Editorial Commentary

The level of estrogen receptor (ER) expression and the length of adjuvant hormonal therapy in ER positive breast cancer

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In an era of increasingly personalized medical treatments, patients receive systemic and local therapies tailored to their specific types and sub-types of cancer. In breast cancer and other cancers, clinical and genomic tumor characteristics associated with recurrence risk in individual patients are taken into consideration for determining the type, and duration of therapy (1). Fohlin *et al.* reported on a re-evaluation of a trial which investigated the length of adjuvant hormonal therapy in estrogen receptor (ER) positive breast cancer (2). The authors addressed the long-term follow-up of a sub-set of patients from this trial performed by the Swedish Breast Cancer Cooperative Group in the last two decades of the twentieth century in Sweden. The trial established that, in the overall population, 5 years of adjuvant tamoxifen was superior to 2 years of adjuvant tamoxifen (2). Concordant results, showing a benefit from longer than 2 to 3 years of adjuvant tamoxifen in prolonging disease-free survival (DFS), have also been reported by a trial from the French Cooperative group (3). The sub-set of 1,210 patients who participated in the Swedish Breast Cancer Cooperative Group trial from 1988 to 1992, when an enzyme immunoassay (EIA) for ER replaced the previous method of isoelectric focusing of ER in tumor cell cytosols, were included in the report (2). The EIA method was adopted in three jurisdictions (South Sweden, South-East Sweden and Stockholm region) which contributed patients to the report (2). Participating patients had stage I to IIIA breast cancer and their benefit from the longer tamoxifen treatment was similar to the benefit observed in the entire ER positive population of the trial (2). When patients were stratified according to the median expression of ER by the EIA assay, a benefit from the 5-year adjuvant tamoxifen duration compared to 2 years of tamoxifen was only evident in the low ER expression group, while the patients with high ER expression had similar breast cancer survival independently of the duration (2 or 5 years) of adjuvant tamoxifen they received (2). When the analysis was performed with tertiles instead of medians of ER expression, the two groups with the lower tertiles of ER expression derived benefit from 5 years of adjuvant tamoxifen compared with 2 years of adjuvant therapy (hazard ratios: 0.61 and 0.64, respectively), while the patients with the highest ER expression tertile had equivalent breast cancer survival independently of the duration of adjuvant tamoxifen.

The data from this report and from a previous report from the same trial suggest that prolongation of adjuvant tamoxifen circumvents hormonal therapy resistance of some cancers with lower ER expression. Other reports have suggested that patients with the more robust ER expression are those that derive the highest benefit from adjuvant hormonal therapy with tamoxifen, while

decreasing ER expression is associated with worse outcomes in patients who received adjuvant tamoxifen without adjuvant chemotherapy (4). This report included patients who received tamoxifen as the only adjuvant therapy and did not focus on the duration of treatment (4). The level of ER expression, as measured by the older methods and the immunohistochemistry (IHC) based method currently used in clinical practice, is one of several factors inversely associated with aggressiveness of ER positive breast cancers and directly associated with endocrine therapy responsiveness (5,6). The prognostic implications of ER level of expression may be less prominent in ER positive patients that receive adjuvant chemotherapy, such as younger patients and high-risk patients with genetic predisposition due to *BRCA1/BRCA2* mutations (7).

Besides uncertainties regarding the breast cancer ER expression levels that derive enhanced gains from longer adjuvant hormonal treatment, another drawback of the Swedish Breast Cancer Cooperative Group study involves the EIA method used which is not the currently used IHC method of ER determination and may not be easily correlated with IHC results of the present day clinical practice. Based on the fact that over four fifths of ER positive breast cancers express ER robustly, at 90% to 100% of tumors cells with the current IHC method, and only about 15% of ER positive cases express the receptor at low levels (1–10%) or intermediate levels (>10% to <90%), several patients with the lower than the median or the two lower tertiles of ER expression by the EIA method, who derived benefit by the prolonged tamoxifen treatment would express ER robustly (90% to 100% of tumors cells) by the IHC method. Therefore, a subset of breast cancer patients with robust ER expression, who remain to be identified, still would require at least 5 years of adjuvant tamoxifen for maximum benefit. Moreover, the calculation of ER expression medians and tertiles for the categorization of patients were based on values in each of the three participating jurisdictions and were not uniform, further complicating any attempt to directly correlate the reported results with the EIA method with the current IHC method. As a result of these considerations, the categorization of ER levels proposed in the Swedish Breast Cancer Cooperative Group study has no direct correlation with levels of ER expression by current IHC methods. The different methods for ER evaluation may also explain the discordant results regarding the groups deriving hormonal therapy benefit. Another factor that may contribute to the observed results is that by design, patients in both arms of the trials recurring before the 2 years would have been excluded from the survival comparisons. The group of patients with early recurrences may be enriched for tumors with the lowest level of ER expression, leaving mostly patients with higher ER expression, who tend to recur later, in the compared arms of the trial.

Before the adoption of IHC based methods, the ER status was determined via radiolabeled ligand binding assays (LBAs), such as the dextran-coated charcoal method. Although these assays were effective, they required fresh tumor tissue, with the associated logistic challenges. The results of LBAs provided a quantitative measurement of ER content, expressed in femtomoles of ER protein per milligram of cytosol protein (8). These assays demonstrated a broad spectrum of ER levels in breast cancers, with higher ER quantities being associated with increased therapeutic benefit from endocrine treatment. The introduction of IHC, which utilizes antibodies to detect ER in formalin-fixed, paraffin-embedded (FFPE) tissue, largely replaced LBAs as well as the EIA method that was used in clinical practice for a brief period (*Table 1*). IHC addressed the logistic limitations of LBA and EIA methods which both required fresh samples. IHC has since become the standard technique for assessing ER status in breast cancer. The IHC method has been evaluated and showed satisfactory correlation of ER expression with the older methods (8,9). A study using samples from the International Breast Cancer Study Group (IBCSG) trials VIII and IX, which included 571 premenopausal and 976 postmenopausal patients, respectively, showed that the concordance between IHC and the EIA method ranged from 74% for progesterone receptor (PR) to 88% for ER (10). Another study demonstrated that the ER status as determined by IHC is more predictive of response to endocrine therapy compared to the LBA method (11). These findings suggest that IHC may be superior to biochemical methods for hormone receptor assessment.

Newer methods of ER testing using messenger RNA (mRNA) assays have been compared with IHC and have shown relatively good concordance, but these assays have not yet been widely adopted for clinical use (12,13) (*Table 1*). Gene-expression assays, such as Oncotype DX (Genomic Health), have been integrated into standard treatment algorithms for IHC ER-positive cancers to assess the potential benefit of adding chemotherapy to endocrine therapy. Similarly, other assays like MammaPrint (Agendia, Amsterdam, Netherlands), Prosigna (PAM-50; NanoString Technologies, Salt Lake City, Utah, USA),

Table 1 Methods for evaluation of the ER in breast cancer

Method	Description	Advantages	Limitations
Enzyme immunoassay (EIA)	Determination of ER in homogenized lysates of tumor tissues using ER antibody coated beads	Quantitative methods with established cut-off	Fresh tissue specimen required
			Several steps involved making analytical validation more complicated
			Not able to discern the topology of detected ER (cancer cells versus normal epithelium and other cells in tumor sample)
Immunohistochemistry (IHC)	Histologic sections of tumors are stained with monoclonal antibodies to ER	May be performed in FFPE specimens	Semi-quantitative method
		Able to discern type of cells stained for the receptor through direct visualization. Direct visualization may also allow for confirmation of heterogeneity of expression	
		Well validated technique used for decades in clinical laboratories	
mRNA based	qRT-PCR based quantification of ER mRNA expression	May be performed in FFPE specimens	Not able to discern the ER mRNA cell provenance (cancer cells versus other cells in tumor sample)
			mRNA may not completely correlate with protein expression due to post-translational regulations

ER, estrogen receptor; FFPE, formalin fixed paraffin embedded; qRT-PCR, quantitative reverse transcription polymerase chain reaction.

EndoPredict (Myriad Genetics, Seattle, Washington, USA), and the Breast Cancer Index (Biotheranostics, San Diego, California, USA) provide prognostic information regarding recurrence risk in patients treated with endocrine therapy and have enhanced the understanding of ER-positive breast cancer behavior defined by IHC measures (14). Most studies validating these assays focus on their prognostic utility (outcomes following treatment) rather than their predictive utility in identifying patients who would specifically benefit from endocrine therapy. Some limited data on the predictive value of ER mRNA expression come from a retrospective analysis of the NSABP B-14 trial, which compared tamoxifen with no endocrine therapy (15). This study showed that higher ESR1 expression, measured by the Oncotype DX assay, was the strongest linear predictor of tamoxifen benefit, with a significant interaction between expression levels and treatment response. ESR1 expression performed better than any of the other 15 genes included in the Oncotype DX assay (13). Although newer ER testing methods may offer advantages over IHC, such as producing more quantitative and reproducible results, the data supporting their ability to predict endocrine therapy benefit are scarce.

One challenge with mRNA-based methods is that non-cancerous tissue mixed with tumor samples can affect test results, especially in cases close to the positive threshold. For instance, tumors classified as IHC ER low positive may be identified as ER-negative by quantitative mRNA testing due to dilution by noncancerous ER-negative tissue. Furthermore, there is limited data on the performance of these alternative assays in patients with IHC-classified ER low positive tumors (15). However, misclassification of ER status in ER low cases remains also a challenge even with IHC methods in use. For example, in one study, up to half of ER low breast cancers (expression between 1% and 10% of tumor cells) were ER negative on retesting (16). Smaller percentages of cancers with higher ER expression at 10% or between 11% and 30% were also ER negative on retesting, suggesting that groups of breast cancers with low ER expression may be misclassified, independently of the method used (16). The therapeutic implications of such misclassifications are obvious, although, arguably,

any benefit of endocrine therapies in these cases would be expected to be limited.

In contrast to shorter adjuvant hormonal treatment, in the years following the trial by the Swedish Breast Cancer Cooperative Group, and with the realization that the risk of late recurrence remained high in ER positive/HER2 negative breast cancers, other trials focused on the prolongation of adjuvant treatment, beyond the 5 years (17). The randomized phase 3 aTTom trial compared 5 years with 10 years of adjuvant tamoxifen in breast cancer patients with ER positive or unknown status and reported an improvement in breast cancer recurrence, breast cancer mortality and overall mortality with longer tamoxifen treatment (17). A translational study from the aTTom trial showed that, in patients with node positive disease, a benefit from extended tamoxifen was present in those with a high Breast Cancer Index [BCI (H/I), the ratio of mRNA expression of *HOXB13* to *IL17BR* genes], while node positive patients with a low BCI (H/I) derived no benefit from extended tamoxifen treatment (18). In the MA.17 study which compared letrozole with placebo after 5 years of adjuvant tamoxifen, high BCI (H/I) was predictive for late recurrence, and was associated with benefit from extended letrozole therapy (19). Additionally, BCI (H/I) was assessed in the transATAC cohort as a prognostic indicator for late distant relapse, proving to be a strong independent predictor of late-distant relapse, particularly in patients who were node-negative at diagnosis (20). In contrast to BCI (H/I), quantitative expression of ER, PR, androgen receptors (AR), the AR/ER ratio and Ki-67 were not co-related with extended tamoxifen benefit (21). The similar ATLAS trial confirmed better survival outcomes with 10 years of adjuvant tamoxifen compared to 5 years.

Other trials of adjuvant hormonal therapy prolongation have also tested aromatase inhibitors as the drugs received during the prolongation phase. The NSABP B-42 trial compared letrozole versus placebo in patients with stage I to IIIA breast cancer who had received at least some duration of aromatase inhibitor therapy during the five first adjuvant years (some patients had received tamoxifen for the first 2–3 years) (22). Although prolongation of treatment using letrozole failed to provide a statistically significant benefit in DFS at a 7-year follow-up, despite an increase from 81.3% with placebo in years 6 to 10 to 84.7% with letrozole, longer follow-up at 10-year confirmed a DFS benefit (hazard ratio =0.85, P=0.01). An evaluation of the genomic Mammaprint signature as a predictor of benefit from extended hormonal therapy revealed that patients with low-risk tumors by Mammaprint had an improved DFS and breast cancer specific survival with extended hormonal therapy, while patients with high risk tumors by Mammaprint had no benefit with extended hormonal therapy (23). Similar to the extended tamoxifen data from aTTom, the BCI (H/I) marker was predictive of benefit from extended letrozole in patients from the NSABP B-42 trial, with patients having a high BCI (H/I) displaying a longer time dependent distant recurrence after 4 years when treated with extended letrozole, while patients having a low BCI (H/I) derived no benefit in distant recurrence with extended letrozole (24). Overall, these analyses suggest that both shorter and longer than 5 years of adjuvant hormonal therapy may have a role for the optimal treatment of subsets of ER positive breast cancer patients.

The clinical importance of shortening the duration of adjuvant hormonal treatments in selected patients at low risk for recurrence cannot be overstated as these treatments have adverse effects and may significantly affect the quality of life of some patients. Since no treatment is entirely free from adverse effects, customizing the length of exposure based on individual patient risk factors has the potential to enhance both patient quality of life and the delivery of efficient health care in endocrine therapy. Considerable resources are dedicated to helping patients with adverse effects stay on treatment, some of whom may derive minimal benefit from longer treatment duration. Such resources may be redirected to patients at higher risk (25).

In conclusion, the report by the Swedish Breast Cancer Cooperative Group, although not directly transferable to modern practice, adds to the increasing evidence arguing for a personalized duration and type of adjuvant hormonal therapy in breast cancer patients. Further research will be needed to clarify the optimal duration of adjuvant hormonal therapies in ER positive breast cancer patients based on disease characteristics and risk of recurrence. The level of ER expression using the current IHC method as a factor influencing the optimal adjuvant hormonal therapy duration should be evaluated in future studies. In particular, clarification of the optimal duration of adjuvant hormonal therapy in patients with ER low (ER expression in 1% to 10% of cells) and ER intermediate (ER expression in 11% to 90% of cells) breast cancers is required and may be evaluated through retrospective examination of these subsets that participated in previous studies or prospectively in adjuvant studies with new hormonal agents, currently in progress.

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Footnote

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