Common Myths about Invasive Lobular Carcinoma (ILC)[1]

Developed by Lobular Breast Cancer Alliance and the LBCA Patient Advocate Advisory Board[2]

Many misconceptions about invasive lobular carcinoma (ILC) exist, sometimes propagated by patients and other times by physicians. Such misconceptions may arise from trying to generalize an individual patient's situation to all patients, from outdated or inadequate research studies, or from common beliefs that have been shared over the years. In the following document, we refer to such generalizations and misconceptions as myths. These have been collected from dialogues within private ILC patient support groups and LBCA page on Facebook, and elsewhere. Each is followed by data relevant to that scenario, which are sometimes nuanced.

Myths vs Facts about ILC

1. ***Myth: There is one type of lobular breast cancer***

Lobular breast cancer has many subtypes and variants: ILC is a heterogeneous disease, meaning there can be differences between tumors from one patient to another, between one tumor to another in the same patient, and even differences within a single tumor. Every patient has a unique tumor, tumor environment, and tumor characteristics, which can behave differently from patient to patient, depending on subtype, grade, presence and amount of Ki67, luminal status, receptor status, genomic characteristics, genetic mutations, somatic mutations, molecular characteristics, and stage (tumor size, nodal status, and presence of metastasis), among other features.

Some examples of different lobular variants are classic (the most common histological variant), alveolar, tubulolobular, solid, pleomorphic, signet-ring, and mixed (including mixed ductal/lobular carcinoma). Some examples of different subtypes, based on molecular characteristics, are Luminal A, Luminal B, HER2-enriched, and basal-like (or triple negative). Other ways to characterize lobular breast cancer are by its receptor status, including HR+ HER2- (the most common subtype), HR+ HER2+, HR- HER2+, and HR- HER2-.

2. ***Myth: "Chemotherapy isn't effective to treat lobular breast cancer."***

There have been several studies that have found that chemotherapy may be less effective in ER+ HER2- breast cancers which are slow growing, as is typically the case, though certainly not always, with lobular breast cancers. Some clinicians even advise their patients that they never treat lobular breast cancer with chemotherapy. However, there have also been recent studies that concluded that

[1] These myths have been compiled from those commonly discussed by patients using two large science/evidence-based Facebook groups for lobular breast cancer, Lobular Breast Cancer (ILC) invasive lobular carcinoma (science & support) and ILC Sisters: Lobular Breast Cancer Support & Evidence-Based Information. Led by members of the LBCA Patient Advocate Advisory Board, more than 13,000 ILC patients from around the world (75% from the US, with the rest from other countries, primarily the UK, Canada, Australia, Ireland, and New Zealand) participate in these groups, of which at least 8,000 patients are active in discussions on a daily basis. The larger of the two evidence-based lobular groups has approximately 600 monthly posts, with over 13,000 comments a month. Moreover, these two groups are recognized and publicized by LBCA, which also manages a public facing Facebook page. Combined, these Facebook forums represent the largest online convening platform for lobular patients globally.

[2] Medical accuracy reviewed by the LBCA Scientific Advisory Board.

when and whether treatment of ILC benefits from chemotherapy is still controversial and understudied.[3]

For a subset of lobular patients, particularly those patients at higher risk of recurrence, chemotherapy can be an appropriate systemic treatment and can effectively lower the risk of recurrence or, in the neoadjuvant setting, can shrink a tumor making it easier to remove surgically. Some research also indicates the low-rate rate of pathological complete response (pCR) in ILC patients is not necessarily associated with poorer distant disease–free or overall survival.[4]

Therefore, it is important that there is much more research on the benefits of chemotherapy in the treatment of ILC and, in particular, on identifying which patients will or won't benefit, when and why, and that sufficient data to warrant new treatment protocols for treatment with chemotherapy for patients with lobular breast cancer is generated to inform evidence-based decision-making.

3. ***Myth: "Tamoxifen doesn't work for lobular"***

Since Dr Otto Metzger's Breast International Group (BIG) 1-98 study was published in 2015,[5] some individuals may have concluded and shared the belief that the findings of the study meant that tamoxifen is not effective, particularly for individuals with ILC. The study compared adjuvant tamoxifen to the aromatase inhibitor, letrozole, in treating postmenopausal women with endocrine-responsive early breast cancer. The findings of the study showed that letrozole had greater magnitude of benefit than tamoxifen in terms of overall survival and distant recurrence-free survival after eight years. The results of the study suggest that an aromatase inhibitor may be "more" effective in treating ILC in many circumstances but NOT that Tamoxifen is not effective. The study did not look at nor conclude that that letrozole is better than the two other aromatase inhibitors, anastrozole and exemestane.

It is important to remember not to make a generalization from one study that the results apply to all types of lobular breast cancer and all circumstances. There are always multiple factors in every breast cancer patient's diagnosis and circumstances that must be taken into account when considering a course of treatment, such as a patient's bone health and other co-morbidities, particularly when there are few studies on endocrine therapy for all lobular breast cancer subtypes, all age groups, menopausal statuses, etc. Some patients have side effects that are not easily manageable and that may necessitate switching between the different drugs – and ultimately – the best endocrine therapy is the one that the patient is realistically able to stay on over time.

In making one's own treatment decisions, it is always worth bringing up studies with your care team and discussing the relevance for your case. It is also a good idea to find out whether the breast cancer treatment protocols have changed and whether there are any that are expressly studying treatment of patients with ILC. Furthermore, while tamoxifen is currently still the standard of care for many

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[3] Trapani D, Gandini S, Corti C, et al. Benefit of adjuvant chemotherapy in patients with lobular breast cancer: A systematic review of the literature and metanalysis. *Cancer Treat Rev*. 2021;97:102205. doi:10.1016/j.ctrv.2021.102205.

[4] Hewlick C. Lobular vs ductal breast cancer: Distinctions in management. *The ASCO Post*. July 10, 2023. https://ascopost.com/issues/july-10-2023/lobular-vs-ductal-breast-cancer-distinctions-in-management/ (accessed Feb 3, 2025).

[5] Metzger Filho O, Globbie-Hurder A, Gusterson B, et al. Relative Effectiveness of Letrozole Compared With Tamoxifen for Patients With Lobular Carcinoma in the BIG 1-98 Trial. *JCO* 2015: 33, 2772-2779. doi:10.1200/JCO.2015.60.8133.

patients and has been quite effective for premenopausal women, there are now studies investigating whether an aromatase inhibitor combined with ovarian suppression may sometimes be a better option in some patients.[6]

4. ***Myth: Any statement suggesting that a specific aromatase inhibitor (AI) is better or worse for ILC than another. We have seen statements such as:***
   "Lobular patients should take letrozole"
   "Lobular patients shouldn't take exemestane"
   "Lobular patients should take anastrozole, as it is superior to the two other AIs"

None of these statements are true. Many come from patients who have heard this from a clinician about their own treatment path or they have read or heard about a particular study but misconstrued the study findings to always be true for all ILC tumors or simply misinterpreted them. For example, some patients conclude from the BIG1-98 study described above that letrozole is superior to the other AIs. In the case of BIG1-98, letrozole was used to represent the class of AIs and not to suggest it was superior to the other two. There have been studies comparing AIs to one another in general breast cancer populations and none suggest that one is better (or worse) in all cases. In addition, there have been no head-to-head studies of all three aromatase inhibitors for lobular patients specifically, so there is a lack of data to argue for superiority of one AI over another for ILC. In addition, there have been findings demonstrating that what is best for one lobular patient may not be best for another because it depends on the patient's specific type of lobular breast cancer, co-morbidities and other circumstances.

We recommend that patients contemplating taking an AI should discuss the differences in the drugs and the possible side effects when determining whether and which one to start and then should continue to talk with their doctors about their experiences on the drug and what changes, if any, might be beneficial. We also always recommend bringing studies and your questions about the findings to your doctor and team rather than drawing conclusions on your own without this consultation about what might be best. We also believe that it is important for lobular breast cancer patients to understand the absolute and relative risk of recurrence when taking any hormone treatment versus taking none, as they may want to factor this important information into their decision-making.

5. Myth: "Lobular is always/frequently/usually/often bilateral" or "Lobular always spreads to the other breast."

While some studies have indicated that lobular breast cancer is more often found in both breasts than other breast cancer types, it is important to note that this does not mean "always," "usually," or "frequently," which are considerable overstatements. Studies to date indicate that cancer in both breasts is still relatively rare, both in invasive lobular breast cancer and in invasive ductal breast cancer. Giannakeas et al's 2021 SEER database study with over 50,000 ILC patients showed that the risk is less than 8% over a 20-year period that patients were studied (compared with 7.8% in IDC)[7].

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[6] Brooks M. Exemestane plus ovarian suppression best in early invasive lobular carcinoma. *Medscape*. May 24, 2024. https://www.medscape.com/viewarticle/exemestane-plus-ovarian-suppression-best-early-invasive-2024a10009tv (accessed Feb 3, 2025).

[7] Giannakeas V, Lim DW, Narod SA. The risk of contralateral breast cancer: a SEER-based analysis. *Br J Cancer*. 2021; 125 (4):601-610. doi:10.1038/s41416-021-01417-7.

The recent study in JAMA on bilateral mastectomy and mortality found the risk of contralateral ILC was 7.1% (and contralateral IDC was 6.7%.)[8]

It is also extremely rare for lobular breast cancer tumors to spread to the other breast later – this is a common patient misconception. Most subsequent (or metachronous) diagnoses of lobular breast cancer in the contralateral (i.e. "other") breast are actually new primary lobular breast cancer diagnoses, not metastases of the original lobular tumor.

6. Myth: "Lobular is always slow growing."

While several landmark or seminal studies have indicated that many subtypes of lobular breast cancer, including the "classic" variant, are slow growing and that this is more often the case than with other non-lobular breast cancers, it is inaccurate to conclude that all lobular breast cancer tumors are slow growing. It is important for lobular breast cancer patients to talk with their doctors to better understand the pathology and characteristics of their own tumors and their tumor grade to be best informed about whether their own tumor is classified as slow growing. Whether a lobular tumor is slow, moderate or fast growing may be a function of multiple characteristics, including overall grade, Ki67 score, or molecular sub-type, etc.

7. Myth: "The Oncotype DX and/or MammaPrint tests aren't relevant and/or reliable for lobular."

The Oncotype DX test is used to assess the risk of early stage, estrogen receptor-positive, HER2-negative breast cancer metastasizing to another part of the body away from the breast and to help determine whether a patient will benefit from chemotherapy. The Oncotype DX test analyzes the activity of 21 genes in tumor tissue that are related to the likelihood that cancer will grow and/or respond to chemotherapy. The initial studies of the efficacy and accuracy of the Oncotype DX test did not analyze efficacy with lobular breast cancer patients, specifically. However, there have been some research studies (such as Weiser et al[9]) that show that there may be prognostic and predictive validity, value and relevance in Oncotype for ILC patients. Regarding predicting the benefit of chemotherapy, there are many nuances and different clinicopathological characteristics that factor into a recommendation by an oncology team for chemotherapy or not and Oncotype scores are only one of these. (See Myth no. 2) In some cases, a patient with a low clinical risk, for example, may have a high genomic risk or vice versa (eg. Abel et al, 2021[10]), which complicates a chemotherapy recommendation. Recent studies have also shown that there may be prognostic and predictive validity for MammaPrint (a 70-gene signature) for ILC patients.[11]

8. Myth: "Lobular always goes to the ovaries/GI tract/stomach/peritoneum"

This statement is not true. While studies have shown that lobular breast cancer tumors may metastasize to other parts of the body, such as the ovaries or GI tract/abdomen/peritoneum, more

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[8] Giannakeas V, Lim DW, Narod SA. Bilateral mastectomy and breast cancer mortality. *JAMA Oncol.* 2024; 10 (9). doi:10.1001/jamaoncol.2024.2212.

[9] Weiser R, Polychronopoulou E, Hatch SS et al. Adjuvant chemotherapy in patients with invasive lobular carcinoma and use of the 21-gene recurrence score: A National Cancer Database analysis. *Cancer*. 2022. doi:10.1002/cncr.34127.

[10] Abel MK, Shui AM, Melisko M, et al. The incidence of discordant clinical and genomic risk in patients with invasive lobular or ductal carcinoma of the breast: a National Cancer Database Study. *npj Breast Cancer* 7, 2021: 156. doi:10.1038/s41523-021-00366-x.

[11] Metzger Filho O, Cardoso F, Poncet C, et al. Survival outcomes for patients with invasive lobular cancer by MammaPrint: Results from the MINDACT phase III trial. *Eur J Cancer*. 2025; 217:115222. doi:10.1016/j.ejca.2025.115222.

often than non-lobular breast cancer tumors do, it is important to note that there is not yet enough data to suggest that this is frequent or to indicate which parts of the body might be the most likely places for metastases beyond the most common sites, which are the bones, as well as the brain, lungs or liver.[12]

9. Myth: "Lobular should always be treated with a double mastectomy."

This generalization stems from decades-old data, with more modern data suggesting that this is not true. Multiple studies support the safety of breast conservation therapy (lumpectomy with radiation) for patients with ILC, and there is no data to suggest that double mastectomy improves long term outcomes in terms of survival. While double mastectomy can reduce the risk of developing a second primary cancer (a new breast cancer), it does not impact the risk of recurrence for the cancer that already formed. Indeed, ILC can recur locally or away from the breast even after mastectomy, which highlights the importance of multimodal therapies such as radiation, hormone blocking medication, and chemotherapy, if indicated. Some patients have a high chance of developing a second primary breast cancer, such as those with germline pathogenic variants (formerly called genetic mutations) in genes like BRCA1 or BRCA2. Even in these cases, the decision about having a bilateral mastectomy is very individualized and must take into account the type of screening/surveillance the patient will undergo after surgery, the risks of more extensive surgery, the type of reconstruction that a patient may or may not want to pursue, and the impact of mastectomy on quality of life.

It is also important to note for those who believe that a mastectomy confers better survival than a lumpectomy that, in fact, mastectomy does not improve overall survival. Recent studies have demonstrated that the overall survival rate of individuals who had a diagnosis of ILC in one breast and underwent lumpectomy and radiation therapy are the same as those who opted for a double mastectomy. In fact, it may also be the case that a mastectomy, especially when not considered medically necessary, may have more adverse effects on quality of life than lumpectomy.[13]

10. Myth: "Lobular never forms a lump" or "lobular isn't a solid tumor"

Many patients read about E-cadherin and its characteristics of forming single lines or sheets of cells, and don't realize that, for some patients, a lump can be felt or even seen protruding through the skin. It may also be the case that some patients did not detect a lump accompanying their initial diagnosis but had a lump at the time of recurrence.

Furthermore, some patients are confused about the distinction between solid and liquid tumors, because of their understanding about E-cadherin causing a lack of cell adhesion. In fact, a solid tumor is made up of a mass of cancer cells, which can grow anywhere in the body, whereas a liquid tumor develops in the blood, bone marrow or lymphatic system, such as leukemia, lymphoma or myeloma. Therefore, lobular breast cancer is always classified as a solid tumor and this classification has nothing to do with whether it forms a detectable lump.

11. Myth: "Lobular breast cancer tumors can't be detected by mammography."

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[12] Mathew A, Rajagopal PS, Villgran V, et al. Distinct pattern of metastases in patients with invasive lobular carcinoma of the breast. *Geburtshilfe Frauenheilkd*. 2017; 77 (6): 660-666. doi:10.1055/s-0043-109374.

[13] Rajan KK, Fairhurst K, Birkbeck B, et al. Overall survival after mastectomy versus breast-conserving surgery with adjuvant radiotherapy for early-stage breast cancer: meta-analysis. *BJS Open*. 2024: 8 (3). doi:10.1093/bjsopen/zrae040.

We are aware of the common experience that many ILC patients have had when being diagnosed and hearing that their tumor had been missed for years by traditional mammography. Many studies have shown that lobular breast cancer is often missed by mammograms and ultrasound. In addition, in a recent survey of breast imagers conducted by LBCA and the Society of Breast Imaging, it was found that breast imagers are also not confident that mammograms alone are sufficient for detecting ILC.[14] Nonetheless, these imaging modalities also continue to effectively detect ILC much of the time, although may be less effective in women with dense breasts.

After completion of treatment, for women who have had a lumpectomy or single mastectomy, it is typically recommended (in the US, but not necessarily everywhere) that yearly mammography should be performed as it has been demonstrated that in this population it significantly improves breast cancer survival.[15] It is important to note that currently 3D mammograms have been found to be better than 2D mammograms for detecting all breast cancers and have a lower false positive rates, even in the case of dense breasts. [16] It may be helpful to inquire about obtaining a 3D mammogram although this imaging modality is not currently available at every medical institution performing breast cancer screening. In cases in which mammogram missed the ILC, supplemental imaging such as US and MRI or a mammogram with contrast may be recommended. As everyone's circumstance is different, the ultimate decision will be decided between the patient and her care team.

The Imaging section III of the LBCA FAQ (https://lobularbreastcancer.org/faq/) has more information about ILC and imaging.

12. Myth: "If my early-stage tumor was not seen, my mets progression won't be seen." Or "Only FES/PET can detect recurrences anywhere including locoregional."

This statement is not true. The type of imaging studies and scans used to identify metastatic ILC depends on the location of the metastatic sites. The available imaging options are currently the same as those for imaging ductal breast cancers and include CT scans, bone scans, FDG PET scans, FES PET scans, and MRI. Bone scans look for evidence of bone remodeling, which often occurs at sites of bone metastases. FDG PET uses glucose metabolism uptake in the body and is a sensitive method for detecting, staging, and monitoring the effects of therapy. However, it may be less sensitive at detecting lobular breast cancer lesions than other types of breast cancer lesions.[17] CT scans, PET scans and/or MRI may be used for identifying lesions in the liver and lung, and MRI can be used to visualize other areas such as the brain for metastasis.[18] A newer radio-pharmaceutical agent, F18 Fluroestradiol (FES), used in PET scans targets the estrogen receptor, and may be used in some cases to image ER+ breast cancer. This imaging agent has been FDA-approved specifically for imaging recurrent or

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[14] Coffey C, Berg WA, Dodelzon K, et al, Breast radiologists' perceptions on the detection and management of invasive lobular carcinoma: Most agree imaging beyond mammography is warranted, *Journal of Breast Imaging*, 2024; 6 (2). doi:10.1093/jbi/wbad112.

[15] Houssami N, Abraham LA, Miglioretti DL, et al. Accuracy and outcomes of screening mammography in women with a personal history of early-stage breast cancer. *JAMA.* 2011; 305(8):790–799. doi:10.1001/jama.2011.188.

[16] Conant EF, Talley MM, Parghi CR, et al, Mammographic screening in routine practice: Multisite study of digital breast tomosynthesis and digital mammography screenings, *Radiology.* 2023 307 (3). doi.10.1148/radiol.221571.

[17] Hogan MP, Goldman DA, Dashevsky B, et al. Comparison of 18F-FDG PET/CT for systemic staging of newly diagnosed invasive lobular carcinoma versus invasive ductal carcinoma. *J Nucl Med*. 2015; 56 (11):1674-1680. doi:10.2967/jnumed.115.161455.

[18] Pesapane F, Downey K, Rotili A, Cassano E, Koh DM. Imaging diagnosis of metastatic breast cancer. *Insights Imaging*. 2020; 11 (1):79. doi:10.1186/s13244-020-00885-4.

metastatic breast cancer. FES PET scans are proving to be helpful in visualizing lobular tumors in certain parts of the body, and other use of FES PET scans are being studied in clinical trials.[19] In order to ensure accurate FES testing, patients may not be on fulvestrant or tamoxifen at the time of the test. FES PET is less effective in detecting lesions in the liver.[20] However, it is acknowledged that FES PET scans are not yet widely available around the world, and therefore a combination of other imaging modalities can be considered. Whole body MRI is under investigation in research studies as it may be valuable to help visualize ILC when traditional CT and FDG PET scans are not useful.[21]

13. Myth: "LCIS always becomes ILC" / "LCIS should be treated with a bilateral mastectomy as it will turn into ILC"

This statement is not true. It is important to note that lobular carcinoma in situ (LCIS) is not considered cancer, despite the name. It is considered a risk factor for any kind of invasive breast cancer and not specifically lobular breast cancer. LCIS is a non-obligate precursor, which means it is not guaranteed to become invasive breast cancer. Typically, monitoring and observation are all that are needed but it is important to discuss your care plan with your team. In some instances, medications can be prescribed that can help reduce the risk of developing breast cancer in the future.[22] If LCIS does become invasive, it will not necessarily become invasive lobular carcinoma. One recent study has also shown that when ILC is diagnosed and LCIS is not also present in the tumor, this is indicative of a poorer prognosis, but further studies are warranted to understand this phenomenon.[23]

14. Myth: Lobular breast cancer starts in the lobules and ductal breast cancer starts in the ducts.

This is a false statement, although it is unfortunately being perpetuated by some very well-respected medical institutions. The fact is there is no sound scientific evidence for this. ILC and IDC can arise in the terminal ductal lobular units (TDLU) in the breast. Additionally, males and mice, both of whom have no lobules, can also develop ILC. LBCA Scientific Advisory Board members have noted that "a combination of the genetic lesion and the cell type that is affected define the lobular phenotype, definitely not simply the anatomic position in the breast."[24]

[19] LBCA. ILC clinical trials. *Lobular Breast Cancer Alliance*. https://lobularbreastcancer.org/ilc-clinical-trials/ (accessed Feb 2, 2025).

[20] Ulaner GA, Jhaveri K, Chandarlapaty S, et al. Head-to-Head Evaluation of ^{18}F-FES and ^{18}F-FDG PET/CT in metastatic invasive lobular breast cancer. *J Nucl Med*. 2021; 62 (3): 326-331. doi:10.2967/jnumed.120.247882.

[21] Bhaludin BN, Tunariu N, Koh DM, et al. A review on the added value of whole-body MRI in metastatic lobular breast cancer. *Eur Radiol*. 2022; 32 (9): 6514-6525. doi:10.1007/s00330-022-08714-6.

[22] Camp M. Lobular carcinoma in situ. Johns Hopkins Medicine. https://www.hopkinsmedicine.org/health/conditions-and-diseases/breast-cancer/lobular-carcinoma-in-situ (accessed Feb 5, 2025).

[23] Mouabbi JA, Raghavendra AS, Bassett Jr RL, et al. Absence of lobular carcinoma in situ is a poor prognostic marker in invasive lobular carcinoma. *European Journal of Cancer*. 2023 (191). 113250. doi:10.1016/j.ejca.2023.113250.

[24] Tabár L, Dean PB, Tucker FL, et al. Breast cancers originating from the terminal ductal lobular units: In situ and invasive acinar adenocarcinoma of the breast, AAB. *Eur J Radiol*. 2022;152:110323. doi:10.1016/j.ejrad.2022.110323.