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Durable palliation of breast cancer chest wall recurrence with radiation therapy, hyperthermia, and chemotherapy

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Abstract

Background and purpose—Chest wall recurrences of breast cancer are a therapeutic challenge and durable local control is difficult to achieve. Our objective was to determine the local progression free survival (LPFS) and toxicity of thermochemoradiotherapy (ThChRT) for chest wall recurrence.

Methods—Twenty-seven patients received ThChRT for chest wall failure from 2/1995 to 6/2007 and make up this retrospective series. All received concurrent superficial hyperthermia twice weekly (median 8 sessions), chemotherapy (capecitabine in 21, vinorelbine in 2, and paclitaxel in 4), and radiation (median 45 Gy). Patients were followed up every 1.5–3 months and responses were graded with RECIST criteria and toxicities with the NCI CTC v4.0.

Results—Twenty-three (85%) patients were previously irradiated (median 60.4 Gy) and 22 (81%) patients received prior chemotherapy. Median follow-up was 11 months. Complete response (CR) was achieved in 16/20 (80%) of patients with follow-up data, and 1 year LPFS was 76%. Overall survival was 23 months for patients with CR, and 5.4 months in patients achieving a partial response (PR) ($p = 0.01$). Twenty-two patients experienced acute grade 1/2 treatment related toxicities, primarily moist desquamation. Two patients experienced 3rd degree burns; all resolved with conservative measures.

Conclusions—ThChRT offers durable palliation and prolonged LPFS with tolerable acute toxicity, especially if CR is achieved.

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Conflicts of interest statement

E.L. Jones, M.D., Ph.D., on speaker's bureau and consultant, BSD Medical; M.W. Dewhirst is a paid consultant and Chair of the Scientific Advisory Board of Celsion, Inc., and is recipient of research contracts from Varian Corporation and GlaxoSmithKline, Inc., M.W.D. and V.J. are recipients of grants from the National Institutes of Health; all other authors had none.

Durable palliation of breast cancer chest wall recurrence with radiation therapy, hyperthermia, and chemotherapy is an approved Duke University Protocol, #00003793.

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Keywords

Breast cancer recurrence; Chest wall; Radiation; Chemotherapy; Hyperthermia

Local recurrence rates of breast cancer after mastectomy alone have been reported as high as 45% for those with T3/T4 or node positive disease [1]. This high rate of failure can be reduced to 2–15% with the addition of postmastectomy radiation therapy (PMRT) and usually chemotherapy as well [2–10], with a corresponding improvement in overall survival [3,4,7]. Treatment for patients that recur in the setting of previous mastectomy and PMRT is quite problematic.

Options for additional therapy may include surgery, chemotherapy, or re-irradiation with or without sensitization (i.e. concurrent chemotherapy or hyperthermia). The utility of further surgery in achieving local control and long-term survival has been reported in several small retrospective series, but the majority of patients are not resectable [11–16]. In the setting of prior radiation therapy, chest wall re-irradiation alone results in complete responses (CR) and long-term local control in relatively few patients [17,18].

Based on the poor results obtained with re-irradiation alone, some investigators advocate combining hyperthermia and radiation in patients that have been previously irradiated, which is supported by randomized and non-randomized studies [19–30]. With its radiosensitizing properties, hyperthermia presumably lowers the radiation dose needed to achieve durable local control, which in turn has potential implications for decreased long-term toxicities in patients with a prior history of radiotherapy. The addition of concurrent chemotherapy to hyperthermia and radiation therapy, constituting thermochemoradiotherapy (ThChRT)), has been evaluated in phase I/II trials by several researchers and found to be well-tolerated, with moderate success [31,32].

Our hypothesis was that the radiosensitizing properties of both chemotherapy and hyperthermia would presumably allow for reduced doses of radiation with equivalent efficacy—an important consideration in patients who received prior radiation—and result in prolonged LPFS and long-term palliation, with limited toxicity.

Material and methods

Patient data

This IRB-approved retrospective study includes 27 patients with chest wall recurrence of breast cancer who received combined modality therapy with concurrent radiation, hyperthermia, and chemotherapy from February 1995 to June 2007 at the Duke University Medical Center. Four patients were treated from 1995 to 1998, and the remaining 23 from 2004 to 2007: competing protocols account for the small number of patients in this series and the gap in entry.

Patients were evaluated in a multidisciplinary setting by medical oncologists, surgeons, and radiation oncologists. All patients had unresectable disease. All patients had biopsy proven invasive cancer recurrence and had imaging to evaluate for distant meta-static disease with PET and or CT, or bone scan in patients that did not have a PET.

Treatment modalities

Radiation therapy—Radiation was delivered in 1.8–2 Gy fractions utilizing either photons or electrons, or a combination of both. In addition to treating the entire chest wall to a median dose of 45 Gy (range 34–50.4 Gy), areas that harbored malignant involvement,

including enlarged locoregional lymph nodes, the flank(s), upper abdomen, back and arms were irradiated. Seven patients received a boost with smaller fields to residual gross disease to a median of 54 Gy (range 45–70 Gy). In patients who had not previously been irradiated (4 patients), or in those who had not had lymph node regions irradiated (16 patients), the supraclavicular fossa was included, and if the internal mammary lymph nodes could be included safely in partly wide tangents, they were treated as well (median dose of 40 Gy, range 34–54 Gy). Tissue equivalent bolus was used when appropriate. Patients were immobilized supine with their arms above their head. Radiotherapy was delivered once daily, on five consecutive days per week, holding only if patients required a toxicity related treatment break.

Hyperthermia—Patients were deemed appropriate hyperthermia candidates if they had superficial tumors, defined as no deeper than 3.0 cm from the skin surface. Hyperthermia was given using microwave spiral strip applicators, operating at 433 MHz and 915 MHz, and 1 MHz/3 MHz ultrasound applicators, depending on the tumor location and patient anatomy. Waterbolus was used between the hyperthermia applicators and the thoracic wall. The water temperature typically varied between 40 °C and 44 °C depending on patient tolerance.

If a patient had extensive disease that could not be encompassed by one hyperthermia applicator (maximum coverage 15 × 15 cm), the involved area was divided into adjacent hyperthermia fields, which were abutting, but not overlapping. The hyperthermia target volume was the gross disease on the chest wall, with a target temperature in tumor of 42–44 °C, as limited by patient tolerance. Maximally allowed temperatures in the adjacent normal tissue and tumor tissue were 43 °C and 50 °C, respectively.

The majority of patients had tumor temperatures measured on the surface due to the superficial nature of the recurrence. When feasible, thermometry catheters were placed in tumor tissue. A sterile, blind-ended interstitial catheter was placed in the tumor using computed tomography guidance as per Radiation Therapy Oncology Group (RTOG) guidelines; 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. Thermometry probes were also placed on the skin and near scar lines within the HT field to monitor normal tissue and surface temperatures. Hyperthermia was administered twice weekly (1–2 h in length, separated by at least 48 h) 30 min prior to irradiation, for a median number of eight treatments (range 1–10). If patients experienced thermal injury related to hyperthermia administration, then it was held until it was deemed that the patient could receive further hyperthermia.

Chemotherapy—All patients received concurrent chemotherapy. The selection of which agent to be given was at the discretion of the administering medical oncologist. Capecitabine (1000 mg/m^2) was given orally twice daily (5 days per week) in 21 (78%) patients, paclitaxel IV (175 mg/m^2) once every 3 weeks in 4 (15%), and vinorelbine IV (25 mg/m^2) once weekly in 2 (7%) patients. No patient received chemotherapy while they were actually undergoing a hyperthermia procedure. Chemotherapy was held/dose reduced if their WBC counts were <2000/μL, or if hand/foot dysesthesias or oral ulcers occurred.

Follow-up

Patients under treatment were seen at least weekly during treatment, more frequently if required. At the completion of ThChRT, they were seen at 4–6 weeks in the radiation oncology department, and then on an alternating basis with medical oncology for as long as the patient remained alive and returned to our institution. Patients lost to follow-up were censored for local progression free survival (LPFS) at their last follow-up but were included in the acute toxicity analysis.

Outcomes

The primary endpoints of this study were CR rates and duration of LPFS. Secondary endpoints included toxicity of ThChRT, incidence of distant metastases (DM), and overall survival (OS). Toxicity was graded using the modified NCI Common Terminology Criteria (CTC, version 4.0). A local progression was defined as any tumor recurrence within the heated/irradiated field. Distant metastases were determined by radiographic examinations with or without subsequent histopathologic confirmation. LPFS and OS were calculated from the last day of radiation therapy administration. Patients that were lost to follow-up were censored for the LPFS analysis. The Kaplan–Meier method was used to compute LPFS and OS [33]. Chi square and log-rank tests were utilized to compare endpoints based on response to therapy (i.e. CR versus PR). All measures were analyzed with statistical software (SAS, Cary, NC, USA), with a 2-sided alpha level <0.05 regarded as statistically significant.

Patients' response to therapy was graded using the RECIST criteria, with confirmation at their first follow-up visit for the patients that returned for follow-up. A complete response (CR) was defined as disappearance of all measurable disease; a partial response (PR) was defined as a 30% decrease in measurable disease; stable disease (SD) was present when neither criteria for PR or PD were met; progressive disease (PD) was assigned when a 20% increase in disease extent was noted, and no CR, PR, or SD was achieved prior to growth [34].

Results

Twenty-seven patients received ThChRT for chest wall recurrence of breast cancer, with a median follow-up of 6 months (range 0–70 months). Seven patients were lost to follow-up regarding local disease outcome, but did have follow-up regarding survival (all seven died of breast cancer). The median follow-up for the remaining 20 patients was 11 months (range 1–70 months). Median time from initial diagnosis to chest wall failure prompting study entry was 27 months (range 5–257 months). The median age was 51 (range 37–75); 96% were Caucasian. One-third of patients initially presented with stage IIIA disease, and 17 patients had nodal involvement at the time of original diagnosis. For full details of patient characteristics at initial diagnosis of breast cancer, see Table 1. At the time of their recurrence, 22 had chest wall disease only; 5 also had distant metastatic disease. The majority of patients had extensive burdens of disease, with diffuse superficial involvement of the entire chest wall. One patient had bilateral supraclavicular matted lymphadenopathy, with no disease on her chest wall and three patients had axillary and or supraclavicular failures in addition to chest wall disease. For individual characteristics of each patient, see Table 2. Twenty-six out of 27 patients completed the prescribed radiotherapy dose. The one patient that did not complete therapy developed rapidly progressive visceral metastatic disease.

Previous therapy

These patients were heavily pre-treated, with 23 (85%) having received prior radiotherapy to a median dose of 60.4 Gy (range 50–67.9 Gy). Similarly high percentage of patients (89%) received prior systemic therapy. Twenty-two (81%) received prior chemotherapy, 9 (33%) received prior hormonal therapy, and 7 (26%) received both. Two patients underwent surgical resection of their chest wall recurrence but had positive margins and extranodal extension of disease.

Local progression free survival

Of the 27 patients treated, none progressed during therapy. Seven were not evaluated for remission status because they did not return for their 1 month follow-up. At the completion of their therapy, two had achieved a CR and five had a PR which were unable to be confirmed. Of the 20 patients that we have a confirmed assessment of disease status 1 month post completion of therapy, 16 (80%) had a CR and 4 (20%) had a PR, for an overall response rate of 100%. Of these 20 patients, 4 (20%) patients developed a local progression within the irradiated/heated treatment field. One-year LPFS was 76%, with four patients having recurred/progressed locally (Fig. 1a).

Overall survival

Median overall survival for the entire cohort was 14.3 months (Fig. 1b). When analyzed by response to therapy, those patients who achieved a CR had a median OS of 23 months, while the partial responders survived a median of 5.4 months ($p = 0.01$) (Fig. 1c). Overall, 14 patients (52%) developed metastatic disease, most frequently to the lungs and liver.

Toxicity

Overall, there were 22 patients who experienced acute grade 1/ 2 toxicities. By far the most frequent was moist desquamation in 17 patients (63%), which was managed conservatively and did not require treatment interruption. Two patients developed clinically asymptomatic fat necrosis by physical examination, which was not pathologically confirmed, nor required therapy.

Thermal injury occurred in nine patients, two of which were small volume 3rd degree burns, both of which resolved. One of the patients developed a 3rd degree burn in a transverse rectus abdominis myocutaneous (TRAM) flap, and hyperthermia was discontinued only after four treatments. After 15 months, this area had healed without further intervention.

Chemotherapy was well tolerated and was administered as prescribed to 23 of 27 patients. There were no hematologic or other toxicities associated with paclitaxel or vinorelbine that required dose reduction or discontinuation. Capecitabine was held for 5 days in two patients secondary to palmar/plantar dysesthesias. It was dose reduced in one other for the same reason. Capecitabine was ultimately discontinued in one patient related to oral ulcers. There were no significant hematologic toxicities associated with its use.

Discussion

The utility of combined modality therapy with hyperthermia rests on several principles. Hyperthermia can be directly cytotoxic and is a known radiosensitizer [35], inhibiting potentially lethal and sublethal damage repair [36]. It is most effective in the S-phase of cell cycle, complementing the relative resistance of this phase to radiation injury [37]. It also alters tumor blood flow and may improve tumor oxygenation [38], which in turn may result in delivery of a higher concentration of chemotherapeutic agents as well as enhance the effect of radiotherapy by decreasing the amount of hypoxia. Hyperthermia may also act

synergistically with the chemotherapeutic agents themselves to enhance cytotoxicity [39]. More than additive effects are seen with cell kill when hyperthermia is combined with alkylating agents, antibiotics and platinum drugs. When hyperthermia is used in conjunction with pyrimidine antagonists, with 5-fluorouracil being the most frequently studied, the effect is seemingly additive [39].

There has been considerable interest in combining hyperthermia with radiotherapy for superficial chest wall recurrences of breast cancer [19–27]. Multiple prospective [19,26] and retrospective [24] studies cite a statistically significant increase in the rate of CR when adding hyperthermia to radiotherapy versus radiotherapy alone, with CR rates typically in the range of 59–66% versus 41–42%, respectively. Complete response rates as high as 95% have been published with the addition of hyperthermia to radiation in a small single institution report [29].

The addition of hyperthermia to radiotherapy and chemotherapy in the setting of chest wall recurrence has been reported previously by two institutions [31,32]. The University of Lübeck treated 25 patients with epirubicin and ifosfamide and only administered one hyperthermia session per week. The radiotherapy also differed in that patients were treated with either conventional fractionation to a mean dose of 52.2 Gy, or hyperfractionated therapy to a mean of 43.3 Gy; the latter was used in patients with extensive disease burden, or those who experienced grade 3 skin toxicities from prior radiotherapy [32]. These investigators reported an overall response rate of 80%, with a CR rate of 44%.

The University of Athens enrolled 15 patients with chest wall recurrence who received concurrent hyperthermia (once every 4 weeks), liposomal doxorubicin and re-irradiation to a dose of 30.6 Gy [31]. The overall response rate was 100%; 80% PR and 20% CR. Only one patient (6.7%) developed moist desquamation.

Comparisons of retrospective series from different institutions are always problematic. Nonetheless, our overall response rate of 100% and CR rate of 80% appear to compare quite favorably to the reports from the above institutions. It remains unclear as to whether the addition of chemotherapy to hyperthermia and radiation improves results. As quoted above, CR rates in the range of 60% have been achieved with hyperthermia and radiation alone without chemotherapy. Because of the very extensive disease present in the great majority of our patients, we believe that the achieved CR rate of 80% represents an improvement over what might have been achieved with radiation and hyperthermia alone. Additional studies will clearly be necessary to demonstrate this, however.

The ThChRT reported herein obviously represents treatment intensification with the risk of worsened toxicity as well. The 63% reported rate of moist desquamation may seem high. However, moist desquamation was an expected consequence of treatment, given the extent of skin involvement of most of these patients and the use of bolus and electrons to maximize the tumor dose to the skin surface. The moist desquamation observed did heal with conservative measures. As far as thermal injury is concerned, only two patients sustained significant thermal injury with small volume 3rd degree burns, which also healed with conservative measures without surgical intervention. One of these patients had recurred in a prior TRAM flap reconstruction. These patients often have compromised skin sensation and thus are less able to report discomfort from hyperthermia. This places them at increased risk for thermal injury and makes them less than ideal candidates for thermal therapy.

Conclusions

Patients experiencing chest wall recurrence of breast cancer that are surgically unresectable, following prior mastectomy and post mastectomy radiotherapy may still experience long-

term LPFS when treated with ThChRT with an acceptable treatment related toxicity. The use of hyperthermia and chemotherapy allows for reduced doses of radiation in these heavily pre-treated patients. The exact role of the various components of this trimodality program is uncertain and further studies are warranted.

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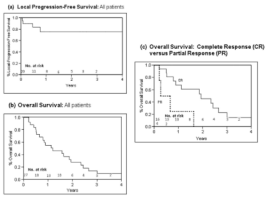

Fig. 1.

(a) Local progression-free survival for all patients (b) overall survival for all patients; (c) and for patients with CR versus PR.

Table 1

Patient characteristics at the time of initial diagnosis of breast cancer.

Patient characteristic	Number of patients (%)
Age	Median 51 (range 37–75)
Histology	
Infiltrating ductal carcinoma	22 (81%)
Infiltrating lobular carcinoma	4 (15%)
Estrogen receptor	
Positive	6 (22%)
Negative	16 (59%)
Unknown	5 (19%)
Progesterone receptor	
Positive	7 (26%)
Negative	14 (52%)
Unknown	6 (22%)
Her2neu	
Not amplified	5 (19%)
Amplified	12 (44%)
Unknown	10 (37%)
T stage	
T0	1 (4%)
T1	9 (33%)
T2	8 (30%)
T3	5 (19%)
T4	3 (11%)
Lymph nodal involvement	
N0	9 (33%)
N1	6 (22%)
N2	8 (30%)
N3	3 (11%)

Table 2

Individual characteristics of patients' chest wall/superficial recurrences and their response to thermochemoradiotherapy.

Patient	Characteristics of chest wall recurrences	Response
1	5 cm nodule surrounded by 9 × 6 cm nodular/erythematous area	CR
2	Multiple bilateral supraclavicular nodes	CR
3	Chest wall nodule and matted axillary LN's resected with + margins/ECE; no gross disease	CR
4	Two nodules s/p resection with involvement of the capsule of her implant which was left intact; no gross disease	CR
5	13 × 6 cm diffuse area of skin infiltration	PR
6	Diffuse erythema on >1/2 her chest wall	uCR
7	Diffuse raised erythematous rash over entire mastectomy scar	CR
8	2 cm nodule in her intact right breast; 2 × 3 cm erythematous rash on her left chest wall	CR
9	6 × 3 cm erythematous nodule	uPR
10	7 × 7 cm erythematous rash on right chest wall; diffuse erythema on left neck/left chest wall	CR
11	Diffuse rash from scar superiorly to clavicle, with satellite smaller areas inferior and medial	CR
12	Diffuse nodules over entire left chest wall, with 3 cm left SCV matted LN's and 4 cm conglomerate of matted left axillary LN's	CR
13	Diffuse nodules throughout entire ipsilateral chest wall	CR
14	15 × 30 cm erythematous rash on ipsilateral chest wall with extension to media upper arm and posteriorly onto her back; +ulceration in her axilla	CR
15	Erythematous rash on entire ipsilateral chest wall extending superiorly to clavicle	uPR
16	Diffuse erythema with multiple nodules	PR
17	Diffuse nodularity of entire chest wall	CR
18	Multiple nodules scattered throughout the chest wall, with synchronous axillary failure status post dissection	CR
19	2 × 0.6 cm ulcerated lesion with 4 × 3 cm satellite nodule	uPR
20	Diffuse erythematous rash extending from her left mid-axillary line contiguously to her right posterior axillary line; 10–20 cm superior to inferior	PR
21	6 × 6 × 4 cm sternal nodule with satellite 3 cm erythematous nodule in the tail of her left reconstructed breast	uPR
22	4 cm left axillary LN, 2 cm sternal nodule, diffuse erythematous rash on right chest wall that extends posteriorly to back	PR
23	Multiple nodules on chest wall and upper inner arm, with erythema/induration extending throughout the ipsilateral chest wall	CR
24	Bilateral SCV LN's with diffuse small erythematous nodules on the left chest wall, with erythema/induration in her right periareolar area	uPR
25	Diffuse erythematous nodules involving her right shoulder/SCV region/entire right chest wall, and her left and right upper abdominal quadrants	uCR
26	3 cm ulcer with diffuse erythema over entire chestwall	CR
27	Diffuse involvement of her chest wall	CR

CR = complete response; PR = partial response; LN = lymph nodes; ECE = extracapsular extension; uCR = unconfirmed CR; uPR = unconfirmed PR.