

Hyperthermia Is Now Included in the NCCN Clinical Practice Guidelines for Breast Cancer Recurrences: An Analysis of Existing Data

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Keywords

Hyperthermia · Radiotherapy · Breast cancer recurrences · Clinical trials

Summary

Background: Hyperthermia has been included in the 2013 National Comprehensive Cancer Network (NCCN) guidelines as an option for the treatment of breast recurrences. The purpose of this article is to demonstrate the important role of hyperthermia as a therapeutic modality by presenting clinical trials on this subject carried out in the last decades. **Materials and Methods:** All relevant trials published since 1987 were retrieved from Medline and reviewed. **Results:** Results show that the addition of hyperthermia to radiotherapy and/or chemotherapy for the treatment of breast cancer enhances treatment response and can increase local control. **Conclusion:** Further studies are required to evaluate potential benefits of hyperthermia in the treatment of other kinds of superficial tumors.

Introduction

Breast cancer is one of the most common types of cancer, and represents a major health problem as the number of cases reported annually is increasing. Although nowadays early detection is feasible, 30% of patients with early stage disease will relapse [1–3]. The treatment of patients with locally advanced breast cancer consists of chemotherapy, followed by radical mastectomy and radiotherapy and in some cases hormonal therapy. Although this combined modality therapy is the treatment of choice in terms of local control, new approaches are still needed for a better clinical outcome [3, 4].

According to the 2013 National Comprehensive Cancer Network (NCCN) guidelines hyperthermia is included in clinical practice for the treatment of breast recurrences. The objective of hyperthermia as a therapeutic modality is to increase the tumor temperature up to 42–45 °C. There are various methods of applying hyperthermia depending on the tumor location [5]. For tumors with a depth of less than 5 cm, such as breast cancer, superficial hyperthermia is mainly used [6]. Superficial hyperthermia in conjunction with radiotherapy and/or chemotherapy has proven to be more effective than radiotherapy or chemotherapy alone [6–8]. The reason for this seems to be that the mechanisms of action of radiotherapy and hyperthermia complement each other. In addition the correct clinical application of hyperthermia is of great im-

portance as thermal parameters such as the minimum or maximum tumor temperature during thermotherapy affect clinical outcome and therapy response [9, 10].

The purpose of this review is to present the clinical trials carried out in the last decades on the subject of applying hyperthermia in conjunction with radiotherapy and/or chemotherapy for the treatment of breast cancer. In more detail this article is commenting on the recent NCCN guidelines which now include hyperthermia for the clinical treatment of recurrent skin lesions from breast cancer, supporting the potential positive role of hyperthermia in the local control of tumor recurrences.

Materials and Methods

All trials included in this report were retrieved from Medline, and were published from 1987 up to now. They refer to the application of hyperthermia in conjunction with radiotherapy and/or chemotherapy in patients suffering from breast cancer and study the benefit of this combined modality treatment. The data collected from each trial depicts the number of patients or breast cancer recurrences and the therapeutic modalities used for their treatment. The studies were divided into 2 categories: comparative studies and 1-arm studies. In the comparative studies a comparison between the clinical outcome of radiotherapy with or without hyperthermia was made. The 1-arm studies report on hyperthermia in conjunction with radiotherapy, but the results are not being compared to those obtained with irradiation only. The main parameters evaluated are response rates, complete and partial response rates, local control, and survival rates. Finally toxicity caused by hyperthermia is reviewed. Data were analyzed to demonstrate the positive effect of hyperthermia on local control of recurrent breast carcinoma.

Results and Discussion

Comparative Studies

First clinical results from comparative studies of thermoradiotherapy (RTHT) versus radiotherapy alone in superficial tumors were published before 1990 and are presented in table 1. Lindholm et al. [11] in 1987 published the results from a study in which patients with superficial recurrent malignant tumors received low-dose radiation therapy with or without local hyperthermia (915 or 2,450 MHz). The majority of the tumors (53%) were mammary adenocarcinomas. The complete as well as the partial response rate were higher in the combined treatment group, showing that hyperthermia when combined with a low dose of radiation can be useful in the palliation of superficial tumor recurrences, especially in cases where higher radiotherapy doses were delivered earlier in a previous treatment. For grade 3 toxicity (desquamation with blisters/moist desquamation) the morbidity rates were 21.2 and 4.2%, respectively, and for grade 4 toxicity (small necrosis or ulceration/massive ulceration) 24.2 and 8.3%, respectively. Finally subcutaneous fat tissue necrosis (grade 4) was reported in 3 patients and 1 patient, respectively. The above results are definitely an evidence-based remark, due to the fact that the penetration depth and consequently either the response or toxicity are related to frequency as well as water-boluses (widely used against skin reactions) [12].

Table 1. Comparative studies on the efficacy of hyperthermia for breast cancer treatment. The results with or without the addition of hyperthermia are presented as well as the toxicity reported for the combined treatment

Study [ref.]	Tumor site	Pat./lesions, n	Treatment	Results		Toxicity of HT
				without HT	with HT	
Lindholm et al. [11]	local recurrences or subcutaneous and/or cutaneous metastases from breast cancers	11/34	Low-dose RT + local HT	CR 35% PR 18% NR 47%	CR 65% PR 29% NR 6%	depending on the operating frequency used and the water bolus: i) 2,450 MHz, no water bolus: severe (33%) to moderate (46%) pain; WHO toxicity > grade 2 45.5% ii) 915 MHz + water bolus: severe (8%) to moderate (34%) pain; WHO toxicity > grade 2 12.5% enhancement of acute skin reactions no increase of late skin reactions pain after HT treatment hypersensitivity in treatment area infections/catheter complications
Gonzalez Gonzalez et al. [13]	chest wall recurrences of breast carcinoma	18 pat.	RT + HT	response rate: 33.3% (3/9)	response rate: 77.7% (7/9)	
Perez et al. [14]	breast cancer		RT + HT	tumors < 3 cm (diameter): 55% (breast)	tumors < 3cm (diameter): 67% (breast)	-

Table 1. Continued on next page

Table 1. Continued

Study [ref.]	Tumor site	Pat./lesions, n	Treatment	Results without HT	Results with HT	Toxicity of HT
Li et al. [15]	advanced/locally recurrent breast cancer	10 primary cases 30 recurrent cases total: 64 lesions	RT for small lesions RT + HT for bigger lesions	CR 36.4%	CR 64.3%	N.A.
Masunaga et al. [16]	locally advanced and/or recurrent breast cancer	26/30	RT + HT	CR + PR primary tumor: 55% recurrent tumor after RT: 84% <i>local control</i> primary tumor: 67% recurrent tumor after operation: 71% recurrent tumor after RT: 75%	CR + PR primary tumor: 91% recurrent tumor after RT: 92% <i>local control</i> primary tumor: 90% recurrent tumor after operation: 80% recurrent tumor after RT: 67%	pain during treatment 2nd degree skin burn (33.3%) moist desquamation (26.7%)
Perez et al. [17]			RT + HT	tumors < 3 cm (diameter): CR 40% (breast)	tumors < 3 cm (diameter): CR 62% (breast)	thermal blistering (30%) no increase of acute/late radiation reactions mild/moderate erythema (50%) severe erythema-desquamation (23%) thermal blistering (11%) ulceration (7%) necrosis (7%) fibrosis (52%) telangiectasia (30%) pigmentation (46%)
Vernon et al. [18]	breast cancer	306 pat.	RT + HT	CR41% previously irradiated pat.: CR 31%	CR 59% previously irradiated pat.: CR 57%	
Sherar et al. [10]	chest wall recurrences	276 pat. RT: 128 RHT: 148	RT + HT	CR 41%	CR 61%	-
Jones et al. [7]	superficial lesions including breast cancer	108 pat.: RT 52 RHT 56 breast cancer: RT 33 RHT 37	RT + HT	CR 42% LC 25% previously irradiated pat.: CR 24% not previously irradiated pat.: CR 51%	CR 66% LC 48% previously irradiated pat.: CR 68% not previously irradiated pat.: CR 65%	thermal injuries : grade 1 25% grade 2 16% grade 3 5% thermometry catheter complications (pain-infections): 11%
Wahl et al. [19]	locally recurrent breast cancer	81 pat.	RT RT + CT RT + HT (54% of pat.)	CR 39% 1-year local DFS 44% (gross disease)	CR 67% 1-year local DFS 58% (gross disease)	induration/fibrosis (34.1%) lymphedema (25%) skin infections (11.4%) soft-tissue necrosis (4.5%) brachial plexopathy (2.3%) pneumonitis (2.3%)

RT = Radiotherapy; CT = chemotherapy; HT = hyperthermia; RHT = RT + HT; CR = complete response; PR = partial response; NR = non-response; LC = local control; SD = standard disease; NC = non-control; PD = progressive disease; DFS = disease-free survival; N.A. = not available.

Another study by Gonzalez Gonzalez et al. [13] also proved the efficacy of the combined treatment. 35 patients with chest wall recurrences of breast carcinoma received hyperthermia in addition to radiation therapy, which was administered within 30 min of irradiation. A comparison between 9 cases that received radiotherapy only and 9 cases that received RTHT showed response rates of 33.3% (3/9) and 77.7% (7/9), respectively. Hyperthermia was well tolerated without severe complications.

A correlation between tumor diameter and response rate was ascertained soon after in a randomized trial by the Radiation Therapy Oncology Group (RTOG) for the evaluation of hyperthermia as a treatment for superficial tumors, including breast cancer. The results revealed an improvement in response especially for lesions that were less than 3 cm in diameter and had received more than 2 hyperthermia treatments (42.5 °C). The incidence of maintaining a persistent response over 12 months was greater for patients that received RTHT than for those who received radiotherapy only, indicating that the addition of hyperthermia offers a more durable complete response [14].

Hyperthermia in conjunction with radiotherapy for advanced or locally recurrent breast carcinoma was applied in 40 patients (10 primary and 30 recurrent) in a study by Li et al. [15]. It was decided that smaller lesions would receive radiotherapy only and bigger lesions would receive RTHT. Despite the greater size lesions that received hyperthermia responded better to the therapy than the lesions that received radiotherapy only.

Effectiveness of hyperthermia when added to radiotherapy for breast cancer treatment was also reported by Masunaga et al. [16]. Patients with primary tumors that received irradiation only had a low rate of complete and partial response and local control, while rates increased with the addition of hyperthermia. For recurrent tumors after surgery the local response rates after radiotherapy were also increased with the addition of hyperthermia. It was concluded that the combined treatment offers an improved clinical outcome in patients suffering from locally advanced and recurrent breast cancer as long as the appropriate heating equipment is used in terms of good quality assurance and acceptable penetration depth.

The role of tumor size was once more confirmed by Perez et al. [17] who demonstrated that hyperthermia in superficial tumors is more effective when the lesion's diameter is less than 3 cm. There was no enhancement of acute or late radiation reactions.

One of the largest studies for the evaluation of hyperthermia was published in 1996 by Vernon et al. [18]. A total of 306 lesions were included in this analysis, and the main endpoint was the complete response rate. Results were obtained from 5 separate randomized trials on the treatment of breast cancer with RTHT (phase III), and proved that hyperthermia offers an advantage when added to radiotherapy mainly in recurrent breast cancer where due to previous radiotherapy lower doses of irradiation should be delivered. Although this advantage was not obvious in all trials, the overall complete response rate was 59% for RTHT and 41% for radiotherapy only.

Sherar et al. [10] conducted a study to determine the relationship between thermal parameters of hyperthermia and the clinical

outcome of patients suffering from chest wall recurrences. A comparison was also made between the response of patients who received RTHT and of those who received radiotherapy only; the overall complete response rates were 61 and 41%, respectively.

Jones et al. [7] in a randomized trial evaluated the role of a thermal dose in the treatment of superficial lesions, including breast cancer. More specifically the main endpoints of this study were treatment response and duration of local control. The patients with heatable tumors were randomized and divided into 2 groups. The first group was treated with radiotherapy only, while the second group was treated with RTHT. The complete response rate and the local control rate both improved with the addition of hyperthermia. The greatest improvement in local control was observed in patients that had already received radiotherapy in a previous treatment.

In 2008 the clinical outcome of patients that received repeat chest wall or breast irradiation after local recurrence was investigated by Wahl et al. [19]. This study included patients with recurrent breast carcinoma from 8 different institutions. Hyperthermia in addition to radiotherapy was given in 54% of patients. The complete response rate was 67 and 39%, respectively, with or without hyperthermia.

One-Arm Studies

Many trials have investigated RTHT for breast cancer treatment without comparing the results to a radiotherapy only group (table 2, online Supplemental www.karger.com/?DOI=376594). The feasibility and efficacy of hyperthermia as a palliative treatment for locally recurrent breast carcinoma was tested by Dragovic et al. [20]. 30 breast cancer patients who had relapsed after treatment with other conventional modalities received low-dose irradiation immediately followed by 1 h of hyperthermia. The results confirmed the contribution of hyperthermia to the palliation of breast recurrences. In addition lesions with a diameter of less than 5 cm responded better to the combined treatment.

Dubois et al. [21] proved that RTHT provides amelioration of local control in the treatment of chest wall recurrences from breast cancer. 34 patients received RTHT, 4 patients received chemotherapy with hyperthermia, and 4 patients received hyperthermia only. It was noted that only those patients who received RTHT responded completely to the therapy and showed improvement in local disease control.

In a trial by Phromratanapongse et al. [22] 44 patients suffering from locally recurrent adenocarcinoma of the breast received RTHT. The response rates were analyzed 1 month after the completion of therapy. 12 months later 67% of patients that had achieved complete response still maintained it. Tumor size was also found to be significantly correlated with clinical outcome.

In order to evaluate multiple field patchwork hyperthermia in conjunction with radiotherapy for the treatment of chest wall recurrences of advanced breast carcinoma 20 patients were enrolled in a study by Engin et al. [23]. The majority of patients (95%) responded completely to the combined treatment which thus pro-

vides effective therapy for extensive diffuse breast cancer lesions. However the mean survival of these patients was unsatisfactory due to the existence of systemic lesions outside of the treated areas.

In an effort to demonstrate the prognostic factors for tumor response and skin damage Lindholm et al. [24] ran a trial including 59 patients who received radiotherapy combined with hyperthermia in a total of 3, 4, or 6 heat treatments. The overall response rate (complete and partial response) was 100%. The number of heating sessions did not influence the response rate. For the majority of patients toxicity was acceptable.

Superficial RTHT was also applied in patients with recurrent breast carcinoma of the chest wall for the evaluation of factors that correlate with local control [25]. At the time of maximum regression the complete response rate was 63%. Survival at 2.5 years was 21%, and at 5 years 8%.

In the Netherlands RTHT is a standard treatment method for previously irradiated patients that have developed breast cancer recurrences for the purpose of local palliation. Van der Zee et al. [26] ran a trial with 134 patients for the evaluation of this treatment. Hyperthermia was applied either with a 433 MHz technique or with a 2,450 MHz technique. Of the 134 patients 119 had macroscopic disease with a complete response rate of up to 71%. The local control rate for all patients including those with microscopic disease was 73%. A comparison of the complete response and local control rates between the 2 hyperthermia techniques was made, and the difference observed was statistically significant for large tumors.

Furthermore studies have shown that simultaneous application of hyperthermia and irradiation offers a better clinical outcome than sequential application. Myerson et al. [27] evaluated this method in patients with superficial tumors. Lesions were mainly head and neck cancers and breast adenocarcinoma. The tumor response for chest wall sites was: complete response 79%, partial response 14%, and non-response 7%.

Feyerabend et al. [28] investigated the efficacy of the combination of chemotherapy with RTHT in patients with inoperable recurrent breast cancer. Chemotherapy and hyperthermia were given once a week 30 min after irradiation. Skin morbidity was acceptable although the triple modality caused significant systemic toxicity. Although the response rate was high local control was only maintained for a few months.

A study by Hehr et al. [29] indicated that for locally recurrent breast cancer the local control achieved depends on many parameters of the combined treatment, including the tumor response to RTHT. 39 women with chest wall recurrences were enrolled and received RTHT, with hyperthermia being delivered before radiotherapy. The 1-year survival rate was 71%, and the 2-year survival rate was 54%.

In 2001 Kouloulias et al. [30] described the experience of the University of Athens Medical School with the combination of RTHT for the treatment of superficial tumors. In this study 88 breast cancer patients with post-mastectomy relapses in the chest wall and 27 patients with relapsed supraclavicular lymph nodes were included. The complete response rates were 85.2 and 70.4%, respectively.

The same team 1 year later published the first study about the efficacy of liposomal doxorubicin in conjunction with RTHT [31]. 15 female patients that suffered from locally advanced recurrent breast cancer were enrolled. All patients responded to the therapy, and more specifically the complete response rate was 20% and the partial response rate 80%.

Ben-Yosef et al. [32] recognized the benefit of hyperthermia when added to radiotherapy, and described their experience with the application of RTHT for the treatment of locally recurrent breast cancer. 15 women received radiation therapy and 45 min of hyperthermia, aiming at 45 °C. 6 of the 15 patients responded completely to the therapy, 4 patients responded partially, and 3 patients did not respond or presented with progressive disease.

Li et al. [33] applied RTHT in patients with locoregionally recurrent breast carcinoma. 41 lesions out of 75 had been previously irradiated. It was shown that hyperthermia offers a clinical benefit when combined with radiotherapy. Skin ulceration was noticed in 14% of patients.

Welz et al. [34] evaluated the contribution of hyperthermia in conjunction with radiotherapy when applied to locally advanced or recurrent breast cancer with marginal resection. In this study 15 patients were enrolled and divided into 2 groups. The first group received RTHT after resection as a primary therapy, and the second group consisted of patients with recurrent tumors who also underwent the same treatment modality. Overall survival was 90% for the first group and 89% for the second group, local control rates were 75 and 81%, respectively, while disease-free survival rates were 64 and 69%, respectively. Concerning all patients the rates for survival, local control, and disease-free survival were 89, 80, and 68%, respectively.

Gabriele et al. [35] based on their experience with the application of hyperthermia in conjunction with radiotherapy proposed that RTHT may be the treatment of choice for superficial recurrences. In their study the efficacy of RTHT was evaluated for patients that had been previously irradiated and had relapsed. After 18 months follow-up, the local control rate was 72.7%, the stable disease rate 20.5%, and the non-control rate 6.8%.

The effectiveness of re-irradiation plus hyperthermia was reported by Oldenborg et al. [36] in 2010. 78 patients with breast recurrences were treated with the combined treatment and responded to the therapy. Local control was high, more specifically the 3-year local control rate was 78% and the 5-year local control rate 65%. The 3- and 5-year survival rates were 66 and 49%, respectively.

Yamamoto et al. [37] reported on a case of a 66-year old woman with recurrent breast cancer, who received radiotherapy and chemotherapy but failed to respond. However, when hyperthermia was added to the other 2 modalities, the patient responded completely.

Finally, Linthorst et al. [38] evaluated the combined treatment and concluded that RTHT can offer good local control without serious toxicity. RTHT was applied in 198 patients suffering from breast cancer recurrences. The 3-year control rate was 83% while the 5-year local control rate was 78%.

Conclusion

The application of hyperthermia in conjunction with other therapeutic modalities is promising for recurrent breast cancer. Reported response rates are high, and the comparison of radiotherapy with or without the addition of hyperthermia as a treatment option shows that hyperthermia offers a benefit in terms of higher response rates, local control rates, and survival rates when the combined treatment is used. More studies are needed to evaluate the role of hyperthermia in the treatment of primary breast cancer lesions since the few currently available results are encouraging. Finally, taking into account the satisfactory results from numerous studies for the application of hyperthermia to head and neck cancers and malignant melanoma, consideration should be given to the integration of hyperthermia in the clinical treatment of other kinds of superficial lesions. Beyond the inclusion of hyperthermia

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in the recent NCCN guidelines for breast skin recurrences, we suggest the evaluation of RTH for other cutaneous lesions and even primary breast cancer lesions.

Supplemental Material

Table 2. 1-arm trials using irradiation and hyperthermia for the treatment of breast cancer. Results and toxicity of the combined treatment are presented

To access the supplemental table please refer to www.karger.com/?DOI=376594.

Disclosure Statement

The authors report no conflict of interest.

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