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EDITORIAL – BREAST ONCOLOGY

Should We Completely Exclude Locoregional Therapy for the Primary Tumor from Our Clinical Practice in De Novo Metastatic Breast Cancer?

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ABSTRACT Locoregional therapy (LRT) for the primary site of breast cancer (BC) is one of the most debated topics in de novo metastatic disease. We have four main randomized controlled trials, three negative and one positive, together with one positive prospectively designed non-randomized study investigating the contribution of LRT to the literature. We aimed to discuss the possible reasons for the positive or negative results of the studies and to identify specific subgroups that may benefit from primary breast surgery.

Keywords Breast cancer · Locoregional therapy · Surgery · Metastatic disease

Locoregional therapy (LRT) for the primary site of breast cancer (BC) is one of the most debated topics in de novo metastatic disease. Khan et al. performed a detailed analysis to evaluate the positive effect of LRT on survival in patients with de novo metastatic BC in the prospectively designed EA2108 trial. Following the authors' finding that early use of LRT does not improve survival, we would like to draw attention to some important points.[1]

Contrary to the results of the EA2108 trial, the MF07-01 trial indicated the positive effect of LRT on survival, whereupon Khan et al. claimed that there was a substantial imbalance in the prognostic covariates of the MF07-01 trial, possibly contributing to better outcomes in the LRT arm compared with systemic therapy (ST) alone.[2] In fact, the most striking imbalance in the MF07-01 trial was the distribution of tumor subtype. Accordingly, patients in the LRT group had higher rates of ER/PR positivity and lower rates of triple-negative tumors than patients in the ST-alone arm. Considering this imbalance, and when analyzed separately for tumor subtypes, it was observed that the overall survival contribution with local treatments was present only in the hormone-positive subgroup. Moreover, despite the small number of patients included, the most striking result is that the contribution of LRT is reduced not only in the presence of multiple lung/liver metastases, but also in the presence of solitary lung/liver metastases and multiple bone metastases. In this regard, although the MF07-01 trial yielded a positive result in the whole population, we can conclude that LRT may contribute to survival in certain patient groups, including hormone positive, solitary bone metastatic disease or low tumor burden termed as oligometastatic disease in especially bone-only disease. Another prospectively designed BOMET MF14-01 trial evaluating the effect of LRT on 505 patients with bone-only metastatic BC, the highest number of patients in literature, showed that LRT prolonged the median 3-year survival compared with ST alone.[3] However, the main shortcoming of MF07-01 and BOMET MF14-01 trials is that CDK4/6 inhibitors, the most potent systemic therapy, were not given, and the contribution of LRT could not be analyzed if given. In the EA2108 study, the poor prognostic patient group was recruited more heavily: the tumor burden was high, the rate of oligometastatic disease was only 12.2%, and the rate of HER-2 and triplet-negative disease was approximately 40%. Therefore, the expectation that LRT might have a survival benefit is actually low. In addition,

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no further analysis was performed for solitary bone metastatic disease or oligometastatic bone-only disease, which may benefit from LRT in the EA2108 study.

Khan et al. state that their results are compatible with the other two studies.[4,5] However, in the Indian study, whose design more closely resembles the EA2108 trial, we see that optimal systemic therapy was not provided to the patients, and therefore the survival time of the patients was much worse compared with the EA2108 trial. In this context, the value of the study is diminished, and conclusions cannot be drawn.[4] In the other negative study, the POSYTIVE trial, we see that analysis was made in a very heterogeneous patient group with a very low number of patients (90 patients).[5] In this regard, despite the negative results of these three studies, the results should be interpreted considering the patient and tumor characteristics included in the studies, the preference for subgroup analysis, heterogeneity of the studies, and the lack of current systemic treatments that may cause bias. Therefore, we think that Khan et al. sharp statement that local treatments should not be used in BC may lead to scientific bias.[1] However, considering the MF07-01 and BOMET MF14-01 trial data, it is seen that performing primary LRT in highly selected patient groups is beneficial in terms of survival. In the EA2108 study, the patient population that could contribute to survival with LRT was not analyzed separately or included a much smaller number of patients. Considering these findings and the shortcomings in the study design of the five published clinical trials, it may be misleading for the patient treatment management to claim strongly that there is no survival benefit of performing LRT in all patients until an ideal clinical trial is conducted.

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REFERENCES

1. Khan SA, Zhao F, Goldstein LJ, et al. Early local therapy for the primary site in de novo stage iv breast cancer: results of a randomized clinical trial (EA2108). *J Clin Oncol*. 2022;20(40):978–87. https://doi.org/10.1200/JCO.21.02006.
2. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage iv breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol*. 2018;25:3141–9. https://doi.org/10.1245/s10434-018-6494-6.
3. Soran A, Dogan L, Isik A, et al. The effect of primary surgery in patients with de novo stage iv breast cancer with bone metastasis only (protocol BOMET MF14-01): a multi-center, prospective registry study. *Ann Surg Oncol*. 2021;28:5048–57. https://doi.org/10.1245/s10434-021-09621-8.
4. Badwe R, Hawaldar R, Nair N, et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. *Lancet Oncol*. 2015;16:1380–8. https://doi.org/10.1016/S1470-2045(15)00135-7.
5. Fitzal F, Bjelic-Radisic V, Knauer M, et al. Impact of breast surgery in primary metastasized breast cancer outcomes of the prospective randomized phase III ABCSG-28 POSYTIVE trial. *Ann Surg*. 2019;269:1163–9. https://doi.org/10.1097/SLA.0000000000002771.