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A comparison of the imaging features of pleomorphic and classical invasive lobular carcinoma

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ABSTRACT

Purpose:

Pleomorphic invasive lobular carcinoma (pILC) is a distinct morphological variant of ILC with a poorer prognosis than classical ILC (cILC). The aim of this study was to ascertain whether the conventional imaging appearances of the two entities differ.

Methods:

A single center retrospective review of conventional imaging was undertaken in 150 consecutive patients with histopathologically confirmed ILC (38 pILC; 112 cILC) between April 2010 and July 2015. Mammographic and sonographic findings were evaluated using the BI-RADS lexicon by a radiologist blinded to pathology and findings in the two groups were compared. The degree of discrepancy between imaging and pathological sizing in the two groups was evaluated using Bland-Altman plots.

Results:

Lesions were mammographically occult in 11% of pILC and 14% of cILC (p=0.56). On mammography, inflammatory features and microcalcification were commoner in pILC than cILC (13% vs. 1%, p<0.01; 25%vs. 5%, p<0.01 respectively). Architectural distortion was more frequent in cILC than pILC (26% vs. 9%, p=0.01).

On ultrasound, pILC more frequently exhibited mixed echogenicity (28% vs. 13%; p=0.04), inflammatory features (8% vs. 0%; p=0.02), echogenic surrounding fat (33% vs. 9%; p<0.01), and posterior acoustic enhancement (10% vs. 1%; p=0.02) than cILC. CILC was more frequently manifested as a focal area of altered echogenicity (24% vs. 8%; p=0.04). Mean elastography stiffness was higher for pILC (174.8 vs. 124.6kPa; p=0.02).

Imaging-pathological size disparity was similar for both subtypes.

Conclusion:

There are differences in the imaging features between pILC and cILC, which reflect the more aggressive nature of pILC.

Keywords

Mammography, ultrasound, pathology, breast, lobular carcinoma

Abbreviations

Pleomorphic invasive lobular carcinoma (pILC); classical invasive lobular carcinoma (cILC); oestrogren receptor (ER); progesterone receptor (PR); human epidermal growth factor receptor (HER2); Breast Imaging Reporting and Data System (BI-RADS).

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Introduction

Pleomorphic invasive lobular carcinoma (pILC) is a distinct morphological variant of invasive lobular carcinoma (ILC) and was first described by Page in 1987[1]. Architecturally, pILC retains the characteristic infiltrative pattern of classical invasive lobular (cILC) carcinoma and its variants. The tumor cells demonstrate a loosely cohesive growth pattern but have certain distinct, pleomorphic, cytologic features characterized by enlarged nuclei with greater nuclear irregularity, hyperchromasia, a single prominent nucleolus along with faintly granular and abundant eosinophilic cytoplasm[1,2].

pILC is a rare subtype of invasive breast cancer and accounts for 1% of all female breast cancer[2,3] and approximately 15% of ILC[2]. Since pILC was formally recognized, studies have attempted to further characterize this variant. Clinically, pILC has a more aggressive behavior than cILC with worse disease free survival and poorer overall prognosis, but the data thus far are limited to small series[3,2]. Attempts to define the imaging features of pILC have also been limited, and to the best of our knowledge, there is only one small retrospective study that evaluated differences in radiological features between pILC and cILC[2]. However, this was limited by small numbers, compared pILC and cILC patients over different time periods, lacked detailed comparison of mammographic and ultrasound features, did not include elastographic data and did not include any comparison of the accuracy of mammographic and ultrasound lesion size estimations. Given the poorer prognosis of pILC, the ability to identify this variant preoperatively could suggest the need for more aggressive treatment and thereby influence preoperative management decisions.

Therefore the aim of this study was to review the mammographic, sonographic, and clinicopathologic features of pILC compared with cILC in a series of consecutive patients with a diagnosis of ILC.

Methods

Study population

This was a single center retrospective analysis of a consecutive series of patients with a diagnosis of either screen-detected or symptomatic ILC. The requirement for informed consent was waived for this study of anonymized imaging data, but institutional approval was received to allow extraction of data from our clinical, pathology and radiology systems. A total of 161 consecutive patients with histopathologically confirmed ILC diagnosed between April 2010 and July 2015 were identified. Of these, five patients with mixed pILC and cILC at final surgical histology were excluded from the study. One patient with cILC was excluded because of non-availability of mammographic and sonographic images, one because of the presence of breast implants which limited the assessment of the lesion, and two because the lesions were ipsilateral recurrences. Two pILC patients were excluded because of non-availability of images. Thus the total cohort

consisted of 150 patients; 112 with cILC and 38 with pILC. 93 patients (62%) had symptoms and 57 (38%) had mammographic screen-detected cancers.

The clinicopathologic features of all patients were assessed through a retrospective review of clinical records and pathologic reports to compare the tumor size, histologic grade, presence of axillary lymph node metastasis, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) status, and the presence of multifocal or multicentric tumors.

Histologic analysis

All patients underwent preoperative core needle biopsy yielding a diagnosis of ILC. Of the 150 patients, 17 did not undergo surgery as a result of significant comorbidities, 15 with cILC and 2 with pILC. Thus the diagnosis of cILC was based on surgical resection in 97 patients (87%) and on core biopsy only in 15 patients (13%), whereas the diagnosis of pILC was based on surgical resection in 36 patients (95%) and on core biopsy only in 2 patients (5%).

The diagnosis and grading of cILC and pILC were carried out using the criteria set out in the NHSBSP guidelines[2]. Essentially the tumor had to show the characteristic growth pattern and cytologic features of invasive lobular carcinoma but with the increased cytological pleomorphism defining the pleomorphic variant. Grading was carried out using the modified method of Elston & Ellis[2].

The assessment of ER, PR and HER2 was carried out as previously described[2,3]. The intensity of ER and PR staining was assessed and scored using the method described by Harvey et al.[2], i.e. Allred Scoring as per NHS BSP guidelines[8]. Cases with a score of 0 or 2 were defined as negative whereas those with a score of 3-8 were positive. HER2 assessment was carried out by immunohistochemistry followed by dual color FISH in cases showing "equivocal (2+)" staining. HER2 positivity was defined using standard criteria[2].

Mammographic examination

All patients underwent two-view digital mammography mammography (craniocaudal and medio-lateral oblique projections) in a single breast unit. Additional views (magnification, spot compression views) were tailored to individual cases.

Sonographic examination

This was performed using a 13MHz linear-array broadband transducer (Supersonic Imagine® system) in a dedicated breast unit either by breast imaging radiologists or an experienced breast sonographer. Quantitative shear wave elastography (SWE) was also performed according to Unit protocol with average mean stiffness from 4 images recorded from the stiffest part of the lesion.

Imaging analysis

One breast radiologist with 25 years of breast imaging experience retrospectively reviewed the mammographic and sonographic images independently, without knowledge of the pathologic findings. Mammographic density was recorded using the ACR Breast Imaging Reporting and Data System (BI-RADS) categorization 5th edition – fatty, scattered fibroglandular, heterogeneously dense and dense. The

abnormalities were interpreted using the BI-RADS lexicon[2]. Lesions were classified as either mass, asymmetry, architectural distortion, microcalcification, skin or trabecular thickening[2], shrinking breast sign or a combination of these features. The shrinking breast sign refers to an apparent decrease in breast glandular tissue volume observed as "shrinking" of the breast on mammography[2,3]. The presence of multifocal or multicentric tumors was recorded; the presence of two or more foci of tumor within the same breast quadrant was defined as multifocal, while the presence of two or more tumors in different quadrants of the same breast was defined as multicentric. In the case of multifocality or multicentricity, each lesion was assessed separately.

Ultrasound findings were recorded as normal, a mass or a focal area of altered echogenicity. The presence or absence of an echogenic halo, bright surrounding fat, skin thickening, subcutaneous or parenchymal edema with increase in echogenicity of the breast parenchyma[9], calcification, echogenicity, and distal effect was noted. Bright surrounding fat (Figure 1) was defined as a subtle, ill-defined increased echogenicity of the fat within a few centimeters of the lesion with no mass-like characteristics, whereas an echogenic halo has a clear cut boundary within 1-2mm of the edge of the central hypoechoic area and appearing to be part of the mass was noted.

For mass measurement, the largest dimension was recorded, and for tumors without mass appearances, the largest measurement between the edges of the area of altered echogenicity was documented. 28 patients with cILC and 10 patients with pILC who received neoadjuvant therapy or did not undergo surgical resection were excluded from imaging-pathologic size agreement analysis.

Statistical analysis

The clinicopathologic, mammographic, and sonographic features of pILC and cILC were compared using the chi-square or Fisher's exact tests for categorical variables, and Student's t-test for continuous variables. Post-hoc tests were performed for multiple comparisons with bivariate analysis and Bonferroni correction. Bland-Altman plots were used to assess the difference in imaging-pathologic size measurements. All statistical analyses were carried out using version SPSS 14.0 version for Windows and P values of <0.05 were considered significant.

Results

In total there were 112 patients with cILC and 38 patients with pILC. There was no significant difference in the mean age of patients in the two groups (Table 1). 11 (29%) of pILC and 46 (41%) of cILC were detected by screening mammography ($p=0.18$). Of 38 patients with pILC, three (8%) had multifocal lesions histopathologically. Of 112 patients with cILC, two patients had bilateral cILC, one had multicentric lesions and eight (7%) had multifocal lesions with one patient having three lesions within the same quadrant. Thus, there were a total of 41 and 124 histologically confirmed pILC and cILC lesions respectively, in 150 patients. The clinicopathologic findings are presented in Table 1.

As would be expected, there was a statistically significant difference in histologic grade, with more grade 2 tumors in the cILC group, while pILC were more frequently grade 3 ($p<0.01$), but there was no statistically significant difference between the two groups with respect to invasive tumor size or lymph node involvement. pILC was more commonly positive for HER2 ($p=0.02$) than cILC.

Mammographic findings

Lesions were mammographically occult in four (11%) patients with pILC and sixteen (14%) patients with cILC ($p=0.56$). Two of the 20 (10%) patients with negative mammography had very dense breast parenchyma (BI-RADS d); five (25%) had heterogeneously dense parenchyma (BI-RADS c) and 7 (35%) had scattered fibroglandular parenchyma (BI-RADS b).

Mammographic evidence of multifocality or multicentricity was uncommon. In the cILC group, one tumor (1%) was considered multifocal, one (1%) multicentric and three (3%) had a synchronous contralateral breast lesion. One (3%) pILC patient had both multifocal and multicentric lesions.

The mammographic findings are presented in Table 2, for a total of 40 pILC and 117 cILC. The most common mammographic appearance was of a mass, observed in 66 of 157 lesions (42%). On mammography, pILC tended to be larger (mean 32mm vs. 20mm, $p<0.01$) and was more likely to present with microcalcification or skin or trabecular thickening (25% vs. 5%, $p<0.01$; 13% vs. 1%, $p<0.01$, respectively) compared with cILC. 91% of pILC with mammographic microcalcification showed malignant calcification within the in situ component (pleomorphic lobular carcinoma in situ) on pathology where it was associated with comedo-type necrosis. This was observed in only 33% of the cILC with microcalcification on mammography. Architectural distortion was the dominant feature in 26% of cILC but only 9% of pILC ($p=0.01$).

Regarding mammographic lesion size, 25 of 54 (46%) measurements for cILC and 11 of 18 (61%) measurements for pILC in unifocal tumors were within 5mm of the histologic size ($p=0.28$). Bland-Altman plots of the differences for cILC and pILC lesions are presented in Figure 2 (a) and (b) respectively. The mean difference between mammographic size and pathologic size for cILC was 13mm, [95% limits of agreement (LoA) -30 to -56mm] and for pILC, 8mm, (95% LoA -21 to -37mm). Mammography systematically undersized all ILC, but there was also a proportional error for cILC in particular, with the differences in size increasing with histologic sizing.

Sonographic findings

Lesions were occult on ultrasound in one (3%) pILC and three (3%) cILC. In 2 (2%) cILC and one (3%) pILC, the tumor was considered multifocal/multicentric. Two (2%) patients had synchronous bilateral cILC lesions on ultrasound. There were a total of 39 pILC and 116 cILC lesions seen on sonography. The most common sonographic appearance was a mass, observed in 118 of 155 (76%) ILC lesions.

The sonographic findings of pILCs and cILCs are presented in Table 3. On sonography, pILC lesions tended to be larger in size (mean 23mm vs. 16mm; $p<0.01$), more often exhibited mixed echogenicity (28% vs. 13%; $p=0.03$) (Figure 3), skin thickening, subcutaneous or parenchymal edema with increase in echogenicity of the

breast parenchyma (8% vs. 0%; p=0.02), bright surrounding fat (33% vs. 9%; p<0.01), and posterior enhancement (10% vs. 1%; p=0.01) than cILC. CILC more frequently demonstrated a focal area of altered echogenicity (24% vs. 8%; p=0.04) than pILC. Mean shear wave elastography stiffness was higher for pILC (174.8 vs. 124.6kPa; p=0.02).

Comparing sonographic measurements with post-surgical pathology, 9 of 23 (39%) ultrasound measurements for pILC and 25 of 70 (36%) ultrasound measurements for cILC in unifocal tumors were within 5mm of the histologic size (p=0.83). Bland-Altman plots of the differences for cILC and pILC lesions are presented in Figure 4 (a) and (b) respectively. The mean difference for cILC was 18mm, (95% LoA -28 to -63mm) and was 17mm, (95% LoA -25 to -58mm) for pILC. There was again a proportional error with differences increasing with histologic size.

Screen-detected vs. Symptomatic

The pILC and cILC tumors were significantly larger in size in the symptomatic compared to screen-detected group [mammography (27 vs. 18mm, p<0.01), sonography (22 vs. 12mm, p<0.01) and pathology (42 vs. 22mm, p<0.01)]. There were more mammographically occult pILC and cILC tumors in the symptomatic compared to screen detected group (19% vs. 4%, p=0.01). The mean shear wave elastography stiffness was also higher for the symptomatic compared to the screen-detected group (143.5 vs. 110.6kPa, p<0.01).

Discussion

pILC is a distinct morphological variant of ILC and has been reported to have a poorer prognosis[4]. Because pILC is a rare subtype of invasive breast carcinoma, previous studies of pILC have been limited by a small number of cases. To our knowledge, there is only one small retrospective study[7] in the literature directly comparing mammographic and sonographic features of pILC and cILC (n=68) in which there were only 22 pILC.

A mammographic diagnosis of ILC is often difficult and a high false-negative rate in the range of 19-43% has been documented[2,3,4]. In our study, pILC was mammographically occult in 11% and sonographically occult in 3% of the cases, and these proportions were not significantly different from those in cILC (14% and 3% respectively).

Our results are consistent with the study from Jung et al.[7] where most pILC and cILC were manifest as a mass lesion on mammography and ultrasound. Interestingly, they reported no significant differences between the mammographic and ultrasound appearances of pILC and cILC. By contrast, we found that pILC exhibited skin or trabecular thickening, or subcutaneous or parenchymal edema with increase in echogenicity of the breast parenchyma significantly more often than cILCs, in keeping with the known more aggressive phenotype of pILC. In addition, microcalcification was more frequently observed on mammography in pILC compared to cILC and we have demonstrated that this is the result of malignant microcalcification associated with comedo-type necrosis within the in situ (pLCIS) component of pILC. The higher frequency of posterior acoustic enhancement can be explained by the greater number of grade 3 tumors, as seen with invasive ductal cancers[2], further support for the concept that pILC are more aggressive, rapidly proliferating lesions. This

may also explain the finding that pILC lesions were significantly larger on mammography and sonography compared to cILC. Likewise, the mean shear wave elastography stiffness was higher for pILC (174.8 vs. 124.6kPa; p=0.02), a finding associated with more aggressive high grade breast cancer[3]. Increased stiffness has been shown to be an independent predictor of lymph node involvement and resistance to neoadjuvant chemotherapy[4,5,6,7]. The differences in findings between the previous imaging study and the current study is likely to be due to the greater numbers and more detailed imaging analysis in the current study.

Our data showed that there was an absolute systematic error with significant underestimation of the sizing of both cILC and pILC at conventional imaging in relation to histologic sizing. The discrepancies in sizing increased as the histologic size increased, for both cILC and pILC, though this difference was less marked for pILC at mammography. Slightly less than half of the ILC measurements on mammography and approximately a third of the measurements on ultrasound were within 5mm of the histologic size.

Our series showed a much higher incidence of grade 3 pILC; indeed only 2 of 124 cILC lesions were grade 3, whereas over 60% of pILC lesions were grade 3. This is consistent with the findings from prior studies[3,8,9] which have also reported poorer clinical outcomes in pILC patients. Invasive lobular carcinoma typically expresses ER and PR[8,9] and does not overexpress HER2. Like Buchanan et al.[10], we found no significant difference in ER or PR negativity between the two groups, but we did find that pILC tumors were more commonly HER2 positive than cILC. HER2 overexpression is associated with poorer prognosis[11,8] and most of the earlier studies also demonstrated that pILC were more often HER2 positive than cILC[29].

We found that pILC and cILC tumors were significantly larger in the symptomatic compared to the screen detected group which are compatible with the findings from a large study by Allgood et al.[8] analyzing data in 19411 women. This, along with higher mean shear wave elastography stiffness value in the symptomatic group, suggests more aggressive tumor.

In this study, while there was a borderline difference in tumor size on pathology, there was no significant difference in the frequency of lymph node positivity, multifocal or multicentric disease or age distribution between the two groups. This may reflect one of the limitations of our study; namely, the smaller number of patients with pILC. We also had to exclude some subjects due to non-availability of mammographic and sonographic images, a further limitation of this retrospective study. In addition, we simplified the categories of mammographic and sonographic findings for analysis. The use of only one reader may also be regarded as a weakness of this study, but the reader was blinded to the histopathologic findings.

In conclusion, there are differences in the clinicopathologic and imaging features of cILC and pILC. On mammography, pILC tend to be larger and more commonly present with skin or trabecular thickening and microcalcification. Similarly, on sonography, pILC are larger than cILC and more frequently presented with mixed echogenicity masses, focal areas of altered echogenicity, bright surrounding fat, skin thickening, subcutaneous or parenchymal edema with increase in echogenicity of the breast parenchyma, and high shear wave elastographic stiffness values. Some of these clinicopathologic, mammographic and sonographic characteristics reflect the aggressive phenotype and poor prognostic features of pILC. The sizing of cILC and pILC lesions was significantly underestimated on mammography and ultrasound, particularly for larger

tumors. Given these characteristics of pILC, we suggest that MRI can be considered in the local staging of pILC as it is for cILC, especially in cases when clinical, mammographic or sonographic disease extent identified the need for a mastectomy. In addition, the preoperative identification of a more aggressive imaging phenotype may suggest the need for more aggressive treatment. Further studies are needed to confirm our findings in a larger cohort and to establish whether the imaging phenotype of pILC indicates a greater likelihood of response to neoadjuvant endocrine therapy.

Conflict of interest

The authors declare that they have no conflict of interest.

Table and Figure legends

Table 1: Clinicopathologic findings of pILC and cILC.

Table 2: Mammographic findings of pILC and cILC lesions.

Table 3: Sonographic findings of pILC and cILC lesions.

Figure 1a: Bland-Altman plots illustrating the size difference between the mammography and pathology against the size average of mammography and pathology for cILC.
Mean difference=13mm (95% LoA -30-56); SD, standard deviation.

Figure 1b: Bland-Altman plots illustrating the size difference between the mammography and pathology against the size average of mammography and pathology for pILC.
Mean difference=8mm (95% LoA -21-37); SD, standard deviation.

Figure 2a: Bland-Altman plots illustrating the size difference between the sonography and pathology against the size average of sonography and pathology for cILC.
Mean difference=18mm (95% LoA -28-63); SD, standard deviation.

Figure 2b: Bland-Altman plots illustrating the size difference between the sonography and pathology against the size average of sonography and pathology for pILC.
Mean difference=17mm (95% LoA -25-58); SD, standard deviation.

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