Featured Article

Thermochemoradiotherapy Improves Oxygenation in Locally Advanced Breast Cancer

Ellen L. Jones,[1] Leonard R. Prosnitz,[1] Mark W. Dewhirst,[1] P. Kelly Marcom,[2] Patricia H. Hardenbergh,[1] Lawrence B. Marks,[1] David M. Brizel,[1] and Zeljko Vujaskovic[1]

Departments of [1]Radiation Oncology and [2]Medical Oncology, Duke University Medical Center, Durham, North Carolina

ABSTRACT

Purpose: **The purpose of this research was to evaluate toxicity, response, and changes in oxygenation (pO_2) in patients with locally advanced breast cancer (LABC) treated with concurrent taxol, hyperthermia (HT), and radiation therapy (RT) followed by mastectomy.**

Experimental Design: **Eighteen patients with LABC were enrolled from October 1995 through February 1999. Treatment consisted of taxol (175 mg/m^2) given every 3 weeks for three cycles. Radiation therapy included the breast and regional nodes with a dose of 50 Gy, followed by a boost to 60–65 Gy for those not undergoing surgery. Mastectomy was performed for patients deemed resectable after this neoadjuvant program. HT was administered twice per week. Oxygenation was measured before the first HT treatment and 24 h after the first HT treatment.**

Results: **Fifteen of 18 patients responded, 6 with a clinical complete response, 9 with a partial clinical response, and 3 nonresponders. Thirteen underwent mastectomy with 3 pathological complete responses. Tumor hypoxia was present in 8 of 13 patients (pO_2 = 4.7 ± 1.2 mmHg). Five patients had well-oxygenated tumors (pO_2 = 27.6 ± 7.8 mmHg). Patients with well-oxygenated tumors before treatment as well as those with significant reoxygenation had a favorable clinical response. Tumor reoxygenation appeared to be temperature dependent and associated with the lower thermal doses.**

Conclusions: **This novel therapeutic program resulted in a high response rate in patients with LABC. Hyperthermia may offer a strategy for improving tumor reoxygenation with consequent treatment response. However, the effect of hyperthermia on tumor reoxygenation appears to depend on thermal dose and requires additional investigation.**

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Requests for reprints: Ellen L. Jones, Duke University Medical Center, Durham, NC 27710. Phone: (919) 681-1675; Fax: (919) 684-8718; E-mail: vujas@radonc.duke.edu.

INTRODUCTION

The treatment of locally advanced breast cancer (LABC) has evolved over the past decade into a multidisciplinary approach, which may include chemotherapy, hormonal therapy, surgery, and radiotherapy. Many different multimodality regimens are currently in clinical use (1–5). The 5-year disease-free survival is typically in the 30–50% range, despite aggressive treatment. Locoregional failure occurs in 10–25% of all patients, whereas distant metastases develop in ~50%. Some patients fail both locally and distantly. Most combined modality regimens have been sequential in nature, often using neoadjuvant chemotherapy followed by various surgical approaches and postoperative radiotherapy. This may result in a treatment program that can take up to a year to complete.

The total treatment time has been shown to adversely affect the treatment outcome in other tumors such as cervix and head and neck cancer (6–9). The presumed mechanism for this is tumor repopulation, which may occur in rapidly proliferating tumors during therapy (10, 11). Although the total treatment time has never been proven to effect outcome in LABC, this variable may be of concern given the aggressive growth rates often seen with this tumor.

This study was designed to assess the feasibility and efficacy of administering concurrent trimodality therapy including hyperthermia, chemotherapy, and radiotherapy followed by surgery and additional adjuvant chemotherapy. The purpose of the concurrent treatment is 2-fold: (*a*) to reduce the overall treatment time; and (*b*) to allow for synergism among the radiation, chemotherapy, and hyperthermia. The study goals were to assess the feasibility and tolerance of this trimodality approach. Additional end points included the clinical and pathological response rates, as well as direct measurements of *in situ* tumor oxygenation.

MATERIALS AND METHODS

Patient and Tumor Characteristics. From November 1995 through February 1999, 18 patients with LABC or inflammatory breast cancer were enrolled onto an Institutional Review Board-approved prospective clinical trial. Written informed consent was obtained. Staging studies included an incisional biopsy, bilateral mammograms, chest X-ray, bone scan, computed tomography (CT) of chest and abdomen, and Multiple-gated Acquisition (MUGA) scan. Also a complete blood count with differential and platelets, blood chemistries, and liver and renal function tests were completed. Patients with a cardiac ejection fraction of <45%, WBC < 3,000 or absolute neutrophil count < 15,000, and platelets < 100,000 were excluded. Patients with distant metastases at presentation or who had received prior therapy were considered eligible. Eleven patients did not have metastases, and 7 patients had distant metastases. The median age was 52. Additional patient characteristics are listed in Table 1.

Table 1 Patient characteristics

Age	Median 51.6 years (range, 40.8–64.5 years)
ER/PR[a] status	
Positive/positive	4
Negative/positive	1
Positive/negative	1
Negative/negative	11
Unknown	1
Tumor grade	
Grade 2/3	1
Grade 3/3	14
Not stated	3
Her-2/*Neu*	
Positive	5
Weakly positive	1
Negative	11
Unknown	1
LVI	
Positive	9
Negative	9
Stage distributions	
T3	3
T4	13
T4 (recurrent)	2
Metastasis	7
No metastases	11

[a] ER, estrogen receptor; PR, progesterone receptor; LVI, lymphovascular invasion.

Treatment Methods. Radiation therapy tangential fields were designed to comprehensively encompass all of the breast tissue, including the tumor and internal mammary nodal regions. On the basis of a planning CT scan obtained in a customized immobilization cradle in the treatment position, the location of the internal mammary vessels was determined relative to the deep border of the tangential fields. If tangential fields that included the internal mammary nodal regions had an acceptable volume of lung (generally defined as $\leq$3.5 cm of lung tissue measured from the posterior border of the tangential field to the internal rib cage at isocenter), that approach was generally used. Alternatively, the internal mammary nodal regions chain was included in a separate *en face* field matched to the medial border of the tangential field using a mixture of photons and electrons. The supraclavicular nodes were treated using a separate field with a nondivergent match to the tangential field. An anterior oblique approach was used with a field typically angled 15° to the contralateral side to include the medial supraclavicular nodes but avoid exit into the spinal cord. Radiation was given at 200 cGy/day to a total of 5000 cGy to the breast, supraclavicular nodes, and internal mammary nodes. A boost to a total dose of 60–65 Gy was delivered for those not undergoing surgery. Tissue equivalent bolus and wedges were used as clinically indicated to assure adequate doses to superficial tumors and minimize target heterogeneity.

Chemotherapy. Taxol (175 mg/m^2) was given every 3 weeks for three cycles. Radiation therapy was begun 2 days after the first taxol dose. Patients received dexamethazone, diphenhydramine, and cimetidine premedication, and dose modifications according to the National Cancer Institute Common Toxicity Criteria (v2.0) were based on the blood counts and interim nonhematological toxicities of the previous cycle. The chemotherapy dose was not reduced unless hospitalization was required for febrile neutropenia, platelet transfusions were required for counts $<$20,000, or if there was significant bleeding.

Hyperthermia. Twice-weekly hyperthermia treatments were administered within 30 min after radiation. First hyperthermia treatment was given after first fraction of radiotherapy. A total of 10 hyperthermia treatments were prescribed to be delivered to the tumor mass with microwaves (433 or 915 MHz) using standard techniques for thermometry selection and placement (12). Patients routinely received Lorazepam or narcotic premedication. Lidocaine HCL (1% solution buffered with 0.1 mEq sodium barcarbonate/ml lidocaine) was used as local anesthesia for placement of the thermometry catheter. Externally applied microwaves were used for any lesions $<$3 cm in thickness. Fiberoptic thermometry probes were placed inside sterile, blind-ended catheters that were inserted into the tumor according to Radiation Therapy Oncology Group guidelines. Temperature measurements were made along the length of the catheter in 5-mm increments every 10 s. Catheter locations were verified during placement by CT scan. Probes were also placed on the skin and near scar lines to monitor surface normal tissues. The treatment goal was to reach 41–41.5°C in $>$90% of measured points for a duration of 60 min. If this was achieved over the course of 10 fractions of HT, the cumulative equivalent minutes 43°C T90 would be $\geq$10. This thermal dose concept has been described earlier (13). Maximal allowable temperatures in the adjacent normal tissue and tumor were 43°C and 48°C, respectively. Applied power was adjusted to reach the desired temperature distribution without exceeding the normal tissue temperatures or tolerance of the patient.

Oxygenation Measurements. Oxygenation measurements (pO_2) were performed during radiotherapy before the first hyperthermia treatment and 24 h after the first hyperthermia treatment using a polarographic device (Eppendorf Netheler Hinz, GmbH, Hamburg, Germany). This technique has been described previously (14, 15). Polarographic electrodes were calibrated before and after the measurements in phosphate-buffered normal saline with room air and 100% nitrogen at room temperature. Location of tumor, assessment of tumor size, and the depth from the skin surface to the peripheral edge of the tumor was determined using CT scan. After determining and marking the insertion site, skin overlying the site was cleansed with betadine and anesthetized with 2% lidocaine. Under CT guidance a 16-gauge needle was inserted and placed at the edge of tumor. The total measurement path was adjusted according to the tumor size, so the measurements were only performed in tumor tissue. The probe was automatically advanced forward in steps of 0.7 mm and subsequent backward step of 0.3 mm with the net increments of 0.4 mm. Multiple probe tracks were obtained with at least 100 distinct pO_2 measurement points collected per tumor per measurement session.

Statistics. Given the small number of patients and Phase I nature of the study, crude rates are used to describe outcomes.

RESULTS

Clinical and Pathological Response and Patient Outcomes. Patients were seen 3–4 weeks after completion of trimodality therapy to score clinical response and finalize plans for mastectomy, as appropriate. Of the 18 patients enrolled, 6 had a clinical complete response (CR), defined as complete absence of tumor on physical examination. Nine patients had a clinical partial response, defined as >50% reduction in initial tumor volume. Three patients had stable disease without clinical response. Thirteen patients underwent mastectomy. Among the 6 patients with a complete clinical response, 3 had a complete pathological response in both breast specimen as well as having no evidence of axillary nodal involvement. The pathological CR rate is, thus, estimated at 23% (95% confidence interval, 5–54%). Fourteen of the 18 patients enrolled are alive with a median follow-up of 11 months since completion of therapy (range, 2.4–40.8). One patient had a local failure. Two patients failed in the contralateral breast or contralateral axilla after complete clinical and partial pathological responses.

Toxicity. The combination of radiation, taxol, and hyperthermia was reasonably well tolerated in the acute setting. Sixteen of 18 patients developed moist desquamation of varying extent, which is not unexpected given the size of tumor, large radiation fields, and use of bolus when appropriate. One of these patients failed to complete the prescribed 5000 cGy due to the acute skin reaction. One patient failed to complete the anticipated 10 hyperthermia treatments because of a third-degree burn. A second patient also developed a small (<1 cm) region of third-degree burn but completed the program. Two additional patients developed second degree burns, and 1 patient had s.c. fat necrosis. Fat necrosis is a thermal injury to s.c. tissues in the absence of cutaneous burn. Two patients developed hematomas associated with the placement of the hyperthermia thermometry catheters. These were self limited and resolved with conservative measures.

Post-mastectomy complications occurred among 9 of the 13 patients who underwent mastectomy. Details are listed in the Table 2. Plastic surgery for reconstruction was not required in any of the cases of dehiscence. All healed with conservative measures.

Table 2 XRT[a]/taxol/HT mastectomy complications by patient

Complications (among 15 patients total)	Incidence
None	4
Delayed healing <2 weeks	1
Delayed healing causing delay in adjuvant chemotherapy (<2 weeks) with infection requiring oral antibiotics and dehiscence ≤25%	4
Delayed healing causing delay in adjuvant chemotherapy (<2 weeks) with infection requiring oral antibiotics and dehiscence >25%	2
Dehiscence ≤25%	1
Dehiscence >25%	1
Multiple complications requiring hospital admission	1
Delay in adjuvant chemotherapy >2 weeks	
Infection requiring iv antibiotics	
Dehiscence >25% requiring debridement in OR	
Planned split thickness skin graft at time of mastectomy with two areas of necrosis 2 × 3 cm, ~80% "take" of graft	1

[a] XRT, x-ray therapy; HT, hyperthermia.

Table 3 Summary of thermal data

Patient no.	No. of treatment	Total CEM 43 T90	Total CEM 43 T50	Average T90 C	Average T50 C
1	11	15.98	206.25	39.65	41.315
2	8	8.29	32.06	38.848	40.361
3	9	21.83	91.92	39.518	40.764
4	8	5.50	31.02	38.893	40.115
5	9	4.72	87.25	38.20	39.78
6	9	5.23	18.93	38.92	39.81
7	10	12.29	81.77	39.554	41.229
8	10	15.61	146.00	39.887	41.401
9	10	46.19	165.50	40.59	39.63
10	9	12.73	200.50	39.08	40.99
11	10	30.36	114.30	40.12	41.24
12	8	2.77	35.79	38.696	39.788
13	9	6.53	27.43	38.77	39.67
14	9	3.84	7.24	38.544	39.124
15	9	22.50	460.50	39.89	41.55
16	10	852.72	4358.88	40.43	44.58
17	2	1.45	381.6	39.13	42.83
18	8	14.66	84.30	39.18	41.12

Thermometry Results. The average number of hyperthermia treatment sessions was 8.7 (range, 2–11). Thermal parameters for each patient are shown in Table 3. The thermal goal of 10 cumulative equivalent minutes 43° T90 was achieved in 10 of 18 patients. There was no evident correlation between increasing thermal dose and improved tumor response. In fact, the opposite trend occurred for all four of the thermal parameters examined. The negative relationship between thermal dose and treatment response was significant for T90°C values ($P = 0.009$; Fig. 1). Furthermore, the response rates were lower in those that have achieved the thermal goal (cumulative equivalent minutes 43° T90 >10) than in those that did not (Fig. 2).

Tumor Oxygenation. Before treatment, tumor oxygenation was measured in 13 of 18 patients, with an average median ± SE pO_2 of 13.5 ± 4.3 mmHg. Tumor hypoxia (median pO_2 < 10 mmHg) was present in 8 of 13 patients (average median ± SE pO_2 = 4.7 ± 1.2 mmHg). The other 5 patients had well-oxygenated tumors (average median ± SE pO_2 of 27.6 ± 7.8 mmHg). Posthyperthermia pO_2 was measured in all of the patients who had baseline measurements. There was a nonstatistically significant increase in pO_2 24 h after the first hyperthermia treatment (average median ± SE pO_2 of 20.4 ± 6.4 mmHg). Patients with hypoxic tumors before treatment had a significant improvement ($P = 0.0002$) in tumor pO_2 after the first hyperthermia treatment (average median ± SE pO_2 increased to 23.3 ± 7.7 mmHg). Tumor oxygenation results are summarized in Table 4. Patients with well-oxygenated tumors before treatment as well as those with significant reoxygenation had a favorable clinical response to treatment (CR or partial response) with an average ± SE increase in pO_2 of 15.8 ± 6.6 mmHg. However, a significant decrease ($P = 0.002$) in average median ± SE pO_2 of 8.3 ± 6.9 was observed in patients who did not respond to treatment (Fig. 3*A*). Furthermore, correlation between changes in tumor reoxygenation and thermal parameter

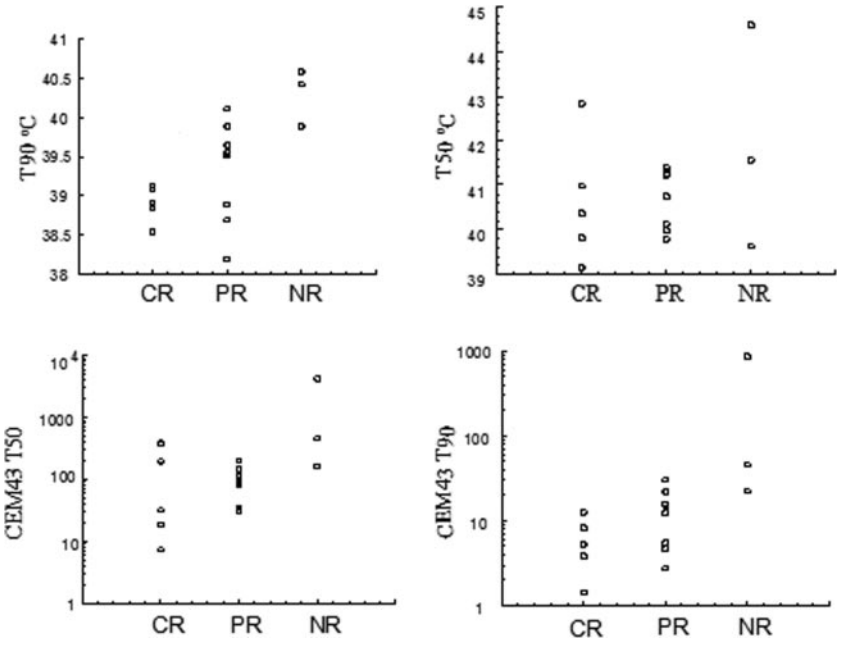

Fig. 1 The correlation between thermal parameters (CEM 43°T_{90}, CEM 43° T_{50}, T90 C, and T50 C) and primary treatment response.

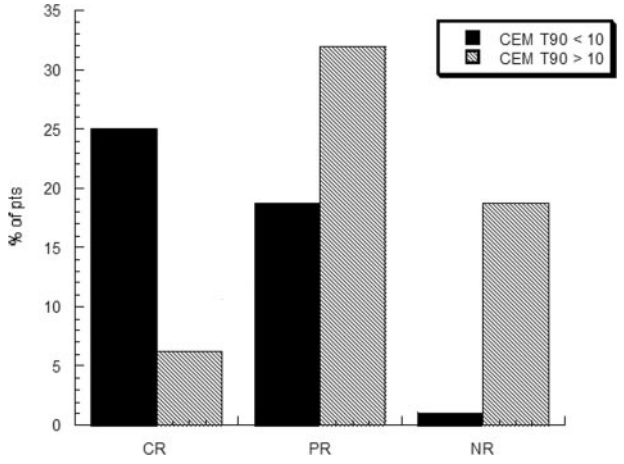

Fig. 2 The correlation between treatment response and achievement of the thermal goal (CEM T90 > 10).

T50°C showed higher temperature to be associated with the loss of reoxygenation effect (Fig. 3*B*).

DISCUSSION

Clinical Considerations. Patients with LABC are at significant risk for locoregional and systemic disease; thus, multimodal therapy has been used in a variety of strategies (1–5). The National Cancer Institute used chemotherapy or chemotherapy with hormonal synchronization to maximal response in a neoadjuvant prospective trial of 107 patients (1). For those patients who achieved a complete clinical response, multiple biopsies were performed, and the pathological response was used to determine the local therapy. Objective clinical responses (partial and complete clinical response) were obtained in 92% of patients. Twenty-nine percent of the overall group of patients had a pathological CR by directed biopsy, not lumpectomy or mastectomy.

A later prospective trial with 89 patients at the University of Michigan used nine cycles of neoadjuvant chemohormonal therapy with pathological complete responders treated with radiation only (2). The overall clinical response rate was 97% (clinical, partial, and CRs), and 28% of patients had a complete pathological response as evaluated by directed biopsies.

The largest study of neoadjuvant chemotherapy for breast cancer patients was conducted by the National Surgical Adjuvant Breast and Bowel Project (4). The patients consisted of a somewhat earlier-stage cohort with palpable, surgically operable breast cancer ($T_{1,2,3}$, $N_{0,1}$, and M_0). In that study, 1523 women were randomized to surgery followed by adjuvant doxorubicin/cyclophosphamide chemotherapy *versus* neoadjuvant adjuvant doxorubicin/cyclophosphamide chemotherapy followed by surgery. An overall pathological CR occurred in only 9% of patients treated with neoadjuvant adjuvant doxorubicin/cyclophosphamide chemotherapy. However, an additional 4% of patients were found to have only residual *in situ* tumor, which resulted in 13% overall pathological CR for invasive tumor. Seven percent of the patients with clinically positive nodes before neoadjuvant therapy were found to have pathological CR at the time of axillary dissection.

Table 4 Summary of pO_2[a] measurement results

	No. of patients	Median pO_2 mmHg	
		Pretreatment	Posttreatment
Hypoxic tumors	8	4.7 ± 1.2	23.3[b] ± 7.7
Well-oxygenated tumors	5	27.6 ± 7.8	32.8 ± 6.8

[a] pO_2, oxygenation.
[b] $P = 0.002$.

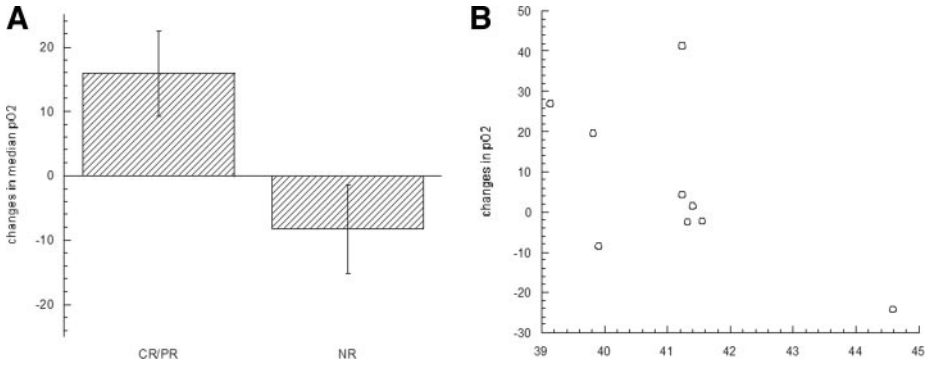

Fig. 3 *A*, changes in average median oxygenation (pO_2) after hyperthermia treatment in responders [complete response (*CR*) and partial response (*PR*)] and nonresponders (*NR*). Patients that responded to treatment are those that experienced an increase in tumor pO_2 after the treatment. *B*, correlation between changes in tumor reoxygenation and thermal parameter T50 C; *bars*, ±SD.

Using a different approach, 36 patients with LABC (stages IIB, III, and IV, supraclavicular adenopathy only) who were initially deemed unresectable with primary wound closure were treated with a course of preoperative 5-fluorouracil and concurrent radiotherapy (3). The objective clinical response rate to this neoadjuvant chemoradiotherapy was 73%, and all were able to undergo modified radical mastectomy with primary wound closure. Seventeen percent of patients had complete pathological response, and 20% had minimal microscopic disease. In our current series, we had a pathological CR rate of 3 patients among 13 patients undergoing mastectomy (23%), but the postoperative complications were relatively common (Table 2).

Thermal Dose Response. The effect of hyperthermia on tumor response in multimodality treatment is a complex issue that involves biological and physiological mechanisms. Interaction and sequence of different treatment modalities certainly introduce another level of complexity. It is well established that hyperthermia can cause and/or enhance direct tissue damage and cell kill, inhibit DNA damage repair, and induce tumor reoxygenation. These effects of hyperthermia are temperature dependent. However, which effect is the most important when given in combination with chemoradiotherapy is not established and may vary over a range of temperature and thermal dose. When compared with other series, thermal doses from the present study are generally lower than thermal doses reported in the clinical trials (Table 5; Refs. 16–18). Higher thermal doses may be more likely to be involved in inhibition of DNA repair and direct cytotoxicity, whereas lower doses may impact mostly on reoxygenation.

This study has shown a paradoxical relationship between thermal dose and treatment response. It appears that patients receiving lower thermal doses tend to respond better to treatment than the patients with higher doses (Figs. 1 and 2). On the basis of our data demonstrating temperature-dependent tumor reoxygenation (Fig. 3*B*) and thermal dose-response relationship (Fig. 1), we believe the thermal dose-response relationship observed in trials with higher thermal doses is related to hyperthermia effects on direct tumor cytotoxicity and DNA damage repair, whereas the reoxygenation effect is the predominant mode of interaction in the dose range for this series.

In this limited dataset, it is important to recognize that one can only generate hypotheses for additional study, because the power to detect true differences between groups is limited. Keeping this caution in mind, we hypothesize that the paradoxical relationship between thermal dose and treatment response is due to temperature-dependent tumor reoxygenation. We propose that reoxygenation and consequent enhancement of clinical response might follow bell shaped curve in relation to thermal dose. In other words, the maximum improvement in tumor oxygenation and treatment response could be achieved only within an optimum range of thermal doses.

Responses are better when tumors are well oxygenated, either before treatment or if pO_2 increases 24 h after the first heat treatment. The benefits of hyperthermia in the clinical setting (other than its cytotoxic and radiosensitizing effects) may result from improvements in oxygenation, as shown earlier in a series of human sarcoma patients (19, 20). Results from several studies in rodent tumors and human tumor xenografts support the notion that an overall improvement in tumor oxygenation can result from lower thermal doses, whereas at higher

Table 5 Summary of thermal parameters from other studies as compared with present results

		Thermal parameter		
Reference	Tumor site	Median T_{50} (°C)	Median T_{90} (°C)	Mean T_{90} (°C)
Oleson *et al.* 1993	Superficial		39.4	
	Sarcoma	41.6		
	Deep	40.1		
Vernon *et al.* 1996	Breast cancer		40.0	
		41.8		
Kapp *et al.* 1995	Breast cancer			40.8
Present study	Breast cancer	40.8		
			39.1	
				39.3

thermal doses tumor oxygenation decreases (21–24). These results are reviewed by Song *et al.* (25). Hyperthermia improves tumor oxygenation in both canine and human soft tissue sarcomas (20, 26). The present study demonstrates that an improvement in tumor oxygenation after hyperthermia treatment can also be achieved in LABC. However, the present results also suggest that tumor reoxygenation decreases with higher thermal doses (Fig. 3*B*), and the failure to reoxygenate is associated with poorer treatment outcome. This result strongly suggests that effectiveness of hyperthermia in this setting is due to its ability to reoxygenate tumors.

Because reoxygenation occurs at lower thermal doses, reassessment of thermal goals for hyperthermia needs to be made. This could also be of importance if hyperthermia is combined with chemotherapy due to the oxygen-dependent activity of some chemotherapeutic agents. In animal studies, improvement in tumor oxygenation has been shown to increase tumor cell killing by cyclophosphamide, 1,3-bis(2-chloroethyl)-1-nitrosourea, Adriamycin, and taxol (27–30). The thermal isoeffect dose relationship for thermochemoradiotherapy may be different from that for thermoradiotherapy.

The time course of hyperthermia-induced improvements in tumor oxygenation is important for combined chemo/radiotherapy/hyperthermia treatment. Horsman and Overgaard (31) reported that the improvements in tumor oxygenation resulting from mild hyperthermia in the C3H mouse mammary carcinoma were transient. Their results suggested that any increase in radiation cytotoxicity resulting from the improved oxygenation would occur only if radiation were given simultaneously or shortly after hyperthermia. In contrast, results from the canine and human sarcoma studies suggest that improvements in oxygenation persist up to 24 h after hyperthermia (20, 26). Similar findings were reported by Iwata *et al.* (32) and Shakil *et al.* (33). In both studies an improvement in tumor oxygenation persisted for periods of up to 24 h after 1 h of 41.5°C hyperthermia treatment (32, 33). Also, persistent improvement in oxygenation was observed in both human sarcoma and breast cancer patients 24 h after hyperthermia (20, 34). The present study confirms that hyperthermia-induced reoxygenation effects on human tumors can last at least for 24 h.

The mechanism of hyperthermia-induced reoxygenation was initially attributed to hyperthermia-induced changes in tumor blood flow (24, 35, 36). It is suggested based on oxygen transport models that at least a 5–10-fold increase in tumor perfusion may be required to achieve the level of improvement in tumor oxygenation observed in canine sarcoma studies (37). Therefore, it is likely that enhanced tumor oxygenation is also influenced by the effect of heat on oxygen consumption and ATP levels. Oxygen consumption and ATP synthesis in the mitochondria are coupled. Because of the pronounced thermosensitivity of the mitochondrial respiratory chain, oxygen consumption after hyperthermia decreases (38, 39). Improved tumor oxygenation is likely a result of the both processes, the decrease in oxygen consumption and an increase in tumor blood flow.

It is also possible that chemotherapy contributes to the long-term reoxygenation. Milas *et al.* (28) have shown that reoxygenation occurs in the MCA-4 murine mammary carcinoma 24 h after taxol treatment. Median pO_2 values increased from 6.2 mmHg in untreated tumors to 10.0 mmHg in treated tumors. The authors suggested that the enhancement of tumor radioresponse by taxol is mediated by reoxygenation of hypoxic tumor cells (28, 29). However, in the present study any contribution of taxol and/or radiotherapy on tumor reoxygenation was accounted for in pO_2 measurements before hyperthermia treatment. Therefore, changes in pO_2 values in this study were primarily affected by hyperthermia.

In conclusion, our earlier findings related to the relationship between tumor oxygenation and thermal dose (26), and results of this study suggest that the changes in tumor oxygenation are temperature dependent and that this relationship may influence treatment outcome. It is also likely that at lower thermal doses (which are easily achievable in clinic) tumor reoxygenation is more relevant for tumor response than the cytotoxic effect itself. This could be particularly important for thermochemoradiotherapy protocols that include chemotherapeutic agents of which the activity is known to be oxygen dependent. However, considering limitations due to the small number of patients in this study, it is important to conduct more clinical studies in which thermal dose parameters and oxygenation are measured to establish more precisely the thermal dose-reoxygenation-response relationship. Therefore, this preliminary study may help to bracket the optimal thermal dose range for combining hyperthermia with radiotherapy and chemotherapy. Furthermore, this regimen resulted in a high rate of pathological CR (23%), favorably comparable with other series of locally advanced breast patients.

This is the first study in human breast cancer patients that demonstrates that changes in tumor oxygenation are temperature dependent and that the improvement in oxygenation may be related to treatment outcome and pathological response. In future studies, we hope to correlate tumor oxygenation with other noninvasive measurements of tumor physiology using magnetic resonance spectroscopy. Ideally, this will be coupled with magnetic resonance-based noninvasive thermometry to determine the full three-dimensional representation of thermal dose, which might then be precisely correlated with the alterations in tumor physiology and subsequent clinical response.

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