Testing for Discordance at Metastatic Relapse: Does It Matter?

Stephen Chia, British Columbia Cancer Agency, Vancouver, British Columbia, Canada

In the articles that accompany this editorial, two studies are reported that challenge the belief that a biopsy at the time of metastatic breast cancer relapse is not routinely required, because it provides no further information in regard to the optimal treatment of an individual patient’s tumor. Amir et al report on a prospective trial assessing the clinical impact of tissue confirmation of metastatic disease in patients with breast cancer, and Niikura et al describe rates of discordance and survival in a large single-institution cohort of patients with human epidermal growth factor 2 (HER2) positive primary breast cancer who had a metastatic tumor biopsy result available. Both of these studies are important for solidifying the results of numerous retrospective studies that have consistently demonstrated a discordant rate for either the estrogen receptor (ER) or HER2 receptor between the primary tumor and metastatic lesion. Although it is rational to attempt a biopsy for confirmation of metastatic disease for prognostic purposes, perhaps more contentious are the potential reasons behind, and the resultant clinical consequences of, an apparent discordant result.

In the pragmatic and well-designed prospective cohort study by Amir et al, patients presenting with evidence suggestive of metastatic disease or who were experiencing progression while receiving a palliative systemic treatment were enrolled. Strengths of the study were that the primary end point of the study was the proportion of patients in whom the biopsy result led to a change in systemic management, with secondary end points including patient-reported outcomes related to patient satisfaction. Neither of these important end points can be properly measured by means of retrospective study. The main conclusion of the study was the finding of discordance in either ER or HER2 in 16% and 10% of patients, respectively. In 14% of all patients enrolled, the biopsy result led to a reported change in management, with 88% of all participants stating they would recommend the biopsy procedure to other patients.

In the retrospective study from the MD Anderson Cancer Centre (MDACC), 182 patients with HER2-positive primary breast cancers were identified, of whom 24% (n = 43) were found to have an HER2-negative metastatic lesion on review. Furthermore, the investigators demonstrated that the patients with a discordant HER2 result (HER2-positive primary disease but HER2-negative metastases) had worse survival than the patients with a concordant HER2 result (hazard ratio, 0.43; P = .003). Strengths of this study were the relatively large cohort of HER2-positive primary breast cancers identified, the attempted central review of HER2 results (for those patients who were originally assessed at other institutions), and correlation of treatments and outcome between discordant and concordant subgroups.

A discordant rate of approximately 25% in either ER or HER2 is well within the range seen in several recent larger retrospective studies as well as one prospective study (BRITS [Breast Recurrence in Tissues Study]). This range of discordance, between 20% and 30%, has been repeatedly demonstrated in these studies despite differences in methodology of assessment for the biomarkers between the primary and relapsed lesions, inclusion of both local and regional relapses with the distant tumors, and heterogeneity in patient populations. Despite these limitations, the similarities in results have led to recent debate that clinicians should routinely consider a biopsy at time of relapse. However, the question now is do we believe that the results will alter clinical practice and improve outcomes enough to justify routine performance of this procedure?

The main reasons for caution involve both the preanalytic and analytic variables associated with immunohistochemical (IHC) assessment based on fine-needle aspiration (FNA) biopsies and the IHC assessment of proteins in formalin-fixed paraffin-embedded tissue (FFPE). Although FNA biopsies are generally easier and less morbid a procedure than core biopsies, the fixative used (eg, cytospin collection fluid v ethanol) to process the cytologic specimen and the methodology used (eg, smears v cell block) can dramatically alter the sensitivity to detect biomarkers. In one comparison study, the sensitivities for assessing ER ranged from as poor as 14% (eg, ethanol fixative for smear prep) to a high of 88% (which still is not optimal) when compared with FFPE tissue sections. This limitation is especially relevant in the study from MDACC, because 71% of the metastatic lesions were evaluated by FNA biopsy. Furthermore, in a recent literature survey led by individuals within the National Cancer Institute Office of Biorepositories and Biospecimens Research, 15 preanalytic variables were identified that were capable of affecting IHC. These 15 identified issues were limited to FFPE-processing variables only; additional variations in tissue type or antigen retrieval techniques are additional sources of variance not addressed in the scope of this article. Discordance between local and central laboratories in the range of 10% to 20% have long been recognized in the context of ER and HER2 testing. However, a recent round-robin review of HER2 testing among three central laboratories involved in large adjuvant trials (NCCTG [North Central Cancer Treatment Group] N9831, BCIRG [Breast Cancer International Research Group] 006, BCIRG 005) with preset methodologies, antibodies, and thresholds demonstrated that a discordant rate of 8% in both HER2 IHC and fluorescent
in situ hybridization status still persisted, further highlighting the role that preanalytic and analytic variables may play in the observed discordance in biomarker testing.

In fact, in the study at hand by Amir et al, when 52 primary tumors were reanalyzed in their central laboratory, five of the tumors (10%) were discordant in either ER or HER2. Thus, their reasoning that retesting of all patient cases for discordance was not necessary because in some cases the original pathology was performed in a central laboratory (n = 42) is not supported by the round-robin exercise described. Interestingly, despite a discordant rate of 26% in either ER or HER2, the biopsy result ultimately led to a change in management in only 14% of all patients. A negative ER or HER2 test in the metastatic lesion, the potential for preanalytic and analytic variables as reasons for discordance, and the subsequent withholding of a hormonal or anti-HER2 agent because of the associated negative biomarker test may have been reasons why in 12% of patients, there was no change in therapeutic strategy despite a discordant result. Furthermore, because the study asked the oncologist whether the biopsy result led to a change in treatment strategy at that point in time, it is unclear if later lines of therapy would continue to be completely based on the study biopsy result.

The ultimate level of evidence to support whether a discordant biomarker result leads to altered patient outcome requires the assessment of its appropriate impact on treatment and then outcome. In the study from MDACC,2 worse survival was demonstrated for the discordant cohort relative to the concordant subgroup, presumably because of appropriate anti-HER2 therapy for the true HER2-positive metastatic breast cancers. A recent study by investigators from the same institution demonstrated that women with HER2-positive metastatic breast cancer treated with trastuzumab had better survival than both the HER2-negative metastatic breast cancer population and the HER2-positive cohort not treated with trastuzumab. The study from the Stockholm Health Care region did demonstrate worse survival in the ER-negative relapsed cohort relative to those experiencing ER-positive relapses regardless of the ER status of the primary cancer.

In conclusion, the available data, including those from the two most recently published studies, demonstrate that a true discordant rate exists between the relapsed lesion and the primary breast cancer. The contribution to this discordance from preanalytic and analytic variables or from true biology based on heterogeneity of clonal populations in breast cancer and treatment is unclear. What seems clear is that the impact on clinical decision making is somewhat more limited. Because the majority of discordance seen in the various studies is in loss of receptor expression, clinicians will continue to struggle with whether to withhold the associated targeted therapy when these agents generally have less morbidity and potential for significant efficacy. Until future studies clearly demonstrate improved patient outcomes are associated with tight adherence to therapeutic strategies based on the most recently biopsied biomarker profile, we will continue to be uncertain as to the value of detecting lost receptor expression on repeat testing at metastatic relapse.

**REFERENCES**


DOI: 10.1200/JCO.2011.36.6385; published online ahead of print at www.jco.org on January 30, 2012