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REVIEW

Is axillary imaging for invasive lobular carcinoma accurate in determining clinical node staging?

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Abstract

Purpose Preoperative evaluation of clinical N-stage (cN) is difficult in breast cancer patients with invasive lobular carcinoma (ILC). Our goal was to assess the predictive value of axillary imaging in ILC by comparing imaging cN and pathologic N-stage (pN).

Methods A single-institution retrospective review was performed for newly diagnosed stage I–III ILC patients undergoing preoperative breast imaging from 2011 to 2016. Clinicopathologic factors; mammogram, MRI, and ultrasound findings; and surgical pathology data were reviewed. Sub-analysis for pN2-N3 patients was performed to determine imaging sensitivity for patients with a larger nodal disease burden. Statistical analysis included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each imaging modality.

Results Of the total 349 patients included, 70.5% were cN0, and 62% were pN0 ($p=0.03$). For all patients, mammogram sensitivity was 7%, specificity 97%, PPV 50%, NPV 72%; ultrasound sensitivity was 26%, specificity 86%, PPV 52%, NPV 67%; MRI sensitivity was 7%, specificity 98%, PPV 80%, NPV 51%. For pN2/N3 patients, 38% were identified as cN0. Mammogram sensitivity was 10%; ultrasound 42%; MRI 65%. Pathology evaluation of N2/N3 patients indicated LN were replaced with ILC but maintained normal architecture. The average largest pathologic tumor deposit (1.5 ± 0.8 cm) correlated with average largest imaging LN size (1.4 ± 0.6 cm) ($p=0.58$).

Conclusion A statistically significant difference between clinical and pathologic N-stage exists for ILC patients. MRI was most sensitive for identification of pN2-N3 patients and should be considered part of routine axillary imaging evaluation for ILC patients.

Keywords Lymph Nodes · Invasive Lobular Carcinoma · Mammogram · Ultrasound · MRI · Clinical Stage

Introduction

In 2020, it is estimated that there will be more than 276,000 new cases of breast cancer and more than 42,000 will succumb to the disease [1]. Invasive lobular carcinoma (ILC) is the second most common histological type of breast cancer comprising 5–15% of all invasive breast cancers [2]. ILC can be challenging to detect with routine breast screening mammography due to the tendency of ILC to grow more diffusely, with neoplastic cells invading the stroma in a single-cell fashion [3, 4]. ILC has differing histologic subtypes that have correlative imaging findings. The "classical histologic ILC" presents mammographically as subtle architectural distortion [5]. Similarly, the gross pathologic examination of ILC are typically poorly demarcated tumors that can be difficult to define macroscopically because of the individual

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cell growth pattern of the malignant infiltrate [4]. In addition, there is often little host reaction or disturbance of the background architecture, which further hinders macroscopic detection and imaging findings [4, 6].

Multiple imaging modalities can be used for detection and diagnostic work-up of ILC. Mammography is the standard breast screening tool but results in a significant occurrence of false negatives, reported as high as 29.9% in ILC, due to the subtle presentation of this cancer [3, 5]. Breast ultrasound is primarily used as a diagnostic imaging tool based on mammogram or exam findings, but has similar challenges to mammography in ILC with often subtle imaging changes [5]. Breast magnetic resonance imaging (MRI) is the most sensitive imaging tool but is not routinely used for screening purposes outside of the high-risk population. However, it is often recommended for ILC patients at the time of diagnosis to improve assessment of the extent of disease within the breast [7]. While prior publications have examined the utility of MRI for assessment of in-breast tumor burden in ILC, none have explicitly reported on MRI use for nodal staging in ILC [2, 5, 7, 8]. Previous studies have reported accurate imaging assessment of nodal burden in ILC is difficult but have not defined this in detail [8, 9]. Preoperative evaluation of axillary metastatic disease in patients with breast cancer provides critical information guiding order of treatment and surgical planning. Therefore, it is important to ensure the optimum preoperative nodal clinical assessment is performed at the time of cancer diagnosis.

The goal of this study was to assess the predictive value of axillary imaging in ILC by comparing imaging clinical N-stage (cN) and pathologic N-stage (pN), considering mammogram, ultrasound, and MRI. In addition, we aimed to assess imaging and pathologic concordance specifically for patients with pN2-N3 disease to advise on optimum axillary imaging for patients with advanced nodal disease.

Methods

Following Institutional Review Board approval, a single-institution retrospective review was performed on women over the age of 18 with newly diagnosed, Stage I-III ILC who underwent preoperative breast imaging and breast cancer surgery from January 2011 to December 2016. Patients were identified using the cancer center tumor registry. Data were collected from the electronic medical record on eligible patients and subsequently entered into REDCap database [10]. Patients were excluded if they did not have preoperative imaging available for review or did not have surgery, and thus did not have surgical pathology evaluation, at our institution.

Clinicopathologic data collected included patient age, race, insurance status, clinical tumor size, receptor status (estrogen, progesterone, HER2), and sequence of treatment. Imaging details focused on tumor size as well as normal versus abnormal lymph node (LN) findings for a mammogram, ultrasound, and MRI. Patients were not required to have all three imaging modalities in order to be included in the study. All available breast and axillary imaging studies were included in the data collection.

If an image-guided LN biopsy was recommended, the results of the image-guided core needle biopsy were documented. Nodal information from surgical pathology was also obtained including N-stage, number of LN examined, and number of LN-positive.

An additional focused pre-planned analysis was performed on patients with pathologic pN2-N3 disease. We evaluated the interpreting breast radiologist and imaging technologist for potentially confounding provider-level factors which could impact imaging findings and outcomes. In addition, the number of axillary nodes visualized, size of nodes visualized, cortical thickness, and morphology were recorded from documentation found in imaging reports. This was correlated to detailed pathology slide review assessing the overall LN size, size of largest tumor deposit, and presence of abnormal morphology. This correlative evaluation provided assessment for possible missed findings on imaging such as an enlarged lymph node on surgical pathology that was not appreciated on preoperative imaging. The pathology-radiology analysis was performed specifically for pN2-N3 patients given this burden of disease should have greater potential for identification on imaging. This pathology-radiology review was not performed on N1 disease as a small burden of disease would not be uncommon to identify in surgical pathology specimens rather than preoperative imaging.

The primary outcomes of interest include the sensitivity, specificity, positive predictive value, and negative predictive value of each individual preoperative breast imaging modality in detecting axillary LN metastasis in patients with Stage I-III ILC. The secondary outcomes of interest were imaging sensitivity for patients with a larger pathologic nodal disease burden (pN2-N3) as well as review of imaging and pathologic data to determine if any imaging features could be used to more accurately predict advanced LN involvement. Statistical analysis was performed using a Chi-Square test and Fisher's t-test.

Results

A total of 349 patients met the inclusion and exclusion criteria. The average age was 63 years old (range 52–74), and most were Caucasian (88.5%) with ER-positive (97.7%) disease. HER2 positivity was uncommon (4.0%) as was triple-negative subtype (1.1%). Tumor mean size was 2.7 cm

Table 1 Patient demographics and tumor details for all patients ($n=349$)

	Mean ± Standard Deviation or Count (%)
Age	63 ± 11
Race (n): Asian	2 (0.5%)
African American	26 (7.4%)
Pacific Islander	2 (0.5%)
Caucasian	309 (88.5%)
Receptors: ER+	341 (97.7%)
HER2+	17 (4.0%)
Triple-Negative	4 (1.1%)
Average Clinical Tumor Size (cm)*	2.7 ± 2.1
Order of Treatment	
Surgery First	307 (88.0%)
Neoadjuvant chemotherapy	42 (12.0%)

*Measurement is recorded as largest single dimension on imaging

Table 2 Imaging modality sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV)

	All Patients (n = 349) (%)	N2–3 Patients ($n=52$) (%)
Mammogram ($n=338$)*		
Sensitivity	7	10
Specificity	97	
PPV	50	
NPV	72	
Ultrasound ($n=329$)*		
Sensitivity	26	42
Specificity	86	
PPV	52	
NPV	67	
MRI ($n=247$)*		
Sensitivity	7	65
Specificity	98	
PPV	80	
NPV	51	

*Number of total patients undergoing each imaging modality. As noted not every patient underwent every imaging modality

(range 0.6–4.8 cm), and the majority of patients (88.0%) underwent surgery as the first step in cancer treatment. Clinicopathologic characteristics are summarized in Table 1. There was a statistically significant difference between clinical and pathologic N0 status ($p=0.03$) with 246 patients (70.5%) identified as cN0 and 218 patients (62.0%) pN0. For all patients, mammogram sensitivity was 7%, specificity 97%, PPV 50%, NPV 72%; ultrasound sensitivity was 26%, specificity 86%, PPV 52%, NPV 67%; MRI sensitivity was 7%, specificity 98%, PPV 80%, NPV 51% (Table 2).

A total of 50 patients were recommended to have an image-guided core needle biopsy of an axillary LN, with 31 (62%) positive for malignancy. The remaining 19 patients had a negative image-guided LN biopsy. Of these 19 with negative image-guided LN biopsy, 4 (21%) had a positive LN on surgical pathology. All of these patients with the false-negative preoperative image-guided biopsy had pN1 disease. Among patients with pN2-N3 disease who were recommended to undergo image-guided LN biopsy ($n=20$), all had a positive preoperative biopsy. No patients with pN2-N3 disease who underwent image-guided biopsy had false-negative results. In total, 20 of the 31 patients (64.5%) with a positive preoperative image-guided LN biopsy had pN2-N3 disease on final pathology.

pN2-N3 disease was identified in 52 total patients. For these patients, 20 (38%) had no abnormal lymph nodes identified on any imaging modality and thus were classified as cN0. The remaining patients either had a positive biopsy as previously noted ($n=20$) or abnormal imaging only on MRI without a finding on ultrasound amenable to percutaneous biopsy ($n=12$). Mammogram sensitivity for N2-N3 patients was 10%, ultrasound sensitivity was 42%, and MRI sensitivity was 65%. (Table 2) Clinical exam was abnormal in two patients, with documented axillary fullness ($n=1$) or a single palpable level 1 node (n = 1) despite normal imaging. These patients did not have an image-guided biopsy preoperatively as there was not an imaging target for this biopsy to be performed. A review of both breast radiologists interpreting imaging and ultrasound technologists performing the imaging demonstrated no trends in patients whose advanced axillary disease was and was not identified on preoperative imaging. Thus, a provider-level factor was not identified in our review.

Of the 52 patients with pN2-N3 disease, 31 (59.6%) had surgical pathology slides available for additional review. Pathology evaluation of these patients identified complete replacement of the axillary LN with ILC but the LN maintained normal architecture, including normal cortical thickness and no evidence of desmoplasia or tissue reaction to the metastasis. (Fig. 1) The average largest pathologic tumor deposit measured 1.5 cm (range 0.7 to 2.3) and correlated to the average largest imaging LN size (1.4 cm, range 0.8 to 2.0) ($p=0.58$). Therefore, imaging may have properly visualized the pathologically abnormal node based on size, but there was no morphologic anatomic change to indicate malignancy in that node.

Discussion

This study examines mammogram, US, and MRI nodal imaging for breast cancer, the incidence of missed advanced nodal disease, and correlation of imaging findings with

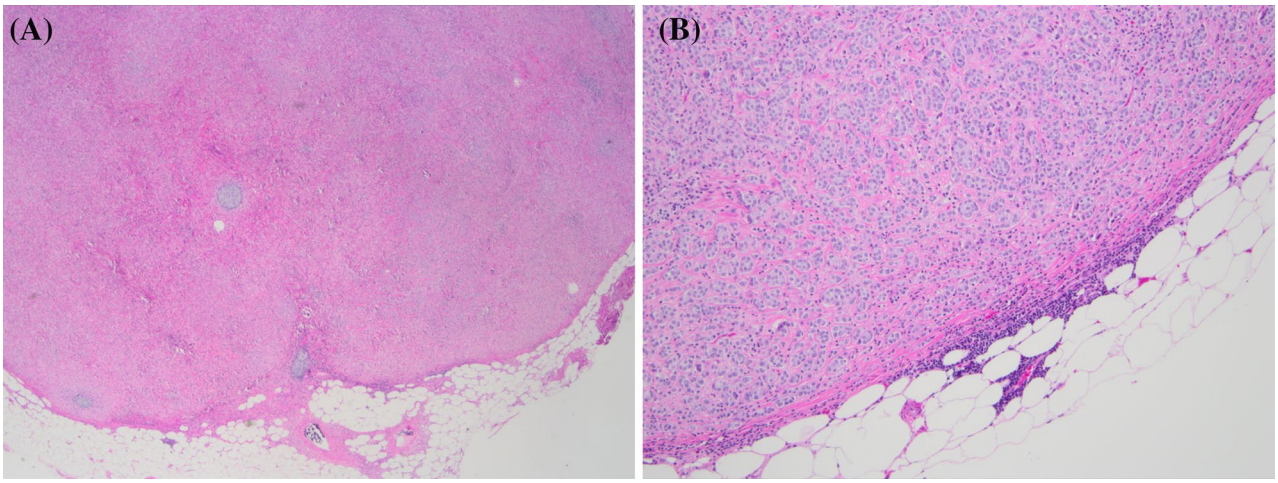

Fig. 1 (**a**) (Left Image) (H&E ×40) Metastatic lobular carcinoma has completely replaced the normal lymph node parenchyma. Three remaining small round residual lymphoid follicles can be seen in the center and subcapsular regions of the lymph node. (**b**) (Right Image) (H&E ×200) Metastatic carcinoma completely replaces the lymph node parenchyma and exists as monotonous epithelial cells in cords, clusters and as single cells with an absence of stromal reaction. The thin capsule can be seen in the lower right corner with a rim of extracapsular lymphoid and adipose tissue. There is no stromal reaction or thickening present within the capsule

pathology evaluation for a large cohort of patients with ILC. There was a statistically significant difference between clinical and pathologic nodal staging for ILC, with 38% of pN2-N3 patients being classified as cN0 based on axillary imaging. For all patients, ultrasound was the most sensitive for detecting nodal involvement, while for pN2-N3 patients, MRI was the most sensitive.

Prior studies have evaluated the sensitivity, specificity, PPV, and NPV for nodal metastasis identification for each breast imaging modality in generalized breast cancer cohorts but not specifically for ILC [11–13]. Prior studies that do focus on ILC have published results comparing US for IDC versus ILC, but have not including other imaging modalities in their evaluation of accuracy of preoperative staging [14–17]. Neal et al. reported one of the largest prior ILC-specific cohorts with an ultrasound false-negative rate for detection of pN2-N3 disease of 4.1% for invasive ductal carcinoma and 17% for ILC ($p < 0.01$), highlighting the difficulty in detection of nodal metastasis with ILC [18]. Our results are in keeping with these prior studies, but with the advantage of delineating sensitivity, specificity, PPV, and NPV for each individual imaging modality in a single cohort. Therefore, from our results, we can evaluate which may be best for predicting nodal status in ILC by considering each individual imaging modality.

Most clinicians could prefer highest sensitivity possible for cN work-up. Despite the potential for over-evaluation with this approach, the significant negative consequences of missing locally advanced disease are far more pressing. First, locally advanced disease often changes the sequence of systemic therapy and surgery with neoadjuvant chemotherapy recommended if advanced nodal disease is identified clinically. Second, surgery is often more extensive as the patient with advanced nodal disease requires axillary dissection if proceeding directly to the operating room. Neoadjuvant chemotherapy allows some patients with advanced axillary disease to safely avoid axillary dissection [19]. While rates of axillary downstaging in ILC are lower than for other types of breast cancer, conversion to pN0 status still occurs in 14% of patients after neoadjuvant chemotherapy, allowing them to safely proceed with sentinel lymph node biopsy rather than full axillary lymph node dissection [20]. Our study is important in that it contributes to the understanding of limitations on clinical node staging and identifies MRI as a modality which can improve clinical nodal staging in ILC patients. This is critical information for surgeons when assessing and counseling patients pre- and post-operatively.

Ultrasound traditionally is the preferred imaging modality for nodal assessment in breast cancer. Indeed, in our patients collectively, ultrasound was the most sensitive test and thus is indicated for clinical axillary staging evaluation in ILC similar to other histologic subtypes of breast cancer. However, based on our results, we recommend MRI also be considered a preferred imaging modality for axillary staging, specifically in ILC. MRI is currently used in patients with ILC due to its demonstrated ability to evaluate in-breast tumor burden, although recent publications have questioned the clinical value of evaluating in-breast tumor burden in these individuals. [7, 21, 22] Our results show that MRI is the most sensitive for detecting advanced nodal disease (pN2–3) and provides new evidence for clinical staging benefit and potential additional value for ILC patients.

One limitation to MRI for nodal staging evaluation is the inability to perform an image-guided LN biopsy with

MRI visualization. Ultrasound with intent to biopsy is indicated following the identification of abnormal LN on MRI. Unfortunately, ultrasound is significantly less sensitive in patients with advanced nodal disease, as demonstrated in our cohort. As a result, ultrasound will not be able to identify the abnormal LN seen on MRI in many individuals. Randomly targeted ultrasound-guided LN biopsy at the time of breast cancer diagnosis is not part of recommended practice, but specific biopsy of abnormal appearing LN is within the standard of care. We attempted via pathology review to determine if a specific subtle morphologic characteristic should indicate biopsy if identified on ultrasound, with the goal to better define which LN warrant biopsy for ILC patients. However, in our cohort, pathologically involved lymph nodes maintained normal architecture (Fig. 1), essentially making them indistinguishable from pathologically benign nodes on imaging. This is likely due to the infiltrative growth of ILC without desmoplastic reaction. As a result of these findings, our institution has implemented an advanced work-up protocol for patients with ILC who have abnormal LN identified on MRI. These patients all proceed to second look ultrasound identify a potential target for biopsy. These patients are closely followed to determine outcomes of second look axillary ultrasound identification of abnormal nodes to target for biopsy and subsequent accuracy of clinical nodal staging. Results of this cohort are currently pending. We recommend a continued high clinical suspicion for LN involvement even if no abnormal nodes are visualized on ultrasound both in terms of counseling patients as well as in terms of surgical decision making.

Specifically, concerning surgical decision making, our results raise the question if it is appropriate to consider the omission of sentinel lymph node biopsy for patients with ILC. Current guidelines suggest consideration for the omission of axillary surgery in cN0 patients over 70 years of age with ER+ HER2- disease, taking into account their other medical comorbidities and impact of this decision on systemic therapy recommendations [23–28]. Our data show that 12% of cN0 patients are pathologically node-positive at the time of surgery, but more concerning is that 38% of N2–3 patients have no imaging indication of nodal involvement preoperatively. Our data also demonstrate that we are not able to reliably predict extent of nodal disease in ILC patients based on preoperative imaging alone given a large proportion of patients with biopsy proven LN involvement preoperatively (64.5%) are found to have advanced (pN2-N3) disease at surgery. While systemic therapy for pN1 disease may not change, certainly patients with pN2-N3 disease would be considered for chemotherapy rather than endocrine therapy alone [29]. Extensive axillary disease may also impact adjuvant radiation recommendations [29]. Thus, patients with ILC do not appear to fall into guidelines for omission of sentinel lymph node procedure in surgery, and this guideline should not be routinely applied to them.

Our study has several limitations which should be considered. Due to its retrospective design, not every patient received every imaging modality. Therefore, with increasing numbers of patients undergoing all imaging modalities for evaluation, there may be variations in the reported sensitivity, specificity, PPV, and NPV. The study design was intended to include the largest number of patients possible for each imaging modality. More narrowly defining the patient cohort to only those who had mammogram, US, and MRI (all three imaging approaches) would be of interest in future studies to directly compare results in identical patients. Furthermore, we did not seek to identify patient or tumor characteristics which have been associated with higher rates of nodal involvement as this is outside the scope of this project and has been previously evaluated [30]. While the patients in our cohort represented an average ILC patient based on tumor size and prognostic marker profile, clinical judgment is still warranted when considering suspicion for nodal status. Finally, all patients at our institution are evaluated by a breast-specific radiologist and breast-specific radiology technologist. Prior studies have demonstrated improvement in cancer detection and staging with specialty-specific radiologists, and thus our results may not apply to practices whose imaging is interpreted by a general non-specialty radiologist [31, 32].

Despite these limitations, our study is important in that it identifies a previously unrecognized role for MRI in evaluating ILC patients and provides data for thoughtful surgical decision making with respect to axillary nodal staging.

Conclusions

Both ultrasound and MRI should be considered for preoperative nodal staging in patients with ILC as their sensitivities vary for patients with limited pN1 versus advanced pN2–3 disease. Even with optimum imaging evaluation, 38% of pN2-N3 patients will be incorrectly classified as cN0 preoperatively. Caution should be used when applying the guidelines considering omission of sentinel lymph nodes to ILC patients.

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Compliance with ethical standards

Conflict of Interest The authors have no financial or non-financial conflicts of interest to report.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. IRB approval was obtained for this study. Ethics approval and consent to participate were not required per IRB.

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