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REVIEW

# The morphologic spectrum of lobular carcinoma in situ (LCIS) observations on clinical significance, management implications and diagnostic pitfalls of classic, florid and pleomorphic LCIS

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**Abstract**
Lobular carcinoma in situ (LCIS) is a non-invasive proliferation of atypical dyscohesive epithelial cells characterized by loss or functional alteration of E-cadherin-mediated cell adhesion. The morphologic spectrum of LCIS encompasses classic (C-LCIS), florid (F-LCIS) and pleomorphic LCIS (P-LCIS), as recently defined by the World Health Organization (WHO) Expert Consensus Group. Atypical lobular hyperplasia (ALH) is also part of this spectrum.
This article highlights the morphologic and immunohistochemical features of the three forms of LCIS and summarizes their management implications and prognosis, with emphasis on F-LCIS and P-LCIS.

**Keywords** Pleomorphic lobular carcinoma in situ (P-LCIS) · Florid lobular carcinoma in situ (F-LCIS) · Upgrade · Risk · E-cadherin

## Introduction

Non-invasive lobular neoplasia encompasses a spectrum of epithelial proliferations characterized by cell dyshesion and loss of cell polarity that fill and distend the terminal duct lobular units (TDLUs) with possible pagetoid involvement of ducts. The WHO Expert Consensus Group categorizes non-invasive lobular neoplasia according to nuclear atypia and architectural features into atypical lobular hyperplasia (ALH) and Lobular Carcinoma In Situ (LCIS), which includes classic LCIS (C-LCIS), florid LCIS (F-LCIS) and pleomorphic LCIS (P-LCIS) [1]. ALH and C-LCIS are often referred together as classic lobular neoplasia (C-LN). All forms of non-invasive lobular neoplasia are both risk indicators and non-obligate precursors of breast carcinoma, but differ in severity.

This review highlights the morphologic features, differential diagnoses, management implications and prognosis of C-LCIS, F-LCIS and P-LCIS. A practical discussion of the applications and pitfalls of immunohistochemistry in the diagnosis of non-invasive lobular neoplasia is included.

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## Classic LCIS

### Morphology

C-LCIS is a proliferation of non-cohesive and non-polarized cells with scant cytoplasm and low-grade nuclear atypia, that fills and expands the TDLUs. Because of cell dyshesion, the cell shape is round, and the nucleus occupies its center, resulting in a "fried egg" appearance. Intracytoplasmic mucin vacuoles are frequent and may indent the nuclei imparting the cells a signet ring morphology. C-LCIS is composed of Type A and Type B cells, alone or in combination [1, 2]. Type A cells are small and have scant cytoplasm; the nuclei are uniform, round to oval, with dense chromatin. Type B cells have a little more cytoplasm and are slightly larger than Type A cells; the nuclei are also slightly bigger and may show some variation in size and shape; the chromatin is vesicular and inconspicuous nucleoli may be present. (Fig. 1). C-LCIS may have focal single-cell apoptosis and/or minute foci of necrosis, but no comedo necrosis [1].

ALH is composed of cells morphologically indistinguishable from those of C-LCIS, but has limited extent, as

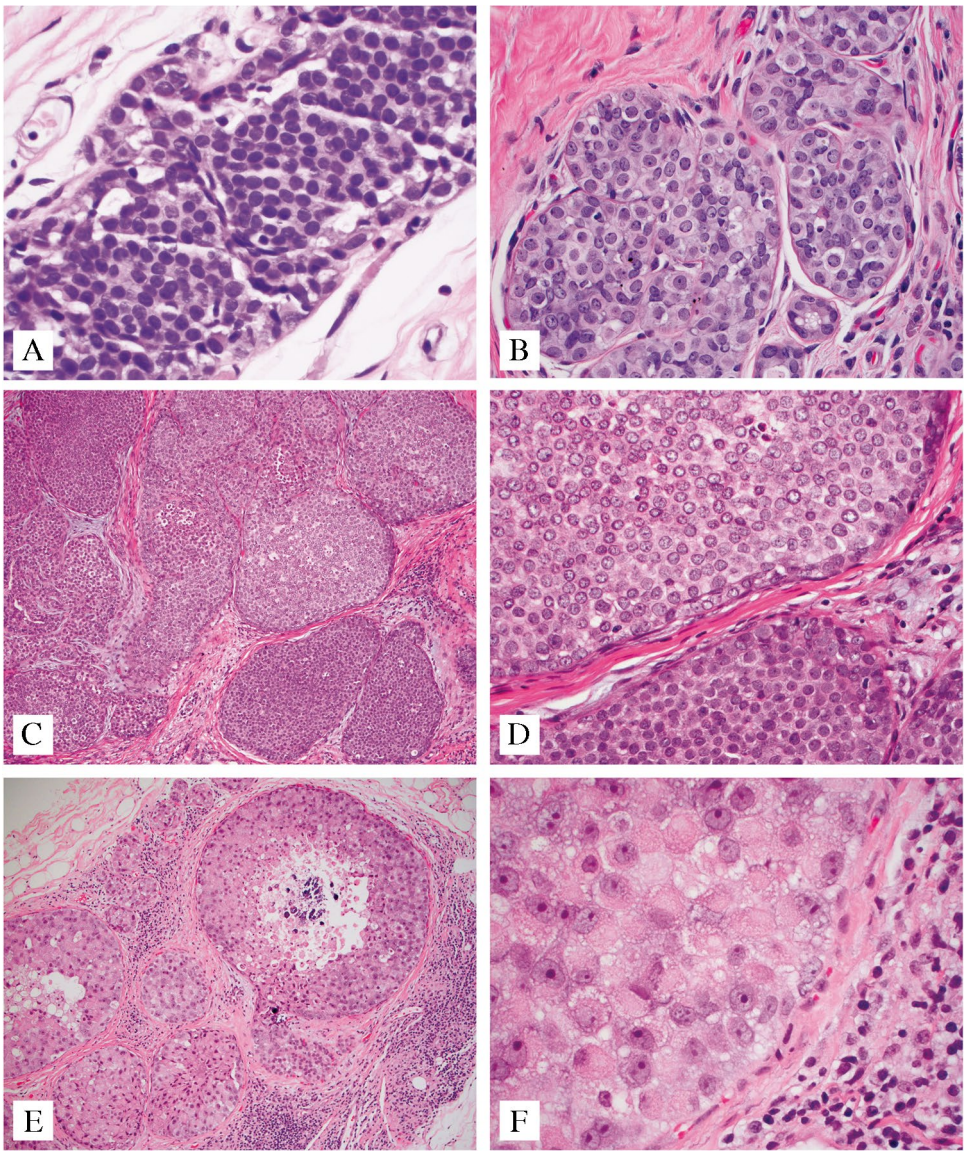


**Fig. 1 LCIS, different morphologies. A: Classic LCIS, Type A cells.** Type A cells are small and have scant cytoplasm. The nuclei are uniform, round to oval, with dense chromatin. **B: Classic LCIS, Type B cells.** Type B cells are slightly larger than Type A cells and have a little more cytoplasm; the nuclei are also slightly enlarged and may show some variation in size and shape; the chromatin is vesicular and inconspicuous nucleoli may be present**. C: Florid LCIS, diagnostic architecture.** Florid LCIS is characterized by massive expansion of the TDLUs. Each expanded acinus or duct fills a high power field of view (at least 40-50 cells across its diameter) and/or little to no intervening stroma is present between the expanded acini and ducts. **D: Florid LCIS, cytomorphology**. Florid LCIS may consists of type A (lower half of image) and/or Type B cells (top half of image). **E: Pleomorphic LCIS, most common architecture.** The acini and ducts are expanded by a solid proliferation of dyshesive epithelial cells. Central necrosis with calcification is evident in this example, but not required for diagnosis. **F: Pleomorphic LCIS, diagnostic cyto**. The cells are round to oval. The nucleus is enlarged (at least 4x the size of normal lymphocytes), the chromatin is coarse, one or more nucleoli are evident. Binucleate cells are present. In this example, the cells have abundant eosinophilic cytoplasm, consistent with apocrine morphology

it involves less than 50% of the acini of the TDLUs, with only minimal expansion [3, 4].

Pagetoid involvement of the extralobular mammary ducts may occur with either C-LCIS and ALH.

In 1941, Foote and Stewart identified LCIS (with morphology now referred to as classic) as the precursor of invasive lobular carcinoma (ILC) based on its morphologic similarity and spatial proximity to the latter [5]. Genetic evidence obtained in the last few decades has confirmed this relationship and documented the critical role of *CDH1*, which encodes E-cadherin, a cell to cell adhesion protein, in the pathogenesis of C-LCIS and ILC [6–11].

**Table 1** Morphologic features of LCIS and ALH

| Morphology | | | | |
|---|---|---|---|---|
| Common features | Non-invasive proliferation atypical epithelial cells characterized by lack of cell cohesion; the atypical cells fill and distends the TDLUs; Pagetoid growth into ducts is possible | | | |
| Type of lesion | ALH | Classic LCIS | Florid LCIS | Pleomorphic LCIS |
| Architecture | The atypical proliferation fills and slightly distends less than 50% of the acini in the TDLUs | The atypical proliferation fills and expands more than 50% of the acini in the TDLUs | 1. Scant to absent stroma between markedly expanded acini of involved TDLUs<br>*and/or*<br>2. Massive acinar expansion, with at least 40–50 cells across the diameter of an expanded acinus or duct | Some expansion of the acini and/ or ducts by a non-cohesive proliferation of epithelial cells |
| Cytologic features | Type A cells (small cells with uniform hyperchromatic nuclei)<br>*and/or*<br>Type B cells (slightly larger cells, nuclei with mild variation in size and shape, vesicular chromatin and small nucleoli) | | | Marked nuclear pleomorphism; nuclei 4x the size of small lymphocytes; nuclear atypia comparable to high-grade DCIS |
| Necrosis | Not present | Single-cell apoptosis or minute foci of necrosis may be present; no comedo necrosis | Comedo necrosis may be present (not required for diagnosis) | |
| Calcifications | May be present, usually rare and minute | | Coarse calcifications may be present (not required for diagnosis) | |

The morphologic features of C-LCIS are summarized in Table 1.

## Differential diagnosis

The differential diagnosis of C-LCIS includes epithelial proliferations of low nuclear grade atypia or benign.

Clear cell change of the epithelium of the TDLUs may mimic focal ALH, but the cells are cohesive and the cytoplasm is clear, whereas in ALH or C-LCIS clear empty spaces occur between the cells, secondary to cell dyshesion.

Low-grade DCIS with predominantly solid growth is a frequent differential diagnosis of C-LCIS. Cell cohesion with a mosaic-like pattern, and focal formation of microacini in a solid low-grade non-invasive epithelial proliferation support a ductal phenotype.

Myoepithelial cells with round to ovoid shape, somewhat abundant clear cytoplasm, possible cytoplasmic vacuolization, and enlarged nuclei, may mimic ALH. The regular distribution of the myoepithelial cells along the basement membrane of the TDLU is a useful diagnostic clue.

C-LN frequently associates with myoepithelial hyperplasia, and different patterns have been described [12]. (see Immunohistochemistry section) C-LN involving foci of collagenous spherulosis may mimic low-grade DCIS [13].

In some cases, C-LN involves a few acini incompletely or partially involves ducts with usual ductal hyperplasia (UDH). These scenarios can mimic UDH, ADH or low-grade DCIS (Fig. 2).

In these settings, the diagnosis rests on the identification of the aforementioned three cell types coexisting in the lesion, namely 1) ductal cells that are either hyperplastic, or are present as an attenuated monolayer or polarized cells around the residual acinar/ duct lumen; 2) dyscohesive C-LN cells with the characteristic "fried egg" morphology admixed with or undermining the ductal/ acinar epithelium; 3) inconspicuous myoepithelial cells with "comma-shaped" nuclei with dense chromatin, usually without any discernible cytoplasm, admixed with the lobular proliferation. In collagenous spherulosis, the myoepithelial cells surround the myxoid and translucent or densely eosinophilic globoid deposits of extracellular matrix characteristic of the lesion.

Immunohistochemical stain for E-cadherin, beta-catenin, p120 and myoepithelial markers can be used to resolve ambiguous cases (see section on immunohistochemistry).

### Clinical presentation, management and follow-up

C-LCIS can occur at any age but is most common in premenopausal women. The median age at diagnosis is 51–55 years. Historically C-LCIS is reported as multicentric in 80% of cases and bilateral in 40% [2]. In two contemporary series, 2–4% of patients with C-LCIS had histologic evidence of C-LCIS in the contralateral breast [14, 15].

The incidence of C-LN is difficult to determine, but it is estimated to range from 0.5% to 4% of benign breast biopsies. Analysis of population data and institutional series shows that in the past few decades the incidence of C-LCIS has increased, especially in postmenopausal women. The increase is estimated to be two- to fourfold since the 1980s [14–18]. This phenomenon may in part be secondary to improved imaging techniques and histopathologic detection, including the use of immunohistochemical stains, and to aging of the population. Hormone-replacement therapy and environmental exposure to hormone-like substances have also been suggested as possible contributing factors, but their role is difficult to assess.

Over time, the surgical management of patients with C-LCIS has changed substantially. While in the 1960s–70s most patients with C-LCIS underwent mastectomy, often bilateral, in the past few decades 50–80% of women with C-LCIS had a surgical excision, and mastectomy was performed only in 10–20% of cases [15, 16, 19, 20].

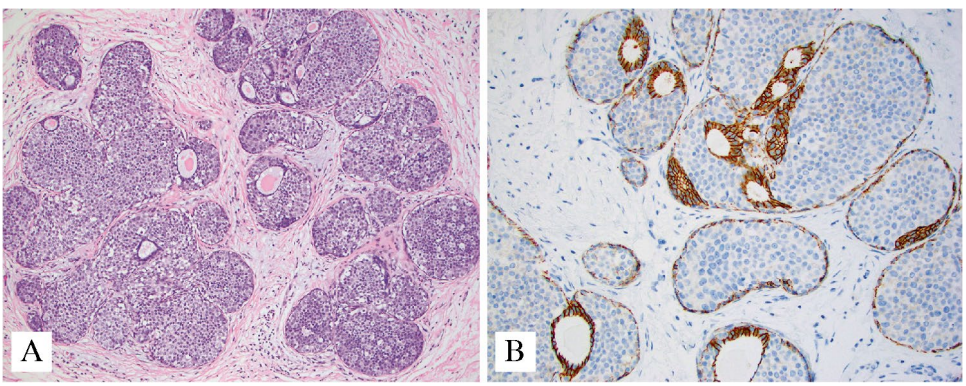


**Fig. 2 Classic LCIS partially involves a TDLU, in a pattern that mimics low-grade DCIS. A:** Classic LCIS composed of Type A cells expands the acini, but focal residual polarized epithelium is present. The resulting pattern mimics low-grade ductal carcinoma in situ. **B:** Classic LCIS shows loss of E-cadherin, while the residual ductal cells are polarized around the lumen of the acini

Women with C-LCIS have an 8–11-fold higher risk of subsequent carcinoma than control populations [3, 21–23]; the risk associated with ALH is increased 3.5–6-fold [3, 24–27].

Contemporary studies assessing the risk of subsequent breast carcinoma in women with C-LCIS show that most cancers are diagnosed in early stages, are hormone-receptor-positive, HER2-negative and of low or intermediate grade. Invasive ductal carcinoma tends to occur equally in both breasts, but ILC is significantly more frequent in the index breast, further supporting the notion that C-LCIS is a precursor lesion [14–16]. The 10- and 20-year breast cancer-specific survival for women with C-LCIS is greater than 95% and 90%, respectively. In a recent population-based analysis, overall survival and relative survival of patients with C-LCIS were 91.5% and 98.5% at 10 years, and 76% and 95.2% at 20 years, respectively. On multivariable analysis, the type of surgical treatment for C-LCIS did not impact long-term survival [16].

In this context, active surveillance of patients with C-LCIS and no suspicious clinical and imaging findings is currently preferred to surgical management [28] and an increasing trend toward no surgery is documented in population studies and institutional series [14, 16].

C-LCIS and ALH express the estrogen and progesterone receptors (ER and PR) and are HER2-negative. Analysis of prospective clinical trials and large single institution series shows that hormone chemoprevention with tamoxifen, or with aromatase inhibitors in postmenopausal patients, reduces significantly the risk of subsequent carcinoma in women with C-LCIS [14, 29–32]. In a study of 1060 women with C-LCIS diagnosed between 1980 and 2009 at one center, 78% chose surveillance and 17% received hormonal chemoprevention. At a median follow-up time of 81 months (range 6–368), 150 patients developed 168 breast carcinoma. The annual incidence rate of carcinoma was 2%, with a cumulative rate of 7% at 5 years and 21% at 10 years. In the group of women who chose hormone chemoprevention with tamoxifen the cumulative risk of carcinoma was only 3% at 5 years and 12% at 10 years [14].

#### Imaging studies and management at needle core biopsy

C-LCIS and ALH usually are clinically and mammographically occult and constitute incidental findings in breast specimens obtained to evaluate other lesions. The surgical management of C-LN identified at core needle biopsy (CNB) remains controversial. In 2019, a multidisciplinary panel of European experts endorsed classification of ALH and C-LCIS in CNB material as B3 lesions. and recommended that "A lesion containing C-LN which is visible on imaging should undergo excision with vacuum-assisted biopsy (VAB). Thereafter surveillance is justified if there is no pathological-radiological discordance and no residual lesion" [33]. The United Kingdom National Health System guidelines also recommend vacuum-assisted excision for second assessment after a diagnosis of C-LN at CNB or VAB [34]. Vacuum-assisted excision as a minimally invasive procedure for removal of an imaging target is uncommon in the USA and Canada. In most contemporary series from North-American institutions, the upgrade rate at follow-up surgical excision of radiology-pathology concordant CNBs yielding C-LN (ALH or C-LCIS) as the highest risk lesion ranges between 1% and 4% [35–40]. In a few series, excision of C-LCIS yielded >5% rate of upgrade [41, 42] and some groups have suggested that surgical excision is not required for ALH but is recommended for C-LCIS [42]. Most of the carcinomas found at excision consist of low-to-intermediate-grade DCIS or of minute foci of hormone receptor-positive HER2-negative well to moderately differentiated invasive carcinoma. Consequently, the current management guidelines by the American Society of Breast Surgeons support clinical and imaging follow-up over surgical excision of lesions yielding only C-LN with radiologic-pathologic concordant findings at CNB [43]. Nonetheless, a 2017 survey of radiologists practicing at 41 academic institutions in the USA found that excision was recommended in 61% of ALH cases, and in 71% of cases of C-LCIS. The authors did not comment on the assessment of radiologic-pathologic concordance [44].

Regardless of regional practice preferences, surgical excision of C-LN is advised if the radiologic-pathologic findings are discordant, another lesion is present which by itself requires further evaluation, or C-LCIS has focal ambiguous features that raise the possibility of F-LCIS or low-grade DCIS.

In most studies, C-LN was identified in the CNB material of a mammographic or sonographic lesion [35–42]. Magnetic resonance imaging (MRI) technology, however, may detect foci of C-LCIS and ALH that are not associated with another lesion and are mammographically and sonographically occult [35, 45–46]. In a series including 31 cases of C-LN detected at MRI-guided CNB, surgical excision yielded carcinoma in 3/14 patients with ALH (21% upgrade; 95% CI: 6-51%) and in 6/17 patients with C-LCIS (35% upgrade; 95% CI: 15-61%) [45]. None of the cases of ALH in another series of MRI-guided biopsies yielded an upgrade, but excision of C-LCIS yielded DCIS in 2/8 cases (25% upgrade; 95% CI: 4-64%) [47]. In a study of MRI-detected high-risk lesions, none of 11 cases of ALH yielded an upgrade, but excision of 48 cases of C-LCIS yielded 3 carcinomas (6.3% upgrade; 95% CI: 2-18%) [48]. It is worth noting that women undergoing MRI evaluation usually are at high risk of breast carcinoma. In one study, 42% of 31 patients with MRI-detected C-LN had a screening MRI, and 58% had a diagnostic MRI, including 12 patients undergoing extent of disease work-up for a concurrent diagnosis of

breast carcinoma [47]. Nonetheless, these data raise the possibility that mammographically and sonographically occult C-LN detected with MRI may carry a higher risk of upgrade at excision than C-LN identified in CNBs targeting mammographic and/or sonographic lesions. Further studies are needed to investigate this hypothesis.

Only a few studies have evaluated the clinical outcomes of women who did not undergo surgical excision following CNB diagnosis of C-LN with radiologic-pathologic concordance. Based on pooled data from over 500 patients with median follow-up time of 2 to 3.7 years, the rates of ipsilateral ILC in women who had surgical versus non-surgical management appear to be comparable, but longer follow-up is needed [42, 48–51].

Reporting of C-LCIS margin status is not required [1], even if C-LCIS occurs in association with invasive carcinoma or near F-LCIS or P-LCIS. Adjuvant radiotherapy and chemotherapy are also not indicated. Hormone chemoprevention with tamoxifen or with aromatase inhibitors in postmenopausal patients significantly reduces the risk of subsequent carcinoma associated with C-LN [14, 29–31].

## Florid LCIS and pleomorphic LCIS

### Morphology

#### Florid LCIS (F-LCIS)

F-LCIS consists of type A and/or type B cells but is characterized by massive expansion of the TDLUs so that an expanded acinus or duct fills a high-power field of view (equivalent to at least 40-50 cells across its diameter) and/or little to no intervening stroma is present between the massively expanded acini and ducts (Fig. 1). Central necrosis and calcifications may be present**,** but they are not required for diagnosis [1]. F-LCIS without associated invasion is rare and only few small series have been published [52–58]. F-LCIS- associated invasive carcinoma usually consists of ILC classic type, but pleomorphic ILC may be found.

#### Pleomorphic LCIS (P-LCIS)

P-LCIS is composed of large non-cohesive cells characterized by marked nuclear atypia and pleomorphism, comparable to those of high-grade DCIS. The cells of P-LCIS are round to oval, have abundant cytoplasm, and often the nucleus is located at one pole of the cell. The nuclei are large (four times the size of a small lymphocyte), round to oval; the chromatin is coarse; one or two prominent nucleoli may be present, and binucleate cells are common [1, 53, 59, 60] (Fig. 1). Although P-LCIS usually shows massive expansion of the acini and comedo necrosis with coarse calcifications, these features are not necessary for its diagnosis, which rests exclusively on the identification of marked nuclear atypia and pleomorphism of the non-invasive neoplastic lobular proliferation. As in the case of F-LCIS, P-LCIS not associated with invasive carcinoma is rare lesion, and only few series have been reported [53, 55, 57–71]. P- LCIS-associated invasive carcinoma usually consists of pleomorphic ILC, but classic ILC or other variant ILC morphologies may occur [72].

Both F-LCIS and P-LCIS tend to be unifocal and show a continuous distribution [54].

F-LCIS and P-LCIS and may coexist in the same case and with C-LCIS. All morphologic variants of LCIS present in a case need to be mentioned in the pathology report.

Rarely, a proliferation consisting predominantly of type B cells and scattered cells with large and pleomorphic nuclei is encountered. The 2019 WHO expert panelists recommend classifying such proliferation as C-LCIS composed of type B cells [1]. This recommendation has great practical utility in the diagnosis of lobular proliferations found in surgical excision specimens. However, information on the upgrade rate of similar lesions identified in CNB material is limited to just a handful of cases [55]. Although none of the lesions yielded carcinoma at excision, no definitive conclusion can be derived, and follow-up excision is still recommended.

The morphologic features of Florid LCIS and Pleomorphic LCIS are summarized in Table 1.

The criteria for the diagnosis of C-LCIS, F-LCIS and P-LCIS are now clearly defined and agreed upon, but no data is available yet on the interobserver diagnostic reproducibility of the three forms of LCIS using the WHO 2019 criteria. In a prior study, six breast pathologists classified 50 cases of non-invasive lobular neoplasia into classic, florid and pleomorphic LCIS. There was substantial interobserver agreement in the diagnosis of C-LCIS (k-value: 0.652) and F-LCIS (k-value = 0.687), but only moderate agreement in the diagnosis of P-LCIS (k-value = 0.565) [73]. The use of E-cadherin immunohistochemical stain has contributed to the identification of F-LCIS and P-LCIS and constitutes an helpful diagnostic tool. Nonetheless some cases continue to be misclassified as DCIS. To avoid possible misdiagnoses, and their management implications, pathologists should consider the differential diagnosis of F-LCIS and P-LCIS if a neoplastic non-invasive epithelial proliferation has exclusively solid pattern and use immunohistochemical stains for E-cadherin and related proteins for its classification. In addition, given the rarity of F-LCIS and P-LCIS unassociated with invasive carcinoma, it is worth reminding clinicians of the differences in the management of

**Table 2** Upgrade rates at excision of florid LCIS and pleomorphic LCIS in CNBs

| Author, Year | Core biopsy | | Carcinoma in excision | | | Upgrade rate (%) |
|---|---|---|---|---|---|---|
| | Diagnosis | n | DCIS | Invasive | Any carcinoma/ all cases | % |
| Chivukula, 2008 [68] | P-LCIS | 12 | 0 | 3 ILC | 3/12 | 25 |
| Carder, 2010 [70] | P-LCIS | 10 | 0 | 1 mIC;<br>2 ILC | 3/10 | 30 |
| Sullivan, 2010 [58] | F-LCIS | 11 | 1 | 4 ILC | 5/11 | 45% |
| | P-LCIS | 17 | 2 | 3 ILC | 5/17 | 29% |
| Niell, 2012 [37] | P-LCIS | 4 | 1 | 2 ILC;<br>1 IDC | 4/4 | 100 |
| D'Alfonso, 2013 [39] | F-LCIS | 8 | 0 | 1 mIC;<br>1 ILC | 2/8 | 25 |
| Flanagan, 2015 [63] | P-LCIS | 17 | 3 | 5 ILC;<br>1 IC | 9/17 | 53 |
| Susnik, 2016 [40] | P-LCIS | 15 | 0 | 4 IC | 4/15 | 27 |
| Fasola, 2018 [62] | P-LCIS | 20 | 2 | 4 ILC | 6/20 | 30 |
| Guo, 2018 [69] | P-LCIS | 25 | 0 | 2 mIC;<br>13 ILC;<br>1 IDC | 16/25 | 64 |
| Desai, 2018 [66] | P-LCIS | 15 | 0 | 3 IC | 3/15 | 20 |
| Nakhlis, 2019 [67] | Variant LCIS | 76 | 10 | 9 ILC;<br>5 IDC;<br>3 IC | 27/76 | 36% |
| Shamir, 2019 [53] | P-LCIS | 8 | 0 | 2 ILC;<br>1 P-ILC | 3/8 | 38 |
| | F-LCIS | 6 | 1 | 1 ILC | 2/6 | 33 |
| Foschini, 2019 [57] | F/P-LCIS | 70 | 3 | 28 IC | 31/70 | 44 |
| Harrison, 2020 [76] | P-LCIS | 17 | 1 | 5 ILC | 6/17 | 35 |
| | F-LCIS | 2 | 1 | 0 | 1/2 | 50 |
| Kuba, 2021 (55) | P-LCIS | 8 | 0 | 1 ILC;<br>1 mIC | 2/8 | 25 |
| | F-LCIS | 24 | 0 | 3 mIC;<br>1 ILC | 4/24 | 17 |

CNB: Core needle biopsy; DCIS; ductal carcinoma in situ; P-LCIS: pleomorphic lobular carcinoma in situ; F-LCIS: florid lobular carcinoma in situ; F/P-LCIS: florid/pleomorphic lobular carcinoma in situ; ILC: invasive lobular carcinoma; IDC: invasive ductal carcinoma; IC: invasive carcinoma; mIC: microinvasive carcinoma; P-ILC: pleomorphic invasive lobular carcinoma

**Table 3** Immunohistochemistry of ALH and LCIS

| | | | | |
|---|---|---|---|---|
| E-Cadherin | Usually absent, may be aberrant (weak cell membrane stain) | | | |
| β-catenin | Usually absent | | | |
| p120-catenin* | Diffuse intracytoplasmic accumulation<br>Cell membrane negative or faintly positive | | | |
| Type of lesion | ALH | Classic LCIS | Florid LCIS | Pleomorphic LCIS |
| ER | Positive | Positive | Positive | Positive in approximately 60% of cases;<br>apocrine P-LCIS usually negative |
| PR | Positive | Positive | Most cases positive, but some negative | Some cases positive;<br>apocrine P-LCIS usually negative |
| HER2 | Negative | Negative | Usually negative, rarely positive | Overexpressed in 20–30% of cases, especially in apocrine P-LCIS |

*p120 is the most useful marker in cases with aberrant e-cadherin expression and is also useful for detection of microinvasion/small foci of invasive lobular carcinoma

F-LCIS and P-LCIS compared to C-LCIS. It should be emphasized that *florid* LCIS is a specific entity, not to be confused with "extensive" classic LCIS.

**Differential diagnosis** The differential diagnosis of F-LCIS and P-LCIS includes solid DCIS with low-to-intermediate nuclear grade and solid DCIS with high nuclear grade, respectively. Cell dyshesion is a feature of F-LCIS and P-LCIS. If comedo necrosis is present, the neoplastic lobular cells located immediately around the necrotic focus tend to have a more noticeable round to oval shape and appear dyshesive, resulting in a "crumbling" appearance of the epithelium. In contrast, the neoplastic cells of DCIS located around a central necrotic focus usually are somewhat cohesive and the apical portion of the cell membrane of adjacent cells tends to have a more continuous and linear appearance. Immunohistochemical stains for E-cadherin and related proteins (beta-catenin and p120) can be used to resolve the differential diagnosis (see section on immunohistochemistry).

## Clinical presentation

P-LCIS and F-LCIS usually occur in association with ILC [53, 54, 57, 61]. In the absence of stromal invasion, F-LCIS and P-LCIS are usually detected mammographically as pleomorphic calcifications, architectural distortion, mass lesion with/ without associated calcifications [52–71]. It is exceedingly rare that F-LCIS or P-LCIS be identified only as an MRI-abnormality. Patients with P-LCIS and F-LCIS have median age of 59–61 years and tend to be older than patients with C-LCIS.

P-LCIS without associated invasive carcinoma was identified in 15/19,678 (0.08%) image-directed CNBs obtained between 2004 and 2017 at one center [66]. No information on the frequency of F-LCIS in breast CNBs is available.

In Europe, including the United Kingdom (UK), P-LCIS is usually classified as a B5a lesion [74, 75]. F-LCIS is not specifically mentioned in the European and UK guidelines, but is usually classified either as B4 (UK) [34] or B5a (other countries) [33]. The identification of P-LCIS and/or F-LCIS in CNB material mandates surgical excision regardless of radiologic-pathologic concordance. The upgrade rates range from 20% to 50% in most series [37, 39, 40, 53, 55, 57, 58, 62, 63, 66–70, 76]. The high rates of upgrade at excision of F-LCIS and P-LCIS may in part be secondary to the difficulty in identifying microinvasive lobular carcinoma, which often requires the use of immunohistochemical stains (see section on immunohistochemistry). The majority of upgrades consist of ILC (Table 2).

Complete surgical excision of F-LCIS and P-LCIS is recommended. Classic LCIS and ALH usually are found near

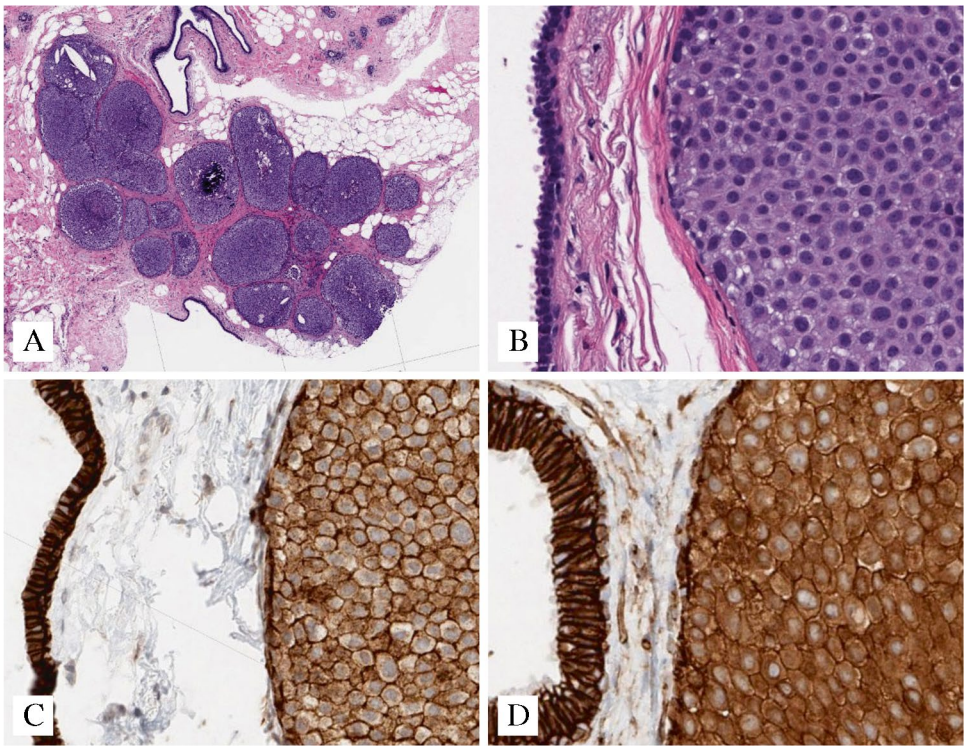


**Fig. 3 Aberrant E-cadherin immunohistochemistry: retained staining in the cell membrane. A:** Mass-forming florid LCIS, secondary to massive expansion of the acini by type A cells. One of the expanded acini has a central calcification. **B:** The LCIS cells (right) are small, round and dyshesive, and have a small nucleus with dense chromatin. Portion of a duct is shown for comparison (left). **C:** In this case, the LCIS cells retain membrane stain for E-cadherin (right), but the intensity of the stain is markedly reduced compared to that of the adjacent ductal epithelium (left). **D:** Diffuse cytoplasmic accumulation of p120 catenin supports a lobular phenotype.

F-LCIS and P-LCIS. In such cases, even though C-LCIS and F-LCIS/ P-LCIS constitute a morphologic continuum, the margin status of C-LCIS is not reported, and no additional surgery is required unless F-LCIS and P-LCIS are still present near the final margin. There is no data on the margin clearance required for the optimal management of F-LCIS and P-LCIS. In a retrospective series [67], DCIS developed in the same quadrant 14 months after excision of an LCIS variant with ≥2 mm margin clearance and no adjuvant radiotherapy. Ipsilateral recurrences of P-LCIS, F-LCIS or ILC have been reported [61, 64, 65, 77] but the number of cases with follow-up information is limited and it remains unclear whether radiotherapy and/or hormone therapy might have been beneficial.

Overall, invasive carcinomas associated with F-LCIS and/ or P-LCIS are ILCs, including classic and pleomorphic ILC, or ILCs with less common morphologies.

Considering that F-LCIS and P-LCIS without associated invasive carcinoma are exceedingly rare, have similar but more complex patterns of genetic alterations than C-LCIS, may show *ERBB2* overexpression/ amplification, and that the invasive carcinomas associated with F-LCIS and P-LCIS consist predominantly of ILC, it is reasonable to conclude that F-LCIS and P-LCIS are morphologic precursors of ILC biologically more aggressive than C-LCIS.

At present, there is no information available regarding the possible benefits of hormone chemoprevention in women with F-LCIS or P-LCIS without associated invasive carcinoma.

While in the AJCC cancer staging 7$^{th}$ ed. [78] classic LCIS was classified both as Tis(LCIS) and a high risk lesion, according to the AJCC staging 8$^{th}$ ed. [79] LCIS is classified only as a high-risk lesion, with no mention of F-LCIS and P-LCIS. No adjuvant radiotherapy is recommended for any type of LCIS. The 2021 NCCN guidelines for the management of patients with breast diseases endorse the same approach [28].

The European Society of Medical Oncology (ESMO) guidelines specify that C-LCIS is a both a non-obligate precursor and a risk factor for subsequent development of invasive cancer in both breasts. ESMO acknowledges that "the pleomorphic variant of lobular neoplasia may behave similarly to DCIS and should be treated accordingly, after multidisciplinary discussion" and (P-LCIS) "…should be considered from a treatment perspective as high-grade DCIS." Accordingly, patients with P-LCIS not associated with invasive carcinoma usually are treated with adjuvant radiotherapy in most European countries. The ESMO guidelines do not mention F-LCIS [80].

## Immunohistochemistry and molecular alterations (C-LCIS, F-LCIS and P-LCIS)

E-cadherin is a transmembrane glycoprotein encoded by *CDH1* (chromosome 16q22.1). By binding the *WNT*-protein complex (β-catenin, α-catenin and p120-catenin),

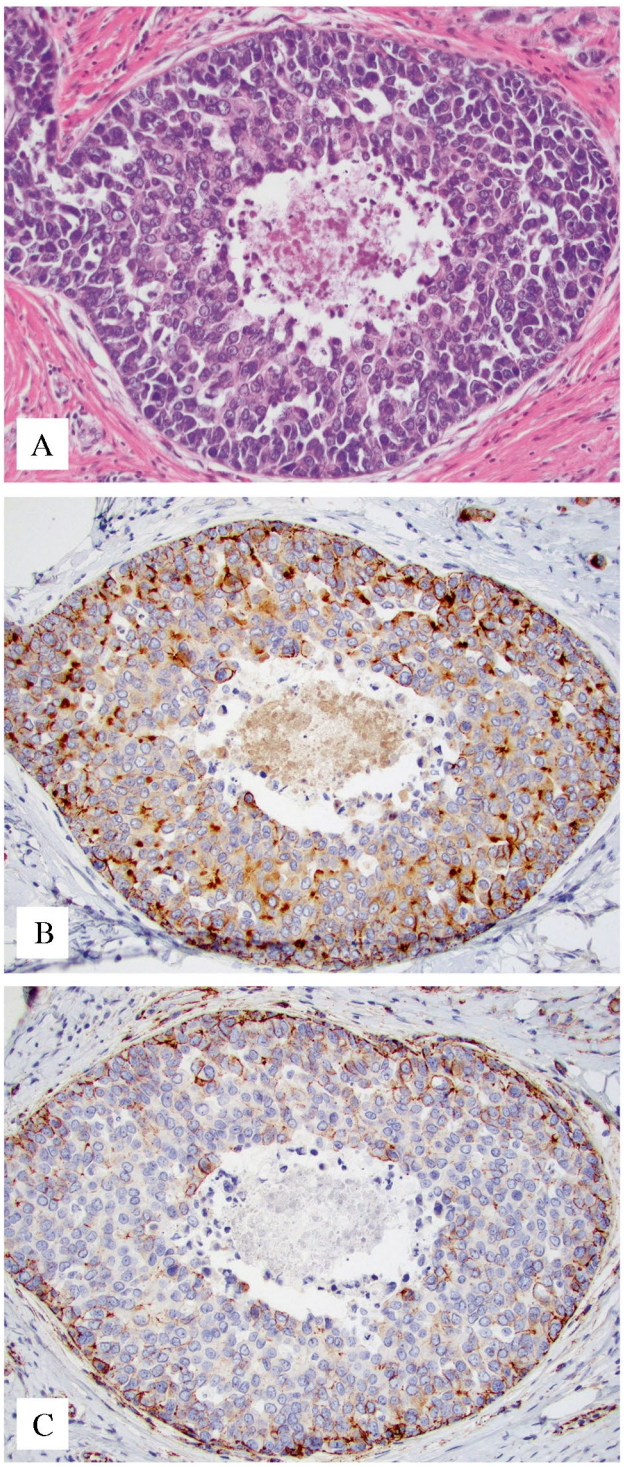


**Fig. 4 Aberrant E-cadherin immunohistochemistry: staining in the Golgi apparatus. A:** An example of Florid LCIS with comedo necrosis. **B:** Immunohistochemistry demonstrates that E-Cadherin accumulates within the cells in conspicuous intracytoplasmic globules consistent with Golgi apparatus. **C:** Loss of beta-catenin expression supports a lobular phenotype.

E-cadherin anchors the cytoskeleton of the cell to the cell membrane, thereby contributing to cell-to-cell adhesion. In the breast, E-cadherin, β-catenin and p120 are located along the cell membrane of the mammary ductal epithelium, whether benign, atypical or neoplastic, except in the apical surface of the cells polarized around a glandular lumen. In the majority of cases, loss of E-cadherin and β-catenin, together with cytoplasmic distribution of p120 catenin characterize non-invasive and invasive lobular neoplasia [5–10] (see Table 3). Approximately 10%–23% of all lobular lesions, including ILCs, retain some membrane expression of E-cadherin (so called "aberrant" expression of E-cadherin) [81–83]. This phenomenon may be due to mutations that impair the function of the protein but do not completely abolish its detection by immunohistochemistry. In addition to *CDH1* mutations or deletions, other possible mechanisms may be involved, such as epigenetic inactivation. In these cases, the expression of E-cadherin in the cell membrane of LCIS is often reduced compared to that of the adjacent ductal epithelium and correlates with loss of function. Consequently, finding weak E-cadherin stain in the cell membrane should not be interpreted as supportive of a ductal phenotype, but rather warrants additional work-up to rule out aberrant expression of E-cadherin. In this setting, loss of β-catenin and cytoplasmic accumulation of p120-catenin provide evidence supportive of a lobular phenotype [83–85].

Sometimes E-cadherin expression in the cell membrane is weak and patchy or may be limited to cells located in the periphery of the lesion, or in its center. In some cases, the E-cadherin stain concentrates in the Golgi apparatus, likely due to impaired protein transfer into the cell membrane. These staining patterns are usually seen in F-LCIS and P-LCIS (Figs. 3, 4, and 5).

When interpreting E-cadherin immunohistochemical stains, one should also remember that the cell membrane of the myoepithelial cells is E-cadherin-positive on the side facing the epithelium, but the stain has a granular "dot-like" distribution. The myoepithelial cells are frequently intermingled with classic LN and three possible patterns have been described [12]. In the "normal" pattern, the nuclei of myoepithelial cells lie flat along the basement membrane of acini and ducts involved by C-LCIS, same as in normal TDLUs and ducts; no myoepithelial hyperplasia is present. In the "perpendicular" pattern, hyperplastic myoepithelial cells interdigitate the outermost layer of C-LCIS and the myoepithelial cell nuclei are arranged perpendicular to the basement membrane. In the "central" pattern, hyperplastic myoepithelial cells are seen in the middle of the acini, intermixed with C-LCIS cells. Knowledge of the latter two patterns is especially useful in the interpretation of E-cadherin

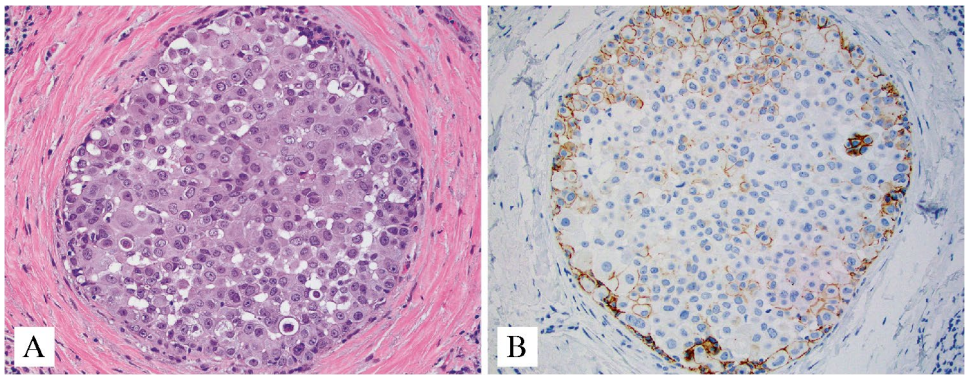


**Fig. 5 Aberrant E-cadherin immunohistochemistry: weak staining of the cell membrane in a patchy distribution. A:** An example of Pleomorphic LCIS. **B:** Immunohistochemistry for E-cadherin demonstrates focal weak membrane stain, especially in the cells at the periphery of the duct.

immunohistochemistry. E-cadherin stain in the myoepithelial cells outlines the cell membrane but appears granular and patchy, has weaker intensity than seen in nearby ductal epithelial cells, and its distribution within the TDLU overlaps that of myoepithelial markers such as calponin (Fig. 6).

C-LCIS is strongly and diffusely positive for ER, PR and AR, but does not express HER2 [53, 59, 86].

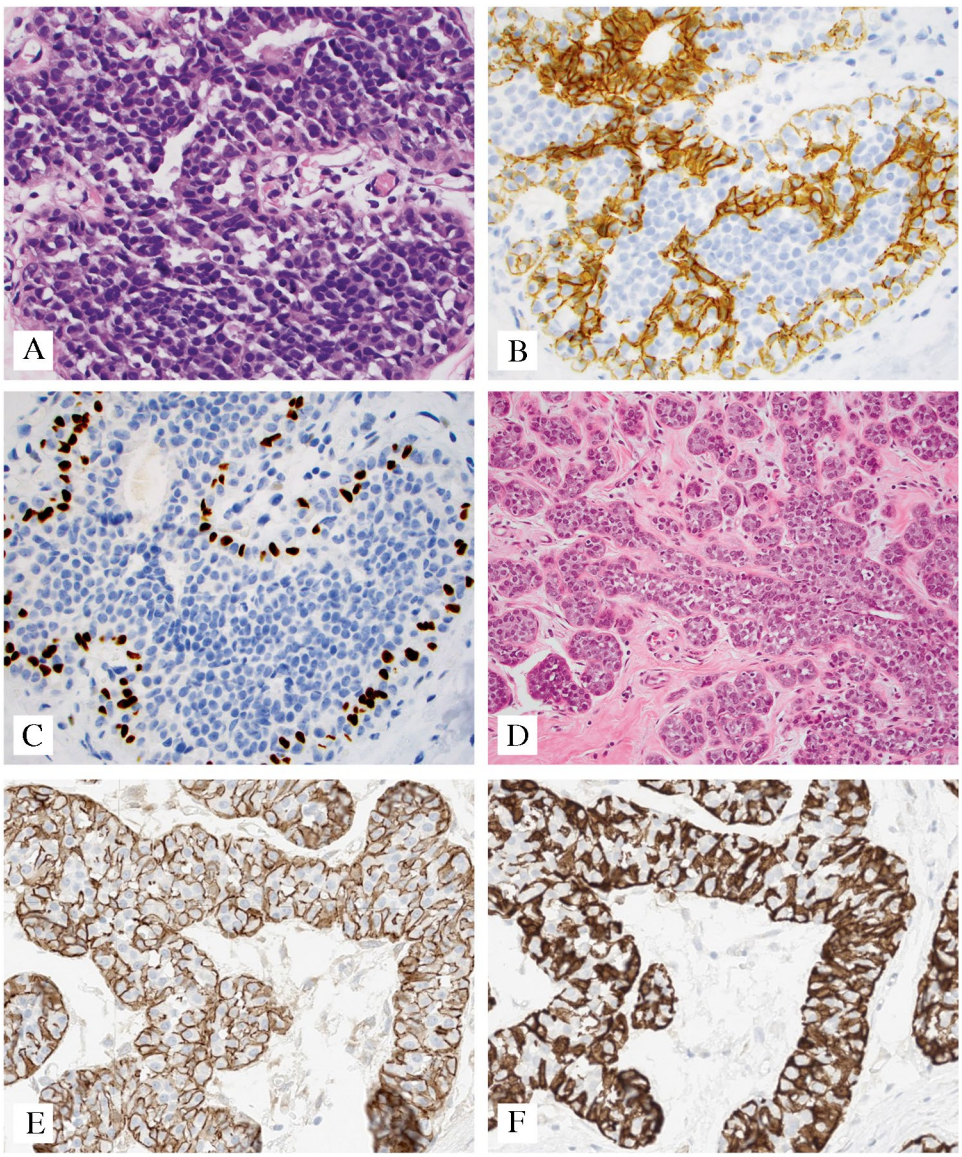


**Fig. 6 Classic LCIS and myoepithelial cells. A-C: Perpendicular pattern. A:** Classic LCIS involves a small duct. **B:** E-cadherin is lost in classic LCIS, but shows granular linear staining in cell membrane of the hyperplastic myoepithelial cells that interdigitate with the outermost layers of classic LCIS. **C:** Many of the p63-positive nuclei of the myoepithelial cells interdigitating with classic LCIS are oriented perpendicular to the basement membrane. **D-F: Central, admixed pattern. D:** Classic lobular neoplasia expands acini and tubules in a case of adenosis. **E:** E-cadherin is lost in the cells of classic lobular neoplasia, but retained in the cell membrane of the hyperplastic myoepithelial cells. **F:** Calponin decorates the hyperplastic myoepithelial cells present centrally within the tubules, intermixed with C-LCIS cells

Assessment of the ER, PR and HER2 status in C-LCIS is not required.

F-LCIS is ER-positive/HER2-negative, but rare cases are HER2-positive [52, 53].

P-LCIS usually is ER-positive/HER2-negative, but it is ER-negative/ HER2-positive in approximately 13–30% of cases, especially P-LCIS with apocrine morphology [53, 55, 59, 60, 64]. P-LCIS with triple negative profile account 17.6% of cases in one series [76] (see Table 3).

All three forms of LCIS usually express AR, regardless of apocrine morphology.

The Ki67 proliferative index of C-LCIS is low (<1-2%) [86]. In F-LCIS, the Ki67 index was reported as "generally low" in one series, [54] and between 2% and 14% in another [53]. The Ki67 index of P-LCIS ranges between 2% and 23% [59–61], although in one series it reportedly ranged between 25% and 90% [68].

Given the frequent association of F-LCIS and/or P-LCIS with (micro)invasion, careful evaluation of foci of periductal inflammation and reactive stromal desmoplasia is recommended. In these cases, the use of "positive" immunohistochemical stains (such as keratins AE1:3 or CK7, ER or p120) highlights foci of (micro) ILC that are not readily detected when only "negative" immunohistochemical stains for myoepithelial markers and/or E-cadherin are applied.

The molecular alterations underpinning C-LCIS and ILC include deletion of 16q, and mutations affecting *CDH1* and *PIK3CA*. Synchronous C-LCIS and ILC shared at least one somatic mutation in 74% of paired samples and paired C-LCIS and ILC were clonal with a confidence of clonality greater than 97% [87]. These and other data support the notion that LCIS is not only a high-risk lesion but also a non-obligate morphologic precursor of ILC. F-LCIS and P-LCIS have genomic alterations similar to those of C-LCIS, including *CDH1* loss/ inactivation, but they are characterized by greater genomic instability, especially apocrine P-LCIS [52, 59, 76, 88–90]. Genomic profiling of F-LCIS and P-LCIS reveled recurrent alterations in ERBB2 and ERBB3 [76, 86, 88–90].

## Conclusions

Classic, florid and pleomorphic LCIS are characterized by altered E-cadherin expression and loss of function. However, they differ substantially in terms of nuclear atypia and architectural features, clinical presentation and behavior, and clinical management. Differences in the clinical management of C-LCIS, F-LCIS and P-LCIS versus C-LCIS are also evident in different parts of the world.

Although data on the different types of LCIS have been gathered in recent years, there is still no definitive and uniform agreement on the biologic potential and optimal management of these lesions.

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## Declarations

**Ethical approval** This article is based on review of published literature and complies with the Institutional Ethical Standards

**Conflict of interest** E. B. has no conflict of interest to declare

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