


# Recommendation of Regional Hyperthermia in the Treatment of Breast Cancer

Integrative Cancer Therapies  
Volume 20: 1–2  
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DOI: 10.1177/1534735420988606  
journals.sagepub.com/home/ict  


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Submitted November 5, 2020; revised December 22, 2020; accepted December 28, 2020

Dear Editor,

We have read with great interest the recent review and updates from Fiorentini et al<sup>1</sup> concerning the application of regional hyperthermia mainly in combination with radio- (RT) or chemotherapy (CT) in your esteemed journal. The authors describe the application of hyperthermia (HT) or “modulated electro-hyperthermia” (mEHT) in a large variety of tumor entities, highlighting the advantages of adding HT to standard treatments.

Concerning breast cancer, the authors list 9 studies: 5 of them address recurrent breast cancer, 2 deal with advanced or recurrent breast cancer, 1 with advanced breast cancer, and the remaining study with liver metastasis of breast cancer. They state that HT combined with RT or CT should be suggested to all patients “with advanced or recurrent [breast cancer] or at high risk of local recurrence.”<sup>1</sup>

We think that this statement is too general and “advanced breast cancer” as a recommended indication is too diffuse. We share the authors’ view that “HT has never gained enough interest among oncologists to become a standard therapy in clinical practice.” However, we proclaim that the key to build up credibility of hyperthermia will be a careful stratification and analysis of disease stages and treatment results. In contrast, general recommendations will certainly not improve the acceptance of hyperthermia. Interestingly, the recommendation for HT has been deleted from the NCCN breast cancer guidelines since version 03.2019 ([https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf)).

To provide a more differentiated analysis, one should at least separate (1) irresectable preirradiated locally recurrent breast cancer (LRBC), (2) irresectable primary, and (3) metastatic disease:

1. Combined HT and RT should strongly be recommended for patients suffering from LRBC in previously irradiated sites, ranging from postoperative situations (“microscopic disease”) to all sizes of irresectable macroscopic LRBC. Since tumor control has a huge impact on quality of life, this applies

to patients with and without additional remote metastasis. The combination with HT allows for a considerable reduction of RT dose without abandoning the aim of effective tumor control. Thereby, re-irradiation with acceptable toxicity can be applied even in patients where re-irradiation alone, using classical doses, is out of option due to expected cumulative toxicity. This recommendation follows the current guidelines of German AGO (<https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma>).

2. The role of HT in the treatment of advanced primary breast cancer as well as for LRBC in sites without previous irradiation should be discussed separately. In these cases, radiotherapy alone using classical doses is an accepted treatment option. Nevertheless, combined HT/RT using reduced doses could be considered and might be advantageous in individual cases.
3. The treatment of distant metastasis (e.g., liver metastasis) with HT and CT as mentioned in the review, is a totally different topic. Since only few data are available supporting such a treatment, we would currently hesitate to give any recommendation.

In addition, a more careful analysis of side effects is necessary. Toxicity of combined HT/RT is especially important since most patients presenting with LRBC in pre-irradiated sites are treated with palliative intent. Toxicity data presented in Table 4 by Fiorentini et al<sup>1</sup> are neither complete (e.g., Linthorst et al<sup>2</sup> reported in detail HT-related thermal

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skin damage) nor correct (e.g., Oldenburg et al<sup>3</sup> reported  $\geq$ G3, not >G3 toxicity of 24%).

Regarding the balance between treatment response and toxicity, we would like to draw attention to our own results published in 2017.<sup>4</sup> Combination with hyperthermia allowed for a reduced total re-irradiation dose of only 20 Gy, using a hypofractionated schedule of  $5 \times 4$  Gy, once a week. A novel technique of contact-free, thermography-controlled water-filtered infrared-A superficial hyperthermia (wIRA-HT) was developed to cover large treatment fields up to a depth of approximately 2 cm. This procedure reduces RT- and HT-related toxicity to a minimum and even allows for repeat re-irradiation using the same dosage and schedule.

Tumor extension being a distinct criterion for prognosis, we have recently proposed a new classification of tumor size in LRBC, demonstrating stratified results for tumor response, local control and overall survival of 201 patients.<sup>5</sup>

For the assessment of the level of evidence and grade of recommendation it must be discussed whether randomized controlled trials (RCT) are feasible or not. Regarding pre-irradiated LRBC, RCTs can be discussed for microscopic disease. In contrast, RCTs are not feasible for macroscopic disease due to the lack of standard treatment options and the heterogeneity of individual situations. Best supportive care as 1 treatment arm would be ethically unacceptable.

In order (a) to improve acceptance of HT and (b) to develop the great potential of HT in cancer therapy, any evaluation and recommendation should consider the heterogeneity of tumor situations, treatment schedules, RT or CT doses and HT techniques used.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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