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. 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, 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. data correctly as “≥G3 toxicity in 24%,” but due to a typographical error it appeared as “>G3.” Linthorst et al. wrote “Cumulative incidence of grade 3 and 4 late toxicity at 5 years was 11.9%,” yet we specify better the Linthorst et al. 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, 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% | 2y. OS = 90%. DFS = 90%. 5y. OS = 50% | >G 3 toxicity in 15% |
| Klimanov 2018 | Metastatic breast cancer | 103 | 53 CHT + HT 50 CHT | Clinical benefit = 76% (HT + HT) vs 42% (HT) P < .05 | | |
| Linthorst 2015 | Recurrent breast cancer | 248 | RT + HT | CR rate 70%. 1, 3, and 5y Local control was 53%, 40%, and 39% | SR at 1, 3, and 5y = 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% | |
| Refaat 2015 | Recurrent or advanced breast cancer | 127 | RT + HT | CR = 52.7%. Local control = 55%, 1% | SR at 1, 3, and 5y = 58%, 29.5%, 22.5% | |
| Linthorst et al. 2013 | Recurrent Breast cancer | 198 | RT + HT | | Median 82mo SR at 3, 5, 10y = 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 carcinoma | 59 | RT + HT | Local control = 70% | | G 3 toxicity in 14% |
| Oldenborg 2010 | Recurrent breast cancer | 78 | RT + HT | 3, 5-year local control rates were 78% and 65% | 3y 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, Wigenraad 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.