Invasive Lobular Carcinoma: A Review of Imaging Modalities

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Invasive lobular cancer (ILC) is the second most common type of breast cancer. It is characterized by a unique growth pattern making it difficult to detect on conventional breast imaging. ILC can be multicentric, multifocal, and bilateral, with a high likelihood of incomplete excision after breast-conserving surgery. This is a review of conventional imaging modalities for detecting and determining the extent of ILC. Review of the literature finds that MRI and CEM surpass conventional breast imaging in terms of sensitivity, specificity, ipsilateral and contralateral cancer detection, concordance, and estimation of tumor size for ILC. Both MRI and CEM have also each been shown to enhance surgical outcomes in patients with newly diagnosed ILC that had one of these imaging modalities added to their preoperative workup.

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1. Introduction

Invasive lobular cancer (ILC) is the second most common type of breast cancer after invasive ductal cancer (IDC) with an estimated 28,785 new cases of ILC in the United States in 2022 [1]. Even though ILC comprises only about 10% of new invasive breast cancer diagnoses, its incidence is high and similar to that of ovarian cancer (estimated 19,880 new cases in 2022) and twice that of cervical cancer (estimated 14,100 new cases in 2022) [1][2]. ILC is associated with older age, more advanced stage at presentation, and larger size and nodal positivity in comparison to IDC [3]. The majority of ILCs are Luminal A intrinsic subtype as evidenced by high estrogen receptor (ER) and progesterone receptor (PR) expression and low HER2 amplification. Histologic subtypes of ILC include classical, pleomorphic, signet ring, solid, alveolar, tubulolobular, and histiocytoid carcinomas [4]. Pleomorphic variants harbor higher rates of HER2 amplification (35%) and triple negative cancers (13%) [5].

ILC is characterized by a unique growth pattern where the stromal invasion causes little disturbance of the normal architecture. Cancer cells grow in single files with minimal desmoplastic stromal response. ILC is characterized by loss of E-cadherin. E-cadherin is a calcium dependent transmembrane protein that maintains tissue integrity by maintaining cell-to-cell adhesion and preventing invasion [6]. It is coded by the CDH-1 gene located on 16q22.1 [7]. Loss of E-cadherin results in loss of alpha-, beta-, and gamma-catenins, while p120-catenin is upregulated and accumulates in the cytoplasm and plays an important role in invasion. Loss of E-cadherin and cytoplasmic accumulation of p120 are present in >90% of ILCs [8].

ILC has been historically difficult to detect on conventional breast imaging as it is often isodense or isoechoic to adjacent normal breast parenchyma and does not present as a palpable mass [9], also making it difficult to discern on clinical examination. Incomplete excision of ILC is common after breast conservation surgery, ranging from 12% to 60% [10][11][12], leading to re-excisions or even mastectomy. Positive margins can also be present after mastectomy with extensive ILC [13]. Moreover, ILC can be multicentric/multifocal and bilateral, making preoperative imaging workup critical to achieve complete resection [14].

2. Mammography and Digital Breast Tomosynthesis

Mammography (MMG) is the most commonly performed breast imaging modality and is the only screening test proven to reduce breast cancer mortality in randomized controlled trials [15]. Identification of ILC on mammography has proven to be a diagnostic challenge, and ILC carries a false negative rate higher than for other invasive cancers [16]. Because of the permeative growth pattern of ILC, up to 30% are mammographically occult and the pathologic size of ILC tumors can be underestimated in up to 70% of mammograms [17]. Mammographic sensitivity for ILC ranges from 34% to 92%, which trends lower than the mammographic sensitivity for IDC ranging from 63 to 98% [16][17][18][19][20]. The sensitivity of digital mammography (DM) is inversely related to breast density [21], which is exacerbated by the subtle findings of ILC. A recent literature review found that the sensitivity of DM across all densities is estimated to be around 34–83% for ILC but only around 8–11% for ILC in dense breasts [17].

The features of ILC on mammography can be subtle and variable. ILC most commonly presents as a spiculated mass (on DM) or architectural distortion (on mammography with tomosynthesis), followed by an asymmetric density or calcifications [22][23]. Less than 1% of ILC presents as well-circumscribed masses with regular borders [16][20]. Utilization of digital breast tomosynthesis (DBT) may improve the sensitivity and area under the curve for detection of ILC compared to digital mammography [24]. In a large multicenter trial, compared to DM alone, DBT identified more invasive breast cancers, and the detection rate for ILC increased from 0.27 to 0.55 per 1000 [25]. Similarly, Krammer et al. reported that DBT detected more ILCs in dense breasts than DM alone with increased sensitivity from 38.9% to 83.3% [26]. DBT significantly increased the conspicuity of ILC lesions (p = 0.002) compared to DM whereas the difference in conspicuity for IDC lesions was not significant (p = 0.2) [23].

While DBT can increase the conspicuity of ILC lesions, it fails to accurately assess tumor size of these lesions. Mann et al. noted that, in patients where ILC tumor was detected by mammography, more than half had an underestimation of tumor size by about 1 cm. In one review of imaging modalities for diagnostic evaluation for patients with suspected or proven ILC, it was referenced that large ILCs (measuring > 3 cm) were found to be particularly difficult to accurately measure on mammography [16]. Likewise, DM has been found to perform poorly for detecting multifocal, multicentric, and bilateral disease [16][17][26]. Overall, DBT can improve the detection of ILC when compared to DM alone, though imaging findings are subtle. It is not an adequate alternative to more sophisticated alternatives such as breast magnetic resonance imaging (MRI) and contrast-enhanced mammography for assessment and pretreatment workup of ILC. Given its superior performance compared to DM alone, it may be an alternative for imaging-guided biopsies of lesions detected by MRI [17].

3. Ultrasonography

Whole-breast ultrasonography (US) is not widely used for breast cancer screening given the higher rate of false positives relative to mammography [27]. However, diagnostic breast US is the imaging modality of choice for further characterization of a palpable abnormality or suspicious mass, distortion, or asymmetry visualized on mammography [28].

US sensitivity for ILC tumor detection is lower than other imaging modalities with sensitivity rates ranging from 68% to 92% [29][30][31]. Unlike mammography, US sensitivity is not impacted by breast density [32].

US has also been found to underestimate ILC tumor size in 18–53% of cases [29][33][34]. US-measured ILC tumor size and volume has also been found to correlate with final pathology to a lesser degree than other imaging modalities [35][36][37]. Vijayaraghavan et al. reported that for ILC tumors there is a median underestimation of tumor size by 3.5 mm (average 27.2%) and a median underestimation of tumor volume by 0.29 cm^3. The extent of ILC tumor size and volume underestimation by US was tumor-size-dependent, increasing with pathology-measured tumor size [37].

ILC does not have a specific appearance on US [38], most commonly presenting as a hypoechoic mass. Similar to mammography, ILC rarely presents as a well-circumscribed mass on US.

US plays a pivotal role in guiding biopsies of suspicious breast masses and detection of lymph nodes metastasis [39], although it still identifies less than 50% of lymph node metastasis [40]. US may play a role in predicting nodal burden in patients with ILC. Increased cortical thickness and loss of fatty hilum on US have been found to be associated with a higher nodal burden in patients with ILC (OR 58.40, 95% CI 5.09–669.71; $p = 0.001$) [30].

Overall, US remains an important imaging adjunct to mammography but likely provides no additional benefit for patients with newly diagnosed ILC given its underestimation of tumor extent and high discordance rate with final pathology.

4. Magnetic Resonance Imaging

Compared to other imaging modalities, breast magnetic resonance imaging (MRI) has the highest cancer detection rate; however, it is typically reserved for screening women at high risk for breast cancer due to cost, accessibility constraints, and false positivity rate [41]. In average-risk women with dense breasts, emerging evidence demonstrates significantly improved cancer detection rates with screening breast MRI compared to DBT, though there is currently insufficient evidence for widespread use in clinical practice [42].

For patients with newly diagnosed breast cancer, current guidelines recommend a preoperative breast MRI for the following groups: to identify occult primary breast cancer in patients with axillary node metastases and a negative mammogram, to better define tumor extent indeterminant by clinical exam and mammogram, to assess for

potential fascia or muscle involvement in patients with invasive breast cancers contiguous with the chest wall, and to screen the contralateral breast in patients with a high risk of breast cancer and patients who are interested in reconstructive surgery after initial resection [43][44][45]. Breast MRI is also traditionally used to determine eligibility and tumor response to neoadjuvant endocrine (NAE) and chemotherapy (NAC) treatments [46].

Recently, breast MRI has been recognized as a useful diagnostic tool in patients with ILC due to various factors. For one, MRI has a much higher sensitivity rate for ILC tumor detection when compared to the other breast imaging modalities (mammography and ultrasonography). The sensitivity rates for MRI range from 83% to 100%, with most studies reporting a sensitivity rate greater than 95% [29][30][35][36][47][48][49]. Furthermore, recent advancements in MRI spatial resolution (e.g., 3T vs. 1.5T) are leading to increased detection of tumors that were previously occult on mammography and ultrasonography [50]. Fewer studies have investigated the specificity rates for MRI but estimates range from 87% to 92.4% [35][49].

An additional benefit of MRI is that breast density does not limit cancer detection rates. In fact, a group of researchers found that supplemental screening with MRI rather than mammography alone in women with very dense breast tissue enhanced detection and reduced the number of interval cancers during the screening period [51].

The literature consistently reports MRI as the imaging modality with the strongest correlation of imaging to pathology tumor size estimate for ILC. Studies report the correlation coefficient for MRI–pathology tumor size as 0.58 to 0.97 with the average mean difference ranging from 1.6 mm to 7 mm [31][33][34][36][47][48][49][52][53][54].

Although MRI appears to be the superior imaging modality for patients with ILC, there is still debate about the accuracy of MRI to determine maximum ILC tumor span [47]. Estimates for tumor size overestimation range from 26% to 36.7% [9][35][48][55][56], while estimates for underestimation range from 13.3% to 59.1% [9][33][34]. Regardless of the degree of under- or overestimation, most studies have found that MRI is consistently more accurate in estimating maximum ILC tumor extent when compared to conventional imaging (mammography and ultrasonography) [52]. Gest et al. performed a logistic regression analysis to investigate whether there are certain factors that may predict discordance between tumor size estimation by MRI and final pathology [57]. Menopausal status (OR 0.27, 95% CI 0.10–0.71; $p = 0.01$), hormone receptor (HR) status (HR negative, OR 1.64, 95% CI 0.27–9.89; HR positive, OR 0.64, 95% CI 0.21–1.88; $p = 0.09$), and NAC (OR 10.33, 95% CI 3.58–29.8; $p < 0.001$) were all independently associated with greater overestimation of tumor size by MRI, while histological size (OR 1.05, 95% CI 1.02–1.08; $p < 0.0001$) and the presence of an additional in situ component (OR 4.66, 95% CI 1.01–21.5; $p = 0.02$) were associated with greater underestimation of tumor size by MRI [57]

One of the main benefits of including MRI as part of the diagnostic workup for patients newly diagnosed with ILC is the detection of additional ipsilateral and/or contralateral breast cancer. The data show that MRI detects an additional lesion in about one-third of patients with ILC and around 65–88% of these additional lesions are confirmed by pathology to be malignant [31][36][52][54][58][59][60][61]. One study found that 7% of patients with newly diagnosed ILC who underwent bilateral breast MRI benefited from early detection of contralateral breast cancer. A

multivariate analysis by Wong et al. found that higher breast density (odds ratio 3.19; 95% CI 1.01 to 10.0) and lymph node positive disease (odds ratio 4.02; 95% CI 0.96 to 16.9) are significantly associated with additional suspicious findings on bilateral breast MRI in patients with ILC [29]. In patients with multifocal/multicentric breast cancer, MRI shows a high sensitivity for the detection of additional cancer foci with sensitivity estimates ranging from 88% to 91.17% [62][63]. Because ILC is more likely to be multifocal, multicentric, and bilateral than other types of breast cancer, patients with newly diagnosed ILC may greatly benefit from a bilateral breast MRI. In addition to earlier detection of additional ipsilateral and/or contralateral malignancies, MRI can also detect potential infiltration of the underlying pectoralis fascia or muscle layer that may not be visible on conventional imaging [31].

Due to the frequent detection of additional lesions, about 25–50% [9][29][35][36][49][52][54][58][64][65] of patients with ILC who undergo a bilateral breast MRI report a change in surgical management from breast-conserving surgery (BCS) towards total mastectomy. The most common changes in surgical management are more extensive unilateral surgery (wider excision or total mastectomy) or the addition of contralateral surgery. One study including patients with all types of breast cancer found that patients with ILC were the most likely to have their surgical management changed by preoperative breast MRI [66].

Another benefit of patients with ILC undergoing a preoperative MRI is the potential for improved prediction of nodal disease burden. MRI has been shown to be comparable to axillary US in the evaluation of axillary nodal status of these patients and an additional axillary US may only be required when there are suspicious nodal findings on MRI [67].

The prediction of nodal status is particularly important for patients with ILC after neoadjuvant therapy (NAC or NAE) as the upgrading or downgrading of axillary lymph nodes influences axillary surgery decisions. A study by Abel et al. found that a post-treatment/preoperative MRI is poor at predicting nodal status in patients with ILC after neoadjuvant therapy [68]. Sensitivity and positive predictive value were significantly higher in clinically node positive patients compared to clinically node negative patients (47.4% vs. 20%, $p = 0.0485$ and 81.2% vs. 40%, $p = 0.0044$) and specificity and negative predictive value were significantly higher in clinically node negative patients compared to clinically node positive patients (78.6% vs. 33.3%, $p = 0.0019$ and 57.9% vs. 9.1%, $p = 0.0005$) [68]. Additionally, for clinically node positive patients only, an abnormal post-treatment/preoperative MRI was associated with a significantly higher proportion of patients with high burden of nodal disease on pathology compared to patients with a normal post-treatment/preoperative MRI (61.1% versus 16.7%, $p = 0.034$) [68]. These results imply that a preoperative MRI may be able to help predict high nodal burden and assist in axillary surgery planning in clinically node positive patients with ILC after neoadjuvant therapy. However, neoadjuvant therapy has been shown to not provide much benefit for patients with ILC tumors especially if clinically node negative [69]. Neoadjuvant therapy is associated with lower rates of downstaging and higher rates of margin positivity in cases changed from total mastectomy to BCS after neoadjuvant therapy [69]. Additionally, neoadjuvant therapy may not improve BCS rate and may lead to higher rates of total mastectomy after initial BCS [34][69]. However, for patients who are candidates for neoadjuvant therapy, studies show that MRI is useful in assessing tumor response after therapy [70]. As a result, for patients with ILC who undergo neoadjuvant therapy, MRI may play a role in assessing tumor response rate and staging after therapy to optimize surgical planning [70].

There continues to be debate in the literature about whether including MRI as part of the diagnostic workup for patients with ILC leads to unnecessary biopsies and mastectomies. In one study by Amin et al., MRI was found to have provided value by identifying additional malignancies and to have caused harm by leading to unnecessary additional biopsies almost equally in the study population of patients with ILC [71]. Rates of unnecessary biopsies due to preoperative MRI in patients with ILC range from 28% to 33.3% [14][71]. Additionally, many researchers have found that there are no unnecessary primary or final mastectomies as a result of patients with ILC undergoing a preoperative MRI [31][52][60][72][73]. Interestingly, a large cohort study by Lobbes et al. found that the likelihood of primary mastectomy as the chosen surgical treatment plan following preoperative breast MRI varied by breast cancer type. Patients with ILC who underwent a preoperative MRI had a lower likelihood of primary mastectomy compared to those who did not undergo an MRI (OR 0.86, 95% CI 0.76–0.99), while patients with IDC who underwent a preoperative MRI had a higher likelihood of primary mastectomy (OR 1.30, 95% CI 1.22–1.39) [74]. Some studies have also found a trend towards lower final mastectomy rates and secondary surgery rates in patients with ILC who undergo a preoperative MRI compared to patients who do not [72][75]. This trend is likely a result of the lower re-excision rates after initial BCS seen in patients with ILC who receive a preoperative MRI [48][54][60][75][76]. A study by Mann et al. found that 27% of patients with ILC in the non-MRI group compared to only 9% of patients with ILC in the MRI group required a re-excision surgery after initial BCS (OR 3.64, 95% CI 1.30–10.20; p = 0.010) [75]. However, many other studies have concluded that there is no difference in re-excision rates between MRI and non-MRI groups in patients with ILC [34][52][65][77][78]. In summary, the addition of preoperative MRI in the diagnostic workup of patients with newly diagnosed ILC is most likely associated with lower reoperation rates and minimal to no increase in the rate of initial or final mastectomies.

Although MRI has a higher sensitivity rate for ILC tumor detection, there has been concern about higher false positive rates compared to conventional imaging. In one study by Stivalet et al., researchers found that MRI sensitivity for ILC tumor detection was 100% at the expense of a 26% false positive rate [30]. The conclusions reached by this study, however, may be limited by its small sample size of only 15 patients with ILC and 31 total ILC masses. Several other studies have found that MRI does not in fact lead to a higher false positive rate in patients with ILC despite its high sensitivity rate [31][79][80]. Ultimately, it is recommended that all new lesions found on MRI should be evaluated by a US-guided or MRI-guided core biopsy to ensure pathologic proof of additional malignancy before a decision is made to change surgical management from BCS to ipsilateral, contralateral, or bilateral mastectomy [14][60]. This “second-look” biopsy by US or MRI can help to mitigate the high false positive rate with MRI and ensure a low rate of unnecessary operations [14][16][60].

In conclusion, some researchers support the addition of MRI to the diagnostic workup for all patients with ILC, especially when there is ambiguity of findings on clinical and conventional imaging (mammography and ultrasonography) [61][70]. However, the research shows that the benefits of adding MRI to the diagnostic workup for patients with ILC are limited to patients who are younger, have dense breasts, poor visualization by mammography, are post-neoadjuvant therapy, and/or are considering BCS [65]. Many societies have yet to determine whether MRI should or should not be included in the preoperative management of patients with ILC. The European Society of Breast Imaging and EUSOMA working group and NCCN recommend the use of preoperative MRI for patients with

ILC [35][60]. For now, the addition of MRI to the diagnostic workup of patients with newly diagnosed ILC remains a case-by-case and institution-by-institution basis.

5. Contrast-Enhanced Mammography

Contrast-enhanced mammography (CEM), also referred to as contrast-enhanced spectral mammography (CESM) and contrast-enhanced digital mammography (CEDM), was approved by the Food and Drug Administration in 2011. CEM combines conventional mammography with administration of intravenous iodinated contrast to provide both morphological and functional information about breast tissue and possible lesions. Commercially available CEM uses a dual-energy technique to generate two images in each projection: a low-energy mammogram similar to a standard mammographic image and a recombined image, highlighting areas of contrast enhancement while suppressing background glandular tissue [81]. Breast Imaging Reporting and Data System lexicon for CEM was recently introduced through the American College of Radiology to standardize interpretation and reporting [82].

In general, CEM is reported to have comparable accuracy to breast MRI, with equal to slight lower sensitivity and similar to slightly higher specificity [83][84][85][86]. In a recent meta-analysis, CEM had an overall 95% sensitivity and 81% specificity for breast cancer detection [87]. Additionally, CEM maintains favorable test characteristics in women with dense breasts, demonstrating a pooled 95% sensitivity and pooled 78% specificity in this cohort [87]. With regard to ILC, small single-center studies report CEM sensitivity ranges of 97–100% [83][88][89].

ILC more commonly presents on CEM as a mass rather than non-mass enhancement [88]. Cancers identified on CEM correlate well with histologic size, significantly outperforming mammography [90]. When comparing tumor size on CEM vs. MRI relative pathologic sizing, some studies show CEM having a superior correlation (Pearson correlation coefficient 0.75 CEM vs. 0.65 MRI, $p < 0.01$) [91] whereas in other studies MRI is superior (0.84 MRI vs. 0.77 for CEM, $p < 0.01$) [92]. In a study of 31 patients with ILC undergoing CEM, masses and non-mass enhancement had similar intraclass correlation coefficients for histologic sizing, 0.851 and 0.819, respectively [89].

The sensitivity of CEM in identifying multifocal, multicentric disease in the preoperative setting has been reported around 97.36–100% [88][89]. CEM has been reported to identify contralateral cancer in 10% [93]. For preoperative assessment of disease extent, CEM has been found to change surgical management in up to 20% of patients, including more extensive surgery in 16% (n = 16%) and conversion to mastectomy in 4% (n = 4) [83]. Given the accuracy of CEM in identifying the extent of disease, the surgical re-excision rate has been reported as low as 6.7% [89]. CEM has been reported to lead to additional biopsies in 12–19% of patients undergoing preoperative evaluation [83][93], though of the additional biopsies, up to 67% proved to be additional foci of invasive carcinoma [83].

The rates of change in surgical procedure and contralateral cancer detection on preoperative CEM are similar to MRI [59][66][71]. Preliminary data suggest that CEM may be equivalent to MRI in patients with breast cancer and a history of breast augmentation [94]. However, CEM does not allow for axillary staging and cannot visualize chest wall or internal mammary lymph nodes [81][95].

For women with breast cancer receiving NAC, MRI has traditionally been the main imaging modality used for assessing tumor response to NAC [96]. Conventional mammography has been of limited use and is not recommended to examine tumor response to NAC. The American College of Radiology grades the various imaging modalities for post-NAC treatment as follows: grade 9 for MRI, grade 8 for US, and grade 7 for mammography [96]. However, with the advent of CEM, which can reveal atypical vascular proliferation in tumors and increase the sensitivity of conventional mammography, studies have now found CEM to be comparable to MRI in determining the efficacy of NAC in breast cancer patients [96][97][98][99]. Some researchers advocate for the use of CEM as an alternative to MRI due to its shorter examination time, greater availability, better patient tolerance, and fewer contraindications [96][99].

Additional advantages of CEM relative to MRI include lower cost [100] and increased patient preference [101]. Exam time and interpretation time are faster with CEM, and there are no contraindications to metallic implants, patient size, or claustrophobia [102]. Disadvantages of CEM include relatively higher risks of contrast reactions [103][104] and potential contrast nephropathy [105] as compared to MRI, although the overall risks remain low. CEM also uses ionizing radiation [106], and CEM-guided biopsy is not yet widely available [107].

Although not specifically focusing on ILC, there are new clinical trials on the horizon investigating the utility of CEM in breast cancer screening and preoperative assessment. An upcoming prospective observational cohort study, Comparison of Breast Cancer Screening with CESM to DBT in Women with Dense Breasts (CMIST), plans to determine if CEM is more accurate than combined DBT and whole-breast US for primary screening in women with dense breasts [108]. Preoperative Contrast Enhanced Mammography in Staging of Malignant Breast Lesions (PROCEM trial) is an ongoing prospective randomized trial to evaluate the added value of CEM in the preoperative staging of breast malignancies [109]. Patients with breast cancer whose primary treatment is surgery will be randomized to no further imaging or CEM. The feasibility study prior to recruitment of this trial found that the treatment plan was changed in 10/47 cases (21%) and that CEM demonstrated improved size estimation with final pathologic size compared to mammogram and ultrasound [110].

6. Conclusions

Clinical examination along with conventional imaging by MMG, DBT, and/or US remains critical to the initial investigation of a new breast concern. However, these imaging modalities underperform in sensitivity, tumor size estimation, and detection of multifocal/multicentric disease for determining the extent of disease in cases of ILC. As a result, subsequent imaging is recommended for the preoperative evaluation of new ILC. Ultimately, the decision to pursue further diagnostic imaging with MRI or CEM should be a shared decision-making process between the patient and provider. Patients should understand the risks and benefits to additional imaging and how the imaging results may impact surgical management, risk of re-excision, and risk of recurrence. Of particular importance is that patients with newly diagnosed ILC interested in BCS are advised to undergo a preoperative MRI or CEM due to the additional information it can offer for surgical planning and management to improve rate of excision with negative margins and reduce reoperation rates.

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