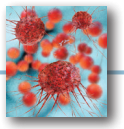

Gene Expression Signatures in Breast Cancer: A Surgical Oncologist's Perspective

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Gene expression can serve to supplement the assessment of recurrence risk now used as the basis for chemotherapy or estrogen ablation recommendations for patients with breast cancer.

The use of systemic chemotherapy and estrogen ablation (EA) for the treatment of breast cancer historically have been based on both the histologic prognostic parameters of the invasive breast cancer and on traditional estimates of recurrence risk. These estimates take into account the patient's age, tumor size, grade, lymphovascular invasion, hormonal receptor status (estrogen receptor/progesterone receptor [ER/PR]), and human epidermal growth factor receptor 2 (HER2) overexpression.[1]

The recent description of 4 primary breast cancer subtypes on the basis of gene expression profiles has led to the identification of more specific gene prognostic signatures.[2] These may serve to supplement, and possibly supersede, the assessment of recurrence risk currently employed as the basis for chemotherapy or EA recommendations for patients with breast cancer. As a result, many patients who would have been treated with chemotherapy previously may now safely avoid it. The information provided by these prognostic signatures may also alter surgical decision making for many patients and, consequently, should be within the purview of dedicated cancer surgeons.

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BREAST CANCER SUBTYPES

The 4 breast cancer subtypes are (1) the HER2 type, these can be ER/PR positive or negative; (2) basal-like tumors, typically ER, PR, and HER2 negative (ER-, PR-, and HER2-); and ER-positive (ER+) or luminal tumors, usually divided into (3) luminal A and (4) luminal B.[2]

HER2 Type

The advent of the first targeted breast cancer therapy, trastuzumab, and its immense salutary effect on survival of patients with previously poor prognoses has made the use of chemotherapy in combination with trastuzumab nearly mandatory in all HER2+ patients with breast cancer. Remarkably, the huge improvement in survival of these formerly doomed patients has led to the recommendation that trastuzumab-containing chemotherapy regimens should be used in the management of even subcentimeter, node-negative patients.[3] This recommendation represents a clear change from the traditional recommendations for chemotherapy, which held that the benefits of systemic chemotherapy were more likely to be seen in patients with tumors in excess of 1 cm and/or who were node positive.

Basal-like Tumors

The discovery of trastuzumab made the basal-like tumor, which is usually ER-, PR-, and HER2- (triple negative), the subtype with the worst prognosis. Further, the natural course of this illness is markedly different from that of ER+/PR+ breast cancer. Nearly all basal-like or triple-negative patients with breast cancer who experience a recurrence do so within the first 5 years after diagnosis.[4] In contrast, nearly 40% of ER+/PR+ HER2- breast cancer survivors experience their first recurrence beyond the 5-year milestone, with many even later in their course.[5] Thus, the patient with triple-negative breast cancer is more likely to benefit from chemotherapy predominantly during the first 5 post-

diagnosis years, as suggested by the Early Breast Cancer Trialists' Collaborative Group meta-analyses.[1]

HER2+ and triple-negative breast cancers account for 20% and 15% of all breast cancers, respectively.[6,7] In both subtypes, the benefit of chemotherapy is immense and chemotherapy will rarely be omitted from the treatment plan. Many of these patients are considered ideal candidates for preoperative chemotherapy (PCT), which results in increased rates of breast-conserving surgery (BCS), decreased positive margin rates at BCS, and decreased need for axillary node dissection. In the setting of PCT, a pathologic complete response (pCR) in the breast and axilla is increasingly recognized as a marker for improved disease-free survival (DFS) and overall survival (OS).[8] For these reasons, preoperative consultation with medical oncologists is now even more important. Many of these patients will benefit from the use of PCT before any surgical treatment is undertaken.

Luminal Type (A and B)

The remaining two-thirds of all patients with breast cancer are ER+, primarily postmenopausal, and fall within the 2 remaining molecular subtypes: luminal A and luminal B. It is for these patients that the relative benefits of chemotherapy vs EA, or both, are currently being debated. For these patients the use of gene prognostic signatures, in concert with traditional histopathologic and clinical risk factors, may alter estimates of recurrence risk and the impact of chemotherapy on survival and recurrence estimates.

It is now evident that even the strongest predictors for breast cancer recurrence—histologic grade, patient age, and nodal status—are inconsistent predictors of the behavior of any individual tumor. While the use of chemotherapy can reduce the risk of metastases in these luminal-type patients with breast cancer, the majority of patients so stratified would survive without chemotherapy.[9]

GENE EXPRESSION SIGNATURE ASSAYS

One of the best demonstrations of the shortcomings of the standard risk predictors for ER+, HER2- breast cancers is provided by the Oncotype DX breast cancer assay's recurrence score (RS) or gene expression signature (GES).[10,11]

Oncotype DX

The Oncotype DX assay is the first commercially available GES assay to illustrate the variability in survival of patients with node-negative, ER+ breast tumors. Sixteen selected cancer proliferative genes are paired with 5 control nonproliferative genes whose relative activity can be measured in paraffin-embedded breast cancer tissue. The ability to retrieve reliable ribonucleic acid (RNA) expression from cancer cells embedded in paraffin was a stroke of genius; it enabled the investigators to correlate the gene expression profile of patient subgroups treated decades earlier with their long-term clinical outcomes and survival.

The normalized summation of the proliferative activity of the 16 cancer proliferation genes in the Oncotype DX assay is expressed as the RS. The RS increases linearly and so does the average rate of distant recurrence in 10 years as a function of the RS. Three risk recurrence groups are defined by the RS: low risk (RS < 18); intermediate risk (RS > 18 to 30); and high risk (RS > 31).[10,11]

Clinical Trials

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial B-14, ER+ node-negative patients were randomized to observation or tamoxifen. In the untreated control patients, a low RS (< 18) was accompanied by a 6.8% risk of metastasis at 10 years, and a high RS (> 31) was accompanied by a 30.5% rate of distant recurrence.[11] In another study, the low RS tamoxifen-treated arm showed a 2.8% risk of breast cancer death at 10 years vs a 15.5% risk in the high RS cohort.[12]

Fast Facts...

- Traditional histopathologic and clinical risk assessment for distant recurrences led to the use of systemic chemotherapy in most patients with breast cancer
- Gene expression signatures (GES) have revealed significant heterogeneity in the biologic behavior of breast cancers
- GES can provide more specific risk estimates for distant recurrence in breast cancer
- GES can help select patients with breast cancer most likely to benefit from chemotherapy and spare those who would not
- Surgical treatment planning can be affected by GES, leading to improved breast-conserving surgery rates

The remarkable significance of the RS is demonstrated when the RS is plotted against patient age, grade, or tumor size.[10] This illustrates the huge variability in these traditional histopathologic and clinical features within a given RS group. For any patient with a low RS, there is marked variability in patient age, tumor grade, or tumor size. A very small or low-grade tumor can have a very high 10-year recurrence rate, as measured by the gene prognostic signature or RS. Similarly, a very large tumor in a young patient can have a very low 10-year recurrence rate or RS. This is due to the heterogeneity of the biology of these cancers, regardless of their favorable or unfavorable histologic features.

In most cases, decisions about chemotherapy in patient who are postmenopausal, node-negative, and ER+ are made by risk estimates based on patient age, tumor grade, and tumor size, without knowledge of their RS. However, the large variability in 10-year rates of metastases and death among patients clearly demonstrates that, for some, chemotherapy affords no benefit. Their RS suggest that their risk of metastases at 10 years is only 2.8% when treated with EA (ie, tamoxifen) and no chemotherapy. In fact, 51% of the patients who are postmenopausal, node-negative, and ER+ in NSABP B-14 fell within the low risk RS category for 10-year distant recurrence, whereas about 27% fell within the high risk (RS > 31) category.[13]

Confidence in the Oncotype DX assay RS stems from the ability of investigators to plot the recurrence rates of distant metastases in patients treated with tamoxifen vs placebo in the NSABP B-14 trial. Their clinical outcomes could be correlated with their GES samples retrieved from paraffin-embedded archival tissue many years after treatment. Corresponding plotting was done for similar patient cohorts treated with chemotherapy with or without tamoxifen in NSABP Trial B-20.

Studies have shown that the additional risk assessment estimate provided by the Oncotype assay causes a change in systemic therapy recommendations from chemotherapy to no chemotherapy in 30% of patients.

Among patients with low RS, the distant recurrence rate at 10 years was 2.2%, whether treated with systemic chemotherapy plus tamoxifen or with tamoxifen alone. Thus, in study participants with low RS, regardless of tumor size, grade, or patient age, 10-year recurrence rates were not affected by the addition of chemotherapy.[13]

Note that, in the absence of the new information provided by the Oncotype gene prognostic signature, nearly all these patients would be treated with systemic chemotherapy. Studies have shown that the additional risk assessment estimate provided by the Oncotype assay causes a change in systemic therapy recommendations from chemotherapy to no chemotherapy in 30% of patients.[14,15] Among patients with high RS, 10-year distant recurrence rates decreased by an absolute 27% with the addition of chemotherapy to tamoxifen. These patients clearly benefited from chemotherapy.[13]

The relative benefits of chemotherapy vs tamoxifen in a third RS group with an intermediate RS of 18-21 awaits publication of the now-closed Trial Assigning Individualized Options for Treatment (TAILORx) trial. This group accounts for 22% of patients who are postmenopausal, node-negative, and ER+ identified by the Oncotype DX assay. Initial reports show no significant benefit from the addition of chemotherapy to tamoxifen in this group.[10]

MammaPrint

Other gene prognostic signatures have recently been validated. Of these, the MammaPrint assay is the best established and validated.[16] The MammaPrint uses a panel of 70 proliferation genes that were selected without bias by scanning the entire human genome. Unlike the Oncotype DX, the MammaPrint panel was randomly selected without any prior knowledge of the role of the proliferation genes in breast carcinogenesis. Furthermore, the reliability of the MammaPrint gene signature is independent of nodal status.[17] This suggests that the intrinsic genetic makeup of the cancer establishes its biologic behavior and supersedes the impact of the traditional assessment of nodal involvement as a significant risk factor for distant metastases.

The MammaPrint GES was developed to identify patients at high risk of recurrence within 5 years of diagnosis; those for whom, as noted earlier, the salutary effect of chemotherapy is most evident.[18] The assay is reliable for both pre- and postmenopausal women and stratifies

patients into 2 risk groups only: high vs low.[19-21] The probability of remaining free of recurrent disease at 10 years is 85% in the low risk GES patients vs 50.6% in those with high risk MammaPrint prognosis signatures.[17]

Subsequent validation trials examined the accuracy of the MammaPrint as a prognostic indicator as well as a predictor of response to chemotherapy. These studies included node-negative, node-positive, pre- and postmenopausal women.[18-23] The risk of metastatic disease within the first 5 years after diagnosis was more significant in the high-risk than in the low-risk group. However, because the MammaPrint signature is independent of ER status, not all MammaPrint low-risk signatures are ER+. This reflects the contribution of unselected proliferation genes to the MammaPrint signature that results in the luminal A and luminal B breast cancer subtypes. In postmenopausal, node-negative patients, 61% may have good prognosis signatures, regardless of ER status.[18,22]

A poor prognosis signature, then, would suggest the use of chemotherapy to prevent early (< 5 years from diagnosis) breast cancer deaths, but would still allow for EA to prevent late (> 5 years after diagnosis) recurrence for patients whose tumors were ER+. It should be noted that these findings also apply to patients treated with contemporary anthracycline chemotherapy regimens.[22] The MammaPrint poor prognostic signature identifies patients at risk for early recurrence who may therefore benefit from chemotherapy, whereas the good prognostic signature identifies patients with a very low risk of distant metastases < 5 years.[22] In the latter group, this low risk may not warrant use of systemic chemotherapy, but treatment with EA would confer a decrease in systemic metastases.

THE SURGEON'S PERSPECTIVE

To the surgeon, as suggested earlier, perhaps more pertinent is the available information on the use of chemotherapy before planned surgery for basal-type triple negative and HER-2+ breast cancers in the setting of luminal ER+ tumors. Mounting evidence suggests that the GES, such as those determined via the Oncotype and MammaPrint assays, can provide a very reliable indication of an individual patient's response to PCT or chemotherapy in the neoadjuvant setting.[24,25] These clinical responses are easily quantitated on physical examination or by imaging in the few months during which a patient can receive PCT.

The MammaPrint poor prognostic signature identifies patients at risk for early recurrence who may therefore benefit from chemotherapy, whereas the good prognostic signature identifies patients with a very low risk of distant metastases < 5 years.

Furthermore, the absence of residual microscopic tumor in the breast and axilla (ie, pCR) after PCT can be predicted by the Oncotype DX RS and the MammaPrint GES. More than 11 reports (5,210 patients) have demonstrated a higher DFS and OS in patients who achieve a pCR after PCT.[8] A pCR in a locally advanced patient with breast cancer can provide the surgeon with a margin-negative surgical procedure (BCS or mastectomy) and inform the patient of the potential for a much better DFS or OS than anticipated from the stage of breast cancer at presentation.

In some patients amenable to BCS at presentation but whose tumor is too close to the chest wall or is proximate to a silicone augmentation prosthesis, the predicted response to systemic chemotherapy or hormonal ablation provided by GES can lead to a decrease in margin-positive rates and salvage of the previous cosmetic augmentation.

In patients at risk for carrying a BRCA mutation, the interval of PCT can be used for appropriate genetic testing and counseling and plastic surgery and gynecologic oncology consultations. Identified BRCA gene carriers may benefit from risk reduction surgery because of their increased breast and ovarian cancer risk. Non-BRCA patients can consider BCS as an option, with decreased margin-positive rates and improved cosmesis. Information provided by GES can be essential to a good surgical outcome and underlines the need for preoperative consultation with medical oncology.[26]

CONCLUSION

Gene expression signatures provide information about the biologic behavior of each individual patient's breast cancer. As new GES are introduced into clinical practice, surgeons must become fully informed about these advances in order to provide truly personalized cancer care plans to our patients.

Author disclosures

The author reports no actual or potential conflicts of interest with regard to this article.

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