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Prognostic performance of Breast Cancer Index in patients with early-stage HR+ HER2+ breast cancer treated with adjuvant trastuzumab: NCCTG N9831 (Alliance)

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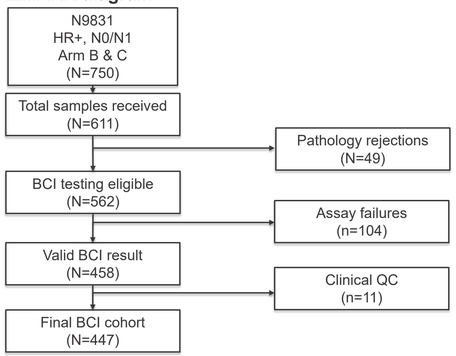
INTRODUCTION

- The Breast Cancer Index (BCI) is clinically validated to stratify patients with hormone receptor-positive (HR+), early-stage breast cancer based on the risk of overall (0-10 years) and late (5-10 years) distant recurrence (DR) with N0/N1 lymph node involvement.[1-4]
- Validation of BCI in patients with HR+ HER2+ breast cancer has been limited, especially in patients treated with adjuvant trastuzumab-based chemotherapy.
- The *HOXB13* and *IL17BR* genes constitute the predictive component of BCI and are known to exhibit an ER-dependent correlation pattern with *HER2*.
- The NCCTG N9831 (Alliance) trial sought to measure the impact of trastuzumab in combination with chemotherapy in N+ HER2+ patients and later included high-risk patients with node-negative (N-) disease.[5]
- We evaluated the prognostic performance of BCI in patients with HR+ HER2+ disease enrolled in the NCCTG N9831 (Alliance) trial treated sequentially or concurrently with the combination of chemotherapy and trastuzumab.

METHODS

- All available tumor specimens from patients with HR+ HER2+ N0/N1 breast cancer in arms B (sequential trastuzumab) and C (concurrent trastuzumab) of the trial were included. BCI testing was performed blinded to clinical outcomes.
- The median follow-up was 12.7 years.
- The primary endpoint was distant recurrence-free interval (DRFI). BCI (N0) and BCIN+ (N1) risk groups were calculated based on pre-specified cutpoints.
- Kaplan-Meier analysis and log-rank testing were used to assess the prognostic significance of BCI/BCIN+ risk groups based on DR. Cox proportional hazard models with and without clinical covariates were used to estimate hazard ratios (HRs), and the associated 95% confidence intervals (CIs).

Figure 1. REMARK diagram



Note: Assay failures resulted from poor RNA quality of previously sectioned specimen (97/104).

RESULTS

Table 1. Clinical characteristics

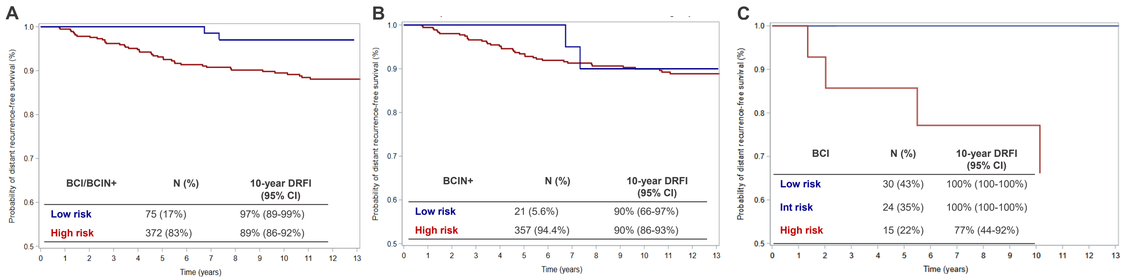
	BCI (N=447)	Non BCI (N=733)	Total (N=1180)	P-value
Treatment Arm, n (%)				0.4605[1]
B	231 (51.7%)	395 (53.9%)	626 (53.1%)	
C	216 (48.3%)	338 (46.1%)	554 (46.9%)	
Age				0.0016[2]
N	447	733	1180	
Mean (SD)	47.8 (10.15)	49.8 (10.13)	49.0 (10.18)	
Median	47.0	50.0	49.0	
Range	22.0-77.0	23.0-79.0	22.0-79.0	
Age Group, n (%)				0.0075[1]
<50	259 (57.9%)	366 (49.9%)	625 (53.0%)	
≥ 50	188 (42.1%)	367 (50.1%)	555 (47.0%)	
Tumor Stage, n (%)				0.0129[1]
1	178 (39.8%)	277 (37.8%)	455 (38.6%)	
2	244 (54.6%)	374 (51.0%)	618 (52.4%)	
3	25 (5.6%)	81 (11.1%)	106 (9.0%)	
4	0 (0.0%)	1 (0.1%)	1 (0.1%)	
Nodal Stage, n (%)				<.0001[1]
0	69 (15.4%)	44 (6.0%)	113 (9.6%)	
1	378 (84.6%)	688 (93.9%)	1066 (90.3%)	
3	0 (0.0%)	1 (0.1%)	1 (0.1%)	
Tumor Grade, n (%)				0.1343[1]
High	280 (62.6%)	430 (60.4%)	710 (61.3%)	
Intermediate	156 (34.9%)	248 (34.8%)	404 (34.9%)	
Low	11 (2.5%)	34 (4.8%)	45 (3.9%)	
Missing	0	21	21	
Breast Surgery Type, n (%)				0.0319[1]
Lumpectomy	194 (43.4%)	272 (37.1%)	466 (39.5%)	
Mastectomy	253 (56.6%)	461 (62.9%)	714 (60.5%)	
ER Status, n (%)				0.1170[1]
Positive	428 (95.7%)	686 (93.6%)	1114 (94.4%)	
Negative	19 (4.3%)	47 (6.4%)	66 (5.6%)	
PR Status, n (%)				0.5483[1]
Positive	328 (73.4%)	522 (71.2%)	850 (72.0%)	
Negative	118 (26.4%)	207 (28.2%)	325 (27.5%)	
Unknown	1 (0.2%)	4 (0.5%)	5 (0.4%)	

[1]Chi-Square p-value; [2]Kruskal-Wallis p-value;

In the BCI translational cohort,

- 58% of patients were younger than 50 years old compared to 50% in the non-BCI cohort
- 40%, 55%, and 5% of patients were T1, T2 and T3 compared to 38%, 51% and 11% in the non-BCI cohort
- 85% of patients had N1 disease, compared to 94% in the non-BCI cohort
- There were significant differences in age, T stage, N stage, surgery type between patients in the BCI cohort and those not in the BCI cohort.

Figure 2. Overall distant recurrence in BCI low vs high risk patients. (A) Overall cohort (N=447), (B) BCIN+ (N+ patients, N=378), (C) BCI (N- patients; N= 69)



- In the overall cohort, BCI/BCIN+ stratified 51 (11%), 24 (5%) and 372 (83%) patients as low, intermediate and high-risk with 10y DRFI rates of 96% (95% CI: 84-99%), 100% (100-100%) and 89% (86-92%), respectively.
- Since the low and intermediate risk groups had few patients and a similar risk of 10y DRFI, they were combined into a single low-risk group.
- For overall 10y DR, BCI/BCIN+ was statistically significant (HR=4.50, 95% CI: 1.09-18.61; p = 0.038) (**Fig 2A**).
- BCI/BCIN+ remained statistically significant in the multivariable analysis, adjusting for age, treatment, and nodal status (HR=7.54, 95% CI: 1.34-42.64; p = 0.022).
- For 378 N1 patients, BCIN+ stratified 21 (6%) and 357 (94%) of patients as low and high-risk with 10y DRFI of 90% (95% CI, 66-97%) and 90% (95% CI, 86-93%), respectively (p = 0.07) (**Fig 2B**).
- Of the 21 patients classified as BCIN+ low-risk, two had BCIN+ scores of 6.75 and 6.73 in close proximity to the cutpoint (6.93) and experienced DR after 5 years, resulting in the same 10y DRFI for both BCIN+ low and high-risk patients. (**Fig 2B**)
- For 69 N0 patients, BCI stratified 54 (78%) and 15 (22%) patients as low and high-risk with 10y DRFI rates of 100% (95% CI, 100-100%) and 77% (95% CI, 44-92%), respectively (p = 0.012) (**Fig 2C**).

CONCLUSIONS

- Breast Cancer Index (BCI) is significantly prognostic for the risk of overall distant recurrence (0-10y) in patients with HR+ HER2+ disease treated with adjuvant trastuzumab-based chemotherapy.
- Optimization of BCI cutpoints may further improve prognostic performance in HR+ HER2+.
- Additional validation in other HR+ HER2+ cohorts treated in the modern setting with anti-HER2-based therapy is warranted, given the small sample size of N0 patients and relatively low DR rate in the late recurrence cohort.
- In summary, these results provide further evidence of BCI's utility to support clinical decision-making for adjuvant endocrine therapies for HR+ HER2+ breast cancer.

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