



Hyperthermia Plus Re-Irradiation in the Management of Unresectable Locoregional Recurrence of Breast Cancer in Previously Irradiated Sites

On May 22, 2020, Buchholz et al¹ published an excellent review of multidisciplinary management of locoregional recurrent (LRR) breast cancer, emphasizing the heterogeneity in manifestations and significant variation in prognosis and preferred treatments.

In that review, the authors recommend considering re-irradiation with hyperthermia “for patients with an isolated LRR after previous postmastectomy radiation who have good performance status.” Regarding the algorithm shown in Figure 2 of the Buchholz et al¹ article, this recommendation applies to isolated unresectable disease as well as to adjuvant re-irradiation after total or partial resection. We fully support this recommendation but consider it too limited. We strongly propose to generally extend it to heavily pretreated patients with unresectable LRR of breast cancer in previously irradiated sites in which another systemic therapy is excluded or is questionable because of treatment resistance or expected toxicity.

For some years, we have focused on new treatment strategies for this group of LRR patients who have the worst prognosis. They suffer from a severe loss in quality of life caused by uncontrolled local tumor growth with symptoms such as ulceration, bleeding, infection, pain, or constriction. Therefore, even patients who present with distant metastasis are likely to benefit from local tumor control and should be considered for re-irradiation.

On the basis of findings from earlier studies using hyperthermia and re-irradiation, we found that the combination with hyperthermia allowed for a reduction of the total re-irradiation dose to just 20 Gy using a hypofractionated schedule of 5 × 4 Gy once per week.² To our knowledge, this is the lowest total re-irradiation dose applied so far in a protocol that aims for effective tumor control. The use of a novel technique of contact-free, thermography-controlled water-filtered infrared-A superficial hyperthermia (39–43°C) allows us to cover large-size lesions and could reduce the risk of thermal skin damage to a minimum.³ In contrast to most reported protocols of radiotherapy and hyperthermia combined, we perform hyperthermia immediately before re-irradiation. Low toxicity of this protocol even allows us to repeat re-irradiation using the same dosage and schedule. This

is especially crucial in the management of lobular carcinoma in situ and ductal carcinoma in situ, and lobular carcinoma in situ, which is often recurring. Results were recently published⁴ for tumor response, local control, and overall survival of 201 patients, including a new classification of tumor size in LRR of breast cancer. There has been a lack of clear definition of tumor extension, which is a distinct criterion for prognosis. The suggested definition of five size classes of local recurrences could help with comparison of data from different protocols and studies using combined hyperthermia and re-irradiation.

The characteristics of unresectable, large-size LRR of breast cancer in pre-irradiated regions do not allow for the design of comparative studies. Randomization of hyperthermia plus re-irradiation with reduced dosages against re-irradiation alone with standard dosage is not feasible because of the expected toxicity of the latter. Comparison of an intervention versus a non-intervention group cannot be ethically justified. The same is true for comparison with a standard treatment; thus, a standard does not exist for patients for whom the aim of tumor control has already been abandoned. Conversely, the lack of comparative studies impedes general acceptance and, in many countries, availability because of the lack of reimbursement. We are interested in remarks and suggestions from the scientific community about strategies to overcome these hurdles.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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