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Pleomorphic Lobular Carcinoma In Situ: Radiologic–Pathologic Features and Clinical Management

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Abstract

Background—Pleomorphic lobular carcinoma in situ (PLCIS) is an unusual variant of LCIS for which optimal management remains unclear.

Methods—We conducted a 15-year (2000–2014) retrospective chart review of the radiologic, pathologic, clinical management, and recurrence rates of patients with PLCIS on diagnostic biopsy. Fifty-one patients were found to have PLCIS either alone or with concomitant breast cancer. Of these, 23 were found to have pure PLCIS on diagnostic biopsy. Rates of upstaging after local excision, positive or close margins, mastectomy, and recurrence associated with pure pleomorphic lobular carcinoma in situ were examined.

Results—Of the 21 patients who underwent surgical excision following diagnostic biopsy, 33.3 % (7/21) were found to have invasive carcinoma, and 19 % (4/23) were found to have ductal carcinoma in situ. Extensive or multifocal PLCIS was present in 47.6 % (10/21) of patients, corresponding to at least one PLCIS-positive or close margin in 71.4 % (15/21). In total, there were 11 local reexcisions in nine patients, and 12 mastectomies. No ipsilateral breast cancer events have occurred, including in those with positive or close surgical margins (mean followup 4.1 years).

Conclusions—Patients with isolated PLCIS on diagnostic biopsy are at high risk of upgrading to invasive cancer or ductal carcinoma in situ at diagnostic excision. PLCIS often is extensive, with high rates of positive or close surgical resection margins. If negative PLCIS margins are pursued, rates of successful breast conservation are low. In light of this and low recurrence rates, caution should be exercised in aggressively treating PLCIS with excision to clear margins.

Classic lobular carcinoma in situ (CLCIS) is an established risk factor for breast cancer that is associated with an 8- to 11-fold increase in the relative risk of breast cancer.^{1–3} CLCIS is not considered an obligate precursor for breast cancer, because subsequent cancers are generally not in the same location as the initial CLCIS lesion and are equally likely to occur in the contralateral breast.⁴ If CLCIS is observed on diagnostic core needle sampling, the

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role of surgical excisional biopsy is debatable given the highly variable 2–40 % upgrade risk or risk of coexisting occult malignancy.^{5–7} In general, CLCIS is not considered a surgically treated entity, and wide surgical excision to obtain negative margins for CLCIS is not recommended.⁸ Rather, interventions are designed to prevent future cancer in either breast. Randomized, controlled trials, namely the NSABP P-01 Tamoxifen Prevention Trial, have demonstrated efficacy of chemoprevention with endocrine therapy for CLCIS.^{9,10}

Pleomorphic lobular carcinoma in situ (PLCIS) is an unusual variant of lobular carcinoma in situ (LCIS) that exhibits histologic and molecular features analogous to those of ductal carcinoma in situ (DCIS).¹¹ Due to these pathologic similarities, it has been suggested that management of PLCIS should mirror that of DCIS rather than CLCIS, including excision to clear surgical margins with or without adjuvant postlumpectomy radiation and endocrine therapy.^{12–15} The risk of concurrent invasive disease, or upgrading, at excision has ranged in prior studies from 0 to 65 %.^{9,12} Following excision, ipsilateral recurrence of PLCIS or of invasive breast cancer has been estimated at 3.8–19.4 %, suggesting that PLCIS may represent a precursor lesion to invasive cancer rather than a marker for increased breast cancer risk.^{12,16}

Current National Comprehensive Cancer Network (NCCN) guidelines state that “clinicians may consider complete excision of PLCIS with negative margins,” but also note that evidence on efficacy and outcomes associated with complete PLCIS excision are lacking.⁸ A recent survey of American breast surgeons highlights this ambiguity. The survey indicated a startling lack of consensus regarding surgical management of PLCIS observed at surgical margins: 53 % recommended no re-excision, 24 % always recommended re-excision, and 23 % recommended re-excision sometimes.¹⁷ In an effort to advance our knowledge on the outcomes and management of PLCIS after diagnostic biopsy, we conducted a 15-year review of PLCIS cases at our institution.^{16,18} The objectives of this study were threefold: (1) to report the radiologic characteristics associated with PLCIS; (2) to report pathologic findings observed after excision of PLCIS, including rates of upgrade to DCIS or invasive cancer; and (3) to examine the clinical management and recurrence rate of patients with PLCIS at our institution.

Methods

All patients diagnosed with PLCIS on core needle, vacuum-assisted, or excisional biopsy between January 1, 2000 and August 30, 2014 were identified through an inquiry of the University of Washington Medical Center (UWMC) pathology database. PLCIS was defined based on standard criteria including dyscohesive, E-cadherin negative pleomorphic cells in which the nuclei have at least a two- to threefold variation in nuclear size (Fig. 1). In total, 51 patients with a breast biopsy including PLCIS were identified. Of these, PLCIS was associated with invasive lobular carcinoma on biopsy in 43.1 % (22/51) of cases and DCIS in 9.8 % (5/51) of cases. PLCIS alone was identified in 47.1 % (24/51) of the biopsies.

A retrospective chart review of the 24 patients with PLCIS alone on core needle ($n = 3$), vacuum-assisted ($n = 14$), or excisional biopsy ($n = 7$) was then conducted. One of the 24 cases was sent to UWMC for pathologic review only, and the electronic medical record

contained no clinical or treatment information. This case was excluded from analysis. The following clinical, pathologic, and radiographic variables were recorded for the remaining 23 patients: patient age, race, menopausal status, personal breast cancer history, first-degree family history, history of hormone replacement therapy, mode of detection, type of biopsy, lesion characteristics on mammogram and magnetic resonance imaging (MRI), and greatest extent of lesion size on imaging. The greatest extent of disease on imaging was measured as suspicious calcifications on mammography or non-mass-like enhancement (NMLE) on MRI. Final pathology included extent of PLCIS and estrogen receptor status. Treatment variables also were collected, including surgical procedures, surgical margins, and receipt of adjuvant endocrine, radiation, and/or chemotherapy. A breast pathologist at the Seattle Cancer Care Alliance (SCCA) had previously reviewed all cases in the UWMC/SCCA multidisciplinary tumor board. The Institutional Review Board of the University of Washington approved this retrospective study.

Results

Patient Characteristics

We identified 23 patients (median age 55 years) with PLCIS alone on biopsy. All patients were female, and three had a previous history of contralateral breast cancer. Of the 23 patients, most were white, postmenopausal, and had no first-degree family history of breast cancer (Table 1).

Radiologic Characteristics of PLCIS

Almost three-quarters of cases (17/23) were detected on screening mammography (Table 1). All but one patient ultimately underwent mammography, and 81.8 % (18/22) were found to have suspicious calcifications that led to biopsy or correlated with clinical areas of concern. Advanced breast imaging with MRI was performed in 70 % of patients, and most commonly revealed non-mass-like enhancement (26.1 %) or no MRI abnormality (21.7 %). The greatest extent of disease on imaging was estimated as 2 cm or greater for 30.4 % (7/23) of patients. Needle sampling was performed for diagnosis in the majority of patients (73.9 %, 17/23).

Pathologic Findings on Excision of PLCIS

All patients found to have PLCIS on needle biopsy (17/23), and the majority of those found to have PLCIS on excisional biopsy (4/6) subsequently underwent surgical (re)excision. Invasive cancer was identified in 33.3 % (7/21) of patients who underwent excision after initial biopsy (Table 2). Invasive lobular carcinoma was the most common cancer identified. There were no cases of isolated invasive ductal carcinoma, and no invasive cancer was discovered subsequent to the first surgical excision. Upgrade to DCIS was observed in 4 of 23 (17.4 %) patients. One patient was noted to have no lesion on excision. Only 12 of 23 (52.2 %) patients had PLCIS alone on definitive surgical pathology. The overall observed upgrade rate to either invasive cancer or DCIS was 47.8 % (11/23).

Of the 22 patients who were observed to have PLCIS (alone or with concomitant cancer) on final surgical pathology, 45.5 % (10/22) were noted to have extensive or multifocal disease.

Among cases with measured extent of PLCIS, 91.7 % (11/12) had lesions 2 cm or greater, and 33.3 % (4/12) had lesions that measured 5 cm or greater. Estrogen receptor (ER) testing was not performed for eight patients. Of the 15 patients who did undergo estrogen receptor testing, 80 % (12/15) were ER-positive (ER+).

Clinical Management of PLCIS

Surgical Management—Twenty-one of 23 patients underwent further excision after initial diagnostic biopsy (Fig. 2). Five patients underwent immediate mastectomy: two were performed for positive PLCIS margins after initial excisional biopsy, one for a 5-cm expanse of NMLE on MRI, another due to concomitant DCIS discovered on contralateral breast imaging, and one had undergone multiple previous breast biopsies. All of these women upstaged to either invasive carcinoma (4/5) or DCIS (1/5) on final pathology. The remaining 16 women underwent local (re)excision. PLCIS involved or was <1-mm from local excision margins in 81.3 % (13/16) and involved margins in 20.0 % (1/5) of patients who underwent mastectomy. Re-excision or mastectomy was performed in 85.7 % (12/14) of patients with positive or <1-mm margins. Three of these patients (2re-excision, 1 mastectomy) had <1-mm PLCIS margins. Both of the re-excision patients underwent a second re-excision, and one had persistently close margins but did not undergo further surgery. Seven patients had persistently positive ($n = 3$) or <1-mm PLCIS ($n = 4$) margins at the time of definitive surgery; 28.6 % (2/7) of these patients had undergone mastectomy or bilateral mastectomy.

More than one-half of patients with PLCIS who underwent excision following initial diagnostic biopsy ultimately underwent mastectomy (12/21), and 66.7 % (8/12) of all mastectomies were bilateral. Contralateral DCIS or invasive cancer was present in five of the contralateral mastectomy specimens. Three cases had abnormal imaging or DCIS-positive biopsies that led to the bilateral mastectomy; the remaining two cases were occult.

Adjuvant Therapy—Of the 12 patients found to have PLCIS alone on definitive excision, most did not receive adjuvant therapy of any kind (Table 3). Chemotherapy was not offered to any patients with pure PLCIS on final pathology. Endocrine therapy was either recommended to or received by 41.7 % (5/12) of patients. Adjuvant radiation was either received or was recommended to 16.7 % (2/12). Four patients who underwent local excision alone had <1-mm PLCIS margins on final excision; none received radiation therapy and two of the four received adjuvant endocrine therapy.

Clinical Outcomes—Among all 23 patients, including the seven patients with positive or <1-mm margins at definitive surgery, there have been no recurrences with mean follow-up 4.1 years (range 5.7 months–9.6 years).

Discussion

PLCIS is a distinct variant of LCIS whose natural history and optimal management is debated. Although the incidence of PLCIS is only estimated to be between 2.7 and 4.4 % of all lobular neoplasias, the prevalence may be higher given the similarities of PLCIS to DCIS and probable misdiagnoses as such in the past.^{6,16} Analogous to DCIS, and consistent with previous reports of PLCIS, we found that almost three-quarters of PLCIS patients presented

with suspicious or pleomorphic calcifications on screening mammography.^{12,16,19,20} With the adoption of more sensitive mammographic technologies, including digital screening mammography and tomosynthesis, combined with a greater awareness of the pathologic entity of PLCIS, there is likely to be a rise in PLCIS diagnoses in the future. At the same time, there remains a clear divide amongst surgeons regarding whether PLCIS should be managed as a marker of increased risk similar to CLCIS or as a preinvasive lesion more akin to DCIS. We sought to further inform the literature regarding the presentation, management, and clinical outcomes of patients diagnosed with PLCIS during a 15-year period.

Recent literature has called into question the routine diagnostic excision of lobular neoplastic lesions detected via needle sampling of screen-detected mammographic abnormalities.^{21,22} This is founded in a negligible (<2–5 %) upgrade rate observed with select cases of pure lobular neoplasia, including focal lobular neoplastic lesions (<4 terminal ductal lobular units), those detected on screening imaging without associated masses, and those found in patients without coexisting risk factors, such as family history. However, our finding that nearly one-half of patients with pure PLCIS on biopsy upgrade to either DCIS or invasive carcinoma on surgical excision supports the practice of routine excisional biopsy following an initial biopsy diagnosis of PLCIS.^{12,23}

Beyond initial diagnostic surgical excision, there is little data to support any one management strategy, a controversy clearly demonstrated in the 2013 study of 358 American breast surgeons' management of PLCIS. Only two studies have reported on the status of surgical margins with PLCIS or the significance of surgical margins' impact on future in-breast cancer events. In a case series of 26 patients who underwent breast-conserving surgery for PLCIS alone or PLCIS with concurrent invasive carcinoma, Downs-Kelly et al. found that 23 % of cases had positive PLCIS margins and 27 % had margins ≥ 1 mm.²⁰ Similarly, 21 % of patients had positive PLCIS margins in a case series of 46 patients by Khoury et al.¹⁶ In our study, 35.8 % of patients had positive PLCIS margins after initial local excision; that percentage increased to 65.2 % with the inclusion of margins ≥ 1 mm. Our study provides further credence to the conclusion that positive or close margins are common in the setting of breast-conserving surgery for PLCIS. This also is consistent with our radiologic and pathologic findings that PLCIS was multifocal and extensive in almost half of cases. The diffuse pathologic extent as well as the high positive/close margin rate observed with breast-conserving surgery contributed to the high mastectomy rate (52.2 %) observed in our patient population. Although only breast-conserving patients were included in their study, Downs Kelly et al. also found that the majority of patients with PLCIS at their institution were treated with mastectomy because of its frequent diffuse, multicentric distribution.²⁴

The primary theoretical goal of excising PLCIS to clear surgical margins is to reduce the risk that residual PLCIS would either evolve or “recur” in the ipsilateral breast as an invasive cancer. However, preliminary data suggest that PLCIS-positive or close margins do not incur an appreciable risk of recurrent PLCIS or cancer on short-term follow-up. Downs-Kelly reported one PLCIS recurrence (3.8 % recurrence rate) in a patient with a positive margin on chemopreventive therapy.²⁰ In the study by Khoury et al. of the six patients who developed local recurrences (PLCIS, DCIS, or invasive cancer) (19.4 % recurrence rate),

four had had PLCIS-positive margins at the time of definitive surgical excision.¹⁶ In contrast to prior studies showing no invasive cancer recurrences, four of the recurrences in Khoury et al's study were invasive cancers (3 lobular).¹² Neither Downs-Kelly et al. nor Khoury et al. were able to show that PLCIS margin positivity was associated with increased risk of recurrence. In our own study of 23 patients with PLCIS during 4-year follow-up, no recurrences of PLCIS, DCIS, or invasive cancer have occurred, including three patients with PLCIS-positive margins and four patients with <1-mm margins at final surgical resection.

In summary, our study shows that PLCIS commonly presents radiographically as extensive calcifications detected on routine screening mammography. A substantial proportion of cases diagnosed as PLCIS alone on needle biopsy upgrade to invasive cancer or DCIS on surgical excision, supporting a recommendation of routine diagnostic surgical excision for these patients. Much like CLCIS, PLCIS often is diffuse and extensive resulting in high rates of positive or close surgical margins. In our own study, we have shown that if negative BCS margins are pursued, high mastectomy, and even bilateral mastectomy, rates ensue. Finally, even with high rates of positive or close PLCIS margins, recurrence risk of invasive cancer appears very low at short-term follow-up. Because PLCIS is a relatively uncommon entity, a randomized, prospective trial may only be made possible through a large cooperative group, such as the Alliance (for Clinical Trials), and is likely to take several years to accrue. Currently, in the absence of larger, combined multi-institutional data on PLCIS outcomes, we support the WHO's stance advising extreme caution for the treatment of PLCIS with aggressive surgical excision, particularly in light of highly effective chemopreventive endocrine agents.²⁵

Conclusions

Current management of PLCIS should include therapeutic excision if isolated PLCIS is identified on biopsy to rule out concurrent invasive carcinoma, but there remains a lack of quality evidence to inform management of surgical margins and adjuvant therapy. PLCIS-positive and close margins are common after breast-conserving therapy but do not appear to significantly increase the risk of early local recurrence. Pursuit of PLCIS-negative margins may result in a higher mastectomy rate without improving clinical outcomes.

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Fig. 1.

Histologic images of classic lobular carcinoma in situ, pleomorphic lobular carcinoma in situ, and ductal carcinoma in situ. **a** Classic lobular carcinoma in situ with enlarged terminal ducts filled with and distended by a population of dyscohesive cells with relatively monomorphic nuclei of low to intermediate grade. Hematoxylin and eosin $\times 200$. **b** Intermediate-grade ductal carcinoma in situ with central comedo-type necrosis involving a single duct. Note the punched out architectural spaces formed by the neoplastic cells and cohesiveness of the cells. Hematoxylin and eosin $\times 200$. **c** Pleomorphic lobular carcinoma in situ involving a terminal duct. The cells are dyscohesive and the nuclei show two-to threefold difference in size and shape. In this example, there are prominent intracytoplasmic vacuoles resulting in a “signet ring” appearance of the cells. Hematoxylin and eosin $\times 400$. **d** Terminal duct filled with both classic lobular carcinoma in situ (*arrowhead*) and pleomorphic lobular carcinoma in situ (*arrow*). The classic lobular carcinoma in situ has a low-grade monomorphic population of cells, whereas the pleomorphic lobular carcinoma in situ has cells with nuclei of varying size and higher nuclear grade. Both populations are dyscohesive and negative for E-cadherin (not shown). Hematoxylin and eosin $\times 200$

Fig. 2. Surgical management of pure pleomorphic lobular carcinoma in situ after needle or excisional biopsy

Table 1
Clinical characteristics and radiologic findings of 23 patients with pleomorphic lobular carcinoma in situ

Characteristics	N	%
Demographics		
Age, median years (range)	55 (36–70)	
White race	20	87.0
Hormone replacement therapy	9	39.1
Postmenopausal	15	65.2
First-degree family history	8	34.8
Radiologic findings		
Mode of detection		
Screening mammogram	17	73.9
Palpable mass/fullness	4	17.4
Screening MRI	2	8.7
Suspicious calcifications on mammogram ^a	18	81.8
Lesion characteristic on MRI		
No MRI	7	30.4
Focus ^b	1	4.3
Mass/space-occupying lesion	4	17.4
Non-mass-like enhancement ^c	6	26.1
No abnormal enhancement	5	21.7
Lesion size on imaging (mm)		
<10	5	21.7
10–20	4	17.4
20–30	2	8.7
30–40	2	8.7
40–50	1	4.3
50	2	8.7
Calcifications, NOS	6	26.1
Multiple lesions on MRI, NOS	1	4.3

MRI magnetic resonance imaging, *NOS* not otherwise specified

^aTotal represents 22 patients who underwent mammogram

^bFocus, <5-mm area of enhancement

^cNon-mass-like enhancement, lesions with abnormal enhancement larger than focus but without space-occupying effect

Table 2
Pathologic outcomes of 23 patients with pure pleomorphic lobular carcinoma in situ on initial diagnostic biopsy

Final pathology	Excisional biopsy (<i>n</i> = 6)		Needle biopsy (<i>n</i> = 17)	
	<i>N</i>	%	<i>N</i>	%
Invasive lobular carcinoma	0	0.0	5	29.4
Invasive lobular and ductal carcinoma	1	16.7	1	5.9
DCIS	0	0.0	1	5.9
DCIS and PLCIS	1	16.7	2	11.8
PLCIS	4	66.7	8	47.1

DCIS ductal carcinoma in situ, *PLCIS* pleomorphic lobular carcinoma in situ

Table 3
Adjuvant therapy in patients with final pathology of pure pleomorphic lobular carcinoma in situ

Adjuvant therapy	PLCIS (<i>n</i> = 12)	
	<i>N</i>	%
Endocrine therapy		
None	7	58.3
Tamoxifen or aromatase inhibitor	3	25.0
Recommended, unknown if administered	2	16.7
Radiation		
None	10	83.3
Adjuvant radiation	1	8.3
Recommended, unknown if administered	1	8.3
Chemotherapy		
None	12	100