Distribution of MammaPrint, BluePrint, and Response Predictive Subtypes based on ImPrint and Reprint in Lobular tumors - A FLEX sub study

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Background

- Invasive Lobular Cancer (ILC) has lower rates of pathologic complete response to neoadjuvant chemotherapy compared to invasive ductal cancer (IDC)[1]
- ILC tumors are biologically heterogeneous and genomic signatures might identify ILC patients that benefit from tailored treatment options.
- The gene expression signature MammaPrint (MP) classifies tumors as having a Low Risk or High Risk of distant recurrence. MP High Risk tumors were further stratified into High 1 and High 2. MP combined with BluePrint (BP), a molecular subtyping signature, categorizes tumors as Luminal A (MP Low Risk), Luminal B (MP High Risk), Basal or HER2 type.
- The signature ImPrint identifies patients who may benefit from immune checkpoint inhibitors
- The signature Reprint identifies patients who may benefit from PARP inhibitors with platinum agents
- Response Predictive Subtypes (RPS), i.e., ImPrint+, ImPrint-/RePrint+ or ImPrint-/RePrint- , used in the I-SPY2 trial[2], combine clinical subtype and these genomic signatures to personalize treatment planning and improve outcomes.

Objective

To determine the distribution of the 3 RPS in HR+ HER2- ILC compared with IDC and mixed ILC/IDC in the FLEX

Methods

- This study includes 1039 women with HR+HER2-ILC, 418 with mixed ILC/IDC and 5939 with IDC enrolled in FLEX registry.
- FLEX (NCT03053193) is a prospective, observational trial that includes patients with stage I-III breast cancer who undergo MammaPrint testing (with or without BluePrint) as standard of care, and consent to full transcriptome and clinical data collection.
- A two-tailed proportional z-test was used to assess differences between ILC and ILC/IDC mixed and IDC as well as between RPS.

Results

Table 1. Clinical Characteristics and Treatment Strategy in patients with HR+HER2- ILC, IDC or mixed ILC/IDC features

	ILC	Mixed IDC/ILC	IDC	P-value	P-value ILC vs Mixed	P-value ILC vs IDC
Age, years (mean(min-max))						
	62.8 (30-99)	61.1 (28-89)	59.9 (23-96)		0.005	<0.001
Ki67						
0-10%	339 (47.9)	119 (38.5)	1,363 (32.9)	<0.001	0.007	<0.001
11-20%	197 (27.8)	102 (33.0)	1,108 (26.7)	0.053	0.111	0.572
>20%	172 (24.3)	88 (28.5)	1,675 (40.4)	<0.001	0.184	<0.001
T Stage						
T1	473 (58.3)	208 (68.2)	3,239 (70.5)	<0.001	0.003	<0.001
T2	263 (32.4)	85 (27.9)	1,240 (27.0)	0.007	0.167	0.002
T3	76 (9.4)	12 (3.9)	114 (2.5)	<0.001	0.004	<0.001
N Stage						
N0	652 (82.6)	227 (77.7)	3,668 (82.8)	0.088	0.081	0.952
N1	137 (17.4)	65 (22.3)	762 (17.2)	0.088	0.081	0.952
Grade						
G1	328 (32.8)	127 (31.7)	1,801 (31.7)	0.784	0.739	0.51
G2	621 (62.0)	250 (62.3)	2,938 (51.6)	<0.001	0.963	<0.001
G3	52 (5.2)	24 (6.0)	950 (16.7)	<0.001	0.646	<0.001
Adjuvant versus Neoadjuvant						
Adjuvant	592 (89.2)	301 (91.2)	3,493 (88.7)	0.376	0.369	0.794
Neoadjuvant	72 (10.8)	29 (8.8)	444 (11.3)	0.376	0.369	0.794
Treatment						
CT only	30 (4.5)	13 (3.9)	294 (7.4)	0.002	0.808	0.007
ET only	465 (69.1)	222 (66.7)	2,275 (57.5)	0	0.48	<0.001
ET+CT	151 (22.4)	82 (24.6)	1,119 (28.3)	0.004	0.487	0.002
Targeted therapy	0 (0.0)	0 (0.0)	2 (0.1)	0.775	NA	1
ET+CT +targeted	4 (0.6)	1 (0.3)	38 (1.0)	0.328	0.883	0.48
ET+targeted	1 (0.1)	1 (0.3)	14 (0.4)	0.684	1	0.617
CT+targeted	1 (0.1)	1 (0.3)	6 (0.2)	0.807	1	1
None	7 (1.0)	7 (2.1)	117 (3.0)	0.013	0.286	0.007
Other	14 (2.1)	6 (1.8)	91 (2.3)	0.804	0.954	0.83

Data presented as n (%), unless otherwise specified, CT Chemotherapy; ET Endocrine Therapy

Figure 1. MP distribution within histologic subtype

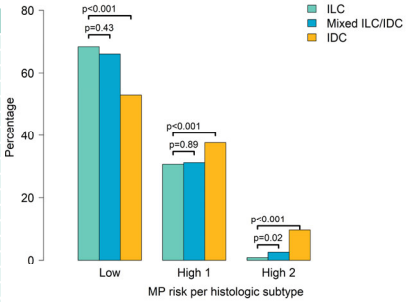

Figure 2. BP distribution within histologic subtype

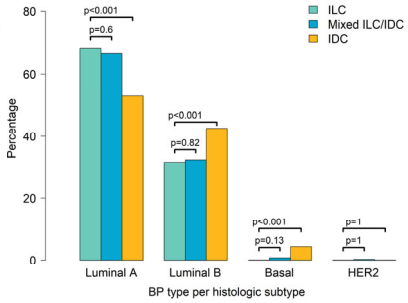

Figure 3. ImPrint+ and RePrint+ distribution within histologic subtype

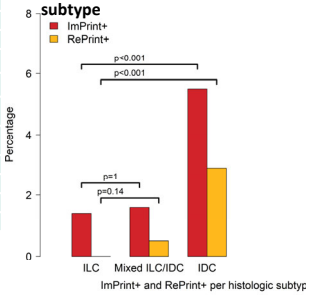

Figure 4. RPS distribution within histologic subtype

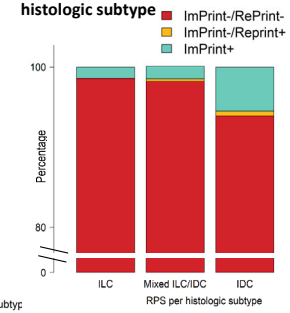

Table 3 frequencies of ImPrint, RePrint and RPS

RPS	ILC	Mixed ILC/IDC	IDC
ImPrint-/RePrint-	970 (98.6)	376 (98.2)	5,322 (93.9)
ImPrint-/RePrint+	0 (0.0)	1 (0.3)	33 (0.6)
ImPrint+	14 (1.4)	6 (1.6)	314 (5.5)

Table 4 p-values frequencies of ImPrint, RePrint and RPS

RPS	P-value	P-value ILC vs Mixed	P-value ILC vs IDC
ImPrint-/RePrint-	<0.001	0.763	<0.001
ImPrint-/RePrint+	0.042	0.624	0.03
ImPrint+	<0.001	1	<0.001

Table 1 and 2

Compared to IDC, patients with ILC are significantly older, have lower Ki67, have higher T stage, have lower grade, and have higher clinical risk, and are less likely to receive chemotherapy

Figure 1 and 2

- ILC patients had a significantly lower percentage of MP High Risk tumors compared to IDC. Among MP High Risk tumors, those with ILC had significantly more MP High 1 than patients with IDC.
- ILC patients had a significant higher percentage of BP Luminal A, and lower percentage of Luminal B, Basal and HER2
- Mixed ILC IDC tumors showed very similar MP and BP distribution compared to ILC

Figure 3 and 4 and Table 3 and 4

- ILC patients are significantly less likely to be ImPrint+ or RePrint+ compared to IDC
- Consequently more ILC patients have RPS ImPrint-/RePrint- compared to IDC, whereas lower frequencies of ImPrint-/RePrint+ and ImPrint+ were found
- These differences were not found for ILC compared to mixed ILC/IDC

Conclusions

- The proportion of MP High Risk is lower in ILC than in IDC, but there is still a substantial proportion of MP High Risk patients in this group.
- Though the percentage of ImPrint+ is lower in ILC, this study revealed a small subset of patients in ILC with potential response to Immunotherapy.
- Mixed ILC tumors are clinically and genomically highly similar to ILC

References: 1. Abel MK ,et al. NPJ Breast Cancer. 2021 2. Wolf D, et al. Cancer Cell, 2022.

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