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Breast Cancer Index (BCI) identifies fewer patients with high risk of late recurrence and high likelihood of benefit from extended endocrine therapy with invasive lobular compared to invasive ductal carcinoma

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INTRODUCTION

- Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) are the first and second most common histologic subtypes of breast cancer[1]. Both IDC and ILC present distinguishing clinicopathologic features that contribute to differences in response to treatment and long-term prognosis.
- Breast Cancer Index (BCI) is a validated gene expression-based assay with two components, the Molecular Grade Index (MGI) and the H/I ratio (*HOXB13/IL17BR*), that evaluate tumor proliferation and estrogen signaling, respectively.
  - Integration of MGI and H/I generates a prognostic BCI score that quantifies the risk of overall (0-10 years) and late (5-10 years) distant recurrence (DR). [4-6]
  - The H/I ratio is the predictive component of BCI and has been shown to predict endocrine response across various treatment regimens.[2-7]
- BCI (H/I) has previously been shown to significantly predict preferential benefit from 5 vs 2.5 years of extended letrozole in the IDEAL (Investigation on the Duration of Extended Letrozole) study designed to directly examine the potential benefit of extended durations of aromatase inhibitor therapy.[8,9]
- The current analysis compared the predictive and prognostic performance of BCI (H/I) in HR+ lobular and ductal tumor types of the BCI Clinical database and the IDEAL study.

METHODS

- The BCI Clinical Database for Correlative Studies is an IRB-approved de-identified database containing >50 clinicopathologic and molecular variables from cases submitted for BCI testing in clinical practice (N=19,126). Molecular variables include BCI Prognostic score, HOXB13/IL17BR ratio (H/I), and Molecular Grade Index (MGI). Clinicopathologic variables were abstracted from pathology reports when available. Chi-squared tests[1] and Kruskal-Wallis tests[2] were used to compare categorical and numeric factors, respectively, between IDC and ILC subgroups.
- Out of the 908 patients from the translational IDEAL cohort, 142 were classified as lobular and 720 as ductal.
- Primary endpoints in this analysis were recurrence-free interval (RFI) for the predictive performance and distant recurrence (DR) for the prognostic performance.
- RNA was extracted from formalin-fixed paraffin-embedded (FFPE) blocks of primary tumors from IDEAL patients and BCI testing was performed by RT-PCR blinded to clinical outcome.
- Kaplan-Meier survival analysis and Cox proportional hazards regression were used to analyze BCI Predictive performance in the lobular and ductal patients from the IDEAL study.

RESULTS

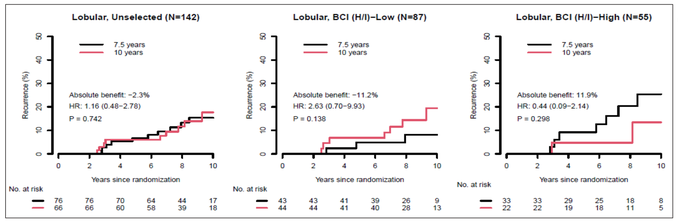
Table 1. The BCI Clinical Database clinicopathological factors

	Ductal(N=3072)	Lobular(N=504)	Total(N=3576)	P-value
Age at Diagnosis				<.001[1]
<=39 years	150 (4.9%)	7 (1.4%)	157 (4.4%)	
40-49 years	675 (22.0%)	91 (18.1%)	766 (21.4%)	
50-59 years	894 (29.1%)	152 (30.2%)	1046 (29.3%)	
60-69 years	991 (32.3%)	170 (33.7%)	1161 (32.5%)	
70+ years	362 (11.8%)	84 (16.7%)	446 (12.5%)	
pT stage				<.001[1]
pT1	1843 (75.8%)	215 (54.2%)	2058 (72.8%)	
pT2	559 (23.0%)	144 (36.3%)	703 (24.9%)	
pT 3	29 (1.2%)	38 (9.6%)	67 (2.4%)	
Unknown	641	107	748	
Grade				<.001[1]
1	882 (29.9%)	153 (35.4%)	1035 (30.6%)	
2	1456 (49.3%)	250 (57.9%)	1706 (50.4%)	
3	615 (20.8%)	29 (6.7%)	644 (19.0%)	
Unknown	119	72	191	
Nodal Status				0.313[1]
N0	1589 (70.9%)	274 (73.5%)	1863 (71.3%)	
N+	652 (29.1%)	99 (26.5%)	751 (28.7%)	
Unknown	831	131	962	
ER				0.179[1]
Negative	22 (1.0%)	1 (0.3%)	23 (0.9%)	
Positive	2098 (99.0%)	345 (99.7%)	2443 (99.1%)	
Unknown	952	158	1110	
PR				0.205[1]
Negative	272 (12.9%)	36 (10.5%)	308 (12.6%)	
Positive	1829 (87.1%)	307 (89.5%)	2136 (87.4%)	
Unknown	971	161	1132	
HER2				<.001[1]
Negative	1807 (87.3%)	338 (97.7%)	2145 (88.8%)	
Positive	262 (12.7%)	8 (2.3%)	270 (11.2%)	
Unknown	1003	158	1161	
Lymphovascular invasion				<.001[1]
No	1488 (76.2%)	274 (89.3%)	1762 (78.0%)	
Suspicious	75 (3.8%)	7 (2.3%)	82 (3.6%)	
Yes	390 (20.0%)	26 (8.5%)	416 (18.4%)	
Unknown	1119	197	1316	

Table 2. Key IDEAL trial clinical characteristics

	Ductal (N =720)	Lobular (N=142)	Lobular BCI (H/I) groups	
			Low (N=87)	High (N =55)
Age at surgery				
<50y	233 (32.4%)	46 (32.4%)	28 (32.2%)	18 (32.7%)
≥50y	487 (67.6%)	96 (67.6%)	59 (67.8%)	37 (67.3%)
pT stage				
pT1	352 (48.9%)	33 (23.2%)	14 (16.1%)	19 (34.5%)
pT2	335 (46.5%)	80 (56.3%)	54 (62.1%)	26 (47.3%)
pT3	21 (2.9%)	26 (18.3%)	17 (19.5%)	9 (16.4%)
pT4	12 (1.7%)	3 (2.1%)	2 (2.3%)	1 (1.8%)
Grade				
1	105 (15.4%)	16 (14.3%)	11 (15.9%)	5 (11.6%)
2	300 (44.1%)	76 (67.9%)	49 (71%)	27 (62.8%)
3	276 (40.5%)	20 (17.9%)	9 (13%)	11 (25.6%)
Nodal status				
N0	186 (25.9%)	38 (26.8%)	27 (31.0%)	11 (20.0%)
N1	406 (56.6%)	67 (47.2%)	41 (47.1%)	26 (47.3%)
N2	101 (14.1%)	28 (19.7%)	13 (14.9%)	15 (27.3%)
N3	24 (3.3%)	9 (6.3%)	6 (6.9%)	3 (5.5%)
ER				
Negative	22 (3.1%)	2 (1.4%)	1 (1.1%)	1 (1.8%)
Positive	697 (96.8%)	140 (98.6%)	86 (98.9%)	54 (98.2%)
Unknown	1	0	0	0
PR				
Negative	133 (19.0%)	25 (17.9%)	10 (11.6%)	15 (27.8%)
Positive	568 (81.0%)	115 (82.1%)	76 (88.4%)	39 (72.2%)
Unknown	19	2	1	1
HER2				
Negative	226 (76.4%)	55 (88.7%)	34 (87.2%)	21 (91.3%)
Positive	70 (23.6%)	7 (11.3%)	5 (12.8%)	2 (8.7%)
Unknown	424	80	48	32
Prior Endocrine therapy				
2–3 yrs TAM–> 3–2 yrs AI	432 (60%)	80 (56.3%)	51 (58.6%)	29 (52.7%)
5 yrs AI	197 (27.4%)	44 (31%)	25 (28.7%)	19 (34.5%)
5 yrs TAM	91 (12.6%)	18 (12.7%)	11 (12.6%)	7 (12.7%)
Prior chemotherapy				
No	225 (31.2%)	49 (34.5%)	25 (28.7%)	24 (43.6%)
Yes	495 (68.8%)	93 (65.5%)	62 (71.3%)	31 (56.4%)

Figure 2. BCI predictive performance in IDEAL study



- The IDEAL BCI study included 142 ILC patients. Similar to the BCI Clinical Database results, ILC was associated with less aggressive disease than IDC (Grade 3: 17.9% vs 40.5%; HER2+: 11.3% vs 23.6%).
- 38.7% and 61.3% of ILC patients were classified as BCI (H/I)-High and -Low, respectively.
- BCI (H/I)-High showed a non-significant absolute benefit of 11.9% (HR=0.44, 95% CI 0.09-2.14; p=0.298) and BCI (H/I)-Low showed no benefit (HR=2.63, 95% CI 0.70-9.93; p=0.138).

Table 3. The BCI Clinical Database Prognostic and Predictive Results

	Ductal (N=3072)	Lobular (N=504)	Total (N=3576)	P-value
BCI Prognostic Risk Category (0-10 years)				<.001[1]
Low Risk	1396 (45.4%)	288 (57.1%)	1684 (47.1%)	
Intermediate Risk	136 (4.4%)	25 (5.0%)	161 (4.5%)	
High Risk	1540 (50.1%)	191 (37.9%)	1731 (48.4%)	
BCI Prognostic Risk Category (5-10 years)				<.001[1]
Low Risk	1396 (45.4%)	288 (57.1%)	1684 (47.1%)	
High Risk	1676 (54.6%)	216 (42.9%)	1892 (52.9%)	
Prognostic and Predictive Results				<.001[1]
Low Risk/ Low Likelihood	1161 (37.8%)	218 (43.3%)	1379 (38.6%)	
Low Risk/ High Likelihood	235 (7.6%)	70 (13.9%)	305 (8.5%)	
High Risk/ Low Likelihood	604 (19.7%)	88 (17.5%)	692 (19.4%)	
High Risk/ High Likelihood	1072 (34.9%)	128 (25.4%)	1200 (33.6%)	
H/I Predictive Category				0.169[1]
Low likelihood	1765 (57.5%)	306 (60.7%)	2071 (57.9%)	
High likelihood	1307 (42.5%)	198 (39.3%)	1505 (42.1%)	

- In the BCI Clinical Database, BCI Prognostic results showed fewer ILC patients at High Risk for late DR than those with IDC (42.9% vs 54.6%, p<0.001).
- BCI H/I Predictive also showed a similar trend (39.3% vs 42.5% High Likelihood) although not statistically significant (p=0.169).
- BCI Prognostic and BCI Predictive results reveal a larger number of ILC patients, who were associated with Low Risk/Low Likelihood of benefit (43% vs 38%) and fewer were called High Risk/High Likelihood of benefit (25% vs 35%) (p<0.001) compared to patients with IDC.

- The BCI clinical database included 3814 patients submitted for BCI testing during years 4-7 post-diagnosis with available histologic subtype data (80.5% IDC; 13.2% ILC; 3.0% mixed; 3.3% other)
- Among those with either ductal (n=3072) or lobular (n=504) cancers (70.9% node-negative and 29.1% node-positive), patients with ILC were older than those with IDC (>70 y: 16.7% vs 11.8%)
- Clinically, ILC was generally less aggressive than IDC (Grade 3: 6.7% vs 20.8%; lymphovascular invasion: 8.5% vs 20.0%; HER2+: 2.3% vs 12.7%; Ki67 Low: 27.9% vs 44.7%; p<0.001 for all comparisons), with the exception that ILC had larger tumors than IDC (T2/T3: 45.9% vs 24.2%)

CONCLUSION

- BCI identified a smaller proportion of patients with ILC at high risk of late DR and high likelihood of EET benefit compared to IDC.
- Preliminary data from the IDEAL study showed that while fewer ILC patients were classified as high likelihood of EET benefit, they still derived similar absolute benefit compared to the overall cohort, while those classified as BCI (H/I)-Low derived no benefit from EET.
- Albeit the small sample size, the results suggests that patients with ILC classified as low likelihood of EET benefit may experience potential harm from longer duration of endocrine treatment.

REFERENCES

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Abstract Number