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Pleomorphic lobular carcinoma in situ of the breast: clinicopathologic review of 47 cases

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Abstract

Background—Pleomorphic lobular carcinoma in situ (PLCIS) of the breast is a distinctive entity, and yet its behavior and management are unclear. The purpose of this study was to review a relatively large number of cases and to evaluate the risk of recurrence.

Methods—Cases of PLCIS (n=47) over a 12 year-period were reviewed. The clinical, radiologic and pathologic findings were recorded. Immunohistochemistry for estrogen receptor (ER), progesterone receptor (PR) and HER2 were performed.

Results—Thirty-one patients had no concurrent or past history of breast cancer, six (19.4%) of which had local recurrence. All tumors (4 invasive carcinoma and two PLCIS) were ipsilateral. Younger age at presentation was a high risk factor for local recurrence with mean and range of 52.5 (44, 59) vs. 60.6 (40, 81) years (p=0.03). Three of 31 patients were treated with radiation therapy (RT), none of which developed local recurrence. PLCIS had an adverse ER/PR/HER2 molecular profile with at least 41.2% of the cases overexpressing HER2. Moreover, at least 11.7% of the cases were triple negative.

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Conclusions—This study included the largest number of patients that had no past or concurrent history of breast cancer with the longest clinical follow-up, providing an insight to the management practices and risk of recurrence from PLCIS.

Keywords

Pleomorphic lobular carcinoma in situ; local recurrence; breast; adjuvant therapy

INTRODUCTION

Lobular neoplasia (LN) that combines atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) is defined as a proliferation of loosely cohesive cells in the terminal duct lobular units. Two variants have been defined by the WHO task force: 1) lesions in which the lobular neoplastic cells show the cytological features of classic LCIS but in which there is marked distention of the involved spaces with areas of comedo necrosis; and 2) lesions that show marked nuclear pleomorphism [equivalent to that seen in high grade ductal carcinoma in situ (DCIS), with or without apocrine features and comedo necrosis, designated as pleomorphic LCIS (PLCIS)] (1). Type 1 lesion is viewed as a form of more extensive and/or florid form of classic LCIS and some clinicians have used the term “mass forming”. The clinical significance of this lesion is unclear. However, it is recommended to be surgically excised (2).

The current consensus is that LN constitutes a risk factor and a non-obligate precursor for subsequent development of invasive carcinoma in either breast in only a minority of women after a long-term clinical follow-up. While managing LN is controversial, excision should be performed for cases of classic LCIS (CLCIS) with comedo necrosis, bulky mass-forming LCIS lesions and cases of PLCIS identified on core needle biopsy, as the risk of concurrent invasive tumor is relatively high at 23% (3). However, in the absence of better information on the natural history of PLCIS, the World Health Organization (WHO) recommended that caution should be exercised in recommending more aggressive management strategies (1). Some authors have suggested treating PLCIS like DCIS only because they have similar clinical presentation (4). An interesting study surveyed 358 breast surgeons on how to manage PLCIS involving the resection margin. About half of the surgeons answered that they would not re-excite, while only about one quarter would (5).

Given the rarity of this lesion, we decided to retrospectively review a relatively large number of cases from three different academic institutions. The aims of the study included retrospective review of the clinical presentation of PLCIS with the radiologic manifestations, as well as the pathologic features including the molecular profile; the incidence of this disease comparing to CLCIS; assessment of the risk and the type of local recurrence subsequent to surgical excision; the role of margin status and the impact of radiation therapy (RT) and hormonal therapy (HT) on the risk of local recurrence.

METHODS

Pleomorphic Lobular Carcinoma in Situ cases identification and histologic classification

Roswell Park Cancer Institute (RPCI) clinical and pathologic databases were searched for PLCIS, LCIS, and DCIS. All PLCIS, CLCIS and solid type DCIS were reviewed by one pathologist (TK). All solid type DCIS cases were stained for E-cadherin, regardless of the cytomorphology. Cases were reclassified as PLCIS based on the complete lack of membranous E-cadherin and the presence of dyshesive pleomorphic cells as suggested by the WHO (1).

Cases from University of Kentucky Medical Center (UKMC) were searched through the Natural Language Search looking for LCIS in breast excisional biopsies for a study period between 2000 and 2012. Cases were retrieved from the University of Pittsburgh Medical Center (UPMC) through a computer-based search in CoPath for a study period between 2000 and 2012, for cases diagnosed as LN (ALH and LCIS) in breast excisions. Hematoxylin and eosin and E-cadherin staining results (already performed as part of routine practice) were reviewed. Cases were exchanged among all three breast pathologists (TK, MD and RK). When there was a disagreement between at least 2 pathologists, the case was excluded from the study.

The classification was based on the histologic and cytomorphologic features. The histologic features included presence of necrosis and macroacinar formation. Necrosis was defined as the presence of central zonal (comedo) type necrosis in at least one duct. Macroacinar feature was defined as massive degree of acinar distention to the point that the acini appeared almost confluent and the stroma barely evident in at least two acini (4). The cells were considered large (grade III nuclei) when their size was at least 4 times larger than that of a mature lymphocyte (6). The percentage of large cells was calculated and recorded. The tumor was considered pleomorphic when at least 10% of the tumor cells showed high grade nuclei. The cell types included were apocrine, non-apocrine, histiocytoid, signet ring and mixed types. Apocrine cells are large with eccentric nuclei, prominent nucleoli and conspicuous eosinophilic cytoplasm. Non-apocrine cells resemble lobular neoplastic cells in the CLCIS. Signet ring cells are those with eccentric nuclei exhibiting the classic cytomorphology of a signet ring. The presence of cytoplasmic mucin alone would not qualify for signet ring type. In histiocytoid cell type, the cytoplasm is foamy and clear resembling histiocytes. When a lesion was composed of at least two of these cell types, each comprising at least 10% of the lesional cells, a mixed cell type was considered.

The following data were recorded: patient's age, race, menopausal status, family history, tumor size, surgery type, and therapy modality (HT, RT). The surgical margin involvement with PLCIS and CLCIS was separately recorded. The margin was considered positive when the lesional cells were present at the inked margin. Family history was defined as presence of breast cancer in at least one of the first or second degree relatives. In addition, personal history of concurrent or past breast cancer was also recorded.

Immunohistochemistry

All cases were stained for E-cadherin. Twenty cases were stained for estrogen receptor (ER), progesterone receptor (PR) and HER2 (table 1). Tissue sections were cut at 5µm, placed on charged slides and dried in a 60°C oven for 1 hour. Upon return to room temperature, the slides were deparaffinized in three changes of Xylene and rehydrated using graded alcohols. Endogenous peroxidase activity was quenched with aqueous 3% hydrogen peroxide for 15 minutes and washed with phosphate buffered saline with 0.05% Tween-20 (PBS-T). Antigen retrieval was then performed. After a PBS-T wash, casein 0.03% (in PBS-T) was used as a block for 30 minutes and then the primary antibody was applied to the slides and left for 30–60 minutes. A PBS-T wash was followed by the biotinylated secondary antibody for 30 minutes. The PBS-T was followed by the streptavidin complex for 30 minutes. PBS-T was used as a wash and the Chromagen 3,3'-diaminobenzidine (DAKO, Carpinteria, CA) was applied for 5 minutes, resulting in brown color reaction product. The slides were counterstained with Hematoxylin.

Standard criteria and scoring systems were used in the evaluation of the IHC results. Allred scoring system was used to assess ER and PR status (7). The scoring for HER2 overexpression was assessed based on the ASCO-CAP guidelines (8). The equivocal cases were not tested by in situ hybridization.

Statistical analysis

Statistical analyses for comparing the groups in regards to categorical variables were performed using Fisher's exact test. A nominal significance level of 0.05 was used. This study has been approved by the internal board review (IRB) in all three participating institutions. No patients' consents were required.

RESULTS

Identification of PLCIS cohort

A total of 47 cases of PLCIS that met the WHO criteria were identified in the three institutions combined. There were 3 cases with concurrent and 13 cases with past history of breast cancer which were excluded from the risk of recurrence analysis. Therefore the total number of cases included in the risk of recurrence analysis was 31.

In RPCI, there were 5 cases reported as PLCIS, all of which were confirmed to be correctly diagnosed on retrospective review, based on diagnostic criteria. There were 36 cases reported as solid type DCIS. Upon retrospective review and staining for E-cadherin, 6 cases were reclassified as PLCIS. One case had equivocal E-cadherin staining and equivocal morphology with cells showing variable degree of cellular cohesion. This case was excluded from the study and was considered a mixed type mammary carcinoma in situ, based on WHO classification (figure 1a and 1b) (1). One case showed PLCIS morphology with weak cytoplasmic staining (figure 1c and 1d). This case was included in the study. There wasn't a single case demonstrating a histomorphology compatible with PLCIS that exhibited membranous immunoreactivity for E-cadherin. One case showed weak membranous staining for E-cadherin but the histomorphology was compatible with DCIS. One case

exhibited mixed cytoplasmic and membranous E-cadherin staining but showed DCIS histomorphology. The last two cases were considered DCIS. There were 310 LN cases at RPCI in the same time period, 3 of which were reclassified as PLCIS. The total number of cases of PLCIS at RPCI was 14. The incidence of PLCIS among all types of LN at RPCI was 14 out of 321 (4.36%). Four cases were excluded from the risk of recurrence analysis due to concurrent or past history of breast cancer.

At the UKMC, there were 12 cases reported as PLCIS. One case was reclassified as DCIS due to a lack of the histomorphologic criteria for LN which was supported by strong membranous staining for E-cadherin. One case was excluded from the risk of recurrence analysis due to the presence of concurrent ipsilateral invasive carcinoma. Seven cases were reclassified as CLCIS, nuclear grade II. The final number of cases was 3.

At the UPMC, there were 32 cases with a reported diagnosis of PLCIS. Three cases were reclassified as CLCIS, nuclear grade II and two cases were excluded from the risk of recurrence analysis due to the presence of concurrent DCIS (one ipsilateral and one contralateral). Nine patients had a past history of breast cancer. Therefore, the final number of cases included in the risk of recurrence analysis was 18. The total number of LN (ALH or LCIS) cases for the period between 2000 and 2012 was not available. However, reportedly the total number of LN cases between 2006 and 2011 was 807 (9). The total number of PLCIS cases in this period was 22. Therefore the incidence of PLCIS in UPMC among all lobular neoplasia was 22 out of 829 (2.7%).

Pleomorphic lobular carcinoma in situ, clinicopathologic findings (all patients, n=47) (table 2)

The majority of patients were postmenopausal (89.4%). The biopsy was performed for mammographic microcalcifications in the majority of the patients 38 (84.4%) (figure 2). One patient presented with nipple discharge and one patient had architectural distortion on mammography. The rest of the patients (n=7) presented with mass detected on mammography. There were 39 (83%) cases with apocrine cells and 40 (85.1%) with necrosis (figure 2). Macroacini were observed in 42 (89.4%) cases. While the signet ring cells were present in 1 (2%) case, histiocytic cells were seen in 5 (10.6%) (figure 2). The median and range of percentage of large cells was 50 (10 to 100). None of these variables had significant correlation with the risk of local recurrence after excluding patients with concurrent or past history of breast cancer.

Pleomorphic lobular carcinoma in situ, clinicopathologic correlation with risk of local recurrence (n=31) (table 3)

Sixteen of 47 (34%) patients had concurrent or past history of breast cancer. These cases were excluded from the risk of recurrence analysis. The median and range of follow-up for these patients was 55.6 (1.6 to 112) months. Three patients received RT, none of which developed tumor recurrence. Six patients had local recurrence [4 invasive carcinoma (3 of lobular type and 1 of no special type) and 2 PLCIS], all recurred ipsilaterally (table 4). All patients who developed local recurrence did not have RT. One patient (not included in the group of patients who had local recurrence) had re-excision after 2 months of surgery with

residual PLCIS. One patient had three recurrences within three years, and eventually underwent a total mastectomy. Tumor recurrence correlated with patients' age, with the younger patients being at risk with mean and range of 52.5 (44–59) vs. 60.6 (40–81), $p=0.03$. Eleven patients received HT, 3 of which developed local recurrence.

Biomarkers

Biomarkers results were available for 25 cases with ER/PR and 17 with ER/PR/HER2 (table 5). Of 25 cases, 21 had necrosis and 22 had apocrine cells. Overall 7 of 25 (28%) cases were negative for ER (figure 3a and 3b), 9 (36%) for PR, and 5 (20%) for both ER and PR. For HER2, 7 of 17 (41.2%) cases were positive (figure 3c and 3d), 8 (47.1%) equivocal and 2 (11.7%) negative. There were at least 2 (11.7%) triple negative cases. Four of the tested cases had local recurrence, including 2 triple positive, one ER-/PR+/HER2-equivocal and one ER+/PR+/HER2-equivocal.

DISCUSSION

PLCIS is a rare form of mammary carcinoma in situ, and its definition, classification, clinical presentation, and management are not entirely clear (1,6,10). Not uncommonly it is misclassified by the pathologist as CLCIS or DCIS (10,11). We have identified 3 cases misclassified as CLCIS and 6 as DCIS in RPCI cohort. For CLCIS cohort, we used the standard criteria set by the WHO for this reclassification. We identified 36 cases in RPCI data reported as DCIS with solid growth pattern. The E-cadherin immunostain was performed to yield 6 (16.7%) cases with negative staining and morphologic features of PLCIS. We did not find any case with PLCIS histomorphology and membranous E-cadherin staining. However, one case showed cytoplasmic staining (figure 1). It has been reported that membranous E-cadherin can be positive in up to 16% of LN and viewed as an aberrant expression (1). One case (2.8%) had equivocal morphology and equivocal E-cadherin staining, and was classified as carcinoma in situ with ductal and lobular features (figure 1). Two cases with ductal morphology had diminished membranous or cytoplasmic E-cadherin staining. It has been reported that E-cadherin could be diminished in a subset of high grade DCIS, particularly those with triple negative profile (6). We agree with Dabbs et al (12) that the lack of E-cadherin, although required, is not sufficient to render a high-grade in situ lesion a PLCIS. Therefore, in our opinion E-cadherin should not be performed routinely on all in situ carcinomas. It would be most useful in confirming the impression that is based on the cytomorphologic evaluation.

Currently the standard of care for patients with PLCIS diagnosed on a core needle biopsy is surgical excision (13). However, it is unclear how to manage the patients with PLCIS after breast conserving surgery, although some suggest that it be treated like DCIS (4). The management of PLCIS involving the resection margin also remains unclear (5).

Due to its rarity, the literature is poor in addressing important issues regarding the definition and management of PLCIS. We found that the incidence of PLCIS relative to all LN is between 2.7% to 4.36%. In the last decade, there have been some studies describing this lesion (table 6) (4,12,14–18). The majority of these studies investigated the pathologic features of this entity with only a few describing its clinical presentation and outcome. Snegi

et al studied ten cases with short follow up time (mean 17 months). None of the studied patients had local recurrence (4). Fadare et al described 6 cases with pure PLCIS. One patient who received RT developed a local recurrence in the form of PLCIS after 7 years (14). Down-Kelly studied 20 cases with a mean follow-up of 46 months. One patient who had been on HT developed a local recurrence after 19 months of initial diagnosis (18). In clinical trial NSABP-B17, 182 patients with LCIS were treated only with local excision without subsequent adjuvant therapy. They found the risk of local recurrence after 5-year follow-up at 9.3%. Interestingly, lobular intraepithelial neoplasia-3 (LIN3) which corresponds to our macroacinic type in our study had a higher risk of recurrence than LIN1 and LIN2. There were 38 cases of LIN3, 6 (15.8%) of which had a local recurrence. In our study we found the risk of local recurrence was 19.4%. It is worth noting that 16 of our cases had follow-up <5 years. In addition, the NSABP-B17 study did not include necrosis among the 16 pathologic variables. While the first factor regarding the follow-up interval would possibly have increased the number of patient who might have developed local recurrence in our study, the second factor related to necrosis may have increased this number for the NSABP-B17 study (19).

Therefore, in order to have a better understanding of the clinical behavior of this relatively newly recognized and poorly studied disease, we collected a relatively large number of cases (n=31). These cases were collected from three different institutions. They had a median follow-up of 55.6 months after excluding cases with concurrent or past history of breast cancer. We found that 6 (19.4%) patients developed local recurrence. Younger patients were at higher risk for local recurrence than older patients. The majority of our cases presented with microcalcifications followed by a presence of mass lesion, consistent with those in previous reports (14,16,20). However, occasionally the patient could present with bloody nipple discharge or distorted tissue on mammography. PLCIS, unlike CLCIS, occurs predominantly in postmenopausal women (21). It is somewhat similar to DCIS which affects a wide range of age with median between 50-years and 59-years (22).

Practicing breast surgeons have variety of management approaches to this disease with at least 25% not performing re-excision for a positive surgical margin (5). In the literature, only one study by Dow-Kelly et al has investigated the significance of margin status in tumor recurrence. There were 17 patients who had positive margin, one of which developed a local recurrence (18). In the current study, 9 patients had positive margins, 2 of which developed a local recurrence. However, in both studies, positive margin status did not have statistical significance, mainly due to the small number of cases and the variability in the adjuvant therapy particularly RT.

We were unable to calculate the risk of local recurrence for PLCIS vs. CLCIS. However, it is known that a woman with CLCIS has a 1%–2% risk of local recurrence annually with an end point of invasive carcinoma (19). Therefore, compared to our cohort of PLCIS who have been followed for a median time of 55.6 months, the risk of local recurrence for CLCIS would be a maximum of 9%. The risk of local recurrence for PLCIS was 19.4%. If we exclude 3 patients treated with RT and 2 patients treated with mastectomy, the risk of local recurrence will increase to 23.1%. Two patients had a local recurrence in a form of PLCIS after 7-months and 21-months, respectively. We believe that these patients had true

recurrence rather than residual disease because they presented with clustered microcalcifications on mammography that were completely excised with negative margins. However, if these cases are considered residual disease, the risk of local recurrence will become 15.4%, which is still higher than that of CLCIS. However, we were unable to determine the natural history of PLCIS or if RT improves local disease control.

The natural history of the disease and the benefit of RT in PLCIS can only be tested in a randomized prospective clinical trial similar to how the DCIS was studied. We explained the possibility of such clinical trial. The patients should be randomized into two groups, one treated with surgical excision and RT and one with surgical excision alone. We calculated the required cases that are needed to be enrolled in a clinical trial with the risk of local recurrence of 15% over a 5-year period. The total number of patients needed is at least 400, 200 in each arm. We have identified a relatively small number of cases (n=47) over a relatively long period of time (12 years) from three relatively large institutions. Moreover, about 34% of these patients had either concurrent or past history of breast cancer, making them ineligible for the proposed clinical trial. Therefore, we think such a clinical trial is neither realistic nor feasible.

Clinical trials had employed tamoxifen in patients with LCIS. After 5 years of therapy, women had 56% risk reduction of developing subsequent invasive carcinoma (23). Evidence from NSABP-B24 and NSABP-B17 clinical trials indicates that tamoxifen alone or with RT is beneficial for women with ER-positive DCIS. However, it is recommended that tamoxifen is an option for consideration and not a necessity (24). In our study, 11 patients received HT, 3 of which developed local recurrence. Two of these three recurred tumors had ER/PR Allred score of 3/8 and 0/5, respectively. However, these markers were not available for the rest of the patients treated with HT. Therefore, it is unclear whether the low ER expression could have played a role in the ineffectiveness of HT. In conclusion, it is unclear if HT is beneficial in improving local control for PLCIS.

Although there was no clear evidence that RT is beneficial or not, some authors recommended it for PLCIS to improve local disease control (4). However, these authors recommended a therapy similar to DCIS only because PLCIS presents like DCIS and has a high risk molecular profile. There was no clinical follow-up on the studied PLCIS patients. In our study, 3 patients received RT mainly due to the misclassification of these lesions as DCIS (1,10,11). It is worth noting that all patients who received RT did not have tumor recurrence. However, it was not statistically significant due to the small number of cases. In Downs-Kelly et al study, 10 of 26 patients received RT, all of which were disease free after a median and range follow-up of 66 (8 to 108) months. One patient who had a positive margin and did not receive RT developed a local recurrence after 19 months (18). In a study with somewhat conflicting results, Fadare et al followed up on 6 patients with PLCIS. One patient who received RT developed a local recurrence of PLCIS 7 years after diagnosis (14). It is unclear, as suggested by the authors, whether RT would have prevented the local recurrence with invasive carcinoma in that case. The other possibility is that RT does not completely prevent local recurrence and DCIS is a good example (24). Therefore, it is still unclear if the patient with PLCIS could benefit from RT.

We performed breast biomarkers of ER/PR/HER2 on representative cases. Interestingly, we found that PLCIS had an adverse biomarkers profile including triple negative in at least 11.7% and HER2+ in at least 41.2% cases. This finding is similar to the biomarker immunoprofile of invasive pleomorphic lobular carcinoma which was reported by us earlier (25). CLCIS is positive for ER/PR in up to 90% of the cases and rarely overexpresses HER2. Overall about 75%–80% of DCIS is ER+ and less so for PR (1). ER/PR/HER2 expression in DCIS is grade-related. ER/PR is expressed in the majority of low grade DCIS and only in about 20% of high grade DCIS. HER2 is overexpressed in up to 60% of high grade DCIS and only in about 10% of low grade DCIS (26). Therefore, we believe that the biomarker immunoprofile for PLCIS is similar to that of high grade DCIS than to low grade DCIS or CLCIS. Our findings are consistent with Chen et al results who studied 31 cases (16). Fadare et al studied 18 cases with necrosis and found all cases being positive for ER and all cases were negative for HER2 (14). In our study, 4 of 21 (19%) cases with necrosis were ER-/PR- and at least 5 of 13 (38.5%) were HER2+. Chen et al compared CLCIS and PLCIS using a panel of IHC and molecular profiling. They found that PLCIS has more aggressive phenotype while genetically related to CLCIS (16). In our study half of the cases had either triple negative or HER2 positive immunoprofile that perhaps contributes to the aggressive phenotype described by Chen et al (15).

We conclude that PLCIS is a distinct clinicopathologic entity. It has features similar to DCIS including an aggressive behavior with a high risk molecular profile and clinical and radiologic presentation. It is still unclear whether PLCIS requires complete excision with RT and/or HT to achieve a local control. However, this study can offer a step forward to suggest such therapy, particularly with the relatively high risk of local recurrence. Since a prospective clinical trial is not feasible, we encourage more reports such as this to increase the number of studied cases in the literature.

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Figure 1.

E-cadherin staining: A, histologic features of mammary carcinoma in situ with ductal and lobular features, note some cohesive cells in figure 1A are displaying cytoplasmic membrane staining for E-cadherin in figure 1B (H&E and E-cadherin 40 $\times$). C, cytomorphic features compatible with apocrine type PLCIS, note the presence of cellular dyshesion, eccentric nuclei, and conspicuous eosinophilic cytoplasm (H&E 40 $\times$); D, cytoplasmic E-cadherin staining (corresponding E-cadherin staining 40 $\times$).

Figure 2.

Histologic and radiologic features of PLCIS. A, back to back acini (macroacini) (H&E, 2×), inset showing apocrine cell morphology of eccentric large nuclei with prominent nucleoli and conspicuous eosinophilic cytoplasm and central comedo type necrosis with microcalcifications (H&E 20×), note this figure correspond to the radiologic picture D; B, signet ring cell (H&E 20×); C, histiocytoid cells (H&E 20×); D, clustered pleomorphic microcalcifications in mammography.

Figure 3. Biomarkers profile; A, PLCIS (H&E 10×), and B, matching ER- staining (ER, 10× with insert 40×); C, PLCIS (H&E 10×), and D, matching HER2+ staining (10×).

Table 1

Characteristics of antibodies used for immunohistochemistry

	Clone	Company	Dilution	Antigen-retrieval
ER	1D5	Dako	1/100	TRS/Vector
PR	PgR636	Dako	1/100	TRS/Steamer
HER2	Rabbit polyclonal	Dako	Prediluted	Epitope retrieval solution
E-cadherin	36B5	Leica	1:50	EDTA

Table 2

Clinicopathologic and radiologic features of all studied cases

Variable (No. of evaluable cases)		Total (n=47)
Age (years)	Median (range)	59.5 (40–88)
Race (47)	AA	6(12.8)
	CA	41(87.2)
Menopause (47)	Pre-	4(8.5)
	Post-	42(89.4)
	Peri-	1(2.1)
Family History (41)	Yes	23(56.1)
	No	18(43.9)
Radiology (45)	Mass	7(15.6)
	Calcifications	38(84.4)
Surgery type (47)	Lumpectomy	40(85.1)
	Mastectomy	7(14.9)
RT (47)	Yes	6(12.8)
	No	41(87.2)
HT (47)	Yes	15(31.9)
	No	32(38.1)
Size-mm (47)	Mean (range)	14.5 (1 to 60)
Margin-PLCIS (43)	Positive	9(20.9)
	Negative	34(79.1)
Margin-CLCIS (43)	Positive	27(62.8)
	Negative	16(37.2)
Necrosis (47)	Yes	40(85.1)
	No	7(14.9)
Apocrine (47)	Yes	39(83)
	No	8(17)
Macroacini (47)	Yes	42(89.4)
	No	5(10.6)
Signet ring (47)	Yes	1(2.1)
	No	46(98)
Histiocytoid (47)	Yes	5(10.6)
	No	42(89.4)
Large cells (47)	Median and range	50 (10 to 100)

Table 3

PLCIS (excluding cases with concurrent or past history of breast cancer) correlation between risk of recurrence and clinical variables

PLCIS		Recurrence (n=6)	No recurrence (n=25)	P value
Age (years)	Mean (range)	52.5(44, 59)	60.6(40, 81)	0.03
Race	AA (5)	1(20)*	4(80)	NS
	CA (26)	5(19.2)	21(80.8)	
Menopause	Post (27)	5(18.5)	22(81.5)	NS
	Pre (3)	1(33.3)	2(66.7)	
	Peri (1)	0(0)	1(100)	
Family history	Yes (16)	4(25)	12(75)	NS
	No (11)	2(18.2)	9(81.8)	
Radiology	Mass (4)	2(50)	2(50)	NS
	Calcifications (27)	5(18.5)	22(81.5)	
Therapy				
Surgery type	Lumpectomy (29)	6(20.7)	23(79.3)	NS
	Mastectomy (2)	0(0)	2(100)	
RT	Yes (3)	0(0)	3(100)	NS
	No (28)	6(21.4)	22(78.6)	
HT	Yes (11)	3(27.3)	8(72.7)	NS
	No (20)	3(15)	17(85)	
Pathology				
Size-mm	Mean (range)	17.2(2, 50)	14.7(3, 60)	NS
Margin-PLCIS	Positive (9)	2(22.2)	7(77.8)	NS
	Negative (21)	4(19)	17(81)	
Margin-CLCIS	Positive (22)	6(27.3)	16(72.7)	NS
	Negative (8)	0(0)	8(100)	
Necrosis	Yes (24)	5(20.8)	19(79.2)	NS
	No (7)	1(14.3)	6(85.7)	
Apocrine	Yes (26)	4(15.4)	22(84.6)	NS
	No (5)	2(40)	3(60)	

* N(%); AA, African America; CA, Caucasian American; RT, radiation therapy; HT, hormonal therapy

Table 4

Detailed clinical findings of patients who developed local recurrence (n=6)

	Case code	PLCIS-RPCI-2*	PLCIS-RPCI-4*	PLCIS-RPCI-10**	PLCIS-RPCI-15	PLCIS UPMC-7	PLCIS UPMC-32
Age-years		46	44	59	53	55	58
Margin							
	PLCIS	-	+	-	+	+	+
	CLCIS	+	+	+	+	+	+
Recurrence							
	Type	IDC	ILC PLCIS	PLCIS	ILC PLCIS	ILC	PLCIS
	Side	Ipsi-	Ipsi-	Ipsi-	Ipsi-	Ipsi-	Ipsi-
	DODx	9/2001	3/2005	5/2009	3/2010	9/2005	5/2010
	DOR	4/2009	2/2010	2/2011	1/2012	2/2012	12/2010
	Time to recur-m	91	59	21	22	77	7
Therapy							
	Surgery	Excision	Excision	Excision	Excision	Excision	Excision
	RT	No	No	No	No	No	No
	HT	Yes	Yes	No	Yes	No	No

* Two cases were misclassified as CLCIS;

** one case was misclassified as DCIS; DODx date of diagnosis; DOR, date of recurrence; RT, radiation therapy; HT, hormonal therapy

Table 5

Biomarkers profile according to the histologic features.

Case#	Code	ER	PR	HER2 IHC	Necrosis	Apocrine	Recurrence
1	PLCIS-UK-8	5	5	2	No	No	No
2	PLCIS UK-2	0	2	1	No	No	No
3	PLCIS UPMC 11	8	3	Na	Yes	Yes	No
4	PLCIS UPMC 14	6	5	Na	Yes	Yes	No
5	PLCIS UPMC 15	5	7	Na	Yes	Yes	No
6	PLCIS UPMC 21	3	0	Na	Yes	Yes	No
7	PLCIS UPMC 24	3	0	Na	Yes	Yes	No
8	PLCIS UPMC 25	8	0	Na	Yes	Yes	No
9	PLCIS UPMC 27	8	4	Na	Yes	Yes	No
10	PLCIS UPMC 28	6	3	3	Yes	Yes	No
11	PLCIS UPMC 3	0	0	Na	Yes	Yes	No
12	PLCIS-RPCI-10	6	5	3	Yes	Yes	Yes
13	PLCIS-RPCI-11	6	8	0	Yes	Yes	No
14	PLCIS-RPCI-12	0	3	2	Yes	Yes	No
15	PLCIS-RPCI-13	0	0	2	Yes	Yes	No
16	PLCIS-RPCI-14	8	8	2	Yes	Yes	No
17	PLCIS-RPCI-15	8	7	2	Yes	Yes	Yes
18	PLCIS-RPCI-2	3	8	3	No	Yes	Yes
19	PLCIS-RPCI-3	8	5	2	Yes	Yes	No
20	PLCIS-RPCI-4	0	5	2	Yes	No	Yes
21	PLCIS-RPCI-5	6	0	3	Yes	Yes	No
22	PLCIS-RPCI-6	6	3	3	Yes	Yes	No
23	PLCIS-RPCI-7	5	0	3	No	Yes	No
24	PLCIS-RPCI-8	0	0	3	Yes	Yes	No
25	PLCIS-RPCI-9	0	0	2	Yes	Yes	No

ER/PR are scored using Allred scoring system (7) incorporating the staining intensity (range from 0 to 3) and percentage of stained cells (0, 0%; 1, <1%; 2, 1% to 10%; 3, 11% to 33%; 4, 34% to 66%; 5 >66%). Then, Allred score is calculated by adding the predominant staining intensity to the proportion of stained cells, which ranged from 0 to 8. HER2 was scored following the ASCO-CAP guidelines (8).

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Negative: 0 (complete absence of staining) or 1 (weak incomplete membranous staining in any proportion of tumor cells or complete membranous non-uniform or weak intensity 10%); Equivocal: 2 (complete membranous non-uniform or weak intensity in >10% of tumor cells); Positive: 3 (uniform intense membranous staining in >30%).

Table 6
Clinicopathologic and follow up data of patients diagnosed with PLCIS: Literature review of published studies

	# cases	Therapy	Margin status	FU time (m)	Recurrence/Therapy	Time to recur-m
Sneige (2002) ⁴	10	L (n=5) M (n=2)	NA	4–32 (mean 17)	None	NA
Fadare (2006) ¹⁴	6	NA	NA	NA	1/RT	84
Simpson (2008) ¹⁵	9	NA	NA	NA	NA	NA
Chen (2009) ¹⁶	31	NA	NA	NA		NA
Sullivan (2010) ¹¹	11	L (n=10) M (n=1) RT: 4	NA	NA	NA	NA
Bagaria (2011) ¹⁷	5	NA	NA	NA	NA	NA
Down-Kelly (2011) ¹⁸	20 6 with IC	RT: 4 HT: 4 RT+HT: 6 None: 10	Positive 17 Negative 9	4–108 (mean 46)	1/HT	19
Current study	31	RT: 3 HT: 11 None: 17	Positive 9 Negative 21	1.6–112 (median 55.6)	6/HT 3; None 3	7–91 (40.5)

IC, invasive carcinoma; L, lumpectomy; M, mastectomy; NA, not available; RT, radiation therapy; HT, hormonal therapy