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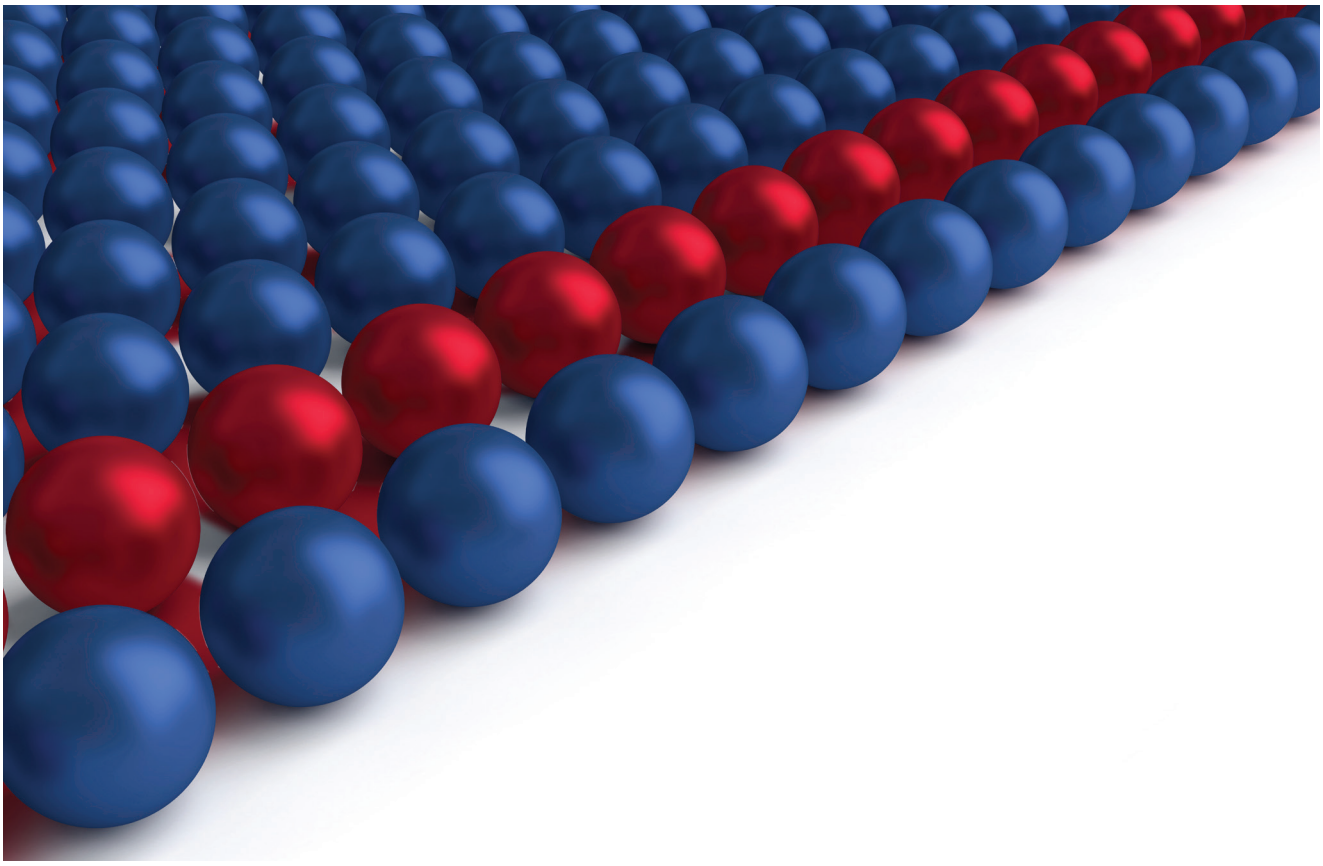
EDUCATIONAL HANDBOOK

Invasive lobular cancer: Current evidence and clinical impact



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Foreword by the Guest Editor

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A complex and multifarious disease, breast cancer encompasses a range of subtypes, each with its unique set of challenges, diagnostic intricacies, and treatment pathways. Among these, invasive lobular carcinoma (ILC) holds a distinct position. Representing 10–15% of all invasive breast carcinomas, ILC emerges as the second most prevalent form of breast cancer, introducing a myriad of challenges in both imaging and diagnosis.

This educational handbook provides an in-depth exploration of ILC. It aims to shed light on its prevalence, explore its epidemiology, and elucidate the unique challenges it presents to the medical community.

ILC is characterized by its small, discohesive cancer cells. These cells, rather than forming a lump, invade surrounding breast tissue in a single-file growth pattern. This behavior of ILC is primarily attributed to the absence of E-cadherin protein expression, a crucial protein that aids in cell adhesion. The lack of this protein results in the unique and challenging growth pattern exhibited by ILC.

In the first article, Dr Rohit Bhargava (University of Pittsburgh School of Medicine) provides a comprehensive exploration of the diverse pathology of ILC. His insights highlight various morphological variants and their associated genetic mutations. As research in this field progresses, the distinct attributes of ILC are becoming more evident. This evolving understanding is paving the way for the development of more personalized and effective treatment strategies in the future.

Drs Randy Yeh and Elena Ochoa-Albiztegui (Memorial Sloan Kettering Cancer Center) provide a detailed analysis of the challenges associated with detecting ILC using standard imaging tests. They emphasize the inherent limitations of mammography, especially when it comes to detecting early stages of ILC. Their insights underscore the importance of adopting a comprehensive imaging approach. By integrating advanced techniques such as magnetic resonance imaging (MRI), positron emission imaging/computed tomography (PET/CT), and contrast-enhanced spectral mammography (CESM), clinicians can achieve a more holistic view of the disease, especially when traditional methods prove insufficient.

The understanding and perceptions of ILC have undergone significant evolution over the years. Its unique infiltrative growth pattern, which often remains undetected in standard imaging, has far-reaching implications. These extend beyond mere diagnostics, impacting surgical decisions, treatment plans, and patient outcomes. The elusive nature of ILC in imaging can sometimes lead to underestimations of the tumor's size and extent, posing challenges for clinicians and surgeons alike.

Drs Rebecca Shatsky and Hemali Batra-Sharma (UC San Diego Health) examine the intricacies relating to the management of ILC. Their article highlights the often infiltrative and hypometabolic nature of ILC metastases, which further complicate detection. They emphasize the pressing need for a tailored approach to ILC treatment. By understanding and acknowledging its unique characteristics, clinicians can devise more effective treatment strategies, ultimately aiming to enhance patient outcomes.

In the final article, Dr Rita Mukhtar (University of California San Francisco) provides a comprehensive review of the surgical challenges posed by ILC. She discusses in detail the two primary surgical techniques – breast conservation therapy and mastectomy. Her insights shed light on the application of these techniques based on the tumor's characteristics and the patient's overall health and preferences. Furthermore, she emphasizes the pivotal role of staging in the treatment decision-making process. The introduction of the Society of Surgical Oncology–American Society for Radiation Oncology (SSO-ASTRO) guidelines has had a significant impact on the surgical management of ILC. By standardizing surgical approaches, these guidelines aim to reduce the frequency of re-excisions, thereby improving patient outcomes and reducing the physical and emotional toll on patients.

This stimulating publication offers readers a profound understanding of the complexities and nuances of ILC. It underscores the need to adopt a strategic, informed, and multifaceted approach to the diagnosis and treatment of ILC. By refining diagnostic strategies, optimizing treatment plans, and staying abreast of the latest research, the medical community can strive to enhance patient outcomes and improve the overall quality of care.

I trust that readers will find this content both educational and deeply insightful.

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Pathology of ILC: a unique subtype

A greater understanding of the pathology of ILC is gradually being developed as the awareness increases and specific techniques are designed to detect and monitor the cancer. Here we examine some of the characteristics and hallmarks of its pathology, which in turn might impact the personalisation of treatment of the disease in future.

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Invasive breast carcinoma of no special type (IBC-NST), also known as invasive ductal carcinoma or IDC and invasive lobular cancer (ILC), which are classified by their different histological features and immunohistochemical profile, are the two main histological types of breast cancer.[1]

ILC is the most common special subtype of breast cancer: it accounts for approximately 15% of all invasive breast carcinomas.[2]

Hallmarks and characteristics

Classical ILC is characterised by small discohesive cancer cells that invade the stroma in a single-file growth pattern. Dysregulation of cell-to-cell adhesion causes the discohesive phenotypes due largely to a lack of E-cadherin protein expression, which is seen in around 90% of cases of ILC and is a feature of all types of ILC.[3] In contrast, only 7% of IDCs have been reported to lack E-cadherin.[4]

Unlike IDC, ILC does not usually destroy breast architecture and grows in single file, concentric patterns around ducts and lobules of the breast.[5]

Classical ILC is associated with low to moderate nuclear pleomorphism and a low mitotic index. It typically shows a luminal A molecular phenotype.[6]

Molecular characteristics

Lack of E-cadherin due to biallelic inactivation of the *CDH1* gene is a key feature of ILC leading to the typical discohesive growth pattern. E-cadherin enables cell–cell adhesion through the formation of adherens junctions between cells, helping to maintain cell viability in the process.[6]

Typically, ILC is characterized as a luminal A subtype as a result of high estrogen receptor (ER)/ progesterone receptor (PR) expression, low human epidermal growth factor receptor 2 (HER2) expression and being a low-grade tumor.[5] Recently, though, HER2 mutations have been found to occur more frequently in ILC (2–15%) than in other breast cancer subtypes, particularly in higher grade tumors.[5]

Immunophenotypical features

The majority (95%) of ILC cases are ER+ and up to 70% express PR, in contrast to IDC, where around 70% of cases express ER and PRs.[6]

HER2 negativity is another feature of ILC, which displays a low rate of *ERBB2* gene amplification.[6] However, not all subtypes share the same ER/PR+ HER2– features. Pleomorphic ILC (especially with apocrine morphology), for example, is more likely to exhibit an ER/PR–, triple negative or HER2+ phenotype.[7]

The tumor immune microenvironment in ER+ breast cancer may be influenced by *PIK3CA* mutation status and that may have implications for ILC.[7]

Phenotypic/morphological characteristics

ILC is classified as breast cancer composed of discohesive cells that are mostly individually dispersed or arranged in single files.[7] However, that is not universally the case; other variants of ILC display their own growth patterns and cytology.

The solid variant of ILC forms large solid sheets of cancer cells, which may be mistaken for other tumors such as lymphoma, often showing intermediate grade nuclei and higher mitotic index.[6]

Tumor cell density in classical ILC is low to moderate and the tumor cells accumulate at the border from connective to adipose tissue or may appear to partially avoid infiltration into the adipose tissue. These features are seen under low power magnification and are characteristic. At higher power magnification, the classic small tumor cells can be seen to have scanty cytoplasm. Mitotic activity is low, and the nuclei vary in shape, although size and chromatin quality are quite consistent.[8]

In addition to the classic form of ILC, there are other subtypes, including pleomorphic (potentially an aggressive form), solid, alveolar, trabecular, solid-papillary, signet-ring cell rich, histiocytoid, and with extracellular mucin (Table 1). Another variant known as ILC with tubular elements (where tubular elements also lack E-cadherin) has also been recently described.[8]

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TABLE 1
ILC variants

Single file growth pattern (classical ILC)
Dissociated growth pattern (classical ILC)
Histiocytoid ILC
Solid ILC
Alveolar growth pattern
Trabecular growth pattern
Plexiform growth pattern
Signet ring cell-rich ILC
ILC with extracellular mucin
Pleomorphic ILC
Solid-papillary ILC
ILC with tubular elements

Ref 8

Alveolar ILC has cells that tend to grow in groups of at least 20 cells, which form globular aggregates.[8]

Pleomorphic ILC shows a greater degree of nuclear atypia (grade 3 nuclear) and pleomorphism, and plasmacytoid features with some cases showing a higher mitotic index but it shares the single-file cell growth pattern with the classical form.[6] Apocrine differentiation is also a common finding in pleomorphic ILC.

The variants are not usually seen as pure forms but more likely occur with the classical type.[2] There are some breast cancer subtypes that are difficult to classify as ductal or lobular. The so called 'tubulo-lobular' variant, once considered a variant of lobular cancer has been shown to express membranous E-cadherin and considered a variant of ductal cancers by many.[9] Additionally, some low to intermediate grade invasive mammary carcinomas with single cell infiltrative growth pattern but with retained membranous expression for E-cadherin are again difficult to classify. We call such tumors lobular-like invasive mammary carcinoma (LLIMCa).[10] These tumors lack the characteristic *CDH1* mutations of ILC but a proportion of them show *CDH1* promoter methylation. Their clinical–pathological features are intermediate between ILC and IDC. The prognosis is related to tumor stage and multivariable prognostic model of Magee Equation score.[10]

A retrospective cohort study of female adults (aged older than 18 years) who were diagnosed with breast cancer from 1990 to 2017 treated at the University of Pittsburgh Medical Center (Magee Women's Hospital and Hillman Cancer Center), Cleveland Clinic, and the Ohio State University Comprehensive Cancer Center, identified 3617 (10.7%) patients with ILC and 30,045 (89.3%) patients with IDC.[11] Compared with IDC, the study found that 88% of ILCs were grade 1 and 2, compared with only 60% of IDC cases in these categories (corrected p <0.001).[11]

ILCs were more frequently higher stage (stage III and IV: 20.7% versus 10.4% in IDC), and more patients were diagnosed with de novo metastatic disease (stage IV: 3.7% ILC versus 2.4% IDC) (corrected p<0.001).[11] ILCs were larger in size (T3 and 4: 14.7% in ILC versus 4.0% in IDC), and there was more nodal involvement at time of diagnosis (N2 and 3: 9.9% in ILC versus 5.5% in IDC) (corrected p < 0.001).[11]

Furthermore, ILCs were more likely to be ER+ (96% versus 77%) and PR+ (81% versus 67%; all corrected p < 0.001). Despite favorable receptor status, ILCs were associated with poorer treatment outcomes. For example, patients with ER+ and HER2– ILC had statistically significantly worse disease-free survival (hazard ratio (HR) = 1.18, 95% CI = 1.01 to 1.38; p = 0.03) and overall survival (HR = 1.32, 95% CI = 1.19 to 1.45; p < 0.001) than ER+ IDC.[11]

Specific gene expression signatures/somatic mutations

CDH1 mutations are seen in the majority of ILC tumors and are a characteristic of the disease.[2] Changes to the *CDH1* gene, located on chromosome 16q22, which codes for E-cadherin, cause loss of the protein.[6] Most *CDH1* mutations are somatic frameshift or nonsense mutations resulting in truncated, non-functional E-cadherin proteins.[8] The second most common change in ILC are *PIK3CA* mutations.[7]

Alterations are also seen in *TP53*, *CCND1* and *FGFR1* genes in patients with ILC.[7] Patients with metastatic ILC are more often found to have mutations in *CDH1*, *NF1*, *PIK3CA*, and *TBX3* than those with metastatic IDC, and tumor mutational burden is higher among patients with ILC than those with IDC.[12]

Among 127 tumor samples of ILC, Ciriello et al found mutated *PIK3CA* genes in 61 samples (48%), compared with 33% (164/490) in IDC samples.[3] *TBX3* (9% versus 2%), *RUNX1* (10% versus 3%) and *FOXA1* (7% versus 2%) mutations were also seen more frequently in ILC samples than those of IDC.[3]

By contrast, alterations usually seen in basal-like tumors were less frequent in ILC, including *TP53* mutations (8% in ILC versus 44% IDC) and focal amplification of *MYC* (6% versus 27%) and *CCNE1* (0% versus 7%).[3] Somewhat unexpectedly, the researchers found differences, including a lower incidence of *GATA3* mutations in ILC compared with IDC (5% in ILC versus 13% in IDC).

Homozygous losses of the phosphatase and tensin homolog (*PTEN*) locus (10q23) were more frequent in ILC as were *PTEN* mutations (8% versus 3%). Collectively, *PTEN* inactivating alterations were identified in 14% of luminal A ILC versus >

3% of luminal A IDC, which, the authors say, made this the third most distinguishing genetic determinant feature between luminal A IDC and luminal A ILC.[3]

In a retrospective cohort study of data from 980 patients with metastatic breast cancer (121 patients with ILC, 792 with IDC and 67 with mixed histology) analysing circulating tumor DNA showed that patients with ILC had a significantly higher number of pathogenic mutations compared with the IDC and mixed histology cohorts (median 3 [IQR 1–6] versus 2 [IQR 0–4] versus 2 [IQR 0–5]) and a significantly lower number of copy number variants (Mann–Whitney U test, $p < 0.05$). Compared with patients with IDC, patients with ILC were found to have significant differences in the single-nucleotide variants (SNVs) of: *CDH1*, *FGFR2*, *IDH2*, *MYC*, *NF1*, *PDGFRA*, *RB1* and *TERT* (Fisher's exact test; all $p < 0.05$), and the copy number variants of: *CCNE1*, *ERBB2*, *MYC* and *PDGFRA* (Fisher's exact test; all $p < 0.05$). Patients with mixed histology were not found to have alterations in *CDH1* or *PTEN*.[13]

While most cases of ILC have low genomic complexity, with low numbers of substitutions, insertions/deletions, and rearrangements, a meta-analysis by McCart Reed et al of 901 ILC cases across four cohorts found considerable genome complexity in tumors associated with:
i. a low number of structural rearrangements but a hypermutation genotype linked to APOBEC mutagenesis, or
ii. tumours with highly rearranged genomes affecting clustered sets of chromosomes, or
iii. tumours exhibiting tumour genomes characteristic of homologous recombination DNA repair deficiency.[2]

TABLE 2

Commercially available gene expression-based tests

Oncotype Dx
EPClin
Prosigna
Breast Cancer Index
LobSig
MammaPrint

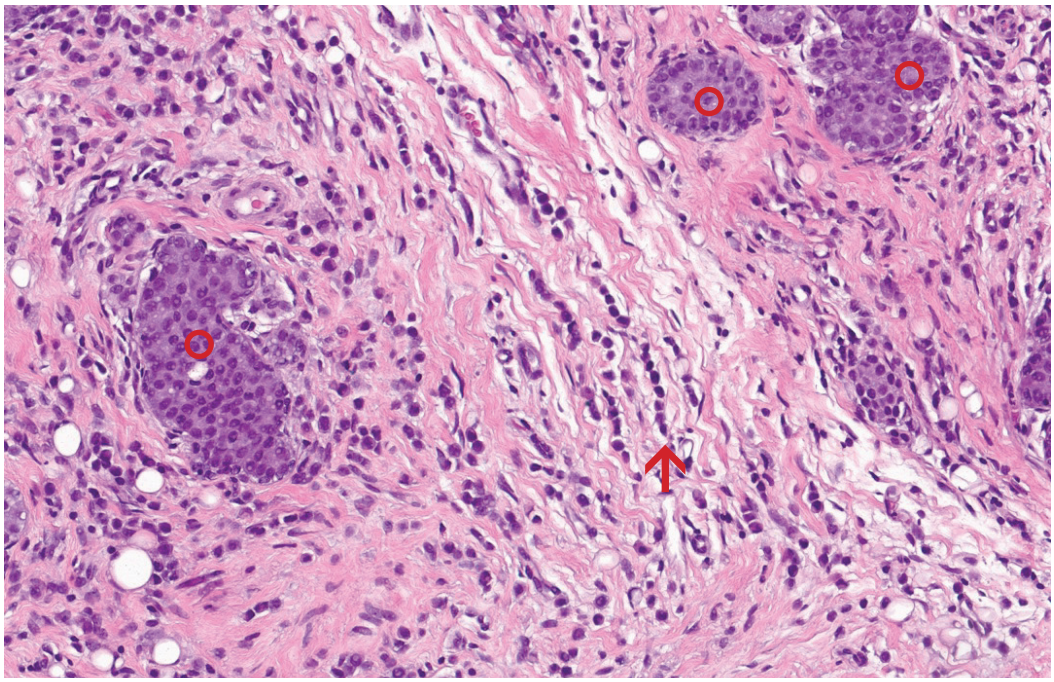
Ref 14

Although the overall pattern of alterations is similar across morphological variants of ILC there are some differences. For example, *ERBB2* and *ERBB3* mutations are more often seen in pleomorphic ILC than classic ILC. Solid ILC variants have been found to be enriched for *ERBB2*, *TP53*, and *ARID1A* mutations; 11p and 6q25.1 (*ESR1*) gains; and 1p36.22 (*ARID1A*) deletions, while the alveolar variant harboured 11q13.3 (*CCND1*) and 11q14 (*PAK1*) gains; mutations in *TP53* and *ERBB2* are seen in mixed, non-classic types.[7]

Future directions

The role of multigene prognostic tests to guide adjuvant treatment is under evaluation and a number of these tests are now commercially available.[14] Table 2 provides a summary.

The utility of some of the tests is still to be determined and uptake has not generally been widespread.[15] Of these, LobSig is the only one that was designed specifically for ILC.[14] It comprises >



ILC and lobular carcinoma in situ (LCIS)
Hematoxylin and eosin-stained section demonstrates single cell infiltrative growth pattern of classical invasive lobular carcinoma. Scattered foci of LCIS are also noted. Arrow represents ILC and circle represents LCIS.

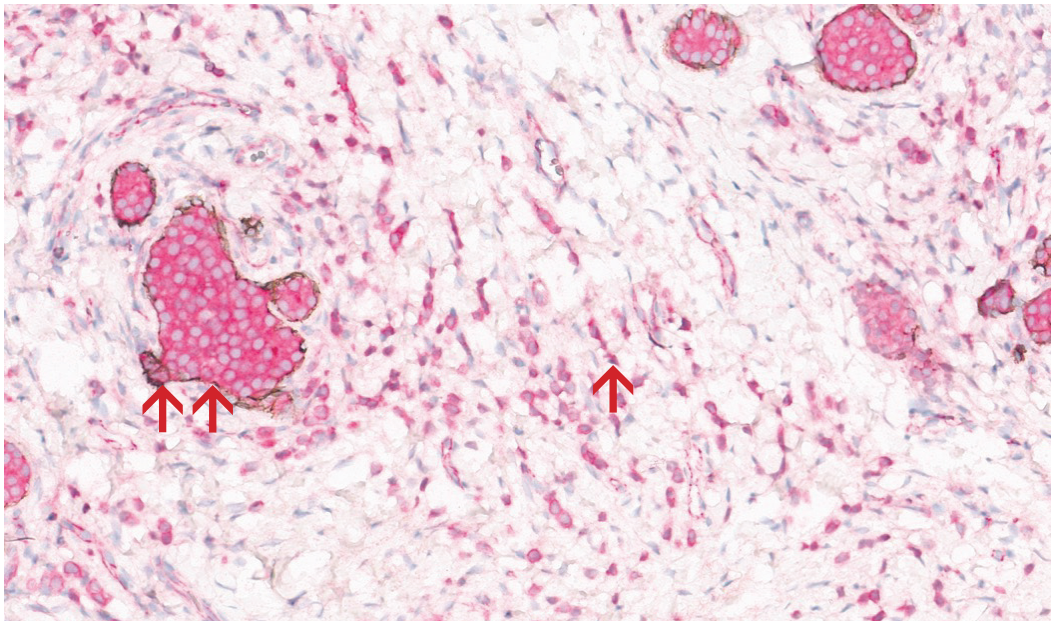
a 194 metagene signature and is a robust method for prognosticating ILC.[15] In their multivariate analysis, McCart Reed at al demonstrated the value of LobSig above individual clinicopathologic features and their data support that LobSig low-risk patients do not require adjuvant chemotherapy.[15] However, it still needs independent validation.

Ongoing trials on ILC are uncovering new potential targets and laying foundations for new management strategies.[14] For example, ROS1 inhibition is currently being explored as a therapeutic strategy in tumours with somatic inactivating *CDH1* mutations in early and metastatic ILC.[14] ROS1 inhibitors have shown significant anti-tumour effects in models of E-cadherin-defective breast cancer, so, in future, it might become important for pathologists to use E-cadherin, p120 to confirm a diagnosis of ILC.[16]

Conclusion

More and more is being discovered about the pathology of ILC. Characteristics that impact treatment response and which, therefore, may be important in improving the personalization of treatment for each individual patient, and thus the patient outcomes, have become apparent. Differences in aspects of pathology have been observed between ILC and other variants, when compared with IDC. Although characteristic pathology is being identified, it does not mean that ILC is homogeneous. Far from it: morphological variants of ILC show differences in genetic mutations, for example.

ILC is an important variant of breast cancer and elucidation of features that differentiate it from other types of cancer will hopefully guide clinicians to an optimal approach to the management of the disease in the future.



ILC and LCIS (dual E-cadherin and p120). A dual e-cadherin (brown) and p120 (red) immunohistochemical stain demonstrates lack of reactivity for E-cadherin and cytoplasmic reactivity for p120 in the tumor cells consistent with a lobular phenotype. Note weak/moderate staining of myoepithelial cells for E-cadherin (brown) around LCIS.
Single arrow points to red p120 cytoplasmic staining in invasive carcinoma. Double arrows point to weak/moderate staining of myoepithelial cells (brown e-cadherin).

FIGURES AND LEGENDS (COURTESY OF DR BHARGAVA)

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The challenges of imaging and diagnosing ILC

As the second most common form of breast cancer, understanding invasive lobular carcinoma (ILC) is vital for clinicians and imaging specialists. This article addresses the intricacies of diagnosing ILC, focusing on the complexities of detecting and treating this type of cancer.

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Invasive lobular carcinoma (ILC) is distinguished by its unique biological and pathological attributes.[1] Unlike other forms of breast cancer, ILC often presents distinct challenges in diagnosis due to its growth patterns and cellular characteristics.[1]

The infiltrative growth pattern of ILC is characterized by its tendency to spread in a linear manner, with cancer cells invading the surrounding breast tissue in a cell-by-cell fashion as opposed to the more common invasive ductal carcinoma (IDC), which forms a discrete tumor mass.[1] This 'single-file' and linear pattern of invasion can make tumors less discernible on standard imaging tests. As a result, ILC might not form a breast lump that is felt during a physical exam or detected on breast imaging.[1,2]

The majority of ILCs are luminal A intrinsic subtype with high estrogen receptor (ER) and progesterone receptor (PR) expression and low human epidermal growth factor 2 (HER2) amplification.[3] Furthermore, other histological characteristics of ILC, including the lack of a cohesive cellular structure, can often be mistaken for normal breast tissue or benign changes, leading to potential delays in diagnosis. This can be particularly challenging as standard imaging techniques such as mammography, might not always detect ILC, especially in its early stages.[1]

What are the implications for diagnosis?

The implications of these challenges are profound. A delayed or missed diagnosis can mean the cancer is detected at a more advanced stage, limiting treatment options and potentially affecting the prognosis.[3] Moreover, the elusive nature of ILC on imaging can lead to underestimating tumor size and extent, which are critical parameters for treatment planning.[4]

Because of these challenges, it becomes evident that a multi-faceted approach to imaging, incorporating various modalities and frequent monitoring, is essential for effectively detecting and managing ILC.

Difficult recognition on screening mammograms

Screening mammograms are a cornerstone of breast cancer detection, designed to identify tumors at their earliest, most treatable stages. However, specific to ILC, these standard screenings often fall short due to the cancer's unique presentation.[5]

The infiltrative growth pattern of ILC contrasts with other forms of breast cancer. Additionally, ILC often exhibits frequent discontinuity, meaning the cancerous cells are not always clustered together but may be interspersed with healthy tissue.[1] This can make the tumor boundaries less distinct and harder to identify on a mammogram, which is based on identifying differences in tissue density between breast cancer tumors and normal breast tissue.[4]

The appearance of ILC on a mammogram can be subtle. Instead of a clear, defined lump, asymmetry is present, which can easily be mistaken for benign breast changes or overlooked entirely.[5] This is particularly concerning because mammograms are the primary tool for early breast cancer detection for many women.

The challenging recognition has multiple implications. If the tumor's true extent is underestimated, it can lead to inadequate surgical margins during initial surgical interventions. This can necessitate further surgeries, increasing the physical and emotional burden on the patient, leading to complications and impacting the overall quality of life and prognosis.[2]

Later stage detection

The combination of its non-lump presentation and unique growth pattern also means that ILC is often detected at a more advanced stage than other breast cancer subtypes. By the time it is identified, the cancer might have spread to a wider area of the breast (Stage II cancer), or metastasized to lymph nodes or distant organs (Stage III or IV).[6]

Diagnosis at a later stage can significantly impact a patient's treatment journey. Larger tumors or those that have spread may require >

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more aggressive surgical approaches, such as a mastectomy instead of breast-conserving surgery.[3] Additionally, later-stage cancers might require more intensive treatments (chemotherapy or radiation), which come with their own set of side effects and challenges. Beyond the physical implications, a later-stage diagnosis can also take a toll emotionally due to a more uncertain prognosis and the potential for a longer, more arduous treatment course.

Imaging modalities

We review the main imaging modalities used below. Recommendations and limitations are outlined in Table 1 and a case study is also presented.

Mammography

As one of the most widely used imaging techniques, mammography plays a pivotal role in the early detection of breast cancers. Low-dose X-rays help visualize the breast's internal structure and morphology, helping to identify any abnormalities or masses. For many breast cancer subtypes, mammography has proven to be an effective screening tool, leading to enhanced patient outcomes.[7]

However, the efficacy of mammography becomes more nuanced in ILC. The 'single file' growth pattern can make it challenging for mammography to detect these subtle changes or capture the "whole picture", often leading to underestimating the tumor's size and extent.[2] Moreover, the architectural distortion (or disruption of normal breast tissue) caused by ILC can sometimes be subtle on mammograms, especially in individuals with dense breast tissue, thus further complicating the detection process and increasing the risk of a delayed or missed diagnosis.[2]

Despite these challenges, it is essential to recognize the value of mammography. While it might have limitations in detecting ILC, it remains effective for identifying and screening other breast cancer subtypes and changes in the breast tissue and continues to be a cornerstone in screening protocols.[7] Its limitations in ILC further underscore the importance of complementing it with other imaging modalities for a more holistic assessment.

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TABLE 1

Benefits and limitations of some of the main imaging modalities

Modality/use	Sensitivity	Benefits	Limitations
Mammography (screening and initial diagnosis)	Sensitivity for ILC ranges from 34% to 92%.[5]	• The widespread use and accessibility of mammography have made it the first line of defense in detecting early signs of breast abnormalities • Mammography has been instrumental in reducing breast cancer mortality rates by facilitating early detection and intervention, reslting in enhanced patient outcomes.[7]	• Effectiveness can be somewhat diminished for ILC • Given ILC's unique infiltrative growth pattern and the associated architectural distortions, especially in individuals with denser breasts, relying solely on mammography for ILC detection might not be sufficient
CESM (screening and diagnosis)	Sensitivity for ILC of 93–100%.[15]	• CESM is emerging as a promising alternative or adjunct to traditional mammography and MRI, especially in cases where these modalities might be inconclusive or not available, respectively • Its ability to highlight vascular changes offers a unique perspective, allowing for a more nuanced assessment of potential malignancies • In the context of ILC, CESM may play a pivotal role. It is especially recommended for individuals who have dense breasts, are unable to undergo MRI, or require a more detailed evaluation following a standard mammogram	• The need for an intravenous contrast agent means that individuals with allergies or renal issues might not be suitable candidates for the procedure • Additionally, like any imaging modality that uses ionizing radiation, there is a radiation exposure consideration with CESM[6] • The procedure might also be more expensive than traditional mammography, potentially posing financial barriers • CESM is a relatively newer modality, so its availability might be limited in certain healthcare settings and impact on long-term outcomes not yet demonstrated
US (screening and initial diagnosis)	Sensitivity for ILC ranges from 68% to 92%.[2]	• In the context of ILC, US is a valuable adjunct to mammography • Its ability to differentiate between solid and cystic lesions and its dynamic imaging can often detect abnormalities that might be missed or appear ambiguous on a mammogram • Thus, incorporating US into the diagnostic process can enhance detection accuracy for patients suspected of having ILC or those with inconclusive mammographic findings	• The unique growth pattern of ILC can sometimes be subtle on ultrasound images. This means that while US might detect the presence of ILC, it can often underestimate the actual size and extent of the lesion • Such underestimations can have profound clinical implications, such as the need for more extensive surgical interventions or even additional surgeries, increasing the physical and emotional burden on the patient

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TABLE 1 (CONTINUED)

Benefits and limitations of some of the main imaging modalities

Modality/use	Sensitivity	Benefits	Limitations
MRI (screening and initial diagnosis, staging and surveillance)	Sensitivity for ILC ranges from 93% to 100%.[5]	• The higher resolution of MRI and its exceptional capability to differentiate between soft tissues offers clinicians a detailed view of the breast's internal structures • Given ILC's unique growth pattern, MRI's precision becomes even more crucial. Accurately gauging the tumor's size and spread is imperative for determining the most appropriate surgical approach, be it breast-conserving surgery or mastectomy • Thus, in cases of uncertainty or when other imaging modalities provide incomplete information, MRI emerges as the go-to choice for a comprehensive assessment of the breasts and axilla	• MRI procedures tend to be more resource-intensive, given their intricate protocols and advanced technology and do not provide disease state information of the whole body.. • Consequently, MRI facilities might not be readily available in all healthcare settings, especially in rural or under-resourced areas. Furthermore, the cost factor can pose a barrier for some patients • Additionally, the lengthier duration of MRI scans compared to other imaging modalities can be challenging for some individuals, especially those who might experience claustrophobia or discomfort during the procedure • As such, while MRI offers a wealth of information, its accessibility and patient experience should be considered when planning diagnostic strategies
FDG PET/CT and FES PET/CT (staging and surveillance)	^{18}F-FDG PET/CT ILC detection rate = 75%; sensitivity and specificity for ILC ipsilateral lesions of 0% and 91.7%[2] FES PET/CT non-ILC sensitivity and specificity = 95% and 80%, respectively[16]	• PET/CT, with its dual capability of providing both functional and anatomical information, becomes invaluable in advanced staging scenarios • By highlighting areas of increased metabolic activity, FDG PET can pinpoint regions of aggressive tumor growth, metastatic spread, or even residual disease post-treatment • This precision becomes crucial in tailoring treatment strategies, ensuring that therapeutic interventions are targeted to the most active disease sites • Furthermore, PET/CT can serve as a real-time monitor as treatments progress, assessing how the tumor's metabolic profile changes in response to therapies • This dynamic feedback can guide clinicians in adapting treatment plans, ensuring that interventions remain effective and responsive to the tumor's evolving behavior	• Given its focus on metabolic activity, FDG PET/CT is inherently more sensitive to tumors with high metabolic rates • Due to lower specificity, FDG PET/CT might not always be the best choice for the initial detection of ILC, especially in the early stages or when the disease presents with a lower metabolic profile • Additionally, the resource-intensive nature of PET/CT, combined with its higher costs and limited availability in some settings, can further relegate it to a secondary or tertiary role in the diagnostic pathway • Thus, while PET/CT offers whole body disease assessment, PET/CT and the particular radiotracer (FDG or FES) should be considered within the context of specific clinical scenarios where its unique capabilities may be appropriate[17]

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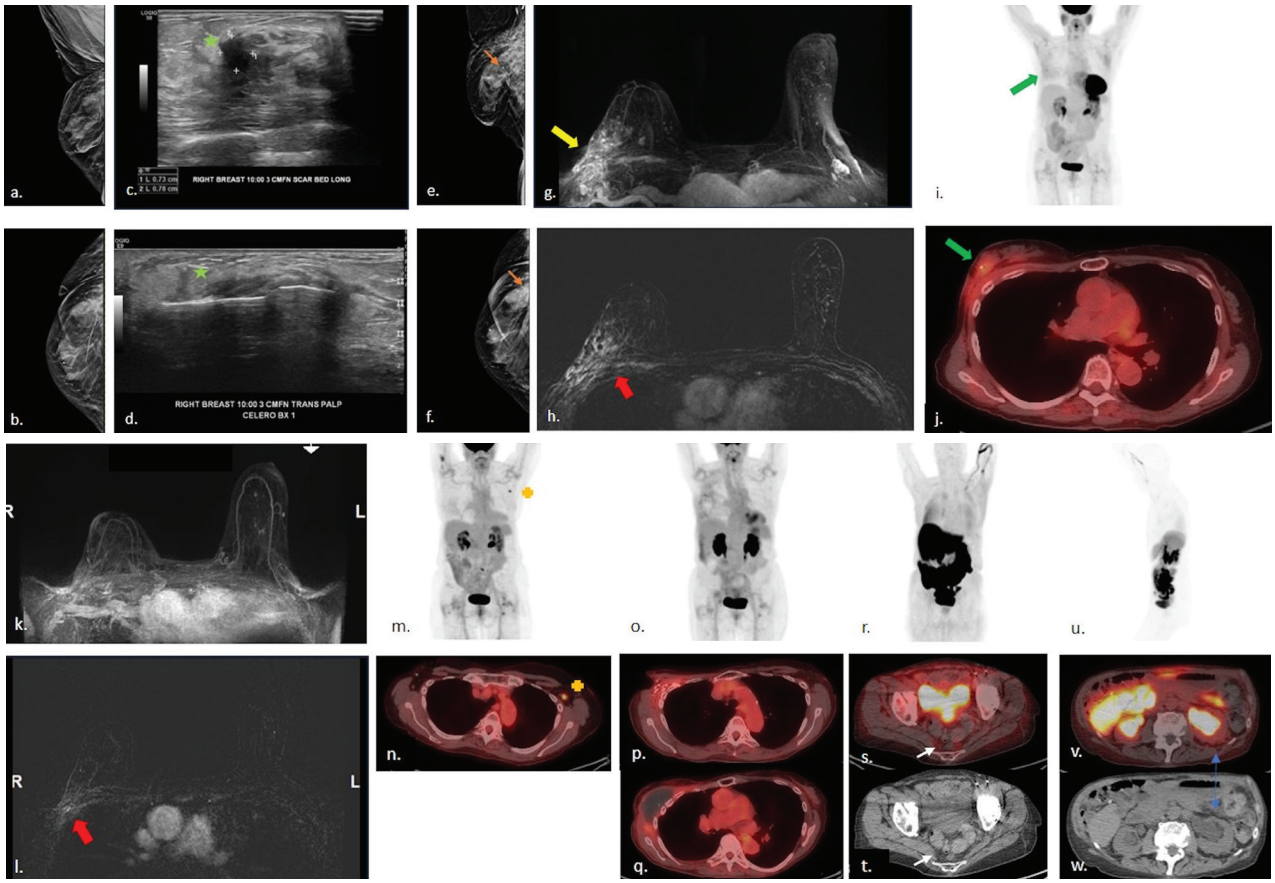
CASE STUDY

55-year-old female diagnosed with right breast ductal carcinoma in situ status post whole excision and whole breast irradiation. 11 years disease-free interval, patient presents with a palpable mass.



Right breast mammogram **(a.)** MLO and **(b.)** CC demonstrate a triangular skin marker correlating to the palpable area with underlying stable global asymmetry in the upper outer breast with an associated distortion along the posterior margin of the asymmetry. US **(c. and d.)** demonstrates a 0.8 cm irregular hypoechoic mass [green star] in the posterior margin of a stable sonographic oval mass. **(d.)** US guided biopsy [green star] yield invasive lobular carcinoma. Physical exam demonstrated a more extensive diffuse involvement of a mass like area in the upper outer quadrant of the right breast with an underestimation of disease with imaging. An MRI was done to further evaluate extent of disease. MRI of the breast MIP. Post biopsy mammogram, ML **(e.)** and CC **(f.)** [orange arrows] depicting biopsy clip. **(g.)** shows the right breast smaller than the left breast due to DCIS prior excision. Subtraction images **(h.)** demonstrate 9:00 axis mass measuring 2.1 cm with biopsy marker and extensive non-mass enhancement spanning 8.3 cm [yellow arrow] involving the intercostal muscles [red arrow] which made her a candidate for neoadjuvant treatment, follow-up by mastectomy as standard of care. A staging FDG PET-CT MIP **(i.)** showed a mildly FDG avid mass [green arrow] [SUV 2.6] in the upper outer breast. Fused images **(j.)** depict the mass with biopsy clip [green arrow] consistent with the biopsy proven invasive lobular carcinoma involving the intercostal muscles and possibly the pectoralis musculature [SUV 2.1], no distant metastases. Post neoadjuvant chemotherapy MRI breast **(k. and l.)** with interval decrease in enhancing recurrent right breast mass biopsy proven invasive lobular carcinoma and enhancing tumor infiltrating posteriorly from this mass into the subcutaneous tissues and intercostal muscles with persistent residual enhancing disease [red arrow]. 3 months after surgery, follow up FDG PET-CT **(m. and n.)** depicts a left axillary subcentimeter avid lymph node [yellow cross] [SUV 5.6]; US guided FNA was negative for malignancy. Two years after mastectomy follow-up FDG PET-CT was obtained due to a new punch biopsy of right axillary skin nodules yielding metastatic lobular carcinoma of the right chest wall **(o.)** FDG PET-CT MIP with no FDG avid lesions suspicious for recurrence, fused images **(p. and q.)** specifically without suspicious FDG avidity in the right axillary skin, biopsy proven chest wall recurrence. Two weeks later, a FES PET-CT was performed, FES PET-CT MIP **(r.)** and lateral FES PET-CT MIP windowed to 8 g/ml **(u.)** without FES avidity in the right axilla/chest wall, **(s. and t.)** however, there was a right perirectal low level tracer avidity slightly above background [SUV 1.3][white arrows] with peritoneal and perirectal fat stranding **(t.)** suspicious for malignancy and **(v. and w.)** mild bilateral hydroureteronephrosis [double pointed blue arrow], probably from peritoneal/retroperitoneal disease.

Contrast-enhanced spectral mammography (CESM)

CESM combines the principles of traditional mammography with the addition of a contrast agent (typically iodine-based).[6] After injection, two X-ray exposures are taken at different energy levels. The high-energy exposure captures the anatomical details, while the low-energy exposure captures the contrast distribution. By subtracting these two images, radiologists obtain a clear picture of areas with increased vascularization, often indicative of malignancies.[8]

CESM's strength lies in its ability to detect lesions that might be obscured in traditional mammography, especially in individuals with dense breast tissue. The contrast agent highlights areas of increased blood flow, a common characteristic of tumors, thus making CESM particularly effective in identifying early-stage cancers or lesions that might not have formed a distinct mass yet.[8] Moreover, CESM can be instrumental in cases where MRI is contraindicated or unavailable.[6]

The ability of CESM to detect subtle changes in vascularization in ILC can be invaluable. The enhanced contrast provided by CESM can help delineate the extent of the disease more accurately than traditional mammography.

Ultrasound

Ultrasonography (commonly known as ultrasound) employs high-frequency sound waves to generate real-time images of the breast's internal structures. It is a useful tool in breast imaging, especially in scenarios where mammography might not offer the most clear picture, such as in individuals with dense breast tissue.[5] The ability of ultrasound to differentiate between solid tumors and fluid-filled cysts provides a distinct advantage, offering a more granular view of any suspicious areas.[1]

Unlike mammography, ultrasound sensitivity is not affected by breast density. However, ultrasound sensitivity of 68–92% for ILC is lower than other modalities.[2] It can fall short in capturing the cancer's full extent and has been found to underestimate tumor size in ILC in 18–53% of cases.[2] This is concerning, as an inaccurate tumor size assessment can influence surgical and treatment decisions, potentially leading to suboptimal outcomes.[1].

Furthermore, while ultrasound is adept at pinpointing abnormalities in the breast, its specificity in discerning benign from malignant lesions might not always be on par with other imaging techniques.[5] This can sometimes result in additional tests or biopsies, which, while crucial for a definitive diagnosis, can be stressful for the patient.

Ultrasound offers a safe, non-invasive, radiation-free method of visualizing breast abnormalities, that when coupled with mammography remains an important imaging adjunct. It is, however, unlikely to provide an additional benefit in newly diagnosed ILC because of its underestimation of the extent of the tumor.[2]

Magnetic resonance imaging (MRI)

As a sophisticated imaging modality, incorporating morphology and contrast kinetics, MRI has become increasingly instrumental in breast cancer diagnostics.[9] Unlike traditional methods, MRI uses magnetic fields and radio waves to produce detailed images of the breast's internal structures. This capability offers unparalleled insights into the tissue, often revealing abnormalities that might be obscured in other imaging techniques, such as mammography and ultrasound.[2]

When focusing on ILC, the role of MRI becomes even more pronounced. MRI can delineate these subtle growth pattern changes more effectively, offering a more precise representation of the tumor's spread and size[2], which is critical if considering breast conserving surgery. This precision is paramount, especially when determining the surgical margins or evaluating the need for additional treatments, making it particularly useful in cases where other modalities are inconclusive, thereby reducing the chances of misdiagnosis or underdiagnosis.[2]

Yet, while MRI's advantages in assessing ILC are evident, it is crucial to acknowledge its limitations. MRI procedures are typically lengthier and more expensive than mammograms or ultrasounds.[2] Neither MRI, US nor mammography image a patient's entire body to assess their whole body status. Additionally, although the sensitivity of MRI is high, its specificity is low, sometimes detecting even benign changes which might lead to unnecessary treatment interventions or anxiety for the patient.[1]

Positron emission tomography/computed tomography (PET/CT)

As an advanced imaging modality, PET/CT offers a unique blend of functional and anatomical insights, making it a powerful tool for disease assessment of the whole body in the oncological landscape.[10] Using radioactive tracers, PET/CT can visualize their accumulation within tumors, shedding light on specific pathological processes; for example, increased glucose metabolism in tumor cells with ^{18}F-Fluorodeoxyglucose (FDG) or functional expression of estrogen receptors on tumor cells with ^{18}F-Fluoroestradiol (FES).[11,12] This imaging, combined with the detailed anatomical views from CT or even MRI, provides a comprehensive picture of the tumor's behavior and location.

The usefulness of FDG PET/CT differs depending on histological subtype (IDC versus ILC), and studies show poorer detection in patients with ILC compared with those with IDC, given the relatively lower uptake of FDG

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in ILC primary and metastatic tumors.[13]

Mechanistically, ILC may be less FDG-avid due to lower tumor microvascularity, cellular density, and number of GLUT transporters compared with IDC.[13,14] More recently, another PET radiotracer – ^{18}F-Fluoroestradiol PET/CT (FES PET) – has shown some promise for improved detection of ILC lesions compared with FDG PET but research is ongoing.[11,15]

As mentioned, where other modalities might struggle to delineate the full extent of ILC, the ability of FDG PET/CT to highlight metabolic hotspots can offer a clearer perspective, ensuring that even subtle areas of disease activity are identified. This precision is particularly crucial when staging the disease as understanding the full extent of the cancer can directly influence treatment strategies.[14]

However, it is not just about detection. The metabolic insights from PET can also play a pivotal role in treatment monitoring. By assessing how the tumor's metabolic activity changes in response to therapies, clinicians can gauge the effectiveness of treatments, allowing for real-time adjustments to care plans.[5]

PET/CT offers many advantages but it is not typically the first port of call for initial ILC detection but rather excels in more advanced stages or when other modalities provide inconclusive results.[10] Its strength lies in its ability to refine treatment strategies, ensuring that care is both targeted and effective.

Conclusion

The diagnostic landscape of ILC highlights the intricate nature of breast cancer and the need for a nuanced, multi-faceted approach to its detection and management. ILC, with its unique growth patterns and cellular characteristics, challenges traditional breast cancer imaging paradigms, requiring a deeper understanding and a more comprehensive diagnostic strategy.

Each imaging modality offers unique strengths and limitations, from the cornerstone of mammography to advanced imaging with FDG or FES PET/CT. While some are excellent for early detection, others excel in disease staging or treatment monitoring. Understanding these nuances and integrating multiple modalities will ensure a holistic and accurate assessment of the disease.

Given these challenges, there is a pressing need for heightened awareness among medical professionals and the public about the unique characteristics of ILC. Enhanced training programs, more frequent use of supplemental imaging modalities, and patient education could all play a role in ensuring that ILC is detected at the earliest possible stage, optimizing outcomes for those affected.

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Management of ILC

There are challenges to tailoring therapy for invasive lobular carcinoma (ILC), in part due to many clinical trials' inclusion criteria requiring measurable disease on imaging which often leads to the exclusion of patients with ILC. Greater understanding of the presentation of ILC is important for improving therapeutic approaches and addressing the current unmet needs in this patient population.

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Invasive lobular carcinoma (ILC) is the second most common subtype of invasive breast cancer, comprising 10–15% of cases.[1] Classic ILC is characterized by the loss of E-cadherin protein expression, and more than 90% of ILC cases are hormone receptor (HR)-positive.[1] Human epidermal growth factor 2 receptor (HER2) amplification is seen in 3–13% of ILC cases and triple-negative ILC comprises 2–9% of cases.[2] There are multiple ILC histologic subtypes; 50% of classic ILC are low grade and luminal A, compared with 60% of mixed non-classical ILC which are high grade and luminal B.[1] The mixed non-classical ILC subtype includes pleomorphic lobular carcinoma, which has a poorer prognosis than other ILC variants.[3]

The distinct biological features of ILC present challenges in its management. In the early stage, rates of pathologic complete response (pCR) after neoadjuvant chemotherapy are low, and mastectomy rates are higher in ILC patients.[3] Endocrine therapy is the cornerstone of HR+ ILC management; however genomic alterations correlate with development of endocrine resistance in advanced ILC. There is conflicting literature on the prognosis of ILC compared to invasive ductal carcinoma (IDC), in part due to the heterogeneity of ILC tumors.[1] A combined analysis of more than 12,000 patients enrolled in 15 International Breast Cancer Study Group clinical trials between 1978 and 2002 found that although prognosis with ILC is better than with IDC in early years, risk of relapse is higher with ILC after six years and overall survival is inferior with ILC compared to IDC after ten years.[4]

A recently published cohort study of more than 225,000 premenopausal women diagnosed with Stage I to III IDC or ILC between 1990 and 2015 found that those with ILC have worse breast cancer-specific survival after ten years following diagnosis compared to those with IDC, highlighting the importance of histologic subtype when determining the duration of endocrine therapy for premenopausal patients.[5]

Multidisciplinary management of early-stage ILC

Currently, the treatment of early-stage ILC is similar to other types of breast cancer and involves a multidisciplinary approach including surgery, radiation, and systemic therapy.[2,3,6,7]

Limitations in detecting the extent of ILC on breast imaging can affect treatment decision-making for early-stage ILC. The sensitivity of mammography in detecting ILC is 34–83%, which is reduced to ~10% in the setting of dense breast tissue.[2] The addition of digital breast tomosynthesis or contrast-enhancement can improve the sensitivity of mammography.[2] Breast MRI has the highest sensitivity for ILC – roughly 93–100% – but may overestimate the size of lesions in 20% of cases, particularly if there is concomitant lobular carcinoma in situ.[2]

Breast conserving surgery is a treatment option for patients with ILC;[3] however, evidence suggests that 17–65% will need a second surgical intervention.[6] Rates of positive margins after surgical resection in ILC are high at 18–60%, but re-excision has been shown to clear the margin in up to 74.2% of cases.[8]

Patients with ILC are more likely to undergo mastectomy, and double mastectomy is not unusual in the setting of bilateral disease.[3,6] There are multiple factors that contribute to this: (1) The disease presentation with ILC is more often with a larger tumor with nodal involvement, and patients can present with multifocal and bilateral disease[2] and (2) Patients with ILC benefit less from neoadjuvant chemotherapy in terms of downstaging disease to enable breast-conserving surgery.[2] A systematic review and meta-analysis of 40 studies involving >87,000 breast cancer patients showed that those with IDC receiving neoadjuvant chemotherapy are significantly more likely to achieve pCR in the breast and axilla compared with those with ILC (breast pCR: 22.1% in IDC versus 7.4% in ILC, OR: 3.03 [95% CI 2.5–3.68] p<0.00001; axillary pCR: 23.6% in IDC versus 13.4% in ILC, OR: 2.01 [95% CI 1.77–2.28] p<0.00001).[9]

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Adjuvant therapy

Given that ILC is often multifocal, adjuvant partial breast irradiation is not recommended in ILC.[2] Local control with adjuvant radiation after breast conservation surgery (with clear margins) or mastectomy appears to be similarly effective for ILC and IDC.[2]

Decision-making regarding adjuvant chemotherapy is guided by clinicopathologic factors and use of prognostic gene expression-based assays.[6] ILC is less likely to be genomically high-risk compared with IDC. Analyses of the National Cancer Database on the utility of the Oncotype DX and the MammaPrint assay in ILC have shown that these genomic assays are prognostic but are less predictive of the benefit of adjuvant chemotherapy in high-risk ILC.[10,11] A systematic review and meta-analysis of eight studies assessed the benefit of adjuvant chemotherapy in localized ILC and did not demonstrate an improvement in overall survival (n=38,387; summary hazard ratio [SHR] 0.99; 95% CI 0.86–1.14).[12] There is a subset of patients with high-risk ILC who can benefit from adjuvant chemotherapy, and tools such as LobSig are in development to refine molecular prognostication for ILC.[1,2,13]

The majority of ILC cases are HR+ and, therefore, endocrine therapy is the cornerstone of adjuvant management. Patients with high-risk, lymph node positive HR+ breast cancer can receive adjuvant abemaciclib with endocrine therapy. A retrospective analysis of clinicopathologic features of breast cancer patients treated at Dana-Farber Brigham Cancer Center between 2016 and 2021 found that patients who were potentially eligible for adjuvant abemaciclib were significantly more likely to have lobular histology, in addition to having other risk factors such as younger age, premenopausal status, and high-risk Oncotype DX recurrence score.[14]

Management of metastatic ILC

The combination of endocrine therapy and a CDK 4/6 inhibitor (CDK 4/6i) is currently the standard of care for first-line treatment of most metastatic HR+ breast cancers. Trials thus far have not been powered to distinguish the efficacy of this combination therapy in ILC compared to IDC.[1] A retrospective study of 2975 patients with HR+/HER2– metastatic breast cancer concluded that the addition of CDK4/6i to endocrine therapy offered a similar magnitude of benefit irrespective of histology.[15] An updated analysis of pooled data from seven trials by the FDA found that patients with IDC and ILC had a longer duration of overall survival when a CDK4/6i was added to an aromatase inhibitor (HRs, 0.75 and 0.66, respectively).[15]

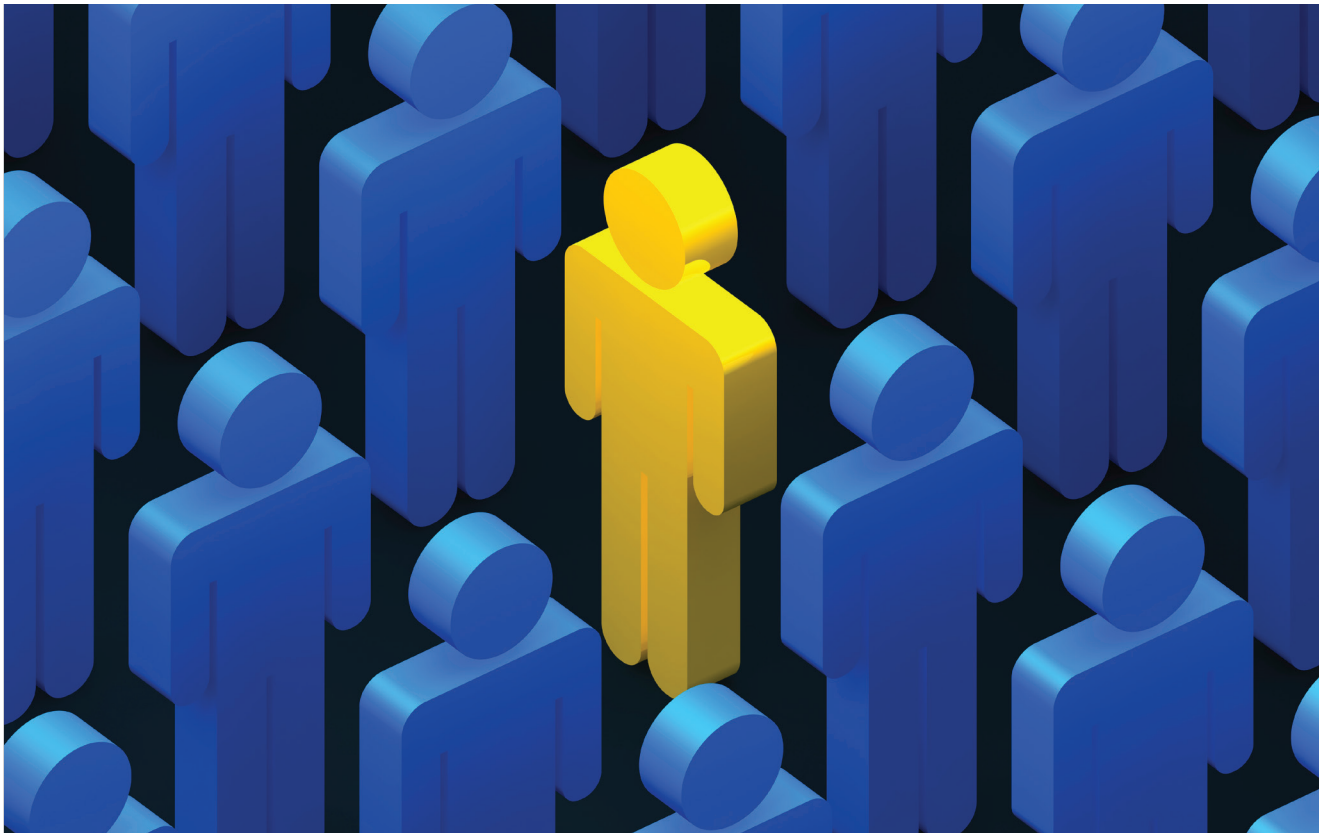
Metastatic ILC demonstrates an increased frequency of mutations associated with endocrine therapy resistance, including in the PTEN/PIK3CA/AKT pathway, *ESR1*, *ERBB2*, *FOXA1*, and *NF1*, which can inform subsequent therapeutic strategies.[15] *PIK3CA*-mutated metastatic ILC can be treated with alpelisib with fulvestrant, which was approved given the improvement in progression-free survival (PFS) in the SOLAR-1 trial.[16] In the BOLERO-2 trial, the combination of exemestane and everolimus, an inhibitor of mTOR which is downstream of PI3K/AKT, improved median PFS compared with exemestane and placebo among postmenopausal HR+/HER2– advanced breast cancer patients with disease recurrence/progression during/after a non-steroidal aromatase inhibitor (7.8 months versus 3.2 months, HR 0.45, 95% CI 0.38–0.54, p< 0.001). A subgroup analysis showed that ILC patients experienced improved median PFS with exemestane plus everolimus compared with the control (6.9 months versus 4.2 months, HR 0.59, 95% CI 0.37–0.95).[17]

Most *ESR1* mutations are acquired after exposure to aromatase inhibitor therapy.[2] In addition to fulvestrant-based endocrine therapy regimens, patients with *ESR1*-mutated ILC have the potential treatment option of elacestrant, which was approved for *ESR1*-mutated advanced HR+/HER2- breast cancer given improvement in PFS demonstrated by the EMERALD trial.[18] *ERBB2* mutations can be found in up to 15% of metastatic ILC cases and may be associated with poor prognosis, but represent an actionable target for therapy.[1,19] The MutHER trial studied neratinib with fulvestrant in HR+ and HER2-mutated, non-amplified metastatic breast cancer patients, 42.5% (n=17/40) of whom had lobular histology; among the evaluable ILC patients, the objective response rate was 38.5% and the clinical benefit rate was 61.5%.[20] In addition, ILC has a higher rate of hypermutation/high tumor mutational burden than IDC (17% versus 7.8%); however, additional studies are needed to further determine the benefit of immunotherapy in this population.[21]

Targeted therapy, antibody-drug conjugates, and immunotherapy have revolutionized the treatment landscape of HER2+ and triple-negative breast cancers, and management of these subtypes of ILC is currently extrapolated from that of IDC. Additional research is needed to tailor management of these presentations of ILC.

Pattern of metastatic dissemination

Compared with IDC, metastases in patients with ILC are more likely to occur in the peritoneum, retroperitoneum, the gastrointestinal (GI) tract, ovaries, and leptomeninges.[1,22] The metastases are usually infiltrative and hypometabolic as opposed to mass forming and hypermetabolic, which makes them difficult to detect with conventional imaging and 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT).[23] Metastatic relapse can occur many years after remission. For >



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The pattern of metastatic dissemination of ILC limits the measurement of disease on conventional imaging, which often leads to the exclusion of patients with metastatic ILC from clinical trials.

example, GI metastases can be detected 15 years after first diagnosis of ILC. As many as 40% of cases of ILC have been found to have GI metastases at autopsy. The GI submucosa is involved first, affecting all layers of the stomach with progression, and can also impact the colon and rectum.[23] Therefore, patients with metastatic ILC can present with bowel obstruction; patients with peritoneal carcinomatosis can present with ascites. Metastatic retroperitoneal disease progresses to retroperitoneal fibrosis, causing ureteral obstruction and hydronephrosis.[23] Although orbital metastases are uncommon in breast cancer, they are more frequently seen with metastatic ILC than with IDC.[24] Patients with metastatic ILC can also present with bone marrow infiltration, manifesting as acute cytopenia(s) out of proportion to therapy-related change; keratin immunohistochemical staining can help detect ILC in bone marrow biopsies that appear negative for involvement by morphologic assessment.[25]

Challenges in clinical trial design and enrollment

Many trials have strict definitions of measurable disease used for eligibility. However, the pattern of metastatic dissemination of ILC limits the measurement of disease on conventional imaging, which often leads to the exclusion of patients with metastatic ILC from such trials.[26] In 2021, 104 trials identified on clinicaltrials.gov specified measurable disease as an inclusion criterion: 29 (27.9%) used Response Evaluation Criteria in Solid Tumors (RECIST) in inclusion criteria; 22 (21.5%) used RECIST as an outcome measure and 48 (46.2%) used RECIST in both inclusion criteria and outcome measures. Five (4.8%) studies used measurable or alternative size criteria. No trials explicitly restricted the study population by histology.[27]

Researchers found that among patients with stage IV breast cancer treated at the University of California, San Francisco (UCSF), there was a significantly lower proportion of ILC patients recruited to trials (based on data from the OnCore clinical trials management system) than in their institutional cancer registry (9.2% versus 17.9%, p=0.005).[27] Among patients with early-stage invasive breast cancer for which RECIST criteria are not routinely used, there was no difference in the proportion of ILC patients enrolled in clinical trials compared to those in their institutional registry.[27]

Utility of PET/CT imaging

Evidence suggests that FDG-PET/CT could be superior to conventional techniques for measuring treatment response. For example, Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) has been found to be largely in agreement with European Organization for Research and Treatment of Cancer (EORTC) >

criteria in relation to progression-free survival and overall survival and the more precise definitions in the PERCIST criteria were considered more straightforward and reproducible between readers than those in EORTC.[24] Studies show that the sensitivity of ^{18}F-FDG PET/CT varies from 95 to 100% for staging metastatic breast cancer, compared with 56–57% for conventional techniques such as contrast-enhanced CT and bone scintigraphy.[28] However, ILC is characterized by low glucose metabolism and, thus, there is little or no uptake of FDG, so ^{18}F-FDG PET/CT is less useful for monitoring disease and treatment response in these patients.[28]

The NCCN guidelines mention that PET/CT utilizing the estrogen receptor (ER) targeting tracer 16α-^{18}F-fluoro-17β-Fluoroestradiol (^{18}F-FES) may be useful for assessing stage IV ER+ disease in certain circumstances.[7] Six prospective clinical trials assessing the utility of ^{18}F-FES PET/CT conducted at Memorial Sloan Kettering Cancer Center demonstrated that ^{18}F-FES PET/CT compared favorably with ^{18}F-FDG PET/CT for detection of metastases in ILC patients.[29]

In 2022, the Society of Nuclear Medicine and Molecular Imaging published Appropriate Use Criteria regarding ^{18}F-FES PET/CT, discussing that this modality may be appropriate for staging ILC and that use of ^{18}F-FES PET/CT is appropriate to help guide consideration of second-line endocrine therapy after progression of metastatic disease.[30]

Conclusion

ILC has distinctive features from other forms of breast cancer. As more is learned about these aspects, clinicians and researchers are beginning to realise that treatment for people with ILC should not necessarily follow the same path as those with other breast cancer types. However, there are challenges to tailoring therapy, in part because patients with ILC are underrepresented in clinical trials compared to those with IDC. Developments in the molecular and clinical understanding of ILC are beginning to point the way towards improved treatment approaches that address the unmet needs in this patient population.

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Surgical management of ILC

Management of ILC, particularly the surgical approach, is influenced by a myriad of factors ranging from the tumor's characteristics to patient preferences. The evolution of surgical techniques has reduced the need for re-excisions and may enhance patient outcomes. There is optimism that future interventions will be even more refined, ensuring the best possible outcomes for patients diagnosed with this unique subtype of breast cancer.

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As noted elsewhere in this handbook, invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer after invasive ductal carcinoma (IDC), accounting for approximately 15% of all invasive breast cancers.[1]

The distinct growth pattern of ILC introduces multiple surgical challenges. From the initial steps of identifying and delineating the tumor to the post-operative management, surgeons face a series of complexities that can influence both the immediate outcomes and long-term prognosis for patients.[2,3]

Staging and its importance in ILC

Staging is an integral component in the management of any cancer, providing a comprehensive snapshot of the disease's progression. At the time of initial diagnosis, 'clinical stage' is determined based on physical examination and imaging studies.[4] The components of stage include the size of the primary invasive tumor, the presence or absence of regional lymph node involvement, and the presence or absence of distant or metastatic disease. Stage ranges from I–IV, with stage IV indicating metastatic breast cancer.

For those with clinical stage I–III disease, a cornerstone of treatment includes surgical excision of the primary tumor and examination of regional lymph nodes via either sentinel lymph node biopsy, targeted axillary dissection, or axillary dissection.[5] At this time, evaluation f the surgical specimens allows for re-calculation of overall stage, termed 'pathological stage'.[6]

This holistic understanding of tumor extent allows clinicians to devise treatment plans tailored to the patient's needs. For instance, early-stage ILC might be managed with breast-conserving surgery followed by radiation and endocrine therapy,[2,5] while advanced stages might require more aggressive treatments like mastectomy or cytotoxic systemic therapies such as chemotherapy.[5]

The components of staging in ILC include:

- Tumor size: This metric indicates how large the tumor is. Tumor size can influence the type of surgery a patient might undergo and can also provide insights into the potential recurrence risk of the cancer[7]
- Lymph node involvement: Lymph node involvement can indicate a higher risk of a cancer spreading to other parts of the body. In ILC, the involvement of axillary lymph nodes is more common than in invasive ductal carcinoma[8,9]
- Distant metastasis: The presence of distant metastases indicates stage IV disease, where treatment is focused on a combination of systemic therapies like endocrine therapy, CDK 4/6 inhibitors, chemotherapy, or targeted therapies[5] The role of surgery in the setting of metastatic ILC is usually limited to palliation or local control.[5,10]

One particular challenge in the staging of ILC is the higher rate of discordance between clinical stage and pathological stage seen in this tumor type.[11,12] Because standard imaging tools have lower sensitivity for diffusely growing tumors like ILC,[13] it is more common that more extensive disease than was initially appreciated is identified at the time of surgery.

Overall, stage both influences treatment recommendations, and also has prognostic implications. Generally, early-stage cancers have a more favorable prognosis than advanced stages. However, factors like tumor grade and hormone receptor status also influence the overall outlook.[2,14] Moreover, staging provides a standardized language for healthcare professionals, ensuring consistent communication about the patient's condition across the multidisciplinary team.

Factors influencing surgical decision-making

The decision-making process for surgery, especially in cases of ILC, is influenced by a myriad of factors. These determinants not only shape the surgical approach but also impact the overall prognosis and quality of life for patients. From the anatomical characteristics of the tumor to the >

personal preferences of the patient, each element plays a crucial role in determining the surgical path for individuals diagnosed with ILC.[12] The sensitivity to neoadjuvant chemotherapy and the implications on surgery, including potential predictors of response to therapy, are also significant considerations in the decision-making process.[2,9] The success rates of re-excision after positive margins can also influence surgical decisions, especially for those facing positive margins after attempted breast conserving surgery (BCS).[12,15] Indeed, the choice between BCS and mastectomy is a critical aspect of surgical management in ILC, with pros and cons for each option.[7,10]

Challenges in the surgical management of ILC

The following challenges encountered during the surgical management of ILC emphasize the need for a comprehensive understanding of the behavior of ILC, ensuring that surgical interventions are both effective and tailored to the disease.

Detection challenges

The growth pattern of ILC can sometimes render tumors less palpable and harder to visualize on standard mammograms. This can lead to underestimations of the tumor's size and extent, influencing surgical decisions.[12,15]

Axillary lymph node challenges

The difficulty in detecting metastases in the axillary lymph nodes can influence decisions regarding the extent of axillary surgery.[9,16]

Achieving clear surgical margins

The linear growth pattern of ILC can make it difficult to delineate the tumor's boundaries. This poses challenges in ensuring all cancerous tissue is removed, which is vital for minimizing risk of recurrence.[13]

While obtaining clear margins is paramount for all types of breast cancer, several studies show that positive margins are more common in ILC than other tumor types.[14,15] Guidelines from the Society of Surgical Oncology (SSO) and the American College for Radiation Oncology (ASTRO) delineate the recommended margin width for invasive breast cancer to be “no ink on tumor”. Analyses have shown these recommendations to be applicable to ILC cases as well.[17]

Society of Surgical Oncology-American Society for Radiation Oncology (SSO-ASTRO) guidelines

The introduction of the SSO-ASTRO guidelines, which defined a negative margin in BCS as "no ink on tumor," has led to fewer return surgeries for ILC patients.[17]

After the adoption of these guidelines, the rate of ILC patients converting to mastectomy decreased from 11.5% to 7.9%.[17]

The introduction of these guidelines provided a standardized approach, clearly defining the acceptable margins for tumor excision.[18] This shift towards a more standardized surgical approach has multiple benefits (Table 1).

Positive margin and re-excision rates

Positive margin rates after mastectomy for ILC differ among studies. One study noted a 10.6% overall positive margin rate, with T3 tumors having a higher rate of 18.7%.[3] For those undergoing BCT for large ILC tumors, clear margins are crucial. In a study of 314 ILC cases treated with BCT, 37.6% had positive margins. Of these, 52.5% underwent re-excision lumpectomies, achieving clear margins in 74.2% of cases.[15]

Re-excision lumpectomy is a surgical procedure that is performed when the initial surgery does not achieve clear margins, indicating that some cancerous tissue might still be present. In the context of ILC, this procedure has gained prominence due to the tumor's infiltrative growth pattern, which can sometimes make it challenging to achieve clear margins at the first attempt.[7] The effectiveness of >

TABLE 1

Benefits of a standardized surgical approach

Minimized surgical risks	Fewer surgeries translate to reduced exposure to surgical risks, such as infections, complications, and extended recovery times
Improved quality of life	Multiple surgeries can be physically draining and emotionally taxing for patients. By reducing the need for additional interventions, patients can experience a smoother recovery trajectory and less disruption to their daily lives
Economic implications *Refs 18,19*	Fewer surgeries also mean reduced medical costs, alleviating the financial burden on both the healthcare system and patients

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re-excision lumpectomy in ILC has been underscored by several studies. Table 2 provides a summary.

Positive margins after surgery

For patients undergoing BCS, positive margins are usually removed surgically, either with a re-excision or with a completion mastectomy. Positive margins can occur even post-mastectomy,[14] adding an element of uncertainty to post-surgical management. In this setting, the optimal management strategy may involve re-excision, post-mastectomy radiation, or both.[5]

Surgical techniques

The surgical approach for ILC is influenced by a combination of the tumor's characteristics, its stage, and the patient's overall health and preferences.[5,7]

While the primary goal remains the complete removal of cancerous tissue, there is an increasing emphasis on preserving the breast's natural form and function, ensuring that patients can lead a fulfilling life post-surgery.[19]

Two primary surgical techniques dominate the landscape of ILC management: breast conservation surgery (BCS) and mastectomy.[5,19] Each offers its own set of advantages and considerations, and the choice between them is often a nuanced decision made in collaboration between the patient and the medical team.

BCS

This approach, also termed lumpectomy, segmental mastectomy, or partial mastectomy, focuses on removing the tumor while preserving as much of the breast tissue as possible.[20]

The goal here is to achieve a balance >

TABLE 2

Benefits of re-excision lumpectomy

Reduced recurrence risk	Achieving clear margins is pivotal in minimizing the risk of local recurrence. Re-excision lumpectomy ensures that any residual cancerous tissue is removed, optimizing long-term outcomes
Preservation of breast tissue	Instead of opting for more aggressive surgeries like mastectomy, re-excision allows for the preservation of more breast tissue, aligning with the goals of breast conservation
Patient satisfaction	For many patients, preserving their breast is of paramount importance. Re-excision lumpectomy can offer a balance between oncological safety and cosmetic outcomes, leading to higher patient satisfaction

Ref 15

between effective cancer removal and aesthetic preservation.

Radiation therapy is typically recommended after BCS for invasive breast cancer.[5] Data on omission or radiation or partial breast radiation in the setting of ILC are lacking. By targeting the remaining breast tissue, radiotherapy reduces the risk of recurrence.

Mastectomy

Mastectomy involves the removal of the entire breast. Depending on the disease's extent, patient preference, and other factors,[7,20] various mastectomy procedures might be considered, including total (or simple) mastectomy, mastectomy with aesthetic flat closure, or mastectomy with reconstruction. Additionally, skin-sparing and nipple-sparing mastectomies can also be safely performed followed by reconstruction, with some data in ILC showing the safety of these approaches.[19]

Conclusion

Management of ILC, particularly the surgical approach, is influenced by a myriad of factors ranging from the tumor's characteristics to patient preferences. The challenges inherent in ILC surgery, stemming from its unique growth pattern, require a strategic and informed approach to ensure optimal patient outcomes. Staging, which provides a comprehensive understanding of the disease's progression to guide clinicians in tailoring treatment plans, is therefore of great importance.

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The evolution of surgical techniques – standardized following the SSO-ASTRO guidelines – reduce the need for re-excisions and enhance patient outcomes. Furthermore, the strategic use of neoadjuvant therapies has shown promise in downstaging tumors, potentially reducing the need for more aggressive surgeries. There is optimism that future interventions will be even more refined, ensuring the best possible outcomes for patients diagnosed with this unique subtype of breast cancer.

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Conclusions

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In this comprehensive handbook, our esteemed group of authors – comprising experts at the forefront of the field – has meticulously dissected the complexities of invasive lobular carcinoma (ILC). This distinct subtype of breast cancer represents 10–15% of all invasive breast carcinomas and is a significant area of study and ongoing research.

This educational handbook provides a panoramic view of ILC, from its unique growth patterns and cellular characteristics to the challenges it presents in imaging, diagnosis, and treatment. These challenges demand a deeper understanding and specialized approach.

ILC's linear and 'single-file' growth pattern, primarily due to the absence of E-cadherin protein expression from *CDH1* gene mutations, makes it challenging to detect using standard imaging tests. This elusive nature can lead to potential diagnostic delays and misdiagnoses due to the limitations of standard mammography in detecting ILC, especially in its early stages. Hence, the need for a multifaceted imaging approach, integrating advanced techniques such as magnetic resonance imaging (MRI), positron imaging emission/computed tomography (PET/CT), and contrast-enhanced spectral mammography (CESM), to ensure accurate and timely diagnosis becomes paramount.

The advancements in imaging technology have been pivotal in identifying and understanding the nuances of ILC, allowing for more targeted and effective treatments.

The pathology of ILC is diverse, with various morphological variants exhibiting different genetic mutations. This diversity is a testament to the complexity of the disease. Molecularly, ILC typically presents as a luminal A subtype, characterized by high estrogen receptor/progesterone receptor (ER/PR) expression. However, recent research indicates a higher prevalence of human epidermal growth factor 2 (HER2) mutations in ILC compared to other breast cancer subtypes, highlighting the evolving nature of our understanding.

This evolving understanding has led to the exploration of new therapeutic avenues, emphasizing the need for ongoing research to fully grasp the molecular intricacies of ILC.

Despite its favorable receptor status, which often leads to an optimistic initial prognosis, ILC has been associated with poorer treatment outcomes compared with invasive ductal carcinoma.

This disparity in outcomes, despite the favorable markers, underscores the complex nature of ILC and the need for a more nuanced approach to its management. >

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The surgical management of ILC is a multifaceted challenge, where staging and the Society of Surgical Oncology–American Society for Radiation Oncology (SSO-ASTRO) guidelines play a vital role in standardizing surgical approaches. These guidelines have been instrumental in reducing the need for re-excisions, thereby improving patient outcomes and minimizing post-operative complications.

The decision between breast conservation therapy and mastectomy is influenced by the size, location, and characteristics of the tumor, as well as the patient's overall health and preferences. The continuous evolution of surgical techniques, combined with the insights provided by the SSO-ASTRO guidelines, ensures that patients receive the most appropriate and effective surgical care.

Furthermore, the biological nuances of ILC present significant challenges in breast cancer management. Its poor detection rate on conventional breast and systemic imaging along with its inferior response to chemotherapy showcase the innate difficulty in treating this subtype.

This resistance to traditional treatments has propelled the exploration of alternative therapeutic strategies, including targeted therapies and immunotherapies, to enhance response rates and outcomes for ILC patients.

The unique nature of ILC metastases, often infiltrative and hypometabolic, complicates detection and underscores the need for a tailored approach to ILC treatment, requiring specialized diagnostic tools and expertise.

While treatments for ILC mirror those for other breast cancers, the efficacy varies, with endocrine therapy in combination with targeted therapies emerging as particularly promising.

The ongoing research and development of new therapeutic agents, specifically targeting the unique characteristics of ILC, are anticipated to revolutionize the treatment landscape.

Clinical trials specifically targeting ILC are limited, hindering therapeutic advancements. This gap underscores the pressing need for a more individualized approach to ILC treatment, and the urgency to invest in research tailored to this subtype.

As research continues to evolve, the medical community is poised to harness this knowledge, refining diagnostic strategies, optimizing treatment plans, and enhancing patient outcomes. The future holds promise as advancements in technology and research methodologies offer new avenues for exploration.

This handbook offers a holistic understanding of ILC, emphasizing the importance of an integrated approach to its management. As we continue to deepen our understanding of ILC, the challenge lies in translating these insights into clinical practice to continue improving patient outcomes and ensuring the best care for those affected.

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