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Biology matters: the clinical impact of single-receptor discordance on breast cancer

The interesting paper by Dieci et al. highlights once again that the estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor type 2 (HER-2) status between primary breast cancer and paired metastases may change. In Dieci's study, discordance rates in the receptor status were 13.4%, 39% and 11.8% for ER, PgR and HER-2, respectively [1], comparable with those of the prospective study conducted by Amir et al. [2]. The exact reason for such discordance has yet to be determined. Possible biological explanations include limited accuracy and reproducibility of receptor assays, intratumor heterogeneity, clonal selection in tumor biology determined by therapy and variable ER-lineage differentiation of putative disseminated breast cancer stem cells during the course of the disease [3].

Whatever the reason, Dieci's single-institution retrospective study also addressed the clinical significance of single-receptor discordance in terms of prognosis, observing that a loss of ER or HER-2 expression resulted in poorer post-recurrence survival (PRS) [1]. We identified a similar discordance rate in our recently published paper: 16.4%, 41.7%, 17.5% for ER, PgR and HER-2, respectively, as well as a trend toward poorer PRS in patients whose tumors showed a loss of ER expression [4] Similarly, other authors reported that patients with ER-positive discordant breast cancer had a significantly shorter time to relapse (TTR) than those with concordant ER-positive disease (1.9 and 4.2 years, respectively; $P = 0.0002$). However, the same analysis was not carried out for the other biological factors [5].

We conducted a study to evaluate the changes in TTR, taking into consideration single-receptor discordance. TTR was calculated as the period from breast cancer diagnosis to the first recurrence. Among 120 patients evaluated, 91 who underwent a biopsy within 3 months from the date of the first relapse were considered suitable for the analysis.

Those whose tumors showed a loss of ER expression experienced a significantly shorter TTR than individuals whose tumors maintained ER positivity (median 45 versus 61 months, respectively). Similarly, a gain in ER expression conferred a longer TTR than stable ER negativity (median 46 versus 19 months, considered globally $P < 0.001$). In contrast, a loss in HER-2 expression resulted in a longer TTR than maintained HER-2 positivity (median 56 versus 16 months). Of note, the four patients whose tumors showed a loss in HER-2 expression had the longest TTR of all the subgroups (median 67 months, globally $P < 0.001$). No significant differences in TTR were observed in relation to the overall PgR discordance.

There is a growing consensus that, if technically feasible metastatic lesions should be biopsied because they may be able to guide treatment choice and may also carry prognostic information. However, discordant results should be interpreted with caution and any decision to change treatment should be based on the clinical behavior of the disease. Further studies are needed to assess whether metastasis biopsy-guided treatment can positively influence the clinical outcome.

A. Farolfi[1]*, T. Ibrahim[1], E. Scarpi[2] & D. Amadori[1]

[1]Osteoncology and Rare Tumors Center;
[2]Unit of Biostatistics and Clinical Trials, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, Italy
(*E-mail: a.farolfi@irst.emr.it)

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disclosure

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