

A Step in the Right Direction

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Although the incidence of breast cancer continues to increase, breast cancer mortality has consistently decreased over the last several years.^{1,2} This decreased mortality appears to be multifactorial, including survival benefits from adjuvant hormonal and chemotherapy,³ and has led to a conundrum that we face as treating physicians. We know that adjuvant therapy benefits patients. The problem is, which patients? Are we willing to forgo treatments that could potentially benefit a particular patient? On the other hand, are we willing to treat all patients with an excellent prognosis to benefit just 1%, 2%, 3%, or maybe 5% of patients? These benefits must ultimately be balanced against the toxicities of adjuvant chemotherapy, which include both psychosocial and physical effects. Most of these adverse effects are short term, but long-term effects are still being discovered.

The article by Paik et al⁴ in this issue of the *Journal of Clinical Oncology* is one of the first to attempt to answer these questions. The recurrence score (RS) has been shown to be associated with prognosis in patients who have estrogen receptor (ER) -positive, node-negative breast cancer and are treated with tamoxifen.⁵ Patients with a high RS have the highest distant recurrence rate. This current analysis expands on the previously published data and finds that patients with high-RS tumors who are treated with chemotherapy have a lower recurrence rate compared with those not treated with chemotherapy. Conversely, patients with a low RS do not benefit from chemotherapy.

Let's start with the scope of the issue. There are an estimated 100,000 new cases a year of lymph node-negative and ER-positive breast cancer in the United States.^{1,2} The number of patients predicted to have a low RS is 51%.⁵ The widespread acceptance of the RS assay could reduce the number of patients for whom chemotherapy is recommended by 50,000 per year in the United States. The 5-year survival rate among patients diagnosed from 1995 to 2001 with localized (node-negative) breast cancer is 96% compared with regional (node-positive) patients, in whom the 5-year survival rate is 81%.¹ These statistics are for both ER-positive and -negative disease. We know that patients with ER-positive breast cancer have a more indolent form of the disease and will continue to have low levels of relapse over many years, so these statistics can be somewhat misleading. We don't know at the current time whether the overall mortality reduction with breast cancer is for all patients regardless of ER status or if this reduction depends on the ER content. These are important issues that are being studied.

The second notable issue was first reported almost 30 years ago: Low ER values significantly predicted which patients would respond to cytotoxic chemotherapy, whereas high ER levels did not.⁶ These data have been confirmed consistently by many studies over the years finding that patients with ER-positive tumors have a

smaller benefit from chemotherapy.^{7,8} The question that the RS model of Paik et al attempts to answer is whether we can clarify which patients with ER-positive disease do benefit from treatment in a clinically relevant manner. The answer appears to be yes. There is a statistically significant benefit from the administration of chemotherapy in these patients who have a high RS, with an absolute reduction in recurrence of 27.6% at 10 years. The model does find higher expression of proliferation genes and lower expression of hormonally regulated genes associated with a chemotherapy benefit. Therefore, cancer researchers might question whether the use of proliferation markers, ER expression, and level of expression alone can predict recurrence without use of the RS. One problem with this singular approach is that ER as measured currently by immunohistochemical methods is not quantitative; results may lead to either false-negative or positive results.^{9,10} Secondly, a consistent measurement of ER as performed by the biochemical method in the Paik article (as shown in Fig 1 of the Paik et al article⁴) shows that there are still many patients with very high ER levels (> 100 fmol/mg) who fall into the high-RS category. The proliferation gene group hazard ratio was almost the same as the RS in the test for interaction with chemotherapy. This suggests the possibility that the use of only a proliferation score may be sufficient to predict a benefit from chemotherapy. This needs to be evaluated further.

The results of the overall study of 2,299 patients showed a definite interaction between age and chemotherapy, whereas those of the subset of 651 patients in the RS study did not. Although the demographics appeared to be similar between the two groups, this result suggests a possible bias in the sampling and that the subgroup might not be representative.

One other cautionary note for the RS data is that the studies used for the generation of the data were done many years ago. Approximately 80% of the tumors in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 study were greater than 1 cm in size, and the remaining 20% were probably close to 1 cm.¹¹ In the Paik et al study, an analysis using 2 cm as a cutoff did not show an interaction of chemotherapy treatment with tumor size.⁴ However, extrapolation of these results to the small tumors often seen in current practice may not be valid. There is a dearth of data, especially prospective randomized data, examining the benefits of chemotherapy for patients with very small tumors (< 1 cm) though guidelines specific for small tumors are present.^{12,13}

Also, though there was no interaction with HER2 status and chemotherapy in the current report; practice has changed here, too. Many patients with HER2-positive tumors will receive adjuvant trastuzumab even with node-negative disease. HER2 status alone predicts which patients will benefit from trastuzumab, and

the RS data in this situation is most likely unnecessary. To clarify this issue, the HER2 status of the tumors in the RS data set should be presented because this important information is not included in the current report, nor in past reports.

Another method, gene expression array, has been used to evaluate breast cancer prognosis. The initial reports have led to a classification of breast cancer into five types: basal, luminal A, luminal B, ErbB-2, and normal basal-like.¹⁴⁻¹⁶ Reports that have been found to predict patients at low and high risk of recurrence include the 70-gene, 76-gene, and wound signatures.¹⁷⁻²⁰ Further work has been reported specifically evaluating the ER-positive subgroup on the basis of differences in genes involved in estrogen signaling.²¹ The poor-prognosis group in this study expressed genes associated with cell proliferation and antiapoptosis and were poorly differentiated, whereas the good-prognosis group expressed genes that were estrogen- and GATA3-regulated and more differentiated. This study stresses the importance of looking much deeper into the biology of breast cancer for more accurate classification of the disease and determination of prognosis.

The RS data have been incorporated into the design of a prospective clinical trial, the Trial Assigning Individualized Options for Treatment (TAILORx).²² This trial will include 11,000 patients with ER- and/or progesterone receptor (PR-) positive, HER2-negative, axillary node-negative breast cancer, which is 1.0 to 5.0 cm or 0.5 to 1.0 cm plus unfavorable features (intermediate or poor nuclear grade and/or histologic grade, or lymphovascular invasion). Patients will all have an RS performed. Those patients who have an RS of less than 11 (29%) will receive hormonal therapy alone. Patients with an RS of 11 to 25 (44%) will be randomly assigned to hormonal therapy plus or minus chemotherapy. Patients with an RS more than 25 (27%) will receive chemotherapy plus hormonal therapy. This trial is designed to reduce overtreatment for those patients benefiting from hormonal therapy alone and to reduce inadequate treatment in those patients who may have been treated with hormonal therapy alone. A trial comparing a 70-gene molecular signature with clinicopathologic criteria is the Microarray In Node-negative Disease may Avoid Chemotherapy (MINDACT) trial.²³ This trial will include 6,000 patients with node-negative disease and T1, T2, or T3 tumors. The goal of the study is to confirm that patients with a low-risk molecular prognosis and a high-risk clinical prognosis can avoid chemotherapy. Patients with tumors at high risk for both clinicopathologic criteria and gene signature receive chemotherapy plus endocrine therapy if ER positive, and those patients at low risk for both undergo hormonal therapy alone or no treatment depending on ER status. The group with the two discordant factors will be randomly assigned to use the clinicopathologic criteria versus the gene signature for treatment decisions. Both of these trials have important implications for the future of thousands of breast cancer patients.

In conclusion, it appears that the RS can be beneficial to predict which patients will definitely benefit and which will not. However, the RS is only a beginning. As technology improves and larger banks of tumor are available for analysis in a prospective fashion, we will most certainly perfect our ability to more precisely predict recurrence and tailor treatments. This will allow us to forego unnecessary treatment in a large number of patients without denying treatments to patients who can most benefit from it.

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Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.