ORIGINAL REPORT

Randomized Trial of Hyperthermia and Radiation for Superficial Tumors

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A B S T R A C T

Purpose

Randomized clinical trials have demonstrated hyperthermia (HT) enhances radiation response. These trials, however, generally lacked rigorous thermal dose prescription and administration. We report the final results of a prospective randomized trial of superficial tumors ($\leq$ 3 cm depth) comparing radiotherapy versus HT combined with radiotherapy, using the parameter describing the number of cumulative equivalent minutes at 43°C exceeded by 90% of monitored points within the tumor (CEM 43°C T_{90}) as a measure of thermal dose.

Methods

This trial was designed to test whether a thermal dose of more than 10 CEM 43°C T_{90} results in improved complete response and duration of local control compared with a thermal dose of $\leq$ 1 CEM 43°C T_{90}. Patients received a test dose of HT $\leq$ 1 CEM 43°C T_{90} and tumors deemed heatable were randomly assigned to additional HT versus no additional HT. HT was given using microwave spiral strip applicators operating at 433 MHz.

Results

One hundred twenty-two patients were enrolled; 109 (89%) were deemed heatable and were randomly assigned. The complete response rate was 66.1% in the HT arm and 42.3% in the no-HT arm. The odds ratio for complete response was 2.7 (95% CI, 1.2 to 5.8; $P = .02$). Previously irradiated patients had the greatest incremental gain in complete response: 23.5% in the no-HT arm versus 68.2% in the HT arm. No overall survival benefit was seen.

Conclusion

Adjuvant hyperthermia with a thermal dose more than 10 CEM 43°C T_{90} confers a significant local control benefit in patients with superficial tumors receiving radiation therapy.

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INTRODUCTION

Hyperthermia (HT), the elevation of tumor temperature to a supraphysiologic level in the range of 40°C to 44°C, is a well-established radiosensitizer. The predominant molecular target of HT appears to be protein.[1] The rationale for combining HT with radiation is multifold. Mechanisms of action are complimentary to the effects of radiation with regard to DNA damage repair,[2] cell cycle sensitivity,[3] and hypoxia.[4] Hyperthermia causes direct cytotoxicity, particularly to cells that are acidotic[5] and nutrient deprived.[4] In addition, HT has effects on tumor blood flow and oxygenation that may enhance tumor radiation response.[6] Preclinical studies have established that hyperthermic radiosensitization depends on temperature achieved and duration of heating.[7] Hyperthermia combined with radiotherapy has improved clinical response, local control, and survival in numerous phase II studies and several randomized trials for patients with breast, cervix, head and neck cancers, melanoma, and glioblastoma multiforme.[8-15]

Despite positive phase III trials, application of HT remains limited. This may

relate partially to the lack of rigorous thermal dosimetric data. The basic premise underlying the need for thermal dosimetry is the ability to write a verifiable prescription for HT. As in any form of therapy, a sound dosimetric basis leads to unambiguous treatment, data reporting, and quality assurance.[16]

This study was designed to test the clinical value of HT delivered within a defined thermal dose range based on dosimetric principles established in the preclinical setting[17] and retrospective analysis of human phase II trials.[18] Quality of treatment was assured using strict application of predefined thermal dose criteria as a test treatment to prospectively determine whether thermal dose prescription could be achieved.

METHODS

Study Design

This randomized trial tested the thermal dose parameter cumulative equivalent minutes at 43°C for 90% of measured points (CEM 43°C T_{90}) as a predictor of response of superficial tumors to local HT plus radiotherapy. The Duke Institutional Review Board approved the study; all patients gave written informed consent. Patients with superficial tumors ≤ 3 cm in depth from the body surface received an initial HT treatment to determine heatability of the tumor (Fig 1). We postulated on the basis of prior preclinical as well as clinical data that the minimum effective thermal dose is 10 CEM 43°C T_{90}.[1,18] The duration of the initial treatment was ≤ 1 hour. Once steady-state temperature was reached, real-time monitoring and calculations were performed to project the thermal dose for 1 hour. The projected dose had to exceed 0.5 CEM 43°C T_{90} for the tumor to be deemed heatable because the plan of heating during the course of radiotherapy was twice a week for a maximum of 2 hours per session. Therefore, if one could not achieve a thermal dose of 0.5 CEM 43°C T_{90} in 1 hour, one would not be able to achieve the minimum effective dose of 10 CEM 43°C T_{90} in 20 hours. Only patients with heatable tumors were randomly assigned. The initial test dose of HT was not to exceed 1 CEM 43°C T_{90}.
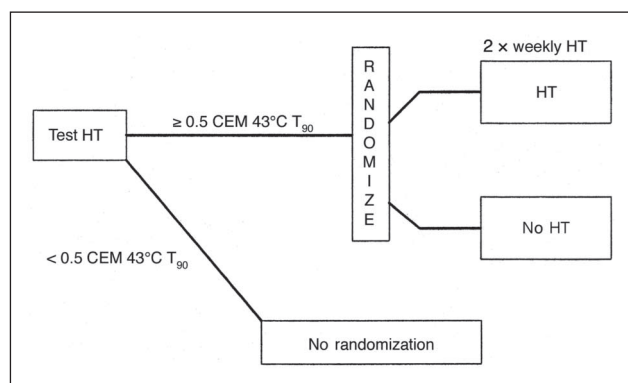

Fig 1. Protocol schema. See Methods for details of thermal dose calculation and heatability criteria.

Patients were also stratified by prior radiotherapy (yes or no) and site of involvement (breast or chest wall, head and neck, melanoma, and other). Patients were randomly assigned to receive no further HT (no-HT arm) or additional HT (HT arm) throughout the course of radiation, delivered twice a week for a maximum of 10 treatments, 1 to 2 hours in length, separated by at least 48 hours, with a targeted CEM 43°C T_{90} between 10 and 100 CEM 43°C T_{90}.

Radiation

Patients were irradiated using megavoltage photons (≥ 4 MV) or electrons with standard fields encompassing gross disease. Treatment fields were individualized for each patient. Patients with chest wall recurrence of breast cancer received tangential photon fields to the chest wall matched to an anteroposterior supraclavicular field if there was no prior radiation.[19] If the chest wall was previously irradiated, electron fields were planned to encompass all gross disease with a minimum 2- to 3-cm margin. Dose fractionation was 1.8 to 2.0 Gy per day, 5 days per week. Previously irradiated patients received between 30 and 66 Gy, depending on location and prior dose. Previously unirradiated patients received 60 to 70 Gy.

Hyperthermia Treatment

Microwave spiral strip applicators, operating at 433 MHz, were used for external heating.[20] Patients routinely received lorazepam or narcotic premedication. A sterile, blind-ended interstitial catheter was placed in the tumor using computed tomography guidance as per Radiation Therapy Oncology Group (RTOG) guidelines[21]; lidocaine HCl (1% solution buffered with 0.1 mEq sodium bicarbonate/mL lidocaine) was used for local anesthesia. Commercially available fiberoptic thermometers were used for temperature monitoring (Luxtron Corporation, Santa Clara, CA). These were moved in a stepwise fashion at 0.5-cm increments throughout the tumor volume using a mechanical device for automated temperature mapping.[22] Thermometry probes were also placed on the skin and near scar lines within the HT field to monitor normal tissue and surface temperatures. Maximally allowed temperatures in the adjacent normal tissue and tumor tissue were 43°C and 50°C, respectively.

Thermal Dose Calculation

Sapareto and Dewey[17] proposed using the Arrhenius relationship to normalize thermal data from HT treatments. The rationale came from the observations that time-temperature histories are not stable, that they vary from patient to patient, and that temperatures within tumors were almost always nonuniform. Using the Arrhenius relationship, it would be possible to convert all time-temperature data to an equivalent number of CEM 43°C T_{90} at a standard temperature. The formulation takes the following form:

$$\text{CEM } 43°C = tR^{(43-T)} \qquad (1)$$

where CEM 43°C is cumulative equivalent minutes at 43°C (the temperature most commonly used for normalization), t is time of treatment, T is average temperature during desired interval of heating, and R is a constant. When the temperature is higher than 43°C, $r = 0.5$. When the temperature is lower than 43°C, $r = 0.25$.

In this protocol, the fiberoptic thermometers completed transits through all locations every 1 minute. The temperature measured at location x at the ith minute during treatment was designated as T_{xi}. The temperature exceeding the temperature at

90% of the locations during the ith minute was designated as T_{90i}. We then used the formula:

$$\text{CEM } 43°\text{C } T_{90} = \sum_{i=0}^{n} R^{43-T_{90i}} \qquad (2)$$

to convert each T_{90i} into an equivalent time at 43°C, and then to sum these equivalent times over the entire treatment duration of n minutes. The CEM 43°C (thermal isoeffect dose) formulation has been used extensively and successfully in clinical trials to assess the efficacy of heating.[7,18,23,24] This is despite the fact that the R values and breakpoints have historically been derived from studies performed on rodent cells and tissues, which are not necessarily equivalent to human cells with respect to the temperature dependence of cell killing rate.

Eligibility Criteria

Patients ≥ 18 years old were required to have histologic proof of malignancy with measurable disease ≤ 3 cm in thickness from the body surface. Patients generally had incurable disease with less than a 50% chance of response to conventional therapy. A Karnofsky performance status of $\geq 70\%$ was required with an expected survival of ≥ 6 months. Metastatic disease was permitted. The tumor was required to be accessible for invasive thermometry placement. Patients were not permitted to have other anticancer therapy within 30 days of protocol enrollment. The criteria for exclusion included pregnancy and patients with cardiac pacemakers or metallic implants incompatible with microwave devices.

Statistical Analysis

The primary end points were complete response (CR) rate and duration of local control. Duration of local control was defined from time of randomization to local recurrence and was equal to zero for non-CR patients. Secondary end points included overall survival, local control at death or last follow-up, and acute or late toxicities associated with thermoradiotherapy.

On the basis of phase II data, we hypothesized that the CR rate for superficial tumors treated with the test dose of HT and radiation would be 50%. For a thermal dose between 10 and 100 CEM 43°C T_{90}, an 80% likelihood of CR was predicted.[18] To detect this difference with a 90% power, 51 patients were required in each treatment group assuming a two-sided level .05 test comparing the two proportions at the end of the trial and a common response rate among the tumor strata. It was planned that 55 patients would be randomly assigned to each treatment group.

Analyses were performed according to the intention-to-treat principle. If a patient had extensive disease that could not be encompassed by one HT applicator (maximum coverage 15 × 15 cm), the involved area was divided into adjacent HT fields, which were abutting but not overlapping. If a patient had more than one HT field, all fields were tested and all fields were deemed heatable before random assignment. Random assignment was performed by patient rather than by field. Thus, for a patient with multiple fields, all fields received either HT or no HT, and all fields received the same radiation dose. If treatment failure occurred at one site, the patient was scored as having local recurrence. Thus, each patient was included in the analyses only once. Patients were censored for purposes of calculating local control if they underwent additional radiation or surgery to the study site without evidence of recurrence. Patients were not censored for the development of distant metastasis or additional systemic therapy. All patients were rigorously observed for local control until death.

Point estimates for response rates, odds ratios (ORs), median duration of local control, and median overall survival and the related 95% CIs are reported. Fisher's exact tests were used to compare the two groups for binary outcome data. Log-rank tests were used to compare the two groups for time-to-event end points; that is, time to local failure and overall survival. Kaplan-Meier time-to-event curves are presented. All reported P values are two-sided.

RESULTS

Study Population

From July 1994 through July 2001, 122 patients were enrolled onto the protocol. Thirteen patients (11%) were deemed to have unheatable tumors; 109 patients were randomly assigned. One patient was randomly assigned but had no measurable disease and hence was excluded from analysis. Two other patients were randomly assigned to no HT but received multiple HT treatments. They were analyzed in the no-HT group (according to the intention-to-treat principle). Among 108 eligible randomly assigned patients, 25 patients had multiple lesions (18 patients in the HT group and seven patients in the no HT group). These patients were included in the analyses only once using the lesion that had the worst treatment outcome. The two groups were balanced with regard to baseline stratification characteristics (Table 1).

Treatment Response

The CR rate in the HT arm was 66%; the CR rate in the no-HT arm was 42% (OR, 2.7; 95% CI, 1.2 to 5.8; Fisher's exact $P = .02$). There was no significant difference in the proportion of patients in each arm who received additional systemic therapy. One patient in each arm was censored for duration of local control during post-treatment follow-up because of additional local surgery.

The improved local response in the high-dose arm resulted in a significant difference in duration of local control between the two arms ($P = .02$). The high-dose arm had 48% local control at death or last follow-up versus 25% in the no-HT arm (OR, 2.8; 95% CI, 1.2 to 6.3). Overall survival was not significantly different between the two groups (Fig 2B).

Among patients in both arms, the median radiation dose if prior radiation given was 41 Gy (range, 18 to 66 Gy) and the median dose if no prior radiation given was 60 Gy (range, 24 to 70 Gy). The improvement in local control was most pronounced for patients who were previously irradiated; 15 of 22 patients in the HT arm (68%) had CR versus four of 17 patients in the no-HT arm (24%). In contrast, for patients without prior radiotherapy, 22 of 34 patients (65%) had CR versus 18 of 35 patients (51%) in the HT and no-HT arms, respectively.

Table 1. Patient Baseline Characteristics and Treatment Summary

	No HT (n = 52)		HT (n = 56)	
Characteristic	No. of Patients	%	No. of Patients	%
Age				
Median	59.3		52.4	
Range	38.4-83.8		18.2-90.9	
Sex				
Male	13		14	
Female	39		42	
Site of disease				
Breast/chest wall	33	63	37	66
Head and neck	6	12	8	14
Melanoma	6	12	5	9
Other	7	13	6	11
Multiple HT fields	7	13	18	32
Prior XRT	17	33	22	39
RT dose, Gy (given on protocol)				
Median	50		55	
Range	18-70		20-70	
Metastasis at enrollment	17 of 51	33	16 of 52	31
Additional systemic therapy	34	65	33	59
Hyperthermia dose, CEM 43°C T_{90}				
Median	0.74		14.3	
Range	0.07-1.49		0.57-36.21	

Abbreviations: HT, hyperthermia; XRT, external radiation therapy; RT, radiation therapy; CEM, cumulative equivalent minutes.

The analysis of local control duration or time to local failure in the face of competing risks is a difficult task.[25,26] Death, additional local surgery, or relapses at distant sites may occur before the end point of local failure is reached. This problem ordinarily requires one to assume that the competing risk factors are independent of the end point of interest—an untestable and potentially implausible assumption. Therefore, in addition to analyzing locoregional control, as illustrated in Figure 2A, we analyzed overall survival and list data on the competing risks (Table 2) and the hazard function for time to local failure (Fig 2C).

Adverse Effects and Safety

Overall, HT was well tolerated (Tables 3 and 4). With regard to thermal injuries, the predominant pattern was of grade 1 and 2 injuries (National Cancer Institute Common Toxicity Criteria, version 3.0). One patient in the HT arm experienced a third-degree burn that measured 1.0×1.5 cm and healed with conservative measures.

Thermometry catheter complications were also infrequent. Three patients had pain associated with the catheter more than 24 hours after treatment, which required over-the-counter pain medication. Two patients had a catheter infection that required topical antibiotics. Radiation toxicities included skin erythema and desquamation that were managed conservatively. Seventeen of 108 patients required a treatment break over the course of radiation related to radiation toxicity.

DISCUSSION

Evidence for the value of adjuvant HT combined with radiation continues to accumulate. A number of phase III trials demonstrate an improved response rate, duration of local control, and survival for a number of tumor sites and histologies.[8-15] For chest wall recurrence of breast cancer, head and neck cancer, esophageal cancer, and melanoma, HT was shown to significantly increase the CR rate. Patients with glioblastoma multiforme were treated with external-beam radiotherapy and brachytherapy boost, and randomly assigned to no HT versus HT during brachytherapy (median CEM 43°C T_{90} in this trial, 14.1). The median time to progression was 33 weeks in the no-HT group and 49 weeks in the HT group, yielding a 2-year survival of 15% v 31% ($P = .008$).[15] The Dutch Deep Hyperthermia Group randomly assigned 115 cervical carcinoma patients with locally advanced disease; CR rates improved from 57% to 83% with the combination of HT and RT compared with RT alone. More importantly, survival at 3 years was 52% for the combined group and 27% for those treated with RT alone.[12]

However, not all randomized studies have been positive. RTOG conducted the first randomized study of radiation and HT versus radiation alone in superficial tumors (RTOG 8104).[27] The study population was patients with primarily chest wall recurrences of breast cancer and head and neck cancers. The CR rate was approximately 30% in both arms. In the subset of tumors less than 3 cm, a better
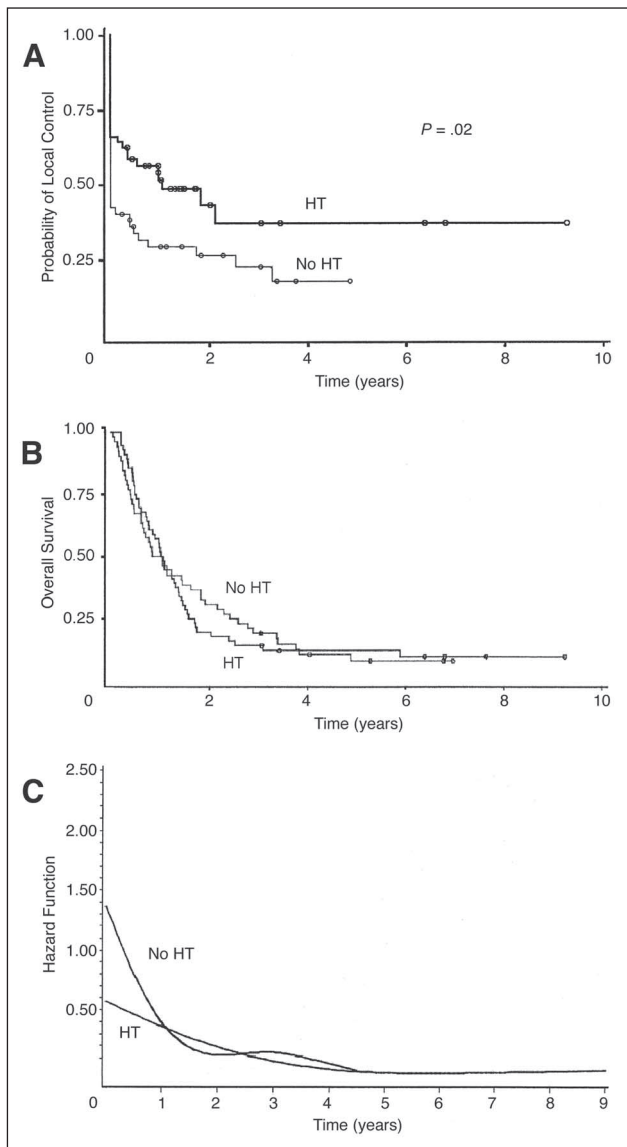
Fig 2. (A) Time to local failure, all patients, log-rank $P = .02$. The primary difference between the two arms occurred at the beginning of the study, corresponding to a significant difference in the complete remission rates in the two arms. (B) Overall survival, all patients, log-rank $P = .84$. (C) Hazard function of time to local failure by arm, all patients, log-rank $P = .02$. Hazard means the risk of having a local failure. Note that the primary difference in the hazard functions between the two arms seemed to have occurred within the first 6 months, likely due to the difference in the complete remission rates in the two arms. The competing risks, including death, were assumed to be independent of this outcome in the two arms. HT, hyperthermia.

Table 2. Local Control Status As of Time of Analysis

Status	No HT (n = 52) No. of Patients	%	HT (n = 56) No. of Patients	%
Local recurrence				
Less than CR	30	58	19	34
Later failure	9	17	10	18
Death (without local treatment failure)	11	21	21	37
Alive with local control	1	2	5	9
Censored: additional local surgery	1	2	1	2

Abbreviations: HT, hyperthermia; CR, complete response.

number of HT treatments and did not prospectively control for cumulative thermal dose.[29,30]

Positive results for the addition of HT were obtained for the combined meta-analysis of five randomized controlled trials with individual patient data for measurable breast cancer lesions for which local therapy was indicated and surgery was not feasible.[8] Among the five studies, a total of 171 patients were randomly assigned to radiotherapy alone versus radiation therapy with HT.

Two articles were subsequently published on thermal dose-response analysis from the individual patients in these trials.[23,24] The first report collected thermal dose data from 120 of the 148 breast cancer patients who were enrolled onto randomized trials from the four collaborating groups: Dutch Hyperthermia Group, Medical Research Council (MRC) at Hammersmith Hospital, the European Society of Hyperthermic Oncology, and the HT group at Princess Margaret Hospital. Five thermal parameters were tested, and two were found to have a significant association with CR rates: max (TD_{min}) and sum (TD_{min}). TD_{min} is the lowest thermal dose recorded at any measurement point during a treatment (TD_{min} is equivalent to the parameter CEM 43°C T_{100}). The sum of TD_{min} is the cumulative thermal dose summed over the series of treatments for a particular patient (ie, CEM 43°C T_{100}).

The definition of CEM 43°C T_{90} in the current study is similar to this end point. Rather than the minimum of all measured points, the CEM 43°C T_{90} defines the thermal

CR rate was noted with radiation and heat (62%) than with radiation alone (40%). However, only 56% of the tumors less than 3 cm and 36% of the lesions $\geq$ 3 cm received adequate HT.[28] It was postulated that the higher response rate in patients with smaller lesions was related to the fact that a larger proportion of the smaller tumors received an adequate thermal dose. Two other negative randomized trials of superficial tumors tested the difference between the

Table 3. HT-Related Toxicities: Catheter Complications

Arm	No. of Patients	Frequency	%
HT	56	6	11
No HT	52	1	2

NOTE. Among those patients in the high-dose arm, three patients had pain associated with the catheter for more than 24 hours and required over-the-counter pain medicines, two patients had infections that required topical antibiotics, and one patient required general first aid for hemorrhage.
Abbreviation: HT, hyperthermia.

Table 4. HT-Related Toxicities: Thermal Burns

Arm	Grade	Frequency	%
HT* (n = 56)	1	14	25
	2	9	16
	3	3	5
No HT† (n = 52)	1	2	4
	2	0	0
	3	1	2

Abbreviation: HT, hyperthermia.
*Overall, 26 burns (primarily first degree) among 56 patients (46%) who received 600 treatments (4.3%).
†Overall, three burns among 52 patients (5.7%).

dose exceeded by 90% of the target volume rather than 100%. Using a categoric relationship with a cutoff of 10 minutes for sum (TD_{min}), the CR rate was 77% for sum (TD_{min}) more than 10 minutes and 43% for sum (TD_{min}) $\leq$ 10 minutes ($P = .022$, adjusted for study center and significant clinical factors). The overall CR rate for the HT and radiation was 61% in these studies, compared with 41% for radiation alone. Max (TD_{min}) and sum (TD_{min}) were associated with local recurrence-free survival and time to local failure.

A similar analysis of thermal parameters was conducted specifically for the Medical Research Council patients.[23] This analysis included 351 HT sessions administered to 101 patients receiving radiotherapy and HT who were entered into phase III concurrent randomized trials for breast cancer. The cumu-lative minimum thermal isoeffective dose (CEM 43°C T_{90}) accrued over the first, first and second, and first three treatment sessions was the only thermal parameter to exhibit a consistent association with CR rate.

This study confirms the results of prior studies with respect to improved CR rate and local control with the addition of HT to radiotherapy. In addition, this study demonstrates that a thermal dose can be prospectively prescribed and delivered, and correlates with outcome. The clinical benefit to adjuvant HT in this study was particularly striking in the group of patients previously irradiated, for whom full-dose additional radiotherapy could not be given (CR rates 24% v 68%). In this study, HT was shown to be an important tool in augmenting the effectiveness of radiotherapy with minimal added toxicity.

In the upcoming era of targeted systemic therapy and improved chemotherapy for micrometastatic disease, the issue of local control may well have increased importance. Efforts are underway to develop three-dimensional noninvasive techniques for monitoring and controlling delivery of HT,[31] which may ultimately make the delivery of a well-defined HT dose feasible and practical for the broader oncologic community.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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