (0–232.8)	8.4 (0.2–74)	23.9 (0.5–180.4)
OCI/PMH	41.1 (40.4–43.0)	0 (0–32.8)	0 (0–58.1)	1.5 (0–25)	2 (0–37)

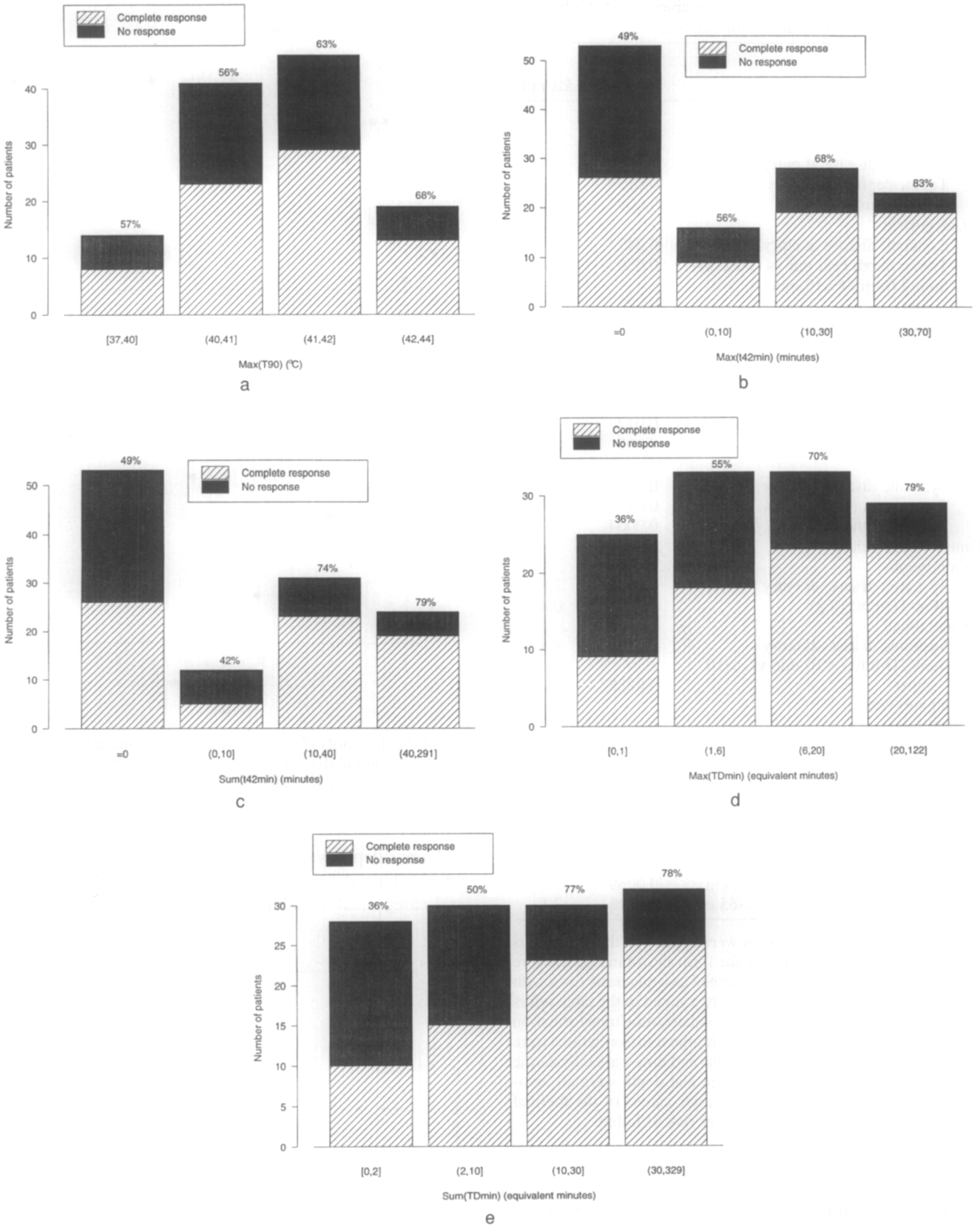

Fig. 1. Distribution of patients receiving hyperthermia according to quality of hyperthermia. Complete responders and non-responders are shown for each category: (a) Max(T90), (b) Max(t42min), (c) Sum(t42min), (d) Max(TDmin), and (e) Sum(TDmin). The percentage of patients achieving CR in each category is given above the appropriate bar.

Table 3. Thermal and clinical variables significantly associated with outcome

	p-Value	Odds ratio
Local response		
Continuous		
Systemic disease at entry	0.12	0.5
Tumor depth (sqrt)	0.015	0.2
Max(TDmin) (log)	0.009	1.5
Categorical		
Systemic disease at entry	0.047	0.4
Tumor depth (≤2 cm vs. >2 cm)	0.030	0.4
Sum(TDmin) (≤10 min vs. >10 min)	0.022	2.8
Local diseasc-free survival		Risk ratio
Continuous		
Systemic disease at entry	0.053	1.6
Tumor area (log)	0.18	1.1
Age (linear term)	0.016	
Age (quadratic term) vertex = 58	0.012	
Max(TDmin) (log)	0.007	0.8
Categorical		
Systemic disease at entry	0.0114	1.7
Tumor area (≤65 cm^2 vs. >65 cm^2)	0.017	1.7
Tumor depth (≤2 cm vs. >2 cm)	0.0064	1.9
Time to local failure		
Continuous		
Systemic disease at entry	0.0530	1.8
Max(TDmin) (log)	0.0249	0.8
Categorical		
Systemic disease at entry	0.0383	1.8
Sum(TDmin) (≤10 min vs. >10 min)	0.0288	0.5
Overall survival		
Continuous		
Systemic disease at entry	0.038	1.7
Age (linear term)	0.053	
Age (quadratic term) vertex = 55	0.030	
Tumor area (log)	0.037	1.3
Sum(TDmin) (log)	0.0018	0.8
Categorical		
Systemic disease at entry	0.0037	2.0
Tumor depth (≤2 cm vs. >2 cm)	0.0069	2.0
Tumor area (≤65 cm^2 vs. >65 cm^2)	0.0018	2.1

The following transformations were applied to the continuous variables as suggested by plots of the form shown in Fig. 2 before modeling took place. 1) Age was treated as a quadratic form with a linear and a quadratic term. The vertex noted in the table refers to the point of lowest hazard. 2) A square root transformation was applied to tumor depth. 3) Logarithmic transformations were applied to Max(TDmin), Sum(TDmin) and tumor area. Systemic disease at entry and larger tumor area and depth were all associated with higher risk of failure. Larger values of the thermal parameters were associated with lower risk of failure.

sured in each treatment, averaged over all treatments) was the only parameter that was significantly associated with outcome in a multivariate analysis. The parameter $T_{min/any}$, equivalent to our Max(TDmin), was not a significant parameter in that analysis although a correlation between T_{max} and T_{min} was demonstrated such that independence of these parameters cannot be assured.

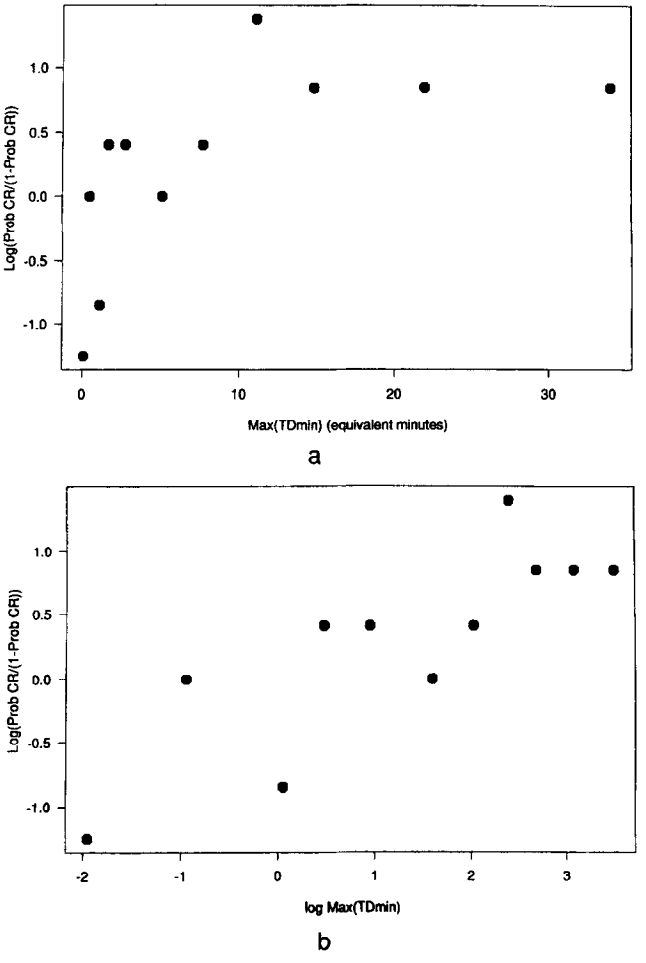

Fig. 2. Scatter plots illustrating (a) the nonlinear relationship between CR probability and Max(TDmin) and (b) the linear relationship between CR probability and log(Max(TDmin)).

Tumor depth was significantly correlated with CR rate when adjusted for other parameters for both continuous and categorical variables. Tumors greater than 2 cm in

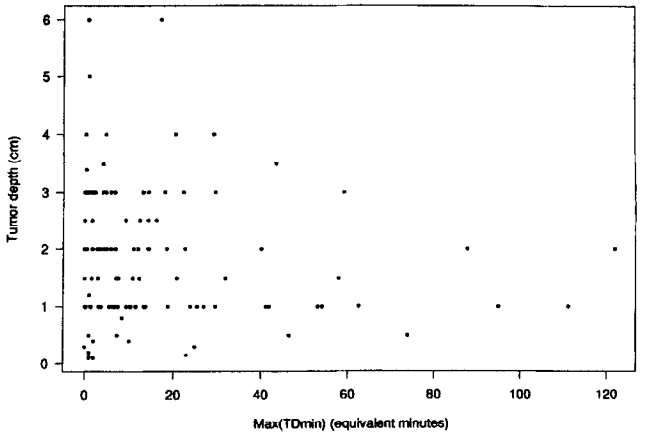

Fig. 3. Scatter plot demonstrating relationship between tumor depth and quality of hyperthermia received as measured by Max(TDmin).

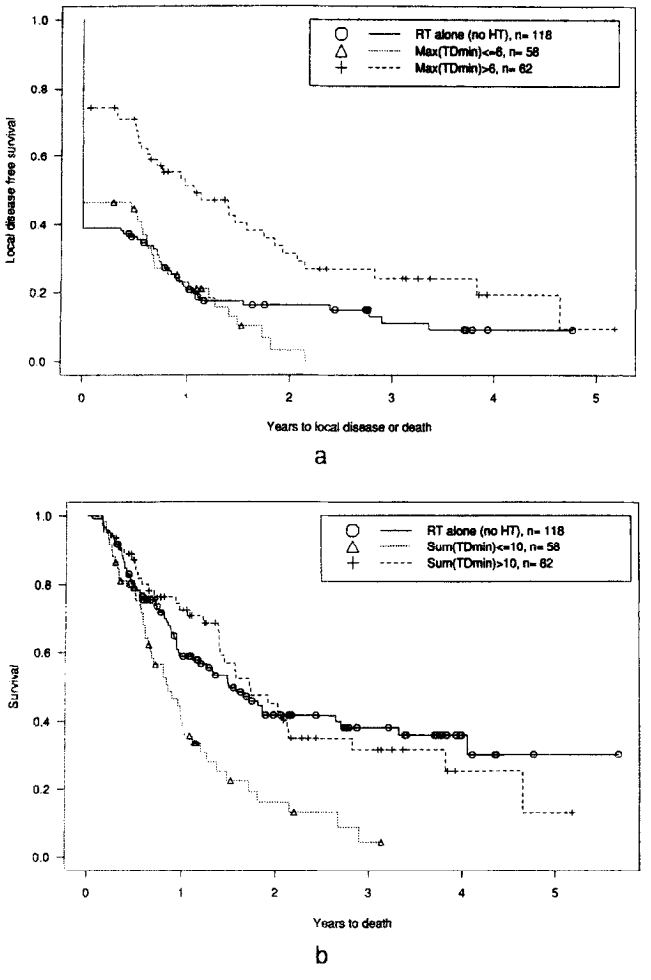

Fig. 4. Kaplan Meier curves for (a) local disease free survival and (b) overall survival. Significant categorical thermal variables are shown in each case with the number of patients in each group noted. The curves for patients receiving radiation alone are shown for comparison.

depth responded significantly worse than those less than 2 cm. This is in accordance with the findings of Overgaard *et al.* (19) for hyperthermia and radiation treatments of metastatic malignant melanoma, and confirms the suggestion of Perez *et al.* (22) that tumor depth is a critical parameter for predicting the likelihood of success of combined treatment of breast cancer recurrences. Both Overgaard *et al.* (19) and Perez *et al.* (22) speculate that the reasons for deeper tumors responding poorly is the inability to heat them, and although we confirm that adequate heating is critical, it is interesting to note that tumor depth correlates with initial CR rate *independently* of the thermal parameters. However, it is possible that the measured temperature distributions in the deeper tumors were not representative of the true distribution if temperature sensors were not located in the deepest areas of the tumor. Our results indicate no correlation between number of hyperthermia sessions and initial complete response rate confirming the findings of previous studies (12–15).

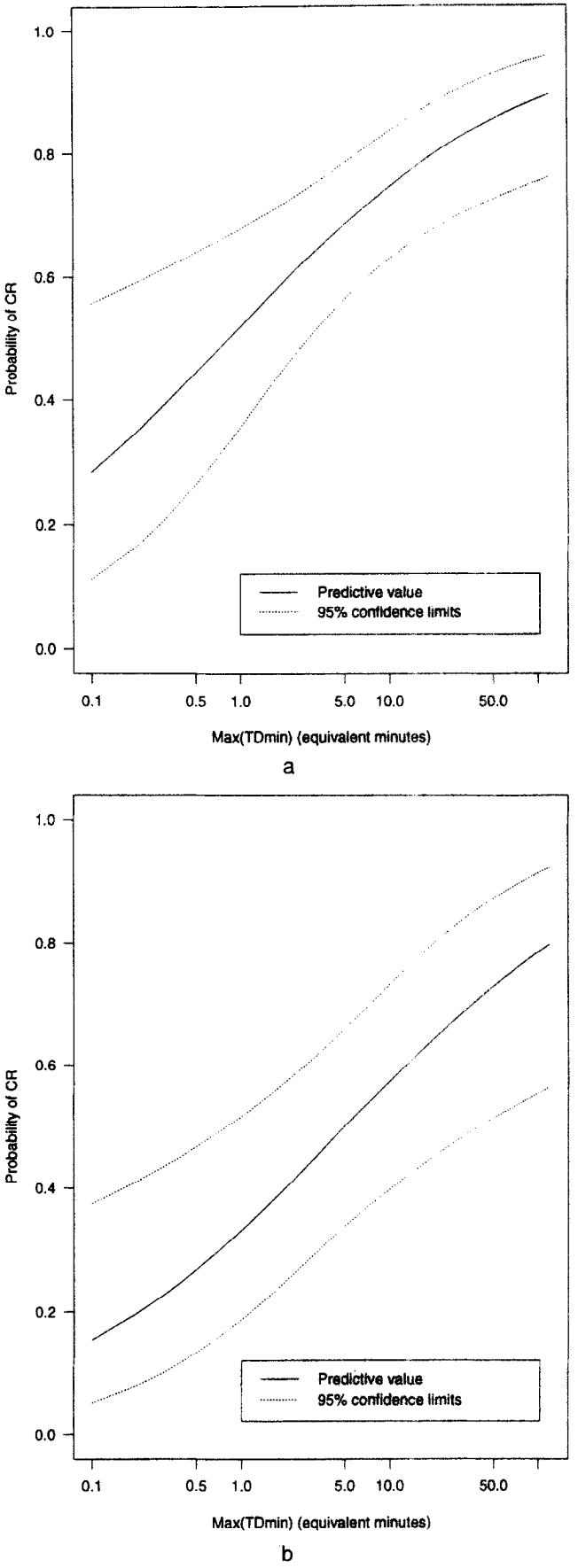

Fig. 5. Thermal response curves for hyperthermia and radiation treatments for two tumor depth categories, (a) ≤2 cm, and (b) >2 cm.

Results of local disease-free survival and time to local failure demonstrate that the initial improvement in complete response achieved with "good" hyperthermia treatments is durable. The Kaplan Meier curves for Max(TDmin) >6 min and Max(TDmin) ≤6 min are parallel for the first 2 years, suggesting that duration of response is equivalent for "good" and "poor" hyperthermia. This agrees with the findings of Dewhirst and Sim (5), who found no thermal dose relationship with duration of local response in the treatment of a variety of canine and feline spontaneous tumors. However, when the animal data were restricted to squamous cell carcinomas, a relationship between thermal dose and duration of local response was found. Arcangeli *et al.* (1, 2) have also suggested such a relationship in a nonrandomized trial of hyperthermia as an adjunct to radiation in the treatment of neck node metastases from head and neck cancer. However, we interpret their data to show only an increase in initial response rate and question whether initial complete responders demonstrate any significant difference in kinetics of tumor regrowth or death as a function of thermal dose. Perez *et al.* (23) detected a nonsignificant difference in duration of response between tumors less than or greater than 3 cm in depth, although whether this was associated with poorer heating in the deeper tumors is unclear.

The response of local recurrences of breast cancer to combined radiation therapy and hyperthermia has been shown in a Phase II trial to be dependent on the radiation dose delivered (26). Consequently, it is likely that dose–response relationships such as the ones we have calculated (Fig. 5) are also dependent on radiation dose. We did not include this variable in the multivariate analysis because the distribution of radiation therapy doses delivered to patients was such that statistically significant associations would be difficult to detect. Sixty-nine percent of patients received between 28.8 and 32 Gy, while the doses delivered to the remaining 31% of patients were evenly spread over the range 16.7 to 74 Gy. Subsequent testing confirmed that radiation dose was not significant as a continuous variable in the multivariate model.

We also investigated whether previous radiation treatment was a significant parameter in the model. This parameter is a surrogate for radiation dose because it determined whether a patient received "palliative" or "radical" radiation doses. This factor also was not significantly associated with outcome. This is probably due to the fact that only 29 of the 120 patients analyzed in this study had no prior irradiation making associations difficult to detect. The difference between this result and the finding that previous radiation therapy was associated with outcome in the overall trial (11) was influenced by the inclusion of patients with tumors in intact breasts (MRC BrI in the overall trial), the majority of whom were given radical radiation doses.

A novel finding from this study is that although the addition of hyperthermia to radiation appears to be associated with no change in overall survival compared to radiation alone, this is not the case if hyperthermia treatments are classified according to the quality of treatment. In our multivariate analysis, Sum(TDmin) was significantly correlated with overall survival, with "poorer" hyperthermia associated with worse overall survival. Further, from Fig. 4 it appears that "poor" hyperthermia added to radiation results in poorer prospects for survival than radiation alone. To our knowledge, no previous study has reported differences in survival depending on quality of hyperthermia when added to radiation. There appears no biological rationale why the quality of local treatment would affect overall survival for disease of this type.

The observed association between quality of hyperthermia and overall survival raises a critical question as to conclusions drawn from all the associations between thermal parameters and outcome that we have observed. Is quality of hyperthermia having a direct effect on outcome, or alternatively, is it merely an indicator for a critical clinical characteristic? For example, one might hypothesize that patients who have more advanced disease during treatment are less able to tolerate high temperatures. In this case, "poor" hyperthermia would be associated with poor response but not because of any direct effect of the hyperthermia treatment. Alternatively, the inability to heat effectively may be indicative of increased local tumor vascularity, and this in turn, is associated with more aggressive disease, and hence, poorer prospects of survival (10, 30). Again, there would be no direct effect of hyperthermia quality even though an association with response were detected. However, there is strong evidence in this study to support the hypothesis that quality of hyperthermia does have a direct effect on outcome. First, the multivariate analyses we have performed demonstrate that the thermal parameters are associated with outcome *independently* from the clinical parameters we have tested for including systemic disease at entry. Second, the associations we have observed were derived from a conservative modelling approach, which gave more weight to the clinical parameters than to thermal parameters yet the thermal parameters remain independently significant.

To investigate this issue further, the patients were divided into two groups, those with and without systemic disease at entry. Systemic disease at entry is an indicator of disease advancement and therefore prospects for an unfavorable outcome. This is demonstrated by the fact that for every outcome studied, systemic disease at entry was a significant parameter. New models were built for these two groups of patients. For those patients with systemic disease at entry we found none of the thermal parameters to be significantly associated with any of the outcomes studied. In addition, these patients were more likely to receive "poor" hyperthermia; only 41% achieved Sum(TDmin) >10 min, whereas for patients with no systemic disease, 62% achieved Sum(TDmin) >10 min (p = 0.018). These data indicate that a selection effect is occurring in that the poorer response in patients receiving "poor" hyperthermia is partly attributable to the fact that

a larger fraction of these patients had systemic disease than those receiving "good" hyperthermia. We suggest that the result in Fig. 4 indicating poorer survival when "poor" hyperthermia is added to radiation compared to radiation alone is due to this selection effect and is not a direct result of the hyperthermia.

For patients with no systemic disease at entry, a significant association with hyperthermia quality was observed with the *same* thermal parameters showing significance as for the analysis of all patients, including overall survival. This indicates that the independent significance of the thermal parameters is robust and is good evidence for the argument that for patients with no systemic disease at entry into the study, good hyperthermia was of direct benefit. However, there remains a possibility that even for this group of patients, hyperthermia quality is a surrogate for some other important prognostic clinical variable that was not measured in the study. For example, concurrent hormonal therapy and initial T-stage were shown to be associated with local control and duration of local control independently of the presence of systemic disease at time of hyperthermia in data from a Phase II trial (14). In our overall trial (11), concurrent systemic therapy was not significantly associated with outcome. Subsequent testing in this model also showed this was not an independently significant clinical parameter.

A further unavoidable weakness of the analysis presented here is that data is combined from several centers. Despite the intended adherence to quality assurance guidelines for thermometry, we suggest that the procedure for temperature measurement may not have been uniform at different centers. As reported earlier (11), the number of temperature sensors varied over a wide range. In addition, the location and depth of the sensors in tissue was not recorded. A number of studies have indicated that the density and location of sensors affects the measured temperature distribution leading to a concern that these may be confounding factors in our results (6, 8). In particular, we have chosen the minimum thermal dose (TDmin) as a descriptor of the treatment, which is expected to be more sensitive to the density and location of sensors than, for example, the 50th percentile of thermal doses measured (4). The minimum was used based on the hypothesis that it is a clinically important measure, despite the fact that it may not be as robust statistically as other measures of the treatment. This issue can be investigated by examining the results from the different centers individually if it is assumed that the density of temperature probes used was reasonably consistent at individual centers. We repeated the analysis using data from the single largest center alone (MRC, 81 patients of the 120 analyzed). The results were consistent with those from the whole data set in that exactly the same thermal parameters were significantly associated with outcome for all the outcomes studied. This confirms the result of our multivariate analysis showing the significance of thermal parameters to be independent of the effect of study center and suggests that the result is robust.

Questions as to the direct role of hyperthermia quality arise due to the nature of a retrospectively analyzed data set. Confirmation of our results must ideally come from prospectively designed randomized hyperthermia dose escalation studies with uniform thermometry standards across all patients. However, these will be very difficult trials to carry out due to the variability in temperature distributions caused by patient and hardware characteristics. Alternatively, retrospective thermal dose studies could be carried out on individual patient groups with very well-defined tumor characteristics (16).

CONCLUSIONS

This study has demonstrated that thermal parameters, and in particular, thermal dose are associated with complete response when hyperthermia is given as an adjunct to radiation for the treatment of superficial recurrences of breast cancer. This is the first such association observed in data from a Phase III trial investigating whether hyperthermia is beneficial in this patient group. The associations observed are due in part to a selection effect of hyperthermia quality in that patients with systemic disease (and, therefore, poorer prospects for a favorable outcome) were more likely to receive poor hyperthermia. However, in the multivariate models, thermal parameters are associated with response independently of systemic disease, indicating that delivering good hyperthermia is of direct benefit. A subgroup analysis leads to the hypothesis that this direct benefit may be limited to patients with no diagnosis of systemic disease at the time of entry into the study.

REFERENCES

1. Arcangeli, G.; Arcangeli, G.; Guerra A.; Lovisolo, G.; Cividalli, A.; Marino, C.; Mauro, F. Tumour response to heat and radiation: Prognostic variables in the treatment of neck node metastases from head and neck cancer. Int. J. Hyperthermia 1:207–217; 1985.
2. Arcangeli, G.; Benasski, M.; Cividalli, A.; Lovisolo, G. A.; Mauro, F. Radiotherapy and hyperthermia. Analysis of clinical results and identification of prognostic variables. Cancer 60:950–956; 1987.
3. Collett, D. Modelling binary data. London: Chapman and Hall; 1991.
4. Corry, P. M.; Jabboury, K.; Kong, J. S.; Armour, E. P.; McGraw, F. J.; LeDuc, T. Evaluation of equipment for hyperthermia treatment of cancer. Int. J. Hyperthermia, 4:53–74; 1988.
5. Dewhirst, M. W.; Sim, D. The utility of thermal dose as a predictor of tumor and normal tissue responses to combined radiation and hyperthermia. Cancer Res. 44:4772s–4780s; 1984.
6. Dewhirst, M. W.; Winget, J. M.; Edelstein-Keshet, L.; Sylvester, J.; Engler, M.; Thrall, D. E.; Page, R. L.; Oleson, J. R. Clinical application of thermal isoeffect dose. Int. J. Radiat. Oncol. Biol. Phys. 3:307–319; 1987.

7. Dunlop, P. R. C.; Hand, J. W.; Dickinson, R. J.; Field, S. B. An assessment of local hyperthermia in clinical practice. Int. J. Hyperthermia 2:39–50; 1986.
8. Edelstein-Keshet, L.; Dewhirst, M. W.; Oleson, J. R.; Samulski, T. V. Characterization of temperature distributions based on assumed mathematical forms. Int. J. Hyperthermia 5:757–777; 1989.
9. Emami, B.; Scott, C.; Perez, C. A.; Asbell, S.; Swift, P.; Grigsby, P.; Montesano, A.; Rubin, P.; Curran, W.; Delrower, J.; Arastu, H.; Fu, K.; Moros, E. Phase III study of interstitial thermoradiotherapy compared with interstitial radiotherapy alone in the treatment of recurrent or persistent human tumors: A prospectively controlled randomized study the radiation therapy oncology group. Int. J. Radiat. Oncol. Biol. Phys. 34:1097–1104; 1996.
10. Horak, E. R.; Leek, R.; Klenk, N.; LeJeune, S.; Smith, R.; Stuart, N.; Greenall, M.; Stepniewska, K.; Harris, A. L. Angiogenesis assessed by platelet/endothelial cell adhesion molecule antibodies as indicator of node metastases and survival in breast cancer. Lancet 340:1120–1124; 1992.
11. International Collaborative Hyperthermia Group; Vernon, C. C.; Hand, J. W.; Field, S. B.; Machin, D.; Whaley, J. B.; van der Zee, J.; van Putten, W. L. J.; van Rhoon, G. C., van Dijk, J. D. P.; Gonzalez Gonazlez, D.; Liu, F. F.; Goodman, P.; Sherar, M. D. Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer—Results from five randomized controlled trials. Int. J. Radiat. Oncol. Biol. Phys. 39:731–744; 1996.
12. Kapp, D. S. Areas of need for continued Phase II testing in human patients. In: Paliwal, B. R., Hetzel, F. W.; Dewhirst, M. W., eds. Biological physical and clinical aspects of hyperthermia. Medical Physics Monograph No. 16. New York: American Institute of Physics Inc.; 1988:424–443.
13. Kapp, D. S.; Petersen, I. A.; Cox, R. S.; Hahn, G. M.; Fessenden, P.l; Prionas, S. D.; Lee, E. R.; Meyer, J. L.; Samulski, T. V.; Bagshaw, M. A. Two or six hyperthermia treatments as an adjunct to radiation therapy yield similar tumor response: Results of a randomized trial. Int. J. Radiat. Oncol. Biol. Phys. 19:1481–1495; 1990.
14. Kapp, D. S.; Barnett, T. A.; Cox, R. S.; Lee, E. R.; Lohrbach, A. R. T. T. and Fessenden, P. Hyperthermia and radiation therapy of local-regional recurrent breast cancer: Prognostic factors for response and local control of diffuse or nodular tumors. Int. J. Radiat. Oncol. Biol. Phys., 20:1147–1164; 1991.
15. Kapp, D. S.; Cox, R. S. Thermal treatment parameters are most predictive of outcome in patients with single tumour nodules per treatment field in recurrent adenocarcinoma of the breast. Int. J. Radiat. Oncol. Biol. Phys. 33:887–899; 1995.
16. Kapp, D. S. Efficacy of adjuvant hyperthermia in the treatment of superficial recurrent breast cancer: Confirmation and future directions. Int. J. Radiat. Oncol. Biol. Phys. 35:1117–1121; 1996.
17. Oleson, J. R.; Sim, D. A.; Manning, M. R. Analysis of prognostic variables in hyperthermia treatment of 161 patients. Int. J. Radiat. Oncol. Biol. Phys. 10:2231–2239; 1984.
18. Oleson, J. R.; Samulski, T. V.; Leopold, K. A.; Clegg, S. T.; Dewhirst, M. W.; Dodge, R. K.; George, S. L. Sensitivity of hyperthermia trial outcomes to temperature and time: Implications for thermal goals of treatment. Int. J. Radiat. Oncol. Biol. Phys. 35:289–297; 1993.
19. Overgaard, J.; Gonzalez Gonzalez, D.; Hulshof, M. C. C. M.; Arcangeli, G.; Dahl, O.; Mella, O.; Bentzen, S. M. Randomised trial of hyperthermia as adjuvant to radiotherapy for recurrence of metastatic malignant melanoma. Lancet 59:540–543; 1995.
20. Overgaard, J.; Gonzalez Gonzalez, D.; Hulshof, M.C.C.H.; Arcangeli, G.; Dahl, O.; Mella, O.; Bentzen, S. M. Hyperthermia as an adjuvant to radiation therapy of recurrent or metastatic malignant melanoma. A multicentre randomized trial by the European Society for Hyperthermic Oncology. Int. J. Hyperthermia 12:3–30; 1996.
21. Parmar, M. K. B.; Machin, D. Survival analysis: A practical approach. Chichester: Wiley; 1995.
22. Perez, C. A.; Gillespie, B.; Pajak, T.; Hornback, N. B.; Emami, B.; Rubin, P. Quality assurance problems in clinical hyperthermia and their impact on therapeutic outcome: A report by the radiation therapy oncology group. Int. J. Radiat. Oncol. Biol. Phys. 16:551–558; 1989.
23. Perez, C. A.; Pajak, T.; Emami, B.; Hornback, N. B.; Tupchong, L.; Rubin, P. Randomized phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors. Final repot by the Radiation Therapy Oncology Group. Am. J. Clin. Oncol. (CCT) 14:133–141; 1991.
24. Sapareto, S. A.; Dewey, W. C. Thermal dose determination in cancer therapy. Int. J. Radiat. Oncol. Biol. Phys. 10:787–800; 1984.
25. Scott, R.; Gillespie, B.; Perez, C. A.; Hornback, N. B.; Johnson, R.; Emami, B.; Bauer, M.; Pakuris, E. Hyperthermia in combination with definitive radiation therapy: Results of a Phase I/II RTOG study. Int. J. Radiat. Oncol. Biol. Phys. 15:711–716; 1988.
26. Seegenschmiedt, H. M.; Karlsson, U. L.; Sauer, R.; Brady, L. W. Jr.; Herbst, M.; Amendola, B. E.; Markoe, A. M.; Fisher, S.; Micaily, B.; Superficial chest wall recurrences of breast cancer: Prognostic treatment factors for combined radiation therapy and hyperthermia. Ther. Radiol. 173:551–558; 1989.
27. Valdagni, R.; Amichetti, M.; Pani, G. Radical radiation alone versus radical radiation plus microwave hyperthermia for N_3 (TNM-UICC) neck nodes: A prospective randomized clinical trial. Int. J. Radiat. Oncol. Biol. Phys. 15:13–24; 1988.
28. Valdagni, R.; Amichetti, M. Report of long-term follow-up in a randomized trial comparing radiation therapy and radiation therapy plus hyperthermia to metastatic lymph nodes in stage IV head and neck patients. Int. J. Radiat. Oncol. Biol. Phys. 28:163–169; 1994.
29. van der Zee, J.; van Putten, W. L. J.; van den Berg, A. P.: van Rhoon, G. C. Wike-Hooley, J. L.; Broeekmeyer-Reurink, M. P.; Reinhold, H. S. Retrospective analysis of the response of tumors in patients treated with a combination of radiotherapy and hyperthermia. Int. J. Hyperthermia 2:337–349; 1986.
30. Weidner, M.; Semple, J. P.; Welch, W. R.; Folkman, J. Tumor angiogenesis and metastasis—Correlation in invasive breast carcinoma. N. Engl. J. Med. 324:1–8; 1991.
31. World Health Organization. WHO Handbook for reporting results of cancer treatment. WHO Offset Publication No. 48. Geneva: WHO; 1979.