

## Collective Wisdom: Lobular Carcinoma of the Breast

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**B**reast cancer researchers have a longstanding fascination for infiltrating lobular carcinomas. Second in frequency only to ductal adenocarcinomas, these tumors are characterized by unique histopathology and (among breast cancers) distinctive clinical biology, both in the primary and metastatic settings. Early hints regarding the underlying sources of this peculiar cancer, in particular the important role of E-cadherin loss, have now been confirmed through comprehensive molecular portraits of the disease. These molecular observations, in turn, go far to explain how lobular carcinomas play out in the clinic, both as regards local control and therapeutic response to systemic therapy. Together, the “collective wisdom” of the laboratory and the clinic paint an interesting portrait of this fascinating disease.

### MOLECULAR BIOLOGY OF LOBULAR CARCINOMAS

Invasive lobular breast carcinoma (ILC) is the second most prominent histologic form of breast cancer and accounts for 10%–15% of invasive breast tumors. On a molecular level, lobular breast cancers are a distinct disease type and should be considered as a unique disease. These molecular underpinnings were recently intensely studied as part of The Cancer Genome Atlas (TCGA) effort on breast cancer, including a recent publication focused on lobular breast cancers.<sup>1</sup> In this publication, 817 breast tumors from the TCGA project, including 490 invasive ductal cancers (IDCs), 127 ILCs, and 88 samples with a mixed IDC-ILC histology, were molecularly profiled on six genomic platforms to develop a comprehensive portrait of the genetic, epigenetic, transcriptional, and proteomic landscape of lobular breast cancers. Comprehensive multiplatform analyses, both supervised and unsupervised, of ILC tumors and across histologic subtypes were performed to identify genomic drivers of ILC oncogenesis.

As expected, low expression of E-cadherin protein, as determined by reverse-phase protein array (RPPA), and

decreased E-cadherin mRNA levels were uniformly observed in ILC cases. In total, 63% of ILC cases had an E-cadherin mutation, and 95% of ILC cases had loss when mutation, DNA copy number, and low gene and/or protein expression were summed together. It is reassuring that this modern study reaffirmed the primacy of E-cadherin loss in lobular breast cancer, and if a biomarker were to be chosen to identify ILC on a molecular level, it would likely be low E-cadherin protein expression and/or DNA mutation of CDH1. Lobular carcinoma's unique histopathologic features and its metastatic patterns undoubtedly have their origins in their impoverished E-cadherin status.

Beyond previously reported CDH1 and PIK3CA mutations (which occur at a 48% frequency in ILC), the TCGA study identified a number of novel ILC-enriched recurrent mutations targeting FOXA1, PTEN, RUNX1, and TBX3. FOXA1 function is particularly intriguing, as it works with the estrogen receptor (ER) to drive the transcriptional output of ER. Interestingly, FOXA1 also plays a similar role in prostate cancer, but in these cancers its cofactor is the androgen receptor.<sup>2</sup> In ILC, we find an increased incidence (9% in ILC vs. 2% in IDC) of FOXA1 mutations, whereas in IDC, we find that GATA3 mutations are considerably enriched in IDC luminal tumors (19% IDC vs. 5% ILC). Within ILC tumors, FOXA1 mutations were found to cluster into a specific region of the forkhead (FK) domain. A broader analysis of FOXA1 mutations in breast and prostate cancer, in which it is also recurrently mutated, confirms two specific hotspots in the FK domain and the C-terminal transactivation domain. Interestingly, these mutational classes were associated with higher FOXA1 messenger RNA and protein expression, and with unique transcriptional changes suggesting different functional effects.<sup>3</sup> More work into why FOXA1 is mutated in ILC, but GATA3 is mutated in IDC, is needed and could possibly reveal some important underlying biology.

Another important finding concerning ILC was the increased incidence of phosphatase and tensin homologue (PTEN)-inactivating events. When including both mutations

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Disclosures of potential conflicts of interest provided by the authors are available with the online article at [asco.org/edbook](http://asco.org/edbook).

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and DNA copy number changes, ILC-luminal A showed a 13% PTEN altered phenotype compared with 3% in IDC-luminal A tumors. This increased mutation frequency of PTEN loss in ILC correspond with decreased PTEN protein expression and was largely mutually exclusive with PIK3CA mutations. Analyses of RPPA protein and phosphor-protein expression data demonstrated increased phosphoinositide-3 kinase/Akt signaling as evident by increased levels of phosphorylated Akt (pS473 and pT308) and downstream Akt substrates including p-p27 and p-p70S6 kinase in ILC tumors; these findings may represent a potential therapeutic opportunity for patients with ILC.

In terms of gene-expression patterns, ILC was found to be of the luminal A subtype in 83% of the cases. Within this ILC-luminal A subset, additional expression subtypes were also identified. These included a subset enriched for stromal and extracellular matrix features, often referred to as the “reactive subtype.”<sup>4</sup> Another ILC expression subtype was enriched for immune cell features/infiltrates, whereas the third group showed a more proliferative expression signature and a concomitant worse patient outcome. Finally, a multiplatform analysis of the mixed histology tumors showed that approximately 80% of these samples could clearly be molecularly classified as either ILC or IDC, with only a few showing a possibly hybrid phenotype. This could have important implications for treatment of patients with mixed ILC-IDC histology, as it suggests they are not a unique group, but instead that their molecular features could be used to classify them as either ILC or IDC.

## SURGICAL ASPECTS OF LOBULAR CARCINOMA

ILC is a distinct subtype of breast cancer that is deserving of particular attention by surgeons. ILCs tend to be insidious as a result of their lack of E-cadherin, causing noncohesive neoplastic cells that permeate through tissue in a single-file pattern. Given its biology, a few areas are of particular concern for surgeons.

### Preoperative Imaging

It is clear that the extent of ILCs tend to be underestimated by conventional imaging (Table 1). Some have suggested that MRI may be useful in this context<sup>5</sup>; however, a recent meta-analysis found that MRI did not significantly reduce positive margin rates in patients with ILC undergoing breast conservation.<sup>6</sup> The concept that MRI could also find occult contralateral disease has also been raised; however, ILCs are no more likely to have a synchronous contralateral cancer than are IDCs.<sup>7</sup> MRI is therefore not routinely recommended in the presurgical workup of patients with ILCs.<sup>8</sup>

### Breast-Conserving Surgery Versus Mastectomy

Regardless of whether neoadjuvant chemotherapy is used or not, ILCs are more often associated with positive margins after breast-conserving surgery.<sup>9–11</sup> Patients with this histologic subtype are more likely to require re-excision, and potentially mastectomy, for margin clearance.<sup>12</sup> Some have suggested that invasive lobular cancers treated with breast

**TABLE 1. Imaging Concordance With Pathologic Tumor Size (Correlation Coefficient)**

Study	MRI	Mammography	Ultrasound	Clinical Exam
Boetes et al <sup>25</sup>	0.81	0.34	0.24	
Francis et al <sup>26</sup>	0.87	0.79	0.56	0.89
Kepple et al <sup>27</sup>	0.88		0.71	
Kneeshaw et al <sup>28</sup>	0.86			0.47
Munot et al <sup>29</sup>	0.97	0.66	0.67	

conservation are more likely to result in local recurrences<sup>13</sup>; however, this has not been borne out in other studies,<sup>9,10,14</sup> and long-term survival rates are no different between breast conservation and mastectomy.<sup>15</sup> Hence, both are considered appropriate in terms of surgical management for this disease. Of note, invasive lobular histology falls into the American Society for Radiation Oncology’s “cautionary” subgroup for the use of accelerated partial breast irradiation,<sup>16</sup> given concerns regarding higher ipsilateral breast tumor recurrences in this population.

### Lymph Node Evaluation

Besides tumor extirpation from the breast, the other key task of the breast surgeon is lymph node evaluation. Although it is clear that sentinel node biopsy is feasible and accurate in patients with ILC, the ability to find micrometastatic deposits particularly on intraoperative evaluation with hematoxylin and eosin staining alone may be challenging given the discohesive nature of the neoplastic cells. Some pathologists have not found this to be problematic.<sup>17</sup> Others, however, may recommend deferral of final diagnosis to permanent sections, at which time immunohistochemistry can be used to draw attention to deposits that otherwise could be missed.<sup>18</sup>

## SYSTEMIC THERAPY FOR LOBULAR CARCINOMA: CHEMOTHERAPY

### Response to Neoadjuvant Therapy

Increasingly, neoadjuvant chemotherapy is part of the multidisciplinary approach to breast cancer, as more novel therapeutics are being evaluated in this setting. However, physicians and patients should be aware that response rates to neoadjuvant chemotherapy are lower for ILC than for its ductal counterpart, as illustrated by the lower rates of pathologic complete response and breast conservation (Table 2).

Why is neoadjuvant chemotherapy relatively ineffective for lobular carcinomas? Is it something intrinsic to the biology of lobular carcinomas per se? Mathieu et al<sup>19</sup> have argued that this relative futility is predictable, in that histologic and biologic factors predicting a poor response to chemotherapy (low histologic grade, high ER content and bcl-2 expression, and low proliferative rates as measured by Ki67 and negative p53 staining) are all more frequent in lobular rather than ductal carcinomas. These, in turn, reflect the luminal A nature of most lobular carcinomas, discussed above.

There is a much smaller body of data evaluating neoadjuvant hormonal therapy for lobular carcinoma. Dixon et al<sup>20</sup>

**TABLE 2. Response to Neoadjuvant Chemotherapy**

Study	No. Patients	pCR (%)	p Value	BCS (%)	p Value
Truin et al <sup>30</sup>	IDC: 3,622	20.2	< .0001	39.4	< .0001
	ILC: 466	4.9		24.4	
Loibl et al <sup>31</sup>	Non-ILC: 7,969	17.4	< .001	71.1	< .0001
	ILC: 1,051	6.2		59.1	
Lips et al <sup>32</sup>	IDC: 601	25	.01	46	.037
	ILC: 75	11		33	
Wenzel et al <sup>33</sup>	IDC: 124	20	.009	79	.001
	ILC: 37	3		51	
Tubiana-Hulin et al <sup>34</sup>	IDC: 742	9	.002	48	.0004
	ILC: 118	1		30	
Cocquyt et al <sup>35</sup>	IDC: 101	15	.0066	50	NS
	ILC: 26	0		38	

Abbreviations: pCR, pathologic complete response; BCS, breast-conserving surgery; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NS, not significant.

evaluated the responsiveness of lobular carcinomas to neoadjuvant letrozole in 61 patients treated for 3 months. Mean tumor volume reduction was 66%, with a high rate of breast conservation (81%). Although we lack any head-to-head comparisons of neoadjuvant endocrine therapy with neoadjuvant chemotherapy (and may never see such a comparison), a primary endocrine approach does not seem unreasonable.

## RESPONSE TO HORMONAL THERAPY

If lobular carcinoma is relatively resistant to standard chemotherapeutic agents, and if this is largely as a result of predictable biology (i.e., higher ER and lower proliferative rates), then what about adjuvant hormonal therapy? Recent data suggest that not all hormonal therapies are equal where lobular cancer is concerned. In particular, tamoxifen appears to be considerably less effective than aromatase inhibition for lobular cancers.

Metzger Filho et al<sup>21</sup> compared the relative efficacies of tamoxifen and letrozole for lobular and ductal carcinomas in the BIG 1-98 trial. This trial was among the first randomized controlled trials of aromatase inhibitor therapy in the adjuvant setting and now has relatively long follow-up (median 8.1 years). Comparing patients by histologic subtype, patients with ILC were far more likely to benefit from letrozole than tamoxifen, regardless of whether patients were luminal A or luminal B like. The 8-year disease-free survival estimate was 66% for tamoxifen compared with 82% for letrozole in the ILC subset (hazard ratio [HR] 0.48) and was 75% for tamoxifen and 82% for letrozole in the IDC subset (HR 0.80). The test for interaction was significantly positive ( $p = .006$ ). These seem, on the face of it, to represent a clinically significant difference and are paralleled by overall survival differences (74% for tamoxifen compared with 89% for letrozole in the ILC subset [HR 0.40]; 84% for tamoxifen and 88% for letrozole in the IDC subset [HR 0.73]).

In contrast, van de Water et al<sup>22</sup> have examined the adjuvant TEAM (Tamoxifen and Exemestane Adjuvant Multinational) trial. This analysis differed considerably in that the

TEAM trial design in that “early switch” (2 to 3 years of tamoxifen followed by 2 to 3 years with an aromatase inhibitor) and “up-front” (5 years with an aromatase inhibitor) strategies were compared for relative benefit in lobular and invasive ductal cancers. The TEAM analysis suggested that endocrine therapy efficacy was similar for IDC and ILC once one had adjusted for ER content. The “early switch” strategy arm might well muzzle the treatment interactions seen in the BIG 1-98 trial.

If, as suggested by the BIG 1-98 analysis, lobular carcinomas are relatively less sensitive to tamoxifen than ductal carcinomas, what molecular changes might underlie these findings? Sikora et al<sup>23</sup> have recently evaluated the response of lobular carcinoma cell lines in vitro. Their work suggests that the ER drives a unique program of gene expression in lobular cancers when compared with ductal carcinomas. Indeed, tamoxifen appears to drive the growth of these cell lines, rather than inhibiting them, although this limited cell line work cannot be safely extrapolated to the clinic.

In contrast to the preclinical results seen with tamoxifen, Arthur et al<sup>24</sup> have recently demonstrated in the neoadjuvant hormonal therapy setting that changes in gene expression in response to letrozole were highly similar between responding ILC and IDC tumors.

## CONCLUSION

Infiltrating lobular carcinoma of the breast represents a biologically distinct subset of breast cancer, a biology defined by specific genetic aberrations in E-cadherin, the high prevalence of ER-positive disease, the relatively low frequency of HER2-positive disease, and specific mutational events revealed by deep sequencing of ILC genomes. This distinctive biology, in turn, affects the presentation, treatment, and—potentially—the prognosis of ILC. Biology affects surgery and preoperative chemotherapy results, and, as recent data suggest, it also affects adjuvant hormonal therapy benefits. Ultimately, an improved understanding of ILC biology should also lead to novel targeted approaches to the conquest of the disease.

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