Role of Hyperthermia in Breast Cancer Locoregional Recurrence: A Review

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Keywords

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Summary

In patients with locoregional recurrences of breast cancer not suitable for resection, subsequent local control is difficult to maintain in previously irradiated areas when reirradiation alone or reirradiation with chemotherapy is used. Due to the limited number of treatment options there is a high risk of subsequent failure and uncontrollable local disease. In this group of patients, local hyperthermia combined with radiotherapy increases the clinical response and local control, adding limited acute and late toxicity, as has been shown in randomized trials. Hyperthermia is an artificial elevation of tissue temperature (range 40–44°C for 30–60 min). If hyperthermia is applied shortly before or after radiation, the effect of radiation is enhanced by influencing intratumoral hypoxia and by inhibiting sublethal damage repair in the tumor. Moreover, hyperthermia combined with radiation reduces the total dose of radiation needed compared to radiation alone, of which a higher dose is needed to obtain the same effect. Few data are available on the combination of radiotherapy and hyperthermia with chemotherapy, although the results of trimodality treatment consisting of reirradiation and hyperthermia together with liposomal doxorubicin are promising. Therefore, this literature review was performed to provide more comprehensive data on the mechanism and use of hyperthermia in locoregional recurrence of breast cancer.

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Introduction

The 10-year incidence of locoregional recurrence after breast-conserving therapy or modified radical mastectomy in women with stage I and II breast cancer is 4–18% [1]; the incidence increases to 28% in patients treated with surgery alone [2]. The 5-year locoregional recurrence rate for locally advanced breast cancer is 20–30% after combination therapy with chemotherapy and radiotherapy, with or without surgery [3–5]. Patients with a local recurrence have a significantly worse outcome with a 10-year distant disease-free survival of 15.4% and an overall survival of 34.8%; these figures are 44.5% and 62.1% ($p = 0.004$), respectively, in patients with local control [6, 7]. Local recurrence occurring more than 2–3 years after primary treatment has a better prognosis (5-year survival of 87–90%) than recurrence occurring within 2–3 years (5-year survival of 38–44%) [8, 9]. Furthermore, the recurrence rate is increased in triple-negative breast cancer and in primary inflammatory breast cancer [10, 11]. In view of the worse outcome in patients affected with a locoregional recurrence, additional therapeutic strategies are needed. Moreover, progression of locoregional recurrences may ultimately cause ulceration with odor, pain and bleeding resulting in considerable physical and mental suffering [12].

The generally recommended treatment for locally recurrent breast cancer after breast conservation is salvage mastectomy. This procedure is relatively successful in controlling local disease, with the incidence of secondary locoregional recurrence after salvage mastectomy ranging from 4 to 37% [13]. The recommended salvage treatment for a locoregional recurrence after mastectomy is high-dose radiotherapy with or without preceding surgery. According to the Dutch national guidelines, the standard treatment for locoregionally recurrent breast cancer in a previously irradiated area is reirradiation to a relatively low dose combined with hyperthermia [14]. Because the tumor load is one of the main predictors

HYPERTHERMIA TECHNIQUES

Fig. 1. Hyperthermia techniques.

of subsequent local failure, surgical resection of the macroscopic tumor before reirradiation with hyperthermia is advised if this is possible without too much damage or mutilation [15–17]. The aim of this review is to provide an overview of the mechanisms and results of the use of hyperthermia in the recurrence of breast cancer.

Literature Search

PubMed, Medline and ClinicalTrials.gov were searched using the keywords 'breast cancer', 'hyperthermia', and 'recurrence'. Preferably, randomized studies were included that were published between 1988 and 2014. Phase II clinical studies were excluded, except for trials with historical relevance or with a large patient population, or with promising data regarding an experimental technique.

Biological Mechanisms of Hyperthermia

Hyperthermia is defined as an artificial elevation of tissue temperature in the range of 40–44°C for 30–60 min. Treatment at these temperatures is cytotoxic for cells in an environment with a low pO_2 and low pH; both these conditions are found within tumor tissue due to insufficient blood perfusion [18].

During hyperthermia, the synthesis of nearly all proteins is stopped except for the heat shock proteins protecting cells from thermal damage and inducing a thermotolerance which influences the antitumor effect. Thermotolerance persists for several days, making heated cells more resistant to additional hyperthermia. If cells are not exposed to heat again, thermotolerance will quickly subside and all cells will lose tolerance at an exponential rate.

Hyperthermia given shortly before or after radiation enhances the effect of radiation by influencing intratumoral hypoxia and by inhibiting sublethal damage repair in the tumor. In addition, the combined treatment has the ability to affect cells in S phase where the radiation is less effective [19].

Hyperthermia combined with radiation reduces the total dose of radiation needed compared to radiation alone when a higher dose is needed to obtain the same effect [20].

To avoid the effect of thermotolerance, the hyperthermia sessions are usually administered weekly concomitant with 1 fraction of radiotherapy if irradiation is delivered on 5 days per week, or bi-weekly when combined with a hypofractionated radiotherapy schedule [21].

Hyperthermia has been under active investigation as a cancer treatment for many years. Although it has been used as a single modality obtaining a high rate of complete response (38.5%) in chest wall recurrences [22], it is not recommended as single therapy since only small and superficial tumors can be adequately heated and the response duration is short. More often, especially during the latter half of the 20th century, hyperthermia is used in combination with radiotherapy and/or chemotherapy. There is a clear rationale for using hyperthermia in order to improve local tumor control and relapse-free survival in patients with high-risk or advanced tumors of different entities [23].

Clinical hyperthermia is directed to safely applying heat to the tumor target volume while avoiding damage to normal tissue. Hyperthermia can be delivered locally (LHT), regionally (RHT) or as whole-body hyperthermia (WBHT) (fig. 1). LHT can be applied by external (external superficial or deep), intraluminal, or interstitial methods, with the volume that can be heated depending on the

Table 1. Selected hyperthermia trials in breast cancer recurrence: Summary of complete response

Author/Year	Study	Treatment	Results (CR)	Toxicity
Perez et al., 1991 [39]	randomized	selected patients; RT + HT vs. RT alone	52% vs. 39%	–
Vernon et al., 1996 [40]	randomized	RT + HT vs. RT alone	59% vs. 41%; 57% vs 31% (in previously irradiated patients)	no increased toxicity
Jones et al., 2005 [41]	randomized	RT + HT vs. RT alone	66.1% vs. 42.3%; 68.2% vs. 23.5% (in previously irradiated patients)	low toxicity
Zagar et al., 2010 [42]	retrospective	pretreated patients; RT + HT + CH	80%	grade 1–2 (desquamation)
Kouloulis et al., 2002 [43]	prospective phase I–II	pretreated patients; LD + RT + HT	20%	mild toxicity
Zagar et al., 2014 [44]	phase I	pretreated patients; LD + RT + HT	17%	grade 3–4 neutropenia (24%) and leucopenia (14%)
Feyerabend et al., 2001 [46]	phase II	RT + CH + HT	44%	acceptable toxicity

CR = Complete response, RT = radiotherapy, HT = hyperthermia, CH = chemotherapy, LD = liposomal doxorubicin.

physical characteristics of the energy source and on the type of applicator [24]. LHT is usually delivered with the superficial method in the treatment of breast cancer recurrence. RHT is applied by perfusion of a limb, organ, or body cavity with heated fluids. When used in combination with cytostatic drugs, the temperature must be lower to avoid unacceptable toxicity [25, 26]. In WBHT, the temperature of 40°C for a longer period in combination with cytokines and cytotoxic drugs is expected to achieve a greater therapeutic index than with a higher temperature [27].

Since the 1980s, several phase II clinical trials have shown an approximate doubling of the complete response rate of solid tumors to the combination of heat and radiotherapy compared with radiotherapy alone. Several phase III randomized trials have also been performed, demonstrating the significant benefit of hyperthermia when added to radiation in diseases such as melanoma, head and neck cancer, locally advanced pelvic tumors, glioblastoma multiforme, rectum cancer, and esophageal cancer [28–38].

Hyperthermia in Breast Cancer Recurrences

In 1988, Valdagni et al. [30] published results on N3 neck nodes after use of radiotherapy combined with microwave superficial hyperthermia. Since then, more than 1,700 patients have been included in randomized trials, showing significantly better results following a combination of hyperthermia with radiotherapy or radiotherapy plus chemotherapy with hyperthermia compared with radiotherapy or radiochemotherapy alone.

In the first randomized trial published in 1991 by Perez et al. [39], no significant increase in local control was found when adding heat to radiotherapy, compared to radiotherapy alone, in patients with superficial measurable tumors. This was due to the poor quality of radiation treatment and an inadequate heating technique. However, a later analysis of that same study evaluating subgroups of patients showed a complete response rate of 52% for the

combined treatment in patients with breast recurrences with a lesion diameter of ≤ 3 cm compared to 39% for radiation alone (table 1).

In 1996, 5 radiation/hyperthermia (RT/HT) phase III trials were jointly analyzed and showed RT/HT to be better than reirradiation alone for locorecurrent breast cancer. The complete response rate of RT/HT was 59% compared to 41% ($p < 0.001$) in the group treated with high-dose conventional radiation or low-dose reirradiation alone. The greatest effect was observed in patients with recurrent lesions in previously irradiated areas (57% RT/HT vs. 31% RT), whereas no increased toxicity was observed. The 3-year local control rate remained better (40% vs. 20%) when hyperthermia was added to radiation [40].

In 2005, results were published of a randomized phase III trial of radiotherapy with or without hyperthermia for superficial lesions, performed at the Duke University (Durham, NC, USA) [41]. Of those patients, 65% had breast cancer or chest wall recurrences. The complete response was 66.1% in the combined treatment group versus 42.3% in the radiation-alone arm. The temperature parameter ‘cumulative equivalent minutes at 43°C exceeded by 90% of monitored points’ (CEM 43°C T90) was a strong predictor of the complete response rate. Patients treated with reirradiation benefitted the most, with complete response rates of 68.2% for the combined treatment versus 23.5% in the radiation-alone group. The toxicity of adding hyperthermia was low and, generally, burns of grade 1 were reported; only 3 patients experienced third-degree burns [41].

Hyperthermia with reirradiation is highly suitable as palliation for inoperable chest wall recurrences after primary treatment. This was shown in a retrospective study of the Duke University, with an overall survival for the entire cohort of 14.3 months. These patients were heavily pretreated with prior radiotherapy (85%) and systemic therapy (89%). Analyzing patients by response, those achieving a complete response (80%) had a median overall survival of 23 months, while partial responders (20%) had a median overall survival of 5.4 months ($p = 0.01$) [42].

In 2002, a phase I/II study with liposomal doxorubicin (Caelix[®]), reirradiation, and hyperthermia administered in locally recurrent breast cancer showed an objective measurable response in all patients, with a complete response of 20%. Best results were obtained when the time between drug infusion and hyperthermia did not exceed 12 h and the temperature T90 exceeded 44°C [43]. In 2014, a similar phase I study of liposomal doxorubicin combined with reirradiation and hyperthermia showed an excellent 5-year disease-free survival (89%) in heavily pretreated patients with locoregionally recurrent breast cancer [44]. The CEM 43°C T90 parameter was correlated with response. These trimodality experiences confirmed the feasibility of reirradiation combined with hyperthermia and liposomal doxorubicin, as well as the correlation between the results and the achieved temperature level, and the importance of the time interval between drug and hyperthermia delivery. Experimental studies demonstrated better results in drug release when temperature-sensitive liposomes containing doxorubicin (Thermodox[®]) were administered instead of free doxorubicin or doxorubicin encapsulated in conventional liposomes. A clinical study is currently recruiting patients with breast cancer recurrences of the chest wall who have failed to respond to at least 2 lines of chemotherapy after mastectomy. Interim results show impressive clinical activity with a response of 50% (ClinicalTrials.gov identifier NCT00826085). Few studies have reported the effectiveness of hyperthermia combined with both radiotherapy and chemotherapy for the treatment of localized recurrent breast cancer except for inflammatory disease [45, 46].

Conclusions

All the above-mentioned studies reach the same conclusion: In a selected group of patients, hyperthermia combined with radio-

therapy increases the clinical response and local control, adding limited acute and late toxicity in patients with locoregional recurrent breast cancer in previously irradiated areas.

Recently, hyperthermia for breast recurrence has been included in the Dutch guidelines. In the National Comprehensive Cancer Network guidelines (NCCN-Breast Cancer, MS-24, 2007), hyperthermia is recommended in the treatment for breast recurrences. Hyperthermia has also been included in the clinical practice guidelines of the European Sarcoma Network Working Group (in the European Society for Medical Oncology (ESMO)) [47].

In the recommendations recently published by the AGO Breast Committee (AGO = Working Group Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie)), the treatment of choice for locally recurrent breast cancer is complete resection, whenever possible; radiotherapy is needed if there has been no prior irradiation [48]. In case of arecurrence in a previously irradiated area, reirradiation is not included. Based on previously reported data, low-dose reirradiation combined with hyperthermia should be added as treatment modality in previously irradiated patients not suitable for resection (see the AGO Recommendations chapter 'Locoregional Recurrence').

We conclude this review with a statement recently made by Januszewski and Stebbing [49] at the Department of Surgery and Cancer, Imperial College of London, UK: 'Scepticism is often justified, but data are increasing and the design of ongoing studies is robust. It is time that this technology is given the attention it deserves.'

Disclosure Statement

All authors listed have contributed sufficiently to the project to be included as authors. To the best of our knowledge, no conflict of interest, financial or other, exists.

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