Integrative Cancer Therapies
Volume 20: 1–2

DOI: 10.1177/1534735420988589
journals.sagepub.com/home/ict
SAGE

Re: Response to Recommendation of Regional Hyperthermia in the Treatment of Breast Cancer

Giammaria Fiorentini, MD[1,3], Donatella Sarti, PhD[1], Cosmo Damiano Gadaleta, MD[2], Marco Ballerini, MD[3], Caterina Fiorentini, MD[4], Tommaso Carfagno, MD[5], Girolamo Ranieri, MD[2], and Stefano Guadagni, MD[6]

Dear Editor,

We read carefully the Letter to the Editor sent by M. Notter et al. and appreciated the interest that these eminent colleagues have shown in our work.[1] Our narrative review has been a great scientific effort to offer useful information to promote hyperthermia treatments (HT) in the daily clinical practice of medical oncologists, surgeons and radiotherapists who practice integrated oncology treatments and palliative medicine as well as that of physicians who do not practice hyperthermia.

In order to write the review for publication in Integrative Cancer Therapies, we selected the most important articles and unfortunately excluded others that would equally deserve to be mentioned, since it was not possible for reasons of space to assemble all the data available on hyperthermia. At the same time, we tried to select the most important information for the tables, often simplifying the data for reasons of exposure and clarity. Our work was not limited to breast cancer alone but reported also data on 8 other types of cancer and it was sincerely our goal to arouse interest in the application of hyperthermia in oncology and not only in a particular type of cancer.

As concerning the recommendation of HT in the treatment of breast cancer of M. Notter et al. we agree about the need to improve the way in which studies are carried out, in particular, the need for a careful stratification and analysis of disease stages. The suggestion to subdivide clinical results according to breast neoplasms (irresectable preirradiated locally recurrent breast cancer, irresectable primary and metastatic disease) is certainly useful for clinical classification and would acquire greater significance if integrated with the well-known classifications of Luminal A, Luminal B, triple-negative/basal-like, HER2-enriched normal-like breast cancer. We will be able to practice locoregional treatments of hyperthermia and radiotherapy in a disease such as breast cancer which is very frequently metastatic at its onset by knowing its clinical and biomolecular parameters.

Regarding the field of metastatic breast cancer, there is currently a growing interest in palliative treatment of both hepatic and other organ metastases, such as pre-irradiated bone metastases, by associating hyperthermia to the metastatic site with systemic chemotherapy and novel immunotherapeutic agents.

This combination can add to the well-known characteristics of blood flow modification, increase in local oxygenation and drug concentration and therefore the efficacy of treatment.

Low doses of radiotherapy and/or HT can increase surface tumor antigens due to immunogenic cell death,[2] and HT increases lymphocyte trafficking and lymphocyte response, creating new avenues of care.

About the inaccuracies contained in Table 1 (see revised Table 1) we would like to specify that we initially recorded the Oldenborg et al.[3] data correctly as "≥G3 toxicity in 24%," but due to a typograpical error it appeared as ">G3."

Linthorst et al.[4] wrote "Cumulative incidence of grade 3 and 4 late toxicity at 5 years was 11.9%," yet we specify better the Linthorst et al.[5] data by adding details in Table 1.

We thank M. Notter et al. for their helpful comments, which add to the utility of our publication

[1]Azienda Ospedaliera "Ospedali Riuniti Marche Nord," Pesaro, Italy
[2]IRCCS Istituto Tumori "Giovanni Paolo II," Bari, Puglia, Italy
[3]Private Clinic Ravenna[33], Ravenna, Italy
[4]University of Siena, Siena, Toscana, Italy
[5]University Hospital Siena, Italy
[6]University of L'Aquila, L'Aquila, Italy

Corresponding Author:
Giammaria Fiorentini, Azienda Ospedaliera Ospedali Riuniti Marche Nord—Oncology, via Lobroso 1, Pesaro 61100, Italy.
Email: g.fiorentini2020@gmail.com

Table 1 (revised). Breast Cancer.

Reference	Type of study	Site	n	Treatment	Tumor response	Survival	HT associated adverse events
De-Colle 2019	Prospective observational study	Recurrent breast cancer	20	RT + HT	Clinical benefit 90%	2 y. OS = 90%. DFS = 90%. 5 y. OS = 50%	>G 3 toxicity in 15%
Klimanov 2018		Metastatic breast cancer	103	53 CHT + HT 50 CHT	Clinical benefit = 76% (CHT + HT) vs 42% (CHT) $P < .05$		
Linthorst 2015[5]		Recurrent breast cancer	248	RT + HT	CR rate 70%. 1, 3, and 5 y Local control was 53%, 40%, and 39%	SR at 1, 3, and 5 y = 66%, 32%, and 18%	Erythema 20%, desquamation 9%, skin necrosis 1%, thermal burns 23%
Oldenborg 2015		Recurrent breast cancer	404	RT + HT	CR = 86%. ORR was 86%. 3-y LC rate was 25%	Median 17 mo and SR at 3 y = 37%	⩾G 3 toxicity in 24%
Refaat 2015		Recurrent or advanced breast cancer	127	RT + HT	CR = 52.7%. Local control = 55, 1%	SR at 1, 3, and 5 y = 58.3%, 29.5%, 22.5%	
Linthorst et al. 2013[4]		Recurrent Breast cancer	198	RT + HT		Median 82 mo SR at 3, 5, 10 y = 75, 60, 36%	G3-4 late toxicity in 11.9%
Takeda et al. 2013		Recurrent or advanced breast cancer	172	Immuno therapy + HT	Clinical benefit 17.6% effective rate of immunotherapy increased from 7.7% to 26.0% using hyperthermia		
Varma et al. 2012		Advanced breast carcinoma	59	RT + HT	Local control = 70%		⩾G 3 toxicity in 14%
Oldenborg 2010[3]		Recurrent breast cancer	78	RT + HT	3, 5-year local control rates were 78% and 65%	3 y survival 66%	G 3 toxicity in 32%

Abbreviations: RT, radiotherapy; HT, hyperthermia; OS, overall survival; SR, survival rate; Clinical benefit, complete response + partial response + stable disease; CHT, chemotherapy.

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.

ORCID iD

Giammaria Fiorentini https://orcid.org/0000-0002-5615-889X

References

1. Notter M, Thomsen A, Grosu AL, Vaupel P. Recommendation of regional hyperthermia in the treatment of breast cancer. *Integr Cancer Ther*. Preprint. 2021.
2. Ahmed A, Tait SWG. Targeting immunogenic cell death in cancer. *Mol Oncol*. Published online November 11, 2020. doi:10.1002/1878-0261.12851. Epub ahead of print. PMID: 33179413.
3. Oldenborg S, Griesdoorn V, Os R, et al. Re-irradiation and hyperthermia for irresectable locoregional recurrent breast cancer in previously irradiated area: size matters. *Radiother Oncol*. 2015;117:223-228. doi:10.1016/j.radonc.2015.10.017
4. Linthorst M, van Geel AN, Baaijens M, et al. Re-irradiation and hyperthermia after surgery for recurrent breast cancer. *Radiother Oncol*. 2013;109:188-193. doi:10.1016/j.radonc.2013.05.010
5. Linthorst M, Baaijens M, Wiggenraad R, et al. Local control rate after the combination of re-irradiation and hyperthermia for irresectable recurrent breast cancer: results in 248 patients. *Radiother Oncol*. 2015;117:217-222.