Hyperthermia Combined with Radiation Therapy in the Treatment of Local Recurrent Breast Cancer

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Abstract

Background: Hyperthermia combined with radiation therapy was shown to be more effective in local recurrent breast cancer than radiotherapy alone, but its use is limited due to technical difficulties, stringent reimbursement policies and because it is time consuming.

Objectives: To report our experience with a simple and convenient XRT + HT delivery system.

Methods: XRT was delivered through either electron or photon beams (total dose 30–40 Gy in previously irradiated fields or 50–70 Gy in non-irradiated fields). Hyperthermia was delivered by a dedicated HT device operating at 915 MHz. The heating session lasted 45 minutes. The maximal tumor surface temperature was set at 45°C and modified according to patient comfort. No intratumoral (invasive) thermometry was used. At least two HT sessions were scheduled to each HT field during the entire XRT treatment period. Tumor response was evaluated every 3 months after completion of treatment. The overall survival was measured from XRT + HT initiation until the last follow-up.

Results: Fifteen women underwent 114 HT treatments delivered through 28 HT fields. Twenty-four HT fields (15 patients) were previously irradiated. There was complete infield response in 10 fields (6 patients), partial response in 8 fields (4 patients), no response or progressive disease in 4 fields (3 patients), and no parameters in 6 fields (5 patients). Eighteen fields (64%) had complete or partial response. Seven patients had outfield recurrence despite wide XRT + HT fields. Ulceration was the only major side effect (three patients, three fields).

Conclusions: The combined HT + XRT delivery system, with no invasive thermometry, is a simple and effective method for treating local recurrent breast cancer.

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Patients with local recurrent breast cancer may present with debilitating ulcerated disease over the entire breast or chest wall. This recurrent tumor is usually treated with systemic/local chemotherapy, surgery and irradiation (or re-irradiation). These treatment modalities are quite effective, but the tumor may become resistant to these modalities with the result that patients succumb to their disease, often with intense pain and suffering. Alternative palliative treatment modalities would be welcome additions to the oncologic armamentarium.

XRT-HT = radiation therapy-hyperthermia

Several randomized studies have confirmed that hyperthermia combined with radiation therapy is more effective than XRT alone in the treatment of various superficially spread tumors, such as local recurrent breast cancer [1], lymph node involvement from head and neck tumors [2], and melanoma [3]. However, HT+XRT is not used in common practice in many radiotherapy units, due to it being time consuming, and because of technical considerations and stringent reimbursement policies.

We describe our relatively simple and convenient method of HT delivery to treat patients with local recurrent breast cancer.

Patients and Methods

Patients with local recurrent breast cancer and a skin and subcutaneous tumor involvement were eligible for this study. Individuals who had a deeper tumor were excluded. Previous treatment modalities could include XRT, any systemic chemotherapy regimen and any topical treatments.

XRT was mainly given through either electron beams or with combined electron and photon beams and aimed to cover the entire tumor site with an additional 1–2 cm of surrounding normal tissue. In cases of previously irradiated fields, the total XRT dose was 30 Gy in 1.8–2.0 daily fractions. An additional 10 Gy was added if no grade 3-4 acute side effects were observed at completion of treatment. In fields that had not undergone earlier irradiation, the dose was 50–60 Gy in similar daily fractions and with a possible additional 10 Gy added at completion of treatment.

Heating sessions were started within 10 minutes after completion of XRT. They were given by means of a dedicated HT device (Medispec, Israel) operating at 915 MHz. This device has a maximal power supply of 50 watts. It has an internal circuit that controls power supply once the planned temperatures have been achieved. The HT field was different from the XRT field and was defined as the area below the hyperthermia applicator, which is a 10x10 cm^2 antenna attached to the tumor site. Several HT fields were needed to cover a large tumor. The heating session continued for a period of 45 minutes. At least two HT sessions were scheduled for each HT field throughout a complete course of radiotherapy. HT treatment to the same HT field was given after an interval of at least 2 days in order to prevent a possible thermo-tolerance. The temperatures were monitored using two thermocouples placed on the tumor site.

Table 1. Treatment parameters and patients' outcome

Patient	Previous XRT	Concurrent chemotherapy	Total XRT dose/dose per fraction	HT field	HT session	Response	Freedom from relapse (months)	Infield side effects	Current status
1	Yes	No	30 Gy/2 Gy	1	3	CR	4	No	DWD
	Yes		"	2	3	CR	4	No	
	No		"	3	3	PR	2	No	
	No		46 Gy/2 Gy	4	3	PR	2	No	
	No		"	5	3	PR	2	No	
2	Yes	No	30 Gy/2 Gy	1	6	NP	24	Blister	DWD
3	Yes	No	36 Gy/2 Gy	1	6	CR	3	Blister	DWD
4	No	Yes (Xeloda)	70 Gy/2 Gy	1	6	CR	+16	Ulcer	AND
5	Yes	No	30 Gy/2 Gy	1	5	NP	+4	No	Unknown
6	Yes	No	50 Gy/2 Gy						
			+14 Gy/2 Gy	1	2	CR	+17	Ulcer	AND
7	Yes	No	30 Gy/2 Gy	1	3	NP	+12	No	AND
	Yes		"	2	3	NP	+12	No	
8	Yes	No	40 Gy/2 Gy	1	5	CR	10	Ulcer	AWD
	Yes		"	2	5	CR	10	No	
	Yes		"	3	4	CR	10	No	
9	Yes	No	30 Gy/2 Gy	1	7	PR	7	No	AWD
	Yes		"	2	5	NP	7	Blister	
10	Yes	Yes (Xeloda)	30 Gy/2 Gy	1	3	CR	+9	No	AWD
	Yes		"	2	3	CR	+9	No	
11	Yes	Yes (Gemzar)	30 Gy/2 Gy	1	7	PR	2	No	AWD
12	Yes	Yes (Taxol)	30.6/1.8 Gy	1	4	P	0	Blister	AWD
				2	2	P			
13	Yes	Yes (navelbine+5fu)	40 Gy/2 Gy	1	6	P	0	No	AWD
14	Yes	Yes (UFT, Iressa)	39.6 Gy/1.8 Gy	1	5	PR	2	No	DWD
	Yes		"	2	3	PR	2		
	Yes		"	3	2	PR	2		
15	Yes	No	30 Gy/2 Gy	1	4	P	0	No	AWD
	Yes			2	2	NP	+8	No	

CR = complete response, PR = partial response, NP = no parameter, P = no response/progression, DWD = died with disease, AND = alive no disease, AWD = alive with disease.

The maximal temperature was set at 45°C and was modified according to the patient's comfort. No invasive thermometry was used.

All study patients were evaluated during the treatment, 1 month after completion of combined XRT+HT treatment, and once during the ensuing 3–6 months. The therapeutic outcome was defined as a complete response, partial response, or no response/progressive disease based on tumor eradication in the hyperthermia field. The duration of response was calculated from the initiation of XRT+HT until the last follow-up.

Results

Between December 2001 and July 2003, 114 HT treatments through 28 HT fields were given to 15 patients in our Division of Oncology's radiotherapy unit. The study patients' characteristics are presented in Table 1. Fourteen of these patients had been previously exposed to XRT, and all 15 had been exposed to various systemic chemotherapy regimens before study entry. Four of the 28 HT fields were not in a previous irradiation site (the HT field could be either in irradiated or non-irradiated fields when there was tumor spread outside of a previous irradiation site). Six of the 15 patients received concurrent chemotherapy during XRT+HT. There was complete and partial response in 10 and 8 fields (6 and 4 patients), respectively. There was a no response/progressive disease result in 4 fields (3 patients) and no parameters for follow-up (treatment was given due to microscopically positive margins) in 6 fields (5 patients). Altogether, there was an infield complete or partial response in 64% of the fields (18/28). Despite the planning for and use of wide XRT+HT fields, there was outfield recurrence in 47% of patients (7/15). The only major and persistent side effect seen in the XRT+HT field was an ulcer and it was observed in 3 fields (3 patients). One ulcer completely and spontaneously resolved (patient 4) [Figure 1] within a few months after completion of treatment, the second one persisted for more than 17 months (patient 6) [Figure 2] with no evidence of tumor recurrence, and the ulcer in the third field was accompanied by tumor recurrence.

Discussion

Several studies that emerged during the last decade reported on the efficacy of combining HT with XRT in the treatment of local recurrent, previously irradiated breast cancer patients. Van der Zee et al. [4] reported 134 patients who had a local control rate of 73%

Figure 1 (Patient 4). [A] An ulcerating tumor in the upper inner left breast. **[B]** One month after completion of the combined XRT + HT treatment. **[C]** A tumor bed scar, 11 months after completion of treatment.

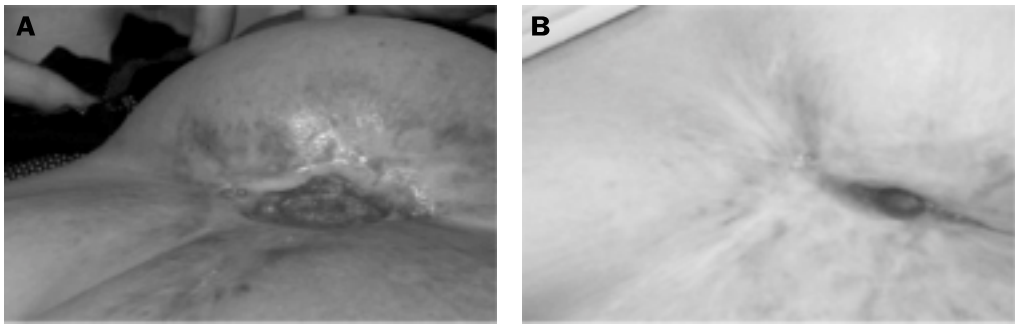

Figure 2 (Patient 6). **[A]** An ulcerating tumor in the lower inner left breast. **[B]** The same site 2 months after completion of the combined XRT + HT treatment. A similar finding as [B] was seen at 17 months.

for a median duration of 32 months. They concluded that this combined treatment is effective and is currently considered a standard treatment in The Netherlands. Vernon et al. [1] presented a multicenter phase III study on the efficacy of XRT+HT or XRT alone in 306 patients: the complete response rate was 59% and 41%, respectively. The greatest effect was observed in patients with recurrent lesions in previously irradiated areas. Other studies investigated the efficacy of combined XRT+HT and chemotherapy: Kouloulias et al. [5] reported 15 patients who were treated with liposomal doxorubicin combined with XRT+HT, and Feyerabend and co-workers [6] reported 25 patients treated with epirubicin and ifosfamide. Both studies demonstrated high remission rates that were similar to previous studies that used different types of chemotherapy. The authors of review articles, either on the treatment of local recurrent breast cancer patients [7] or on the role of hyperthermia in cancer patients in general [8,9], reached a similar conclusion on the beneficial effect of the combined modality. In our study, all patients but one had been exposed to previous irradiation (24 out of 28 HT fields) and the response rate was 64%. These results are similar to those reported in the literature.

We did not deliver HT as a sole treatment since it produced an inadequate response and one that continued for only a short time [10]. In addition, our protocol was to deliver the HT within 10 minutes of XRT delivery since a longer delay may decrease its effectiveness [11].

Although many studies confirm the benefit of using HT in conjunction with XRT, this modality is not in common practice in most radiotherapy units throughout the world, partly due to the negative results of the RTOG study [12], which evaluated XRT+HT in various superficial tumors. That study was criticized for inappropriate selection of HT devices and for the enrollment of unsuitable patients who had deeper tumors. Several more recent phase III studies [1–3,13] reported on the beneficial effect of the combined approach compared to XRT alone. The use of HT is limited by several other factors: a) the patient's discomfort secondary to invasive thermometry, b) the need for expert medical staff, c) a rather lengthy treatment time (30–90 minutes of HT delivery), d) the need for a strict time schedule (treatment should be started immediately before or after XRT), and e) stringent reimbursement policies. We addressed and tried to overcome some of these issues; for example, we intentionally omitted the invasive thermometry that is inconvenient for the patients and requires a physician's time, and we used only superficial thermo-couples that, in turn, had the additional task of regulating the maximal allowed temperature in the tumor. This self-regulation helped us to reach the maximal temperature in a shorter time. If the patient complained of any pain, we decreased either the maximal temperature or the power supply. A radiation technologist can carry out this simple operation throughout the entire treatment, thereby markedly reducing the onsite time of the medical physicist and the physician.

Eliminating invasive thermometry means that there was no accurate measurement of temperature in the tumor, which questions the quality of HT delivery [14] and indicates the need for non-invasive thermometry [15]. Nevertheless, the outcome in our study patients is very similar to that of patients in studies that did use invasive thermometry. We chose not to decrease the HT time, based on our previous *in vivo* study [16] that was aimed to

shorten the HT time in mice treated with liposomal doxorubicin+HT. In that study we found that a 30 minute HT session was better than a 5 minute session. In addition, time is needed to build up the required amount of heat, which is substantially different among patients and perhaps should not be included in estimating the overall treatment time.

The reimbursement policy is still a problematic issue since the cost of HT is approximately $250–300 for each session and, in most countries, is only partially covered by medical insurance. Nevertheless, the positive clinical results and the convenience of this treatment modality will probably change the attitude of radiation oncologists and medical carriers to this therapeutic approach.

In conclusion, XRT+HT is effective in treating patients with local recurrent breast cancer. Based on our experience, we recommend this simple method of HT delivery without invasive thermometry for use in a busy radiotherapy unit.

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