The Role of Novel Assays in the Prediction of Benefit from Extended Adjuvant Endocrine Therapy for Breast Cancer

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Abstract

Endocrine therapy in the adjuvant setting has been shown to decrease the risk of recurrence and improve survival in women with hormone receptor-positive, early-stage breast cancer. Well-established prognostic and predictive markers including estrogen-receptor, progesterone-receptor, and HER2 status help classify patients into risk groups based on tumor biology and behavior, and further determine which patients may benefit from specific therapies. The standard duration of adjuvant endocrine therapy had been 5 years, but more recently studies have demonstrated a benefit for extending therapy to 10 years. Longer treatment carries some associated risks, so it is integral to the management of patients with early-stage breast cancer to determine who will benefit from extended adjuvant endocrine therapy and who will not, thus sparing women who will not benefit the toxicities of longer therapy. Assays including the 21-gene recurrence score (onco*type* DX®), PAM50 Risk of Recurrence, EndoPredict, and Breast Cancer Index are in various phases of development and validation, and function to risk-stratify women into groups based on likelihood of benefit from extended adjuvant endocrine therapy. These tests will likely play a vital role in moving forward to a world of personalized care in early-stage breast cancer.

Key words: breast cancer, extended adjuvant endocrine therapy, PAM50, EndoPredict, Breast Cancer Index

For women with hormone receptor-positive, early-stage breast cancer, tamoxifen for 5 years had been the standard-of-care endocrine therapy for several decades.[1-3] More recently, the benefit of extending the duration of therapy either with an aromatase inhibitor (AI) from year 5 to year 10 or, for tamoxifen, for 10 years has been evaluated in large multinational clinical trials, and has demonstrated an association with an approximate 2.5% to 4% absolute reduction in risk of recurrence and up to a 2.8% reduction in risk of breast cancer mortality.[4-6] Current guidelines from the American Society of Clinical Oncology (ASCO) reflect these studies and recommend that premenopausal women who have completed 5 years of adjuvant tamoxifen be offered the option to continue tamoxifen for a total duration of 10 years. Additionally, postmenopausal women who have received 5 years of adjuvant tamoxifen should be offered the option of continuing tamoxifen or switching to an AI to complete a total duration of 10 years of adjuvant endocrine therapy.[7]

Not unexpectedly, some side effects were seen with these therapies. Notably, with AIs, an excess risk of hot flashes, arthritis, arthralgia, myalgia, and osteoporosis was seen.[4] With 10 years versus 5 years of tamoxifen, there was an excess risk of pulmonary embolism (41 vs 21 events; relative risk [RR], 1.87; P = .01) and endometrial cancer (116 vs 63 events; RR, 1.74; P = .0002), which was associated with a 0.2% increased rate of endometrial cancer-related mortality.[5] Thus, while studies demonstrated the superiority of extended adjuvant endocrine therapy, the benefits overall were modest, and it is apparent that this is a treatment that will benefit only a few. There is a clear clinical need to identify patients who will benefit from this therapy and, conversely, patients who will do well regardless and can be spared the excess toxicity and cost.

We will focus this review on studies that provide prognostic data regarding the chance of recurrence in women who remain disease-free after 5 years of endocrine therapy. This will include a discussion of standard histopathological factors, 21-gene recurrence score (onco*type* DX®), Prediction Analysis of Microarray Risk of Recurrence (PAM50 ROR), EndoPredict (EP), HOXB13/IL17BR (H/I), and Breast Cancer Index (BCI).

Biomarker Studies

Kennecke et al[8] interrogated the British Columbia Breast Cancer Outcomes database and identified 1086 women who were disease-free after 5 years of tamoxifen. Statistically significant predictors of breast cancer recurrence at 10 years from diagnosis included larger tumor size (RR of a T2 vs a T1 tumor, 1.6; P =.049) and nodal status (patients with 1-3 positive nodes had

RR of 1.7; patients with 4 to 9 positive nodes had RR of 3.0 compared with node-negative patients).

An analysis of data from the NSABP B-14 and B-28 trials, conducted by Wolmark et al,[9] at a median follow-up of 14.5 years and 11.2 years, respectively, demonstrated the ability of the 21-gene recurrence score (onco*type* DX) to predict late distant recurrence after 5 years as a function of estrogen receptor expression. In NSABP B-28 patients, the recurrence score was strongly associated with distant recurrence after 5 years in women with tumors characterized by higher quantitative estrogen expression (log rank *P* = .001), and this finding was confirmed in NSABP B-14 patients (*P* = .004), where the risk of recurrence in years 5 to 15 was 6.8%, 11.2%, and 16.4% for those with low, intermediate, and high recurrence scores, respectively.

The PAM50 ROR score is calculated using the expression profile of a 46-gene subset of 50 selected genes of the 4 intrinsic subtypes (PAM50),[10] a proliferation score (18-gene subset), and tumor size.[11] The ability of PAM50 ROR to predict risk of distant recurrence was shown in a 10-year analysis of samples from the ABCSG-8 trial with the creation of 3 distinct risk groups, with distant recurrence-free survival (DRFS) rates of 96.7%, 91.3%, and 79.9% for the low-, intermediate-, and high-risk subgroups, respectively.[12,13] In order to address the potential utility of PAM50 ROR for determining the risk of late recurrence, Sestak and colleagues[14] analyzed combined data from the TransATAC trial, the correlative science study from a subset of patients participating in the ATAC trial that randomized patients with estrogen receptor–positive (ER+) disease to either 5 years of tamoxifen or anastrozole, and ABCSG-8, a randomized trial comparing 5 years of tamoxifen with 2 years of tamoxifen followed by 3 years of anastrozole in postmenopausal women. The analysis demonstrated that PAM50 ROR had significant independent prognostic value in predicting outcome in years 5 to 10.[12,14,15] The risk of distant recurrence during this time period was 16.6%, 8.3%, and 2.4% in the high-, intermediate- and low-risk groups, respectively. Patients in the PAM50 ROR high-risk group had a 6.9-fold higher risk of late distant recurrence, and those in the intermediate-risk group had a 3.3-fold higher risk of late distant recurrence compared with those in the low-risk group. The PAM50 ROR was also found to have more prognostic value for late distant recurrence compared with the clinical treatment score (comprising nodal status, tumor size, grade, age, and treatment)[16] in the HER2-negative/node-negative subgroup.[15]

The EndoPredict (EP) is based on an analysis of 964 tumor specimens from patients in the ABCSG-6 (tamoxifen-only arm) or ABCSG-8 trials.[12,17,18] This gene expression test includes 8 cancer-related genes of interest and 3 reference genes, and classifies patients into 2 recurrence risk groups. The EPclin score combines the EP score with nodal status and tumor size, and was validated as a predictor of overall and late recurrences, with 10-year distant recurrence rates of 4% and 4% in EPclin low-risk and 28% and 22% in EPclin high-risk patients in ABCSG-6 (*P* <.001) and ABCSG-8 (*P* <.001) trials, respectively.[19] In a follow-up study by Dubsky et al[20] that included 1702 patients from ABCSG-6 and ABCSG-8 trials, 49% were classified as EP low-risk and experienced an improved freedom from distant recurrence at more than 5 years (HR, 3.28; *P* = .002). The EPclin score had the best predictive performance for late-relapse events beyond 5 years (HR, 6.25; *P* <.001). The absolute freedom of distant recurrence after 10 years of follow-up was 98.2% and 87.7% for EPclin low-risk and EPclin high-risk, respectively. In both of these studies, EPclin outperformed standard histopathological factors.[20]

The HOXB13/IL17BR (H/I) is a 2-gene ratio that was developed for prediction of recurrence risk in patients with ER+, node-negative, early-stage breast cancer, and has been shown to be a strong independent prognostic factor in these patients.[21] The H/I was evaluated as a prognostic and predictive factor for late recurrence by Sgroi and colleagues.[22] They performed a nested case-control study of tumors from 83 patients with recurrences matched to 166 nonrecurrences in subjects receiving letrozole and placebo in the MA.17 study. In the low-H/I group, the overall prognosis was good regardless of treatment arm, with a 5-year RFS of 87% in the placebo group and 91% in the letrozole group. In contradistinction, in the high-H/I group, a statistically significant benefit of letrozole was observed (*P* = .007), with a 5-year RFS of 73% in the placebo group and 89.5% in the letrozole group.[22]

The Breast Cancer Index (BCI) assay combines the H/I ratio and the Molecular Grade Index (MGI), which is a 5-gene predictor, including tumor grade and proliferation, that has been shown to be highly prognostic in patients with ER+ breast cancer.[23-26] A retrospective analysis, which included 317 patients with node-negative disease treated with 2 to 5 years of tamoxifen from the Stockholm trial and 358 patients from a multi-institutional cohort of patients with node-negative ER+ disease receiving tamoxifen, showed that BCI predicted risk of recurrence in years 5 to 10. In the BCI low-risk group, which comprised 55% to 65% of patients, a low risk of recurrence was observed in years 0 to 5 (DRFS at 5 years, 98% and 95.9%) and years 5 to 10 (DRFS at 10 years, 97.2% and 97.5%) for the Stockholm and multi-institutional cohorts, respectively. By way of comparison, the DRFS at years 5 to 10 for the BCI-high risk group was 89.9% and 85% for the respective cohorts.[24]

A recent study sought to compare the utility of the BCI assay, the 21-gene recurrence score (onco*type* DX), and an immunohistochemical (IHC) model, IHC4, as predictors of early and late recurrence in patients with ER+ early-stage disease. The IHC4 is a prognostic model that measures protein expression of 4 IHC biomarkers: ER, PR, HER2, and Ki-67.[16] Archival material was obtained from 665 patients with node-negative disease who were participating in TransATAC.[16,27,28]

Multivariate analysis showed that the BCI-linear test was a

stronger predictor for overall distant recurrence compared with the 21-gene recurrence score and IHC4. While the BCI assay, 21-gene recurrence score, and IHC4 were all significantly prognostic for early distant recurrence, only BCI was significant for late distant recurrence (HR, 1.95; *P* = .0048). Furthermore, for both early and late distant recurrence, the BCI was able to identify 2 risk populations with distinct differences in distant recurrence rates. For the high-risk versus the low/intermediate-risk group, the HR for early distant recurrence (5 years) was 4.61. For late distant recurrence (5 to 10 years), the HR was 2.94 for the high/intermediate-risk versus the low-risk group. The subgroup of patients (61%) who were classified into the BCI low-risk group experienced a very low risk of recurrence of 3.5% in years 5 to 10. Furthermore, BCI may also have a role in evaluating risk of distant recurrence in the node-positive population as well, with 10 year rates of distant recurrence of 25.0%, 33.4%, and 52.3% for BCI low-, intermediate-, and high-risk groups, respectively (HR, 1.41 for intermediate-risk; HR, 1.69 for high-risk; BCI low-risk as reference; *P* = .0045).[28] In the MA.14 trial, which randomly assigned 667 women with ER+ tumors to 5 years of tamoxifen with or without 2 years of octreotide, in the node-positive patients (n = 116), higher continuous BCI was associated with shorter RFS (HR, 1.49; *P* = .002) at a median follow-up of 9.8 years.[29]

These studies support the ability of BCI to risk-stratify patients with early-stage breast cancer, and to identify a rather large subgroup of patients with a low risk of recurrence beyond 5 years. Data suggest that these assays may help guide clinicians in determining which women with early-stage, hormone receptor–positive breast cancer may benefit from extended adjuvant endocrine therapy. However, ASCO does not recommend the 21-gene recurrence score (oncotype DX), PAM50, EP, or BCI in the decision-making process of 5 versus 10 years of adjuvant endocrine therapy, but rather supports 10 years' duration.

Ongoing studies aim to shed light on current optimal management of extended adjuvant endocrine therapy. The NSABP B-42 trial is determining whether extended letrozole will improve DFS in women who have completed 5 years of endocrine therapy that includes 2 to 5 years of an AI. The MA.17R trial is addressing the question of whether adjuvant AI therapy for longer than 5 years is better than 5 years alone. The Different Durations of Adjuvant Anastrozole Therapy After 2 to 3 Years Tamoxifen Therapy in Breast Cancer (DATA) trial is comparing 3 years versus 6 years of anastrozole after 2 to 3 years of tamoxifen. The Secondary Adjuvant Long-term Study with Arimidex (SALSA) trial is evaluating 2 years versus 5 years of extended anastrozole therapy. The Study of Letrozole Extension (SOLE) trial involves comparison of continuous and intermittent extended letrozole therapy.

Additionally, it is important to note that data exist indicating that women who have received 5 years of adjuvant endocrine therapy can still gain benefit from extended adjuvant endocrine therapy even if they have been off treatment for a period of time. An analysis from the MA.17 trial examined outcomes in women originally assigned to placebo who, following unblinding, chose either to remain off therapy or switch to letrozole. After a median of 2.8 years off tamoxifen, those who chose letrozole compared with those who remained off therapy had a significant improvement in DFS (HR, 0.37; 95% CI, 0.23-.61; *P* = .0001) and distant DFS (HR, 0.39; 95% CI, 0.20-0.74; *P* = .004).[30] The results of the LATER trial[31] were recently presented and confirmed these findings, despite being closed early due to poor accrual. This trial randomized 360 postmenopausal women with hormone receptor–positive, early-stage breast cancer who were free of breast cancer and had completed at least 4 years of adjuvant endocrine therapy more than 1 year prior to enrollment to 5 years of letrozole or observation. The late reintroduction of letrozole was associated with a 7.3% reduction in the incidence of invasive breast cancer events (*P* = .001).

Summary

Various molecular-based tests have been developed, including the BCI, 21-gene recurrence score, PAM50 ROR, and EP, which have the ability to more accurately separate women into specified risk groups, and may help determine which patients may benefit from a longer duration of endocrine therapy. These assays show promise; however, their routine clinical use will require confirmation in additional studies. Many of the ongoing trials of extended adjuvant endocrine therapy are collecting biospecimens and will be a rich source of validation for these and future studies of predictive markers.

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