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Commentary

To Biopsy or Not to Biopsy: Is That the Only Question?

SHAHEENAH DAWOOD,[a] ANA M. GONZALEZ-ANGULO[b]

[a]Department of Medical Oncology, Dubai Hospital, Dubai, UAE; [b]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

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The last two decades have seen some exciting advances in the realm of breast cancer biology and management. Gene expression profiling studies have reaffirmed the long-standing concept that breast cancer is not a homogeneous disease but a heterogeneous one composed of at least six distinct subtypes, each with a unique prognostic outcome [1]. Advances in the management of early-stage breast cancer, including the incorporation of a multidisciplinary approach, polychemotherapy regimens, and biological agents, have all contributed to improving the prognostic outcome. However, ~20%–30% of women with early-stage breast cancer still recur [2], and despite advances in management, metastatic disease is not curable.

The management of metastatic breast cancer is guided by both molecular markers and the burden of disease indicating when endocrine therapy and human epidermal growth factor receptor (HER)-2–directed therapy are appropriate. Indeed, the introduction of trastuzumab into the treatment paradigm for women with HER-2^+ metastatic breast cancer has clearly been shown to have transformed this once aggressive disease into one with a prognostic outcome that is far superior to that of women with HER-2^- metastatic disease [3]. Discordance in molecular markers between primary and metastatic disease was reported as early as the 1970s. However, with the advent of numerous agents directed at specific molecular markers and the growing knowledge that each subtype of breast cancer has a unique and distinct natural history that can guide the aggressiveness of treatment, over the last few years there has been a growing interest to determine whether molecular markers remain static between primary and metastatic lesions or a real discordance exists that could potentially have an impact on management and, indeed, the subsequent prognostic outcome [4]. This has in turn spurned numerous small retrospective studies (with discordance rates reported in the range of 10%–35%) for which the interpretation of results has largely been hampered by the use of different techniques to evaluate receptors in the primary and metastatic disease.

In the current retrospective study that accompanies this commentary, Macfarlane and colleagues [5] report on a relatively large cohort of 160 women in British Columbia with recurrent breast cancer whose primaries were diagnosed in 1986–1992 and for whom tissue samples were available for both the primary and the biopsied metastatic lesions. Excluding patients with in-breast recurrences and new breast primaries, the authors reported an overall discordance in receptor status of 19.1% between primary and metastatic lesions. Interestingly, the authors further reported that 5% of tumors had a hormone receptor change from positive to negative, 9.4% had a hormone receptor change from negative to positive, 3.8% had a HER-2 change from positive to negative, and 1.3% had a HER-2 change from negative to positive. Riding closely on the heels of this study are two new studies asking a similar question. Amir and colleagues [6] reported on the largest prospectively designed study that investigated the rate of discordance in receptor status. Those authors reported discordance rates of 16%, 40%, and 10% for estrogen receptor, progesterone receptor, and HER-2, respectively. Niikura and colleagues [7] retrospectively looked at 182 women with HER-2^+ breast cancer and reported a change in HER-2 status from positive to negative in 24% of cases.

Several hypotheses have been used to try to explain the changes in receptor status seen between primary and metastatic lesions [4]. Limited accuracy and reproducibility of receptor assays stemming from differences in tissue fixation, antigen retrieval, and staining methods as well as subjective scoring resulting in interobserver variability may be one expla-

Correspondence: Shaheenah Dawood, M.R.C.P. (U.K.), M.P.H., Department of Medical Oncology, Dubai Hospital, Department of Health and Medical Services, P.O. Box 8179, Dubai, UAE. Telephone: 97150-7289797; Fax: 97143527776; e-mail: Shaheenah@post.harvard.edu Received December 7, 2011; accepted for publication December 16, 2011; first published online in *The Oncologist Express* on January 20, 2012. 1083-7159/2012/$40.00/0 http://dx.doi.org/10.1634/theoncologist.2011-0432

nation for the reported discordance in receptor status. In the study reported by Macfarlane and colleagues [5], the investigators dealt with this problem to a certain extent by using identical methodology, scoring, and antibodies to evaluate receptor status for both the primary and the biopsied metastatic tumors, thereby reducing potential errors in reporting the receptor status. However, as the authors correctly point out, the majority of the formalin-fixed primary tissue samples were >15 years old and the possibility of antigen loss contributing to at least some of the discordance observed cannot be excluded. Perhaps an additional method of reducing reporting errors may be to use confirmatory tests such as a fluorescence in situ hybridization assay for HER-2 and an mRNA method of measurement for determining hormone receptor status among cases that are reported as discordant [4].

Intratumor heterogeneity that can subsequently result in sampling error is another possible explanation for the reported discordance. However, the occurrence of small pockets of a different subtype of disease that essentially expresses different molecular markers from the main disease bulk is rare. These pockets of disease are perhaps, however, becoming more apparent with the increasing use of preoperative chemotherapy that incorporates targeted biological agents. Indeed, this was illustrated in a study by Mittendorf and colleagues [8] wherein the authors reported that 32% of tumors from women with HER-2$^+$ disease who had received preoperative chemotherapy with trastuzumab and did not achieve a pathological complete response had a change in HER-2 status from positive to negative.

A true genetic switch in the biology of the disease, whereby the molecular profile and thus subtype of the disease changes, is another hypothesis that has been put forward to explain the observed discordance in receptor status between primary and metastatic breast cancer lesions. The limited available molecular profiling data from studies that have looked at this specific question indicate that the genomic features of breast cancer remain largely stable during the natural course of the disease [4, 9]. However, those studies were conducted on tumor samples acquired in the pretrastuzumab era and thus must be viewed with caution. Indeed, if one looks at the discordance rates reported by Macfarlane and colleagues [5], they appear to be much smaller than those reported by both Amir and colleagues [6] and Niikura and colleagues [7]. This may be explained by the fact that, compared with the other two studies, the diagnosis of primary breast cancer in the study by Macfarlane and colleagues [5] predated the widespread use of hormone therapy and polychemotherapy, as evidenced by the fact that less than half of the women with hormone receptor–positive disease received adjuvant hormone therapy as well as the fact that approximately half of the overall cohort did not receive any form of adjuvant systemic treatment. Indeed, Niikura and colleagues [7] reported a significantly higher discordance rate among women who received chemotherapy than among those who did not. If one accepts the hypothesis of a genetic switch to be true, the increasing use of newer chemotherapeutic and biological agents in both the adjuvant and metastatic settings is likely to lead to a higher discordance rate.

Regardless of the biological explanation, the results reported on the observed receptor discordance have given way to several important questions. How will these results impact everyday clinical practice? Certainly a change from a negative to a positive receptor status will impact management in that targeted therapy may then be incorporated into the treatment plan. Conversely, a change from a positive to a negative status would not only avoid the use of these agents and their related side effects but also would considerably cut down on unnecessary costs. Do such changes in receptor status impact decision making in the clinic? The results of the study by Amir and colleagues [6] indicate that the answer to this question is "yes," with the authors reporting that biopsy led to a change in management in ~14% of women. If biopsy of recurrence or metastatic lesions is the standard of care, when should one biopsy? If we believe in the hypothesis of a true genetic switch or in the hypothesis of intratumor heterogeneity, both would plausibly be influenced by exposure to both chemotherapeutic and biological agents. Thus, the timing of exposure to these agents may help guide the timing of biopsy. Should we only biopsy a first recurrence? Should we biopsy after progression on each line of treatment? Unfortunately, most of the studies published thus far have not been able to answer these questions. In the study by Macfarlane and colleagues [5], although timing of the biopsy was not a mandate, among the discordant cases, biopsies of recurrent lesions were obtained before administration of first-line treatment for metastatic disease. Are metastatic lesions the same or different? For example, could a patient with a local recurrence and simultaneously detected liver metastases have two different subtypes? And if so, should both be biopsied? At the present time, the data indicate that heterogeneity in receptor status among different metastatic sites is a rare phenomenon [10]. Perhaps, ultimately the most important question is whether or not a change in receptor status and a subsequent change in management will ultimately impact the prognostic outcome. Evidence of the influence of discordance in receptor status on prognostic outcome has been conflicting, ranging from an associated poor prognostic outcome to no influence at all. In the study by Amir and colleagues [6], a change in management based on a receptor status change was used to describe the lack of difference in prognostic outcome between discordant and nondiscordant cases.

In conclusion, the mounting evidence of discordance in receptor status between primary and metastatic breast cancer lesions is a phenomenon we can no longer ignore. There appears now to be a consensus that, if technically feasible and easily accessible, metastatic lesions should be biopsied, and this recommendation has now been incorporated into the 2011 National Comprehensive Cancer Network guidelines [11]. However, interpretation of the discordance results should be done with caution and any change in treatment should be done in conjunction with clinical judgment based on the clinical behavior of the disease. False-negative and false-positive results may still occur and ultimately may adversely impact outcome because of changes in management. Indeed, an inaccurate change from a positive receptor status to a negative receptor status may be more detrimental than a change from a negative

receptor status to a positive receptor status. As our treatment protocols evolve to incorporate more biological agents, we are likely to see higher rates of discordance, which will ultimately lead to more questions than answers!

Author Contributions

Conception/Design: Shaheenah Dawood, Ana M. Gonzalez-Angulo
Data analysis and interpretation: Shaheenah Dawood
Manuscript writing: Shaheenah Dawood, Ana M. Gonzalez-Angulo
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