

High Prevalence of HER2-Low and Increased TIL Levels in ILC Patients with Residual Disease Following Neoadjuvant Therapy Provides a Rational for use of HER2-Antibody-Drug Conjugates or Immunotherapy Approaches

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Background

Invasive lobular carcinoma (ILC) accounts for 5-15% of breast cancer (BC). Most ILCs are hormone receptor positive (HR+), HER-negative (HER2-) and lack associated tumor infiltrating lymphocytes (TILs), a state referred to as “immune desert”. The benefit of chemotherapy in reducing ILC recurrence is unclear, while endocrine therapy (ET) plays a key role for patients with ILC. For patients with locally advanced disease, neoadjuvant ET or chemotherapy may be warranted to downstage ILC and permit breast conservation. However, pathological complete response (pCR) after neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET) in patients with ILC is significantly lower than that observed in no special type (ductal) carcinomas. Although tumor-infiltrating lymphocytes (TILs) predict response to neoadjuvant therapies in HER2-positive BC, their role in HER2-Low ILC is unknown. However, TIL counts > 5% in ILC have been previously correlated with decreased survival. HER2-Low BC are defined by an immunohistochemical score of 1+ or 2+ with a negative HER2 FISH test. The prevalence and implications of HER2-Low in ILC are currently poorly characterized.

Methods

Patients with ILC treated from 2018 to 2022 at our institution were identified from a breast cancer database. HER2-Low status was correlated with clinicopathologic features including TILs and treatment response among patients with HR+/HER2- ILC treated with neoadjuvant therapy (NAT) at our institution. Stromal TILs were quantified as < 5%, 5 to 10%, >10%.

Results

	# of patients	%
Cohort Patients	196	
Female	196	100%
Mean Age	63	
Tumor grade		
Low	35	18%
Intermediate	144	73%
High	15	9%
HR status		
HR Positive	192	98%
HR Negative	4	2%
HER2 status		
HER2 Negative	185	94%
HER2-Low	97	52%
HER2 zero	88	48%
HER2 Positive	11	6%
NAT regimen	37	19%
Chemotherapy	13	35%
Endocrine therapy (NET)	24	65%

Table 1: Clinical and pathological characteristics of 196 patients with ILC diagnosed between 2018-2022. The majority of ILC were HR+/HER2- (94%), intermediate to low grade (91%), and HER2-Low (52%).

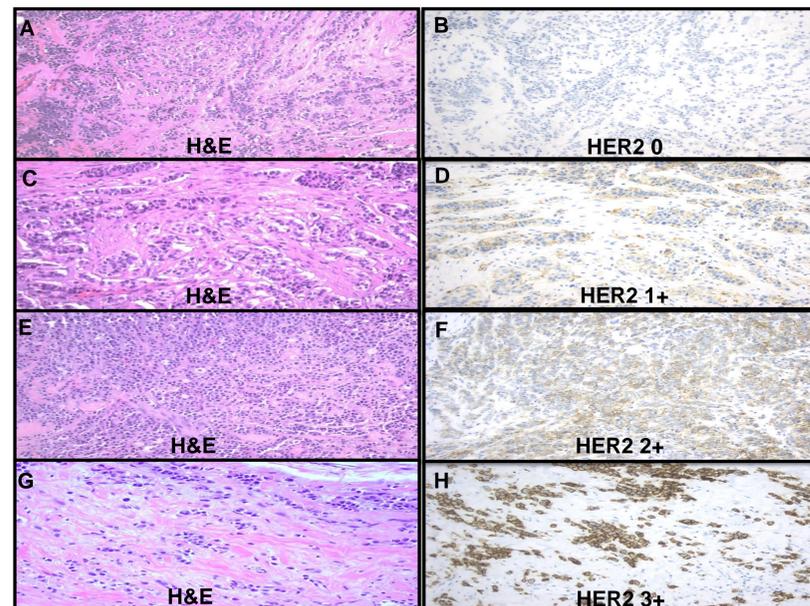


Figure 1: Immunohistochemical staining for HER2.

	HER2 zero	%	HER2 low	%
Total	14	38%	23	62%
Tumor size				
pT1	2	14%	3	13%
pT2/pT3	11	79%	20	87%
Lymph nodes				
pN0	2	14%	7	30%
pN1 or more	12	86%	14	61%
Grade				
G1	2	15%	5	22%
G2/G3	12	85%	18	78%
Multifocal tumor	9	64%	19	82%
TILs (>5%)	5	35%	15	65%
TLS	2	14%	11	48%
Tumor response				
RCB I	0	0%	2	9%
RCB II/III	14	100%	21	91%

Table 2: Among the HR+/HER2- patients, 13 received neoadjuvant chemotherapy and 24 received NET. The majority (81%) were intermediate or high combined histologic grade and 7 (19%) had an intermediate or high proliferative rate. Collectively, most were cT2/cT3 (84%), multifocal (76%) and lymph node positive (70%). 54% had > 5% stromal TILs, 35% had associated tertiary lymphoid structures (TLS), and 24 (65%) had both. No difference in clinicopathologic features was observed between HER2-0 and HER2-Low.

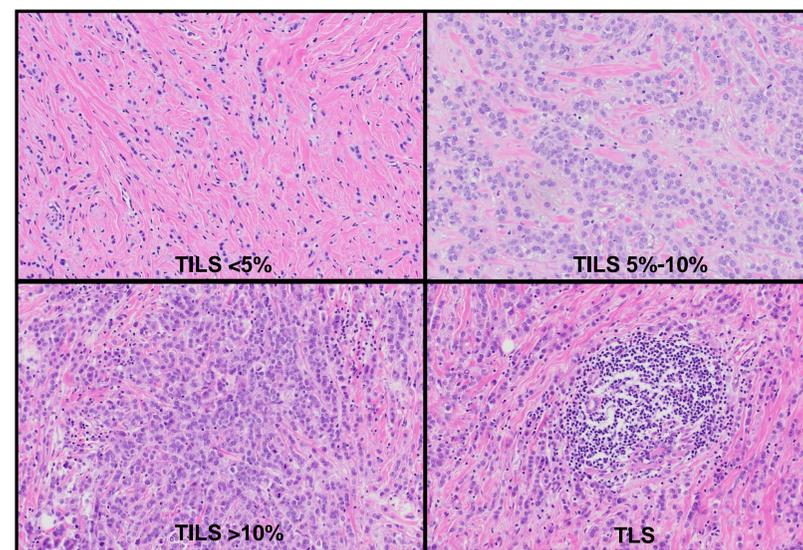


Figure 2: TILs and TLS (tertiary lymphoid structures) in ILC.

Figure 3: HER2-Low tumors were associated with higher TILs and presence of tertiary lymphoid structures (TLS) (65% vs 35% showed > 5% stromal TILs; 78% vs 24% had > 5% TILs and/or TLS, Fisher's test p= 0.0395).

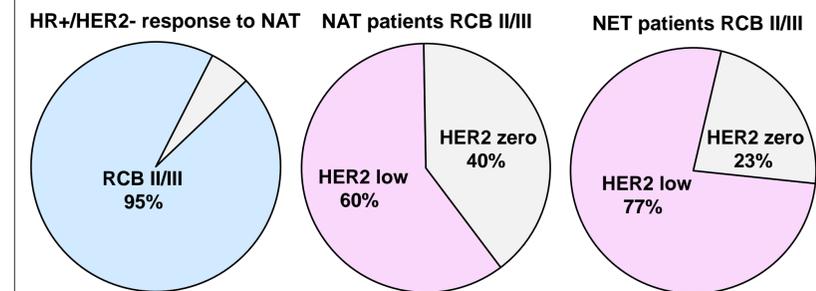
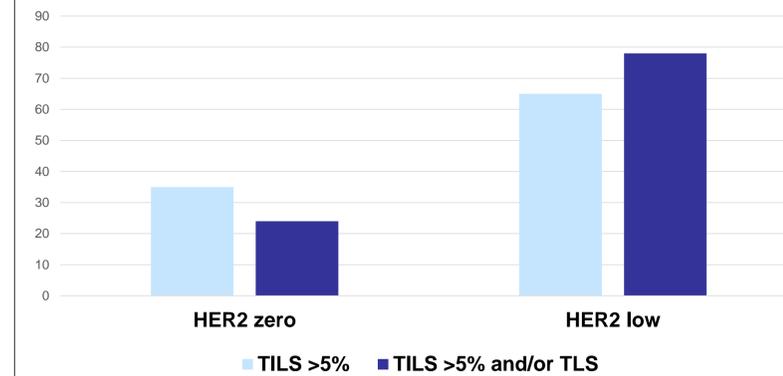


Figure 4: No patients achieved pCR and 95% were RCB II/III. Among patients with RCB II/III, 60% of those who received NAT and 77% of those who received NET were HER2-Low.

Conclusion

HER2-low status is common in ILC patients who receive NAT and is associated with higher TIL levels than HER2-0 tumors. The high prevalence of residual disease after NAT in HER2-low ILC suggests treatment resistance, and alternative treatment approaches are warranted. These could include antibody drug conjugates (ADCs) and/or immunotherapy-based approaches.