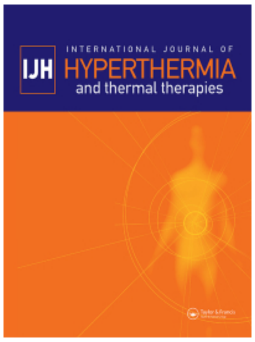

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REVIEW ARTICLE

Hyperthermia combined with radiation therapy for superficial breast cancer and chest wall recurrence: A review of the randomised data

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Abstract
Hyperthermia has long been used in combination with radiation for the treatment of superficial malignancies, in part due to its radiosensitising capabilities. Patients who suffer superficial recurrences of breast cancer, be it in their chest wall following mastectomy, or in their breast after breast conservation, typically have poor clinical outcomes. They often develop distant metastatic disease, but one must not overlook the problems associated with an uncontrolled local failure. Morbidity is enormous, and can significantly impair quality of life. There is no accepted standard of care in treating superficial recurrences of breast cancer, particularly in patients that have previously been irradiated. There is a substantial literature regarding the combined use of hyperthermia and radiotherapy for these superficial recurrences. Most of it is retrospective in nature, but there are several larger phase III randomised trials that show an improved rate of clinical complete response in patients treated with both modalities. In this review article, we will highlight the important prospective data that has been published regarding the combined use of hyperthermia and radiation.

Keywords: *breast cancer recurrence, hyperthermia, radiation*

Introduction

Patients with chest wall/superficial breast cancer recurrences are a heterogeneous group, but the unifying principle is that they have failed standard therapy. Local recurrence rates after mastectomy range from 5% to 45%, thus prompting the consideration of adjuvant radiation therapy [1–7]. The use of post-mastectomy radiotherapy has been demonstrated to dramatically decrease this risk of failure to 2% to 15%, as well as promote a survival advantage [6, 8, 9]. When patients do fail locally, morbidities include pain, ulceration, bleeding, lymphoedema, brachial plexopathy, as well as the psychological distress of having visible local disease [10, 11]. A significant proportion of patients who experience a chest wall failure will also develop distant metastatic disease, prompting some to treat patients with local recurrence palliatively [5, 6, 12–16]. However, with aggressive local therapy, some patients are able to have long disease-free intervals [17–23].

Hyperthermia (HT) in the clinical context of a radiosensitiser for superficial tumours is defined as temperatures that are above normal physiological conditions, ranging from 40° to 45°C. The earliest report of its use in the treatment of breast cancer was more than 5000 years ago, described on an Egyptian papyrus [24]. In the modern era, its use in conjunction with radiotherapy (RT) is based on several

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Table I. Complete response (CR) rate in randomised trials involving irradiation with or without hyperthermia for chest wall recurrence/superficial breast cancer.

Study	Number of patients	Tumour type	Heat (%)	No heat (%)
Perez et al. [30]	236	Superficial tumours (primarily chest wall and neck nodes)	32	30
Jones et al. [31]	108	Superficial tumours (primarily chest wall and neck nodes; melanoma)	66 (no prior RT)	42
			68 (prior RT)	24
Vernon et al. [32]	306	Chest wall (some intact breast)	59	41
Kapp et al. [34]	70	Superficial tumours (primarily chest wall and neck nodes; melanoma)	52 (6 HT)	51 (2 HT)
Engin et al. [42]	41	Superficial tumours (primarily chest wall and neck nodes)	55 (8 HT)	59 (4 HT)

RT, radiotherapy; HT, hyperthermia.

biological principles, including its ability to affect cells in S phase, a portion of the cell cycle where radiation is less effective [25]. In addition to being directly cytotoxic, hyperthermia can inhibit sub-lethal damage repair and improve oxygenation, thus limiting the degree of hypoxia that hampers the effectiveness of radiotherapy [26–28]. Utilising hyperthermia as a radiosensitiser, by definition, would reduce the dose of radiation needed to get the same effect as in its absence [29]; this is especially important in women who received prior irradiation for their breast cancer, when one worries about increased normal tissue toxicity. Furthermore, doses for treating disease in a previously irradiated fields are often more limited, which increases the importance of tumour sensitisation.

Randomised data

There are numerous reports in the literature detailing the results of combined hyperthermia and radiation therapy for chest wall/superficial recurrences of breast cancer [30–42]. Many are single institution retrospective accounts, but there are several large prospective randomised trials with a primary endpoint of percentage achieving a clinical complete response (CR) [30–32, 34] (Table I).

The first randomised trial was run by the Radiation Therapy Oncology Group (RTOG), protocol 8104, and included 307 patients with superficially measurable tumours, 245 of which had single lesions and were available for analysis. Their treatment consisted of a radiation dose of 32 Gy, given in 4 Gy twice weekly fractions, with two hyperthermia sessions (goal 42.5°C, 45–60 min). Approximately 30% (68 patients) of those included had superficial disease in the breast or chest wall. Their primary endpoint was rate of CR, and overall, they did not find a statistically significant increase in local control with the addition of heat to radiotherapy [30]. On subset analysis, those patients with breast or chest wall/flank lesions had a CR rate of 62% with the addition of heat, compared to 40% without. In addition, patients with a lesion diameter <3 cm had a CR rate of 52% with heat, versus 39% with radiotherapy alone ($p = 0.02$). A caveat of their results that was pointed out, which has been borne out in other studies, was the quality of treatment delivered. Only 52% in the combined HT/RT group received full RT dose and 8 HT treatments; 42% and 31% of lesions <3 cm and >3 cm received 'good' heating, respectively, defined as at least 4 HT sessions of 42.5°C for 45 min at the temperature reference point [30]. The authors noted that the poor survival of their patients (22% alive at 1 year), could also help explain their low control rates, in that patients need to survive long enough for full clinical impact to be appreciated in both arms. All toxicities were similarly balanced in the two groups, except that 30% of the patients who received RT and HT developed thermal blisters, versus 0% in the RT only arm. No mention was made as to the severity of the thermal injury, nor to the methods of treatment if necessary.

Shortly after RTOG 8104 began accruing patients, both Stanford and Thomas Jefferson Universities ran single institution randomised trials to address the question of whether one or two hyperthermia treatments should be given weekly [34, 42]. Both of these trials, which included a heterogeneous group of patients (mostly chest wall), found no difference in rate of CR if HT was given once or twice weekly. Radiotherapy was similar in the two trials for recurrences in the previously unirradiated chest, but when patients with chest wall recurrences required re-irradiation, the fractionation was different. Thomas Jefferson utilised a more hypofractionated regimen (40 Gy in 4 Gy fractions), whereas Stanford used more traditional fractionation (21.6–36 Gy in 1.8–2 Gy fractions). Both trials evaluated similar thermal profiles and both found T_{min} to be the only thermal predictor for durable local control. The Stanford trial found a trend for increased local control with a $T_{min} \geq 41°C$, versus <41°C ($p = 0.08$), whereas the Thomas Jefferson found a median local control to be 12 months with a $T_{\min} \leq 39.5°C$, versus 23 months for a $T_{\min} > 39.5°C$ ($p = 0.01$).

Thermal injury was not statistically different in patients treated with one versus two weekly HT sessions. In the Stanford analysis, only 3/58 patients' complications required medical treatment, and 2/58 required surgical intervention [34]. Nearly 40% of the patients at Thomas Jefferson were reported to have no skin reactions related to therapy; 11/56 heated fields developed thermal blistering, which was equally balanced between the two groups [42].

The reason this question was posed deals with the phenomenon of thermotolerance; that is, that most mammalian cells become resistant to the effects of heat at temperatures below 43°C, or at 37°C after exposure to temperatures greater than 43°C [43]. As more research has been done in this area, the tolerance to heat has been found to be related to heat shock proteins (HSPs), which are up-regulated by hyperthermia [44]. As a consequence, most advocate an interval between HT sessions of at least 48–72 h, so as to allow adequate time for their removal. However, there is some data to suggest that thermal radiosensitisation is not subject to thermotolerance. Armour et al. found that the protein synthesis inhibitor cycloheximide prohibited the induction of thermotolerance, but did not influence radiation sensitisation [45]. Given this biological finding, a more aggressive hyperthermia fractionation scheme may be warranted, but to date has not been attempted.

The largest collection of prospective data for combining radiotherapy and hyperthermia for the treatment of superficial breast cancer was compiled in a collaborative effort by the UK Medical Research Council, European Society for Hyperthermic Oncology, Dutch Hyperthermia Group and the Princess Margaret Hospital/Ontario Cancer Institute [32]. There were five simultaneous ongoing prospective trials being conducted by the aforementioned groups. Due to poor patient accrual it was decided to pool their data so as to increase statistical power. As one might expect, by combining multiple trials there is a large degree of heterogeneity in the patient populations, as well as the treatment delivered. In this meta-analysis of the European and Canadian series there were three identifiable patient groups: untreated primary inoperable breast cancer, recurrent disease in sites not previously irradiated, and those with recurrences in sites having previously been irradiated; 71% had recurrences on their chest wall [32].

Radiotherapy was administered 'radically' (range of 'effective' dose 60–69.3 Gy) if the patient's failure was not in a previously irradiated field, or 'palliatively' (range 39.8–47.2 Gy) if it had been [32]. Their goal with respect to hyperthermia was to achieve a minimum intratumour temperature of 43°C (42.5°C in one of the five trials). Their primary endpoint was the rate of CR, which was 59% and 41% with and without hyperthermia, respectively ($p < 0.001$, OR 2.3, 95%CI 1.4–3.8). In patients that had previously been irradiated, their rate of CR was 57% versus 31% (OR 4.7, 95%CI 2.4–9.5), and this was with 'palliative' doses of radiation. This represents a significant improvement in complete response with the addition of hyperthermia to irradiation. While overall survival was not a primary endpoint of this collection of trials, it was evaluated on subset analysis. There was no statistically significant difference in survival in patients irradiated with or without hyperthermia, due largely in part to the high percentage of patients that developed metastatic disease in both groups; median overall survival was 18 months, regardless of randomisation. However, given the natural history of recurrent breast cancer, a local therapy would not necessarily be expected to improve overall survival.

It should be noted that the majority of patients did not reach the minimum intratumour temperature defined at the outset of the trial. Sherar et al. examined the thermal dosimetry of 120 patients that were enrolled, and sought to find reliable treatment parameters that might predict for response to therapy [46]. Five thermal endpoints were evaluated, of which two were found to be correlated with rates of CR; the Max ($TD_{\min}$), and the Sum ($TD_{\min}$), with the $TD_{\min}$ being the lowest recorded temperature during treatment. They highlighted that those patients without distant metastatic disease at entry – difficult to extrapolate from, as only one of the five trials vigorously evaluated for distant disease prior to enrolment – had better outcomes, including increased CR rate, local disease-free survival, time to local failure and overall survival, with improved quality of hyperthermia (with cut-offs of ≤ 10 or > 10 min) [46].

With respect to toxicity of HT combined with RT, the authors note that 'a small number' of patients did not complete their planned HT secondary to pain; they did not cite exactly how many. They found little difference in the rates of erythema and desquamation with the addition of HT to RT, but reported an 11% rate of thermal blistering in the combined group, versus a 2% rate in the RT alone patients [32]. They noted that acute treatment-related toxicities healed with conservative measures alone. Three late treatment-related complications were identified in patients receiving HT plus RT (bone necrosis, bone fracture and brachial plexopathy), thus underscoring the importance of long-term follow-up of surviving patients [32].

The most recently reported phase III trial of radiotherapy with or without hyperthermia was from Duke University [31]. This study was rigorous in terms of meeting thermometry/thermal dose guidelines and included a 'test dose' of hyperthermia before randomisation to ensure that all patients were indeed heatable. Of the 122 patients enrolled, 108 patients were deemed heatable and were randomised. Of those patients, 65% had disease in their breast or chest wall. Overall, the CR rate was 66.1% for patients treated with both heat and radiotherapy, versus 42.3% in the radiotherapy alone arm ($p = 0.02$, OR 2.7, 95%CI 1.2–5.8). The thermal parameter used was the number of cumulative equivalent minutes at 43°C exceeded by 90% of monitored points within the tumour (CEM 43°C T_{90}), which is similar to one of the two endpoints evaluated by Sherar et al. found to have a significant effect on CR (i.e. sum (TD_{min}), which is the CEM 43°C T_{100}) [46, 47]. Jones et al. found that the CEM 43°C T_{90} was a strong predictor for CR, as was found in a Medical Research Council analysis of their data [48]. Like the Vernon meta-analysis [32], the patients that had the greatest benefit were those that had previously received radiation therapy, with CR rates of 68.2% and 23.5%, with and without hyperthermia, respectively. Not surprisingly, there were no differences in overall survival between the two groups.

As was the case with the previous trials, toxicity with the addition of HT to RT was manageable. Thermal burns occurred in 45% of patients randomised to HT plus RT, versus 5.7% in the RT alone group. Nearly half of the burns in the combined modality arm were first degree, with only three patients experiencing third-degree burns [31]. Catheter-related toxicities were reported in six patients, which included pain requiring over the counter analgesics in three, infection requiring antibiotics in two, and wound management for bleeding in one [31].

Conclusions

While there are some differences in the series on superficial hyperthermia and radiation, there seems to be one unifying theme. In a select group of patients, the addition of hyperthermia to radiotherapy increases the eradication of local tumour, with a modest increase in largely self-limited toxicity. While attainment of CR is a worthwhile study endpoint, one must also consider the need to address palliation of symptoms, in that the majority of these patients will ultimately succumb to their distant disease. In the modern era of 'targeted' therapy, the issue of local control will increasingly become more important. Future applications of hyperthermia combined with radiotherapy for should include the addition of targeted biological agents in the hopes of increasing the CR rate and hopefully translating into prolonged disease-free survival. Liposomal doxorubicin has been combined with radiotherapy and hyperthermia by one group and warrants further evaluation in the future [49]. Efforts must be taken to provide reproducible, efficacious heating of tumours so that the synergistic effect of combining radiotherapy and hyperthermia can be optimised. With rigorous thermal dosimetry and careful treatment technique, the addition of heat to radiotherapy can result in long-term local control of breast cancer chest wall recurrences.

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