Original Study

The Utility of Breast Cancer Index (BCI) Over Clinical Prognostic Tools for Predicting the Need for Extended Endocrine Therapy: A Safety Net Hospital Experience

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Abstract

In this retrospective chart review, we evaluated 2 tools that help providers decide which early-stage hormone-receptor positive breast cancer patients should be offered extended endocrine therapy (EET) beyond 5 years. The Breast Cancer Index (BCI) is one such tool and allowed for more patient-specific treatment recommendations. In our population, recommendation for EET was better correlated with high BCI benefit.

Introduction: Extended endocrine therapy (EET) benefits select patients with early-stage hormone-receptor positive (HR+) breast cancer (BC) but also incurs side effects and cost. The Clinical Treatment Score at Five Years (CTS5) is a free tool that estimates risks of late relapse in estrogen-receptor positive (ER+) BC using clinicopathologic factors. The Breast Cancer Index (BCI) incorporates 2 genomic assays to estimate late relapse risk and likelihood of benefit from EET. This retrospective study assesses the utility of BCI in selecting EET candidates in a safety net hospital. **Materials and Methods:** We performed a retrospective chart review on 69 women with early-stage HR+, HER2- BC diagnosed at our institution from December 2009 to February 2016 on whom BCI was submitted. The CTS5 score was also calculated to assess clinical risk of late relapse. **Results:** Median age was 53 years. All patients included in our analysis had early ER+ HER2-negative BC. Roughly half of the patients (55%) were postmenopausal and 61% were of Hispanic origin. A total of 34 patients (49%) were deemed high-risk (>5%) for late relapse by CTS5, compared to 42 (61%) by BCI. BCI identified 31 (45%) patients that would benefit from EET and of those, 74%% were advised EET. 16 (47%) clinical high-risk patients were advised against EET due to low benefit predicted by BCI. In the clinical low risk group, 9 (26%) were recommended EET based on high benefit predicted by BCI. **Conclusion:** BCI is reasonable to consider in early-stage HR+ BC and offered clinically relevant information over clinical pathologic information alone.

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Introduction

The majority of breast cancers diagnosed in the United States are hormone-receptor (HR) positive, ranging from 60% to 90% of new breast cancer diagnoses depending on the region.[1,2] The role of adjuvant endocrine therapy for 5 years after local therapy (surgery and radiation) for women diagnosed with early-stage HR+ breast cancer is well established, with improvement in disease free survival and overall survival.[3-5] While patients with HR negative disease tend to present with recurrence earlier in follow up, HR+ breast cancer is more likely to present with late recurrence (after 5 years),[6] thought to be due to biological mechanisms unique to this cancer subtype.[7] Therefore, a significant portion of patients (ranging from 10%-41% depending on tumor (T), nodal (N) status, and tumor grade) continue to suffer from late relapse of disease with this treatment paradigm.[8,9] To mitigate this risk, several trials have investigated the benefits of EET beyond 5 years, showing a notable albeit small absolute reduction in late recurrence risk (2%-5%).[10,11] However,

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EET also carries with it an increased risk of side effects as well as higher cost.[12,13] Therefore, it is essential that it is not recommended to patients who will not benefit. Various tools such as web-based risk calculators and genomic assays have been developed to estimate the recurrence risk in ER-positive breast cancer. [9,14,15] Two of these tools are the Clinical Treatment Score at Five Years (CTS5) and the Breast Cancer Index (BCI).

The CTS5 is a web-based prognostic tool that predicts the risk of late distant recurrence of breast cancer after 5 years of adjuvant endocrine therapy based on the clinicopathologic features of a patient's disease.[15] It incorporates age, tumor size, nodal status, and grade and was initially developed based on studies of post-menopausal women. Further study indicated that CTS5 had a good discriminating power for long-term recurrence risk of HER2- patients, irrespective of menopausal status.[16] However, for HER2+ postmenopausal patients, the model had less effective prognostic value and it was suggested that further large-scale studies are warranted to assess its prognostic value in HER 2+ BC.[16] CTS5 is calculated using the following formula: $CTS5 = 0.438 \times \text{nodes} + 0.988 \times (0.093 \times \text{size} - 0.001 \times \text{size}^2 + 0.375 \times \text{grade} + 0.017 \times \text{age})$.[16] Results of this score are reported as low risk (<5%), medium risk (5% to 10%), and high risk (>10%) of late distant recurrence, and these risk categories are used to identify patients who may benefit from EET.[15]

Breast Cancer Index (BCI) is a validated bio-marker test that incorporates 2 distinct genomic assays to estimate late relapse risk and likelihood of benefit from EET in patients with HR positive breast cancer.[17-19] For prognostication, the test combines the HOXB13/IL17BR (H/I) ratio and the molecular grade index (MGI), 2 gene expression-based biomarker panels that reflect important estrogen signaling and proliferation pathways in breast cancer.[20] BCI presents prognostic information using an algorithmic combination of the H/I ratio and MGI, providing risk of overall and late distant recurrence of breast cancer that is specific to each patient.[20] However, what sets it apart from other risk calculators is its ability to predict the likelihood (high versus low) that a patient will benefit from EET using H/I ratio.[20] It has been validated in women with HR+, lymph node negative or lymph node positive (with 1-3 positive nodes) early stage, invasive breast cancer who are distant recurrence-free.[20] Notably, HER2+ patients made up only a small percentage of the populations of BCI validation studies (around 7%-13%).[17,20-22] The limited sample size and the event rates made analyzing this subgroup somewhat challenging. Results for relapse risk are divided into high (≥5%) and low (<5%) risk, whereas benefit is divided into high (should receive EET) and low (should not receive EET).

In contrast with the CTS5 score, which can be easily calculated by the individual provider free of charge, the BCI assay does also incur a cost. In safety net hospitals, reliance on public funding makes the cost-effectiveness of their services essential to continued delivery of subsidized care to the indigent population in the area where such hospitals are located. Therefore, weighing the cost of BCI against its benefits is especially important in this setting. The objective of this retrospective study was to assess the utility of BCI in selecting candidates for EET in a safety net hospital.

Materials and Methods

Study Site

Parkland Memorial Hospital (PMH) is one of the largest county hospitals in the US, and the only one located in Dallas. Its reliance on public funding makes the cost-effectiveness of its services essential to its continued delivery of free care to the indigent population of this large metropolitan area.

Study Population

In 2009, the medical oncology group at PMH made the decision to utilize BCI as a tool to assist in making recommendations regarding EET in women with early breast cancer. BCI has been validated in women with HR+, lymph node negative or lymph node positive (with 1-3 positive nodes) early stage, invasive breast cancer who are distant recurrence-free.[20] BCI was offered to all patients who were eligible based on these criteria and submitted if the patient consented to the test. All consecutive breast cancer patients diagnosed at PMH from December 2009 to February 2016 on whom BCI was submitted were evaluated (83 women). A total of 14 HER2 positive patients were excluded, because CTS5 has not been validated in these patients as explained above. Our final study population therefore consisted of 69 patients who met the above criteria.

Data Collection and Analysis

Demographic and clinical data were collected through retrospective chart review. Demographic data was collected as detailed in Table 1. Clinical data pertained to each patient's breast cancer diagnosis and included stage, grade (using final surgical pathology), Ki-67, HR status, receipt of chemotherapy, type of endocrine therapy received, BCI results, and whether EET was recommended by their provider. CTS5 score was calculated for all patients to assess risk of late recurrence based on clinicopathological features. Calculation is as previously published and is detailed in Table 2.[15]

To analyze the overlap between the predictions of both BCI and CTS5, the patient population was grouped based on BCI risk of relapse (high [≥5%] vs. low [<5%]), clinical risk of relapse (high [≥5%] vs. low [<5%] as predicted by CTS5 score), and BCI predicted benefit of EET (high vs. low). Various combinations of these groups were then analyzed based on the percentage of each who were recommended EET to determine whether BCI had any benefit in optimizing EET delivery over CTS5 in our study population

Ethics

This study was approved by the Institutional Review Board of UT Southwestern Medical Center.

Results

Eighty-three patients were identified in whom the BCI was submitted between 2009 and 2016. Fourteen of these cases were HER2-positive and were excluded, with 69 patients included in the final analysis. Patient characteristics are summarized in Table 1. The median age of this population was 53 years old, and the majority (61%) were Hispanic (Table 1). Slightly more than half (55%) of the patients were postmenopausal (Table 1). All patients had early-stage

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Table 1 Demographics, Tumor Characteristics, and Therapy Details, n = 69

Characteristic	
Age (years)	
Range	27-76
Median	53
Mean	54
Race	n (%)
Caucasian	5 (7.2)
African-American	19 (27.5)
Asian	2 (2.9)
Hispanic	42 (60.8)
Other	1 (1.4)
Menopausal status	n (%)
Premenopausal	31 (44.9)
Postmenopausal	38 (55.1)
Stage	n (%)
I	31 (44.9)
II	37 (53.6)
III	1 (1.4)
Tumor size range in mm	4-60
T stage	n (%)
T1	37 (53.6)
T2	29 (42.2)
T3	3 (4.3)
N stage	n (%)
Node negative	48 (69.6)
Node positive	21 (30.4)
Grade	n (%)
1	23 (33.3)
2	37 (53.6)
3	9 (13.0)
Ki-67	n (%)
≤20%	37 (53.6)
>20%	32 (46.4)
Hormone receptor status	n (%)
ER+PR+	55 (79.7)
ER+PR-	14 (20.3)
Chemotherapy	n (%)
Adjuvant	24 (34.8)
Neoadjuvant	5 (7.2)
None	40 (58.0)
Adjuvant endocrine therapy*	n (%)
TAM	14 (20.3)
AI	46 (66.7)
Both	9 (13.0)

Abbreviations: AI = aromatase inhibitor; ER = estrogen receptor; PR = progesterone receptor; TAM = tamoxifen.
*Includes extended therapy beyond 5 years.

estrogen-receptor (ER) positive breast cancer and 55 (80%) were also progesterone-receptor (PR) positive (Table 1). Most tumors were low to intermediate grade (23 [33.3%] grade 1, 37 [53.6%] grade 2, and 9 [13%] grade 3) (Table 1). Twenty-one (30%) patient's had lymph node positive breast cancer, with up to 3 positive lymph nodes (Table 1). Five (7%) of patients received neoadjuvant chemotherapy, and 24 (35%) received adjuvant chemotherapy (Table 1).

In our population, the BCI assay was requested 4-8 years from diagnosis (median 5 years). BCI identified 42 (61%) patients at high (greater than 5%) risk for late relapse, while CTS5 predicted that 34 (49%) patients fell into this category (Table 2). The majority (71%) of patients identified as high risk by BCI were also identified by CTS5. A similar trend was seen with prediction of patients at low (less than 5%) risk of relapse. Twenty-seven (39%) of patients were identified by BCI, and 35 (51%) by CTS5 (Table 2). In other words, 66% of patients identified as low risk of late relapse by CTS5 were also identified by the BCI assay.

BCI identified 31 (45%) patients that would derive high benefit from EET and 23 (74%) of those patients were advised to take EET. When examined by risk of relapse, 87% of those deemed high risk by BCI and 29% deemed low risk were advised EET based on the benefit prediction of BCI. Sixteen (47%) of patients designated as high risk for late relapse by CTS5 were advised against EET due to low benefit predicted by BCI. Similarly, 9 (26%) of patients who were identified as being low risk for late relapse by CTS5 were still recommended EET based on high benefit predicted by BCI (Table 2).

Discussion

Recent clinical trials have shown that EET imparts modest benefit in the reduction of risk of late recurrence in HR+ breast cancer, but this comes at the cost of increased morbidity and financial burden.[3-5] The diverse prognosis and disease heterogeneity of breast cancer need to be considered when deciding on the duration of endocrine therapy. Web-based tools such as CTS5 are useful in this regard, as they predict the risk of late distant recurrence of breast cancer after 5 years of adjuvant endocrine therapy based on the clinicopathologic features of a patient's disease.[14,15] CTS5 in particular incorporates tumor size, grade, patient age, and number of nodes involved, and categorizes patients as low risk (<5%), medium risk (5%-10%), and high risk (>10%) of late distant recurrence.[15] However, tools like this do not directly inform providers of the benefit EET will provide for a given patient, as increased risk of recurrence does not directly correlate to benefit from EET.[20] Given the risk of adverse effects and financial burden of EET, it is crucial to avoid advising it to patients who are unlikely to benefit, regardless of their risk of late relapse.[10-13]

To this end, BCI is reasonable to consider in early-stage HR positive breast cancer to predict both risk of late relapse and likelihood of benefit from EET. It accomplishes both functions by combining the results of 2 gene expression-based biomarker panels (the H/I ratio and MGI), which together reflect a given patient's tumor proliferation status based on the estrogen signaling and proliferation pathways of their cancer cells.[20] By running this kind of individualized genomic assay, providers gain insight into the unique

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Table 2 BCI and CTS5 Data, n = 69

Characteristic	n (%)	EET recommended, n (%)
BCI high risk, n = 42 (60.9)		
Clinical high risk	30 (71.4)	15 (50.0)
Clinical low risk	12 (28.6)	7 (58.3)
BCI low risk, n = 27 (39.1)		
Clinical high risk	4 (14.8)	0 (0)
Clinical low risk	23 (85.2)	2 (8.7)
BCI high risk, n = 42 (60.9)		
High benefit	24 (57.1)	21 (87.5)
Low benefit	18 (42.9)	0 (0)
BCI low risk, n = 27 (39.1)		
High benefit	7 (25.9)	2 (28.6)
Low benefit	20 (74.1)	0 (0)
Clinical high risk, n = 34 (49.3)		
BCI high benefit	18 (52.9)	15 (83.3)
BCI low benefit	16 (47.1)	0 (0)
Clinical low risk, n = 35 (50.7)		
BCI high benefit	13 (37.1)	9 (69.2)
BCI low benefit	22 (62.9)	0 (0)
Total patients	69 (100)	24 (34.8)

Abbreviations: BCI = Breast Cancer Index; EET = extended endocrine therapy.
Clinical high risk = CTS5 intermediate or high risk, which indicates a ≥5% risk of late relapse.
Clinical low risk = CTS5 low risk, which indicates a <5% risk of late relapse.
BCI high risk indicates ≥5% risk of late relapse.
BCI low risk indicates <5% risk of late relapse.

biology of their patient's tumor and can provide specifically tailored treatment recommendations that help prevent prescription of EET to patients who will not benefit.[20]

The validity of BCI's prediction of late relapse risk, as well as likelihood of EET benefit using the H/I ratio has been examined in different cohorts with positive results, specifically in the Stockholm, MA.17, Trans-aTTom, and IDEAL trials.[17,18,20,23] A more recent study examining the effect of BCI-H/I for EET benefit prediction in the NSABP B-42 trial found no statistically significant benefit of EET by BCI-H/I interaction with regard to recurrence- free interval. However, in a time-dependent analysis examining distant recurrence, BCI-H/I-High patients had statistically significant benefit from EET after 4 years, while BCI-H/I-Low pts did not.[24] More detailed analysis of this new data is ongoing and longer follow up planned.[24] Despite these recent trial results, the totality of the data continues to support the validity of BCI.

The benefit of BCI also must be weighed against the cost of running the test, a consideration that is especially important at a safety net hospital. As millions of Americans remain without health insurance, it falls on safety net hospitals to provide them with optimal care while also effectively utilizing the limited resources they are given.[25] Therefore, frequent reassessment of the allocation of these resources and whether or not investment in BCI is worthwhile is necessary, and that is what we sought to do in this study.

Our study objective was to understand the utility and impact of a genomic tool (BCI) in determining the need for EET. We also compared the results of this genomic assay to risk of late breast cancer relapse based on clinicopathologic features as predicted by CTS5. In our population, consisting of a relatively even number of patients with clinically high and low risk disease, the risk prediction component of the BCI assay was well correlated with that of the CTS5 score. Differences between the 2 tests were similar to those reported in prior analyses (39% low risk by BCI vs. 51% by CTS5 in our study [12% difference], compared to 54% low risk by BCI vs. 61% by CTS5 [7% difference] found by Foldi et al. in their analysis of 119 patients with stage I or II ER-positive breast cancer.)[26] However, the benefit prediction component of the BCI assay both prevented the use of EET in 16 (47%) clinically high risk patients and added EET to the treatment of 9 (26%) clinically low risk patients.

To our knowledge, this is the first study assessing the utility of BCI in identifying patients for EET in a safety net hospital. Our population is additionally unique in that the majority (61%) were Hispanic. While a registry study is underway collecting ethnicity information on enrolled patients, past BCI validation studies did not collect ethnicity data.

The use of BCI results over CTS5 score in recommendation of EET is gaining support, with the National Comprehensive Cancer Network (NCCN) unanimously supporting the use of BCI to deter-

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mine benefit of EET for the first time in 2021, although evidence in support of BCI is classified as level 2A (lower level).[27] This study further explores the benefit of this genomic assay by evaluating its utility alongside the CTS5, a prognostic tool with little to no investment required.

This is a single-center, retrospective study with a small population size and therefore carries the limitations inherent in these characteristics. Further study with a larger population is needed to assess whether the number of patients whose EET recommendation based on BCI benefit contradicted that of their CTS5 risk score was statistically significant. We are additionally unable to account for the impact of GNRH use on our results. However, given the notable side effects and cost of EET, the fact that any number of patients in our population avoided EET based on a lack of benefit predicted by the BCI assay could justify the expense that the test incurs at a safety net hospital. Further study is also recommended to quantify whether money saved through avoiding unnecessary EET offsets the additional cost of BCI in this setting.

Clinical Practice Points

- HR+ breast cancer is more likely to present with late recurrence compared to HR negative breast cancer. Several trials have shown extended endocrine therapy (EET) beyond 5 years reduces late recurrence risk.
- Various tools exist to help determine which patients should be offered EET. The Clinical Treatment Score at Five Years (CTS5) is a free calculator that predicts the risk of late distant recurrence of breast cancer after five years of adjuvant endocrine therapy based on the clinicopathologic features of a patient's disease. However, not all patients at high risk of recurrence will benefit from EET.
- The Breast Cancer Index (BCI) incorporates two genomic assays to estimate both late relapse risk and likelihood of benefit from EET.
- This retrospective study assesses the utility of BCI in selecting EET candidates. We found that sixteen (47%) patients designated as high risk for late relapse by CTS5 were advised against EET due to low benefit predicted by BCI. Similarly, 9 (26%) patients identified as being low risk for late relapse by CTS5 were still recommended EET based on high benefit predicted by BCI.
- Both outcomes indicate that BCI is reasonable to consider in early-stage HR+ breast cancer patients to guide decision-making regarding EET, as it will increase delivery of effective treatment to patients who would otherwise miss out while decreasing unnecessary morbidity and cost to patients who are at high risk of late relapse but would not benefit from EET.

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Disclosure

The authors have stated that they have no conflicts of interest.

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