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## CLINICAL VIGNETTE

# Discordant Metastatic Breast Cancer Markers

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### Clinical Presentation

Patient is 63-year-old post-menopausal female with a past medical history significant for a clinical stage II (cT2N0) left sided estrogen receptor negative (ER-), progesterone receptor negative (PR-), HER2 overexpressed breast. At the time of diagnosis, the primary tumor measured 3.5cm in greatest dimension and no lymph node involvement was noted. She completed six cycles of neoadjuvant, pertuzumab, trastuzumab, carboplatin and docetaxel. She subsequently underwent a breast conserving lumpectomy with sentinel lymph node biopsy which revealed a complete pathologic remission (ypT0N0). The patient then completed standard external beam radiation therapy and a year total of adjuvant trastuzumab.

She presented two years later after completing her adjuvant therapy with a 1 month history of progressive left rib pain and lower back pain. CT revealed multiple bone lesions but no visceral masses. A CT-guided biopsy of the lumbar vertebra revealed an invasive ductal carcinoma that was ER-, PR- HER2 not-overexpressed and morphologically similar to the primary malignancy. She began capecitabine. Repeat imaging after 4 months revealed a complete remission.

### Case Discussion

This case highlights an important concept in the management in breast cancer. Molecular markers are playing an increasing role in the management metastatic breast cancer, guiding when endocrine therapy, chemotherapy, and targeted therapy is appropriate. However, confirmatory biopsies of suspected metastases are not always performed in the routine oncologic care setting.<sup>1</sup> Treating recurrences based on the original pathology rather than obtaining fresh tissue has been a common practice. This practice can be explained by the following. Biopsies are inherently invasive and carry risk of morbidity. Discordance in tumor characteristics between primary and metastatic breast cancer has been described for more than 30 years, discordance data in tumor characteristics between primary and metastatic breast cancer had been considered unreliable due to wide variation and non-reproducibility.<sup>2</sup>

Within the last 10 years, laboratory assays for receptor testing have improved and results are more reproducible although a wide variance in reported values persists. The reasons for wide range in values include: type of biopsy performed (FNA vs core), site of biopsy and fixative used. Both retrospective and

prospective trials demonstrate marker discordance. Expression of the estrogen and progesterone receptors in metastatic breast cancer have been reported to be discordant in up to 15-40% and 15-30%, respectively.<sup>2</sup> The discordance rate for HER2 expression is between 10-24%.<sup>3</sup>

In a recent prospective cohort study,<sup>4</sup> 121 patients with evidence suggestive of metastatic disease or with progression while during treatment were enrolled. The primary end point of the study was the proportion of patients in whom the biopsy result led to a change in treatment. Discordance in ER, PgR, and HER2 between the primary and the metastasis was 16%, 40%, and 10%, respectively. Biopsy led to a reported change of management in one of 7 (14%) of women (95% CI, 8.4% to 21.5%). These findings are similar to the findings of the prospective BRITS trial where switch in receptor status led to a change in the subsequent treatment plan for one in 6 patients (17.5%).<sup>3</sup>

Altering treatment after biopsy, has not conclusively shown improvement in overall survival or progression free survival. The clinical studies to date have not been powered with sufficient patients per cohort to draw any significant conclusions. Despite this limitation, it may be of value to recommend biopsy of metastatic lesions. Recently approved treatments have included agents that target the mammalian target of rapamycin (mTOR) inhibitors and cyclin dependent kinase pathway inhibitor. These agents appear to have increased efficacy and significant less toxicity than traditional intravenous chemotherapy in specific sub-groups.

In the case above, re-biopsy of a metastatic site was completed without significant morbidity. Detection of the change in receptor status resulted in significant changes in the chemotherapy regimen with a complete remission. Future clinical trials are needed to confirm the clinical benefit of this change in treatment paradigm.

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