Estrogen Receptor Expression in Breast Cancer

We Cannot Ignore the Shades of Gray

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In this issue of the Journal, Gomez-Fernandez et al report their experience with estrogen receptor (ER) immunohistochemical expression in 278 patients with recurrent and/or metastatic breast cancer. By using ER antibody 1D5, they found that 9 of 159 previously positive cases (5.7%) did not express ER in their metastatic or recurrent sites. In addition, of 119 initially ER– primary breast cancers, no cases changed to a positive ER status in the metastatic or recurrent sample. The conclusion of the study is that ER status, using well-fixed tissues and the 1D5 antibody, remains stable through disease progression.

In breast cancers that originally test positive for ER expression (particularly those that are strongly positive), it does not seem to be necessary to routinely repeat ER staining except for diagnostic purposes (ie, to confirm metastatic disease is from a previously ER+ breast primary site). Not only are oncologists loathe to withhold hormonal therapy if a case was considered previously ER+, it is difficult to be confident that the more recent result is not a false-negative. As emphasized by Gomez-Fernandez et al,1 because of a lack of internal controls in metastatic sites, it is often not possible to exclude poor antigen preservation in these cases. The deleterious effects of decalcification in bone marrow tissue stained for ER is one possible source of poor antigen preservation. Others have reported similar findings when comparing ER in breast needle core biopsy specimens to the final surgical specimen, with the most common change in ER being “false-negative” results in the final surgical specimen, possibly owing to worse fixation of larger specimens.2,3

But what to do with cases that originally test ER– or only weakly positive? If the initial result is a false-negative, potentially beneficial hormone therapy will be withheld. In the study by Gomez-Fernandez et al,1 there were no cases that changed from initially negative for ER expression to positive for ER expression at the metastatic or recurrent site. So no new candidates for hormonal therapy were identified. Are we to then assume that repeated testing in previously ER– cases is not warranted?

The rate of false-negative ER staining of initial core needle biopsy specimens is estimated to be as low as 2% to 3%.2 It is not mentioned in the study by Gomez-Fernandez et al1 if their initial ER determination was performed on needle core biopsy or excision specimens. However, they do have the benefit of a reported well-controlled 12- to 48-hour fixation period, which has been shown to be essential in ensuring accurate ER assessment by immunohistochemical analysis.4

But even with adequate fixation, the possibility of inadequate sampling of a heterogeneous cancer with weak ER expression will always be an issue in ER “negative” or weakly positive cases. Or will it? The authors report that in their hands, ER staining is dichotomous, with each case being completely negative or positive in more than 90% of cells. This report suggests that by using their methodological approach, cases with heterogeneous or weak ER expression simply are effectively converted to a stronger positive result. Although this group and others have previously reported the potential advantages of dichotomization of ER antibody staining, this practice is by no means standard.5,6 And as has been discussed previously in these pages, although the majority of ER+ cases have strong and uniform staining, there is a smaller group of breast carcinomas that exhibits weak to intermediate expression of hormone receptor expression in breast cancers and a valid
means to score it, we ignore the potential importance of variability in response to hormonal and other adjuvant therapies that might be due to “phenotypic drift” or clonal selection with treatment and tumor progression.\(^7,8\) We can, but should not, artificially eliminate the biologic shades of gray.

The original ER immunohistochemical validation study by Harvey and colleagues\(^8\) comparing response to tamoxifen with the level of ER in breast carcinoma showed a wide range of semiquantitative expression levels by ligand binding assay and immunohistochemical analysis. Cases with as little as 1% of cells weakly staining gained some objective benefit from tamoxifen, providing the rationale for and validation of the Allred scoring system (which takes into account the intensity of the stain and the proportion of cells that are positive) and the cut point (Allred score 3) for a “treatable” positive result. More recently, studies using reverse transcription–polymerase chain reaction have reiterated the significance of wide biologic distribution of ER messenger RNA expression.\(^10\)

ER status is usually stable over time; however, it remains problematic when conclusions about phenotypic (and, likely, true biologic) variation are drawn from data sets in which ER reactivity is expressed as a dichotomous variable. Carcinomas with low Allred scores are reproducibly identified when the assay reflects true variation. Similarly, potentially important changes in Allred score with disease progression—data points that may be just as biologically relevant—may be missed if low levels of expression are not reliably separated from stronger positive levels. It is precisely because these cases may not have as robust a response to hormonal therapies or a response that changes over time that it remains important to report the level of ER expression in a manner that accounts for the true phenotypic variability in expression and response to therapy.\(^8,11\) In this context, my initial question can be answered: cases that are ER– or weakly positive in an initial needle core or excisional biopsy specimen should undergo repeated ER testing on a subsequent surgical specimen, if available.

Clearly, there is a need for a testing standard to ensure consistent (and, I hope, more accurate) use of ER expression as a predictor of response to hormone therapy. HER2 testing was the first marker to benefit from reasoned testing and interpretive guidelines (National Comprehensive Cancer Network and American Society of Clinical Oncology/College of American Pathologists),\(^12,13\) and consensus recommendations for ER testing by immunohistochemical analysis will be disseminated in the near future. These recommendations will continue to emphasize appropriate fixation and semiquantitative assessment.\(^14\) Until there is a superior clinically validated immunohistochemical approach or scoring method, the use of semiquantitative ER reporting should continue.

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References