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Comment

Randomized trials in accelerated partial breast irradiation: “Two wrongs don’t make a right!!”

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We congratulate Marta et al.⁷ for their effort for this systematic review on accelerated partial breast irradiation (APBI). Unfortunately, as mentioned by the authors “wide confidence intervals and high risk of inconsistency precluded a sound conclusion”.... We would like to comment on two major issues regarding the concept of APBI and the methodology considered by the authors of that work.

First, we definitely believe that intra-operative radiotherapy (IORT) procedure should no longer be considered as an “APBI technique” concept similar to other techniques using a twice-daily fractionation following one week. One of the advantages of IORT is to achieve (with a single fraction of 20 Gy) a precise treatment during surgery procedure. However, the results of published randomized trials, either using low energy X-ray (Intrabeam),¹ or electron beam (Eliot)² were both clearly unfavorable to IORT, in terms of local recurrence rates, as compared to standard whole breast irradiation (WBI). In addition, many comments have been published regarding the IORT limitations that could explain these local failures such as:

- (i) Possibility of delivering a very limited dose to occult foci away from the surgical margins: for example, using Intra-beam device to deliver 20 Gy in 1 fraction, the physical radiation dose delivered at 10 mm and 27 mm depth are only 5 Gy, 1 Gy, respectively.

- (ii) Inability of radiation to deliver curative doses beyond the first few millimeters, with only 15.5 Gy at 2 mm. In addition, this could even limit the dose due to the remaining seroma in the lumpectomy cavity during IORT, even if some recent reports have postulated that IORT can modify favorably the biologic activity of surgical wound fluid and mediate radiation damage through environmental factors secreted by irradiated cells that induces a “bystander effect”.³
- (iii) Absence of patients’ selection according to the tumor biology in these trials.

Finally, the fact that IORT trials were mixed with the other fractionated APBI techniques results could create confusion and raise doubts about the reported results. We then suggest that IORT data should be analyzed separately from the other APBI modalities.

The second point concerns the methodology. The authors applied the PRISMA guidelines to conduct this systematic review of the literature.⁴ Of note, some methodological key points have not been respected. According to the PRISMA guidelines, a systematic review protocol should have been previously published on a repository such as Prospero.⁵ But most importantly, there is an obvious lack of consistency among the included studies as the planning target volume (PTV) is significantly different between them; this is considered a major

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<https://doi.org/10.1016/j.rpor.2019.08.004>

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parameter in respect to local control in breast cancer. Furthermore, there is a significant difference among the different studies with regard to adjuvant treatment, such as duration and/or type of endocrine therapy, and in tumor characteristics as some studies included DCIS in more than 10% of patients or grade III carcinoma in more than 20% of patients compared to others which included none. Those inconsistencies between studies lead to limitations of the internal validity of the systematic review.⁶ The authors reported in their methodology that they are calculating the I^2 statistic to quantify heterogeneity between studies. However, while the results are reported in supplementary material, those are only partially estimated and reported, as it has only been estimated for a fraction of the included studies (external beam radiotherapy only) and reported without a confidence interval. The estimated I^2 reported moderate heterogeneity among the results; however, a more accurate estimation and presentation of the I^2 would probably have reported a higher degree of heterogeneity for the reasons mentioned before.

Finally, the limitations in the trials selection and the limited consistency of the methodology made it very difficult to draw any conclusions from this study in which the quote “two wrongs don’t make a right!!” is more than ever valid for such data.

Conflict of interest

None declared.

Financial disclosure

None declared.

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