5 Minute JournalClub

POST-SABCS Issue 3, 2013

Performance of the Breast Cancer Index℠ versus Oncotype DX® Recurrence Score® and IHC4 in Predicting Late Recurrence of Breast Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. This unique conference provides many clinicians and scientists from around the world a forum for discussing critical issues in the prevention and management of breast cancer. Therefore, SABCS is targeted by many members of the clinical research community as the optimal time to unveil new clinical data. This creates an environment in which yearly published results from a plethora of ongoing clinical trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes.

Although SABCS currently offers online access to the vast majority of the poster and plenary presentations from the annual meeting, the absence of expert assessment concerning practical applications may yield confusion among community oncologists who are challenged almost daily to appropriately apply a multitude of scientific findings across diverse tumors. Thus, identification of those data sets with immediate or impending relevance to the delivery of quality breast cancer care, in conjunction with professional commentary to address resultant practice ambiguity, may prove vastly beneficial to those physicians who are unable to make the annual pilgrimage to San Antonio. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS, including expert perspectives on how these new evidence-based concepts can and should be incorporated into on- and off-protocol patient care. This activity will assist medical oncologists, radiation oncologists, breast/general surgeons, nurses and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the EndoPredict® signature together with a predefined combination of clinicopathologic factors and molecular data as a predictor of late metastases for patients with estrogen receptor-positive and HER2-negative breast cancer.
- Assess the utility of the Onco*type* DX® Recurrence Score® in predicting benefit from the addition of paclitaxel to adjuvant doxorubicin/cyclophosphamide for patients with lymph node-negative and estrogen receptor-positive breast cancer treated concurrently with endocrine therapy.
- Compare the performance of the Breast Cancer Index℠ biomarker to that of the Onco*type* DX Recurrence Score and IHC4 score as prognostic factors for distant recurrence of hormone receptor-positive, lymph node-negative primary breast cancer.
- Determine the impact of metabolic syndrome on breast cancer recurrence for patients with high-, intermediate- or low-risk disease as defined by the 21-gene Onco*type* DX Recurrence Score assay.
- Appraise the reproducibility of IHC-based Ki-67 biomarker assays and ongoing strategies to increase concordance in analysis and scoring methods.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee, Consulting Agreements and Speakers Bureau: Amgen Inc, Bristol-Myers Squibb Company, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Research Support: Genentech BioOncology, GlaxoSmithKline, Sanofi.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: April 2013
Expiration date: April 2014

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POST-SABCS Issue 3, 2013

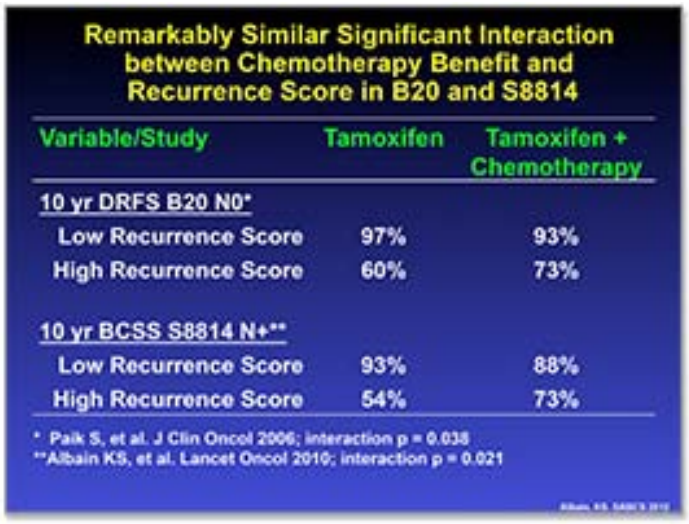
Adjuvant chemotherapy for patients with node-positive luminal A breast cancer

To go directly to slides and commentary for this issue, **click here**.

The December San Antonio Breast Cancer Symposium (SABCS) once again featured a bounty of papers focused on tissue predictors of response to systemic agents, and although none will shake up clinical practice like Dr Soon Paik's legendary 2004 SABCS presentation documenting the predictive value of the 21-gene Recurrence Score® (RS) in tumor samples from patients on the NSABP-B-20 trial of tamoxifen alone or with chemotherapy (CT), on a macro level these translational and clinical findings contribute significantly to our knowledge base and help further divide this disease into specific biologic subsets. However, other than being an outlet for new research data, SABCS is also an exceptional educational event where fascinating sessions often provide new perspectives on patient care.

To that end, the spectacular clinical science symposium on the first day of the conference included a thoughtful and thought-provoking overview by Dr Kathy Albain on the critical and controversial issue of adjuvant treatment for patients with the common luminal A phenotype, defined by Dr Charles Perou and others as having high ER and normal HER2 levels and relatively low proliferation. Dr Albain noted that last year's international meta-analysis demonstrated an overall benefit of CT in ER+ tumors, but the emergence of contemporary assays like the RS has now identified patients with ER+ tumors who are less likely to benefit from CT.

A critical issue in this regard is the patient with a node+ tumor, and to explore this Dr Albain took a unique tack by directly comparing the results of her work (presented in SABCS 2010) evaluating the RS in available tissue from the SWOG-8814 node+ study to the findings from Paik's initial evaluation of the assay in node-negative tumors from B-20. Interestingly, there was a remarkably similar correlation between CT benefit and RS in B-20 and S8814. However, more than 2 years later



controversy still surrounds the issue. Dr Albain referred to a 2012 ***JCO* editorial** by Dr Dan Hayes in which he enthusiastically supported enrolling eligible patients on the ongoing RxPONDER node+ trial but vehemently objected to withholding CT (and the potential to improve the chance of remaining disease free) in such individuals outside a study setting. As is often the case with education sessions of this type, Dr Albain did not provide a definitive recommendation about the use of tissue predictors in node+ disease, but at **our CME symposium that evening** a number of the faculty members, including Drs Hal Burstein, Kim Blackwell, George Sledge and Cliff Hudis, noted that they will selectively obtain a RS in patients with node+, ER+, HER2-negative tumors and a low nodal burden.

After hearing Dr Albain's talk, I invited her to participate in an audio interview, during which she was particularly enthused about the next generation of prospective trials, including TAILORx and RxPONDER (RS in node-negative and node+ settings) and MINDACT and I-SPY 1 (70-gene signature in the adjuvant and neoadjuvant settings), which have the potential to drastically shift how predictive assays are employed in clinical practice. However, until these trials begin to report, oncologists must make these difficult decisions with a less than optimal evidence base and keep abreast of incremental steps forward. In that regard, here's the bottom line on the most recent crop of related SABCS data sets.

1. More on RS in node+ tumors

A prominent SABCS paper focused on another retrospective/prospective analysis of tissue in patients with ER+ tumors in a large Phase III trial (NSABP-B-28, evaluating AC alone or with paclitaxel in patients with node+ disease) and provided additional evidence that RS can predict outcome in this population. Interestingly, the incremental gain from paclitaxel was not correlated with RS, but the analysis was underpowered to make that determination.

2. Molecular profiles to predict risk of delayed recurrence (DR) in patients completing 5 years of adjuvant endocrine treatment

The SABCS presentation of the ATLAS trial of 5 versus 10 years of tamoxifen was yet another data set demonstrating the critical role of DR in ER+ tumors, and 2 early but encouraging papers reported on novel RT-PCR assays to identify patients at particular risk for these events. The first looked at the **"EndoPredict® Score"** in tissue from 2 major Austrian trials, and the second examined the **"Breast Cancer Index"** versus RS and IHC4 in 665 primary tumor samples from the TransATAC tissue bank. Although not definitive, it appears that these or other similar assays may one day be able to provide important input on the critical clinical decision of extending endocrine treatment to 10 years or more while also yielding clues about specific genes correlated with the almost mysterious syndrome of DR, particularly in luminal A tumors.

3. Another dagger in the heart of Ki-67

Show this abstract to your friendly local pathologist the next time he or she offers a home brew that can save you the cost of a RS. After reviewing these scary numbers on lack of Ki-67 reproducibility among pathologists, unless perhaps Dr Mitch Dowsett or Dr Matt Ellis is doing your assay, you may want to rethink this approach.

4. Correlation between metabolic syndrome (MS) and breast cancer recurrence in luminal A tumors

This fascinating effort from Dr Albain's group attempted to determine whether the presence of MS is predictive of breast cancer recurrence in RS subtypes. In addition to documenting an overall eye-popping 27% rate of MS (glucose intolerance/diabetes and 2 other factors, including hypertension, dyslipidemia, central obesity and microalbuminemia) among the 332 patients in the study, of great interest was the correlation of MS and recurrence rate in patients with low RS. This intriguing finding suggests that the work of Dr Rowan Chlebowski and many others demonstrating a link between recurrence and metabolic factors like diet, obesity and exercise may be particularly relevant in luminal A tumors.

Next on this series: SABCS papers on CT, including a surprising potentially practice-changing paper on "pseudoadjuvant" treatment for patients with resected local recurrences rendered Stage IV with no evidence of disease.

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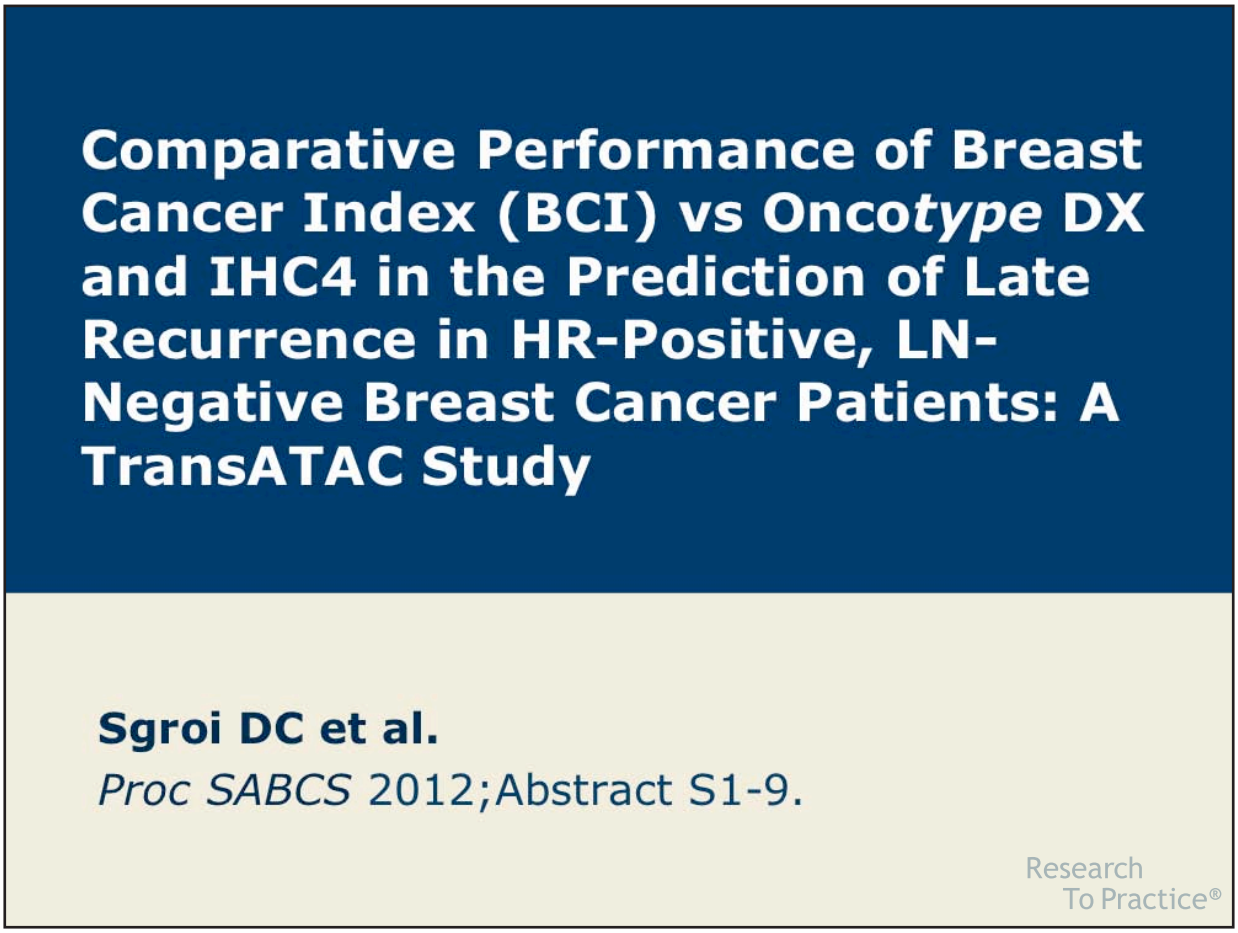
Performance of the Breast Cancer Index versus Onco*type* DX Recurrence Score and IHC4 in Predicting Late Recurrence of Breast Cancer

Presentation discussed in this issue

Sgroi DC et al. **Comparative performance of Breast Cancer Index (BCI) vs Onco*type* Dx and IHC4 in the prediction of late recurrence in HR-positive, LN-negative breast cancer patients: A TransATAC study.** San Antonio Breast Cancer Symposium 2012;**Abstract S1-9**.

Slides from a presentation at SABCS 2012 and transcribed comments from a recent interview with Lisa A Carey, MD (1/17/13)



Background

- More than 50% of late recurrences for patients with estrogen receptor (ER)-positive breast cancer (BC) occur after 5 years from diagnosis, making residual risk of recurrence a substantial concern (*Lancet Oncol* 2010;11:1135).
- Current multigene signatures have significant prognostic performance in predicting early recurrence 0 to 5 years post-diagnosis (*JNCI* 2006;98:1183; *Lancet Oncol* 2010;11:55).
- However, these signatures have limited performance in predicting the risk of late recurrence (>5 years).
- **Study objective:** To determine whether the BCI biomarker adds prognostic information to clinical variables in predicting distant recurrence in patients with ER-positive, lymph node (LN)-negative BC enrolled on the TransATAC trial.

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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Breast Cancer Index (BCI)

- The BCI is a PCR-based assay that stratifies patients into 3 risk groups and has been shown to predict distant recurrence beyond clinical and pathophysiological parameters.
- It consists of 2 independently developed biomarkers.
  - HOXB13:IL17BR (H/I) gene expression ratio: Prognostic and predictive for extended adjuvant hormonal therapy benefit
  - Molecular Grade Index: A set of cell cycle-related genes that predicts for distant recurrence beyond tumor grade
- The BCI Linear Model was trained on the untreated arm of the Stockholm Trial and was the BCI model used in the current analysis.

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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Design for Sample Analyses

Eligibility (n = 1,102)

Centrally confirmed hormone receptor-positive, LN-negative primary tumor
Prior tamoxifen or anastrozole alone
No adjuvant chemotherapy
Sufficient residual RNA for BCI
Available Onco*type* DX® Recurrence Score® (RS) and IHC4 scores
Database of 10-year follow-up

↓

Final study cohort
665 primary tumor samples,
LN-negative and matched for BCI, IHC4 and RS

- **Primary endpoint:** Distant recurrence
- Measurements included the analysis of overall distant recurrence (0-10 years), early distant recurrence (0-5 years) and late distant recurrence (5-10 years)

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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BCI Identifies 3 Risk Groups* (All Patients, 10-Year Follow-Up)

Risk group (n, %)	10-y rate of distant recurrence	Hazard ratio†
BCI-low (n = 390, 58%)	4.2%	Reference
BCI-intermediate (n = 166, 25%)	18.3%	2.89
BCI-high (n = 109, 17%)	30.0%	4.86

* $p < 0.0001$; † Adjusted for Clinical Treatment Score (CTS), an algorithm consisting of nodal status, tumor size and grade, age and treatment

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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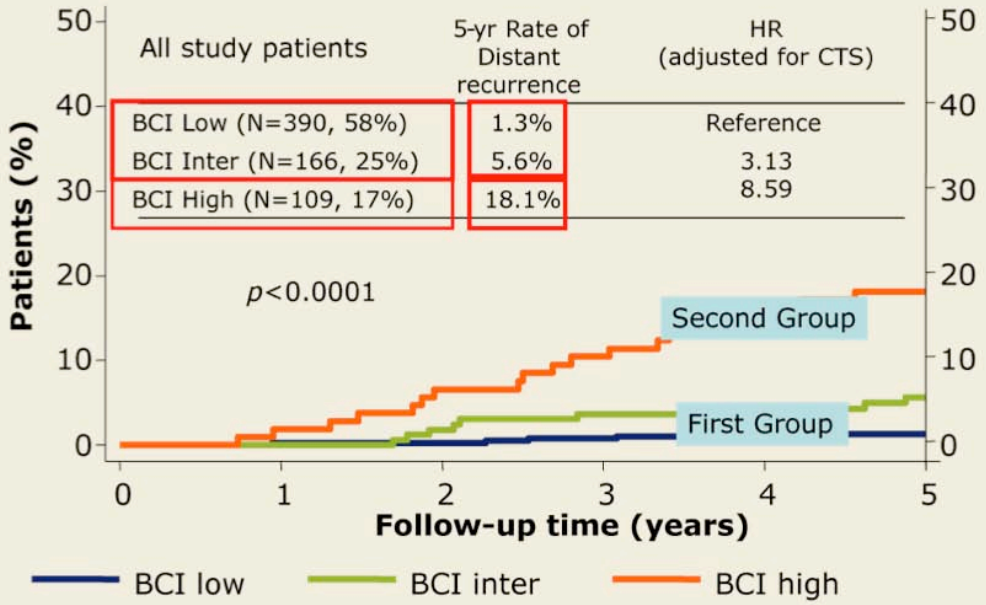
BCI Identifies 2 Early Recurrence Risk Groups



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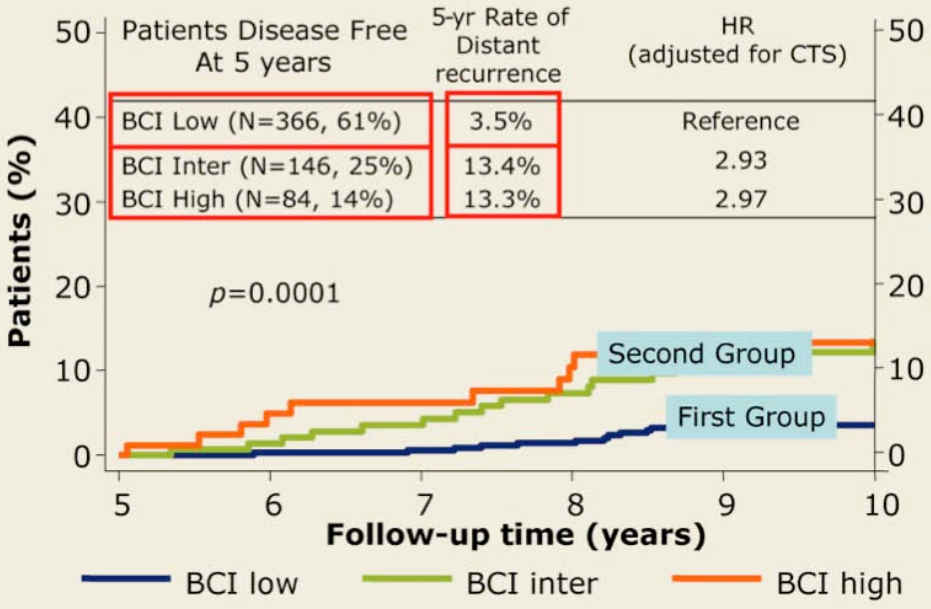
BCI Identifies 2 Late Recurrence Risk Groups



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Comparative Prognostic Performance for 0 to 10 Years

Assay type	LR χ^2 statistical analysis*		
	Univariate	Multivariate†	*p*-value
BCI	48.9	22.7	$p < 0.0001$
IHC4	39.2	22.9	$p < 0.0001$
Oncotype DX RS	25.2	13.8	$p = 0.0002$

* The likelihood ratio (LR) test was used to measure the amount of additional information provided by the BCI biomarker beyond CTS, and it allowed for a head-to-head comparison with the IHC4 and Oncotype DX RS assays.

† Multivariate analysis of LR χ^2 test was always adjusted for CTS.

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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Comparative Prognostic Performance for Early and Late Distant Recurrence

Early recurrence (0-5 years)	LR χ^2 statistical analysis		
	Univariate	Multivariate	*p*-value
BCI	34.7	15.4	$p < 0.0001$
IHC4	43.6	28.8	$p < 0.0001$
Oncotype DX RS	28.9	18.2	$p < 0.0001$
Late recurrence (5-10 years)	**Univariate**	**Multivariate**	***p*-value**
BCI*	16.6	8	$p = 0.0005$
IHC4	4.8	1.6	$p = 0.2$
Oncotype DX RS	2.2	0.5	$p = 0.5$

* Only the BCI assay demonstrated sustained significant prognostic performance.

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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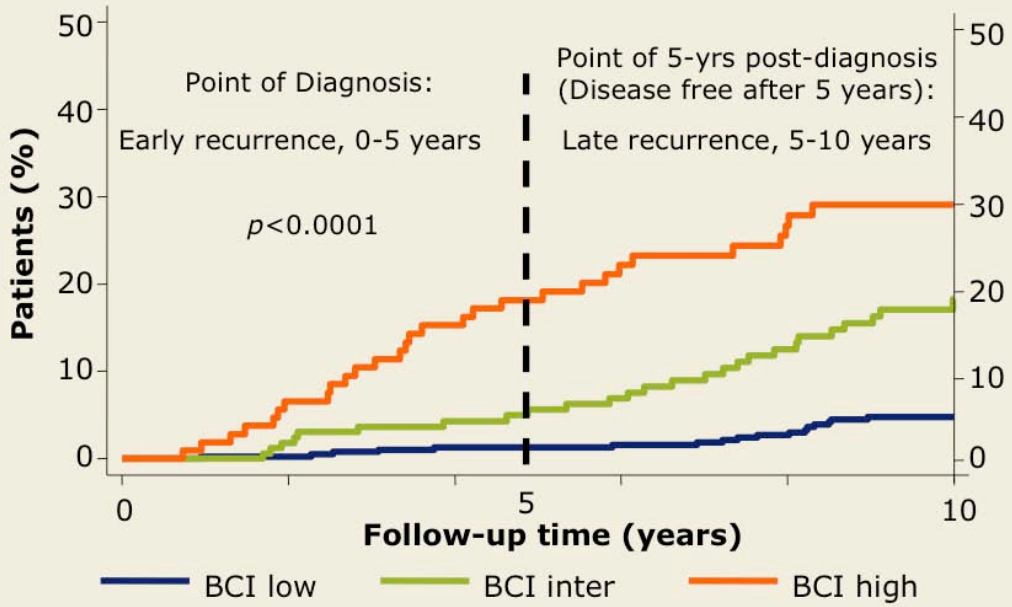
Ten-Year BCI Analysis of Early and Late Recurrence



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Author Conclusions

- BCI significantly predicts a 10-year distant recurrence rate beyond CTS for patients with ER-positive, LN-negative BC.
- BCI is a significant prognostic factor beyond CTS for predicting late distant recurrence of 5 to 10 years.
- Onco*type* DX RS and IHC4 scores are not significant prognostic factors for late distant recurrence of 5 to 10 years.
- The performance of BCI for patients at good risk with LN-negative, ER-positive primary tumors identified the following 2 groups at the point of diagnosis:
  - Those at low risk of early recurrence, who are adequately treated with endocrine therapy (ET)
  - Those at high risk of early recurrence, who do not benefit adequately from simple ET and should be considered for additional therapy (chemotherapy or other)

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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Author Conclusions (Continued)

- At the point of a follow-up of 5 years disease free, BCI identified 2 groups of patients:
  - Those at low risk of late recurrence, who do not need subsequent therapy
  - Those at significant risk of late recurrence, who should be considered for additional or alternative systemic adjuvant therapy

Sgroi DC et al. *Proc SABCS* 2012;Abstract S1-9.

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Investigator Commentary: Comparative Performance of BCI vs RS and IHC4 in Predicting Late Recurrence for Hormone Receptor-Positive, LN-Negative BC

This is a subset study of the BCI in tumors from 665 patients on the large TransATAC trial with HR-positive, LN-negative BC who had received prior tamoxifen or anastrozole only. One must be cautious when interpreting data about the efficacy of a biomarker when including subsets on which the biomarker (IHC4) was trained. It is now being recognized that ER-positive BC carries a constant ongoing risk of relapse beyond the first 5 years. Because the biology that differentiates risk of early versus late relapse is not fully understood, many therapeutic studies are being conducted in this field.

After 10 years of follow-up, this study showed that BCI was prognostic. If the BCI is classified into low-, intermediate- and high-risk groups, patients in the low-risk group had <5% risk of relapse. The intermediate- and high-risk groups had 18% and 30% risk of relapse, respectively. In the first 5 years, it seemed that the low- and intermediate-risk groups had an especially low risk of relapse when grouped together. After year 5, patients with low risk of relapse had a low BCI and the intermediate- and high-risk BCI groups had a 13% risk of relapse. However, for years 5 to 10, the RS score didn't perform well from a prognostic standpoint. These data are interesting, and I believe it's highly important that we get a grip on identifying patients who need to receive extended adjuvant therapy.

Interview with Lisa A Carey, MD, January 17, 2013