Validation of the prognostic performance of Breast Cancer Index (BCI) in hormone receptor-positive (HR+) postmenopausal breast cancer patients in the TEAM trial

Validation of the Prognostic Performance of Breast Cancer Index in Hormone Receptor–Positive Postmenopausal Breast Cancer Patients in the TEAM Trial

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ABSTRACT

Purpose: Patients with early-stage hormone receptor–positive (HR^+) breast cancer face a prolonged risk of recurrence even after adjuvant endocrine therapy. The Breast Cancer Index (BCI) is significantly prognostic for overall (0–10 years) and late (5–10 years) distant recurrence (DR) risk in N0 and N1 patients. Here, BCI prognostic performance was evaluated in HR^+ postmenopausal women from the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial.

Experimental Design: 3,544 patients were included in the analysis (N = 1,519 N0, N = 2,025 N^+). BCI risk groups were calculated using pre-specified cutoff points. Kaplan–Meier analyses and log-rank tests were used to assess the prognostic significance of BCI risk groups based on DR. Hazard ratios (HR) and confidence intervals (CI) were calculated using Cox models with and without clinical covariates.

Results: For overall 10-year DR, BCI was significantly prognostic in Ni0 (N = 1,196) and N1 (N = 1,234) patients who did not receive prior chemotherapy ($P < 0.001$). In patients who were DR-free for 5 years, 10-year late DR rates for low- and high-risk groups were 5.4% and 9.3% (N0 cohort, N = 1,285) and 4.8% and 12.2% (N1 cohort, N = 1,625) with multivariate HRs of 2.25 (95% CI, 1.30–3.88; $P = 0.004$) and 2.67 (95% CI, 1.53–4.63; $P < 0.001$), respectively. Late DR performance was substantially improved using previously optimized cutoff points, identifying BCI low-risk groups with even lower 10-year late DR rates of 3.8% and 2.7% in N0 and N1 patients, respectively.

Conclusions: The TEAM trial represents the largest prognostic validation study for BCI to date and provides a more representative assessment of late DR risk to guide individualized treatment decision-making for HR^+ patients with early-stage breast cancer.

Introduction

Advancements in adjuvant endocrine therapy for early-stage hormone receptor–positive (HR^+) breast cancer have led to improved survival and reduced recurrence of disease (1–3). Even so, patients with breast cancer face a substantial and prolonged risk of recurrence with over 50% of recurrences occurring after the first 5 years from diagnosis (4–7). An Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that the risk of distant recurrence (DR) between 5 and 20 years after 5 years of adjuvant endocrine therapy for ER-positive breast cancer was strongly correlated with nodal status with an absolute risk of 13%, 20%, and 34% for patients with N0, N1, and N2 disease even with T1 tumors, respectively (6). Consequently, N^+ patients are more likely to be treated with extended endocrine therapy (EET) than N0 patients (1). However, more intensive therapies may also expose patients to a greater risk of side effects. Genomic assays that inform prognosis and predict response to therapy can help assess risk versus benefit and have been incorporated into clinical decision-making (8).

The Breast Cancer Index (BCI) is a gene expression-based biomarker comprising two complementary functional domains that interrogate different biological pathways: The Molecular Grade Index that assesses proliferative status based on the expression levels of five cell-cycle–associated genes and the *HOXB13:IL17BR* expression ratio (H/I) that interrogates estrogen signaling in HR^+ breast cancer. The combined index, BCI, has been shown to significantly stratify patients with N0 disease based on the risk of overall (0–10 years) and late (5–10 years) DR (9–11). For patients with breast cancer with 1 to 3 positive nodes (N1), an updated prognostic model ($BCIN^+$) that integrates BCI with tumor size and grade was developed and validated with significantly improved prognostic performance (12). Recently, new cutoff points for both BCI and $BCIN^+$ models that were specifically optimized for late DR were developed using N0 patients from the TransaTTom study (13) and N1 patients from the IDEAL trial (14), which showed improved prognostication by identifying low-risk groups with an even lower risk of late DR.

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Translational Relevance

Accurate prognostication of hormone receptor–positive (HR^+) patients with early-stage breast cancer is important to inform adjuvant therapy selection. This study evaluated the Breast Cancer Index (BCI) prognostic models in a cohort of postmenopausal women from the Tamoxifen and Exemestane Adjuvant Multinational trial confirming that BCI and $BCIN^+$ are significantly prognostic for overall and late distant recurrence (DR) in N0 and N1 patients. This study further refines the identification of women at low risk of DR, using the BCI prognostic score, who may be spared from extended endocrine therapy (EET) due to their low absolute risk and modest benefit from longer endocrine therapy. Women at high risk of late DR should receive EET based on BCI-predictive results. In summary, BCI may inform personalized decision-making for adjuvant therapies by providing independent prognostic information.

This study evaluated the BCI and $BCIN^+$ prognostic models in a cohort of women from the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial (registered with ClinicalTrials.gov, NCT00279448, NCT00032136, and NCT00036270; ref. 15). BCI and $BCIN^+$ were assessed for their ability to significantly stratify HR^+ patients with breast cancer based on the risk for overall (0–10 years) and late (5–10 years) DR.

Materials and Methods

Study design and patients

Tumor samples in this study were derived from patients previously enrolled in the TEAM trial. The TEAM trial is a prospective phase III trial that examined disease-free survival (DFS) after 5 years of either aromatase inhibitor (AI) monotherapy or sequential therapy, consisting of tamoxifen for 2.5–3 years followed by an AI to complete 5 years of endocrine therapy (15). Postmenopausal HR^+ women (9,766 patients) were randomly assigned to AI monotherapy (4,904 patients) or TAM-AI sequential therapy (4,875 patients). Results of the study showed no difference in DFS at 5 and 10 years between the two groups of patients (15, 16). Patients from the translational pathology cohort with available RNA samples for BCI testing were assessed in this study ($N = 4{,}086$). Patients were excluded if they had received neoadjuvant chemotherapy. Hormone receptor status was defined locally at a cutoff point of 1% for ER or PR.

The TEAM trial was done in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonization, and Good Clinical Practice. Appropriate approvals from the ethical committee were obtained. All patients provided written informed consent.

BCI assay

BCI gene expression analysis was performed by RT-PCR blinded to clinical outcome (Biotheranostics Inc., A Hologic Company), as previously described (9). BCI and $BCIN^+$ scores were calculated for N0 and N1 patients, respectively, and pre-defined cutoff points were used to stratify patients into overall (0–10 years) risk groups: BCI-Low, BCI-Intermediate, and BCI-High for N0 patients as well as $BCIN^+$-Low and $BCIN^+$-High (9, 12). To evaluate late DR in N0 patients, BCI-Intermediate and BCI-High risk groups were grouped together and re-categorized as BCI-High (9, 12). In addition, new cutoff points (4.4 for N0 and 1.8 for N1) were previously optimized for late DR based on the classification of a low-risk group with <5% risk of 5–15 years late DR using N0 patients from the Trans-aTTom study (13) and N1 patients from the IDEAL trial (14) were also used to further evaluate BCI and $BCIN^+$ prognostic performance.

Study endpoints

The primary endpoint was time to DR, defined as the time from randomization in the main trial to the first recurrence at distant sites. Contralateral disease, locoregional recurrences, and other secondary primary cancers were neither counted as events nor censored. Death before DR was treated as a censoring event. The secondary endpoint was time to recurrence, defined as the time from randomization to first locoregional or DR. The primary objective was to evaluate the prognostic performance of BCI and $BCIN^+$ for overall (0–10 years) and late DR (5–10 years) risk in postmenopausal women with HR^+ N0 and N1 breast cancer, respectively. The secondary objective was to evaluate the prognostic performance of BCI and $BCIN^+$ in the subset of patients with $HER2^-$ disease. Overall DR risk (0–10 years) was evaluated within the subset of patients that did not receive chemotherapy and late DR risk (5–10 years) was evaluated within the subset of patients that remained DR-free for at least 5 years, independent of having received chemotherapy or not.

Statistical analyses

Analyses were prespecified in a Statistical Analysis Plan before unblinding. Kaplan–Meier analysis and log-rank test were used to compare the differences between BCI and $BCIN^+$ risk groups for overall (0–10 years) and late (5–10 years) DR risk. Hazard ratios (HR) and the associated 95% confidence intervals (CI) were estimated using Cox proportional hazards regression analysis. Multivariate models were adjusted for standard clinicopathological variables, including age, tumor size, tumor grade, and treatment. Ten-year risk of DR, as a function of continuous BCI and $BCIN^+$ risk score, was estimated from a Cox model based on Breslow estimate (17). A two-sided P value of less than 0.05 was considered statistically significant. All analyses were performed using SAS statistical package.

Data availability

The data analyzed in the current study are not publicly available because they contain patient data and proprietary information. Aggregated data analyzed in the study are included in the article. Qualified researchers may contact the corresponding author with reasonable requests to view additional data.

Results

Patient characteristics

Patient and tumor characteristics for the translational cohort and the parent TEAM trial are summarized in **Table 1**. Of the 9,766 patients evaluated in TEAM, 4,086 had tissue available for analysis and 3,544 patients were included in the final analysis, consisting of 1,519 HR^+ N0 and 2,025 N1 patients (**Fig. 1**).

Distributions of age, ER status, PR status, adjuvant radiotherapy and chemotherapy were similar between patients in the TEAM trial and the translational BCI cohort (**Table 1**). Compared with the parent TEAM trial, more patients in the translational cohort had T2 (45% vs. 37%), poorly differentiated tumors (34% vs. 27%), node-positive disease (57% vs. 47%), and mastectomy (47% vs. 44%), largely due to the exclusion of US study sites that had the lowest risk population of patients among the 9 countries that participated in the TEAM trial.

Table 1. Patient characteristics.

	TEAM trial ($N = 9,766$)	BCI cohort ($N = 3,544$)
Age at randomization, years		
<50	331 (3%)	88 (3%)
50–59	3,017 (31%)	1,057 (30%)
60–69	3,731 (38%)	1,350 (38%)
≥70	2,687 (28%)	1,049 (30%)
Histological grade		
Well differentiated	1,677 (19%)	412 (12%)
Moderately Differentiated	4,797 (54%)	1,874 (54%)
Poorly differentiated	2,438 (27%)	1,197 (34%)
Not known	854	61
Tumor size		
T1	5,691 (58%)	1,769 (50%)
T2	3,591 (37%)	1,597 (45%)
T3–T4	457 (5%)	177 (5%)
T0/T *in situ*	6	0
Not known	21	1
Nodal status		
N0	5,113 (53%)	1,519 (43%)
N1	4,109 (42%)	2,025 (57%)
N2–3	478 (5%)	
Not known	66	
ER status		
Positive	9,585 (98%)	3,480 (98%)
Negative	176 (2%)	63 (2%)
Not assessed	5	1
PR status		
Positive	7,301 (81%)	2,419 (79%)
Negative	1,724 (19%)	644 (21%)
Not assessed	741	481
HER2 status		
Positive	560 (13%)[a]	430 (13%)
Negative	3,825 (87%)[a]	2,966 (87%)
Not assessed	1,735[a]	148
Most extensive surgery		
Mastectomy	4,333 (44%)	1,671 (47%)
Wide local incision	5,423 (56%)	1,871 (53%)
No resection	3 (<1%)	0 (0%)
Not known	7	2
Adjuvant radiotherapy		
Yes	6,697 (69%)	2,263 (64%)
No	2,976 (31%)	1,276 (36%)
Not known	93	5
Adjuvant chemotherapy		
Yes	3,513 (36%)	1,110 (31%)
No	6,248 (64%)	2,430 (69%)
Not known	5	4
Histology		
Ductal	3,696 (60%)	2,667 (75%)
Lobular	809 (13%)	498 (14%)
Mixed	226 (4%)	143 (4%)
Mucinous	12 (<1%)	8 (<1%)
Medullary	3 (<1%)	2 (<1%)
Papillary	6 (<1%)	2 (<1%)
Tubular	10 (<1%)	3 (<1%)
Other[b]	6 (<1%)	3 (<1%)
NOS[c]/Missing	1,352 (22%)	218 (6%)

[a]HER2 status only available for patients in pathology sub study ($n = 6,120$).
[b]Other histological subtypes: *In situ*, Bifocal, Cribiform, Multifocal, Neuroendocrine.
[c]Not otherwise specified.

Performance of BCI and BCIN± for overall DR

Using previously established cutoff points (9, 12), BCI stratified N0 patients ($N = 1,196$) who did not receive chemotherapy into three distinct risk groups for overall DR: 47% ($N = 567$) into a BCI low-risk group with a 10-year DR rate of 7.8% (95% CI, 4.9–10.5), 29% ($N = 343$) BCI intermediate-risk with a 10-year DR rate of 14.1% (95% CI, 9.9–18.1), and 24% ($N = 286$) BCI high-risk with a 10-year DR rate of 23.5% (95% CI, 17.9–28.7; **Table 2** and **Fig. 2A**). BCI was significantly prognostic for overall DR in N0 patients with a multivariate HR of 2.16 (95% CI, 1.32–3.52) for intermediate-risk and 3.89 (95% CI, 2.42–6.24) for high-risk versus low-risk groups, respectively ($P < 0.001$; **Table 2** and **Fig. 2A**).

Similarly, using previously defined cutoff points (12), BCIN$^+$ stratified N1 patients ($N = 1,234$) who did not receive chemotherapy into two prognostic groups for overall DR (**Table 2** and **Fig. 2B**). The BCIN$^+$ low-risk group comprised 23% of patients ($N = 286$) with a 10-year DR rate of 10.1% (95% CI: 6.2–13.8). The BCIN$^+$ high-risk group included 77% of patients ($N = 948$) with a 10-year DR rate of 24.6% (95% CI, 21.5–27.6; **Table 2** and **Fig. 2B**). BCIN$^+$ was significantly prognostic with a multivariate HR of 2.62 (95% CI, 1.72–3.98; $P < 0.001$; **Table 2** and **Fig. 2B**).

In the N0 subset of patients who did not receive chemotherapy, 82% ($N = 978$) were HER2$^-$. BCI was significantly prognostic for overall DR ($P < 0.001$) with a multivariate HR of 2.51 (95% CI, 1.41–4.47) for intermediate-risk and 5.00 (95% CI, 2.83–8.84) for the high-risk versus low-risk groups (**Table 2** and **Fig. 2C**). Over half (51%, $N = 498$) of N0 HER2$^-$ patients were in the BCI low-risk group, with a 10-year DR rate of 6.8% (95% CI, 3.8–9.7), whereas 29% ($N = 280$) and 20% ($N = 200$) of N0 HER2$^-$ patients were in the BCI intermediate and BCI high-risk groups, with a 10-year DR rate of 12.6% (95% CI, 8.2–16.8) and 22.7% (95% CI, 16.1–28.9), respectively (**Table 2** and **Fig. 2C**).

Among N1 patients who did not receive chemotherapy, 86% ($N = 1,067$) were HER2$^-$. BCIN$^+$ significantly stratified these patients into two risk groups with a multivariate HR of 2.37 (95% CI, 1.53–3.67) for overall DR ($P < 0.001$; **Table 2** and **Fig. 2D**). The low-risk group consisted of 24% of patients ($N = 258$) with a 10-year DR rate of 10.5% (95% CI, 6.3–14.5) and the high-risk group included 76% of patients ($N = 809$) with a 10-year DR rate of 23.7% (95% CI, 20.4–27.0; **Table 2** and **Fig. 2D**).

In both the overall and HER2$^-$ cohort, the risk of overall DR increased exponentially with higher BCI and BCIN$^+$ scores (Supplementary Fig. S1).

Performance of BCI and BCIN± for late DR

Among the 3,544 patients in this study, 82% ($N = 2,910$) were DR-free for at least 5 years, including 1,285 N0 and 1,625 N1 patients. Among these patients, 21% and 41% of the N0 and N1 patients received prior chemotherapy, respectively. For late DR, BCI significantly stratified these 1,285 N0 patients into two prognostic groups with a multivariate HR of 2.25 (95% CI, 1.30–3.89; $P = 0.004$; **Table 2** and **Fig. 3A**): 49% ($N = 633$) were low-risk with a late DR rate of 5.4% (95% CI, 3.0–7.8) and 51% ($N = 652$) were high-risk with a late DR rate of 9.3% (95% CI, 6.7–11.8).

BCIN$^+$ significantly stratified 1,625 N1 patients with respect to risk of late DR into low- and high-risk groups with a multivariate HR of 2.67 (95% CI, 1.53–4.63; $P < 0.001$; **Table 2** and **Fig. 3B**). The low-risk group, consisting of 21% of N1 patients ($N = 349$), had a late DR rate of 4.8% (95% CI, 2.3–7.3), whereas the high-risk group, comprising 79%

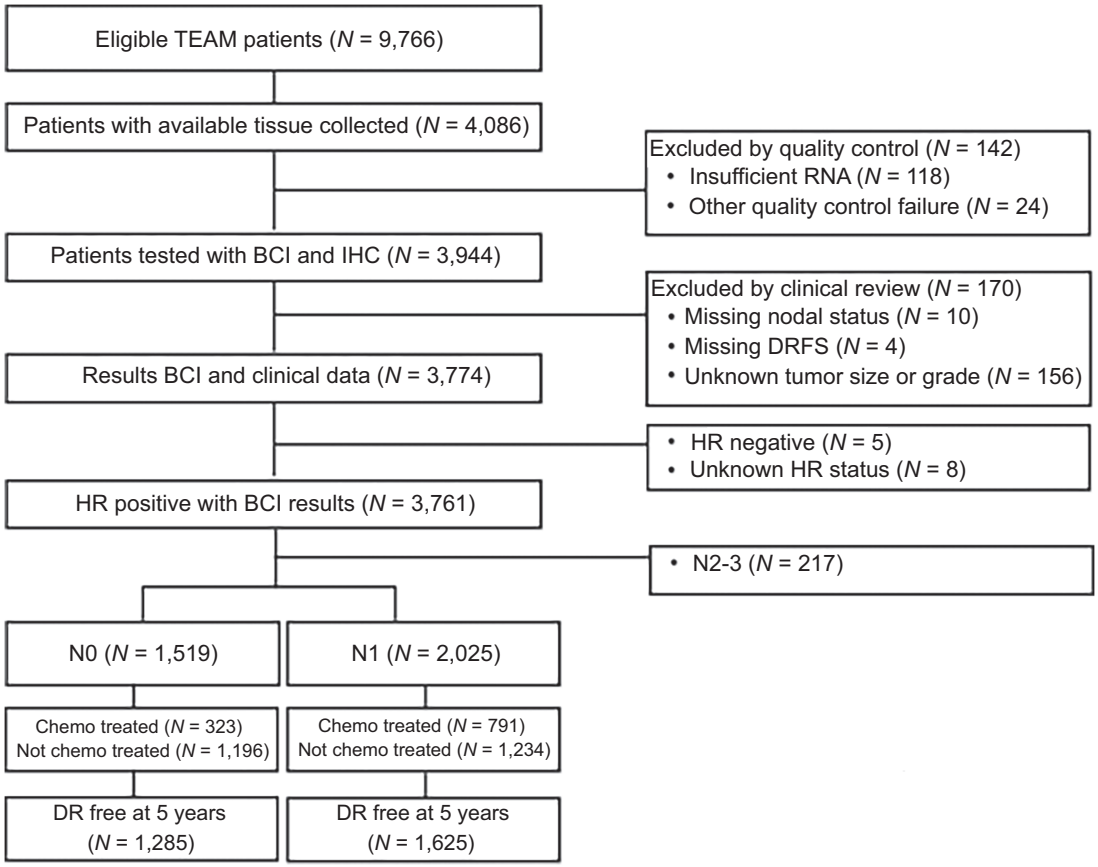

Figure 1.
Case flow diagram.

of N1 patients ($N = 1,276$), exhibited a late DR rate of 12.2% (95% CI, 10.1–14.2; **Table 2** and **Fig. 3B**).

In the HER2$^-$ subsets, BCI and BCIN$^+$ remained significantly prognostic for late DR in N0 and N1 patients, respectively ($P = 0.006$ and $P < 0.001$; **Fig. 3C** and **D**). Out of 1,063 N0 HER2$^-$ patients, BCI classified 52% ($N = 556$) into a low-risk group with a late DR rate of 5.3% (95% CI, 2.6–7.9) and 48% ($N = 507$) into a high-risk group with a late DR rate of 9.0% (95% CI, 6.1–11.8),

Table 2. Prognostic performance of BCI and BCIN$^+$ for overall and late DR in all patients with N0 and N1 breast cancers, as well as in HER2$^-$ subsets, respectively.

		All patients				HER2$^-$ subset			
BCI/BCIN$^+$ groups		*N*	10-y DR, % (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)	*N*	10-y DR, % (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Overall DR (0–10 years) in patients not treated with chemotherapy									
N0	**Low**	567	7.8 (4.9–10.5)	—	—	498	6.8 (3.8–9.7)	—	—
	Intermediate	343	14.1 (9.9–18.1)	2.14 (1.35–3.40)	2.16 (1.32–3.52)	280	12.6 (8.2–16.8)	2.35 (1.36–4.04)	2.51 (1.41–4.47)
	High	286	23.5 (17.9–28.7)	3.94 (2.56–6.06)	3.89 (2.42–6.24)	200	22.7 (16.1–28.9)	4.56 (2.73–7.61)	5.00 (2.83–8.84)
N1	**Low**	286	10.1 (6.2–13.8)	—	—	258	10.5 (6.3–14.5)	—	—
	High	948	24.6 (21.5–27.6)	2.68 (1.77–4.07)	2.62 (1.72–3.98)	809	23.7 (20.4–27.0)	2.46 (1.59–3.81)	2.37 (1.53–3.67)
Late DR (5–10 years) in patients DR free for 5 years									
N0	**Low**	633	5.4 (3.0–7.8)	—	—	556	5.3 (2.6–7.9)	—	—
	High	652	9.3 (6.7–11.8)	2.10 (1.26–3.50)	2.25 (1.30–3.88)	507	9.0 (6.1–11.8)	2.18 (1.23–3.88)	2.53 (1.37–4.67)
N1	**Low**	349	4.8 (2.3–7.3)	—	—	311	5.1 (2.3–7.8)	—	—
	High	1,276	12.2 (10.1–14.2)	2.68 (1.54–4.66)	2.67 (1.53–4.63)	1,083	12.1 (9.9–14.3)	2.50 (1.41–4.45)	2.49 (1.40–4.44)

Note: Multivariate analysis was adjusted for age, tumor size, tumor grade, and treatment for N0 subsets, but excluded tumor grade for N1 subsets due to confounding with BCIN$^+$.

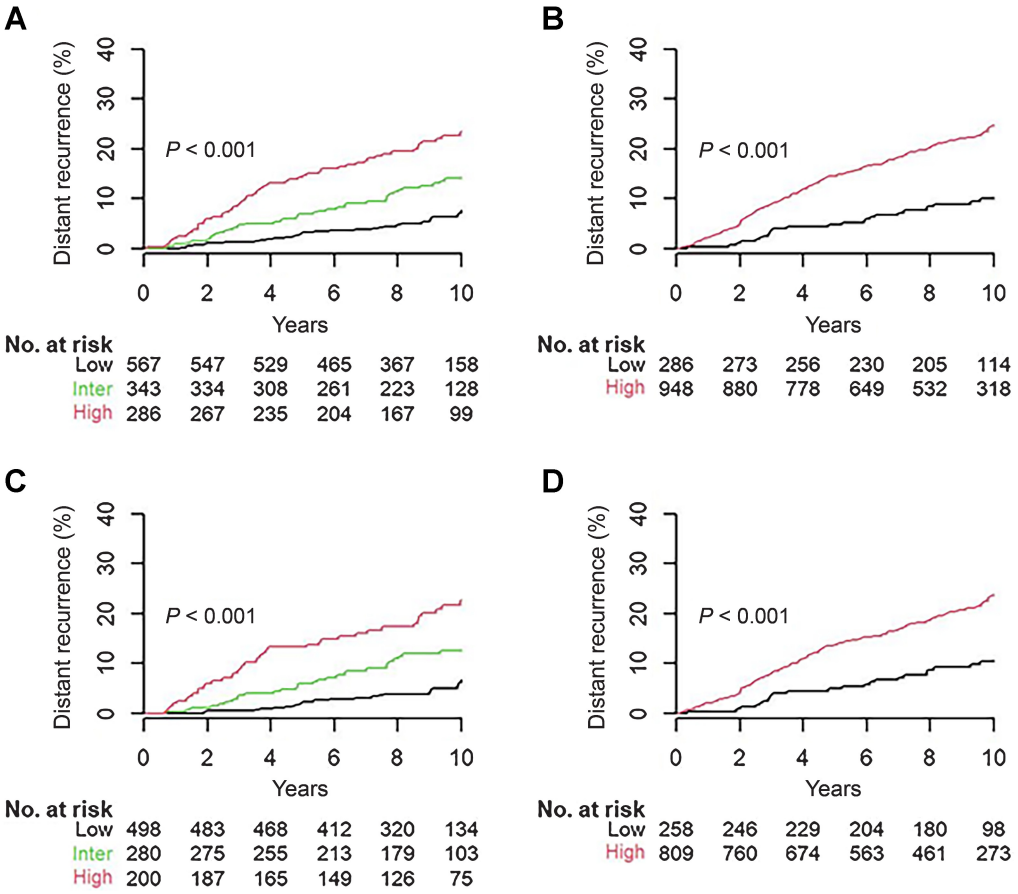

Figure 2.

Prognostic performance of BCI and BCIN$^+$ for overall 10-year risk of DR in N0 and N1 patients who did not receive adjuvant chemotherapy. **A,** BCI stratification in 1,196 N0 patients. **B,** BCIN$^+$ stratification in 1,234 N1 patients. **C,** BCI stratification in 978 N0 HER2$^-$ patients. **D,** BCIN$^+$ stratification in 1,067 N1 HER2$^-$ patients

resulting in a multivariate HR of 2.53 (95% CI, 1.37–4.67; **Table 2** and **Fig. 3C**).

In the late DR analysis, 85% of N1 patients ($N = 1,394$) were HER2$^-$. BCIN$^+$ stratified 22% of patients ($N = 311$) into a low-risk group with a late DR rate of 5.1% (95% CI, 2.3–7.8), and 78% patients ($N = 1,083$) as high-risk with a late DR rate of 12.1% (95% CI, 9.9–14.3), resulting in a multivariate HR of 2.49 (95% CI, 1.40–4.44; **Table 2** and **Fig. 3D**).

Similar to the findings for overall DR, the risk of late DR increased with higher BCI and BCIN$^+$ scores in both the overall and HER2$^-$ cohort (Supplementary Fig. S2).

Performance of BCI and BCIN± with optimized cutoff points for late DR

Previous work demonstrated that alternative BCI cutoff points specifically optimized for late DR resulted in improved prognostic performance for both BCI and BCIN$^+$ (13, 14). Using these optimized cutoff points, BCI significantly stratified 1,285 N0 patients into two prognostic groups ($P = 0.002$; **Fig. 4A**): a low-risk group consisting of 34% of N0 patients ($N = 439$) with a late DR rate of 3.8% (95% CI, 1.5–6.0) and a high-risk group, including 66% of N0 patients ($N = 846$) with a late DR rate of 9.1% (95% CI, 6.8–11.4) resulting in a multivariate HR of 2.63 (95% CI, 1.36–5.12; **Fig. 4A**; Supplementary Table S1). BCIN$^+$ also significantly stratified the risk of late DR in 1,625 N1 patients using the optimized cutoff points ($P < 0.001$; **Fig. 4B**). The low-risk group, consisting of 16% of N1 patients ($N = 279$), exhibited a late DR rate of 2.7% (95% CI, 0.7–4.7), whereas the high-risk group, comprising 84% of N1 patients ($N = 1,346$), demonstrated a late DR rate of 12.3% (95% CI, 10.3–14.3), resulting in a multivariate HR of 4.34 (95% CI, 2.03–9.28; **Fig. 4B**; Supplementary Table S1).

In HER2$^-$ patients, BCI and BCIN$^+$ demonstrated statistically significant prognostication using the optimized cutoff points ($P = 0.002$ and $P < 0.001$; **Fig. 4C** and **D**). In the N0 HER2$^-$ subset ($N = 1,063$), BCI stratified 37% of patients ($N = 388$) into low-risk with a late DR rate of 3.1% (95% CI, 0.9–5.3) and 63% of patients ($N = 675$) into high-risk with a late DR rate of 9.0% (95% CI, 6.4–11.6), resulting in a multivariate HR of 3.22 (95% CI, 1.50–6.93; **Fig. 4C**; Supplementary Table S1). In the N1 HER2$^-$ subset ($N = 1,394$), BCIN$^+$ stratified 17% of patients ($N = 249$) into a low-risk group with a late DR rate of 2.6% (95% CI, 0.5–4.7) and 83% of patients ($N = 1,145$) into a high-risk group with a late DR rate of 12.3% (95% CI, 10.1–14.5), with a multivariate HR of 4.44 (95% CI, 1.95–10.11; **Fig. 4D**; Supplementary Table S1).

Discussion

In this translational TEAM study, consistent with previous BCI validation studies (9, 12, 13), BCI and BCIN$^+$ were confirmed to be

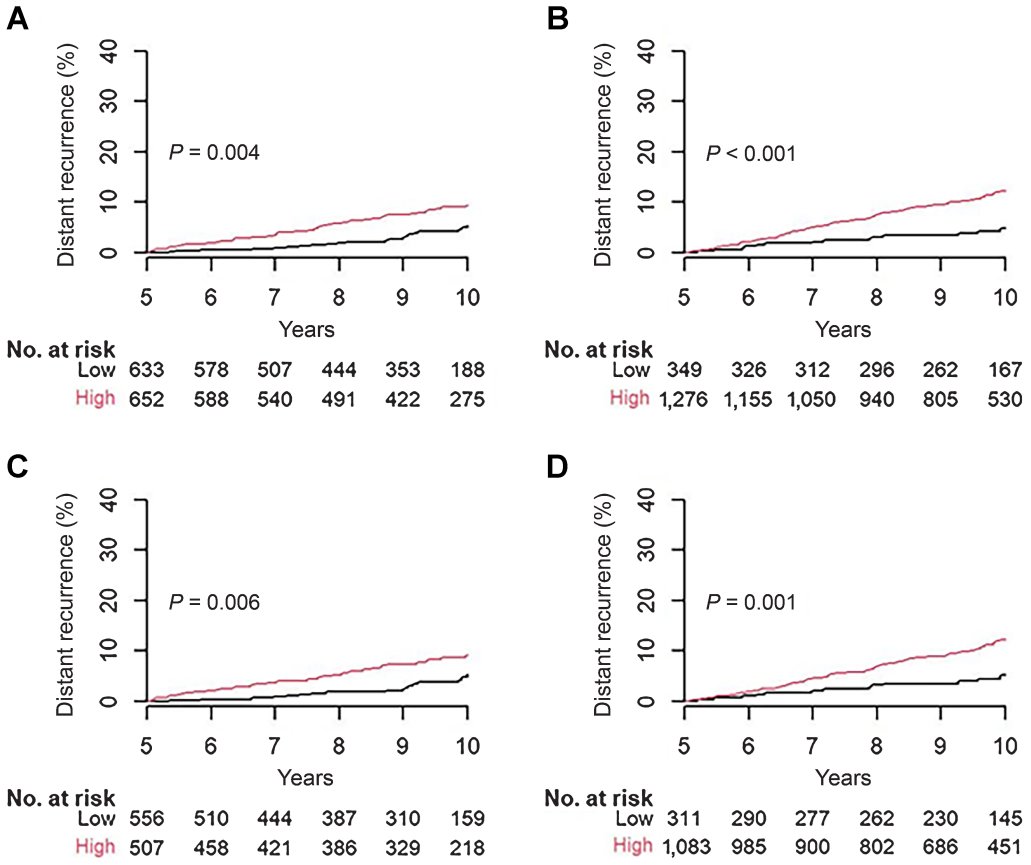

Figure 3.

Prognostic performance of BCI and BCIN$^+$ for late DR in N0 and N1 patients who were DR free at 5 years. **A,** BCI stratification in 1,285 N0 patients. **B,** BCIN$^+$ stratification in 1,625 N1 patients. **C,** BCI stratification in 1,063 N0 HER2$^-$ patients. **D,** BCIN$^+$ stratification in 1,394 N1 HER2$^-$ patients.

significantly prognostic for risk of overall and late DR in postmenopausal women with N0 and N1 HR$^+$ breast cancer, respectively. These results suggest that BCI demonstrates the ability to inform on two important clinical decision points in the management of these patients. At time of diagnosis, 24% of N0 and 77% of N1 patients were classified by BCI and BCIN$^+$ as high-risk, who did not benefit sufficiently from endocrine therapy alone with 10-year DR risks of 23.5% and 24.6%, respectively. These patients might be a group for whom additional therapy could be considered. At the time point of 5 years after diagnosis, 49% of N0 and 21% of N1 patients were classified by BCI and BCIN$^+$ as low-risk with a 10-year late DR risk of 5.4% and 4.8%, respectively, after receiving only 5 years of endocrine therapy. In particular, with the new alternative cutoff points optimized specifically for late DR, the low-risk patients identified by BCI and BCIN$^+$ demonstrated a very low 10-year risk of late DR of 3.8% and 2.7% for N0 and N1 patients, respectively, suggesting 5 years of endocrine therapy might be sufficient for these patients.

Traditionally, clinical and pathologic factors such as tumor size, tumor grade, and extent of nodal involvement have been used to assess the risk of late DR (18, 19). In particular, the Clinical Treatment Score post-5 years (CTS5) has been described as a prognostic tool to estimate the risk of late DR based on age, tumor size, grade, and nodal involvement (20). However, these measures can be limited in their prognostic power. For example, in an EBCTCG meta-analysis, pN1 patients with small tumors (T1) had a risk of late DR of 7%, 14%, and 20% between years 5 to 10, 5 to 15, and 5 to 20, respectively (6). In addition, an analysis of CTS5 in the TEAM and IDEAL trials showed that CTS5 not only overestimated the risk of late DR for high-risk patients, but also did not predict the benefit of EET (21). Thus, identification of patients with a limited risk of late DR can be challenging based on clinicopathologic factors alone.

This study has shown that BCI and BCIN$^+$ remained statistically significant for N0 and N1 patients in multivariate models adjusted for age, tumor size, tumor grade, and treatment, consistently demonstrating that BCI and BCIN$^+$ provide independent prognostic information beyond clinicopathological factors. Two other gene expression-based classifiers have been shown to prognosticate late DR in HR$^+$ breast cancer (22, 23). The PAM50-based ROR score identified a low-risk group with 2.3% and 3.3% risk of 5–10 years late DR for N0 and N1 patients in the combined ABCSG-8/ATAC cohorts, respectively (22). Similarly, the EPclin score was able to identify a low-risk group with 3.1% and 13.0% risk of 5–15 years late DR for N0 and N1 patients in the combined ABCSG-6/8 cohorts, respectively (23). However, neither of them has been demonstrated to be predictive of benefit from EET. On the other hand, although the 70-gene assay did not specifically conduct studies on the late DR risk in patients who remained DR-free at 5 years, it classified 16% of tamoxifen-treated patients from the STO-3 study as an "ultralow-risk" group with a 97% cumulative 20-year breast cancer–specific survival (24). In the same STO-3 study, BCI was also able to derive a minimal risk group, including 27% of tamoxifen-treated

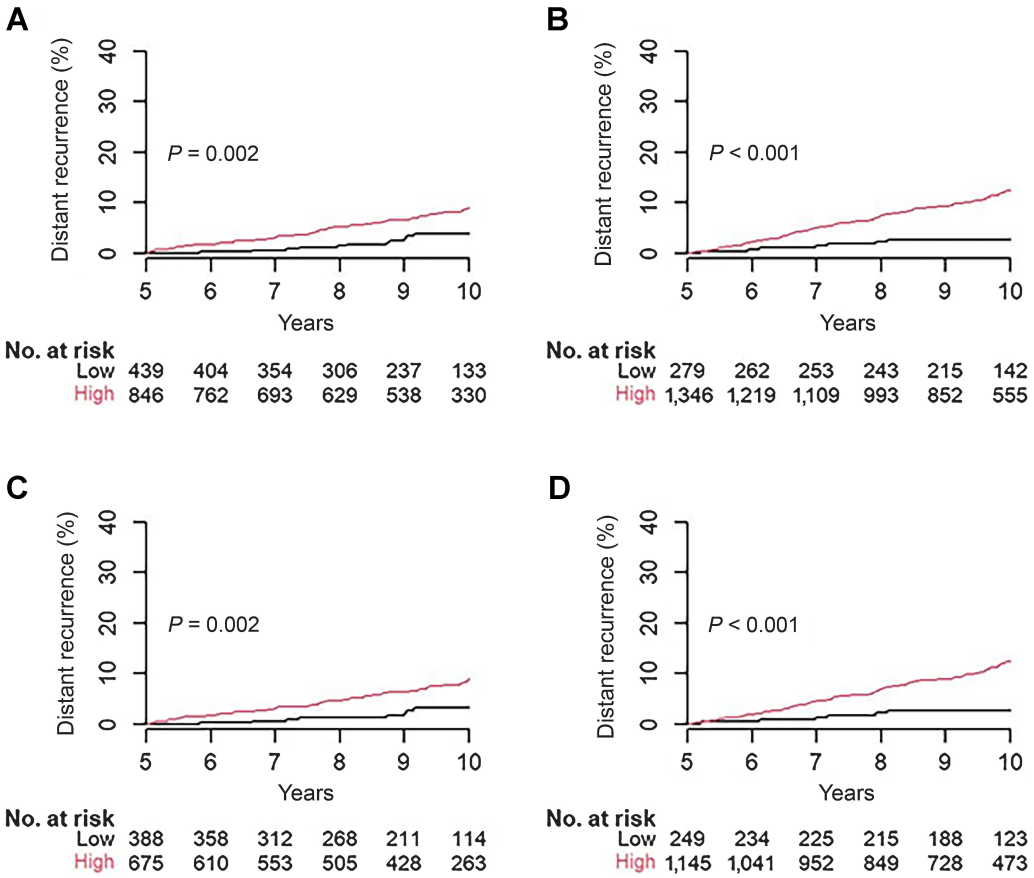

Figure 4.

Prognostic performance for late DR with optimized BCI/BCIN$^+$ cutoff points. **A,** Stratification of risk of late DR in N0 patients ($N = 1,285$) by BCI. **B,** Stratification of risk of late DR in N1 patients ($N = 1,625$) by BCIN$^+$. **C,** Stratification of risk of late DR in N0 HER2$^-$ patients ($N = 1,063$) by BCI. **D,** Stratification of risk of late DR in N1 HER2$^-$ patients ($N = 1,394$) by BCIN$^+$.

patients with a 98% cumulative 20-year breast cancer–specific survival (24). In summary, BCI provides both prognostic and predictive information in the late recurrence and extended endocrine treatment setting and has been recognized by NCCN and ASCO to predict benefit of EET (25, 26).

N1 patients are at significantly greater risk of recurrence (4–6) and have lower rates of both DFS and overall survival when compared with N0 patients (27–30). Consequently, N1 patients are recommended to receive additional treatment than N0 patients, including EET, adjuvant chemotherapy, and ovarian suppression (25, 31). However, previous BCI results in Trans-aTTom indicate that nearly half of all N1 patients did not derive significant benefit from longer duration of tamoxifen treatment (32). Furthermore, even though endocrine therapy is generally better tolerated compared with chemotherapy, adverse side effects are both common and significant, and can include vasomotor symptoms and sexual dysfunction; osteoporosis, skeletal fractures, and musculoskeletal symptoms associated with AIs; and endometrial cancer and venous thrombosis associated with tamoxifen (33–35). Thus, an accurate personalized assessment of risk and benefit for each patient, as offered by BCI, is important for adjuvant therapy decision-making.

More importantly, the BCI (H/I) ratio has been extensively validated as a predictive biomarker for the benefit of EET, including either tamoxifen or AIs (32, 36–38). On the basis of this clinical evidence, BCI has been recognized by national guidelines such as NCCN and ASCO (25, 26). When combining both BCI prognostic and BCI (H/I)-predictive results based on the optimized prognostic cutoff points, 56% of patients were BCI (H/I) predictive of low-likelihood to benefit and thus could be spared from potential toxicities of EET (Supplementary Table S2). Among these patients, those classified as BCI prognostic high-risk could consider other alternative therapeutic approaches to address their residual high risk of late DR. On the other hand for those predicted to be high-likelihood to benefit by BCI (H/I), using the predicted benefit of 58%–62% relative risk reduction estimated from previous BCI predictive studies (32, 36–38), 38% of patients were also BCI prognostic high-risk, with absolute risk of late DR between 9.1% and 12.3%, and might be able to derive an estimated 5%–9% absolute recurrence risk reduction from EET; whereas 6% of patients who were BCI prognostic low-risk might only derive a modest benefit of 2%–3% with EET, therefore, their treatment decision should be made on an individual patient basis. In summary, BCI adds important information to better manage HR$^+$ patients with breast cancer to personalize EET decision-making.

This study has strengths and limitations. The study was a retrospective analysis of a prospective clinical trial representing the largest BCI validation study to date that included both N0 and N1 patients. In addition, the treatment regimen represented contemporary endocrine therapy in the US with 5 years of either an AI or a sequence of

tamoxifen and AI for postmenopausal women. Although the analysis was retrospective, the study was prospectively defined in a Statistical Analysis Plan and BCI testing was conducted blinded to clinical outcome.

In summary, this study has confirmed the independent prognostic ability of BCI for both overall and late DR in HR^+ postmenopausal patients, irrespective of nodal status, who were treated with adjuvant endocrine therapy, including an AI as part of primary adjuvant endocrine therapy. On the basis of these results, BCI provides clinically important information to facilitate the selection of treatments at two important decision points in the management of HR^+ breast cancer: first at time of diagnosis for potential chemotherapy benefit and second at 5 years following diagnosis to predict the benefit from extended endocrine treatment.

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Authors' Contributions

J.M.S. Bartlett: Conceptualization, resources, supervision, investigation, writing–review and editing. **K. Xu:** Formal analysis, writing–review and editing. **J. Wong:** Writing–review and editing. **G. Pond:** Data curation, formal analysis. **Y. Zhang:** Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing–original draft. **M. Spears:** Writing–review and editing. **R. Salunga:** Formal analysis, methodology. **E. Mallon:** Writing–review and editing. **K.J. Taylor:** Writing–review and editing. **A. Hasenburg:** Writing–review and editing. **C. Markopoulos:** Writing–review and editing. **L. Dirix:** Writing–review and editing. **C.J.H. van de Velde:** Writing–review and editing. **D. Rea:** Writing–review and editing. **C.A. Schnabel:** Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing. **K. Treuner:** Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing. **J. Bayani:** Formal analysis, writing–review and editing.

Note

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