

Lobular Breast Cancer

Different Disease, Different Algorithms?



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KEYWORDS

- Invasive lobular carcinoma • E-cadherin • The Cancer Genome Analysis
- Breast conservation • Mastectomy • Chemotherapy • Aromatase inhibitors

KEY POINTS

- Invasive lobular breast cancer is a biologically unique entity, distinct from invasive ductal cancer.
- The characteristic molecular features of invasive lobular carcinoma (ILC) include its largely ER-positive and low-grade nature, and loss of E-cadherin protein expression.
- Tumor biology is of key importance in designing treatment approaches.
- Harnessing the growing knowledge of the molecular features inherent to lobular cancer holds promise for the next generation of tailored therapies.

INTRODUCTION

Invasive lobular carcinoma (ILC) is the second most common histologic form of breast cancer, comprising 10% to 15% of invasive tumors.¹ ILC is now recognized as a biologically distinct disease from the more common invasive ductal carcinoma (IDC), with a unique molecular pathogenesis and consequential implications on diagnosis and treatment. An understanding of these differences is of utmost importance to tailor management strategies. Ongoing investigations of the genomic basis of breast cancer are paving the road for novel approaches to treatment of ILC.

EPIDEMIOLOGY

The mean age of diagnosis of ILC is 57 years.² Risk factors include age at menarche, age at first birth, and use of hormone therapy, emphasizing the role of estrogen

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exposure in pathogenesis. This relationship is also observed for most IDCs, but is more pronounced for ILC.³ The incidence of ILC in the Western world has generally mirrored trends in use of hormone replacement therapy, with a steep increase between 1975 and 2000 and a decline between 2000 and 2004, but now increasing since 2005 with an unclear cause.⁴

Hereditary ILC is uncommon, but may be seen as a secondary tumor in families with hereditary diffuse gastric cancer syndrome, caused by a germline mutation in the tumor suppressor gene, CDH1. ILC otherwise accounts for a minority of cancers associated with known susceptibility genes, comprising less than 10% of cancers in patients with BRCA2 mutations, and less than 5% of cancers in patients with BRCA1 or TP53 mutations.⁵

HISTOLOGY

Classic ILC is histologically characterized by discohesive cells infiltrating the breast stroma in a single-file pattern² with a limited host inflammatory response (Fig. 1A).⁶ Observed loss of membranous E-cadherin staining by immunohistochemistry may be a useful adjunct to confirm the diagnosis (see Fig. 1B). Several nonclassic forms of ILC have also been described, distinguished by morphology (alveolar, solid, dispersed, trabecular, and mixed) and cytology (apocrine, pleomorphic, signet ring, histiocytoid, and tubulolobular).⁵ These variant forms show the typical cytologic

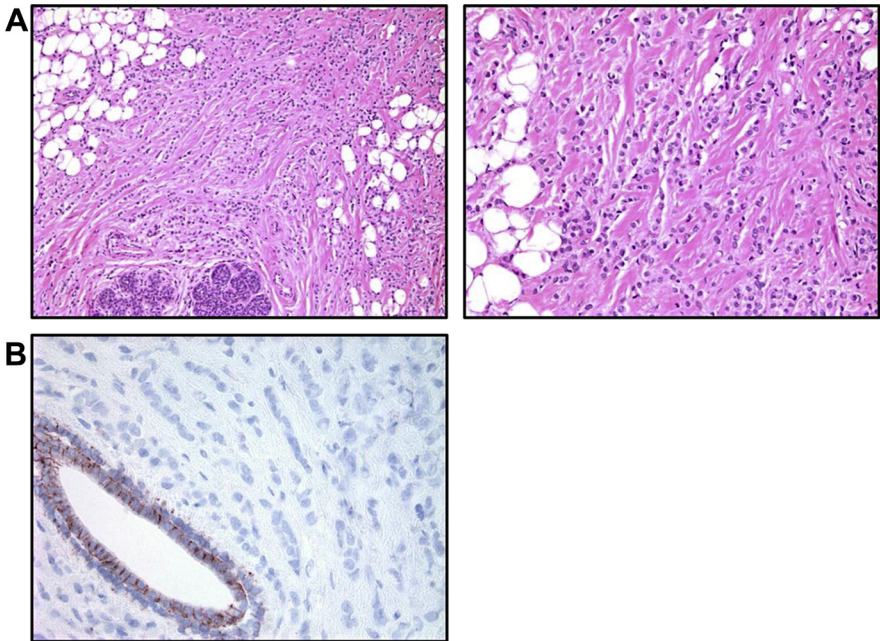


Fig. 1. (A) Hematoxylin and eosin staining, 10 \times and 20 \times magnifications, depicting the classic "single-file" morphology of ILC. (B) Immunohistochemistry of paraffin-embedded breast cancer tissue showing characteristic loss of membranous E-cadherin in lobular carcinoma. (Courtesy of Dr Stuart J. Schnitt, MD, Chief of Breast Oncologic Pathology, Dana-Farber/Brigham and Women's Cancer Center; Associate Director, Dana-Farber Cancer Institute/Brigham and Women's Hospital Breast Oncology Program; Professor of Pathology, Harvard Medical School.)

features of classic ILC, but display differing growth patterns. In the alveolar variant, cells are organized in globular arrangements, whereas the solid variant displays sheets of uniform cells with high frequency of mitoses. Conversely, the low-grade tubulolobular variant displays linear cells with tubular glands. The most aggressive pleomorphic variant of ILC exhibits greater atypia, nuclear pleomorphism, and frequent mitoses, with variable degrees of apocrine differentiation.²

Associated lobular neoplasia (LN), which refers to the noninvasive proliferative lobular lesions inclusive of atypical lobular hyperplasia and lobular carcinoma in situ (LCIS), is observed in more than 50% of classic ILCs.² The reported incidence of pure LN ranges from 0.5% to 4%,² and typically presents in younger women than does ILC. Histologically, LN displays pagetoid terminal duct involvement in more than 70% of cases. There exist 2 types of LN, type A (classic cellular features) and type B (larger, atypical cells with prominent nucleoli), with a small subgroup displaying pleomorphic cells with apocrine features and more aggressive biology, termed pleomorphic LCIS.²

LN is considered a risk factor for the subsequent development of invasive cancer of either the ductal or the lobular phenotype. The increased risk ranges from 1% to 2% per year and is conferred equally to both breasts.⁷ Recent work demonstrating shared molecular alterations between LCIS and synchronous ILCs in a significant proportion of cases has also reopened the notion that some LCIS lesions may behave as nonobligate precursors of ILC.²

MOLECULAR BIOLOGY

More than 90% of ILCs are estrogen receptor (ER) positive and they are largely classified as luminal A at the level of the transcriptome, although this proportion is lower in more aggressive variants,⁵ with highest rates of ER positivity observed in the classic form and alveolar variants, and lowest rates of ER positivity observed in pleomorphic ILCs (10%).² HER2 overexpression is rare, seen in only 3% to 5% of classic ILCs, but present in up to 80% of the more aggressive pleomorphic subgroup.^{2,4}

Loss of E-cadherin expression is the most consistently reported hallmark feature of ILC (see **Fig. 1B**), demonstrated in up to 90% of cases, and thought to play a crucial role in pathogenesis.² E-cadherin is a calcium-dependent transmembrane protein involved in adherens-type junctions between epithelial cells, the loss of which predisposes to neoplastic proliferation. E-cadherin dysregulation results from somatic mutations in the CDH1 gene on chromosome 16q22.1, reported in 30% to 80% of ILCs, as well as by loss of heterozygosity at the CDH1 locus.^{2,8} However, E-cadherin positivity does not, by itself, exclude a lobular neoplasm, and not all ILCs harbor CDH1 mutations. Other markers frequently expressed in ILC include GCDFP-15, seen in up to 90% of pleomorphic and signet ring subtypes,² cyclin D1 (80%), cathepsin D (86%), Bcl-2 (89%), and Ck 34BetaE12.²

In the Cancer Genome Analysis study, mutations in several key genes were found more frequently in ILC as compared with IDC, including CDH1 (63% in ILC vs 2% in IDC), P1K3CA (48% vs 33%), FOXA1 (7% vs 2%), RUNX1 (10% vs 3%), and TBX3 (9% vs 2%), respectively.⁴ Conversely, GATA3 mutations were enriched in IDC (5% in ILC vs 13% in IDC). Importantly, when the analysis was limited to luminal A cancers, several alterations remained significantly more common among ILCs versus IDCs, as summarized in **Table 1**.⁴ A later analysis of 417 ILCs by Desmedt and colleagues⁹ reported that more than half of the cases contained a mutation in PIK3CA, PTEN, or AKT1, and there was also an increased frequency of HER2, HER3, FOXA1, and ESR1 alterations.

Gene	Q Value ^a
CDH1	1.4E-30
FOX1A	0.065
PIK3CA	Not stated
PTEN	0.035
RUNX1	Not stated
TBX3	0.05

^a Depicted "q value" represents a *P* value that is adjusted for the proportion of expected false positives.

Data from Ciriello G, Gatza ML, Beck AH, et al. Comprehensive molecular portraits of invasive lobular breast cancer. *Cell* 2015;163:506–19.

CLINICAL PRESENTATION AND DIAGNOSIS

ILC may pose a diagnostic challenge because of its inherently insidious and infiltrative growth pattern. Although some patients present with an ill-defined palpable mass, others may display only vague skin thickening or diffuse nodularity, or disease may be clinically occult.² In keeping with their indolent phenotype, ILCs are not frequently associated with calcifications and have an innately discohesive growth pattern. As such, ILCs frequently display a scattered radiological appearance. Compared with IDCs, ILCs are more often mammographically occult, with sensitivity as low as 57% to 76%² and false negative rates as high as 25%.¹⁰ These tumors also tend to be poorly circumscribed, which may limit the accuracy of both breast and axillary ultrasound. The sensitivity of ultrasound-guided fine-needle aspiration of lymph nodes in ILC is low, reported to be less than 40% in cases of pure ILC.^{11,12} **Table 2** summarizes reported correlations between pathologic and radiologic tumor size as visualized by mammogram, ultrasound, and MRI.^{13–17}

The utility of preoperative MRI in the workup and staging of lobular cancers remains controversial, with mixed data on resultant rates of mastectomy or reexcision after breast conservation. A recent large meta-analysis found that preoperative MRI increases rates of mastectomy for all cancer histologies, suggesting an unfavorable overestimation of the extent of disease.¹⁸ On subset analysis of 766 ILC patients, although there was some reduction in the rate of reexcision after breast-conserving

Study	Mammogram	Ultrasound	MRI
Boetes et al, ¹⁶ 2004 (n = 34)	0.34	0.24	0.81
Francis et al, ¹³ 2001 (n = 22)	0.79	0.56	0.87
Kepple et al, ¹⁷ 2005 (n = 29)	—	0.71	0.88
Kneeshaw et al, ¹⁵ 2003 (n = 21)	—	—	0.86
Munot et al, ¹⁴ 2002 (n = 20)	0.66	0.67	0.97

All values are reported as correlation coefficient.

Data from Mamtani A, King TA. Lobular breast cancer. *Complex General Surgical Oncology*, in press.

surgery (BCS) (odds ratio [OR] 0.56, $P = .031$), this observation was likely attributable to an increased likelihood of upfront mastectomy (adjusted OR 1.64, $P = .034$).¹⁸

American Joint Committee on Cancer TNM guidelines are used to stage all breast cancers, regardless of histology. The assessment of tumor size (T) category may be more complicated in ILCs, which often present in a multifocal or multicentric fashion.² In such cases, the T category is based on the size of the single largest mass, not an additive sum of multiple tumors. Many studies, including a large Surveillance, Epidemiology, and End Results (SEER) registry analysis of 263,408 patients with IDC or ILC, report that patients with ILC are more likely to present with tumors measuring greater than 2 cm at the time of diagnosis, as compared with IDC.¹⁹ It is also well documented that the invasive lobular histology is an independent predictor for the likelihood of nodal micrometastases,²⁰⁻²² thought to be another demonstration of the underlying discohesive biology. Finally, although metastatic disease most commonly presents in the bones, lungs, and the central nervous system, ILCs display a fascinating predilection for gastrointestinal, peritoneal, and ovarian metastases.² The overwhelmingly ER-positive nature of ILCs also results in more frequent development of late metastases.

MANAGEMENT

The contemporary, multidisciplinary approach to the treatment of breast cancer includes individually tailored surgery, radiotherapy (RT), and systemic therapy. Although the overarching concepts of treatment are common among all breast cancer types, the largely ER-positive phenotype of ILC is central to the principles of management and the observed responses.

Surgery and RT provide locoregional control. The course of surgery, regardless of histology, is determined by the TNM stage at presentation. An operable cancer may be approached with upfront surgery if amenable, or undergo surgery after preoperative neoadjuvant therapy, if appropriate.

UPFRONT SURGERY

Patients with early-stage breast cancer are generally candidates for upfront surgery, either with BCT or mastectomy. BCT involves lumpectomy with negative margins followed by RT.

Factors that determine eligibility for BCT are shared between ILC and IDC. To be a candidate for BCT, patients must have tumors that can be removed with negative margins and acceptable cosmesis and must be able to receive RT thereafter. Accordingly, contraindications to BCT include cancers that are too large or diffuse for an acceptable oncologic and cosmetic result. In addition, any current or prior circumstances that preclude irradiation, such as a history of prior chest wall radiation, significant connective tissue or collagen vascular disease, and first trimester of pregnancy, are also contraindications. Determination of BCT candidacy can generally be made with greater than 95% accuracy by clinical examination and mammography alone.²³ Mastectomy is indicated for patients with contraindications to BCT, and those who prefer mastectomy.

Several randomized trials with long-term follow-up have demonstrated similar rates of locoregional recurrence (LRR) and survival with BCT and mastectomy for early-stage cancers.^{24,25} Long-term survival is also shown to be equivalent with the use of BCT or mastectomy among a population of ILCs alone, but is dependent upon obtaining negative margins.²⁶ This is particularly true in the contemporary era of

systemic therapies increasingly tailored to tumor biology, known to further reduce rates of LRR.^{25,27,28}

The innately infiltrative growth pattern of ILC and difficult preoperative assessment of extent of disease have historically led surgeons to question the feasibility of BCT in ILC.²⁹ Mixed results have been reported; some studies demonstrate no significant increase in reexcisions to achieve negative margins,³⁰ whereas others have found an association with positive lumpectomy margins^{29,31} and a higher likelihood of reoperation to obtain negative margins in ILC.^{31,32} Despite these varying findings, when negative margins are obtained, patients with ILC are no more likely to experience LRR after BCT (**Table 3**), with contemporary rates ranging from 3.1% to 5.7%.^{10,33–35} As defined by the recent consensus guidelines, “negative” margins are defined as no ink on tumor and include a subset analysis showing no benefit to a wider margin for ILC.³⁶ Based on these findings, the consensus panel concluded that these general recommendations should not be altered for lobular histology.³⁶

The surgical approach to the axilla is similarly shared between ILC and IDC, although data on the patterns of nodal involvement in ILC vary, with some studies reporting no difference in the likelihood of axillary involvement when compared with IDC and others reporting an increased likelihood of nodal involvement.^{19,37} Lobular histology has however been shown to independently predict for micrometastatic disease,^{20–22} consistent with a discohesive biology.

Sentinel node biopsy (SLNB) is the standard method of axillary assessment for clinically node-negative patients and is equally feasible in both ILC and IDC.³⁸ Indications for axillary dissection (ALND) in clinically node-negative patients have been in evolution over the past decade, a decision related both to the nodal burden and to the breast surgery being performed.

Clinically node-negative (cN0) patients with a negative SLNB do not require ALND. Among women undergoing BCT, the ACOSOG Z0011 trial demonstrated low LRR rates and similar survival with SLNB alone as compared with ALND among early-stage, cN0 patients found to have 1 to 2 positive sentinel lymph nodes (SLNs).³⁹ The IBCSG 23-01 trial reported similar results for patients with micrometastatic disease in 1 to 2 SLNs, yet also included patients having mastectomy.⁴⁰ The AMAROS trial similarly showed noninferiority of SLNB and axillary irradiation compared with ALND in patients with 1 to 2 positive SLNs undergoing BCT or mastectomy.⁴¹ These contemporary trials have allowed safe omission of ALND in select patients without a compromise in long-term outcomes.

Table 3

Local recurrence of lobular cancers after breast conservation therapy

Study	Stage	Received Adjuvant Therapy (%)	Follow-up (y)	Local Recurrence (%)
Braunstein et al, ³³ 2015 (n = 79)	1–2	90	9.9	4.4
Galimberti et al, ³⁵ 2011 (n = 382)	1–3	95	8.4	5.7
Molland et al, ¹⁰ 2004 (n = 76)	1–3	69	3.6	3.9
Sagara et al, ³⁴ 2014 (n = 384)	1–3	96	6	3.1

Data from Mamtani A, King TA. Lobular breast cancer. *Complex General Surgical Oncology*, in press.

Patients who are clinically node positive should have the presence of axillary disease confirmed by fine-needle aspiration or core biopsy. In this setting, those having upfront surgery will require ALND. The management of the axilla in patients with nodal metastases who receive preoperative neoadjuvant therapy is discussed in the following section.

SURGERY FOLLOWING NEOADJUVANT THERAPY

Patients with locally advanced cancers should generally receive neoadjuvant therapy before proceeding to surgery. This approach affords an opportunity for downstaging of locally advanced disease without compromising survival and allows BCS in more patients who would otherwise need mastectomy. Neoadjuvant therapy also decreases the need for ALND⁴² and provides insight into *in vivo* tumor chemosensitivity.

Patients with ILC are significantly less likely than those with IDC to experience a pathologic complete response (pCR) to neoadjuvant chemotherapy (NAC), ranging from 0% to 11% (Table 4).^{43–51} In a meta-analysis including 1764 ILCs and 12,645 IDCs, IDCs had a significantly higher pCR rate (OR 3.1) and ability to undergo BCS (OR 2.1).⁵² This is consistent with growing evidence that tumor biology is the principal determinant of response to NAC. The high ER-positivity and low proliferative rates in ILC predispose to a lesser response, a trend seen in most ER-positive breast cancers regardless of histology.^{46,51} Expectedly, studies also show limited success in tumor downstaging to BCT in ILC.^{48,53} Notably, despite having a reduced response to NAC, ILCs treated in this manner have very low LRR rates and no survival disadvantage when compared with all-comers undergoing BCT after NAC.^{51,53} BCT rates in ILC after NAC are still increased from the otherwise anticipated baseline, supporting consideration of this approach for locally advanced ILCs.^{48,54} Recent data suggest that although overall rates of pCR are low in ILC after NAC, lack of progesterone receptor expression and poor differentiation may identify those with the highest likelihood of benefit.⁵⁵

An area of growing interest is the management of the axilla after NAC, with a recent prospective study demonstrating avoidance of ALND in 48% of biopsy-proven node-positive patients who downstaged to cN0 after NAC and had at least 3 negative SLNs

Table 4
Pathologic complete response to neoadjuvant chemotherapy among lobular versus other breast cancers

Study	N		pCR (%)		P
	ILC	Non-ILC	ILC	Non-ILC	
Cocquyt et al, ⁴³ 2003	26	101	0	15	.007
Cristofanilli et al, ⁵⁰ 2005	122	912	3	15	<.001
Delpech et al, ⁴⁹ 2013	177	1718	3	14	<.001
Lips et al, ⁴⁶ 2012	75	601	11	25	.01
Loibl et al, ⁴⁷ 2014	1051	7969	6	17	<.001
Mathieu et al, ⁵¹ 2004	38	419	0	11	.04
Truin et al, ⁴⁸ 2016	466	3622	5	20	<.0001
Tubiana-Hulin et al, ⁴⁴ 2006	118	742	1	9	.002
Wenzel et al, ⁴⁵ 2007	37	124	3	20	.009

Data from Mamtani A, King TA. Lobular breast cancer. *Complex General Surgical Oncology*, in press.

resected.⁴² Several trials are underway to further investigate these approaches and to document long-term local-regional control. As ILCs will constitute small subsets of these studies, it is unlikely that recommendations for management of the axilla will differ between IDC and ILC.

Given the known ER-rich nature of most ILCs and favorable results in small retrospective studies, there is growing interest in neoadjuvant endocrine therapy (NET) for ILC. In one study, neoadjuvant letrozole was used for 3 or more months in 61 postmenopausal women with locally advanced cancers, after which they proceeded to surgery or continued on letrozole if tumors remained too large for BCS. At the time of publication, although there were no pCRs observed, the mean reduction in tumor volume was 66%, and the rate of successful BCS was 81% among 31 patients who had undergone surgery.⁵⁶ The PROACT trial demonstrated aromatase inhibitors to be as effective as tamoxifen for tumor downstaging in postmenopausal women with ER-positive disease.⁵⁷ The IMPACT trial showed similar results, randomizing patients to neoadjuvant tamoxifen, anastrozole, or both, showing equivalent tolerance and efficacy, but was unable to predict for outcome.⁵⁸ More recently, the ACO-SOG Z1031 trial randomized stage II–III patients with ER-positive disease to 1 of 3 NET regimens and found marked improvements in surgical outcomes after NET, with the most favorable results in luminal A tumors.⁵⁹ Ongoing trials of relevance include the ALTERNATE trial, which randomizes women with ER-positive cancer to anastrozole or fulvestrant or a combination, and the PELOPS trial, which will assess response to preoperative endocrine therapy with or without the addition of palbociclib among patients with ILC.

RADIOTHERAPY

BCT by definition includes margin negative lumpectomy followed by adjuvant RT. Adjuvant whole-breast RT reduces the risk of both LRR and death from breast cancer after BCS.²⁴ Additional regional nodal irradiation may be indicated for those with involved lymph nodes or high-risk features. It is noteworthy that omission of RT may be considered in elderly women with early-stage ER-positive tumors, with small increases in absolute risk of LRR but no difference in mastectomy-free survival, disease-specific survival, or overall survival (OS).⁶⁰ Accelerated partial breast irradiation (APBI) is a newer technique involving more focused RT delivered in higher doses over a shorter time span. Notably, the recent American Society for Radiation Oncology guideline update categorizes lobular histology for “cautionary” use of APBI outside of a clinical trial.⁶¹

Selected patients may benefit from the use of RT after upfront mastectomy, determined by consideration of macrometastatic nodal deposits, large tumor size, and high-risk disease features. Similar to surgical trials, ILC patients comprise a minority in RT trials. A SEER study including 12,703 ILC patients treated from 2004 to 2009, of which 26% had a definite indication for post-mastectomy RT, found an improved 5-year breast cancer-specific survival from 80.9% to 84.7% ($P = .0003$) among ILC patients, a benefit to the same degree as IDC.⁶² These data support continued consideration of RT using existing criteria, regardless of histology. The implications of margins at mastectomy remain controversial among radiation oncologists, with no data to support a definite benefit of RT after upfront mastectomy with close margins.

Considerations for RT in patients who undergo preoperative neoadjuvant therapy followed by surgery are similarly related to nodal burden, tumor size, and high-risk features, in addition to the response of disease to neoadjuvant therapy. Awaited data from ongoing trials including the NSABP B-51 trial will provide further insight.

ADJUVANT SYSTEMIC TREATMENT

Systemic adjuvant therapy is driven largely by tumor biology, rather than histology. Generally, patients with hormone receptor–positive cancers receive endocrine therapy, applicable to the vast majority of ILCs. Chemotherapy is offered for locally advanced cancers and considered for early-stage cancers with high-risk features such as large size, nodal involvement, high grade, high 21-gene recurrence scores, and more aggressive tumor biology, including triple-negative and HER2-positive receptor status. Although HER2 positivity is rare in most ILCs, this is overexpressed in up to 80% of pleomorphic ILCs, comprising a subset of patients who are more likely to benefit from targeted anti-HER2 therapy.²

Contemporary systemic therapies have a major impact on both locoregional and distant disease control,²⁵ and disease biology determines the efficacy of various therapies. Low rates of local recurrence (approximating 3%) are reported with 12-year follow-up among ER-positive patients who receive endocrine therapy, most relevant to ER-positive ILCs.²⁵ Randomized trials have demonstrated a measurable response in ILC to systemic hormonal and chemotherapy.^{28,63,64} These studies include patients with ER-positive and ER-negative tumors, and hormone receptor status is evidently the chief determinant of response. Interestingly, studies of the utility of Oncotype Dx in ILC have shown that ILCs rarely (less than 2%) have a high recurrence score, as compared with rates approximating 20% in IDCs.⁶⁵

Support for adjuvant endocrine therapy comes from trials demonstrating significant reduction in risk of recurrence at 15 years, summarized in a large Early Breast Cancer Trialists Collaborative Group meta-analysis.²⁷ Although studies specific to ILC remain limited, some data suggest a greater benefit with aromatase inhibitors compared with tamoxifen. In a retrospective analysis of the prospective BIG 1-98 trial, a greater benefit was observed with letrozole than tamoxifen among ILCs, with disease-free survival of 82% with letrozole versus 66% with tamoxifen at 8-year follow-up, and OS of 89% with letrozole versus 74% with tamoxifen.⁶³ One possible explanation for this differential response includes a paradoxical *de novo* resistance to tamoxifen and resultant proliferative response, which was observed in an *in vitro* study of ILC cell lines.⁶⁶ Conversely, the Tamoxifen and Exemestane Adjuvant Multinational trial, which randomized patients to exemestane alone, or an “early-switch” from tamoxifen for a total of 5 years, showed similar efficacy of both regimens for IDC and ILC. There was evidence of an effect of ER content, with benefit from monotherapy for ER-rich patients, as compared with a benefit from sequential treatment of ER-poor patients, regardless of histology.⁶⁴

There are no randomized trials examining adjuvant chemotherapy regimens specifically in ILC. Although retrospective analyses do not show any definite reasons to deny adjuvant chemotherapy to ILC patients who otherwise meet indications for treatment, the limited response of classic ILCs to chemotherapy in the neoadjuvant setting suggests low chemosensitivity. In a retrospective study of 3685 postmenopausal patients with ILC and 19,609 postmenopausal patients with IDCs, treated either with adjuvant hormonal treatment alone or with hormonal treatment and chemotherapy, 10-year survival among ILC patients was 68% with hormonal treatment alone and 66% with combination therapy ($P = .45$), suggesting a limited benefit of chemotherapy in patients with ILC already receiving hormonal therapy.⁶⁷ However, chemotherapy may be more valuable for the minority of ILCs with ER-negative or HER2-positive subtype. In a retrospective subset analysis of the prospective phase III Herceptin Adjuvant trial of patients with HER2-positive tumors, there was a similar benefit after 1 year of adjuvant trastuzumab among ILCs and IDCs (disease-free survival hazard ratio [HR] 0.63

vs 0.77, $P = .49$) at 4 years of follow-up.²⁸ Presently, standard treatment with adjuvant trastuzumab is recommended for HER2-positive ILCs.

OUTCOMES

In keeping with the luminal A phenotype, outcomes and prognosis in ILC are generally favorable. In a large SEER study of 263,408 women (27,639 with ILC and 235,769 with IDC) treated between 1993 and 2003, a stage-matched analysis showed that the 5-year disease-free survival was significantly better for ILC than IDC, with an overall 14% survival benefit (HR 0.86) on multivariate analysis.¹⁹ Although overall stage-corrected prognosis is favorable, some think that this may be offset by a higher stage at presentation,⁶⁸ and higher rates of late metastases in atypical locations. Pleomorphic ILCs are also a known exception, shown in retrospective series to present with larger tumor size, more nodal positivity, and frequently require mastectomy.⁶⁹

SUMMARY AND FUTURE DIRECTIONS

Lobular breast cancer is increasingly recognized as a distinct disease from ductal cancer, with a unique molecular pathogenesis and differing genomic profile. Presently, locoregional and systemic treatment approaches remain shared among all breast cancer types. Continual discoveries of the molecular basis of this disease hold potential for advances in therapy and will pave the way for development of treatment algorithms tailored specifically to lobular disease.

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