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# Pleomorphic and florid lobular carcinoma in situ of the Breast: A systematic review of current evidence and knowledge gaps

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## ABSTRACT

*Introduction:* Pleomorphic (PLCIS) and florid (FLCIS) lobular carcinoma in situ are uncommon entities, characterized by significant architectural distortion and cellular atypia. Their rarity poses three key clinical challenges: diagnostic variability, histologic upgrade and risk of local recurrence (LR). Currently, no standardized management guidelines exist. This systematic review provides the most comprehensive synthesis to date of the available evidence on clinical, radiologic, pathologic, and molecular characteristics of P/FLCIS, and evaluates outcomes associated with different treatment strategies.

*Methods:* A systematic literature search was conducted across major biomedical databases up to June 2025. Eligible studies were original case series reporting primary data on P/FLCIS.

*Results:* From 5402 screened records, 38 studies were included, comprising 629 total cases: 411 PLCIS, 98 FLCIS, and 120 categorized as LCIS with pleomorphic or non-classic features. The pooled upgrade rate was 35.3% (PLCIS 35.1%, FLCIS 33.3%; $p = 0.843$), predominantly to invasive carcinoma (28.8%). Among 258 pure P/FLCIS cases with available follow-up (median, 50 months) the overall LR rate was 12.4% (PLCIS 13.1%, FLCIS 9.1%; $p = 0.618$), with invasive recurrences representing the majority (62.5%; $p = 0.04$). Margin status was significantly associated with risk of LR (positive margins 38.2%, close margins (<2 mm) 20.0%, negative margins 3.0%; $p < 0.001$). Data on adjuvant treatments were inconsistent and heterogeneous.

*Conclusions:* Given the high upgrade rate and significant risk of LR for P/FLCIS, complete surgical excision with negative margins is strongly advised to ensure definitive diagnosis and reduce future breast events. The role of

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adjuvant therapies remains unclear, highlighting the urgent need for standardized, multicenter studies to guide optimal clinical management.

**Glossary**

| | |
|---|---|
| LCIS | lobular carcinoma in situ |
| CLCIS | classic lobular carcinoma in situ |
| PLCIS | pleomorphic lobular carcinoma in situ |
| APLCIS | apocrine pleomorphic lobular carcinoma in situ |
| FLCIS | florid lobular carcinoma in situ |
| AFLCIS | apocrine florid lobular carcinoma in situ |
| LCIS-PF | lobular carcinoma in situ with pleomorphic features |
| NC-LCIS | non-classic lobular carcinoma in situ |
| DCIS | ductal carcinoma in situ |
| IC | invasive carcinoma |
| ILC | invasive lobular carcinoma |
| IDC | invasive ductal carcinoma (invasive carcinoma of no-special type) |
| BCS | breast conserving surgery |
| LR | local recurrence |
| RT | radiotherapy |
| ET | endocrine therapy |
| ER | estrogen receptors |
| PR | progesteron receptors |
| HER2 | Human Epidermal Growth Factor Receptor 2 |
| CDH1 | Cadherin-1, the gene that encodes the protein *E*-cadherin |
| ERBB2 | Erythroblastic Oncogene B2 the gene that encodes the HER2 protein |
| MRI | magnetic resonance imaging |
| CNB | core needle biopsy |

## 1. Introduction

Lobular carcinoma in situ (LCIS) of the breast was first described in 1941 by Foote and Stewart as a potential precursor of invasive carcinoma (IC) [1]. In current practice it is primarily considered a risk indicator for the development of IC, with rates of cancer development well documented at 1–2% per year [2]. In addition to classic LCIS (CLCIS), the latest edition of the World Health Organization (WHO) Classification of Breast Tumors [3] now clearly recognizes two other distinct subtypes: pleomorphic LCIS (PLCIS) and florid LCIS (FLCIS).

Pleomorphic and florid LCIS (P/FLCIS) were first described in 1996 [4] and 2002 [4], respectively. A distinct rare morphologic subtype, apocrine PLCIS (APLCIS), was first characterized by Eusebi et al., in 1984 [5], and is increasingly recognized for its unique molecular features and potentially more aggressive behavior. Given the rarity of these lesions and significant variability in diagnostic criteria prior to their formal WHO definition, the development of consensus management guidelines has been challenging. Older studies often failed to clearly distinguish CLCIS from non-classical variants, leading to potential misclassification and limiting the reproducibility and specificity of reported outcomes. Although PLCIS is suspected to carry an increased risk of progression to IC, robust data on long-term outcomes are still lacking [6,7].

Histologically, these variants are more complex than CLCIS, with a higher risk of concurrent IC; yet classification varies across countries. In the United States, PLCIS and FLCIS are generally considered as high-risk lesions. In Europe, while CLCIS diagnosed on preoperative biopsy is typically classified as a lesion of uncertain malignant potential (B3), both PLCIS and FLCIS are usually categorized as malignant, in situ, lesions (B5a). In the United Kingdom, FLCIS is instead classified as a lesion suspicious for malignancy (B4) according to the Royal College of Pathologists guidelines [8–12].

While surgical excision is generally recommended, there is lack of consensus on requirements to obtain clear margins or the role of adjuvant radiotherapy (RT) and endocrine therapy (ET) in reducing the risk of recurrence. The European Society of Medical Oncology (ESMO) [13] endorses treatment recommendations for PLCIS based on its histologic similarity to ductal carcinoma in situ (DCIS), advocating for wide local excision and consideration of adjuvant RT.

The National Comprehensive Cancer Network (NCCN) guidelines [14] recommend complete excision with negative margins for non-classic LCIS (PLCIS and/or FLCIS) diagnosed on core biopsy. However, no standardized recommendations for additional treatments are provided, owing to the limited available evidence, and state that management beyond surgery should be individualized.

The American Society of Breast Surgeons recommends surgical excision with negative margins for PLCIS and FLCIS; however, the guidelines explicitly acknowledge that there are limited data defining what constitutes an adequate negative margin. Based on pooled retrospective studies, a 2-mm margin is proposed as an acceptable and safe cutoff, although this threshold is not supported by high-level clinical data [15]. Notably, the NCCN and ASBrS guidelines are currently the only international recommendations specifically addressing FLCIS, further highlighting the lack of standardized definitions and a solid evidence base in this setting.

In light of these notable gaps in knowledge we conducted a systematic review to address three key clinical challenges: diagnostic variability, histologic upgrade and risk of local recurrence (LR). Here we define the pathological and clinical characteristics of P/FLCIS, evaluate the available evidence on rates of upgrade to invasive cancer and describe long term outcomes following surgical management with or without adjuvant therapies in patients with pure P/FLCIS.

## 2. Methods

### 2.1. Literature search strategy

A systematic review was conducted to explore the available literature reporting cases of pure PLCIS and/or FLCIS. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [16]. A comprehensive search was carried out across PubMed, Google Scholar, Scopus, BioMed Central, and Mendeley covering all relevant publications from database inception through June 1, 2025. Articles were identified using combinations of the following keywords: “pleomorphic lobular carcinoma in situ”, “florid lobular carcinoma in situ”, “PLCIS”, and “FLCIS”. No date restrictions were applied. In addition, the reference lists of selected articles were manually screened to identify additional eligible studies.

### 2.2. Study selection

All retrieved records were imported into Rayyan [17], an artificial intelligence–assisted platform for title and abstract screening. Two authors (M.F. and D.P.) independently assessed full texts to identify

eligible studies. Inclusion criteria comprised original, English-language articles reporting primary data on pure PLCIS and/or FLCIS without concurrent IC and/or DCIS on preoperative biopsy and/or final surgical pathology. Recurrence outcomes and adjuvant treatment data were analyzed only for cases confirmed as pure P/FLCIS on the surgical specimen. Exclusion criteria included non-English articles, review papers, conference abstracts, case reports, letters to the editor, commentaries, and any articles not accessible via the authors' institutional libraries. Studies focusing exclusively on invasive and/or microinvasive pleomorphic and/or florid lobular neoplasia, or on CLCIS, were also excluded. Discrepancies during screening were resolved by a third author (F.M.).

### 2.3. Data extraction

Extracted data included LCIS subtypes (PLCIS, APLCIS, FLCIS), clinical, radiologic, pathologic, genetic and molecular features; surgical management and upgrade rates; margin status; adjuvant treatments; and recurrence outcomes. One author (M.F.) conducted the initial data extraction using a standardized Excel spreadsheet developed a priori, which was subsequently cross-verified by a second author (D.P.), who independently reviewed all included articles to ensure consistency and accuracy.

In accordance with scoping review methodology, no formal assessment of methodological quality or risk of bias was performed. Findings from the included studies were synthesized descriptively and presented in narrative form.

### 2.4. Statistical analysis

Descriptive statistics were used to summarize clinical and pathological features across studies. Differences in recurrence rates and upgrade rates between subgroups were assessed using the Pearson chi-square test or Fisher's exact test, as appropriate. The Mann–Whitney *U* test was applied to compare time-to-recurrence distributions between invasive and in situ recurrences. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the relative risk of recurrence based on surgical margin status and to compare upgrade risk between PLCIS and FLCIS. All statistical tests used a two-sided 5% significance level, and a p-value $<0.05$ was considered statistically significant. Post-hoc power analysis was conducted using Cohen's h effect size for proportions. Statistical analyses were performed using the RStudio software (RStudio: Integrated Development for R. RStudio, Inc.; Boston, MA).

## 3. Results

### 3.1. Search results

A total of 5402 records were identified through the initial database search. After removing 5002 duplicates, 400 titles and abstracts were screened for relevance, resulting in 44 full-text articles retrieved and assessed for eligibility. No additional studies were identified through reference list screening. Following full-text review, 6 articles were excluded based on the predefined eligibility criteria, leading to a final total of 38 studies included in this review. The study selection process is illustrated in the PRISMA flow diagram (Fig. 1). All included studies were retrospective case series reporting on PLCIS and/or FLCIS, published over a period of more than two decades, from 2002 to 2025. No randomized controlled trials, prospective cohort studies, or meta-analyses were identified. A detailed overview of the included studies, along with their primary focus, is presented in Table 1.

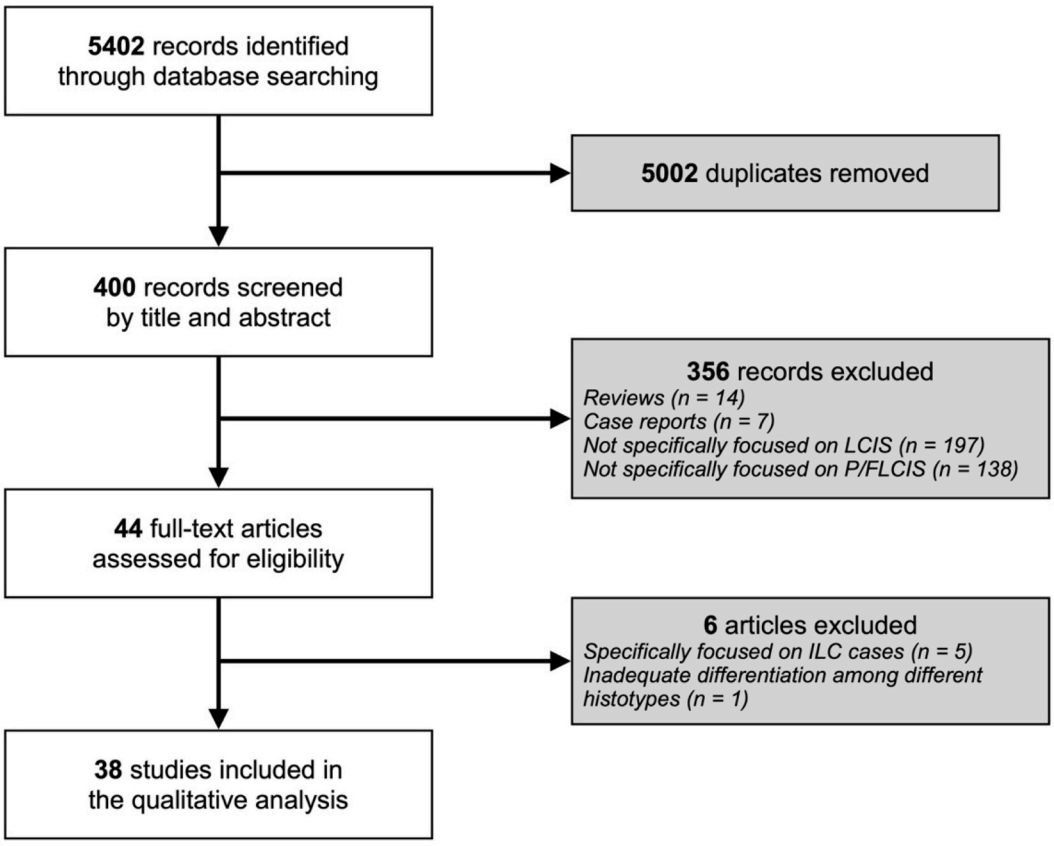


**Fig. 1.** Preferred Reporting Items for Systematic Review and Meta-Analyses Flow Diagram. LCIS, lobular carcinoma in situ; P/FLCIS, pleomorphic/florid lobular carcinoma in situ; ILC, invasive lobular carcinoma.

**Table 1**
Summary of the included studies.

| Original articles | | Study Period | LCIS variant | Overall reported cases |
|---|---|---|---|---|
| Sneige et al., 2002 (USA) | [18] | 1997–2000 | PLCIS[a] | 10 |
| Palacios et al., 2003 (Spain) | [19] | Not available | PLCIS | 29 |
| Mahoney et al., 2006 (USA) | [20] | 1999–2004 | PLCIS | 2 |
| Lavoue et al., 2007 (France) | [21] | 2000–2005 | PLCIS | 3 |
| Hwang et al., 2008 (USA) | [22] | 1996–2006 | PLCIS/FLCIS[b] | 7/6 |
| Chivukula et al., 2008 (USA) | [23] | 2002–2007 | PLCIS | 12 |
| Chen et al., 2009 (USA) | [7] | Not available | PLCIS/APLCIS | 18/13 |
| Carder et al., 2010 (UK) | [24] | 2002–2009 | PLCIS | 10 |
| Sullivan et al., 2010 (USA) | [25] | 2001–2005 | PLCIS/FLCIS[b] | 17/11 |
| Purdie et al., 2010 (UK) | [26] | 2000–2009 | PLCIS | 3 |
| Downs-Kelly et al., 2011 (USA) | [27] | Not available | PLCIS | 26 |
| Lewis et al., 2012 (USA) | [28] | 1991–2001 | PLCIS | 2 |
| Niell et al., 2012 (USA) | [29] | 2005–2010 | PLCIS | 4 |
| Shin et al., 2013 (USA) | [30] | Not available | FLCIS | 20 |
| D'Alfonso et al., 2013 (USA) | [31] | Not available | PLCIS/FLCIS | 2/8 |
| Khoury et al., 2014 (USA) | [32] | 2000–2012 | PLCIS/APLCIS | 8/39 |
| Meroni et al., 2014 (Italy) | [33] | 2001–2009 | PLCIS | 12 |
| Flanagan et al., 2015 (USA) | [34] | 2000–2014 | PLCIS | 23 |
| Szynglarewicz et al., 2015 (Poland) | [35] | 2004–2014 | PLCIS | 5 |
| Blanco et al., 2015 (USA) | [36] | 2001–2012 | PLCIS | 20 |
| Susnik et al., 2016 (USA) | [37] | 2008–2012 | PLCIS/FLCIS[b] | 15 |
| Fasola et al., 2017 (USA) | [38] | 1998–2012 | PLCIS | 20 |
| DeBrot et al., 2017 (USA) | [39] | 1995–2012 | PLCIS | 16 |
| Guo et al., 2017 (USA) | [40] | 2006–2017 | PLCIS | 37 |
| Masannat et al., 2018 (UK) | [41] | Not available | PLCIS | 77 |
| Desai et al., 2018 (USA) | [42] | 2004–2017 | PLCIS | 18 |
| Savage et al., 2018 (USA) | [43] | 1999–2016 | PLCIS | 21 |
| Hoffmann et al., 2019 (USA) | [44] | 2008–2018 | PLCIS/FLCIS | 26 |
| Foschini et al., 2019 (Italy) | [45] | Not available | PLCIS/FLCIS | 70 |
| Shamir et al., 2019 (USA) | [46] | 1997–2017 | PLCIS/APLCIS/FLCIS | 5/7/9 |
| Shamir et al., 2020 (USA) | [47] | 1997–2017 | PLCIS/APLCIS/FLCIS | 8/2/6 |
| Harrison et al., 2020 (USA) | [48] | 2006–2017 | PLCIS/APLCIS/FLCIS | 9/8/2 |
| Zhong et al., 2020 (USA) | [49] | 2010–2019 | APLCIS | 11 |
| Singh et al., 2020 (USA) | [50] | 2007–2017 | APLCIS/FLCIS | 14/22 |
| Kuba et al., 2021 (USA) | [51] | 2007–2019 | PLCIS/APLCIS/FLCIS/AFLCIS | 7/5/18/6 |
| Meurs et al., 2024 (Netherlands) | [52] | 2011–2019 | PLCIS | 129[c] |
| Desai et al., 2025 (USA) | [53] | 2012–2023 | FLCIS | 20 |
| Ferrucci et al., 2025 (Italy) | [54] | 2012–2021 | PLCIS/FLCIS | 35/23 |

Abbreviations: USA, United States of America; UK, United Kingdom; PLCIS, pleomorphic lobular carcinoma in situ; FLCIS, florid lobular carcinoma in situ; APLCIS, apocrine pleomorphic lobular carcinoma in situ; AFLCIS, apocrine florid lobular carcinoma in situ.

[a] PLCIS is defined as pleomorphic lobular and ductal lobular carcinoma in situ (PL/DLCIS).

[b] FLCIS is defined as LCIS with necrosis.

[c] of which 107 underwent surgical excision.

### 3.2. LCIS subtypes: reporting patterns, histopathologic features, and diagnostic challenges

PLCIS was more frequently investigated than FLCIS, with 24 studies (63.2%) reporting exclusively on PLCIS, 12 (31.6%) on both PLCIS and FLCIS, and 2 (5.3%) on FLCIS alone. Sneige et al. [18] were the first to report PLCIS as an isolated lesion without coexisting IC, describing it as pleomorphic lobular and ductal lobular carcinoma in situ (PL/DLCIS). In three studies [39,44,51], an additional borderline variant - LCIS with pleomorphic features (LCIS-PF) - was distinguished from classic PLCIS. Eight studies [7,32,46–51] reported APLCIS cases, suggesting that this rare morphologic subtype may display a higher degree of neoplastic complexity compared with conventional PLCIS. Among these, one study [49] focused exclusively on this variant, while another [7] provided a separate analysis distinct from conventional PLCIS.

FLCIS was first described as an isolated lesion by Hwang et al. [22] in a study investigating the surgical management of LCIS identified on core biopsy. In three studies [22,25,37], FLCIS was referred to as “LCIS with necrosis”, while D'Alfonso et al. [31] were the first to explicitly adopt the term “florid” to designate this distinct variant. Only one study describes six FLCIS cases with apocrine features [51].

Among the 38 included studies, 14 reported histologic evidence of necrosis [7,23–25,27,30,46,48–51,53,54], observed in a total of 216/295 (73.2%) P/FLCIS cases; 8 studies [7,17,23,24,27,30,49,54], described pathological calcifications in 143/163 (87.7%) cases; and 5 studies [17,24,46,49,54] reported synchronous CLCIS in 59/89 (66.3%) cases. Histopathological features from studies reporting comprehensive data are summarized in Table 2. Microscopic morphology of PLCIS and FLCIS are illustrated in Supplementary Figure 1.

Significant morphologic overlap between PLCIS and solid high-grade DCIS has been reported to contribute to diagnostic challenges and risk of misdiagnosis. Among six studies [24,25,39,50,51,54], a total of 21/156 cases initially diagnosed as DCIS on core needle biopsy were reclassified as PLCIS on final surgical specimen, corresponding to an overall misdiagnosis rate of 13.5%. Diagnostic clues favoring P/FLCIS over solid DCIS included the absence of cribriform architecture, cellular dys-cohesion with loss of polarization, and frequent coexistence with CLCIS.

Of note, the vast majority of the studies included in this review systematically applied *E*-cadherin immunostaining to confirm their diagnoses of P/FLCIS, with loss of *E*-cadherin expression reported in almost all cases [7,18,19,21–27,29–34,36,38–40,42,44–54]. Other authors specified that *E*-cadherin staining was performed selectively, primarily to support a definitive lobular classification in diagnostically challenging cases [22,35,37,41–43]. In four studies, immunohistochemical analysis of p120 was also performed, yielding concordant results [23,48–50]. β-Catenin immunostaining was used in conjunction with *E*-cadherin in two studies [40,48]. Finally, two studies did not report the use of immunohistochemistry for diagnostic confirmation

**Table 2**
Clinicopathologic, radiologic, and immunophenotypic features of reported P/FLCIS cohorts with complete data.

| Authors | Cases | Mean or median age (range) | Radiographic features | Pathologic features | Median size (range) | Immunohistochemical features[c] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ER+ | PR+ | HER2+ |
| Sneige et al. [18] | 10 PLCIS | 50.8[a] y (44–64) | 4/10 (40%) architectural distortion and calcifications<br>1/10 (10%) spiculated mass<br>4/10 (40%) calcifications<br>1/10 (10%) not available | 8/10 (80%) calcifications<br>4/10 (40%) associated CLCIS | NA | 10/10 (100%) | NA | 0/10 (0%) |
| Chivukula et al. [23] | 12 PLCIS | 61.4[a] y (45–77) | 11/12 (92%) calcifications<br>1/12 (8%) mass lesion | 12/12 (100%) necrosis<br>12/12 (100%) calcifications<br>2/12 (17%) associated ADH<br>4/12 (33%) associated ALH | 10 mm (1–21) | 11/12 (92%) | 5/12 (42%) | 3/12 (25%) |
| Chen et al. [7] | 31 PLCIS | 55[a] y (NA) | 21/31 (68%) macrocalcifications<br>4/31 (13%) microcalcifications with nodule/architectural distortion/ density<br>2/31 (7%) architectural distortion/ density | 18/31 (58%) comedonecrosis<br>4/31 (13%) punctate necrosis<br>29/31 (94%) calcifications<br>13/31 (42%) apocrine | NA | 18/18 (100%)<br>3/13 (23%)* | 17/18 (94%)<br>2/13 (17%)* | 0/18 (0%)<br>4/13 (31%)* |
| Carder et al. [24] | 10 PLCIS | 63[a] y (56–67) | 5/10 (50%) granular calcifications<br>3/10 (30%) punctate calcifications<br>1/10 (10%) segmental calcifications<br>1/10 (10%) variable calcifications<br>7/10 (70%) single cluster<br>1/10 (10%) two clusters<br>2/10 (20%) three clusters | 10/10 (100%) necrosis<br>10/10 (100%) calcifications<br>9/10 (90%) associated CLCIS | 10 mm (4–28) | 4/7 (57%) | NA | 0/1 (0%) |
| Sullivan et al. [25] | 17 PLCIS<br>11 LCIS-N (FLCIS) | 56[a] y (41–70) | 25/28 (89%) calcifications<br>3/28 (11%) mass | 6/7 (86%) necrosis | NA | NA | NA | NA |
| Downs-Kelly et al. [27] | 26 PLCIS | 58[a] y (35–76) | 18/26 (69%) suspicious calcifications<br>3/26 (12%) benign calcifications<br>2/26 (8%) indeterminate calcifications<br>1/26 (4%) amorphous calcifications<br>1/26 (4%) pleomorphic calcifications<br>1/26 (4%) architectural density<br>1/26 (4%) hypoechoic mass | 15/26 (58%) necrosis<br>25/26 (96%) calcifications | NA | 26/26 (100%) | NA | NA |
| Shin et al. [30] | 20 FLCIS | 61[a] y (42–81) | 13/14 (93%) calcifications<br>1/14 (7%) mass lesion | 11/20 (55%) punctate necrosis<br>6/20 (30%) comedonecrosis<br>3/20 (15%) punctate + comedonecrosis<br>20/20 (100%) calcifications | NA | 12/13 (92%) | NA | 2/11 (18%) |
| Khoury et al. [32] | 47 PLCIS | 56.6[a] y (40–81) | 7/47 (15%) mass<br>38/47 (81%) calcifications<br>1/47 (2%) distortion | 40/47 (85%) necrosis<br>39/47 (83%) apocrine<br>42/47 (89%) macroacini<br>1/47 (2%) signet ring cells<br>5/47 (11%) histiocytic cells | 14.5 mm (1–60) | 18/25 (72%) | 16/25 (64%) | 7/17 (41%) |
| DeBrot et al. [39] | 11 PLCIS | 57[a] y (NA) | 7/11 (64%) calcifications<br>3/11 (27%) enhancement | Not available | NA | 9/11 (82%) | NA | 0/11 (0%) |
| | 5 LCIS-PF | 49[a] y (NA) | 2/5 (40%) calcifications<br>2/5 (40%) enhancement | Not available | NA | 5/5 (100%) | NA | 0/5 (0%) |
| Desai et al. [42] | 15 PLCIS alone on biopsy<br>3 PLCIS after surgery | 52[b] y (48–74) | 13/18 (72%) calcifications<br>4/18 (22%) asymmetry<br>1/18 (6%) asymmetry and calcifications<br>5/8 (63%) hypo or anechoic mass | Not available | NA | 14/15 (93%) | 11/15 (73%) | NA |
| Hoffman et al. [44] | 13 PLCIS<br>10 LCIS-PF<br>3 FLCIS | 54[b] y (40–70) | 22/26 (85%) calcifications<br>9/13 (69%) non-mass enhancement<br>3/13 (23%) irregular mass | Not available | 22.1 mm (7–53) | 20/21 (95%) | 19/21 (91%) | NA |
| Shamir et al. [46] | 12 PLCIS | 61[a] y (42–83) | 6/12 (50%) calcifications<br>2/12 (17%) non-mass enhancement<br>2/12 (17%) mass<br>1/12 (8%) architectural distortion | 7/12 (58%) apocrine<br>9/12 (75%) associated CLCIS | 39 mm (1.8–10) | 7/10 (70%) | 3/10 (30%) | 2/10 (20%) |
| | 9 FLCIS | 56[a] y (40–86) | 3/4 (75%) non-mass enhancement<br>1/4 (25%) mass [among cases without necrosis] | 5/9 (56%) necrosis<br>9/9 (100%) associated CLCIS | 36 mm (0.4–8.2) | 6/6 (100%) | 5/6 (83%) | 0/6 (0%) |

(*continued on next page*)

**Table 2** (*continued*)

| Authors | Cases | Mean or median age (range) | Radiographic features | Pathologic features | Median size (range) | Immunohistochemical features[c] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ER+ | PR+ | HER2+ |
| | | | 5/5 (100%) calcifications [among cases with necrosis] | | | | | |
| Zhong et al. [49] | 11 APLCIS | 66[a] y (46–83) | 9/11 (82%) calcifications<br>2/11 (18%) hyper density<br>2/11 (18%) enhancement | 5/11 (45%) necrosis<br>9/11 (82%) calcifications<br>7/11 (64%) associated CLCIS<br>5/11 (45%) associated FLCIS | 10 mm (4–17) | 9/11 (82%) | 5/11 (45%) | 4/11 (36%) |
| Singh et al. [50] | 14 APLCIS<br>22 FLCIS | 57[a] y (NA) | 28/36 (78%) calcifications<br>3/36 (8%) enhancement<br>3/36 (8%) mass<br>2/36 (6%) distortion | 18/36 (50%) necrosis | NA | 16/21 (76%) | NA | 2/6 (33%) |
| Harrison et al. [48] | 17 PLCIS | | Not available | 15/17 (88%) necrosis<br>8/17 (47%) apocrine cytology<br>8/17 (47%) signet ring cell features<br>4/17 (24%) stromal lymphocytic infiltrate | NA | 12/17 (71%) | 12/17 (71%) | 2/17 (12%) |
| | 2 FLCIS | | Not available | Not available | | 2/2 (100%) | 2/2 (100%) | 1/2 (50%) |
| Kuba et al. [51] | 8 PLCIS | 62.5[b] (45–75) | 6/8 (75%) calcifications<br>1/8 (13%) non-mass enhancement<br>1/8 (13%) mass | 5/8 (63%) necrosis<br>5/8 (63%) apocrine<br>3/8 (37.5%) associated with FLCIS | NA | 26/32 (81%) | NA | 4/31 (13%) |
| | 24 FLCIS | 61[b] (48–79) | 17/24 (71%) calcifications<br>4/24 (17%) non-mass enhancement<br>2/24 (8%) mass<br>1/24 (4%) architectural distortion | 17/24 (71%) necrosis<br>6/24 (25%) apocrine | | | | |
| | 4 LCIS-PF | 52.5[b] (49–73) | 1/4 (25%) calcifications<br>3/4 (75%) non-mass enhancement | Not available | | | | |
| Desai et al. [53] | 20 FLCIS | 57[b] y (35–77) | 8/18 (44.4%) calcifications<br>2/18 (11.1%) mass with suspicious calcifications<br>3/18 (16.7%) mass without suspicious calcifications<br>1/18 (5.6%) asymmetry with suspicious calcifications<br>1/18 (5.6%) asymmetry without suspicious calcifications<br>3/18 (16.7%) non-mass enhancement | 13/18 comedonecrosis<br>1/18 single cell necrosis | NA | 15/18 (83.3%) | NA | NA |
| Ferrucci et al. [54] | 20 PLCIS | 60[b] y (41–75) | 8/20 (40%) calcifications<br>6/20 (30%) architectural distortion<br>5/20 (25%) calcification with architectural distortion<br>1/20 (5%) not evidence of disease<br>11/20 (55%) hypoechogenic<br>1/20 (5%) hyperechogenic<br>11/20 (55%) irregular margins<br>1/20 (5%) regular margins<br>3/11 (27.3%) mass like enhancement<br>8/11 (72.7%) non-mass like enhancement | 11/20 (55%) necrosis<br>12/20 (60%) calcifications<br>14/20 (70%) associated CLCIS | 15 mm (9–25) | 7/9 (77.8%) | 6/9 (66.7%) | NA |
| | 17 FLCIS | 52[b] y (48–58) | 9/17 (52.9%) calcifications<br>5/17 (29.4%) architectural distortion<br>2/17 (11.8%) calcification with architectural distortion<br>1/17 (5.9%) not evidence of disease<br>12/17 (70.6%) hypoechogenic<br>1/17 (5.9%) hyperechogenic<br>11/17 (64.7%) irregular margins<br>2/17 (11.8%) regular margins<br>2/6 (33.3%) mass like enhancement<br>4/6 (66.7%) non-mass like enhancement | 14/17 (82.4%) necrosis<br>13/17 (76.5%) calcifications<br>7/17 (70%) associated CLCIS | 14 mm (8–16.5) | 1/1 (100%) | 1/1 (100%) | NA |
| | 6 P/FLCIS | 60[b] y (57–66) | 2/6 (33.3%) calcifications<br>1/6 (16.7%) architectural distortion<br>3/6 (50%) calcification with architectural distortion<br>4/6 (66.7%) hypoechogenic<br>1/6 (16.7%) hyperechogenic<br>4/6 (66.7%) irregular margins | 4/6 (66.7%) necrosis<br>5/6 (83.3%) calcifications<br>0/6 (0%) associated CLCIS | 17.5 mm (13–23) | 3/3 (100%) | 1/3 (33.3%) | NA |

(*continued on next page*)

**Table 2** (*continued*)

| Authors | Cases | Mean or median age (range) | Radiographic features | Pathologic features | Median size (range) | Immunohistochemical features[c] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | ER+ | PR+ | HER2+ |
| | | | 1/6 (16.7%) regular margins<br>1/2 (50%) mass like enhancement<br>1/2 (50%) non-mass like enhancement | | | | | |

Abbreviations: PLCIS, pleomorphic lobular carcinoma in situ; FLCIS, florid lobular carcinoma in situ; APLCIS, apocrine pleomorphic lobular carcinoma in situ; PL/DLCIS, pleomorphic and ductal lobular carcinoma in situ; LCIS-PF, lobular carcinoma in situ with pleomorphic features; NC-LCIS, non-classic lobular carcinoma in situ; CLCIS, classic lobular carcinoma in situ; ER, estrogen receptor; PR, progesterone receptor; HER2, Human Epithelial Receptor 2; NA, not available.

[a] mean.

[b] median.

[c] *E*-Cadherin immunohistochemistry was performed in all studies included in this table, and loss of *E*-cadherin expression was reported in 100% of the cases.

[20,28].

### 3.3. Upgrade rates

The rate of upgrade from pure P/FLCIS on core biopsy to IC and/or DCIS on final surgical pathology was evaluated based on pooled data from 28 studies (Table 3). A total of 613 P/FLCIS cases were identified on pre-operative biopsy; these included 412 PLCIS (9 APLCIS), 98 FLCIS (6 FLCIS with apocrine features, AFLCIS), and 103 cases categorized as LCIS-PF (n = 14) [44,51] or non-classic LCIS (NC-LCIS, n = 89) [45,50]. The NC-LCIS group comprised both PLCIS and FLCIS cases, but the two entities were not distinguished in the original reports.

Considering only cases with complete data, surgical excision was performed after the initial biopsy in 603/610 (98.8%) cases, while the remaining 7 patients did not undergo surgery and had no available follow-up. Overall, histologic upgrade to IC or DCIS was reported in 213/603 cases, corresponding to a pooled upgrade rate of 35.3%. Specifically, after excluding 5 unspecified cases, 172/598 (28.8%) were upgraded to IC, including 11 cases of microinvasive carcinoma (1.8%), while 36/598 (6%) were upgraded to DCIS. Among PLCIS cases, the overall upgrade rate was 35.1% (138/393; 28.7% to IC and 6.4% to DCIS), while in FLCIS cases the upgrade rate was 33.3% (30/90; 26.7% to IC and 6.7% to DCIS). No significant difference in upgrade rates was observed between the two groups (p = 0.843; OR 1.06, 95% CI: 0.66–1.70; Cohen's h = 0.028). Among upgraded cases, invasive lobular carcinoma (ILC) represented the most frequent histological pattern, accounting for 71.7% (99/138) of PLCIS-associated and 63.3% (19/30) of FLCIS-associated invasive lesions.

### 3.4. Immunohistochemical and molecular features

Immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) in P/FLCIS cells was reported in 16 studies comprising 293 cases. Based on available ER/PR and HER2 data (with incomplete overlap across assays), and assuming independence between ER and PR, the estimated proportion of hormone receptor positive/HER2-cases was 133/168 (79.4%) in PLCIS, 32/40 (80.0%) in FLCIS, 11/24 (44.4%) in APLCIS, and 60/74 (80.7%) in undistinguished cases. The specific immunohistochemical pattern distribution by histological subtype is detailed in Supplementary Figure 2. Despite the limited sample size, ER and PR positivity appeared to be lower in the APLCIS subgroup compared to P/FLCIS, while HER2 positivity was notably higher (8/24 cases, 33.3%). Only three studies [7,49,51] evaluated androgen receptor expression, which was reported as positive in all analyzed cases (21 PLCIS, 10 APLCIS and 22 FLCIS).

Four studies (Table 4) investigated the molecular and genomic profile of PLCIS and FLCIS. Overall, 57 PLCIS and 28 FLCIS cases were characterized using a variety of genomic techniques [7,30,47,48].

Somatic mutations in CDH1 were the most frequent alteration, identified in 33/35 (94.3%) P/FLCIS cases, supporting its role as an early and essential driver of lobular neoplasia. Other frequently mutated genes included ERBB2 in 19/35 (54.3%) cases and PIK3CA in 15/35 (42.9%) cases.

P/FLCIS harbor several recurrent copy number variants (CNVs), that are also consistently found in lobular cancers, including loss of 16q in 71/75 (94.7%) cases, gain of 1q (61/75, 81.3%) and 11q (16/35, 45.7%), and loss of 17p in 31/75 (41.3%) cases.

### 3.5. Radiologic features

Nineteen studies (Tables 2 and 3) provided data on the radiologic characteristics of P/FLCIS. Mammography was the primary method of detection described across all series. Although less frequently reported, in select cases presenting as a mass lesion, ultrasound provided additional information, particularly with regard to margins (typically described as irregular) and echogenicity (generally hypoechoic). In select cases, magnetic resonance imaging (MRI) was performed to better delineate disease extent. The most frequent radiologic finding for both PLCIS and FLCIS was the presence of mammographic calcifications, observed in 328/442 (78.7%) pooled cases. Architectural distortion was reported in 49/285 (17.2%) cases, while the presence of a radiologically detectable mass - identified on mammogram, ultrasound, or MRI - was noted in 75/377 (19.9%) patients. The predominant MRI feature was non-mass enhancement, documented in 49/208 (23.5%) cases.

Savage et al. [43] uniquely focused on imaging characteristics with the aim of distinguishing between pure PLCIS and cases subsequently upgraded to IC or DCIS. They reported that the median extent of calcifications was significantly larger in upgraded lesions compared to pure PLCIS (28 mm vs. 11 mm, respectively). Foschini et al. [45] further investigated predictive radiologic features in a series of 117 patients with P/FLCIS and, through multivariate analysis, identified the linear extent of microcalcifications as an independent predictor of upgrade. In their series, all upgraded cases exhibited microcalcifications extending over 20 mm.

### 3.6. Surgical treatment

Pooled data from 33 studies reported a total of 517 patients who underwent surgery for pure P/FLCIS with available outcomes (Tables 3 and 5). Breast-conserving surgery (BCS) was the most frequent approach (402/517, 77.7%), while mastectomy was performed in 82/517 (15.9%) cases, 64/82 unilateral (78.0%) and 18/82 bilateral (21.9%). A minority of patients (33/517, 6.4%) underwent excisional biopsy alone.

Among the twelve studies that reported mastectomy as a treatment modality, only four [34,43,44,54] explicitly reported the indications for mastectomy. The most common reason was positive margins following excisional biopsy or lumpectomy (4/15, 26.7%). Other indications included risk-reducing mastectomy for contralateral disease (2/15, 13.3%), patient preference (2/15, 13.3%), multifocal disease (3/15, 20%), high lesion-to-breast volume ratio (2/15, 13.3%), multiple diagnostic biopsies (1/15, 6.7%), and prophylactic mastectomy in a BRCA2 mutation carrier (1/15, 6.7%).

Axillary lymph node staging was rarely reported as only one study

**Table 3**
Upgrade rate of P/FLCIS cases screened on pre-operative biopsy.

| Authors | Indications to biopsy | Pre-operative Diagnosis | Primary Surgery | Pure P/FLCIS cases | IC cases | mIC cases | In situ cases | Upgrade rate |
|---|---|---|---|---|---|---|---|---|
| Mahoney et al. [20] | 1 calcifications on MMX<br>1 mass on MMX | 2 PLCIS | 2 excisional biopsies[a] | 1 PLCIS | 1 ILC | 0 | 0 | 1/2 (50.0%) |
| Lavoue et al. [21] | Not available | 5 PLCIS | 5 surgical excisions[c] | 2 PLCIS | 3 ILC | 0 | 0 | 3/5 (60.0%) |
| Hwang et al. [22] | Not available | 7 PLCIS | 7 surgical excisions[c] | 4 PLCIS | 0 | 0 | 3 DCIS | 3/7 (42.9%) |
| | Not available | 6 LCIS-N (FLCIS) | 6 surgical excisions[c] | 3 LCIS-N (FLCIS) | 1 ILC T1b | 1 mIC | 1 DCIS | 3/6 (50.0%) |
| Chivukula et al. [23] | Not available | 12 PLCIS | 1 excisional biopsy[a]<br>1 lumpectomy[b]<br>8 segmental mastectomies<br>1 unilateral mastectomy<br>1 bilateral mastectomy | 7 PLCIS<br>2 LCIS | 1 classic ILC T1aN0<br>1 pleomorphic and classic ILC T1cN0 (i+)<br>1 pleomorphic ILC T1aNX + DCIS | 0 | 0 | 3/12 (25.0%) |
| Carder et al. [24] | Not available | 10 PLCIS | 8 wide local excisions[b]<br>2 excisional biopsies[a] | 6 PLCIS<br>1 CLCIS | 1 ILC T1bN1(5/9)<br>1 ILC T1cN0 | 1 mILC | 0 | 3/10 (30.0%) |
| Sullivan et al. [25] | 14 calcifications on MMX<br>3 masses on MMX | 17 PLCIS | 13 lumpectomies[b]<br>4 mastectomies | 12 PLCIS | 3 ILC | 0 | 2 DCIS | 5/17 (29.4%) |
| | 11 calcifications on MMX | 11 LCIS-N (FLCIS) | 8 lumpectomies[b]<br>3 mastectomies | 6 FLCIS | 4 ILC | 0 | 1 DCIS | 5/11 (45.5%) |
| Purdie et al. [26] | 2 punctate calcifications on MMX<br>1 architectural distortion on MMX | 3 PLCIS | Not available | 1 PLCIS | 1 pleomorphic ILC G2 T1b | 1 mIC | 0 | 2/3 (66.7%) |
| Lewis et al. [28] | Not distinguished | 2 PLCIS | 2 surgical excisions[c] | 2 PLCIS | 0 | 0 | 0 | 0/2 (0.0%) |
| Niell et al. [29] | 4 calcifications on MMX | 4 PLCIS | 4 excisional biopsies[a] | None | 1 ILC G2 T1a<br>1 ILC G2 T1b | 1 IDC G2 + DCIS | 1 DCIS G1 | 4/4 (100%) |
| D'Alfonso et al. [31] | Not distinguished | 5 FLCIS | 5 excisional biopsies[a] | 4 FLCIS | 0 | 1 mILC | 0 | 1/5 (20%) |
| | | 3 F/NF-LCIS | 3 excisional biopsies[a] | 2 F/NF-LCIS | 1 classic ILC T1c | 0 | 0 | 1/3 (33.3%) |
| | | 2 PLCIS | 2 excisional biopsies[a] | 2 PLCIS | 0 | 0 | 0 | 0/2 (0.0%) |
| Meroni et al. [33] | Not distinguished, | 12 PLCIS | 12 surgical excisions[c] | 2 PLCIS<br>4 LCIS | 5 ILC | 0 | 1 DCIS G3 | 6/12 (50.0%) |
| Flanagan et al. [34] | 18 suspicious calcifications on MMX<br>4 mass/space occupying lesion on MRI<br>1 focus enhancement on MRI | 23 PLCIS | 16 lumpectomies[b]<br>5 bilateral mastectomies<br>2 excisional biopsies[a] | 12 PLCIS | 5 ILC<br>2 ILDC | 0 | 4 DCIS | 11/23 (47.8%) |
| Szynglarewicz et al. [35] | 5 hypoechoic, irregular masses with posterior shadowing on US (BIRADS 5) | 5 PLCIS | 5 surgical excisions[c] | None | Not available | Not available | Not available | 5/5 (100%) |
| Susnik et al. [37] | Not distinguished | 15 PLCIS | Not available | 11 PLCIS | 4 IC | 0 | 0 | 4/15 (26.7%) |
| Fasola et al. [38] | 20 abnormalities on MMX, the majority of which suspicious calcifications | 20 PLCIS | Not distinguished | 14 PLCIS | 3 classic ILC<br>1 pleomorphic ILC | 0 | 2 DCIS | 6/20 (30.0%) |
| Guo et al. [40] | Not distinguished | 25 PLCIS | Not distinguished | 9 PLCIS | 13 ILC<br>1 IDC | 2 mIC | 0 | 16/25 (64.0%) |
| Masannat et al. [41] | Not available | 22 PLCIS | Not available | 14 PLCIS | 7 IC | 0 | 1 DCIS | 8/22 (36.4%) |
| Desai et al. [42] | 13 calcifications on MMX<br>4 asymmetries on MMX<br>1 asymmetry and calcifications on MMX<br>5 hypo or anechoic mass | 15 PLCIS | 11 wide local excisions[b]<br>4 mastectomies | 12 PLCIS | 3 IC | 0 | 0 | 3/15 (20.0%) |
| Savage et al. [43] | 16 fine pleomorphic calcifications on MMX<br>2 architectural distortions with faint amorphous calcifications on MMX<br>1 circumscribed mass on MMX + US<br>1 regional clumped non-mass enhancement on MRI | 21 PLCIS | 16 lumpectomies[b]<br>2 bilateral mastectomies<br>2 bilateral mastectomies after lumpectomies<br>1 no further surgery after CNB | 16 PLCIS | 2 ILC | 0 | 1 DCIS G3<br>1 DCIS G1 | 4/20 (20.0%) |

(*continued on next page*)

**Table 3** (*continued*)

| Authors | Indications to biopsy | Pre-operative Diagnosis | Primary Surgery | Pure P/ FLCIS cases | IC cases | mIC cases | In situ cases | Upgrade rate |
|---|---|---|---|---|---|---|---|---|
| Hoffmann et al. [44] | 22 calcifications on MMX<br>9 non-mass enhancement on MRI<br>3 irregular masses on MRI | 13 PLCIS<br>10 LCIS-PF<br>3 FLCIS | 14 lumpectomies[b]<br>7 bilateral mastectomies<br>2 unilateral mastectomies<br>3 excisional biopsies[1] | 7 PLCIS<br>4 LCIS-PF<br>3 FLCIS<br>9 PLCIS or LCIS-PF | 2 ILC | 0 | 1 DCIS | 3/26 (11.5%) |
| Foschini et al. [45] | 61 microcalcification on MMX<br>9 dense area on MMX | 70 P/FLCIS | Not available | 39 P/FLCIS | 28 IC | 0 | 3 DCIS | 31/70 (44.3%) |
| Shamir et al. [46] | 6 calcifications on MMX<br>2 non-mass enhancement on MRI<br>2 masses on MMX<br>1 architectural distortion on MMX<br>1 palpable mass with sclerosing lesion on CNB | 5 PLCIS | 1 local excision[3]<br>2 mastectomies<br>1 mastectomy after local excisions<br>1 no excision for contralateral metastatic ILC | 2 PLCIS | 1 ILC<br>1 pleomorphic ILC | 0 | 0 | 2/4 (50%) |
| | | 7 APLCIS | 3 local excisions[c]<br>1 mastectomy<br>2 mastectomies after local excision<br>1 lost to follow-up | 3 APLCIS | 1 ILC | 0 | 0 | 1/4* (25%) |
| | 5 calcifications on MMX<br>3 non-mass enhancement on MRI<br>1 mass on MMX | 9 FLCIS | 2 local excisions[c]<br>2 mastectomies<br>2 mastectomies after local excision<br>3 no excision | 4 FLCIS | 1 ILC | 0 | 1 DCIS | 2/6 (33.3%) |
| * Two patients have no available upgrade data because they underwent surgical excision at other institution | | | | | | | | |
| Harrison et al. [48] | Not available | 17 PLCIS | Not available | 11 PLCIS | 5 ILC | 0 | 1 DCIS | 6/17 (35.3%) |
| | Not available | 2 FLCIS | 2 surgical excisions[c] | 1 FLCIS | 0 | 0 | 1 DCIS | 1/2 (50.0%) |
| Singh et al. [50] | 28 calcifications on MMX<br>3 non-mass enhancement on MRI<br>3 masses on MMX<br>2 architectural distortions on MMX | 36 NC-LCIS with<br>19 NC-LCIS eligible to upgrade* | 19 wide local excisions[b] | 11 NC-LCIS<br>2 benignities | 5 ILC | 0 | 1 DCIS | 6/19 (31.6%) |
| * 27 patients with available surgical excision information; 8 patients with microscopic invasion on needle biopsy. | | | | | | | | |
| Kuba et al. [51] | 24 calcifications on MMX<br>8 non-mass enhancement on MRI<br>3 masses on MMX<br>1 architectural distortion on MMX | 3 PLCIS<br>2 APLCIS<br>3 apocrine PLCIS + FLCIS | 6 lumpectomies[b]<br>2 mastectomies | 6 PLCIS | 1 ILC | 1 mIC | 0 | 2/8 (25.0%) |
| | | 18 FLCIS<br>6 AFLCIS | 22 lumpectomies[2]<br>2 mastectomies | 20 FLCIS | 1 multifocal ILC | 3 mIC | 0 | 4/24 (16.7%) |
| | | 4 LCIS-PF | 4 lumpectomies[b] | 4 LCIS-PF | 0 | 0 | 0 | 0/4 (0.0%) |
| Meurs et al. [52] | Not available | 107 PLCIS | 83 lumpectomies[b]<br>24 mastectomies | 73 PLCIS | 23 classic ILC<br>1 pleomorphic ILC<br>2 IDC<br>1 tubular IC | 0 | 7 DCIS | 34/107 (31.8%) |
| Desai et al. [53] | 8 calcifications<br>2 mass with suspicious calcifications<br>3 mass without suspicious calcifications<br>1 asymmetry with suspicious calcifications<br>1 asymmetry without suspicious calcifications<br>3 non-mass enhancement | 20 FLCIS | 18 surgical excisions[c]<br>2 active surveillance and endocrine therapy | 9 FLCIS | 8 ILC | 0 | 1 DCIS | 9/18 (50%) |
| Ferrucci et al. [54] | Not available | 33 PLCIS | 33 surgical excisions[c] | 19 PLCIS<br>3 PLCIS + FLCIS | 7 ILC<br>3 IDC | 0 | 1 DCIS | 11/36 (30.6%) |
| | Not available | 15 FLCIS | 15 surgical excision[c] | 9 FLCIS<br>2 PLCIS + FLCIS | 2 ILC<br>1 IDC | 0 | 1 DCIS | 4/15 (26.7%) |

Abbreviations: LCIS, lobular carcinoma in situ; PLCIS, pleomorphic lobular carcinoma in situ; FLCIS, florid lobular carcinoma in situ; P/F-LCIS, pleomorphic and florid lobular carcinoma in situ; LCIS-N, lobular carcinoma in situ with necrosis; NC-LCIS, non-classic lobular carcinoma in situ; LCIS-PF, lobular carcinoma in situ with pleomorphic features; F/NF-LCIS, florid and non-florid lobular carcinoma in situ; APLCIS, apocrine pleomorphic lobular carcinoma in situ; AFLCIS, apocrine florid lobular carcinoma in situ; IC, invasive cancer; mIC, microinvasive cancer; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; mILC, microinvasive lobular carcinoma; MMX, mammogram; US, ultrasound; MRI, magnetic resonance imaging; CNB, core needle biopsy.

[a] Surgical biopsy, defined as excision of the lesion performed primarily for diagnostic purposes, without specific attention to achieving negative margins.

[b] Wide local excision or lumpectomy, defined as excision of the lesion performed primarily for therapeutic purposes, with the aim of achieving negative surgical margins.

[c] Breast-conserving surgery, with no further specification about the surgical procedure.

**Table 4**
Chromosomal alterations in P/FLCIS cohorts.

| Chromosomal alteration | Gene associated | Chen et al. [7] | | | Shin et al. [30] | Shamir et al. [47] | | Harrison et al. [48] |
|---|---|---|---|---|---|---|---|---|
| | | 21 PLCIS | 8/21 APLCIS | 20 CLCIS | 20 FLCIS | 9 PLCIS | 6 FLCIS | 19 P/FLCIS |
| 1q gain | – | 75% | Not specified | 69% | 80% | 88.9% | 83.3% | 84.2% |
| 3q loss | PIK3CA | – | 22% | – | – | – | – | – |
| 6p gain | – | – | 15% | – | – | – | – | – |
| 7q loss | – | – | – | – | – | – | – | 10.5% |
| 8p loss | – | 5% | – | 0% | 25% | 44% | 33% | 15.8% |
| 8q gain | – | – | – | – | – | 33% | 33% | – |
| 11q gain | CCN1D | 14% | 38% | 5% | 25% | – | – | – |
| 11q loss | – | – | – | – | 50% | 44% | 33% | – |
| 12p loss | KRAS | – | – | – | – | – | – | 15.8% |
| 13q loss | RB1 | – | 25% | – | – | 44% | 17% | – |
| 16p gain | – | 14% | 36% | 0% | – | 22% | 33% | 15.8% |
| 16q gain | CBFB | – | – | – | – | – | – | – |
| 16q loss | CDH1 | 85% | Not specified | 76% | 100% | 100% | 100% | 94.7% |
| 17p loss | TP53 | 23% | 45% | 10% | 40% | 56% | 17% | 52.6% |
| 17q gain | ERBB2 | 10% | 25% | 0% | – | 33% | 17% | – |
| 18q loss | – | – | – | – | – | 44% | 17% | – |

Abbreviations: PLCIS, pleomorphic lobular carcinoma in situ; APLCIS, apocrine pleomorphic lobular carcinoma in situ; CLCIS, classic lobular carcinoma in situ; FLCIS, florid lobular carcinoma in situ; P/F-LCIS, pleomorphic and lobular carcinoma in situ.

[54] described four patients with pure PLCIS who underwent sentinel lymph node biopsy (SLNB), suggesting this practice is not commonly adopted in the absence of known IC.

### 3.7. Surgical and oncological outcomes

The mean patient age reported across studies ranged from 49 to 66 years. When accounting for sample size, the weighted average age was 51.8 years, based on data from 298 patients. After excluding cases upstaged to IC or DCIS upon excision, we identified 393 pure P/FLCIS cases. Restricting the analysis to studies reporting at least one surgical or oncological outcome (n = 15, Table 5) yielded 258 patients, who represent the subgroup with available follow-up data. This pooled population comprised 194 pure PLCIS cases (including 43 APLCIS, 12 LCIS-PF and 22 with synchronous PLCIS and FLCIS), 44 pure FLCIS cases (including 6 AFLCIS), and 20 undistinguished P/FLCIS cases.

Data on surgical margin status was available for 197/258 (76.4%) patients. The overall rate of positive, close (<2 mm) and negative margins was 34/197 (17.3%), 30/197 (15.2%), and 133/197 (67.5%), respectively. Margin status by LCIS subtype is shown in Table 6.

Across the included studies, follow-up data were heterogeneous, with a pooled median follow-up of 50 months, and an overall range of 1.6–189 months. The overall ipsilateral breast event rate among patients with available follow-up was 32/258 (12.4%), comprising 20 IC (62.5%), 1 DCIS (3.1%), and 11 recurrent P/FLCIS (34.4%). Invasive recurrences were significantly more frequent than in situ events ($p = 0.04$).

One patient with PLCIS developed an invasive LR with locoregional axillary involvement (after 43 months), while another experienced synchronous invasive LR with distant metastases (after 87 months) and subsequently died—the only reported disease-related death.

Recurrence occurred more frequently in PLCIS (24/194, 12.4%; rising to 28/214, 13.1%, when the 20 undistinguished cases were included), than in FLCIS cases (4/44, 9.1%), although this difference did not reach statistical significance ($p = 0.618$). Focusing specifically on invasive/DCIS recurrences, 19/28 (67.9%) PLCIS events were invasive/DCIS, whereas half of FLCIS recurrences were invasive (2/4). Data on margin status was available for 23/32 reported recurrences. Notably, recurrence rates were strongly associated with surgical margin status ($p < 0.001$) (Table 5). Patients with positive margins experienced recurrence in 13/34 cases (38.2%; 95% CI, 24.9%–54.9%), while those with close margins in 6/30 cases (20%; 95% CI, 9.5%–37.3%). In contrast, patients with negative margins showed a markedly lower recurrence rate of 4/133 cases (3.0%; 95% CI, 1.2%–7.5%). Compared with negative margins, positive margins conferred a nearly 20-fold higher recurrence risk (OR 19.9, 95% CI 6.4–76.4; $p < 0.001$), while a significant linear trend across margin categories was confirmed (Cochran-Armitage $Z = 5.91$, $p < 0.001$). A subgroup analysis of recurrence by histologic subtype and margin status further confirmed this trend. In PLCIS, recurrence occurred in 10/31 (32.3%) patients with positive margins, 6/24 (25%) with close margins, and 4/113 (3.5%) with negative margins; the difference across groups remained significant within this subset ($p < 0.001$). In FLCIS, recurrence was reported in 3/3 patients with positive margins, and in none of the 5 patients with close margins or 12 with negative margins. Margin status was unavailable for 9 of the 32 patients who experienced recurrence.

In the apocrine subgroups, overall pooled analysis identified 7 recurrences among 43 APLCIS cases (15%) [32,46,49,51]. Zhong et al. specifically analyzed 11 cases of pure APLCIS reporting, with a mean follow-up of 57 months, an invasive recurrence rate of 18% (2/11) with no instances of metastasis or cancer-related mortality [49]. Kuba et al. reported 6 cases of pure AFLCIS, with 1 invasive recurrence (16.7%) occurring in a case with negative margins after 59 months [51].

Among all P/FLCIS cases, the overall median time to recurrence was 43 months (IQR, 22–66), significantly longer for invasive events—57.5 months (IQR, 41.5–70.5)—compared with 22 months (IQR, 17.5–31) for in situ recurrences ($p = 0.017$). Patients with positive or close margins experienced earlier recurrence, with a median time of 34 months, compared to 65.5 months among those with negative margins, yielding a mean difference of approximately 19.4 months. This difference approached borderline statistical significance ($p = 0.07$).

### 3.8. Adjuvant treatments

Among the studies included in this review, only ten (Table 5) studies including 177 patients reported data on adjuvant treatments. Across the available data, 14/177 (7.9%) patients received RT, 66/177 (37.3%) received ET, 8/177 (4.5%) received both, and 95/177 (53.7%) patients did not undergo any form of adjuvant treatment. No cases of adjuvant chemotherapy were documented. None of the included studies provided

**Table 5**
Surgical treatment, final margin status and clinical outcomes in definitive pure P/FLCIS cohorts.

| Authors | Pure cases | Surgical treatment | Adjuvant treatment | Final positive margins | | Final close margins | | Final negative margins* | | Total recurrence rate | Mean or median follow-up (range), months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Recurrences | N | Recurrences | N | Recurrences | | |
| Sneige et al. [18] | 10 PL/DLCIS | 5 lumpectomies<br>2 unilateral mastectomies<br>3 NA | NA | 0 | None | 1 | 1 PL/DLCIS after 12 mo | 6 | None | 1/7 (14.3%) | 17[a] (4–32) |
| Downs-Kelly et al. [27] | 20 PLCIS<br>6 PLCIS with micro invasion (≤1 mm) | 26 wide local excisions | 4 HT<br>4 RT<br>6 HT + RT<br>10 none | 6 | 1 PLCIS after 19 mo [previous HT and treated with mastectomy] | 11 | None | 9 | None | 1/26 (3.9%) | 46[a] (4–108) |
| Khoury et al. [32] | 31 PLCIS | 29 wide local excisions<br>2 unilateral mastectomies | 11 HT<br>3 RT<br>17 none | 9 | 1 ILC + PLCIS after 59 mo [previous HT, treated with excision + HT]<br>1 ILC + PLCIS after 22 mo [previous HT, treated with excision + HT]<br>1 ILC after 77 mo [treated with excision]<br>1 PLCIS after 7 mo [treated with excision] | 0 | None | 21 | 1 IDC after 91 mo [previous HT, treated with excision + HT]<br>1 PLCIS after 21 mo [treated with excision] | 6/30* (19.4%) | 55.6[b] (1.6–112) |
| * Recurrence data reported for 30/31 cases | | | | | | | | | | | |
| Meroni et al. [33] | 2 PLCIS | 2 surgical excisions | None | 0 | None | 0 | None | 2 | 1 IDC after 7.6 y | 1/2 (50%) | 4.3–7.6 y |
| Flanagan et al. [34] | 12 PLCIS | 2 excisional biopsies<br>10 local excisions | 3 HT<br>1 RT | 3 | None | 4 | None | 5 | None | 0/12 (0%) | 49.2[a] (5.7–115.2) |
| Fasola et al. [38] | 12 PLCIS | 11 excisional biopsies<br>1 NA | NA | 2 | None | 0 | None | 10 | None | 0/12 (0%) | NA |
| DeBrot et al. [39] | 11 PLCIS | 8 local excisions<br>3 mastectomies | 3 HT | 2 | None | 3 | 1 mILC. ILC after 63 mo<br>1 IDC G3 T1b after 56 mo<br>1 DCIS G2 after 66 mo [previous HT] | 3 | None | 3/11 (27.3%) | 67[b] (34–189) |
| | 5 LCIS-PF | 4 local excisions<br>1 mastectomy | | 3 | 1 multifocal classic ILC G3 after 45 mo | 0 | None | 1 | None | 1/5 20% | |
| Desai et al. [42] | 15 PLCIS | 11 wide local excisions<br>2 unilateral mastectomies<br>2 unilateral mastectomies after wide local excisions | 6 HT<br>1 RT<br>1 HR + RT<br>7 None | 1 | 1 PLCIS after 16 mo [previous HT] | 0 | None | 14 | 1 ILC with metastases after 87 mo [previous RT] | 2/15 (13.3%) | 21[b] (2–160) |
| Savage et al. [43] | 16 PLCIS | 12 lumpectomies<br>2 bilateral mastectomies after lumpectomies,<br>2 bilateral mastectomies | 8 HT<br>2 RT | 1 | None | 0 | None | 15 | None | 0/16 (0%) | 40.8[b] (15.6–110.4) |
| Hoffman et al. [44] | 4 LCIS-PF | 3 lumpectomies<br>1 lumpectomy with re-excisions | 2 HT | 0 | None | 2 | None | 2 | None | 0/4 (0%) | 54[a] (0.67–126) |

(*continued on next page*)

**Table 5** (*continued*)

| Authors | Pure cases | Surgical treatment | Adjuvant treatment | Final positive margins | | Final close margins | | Final negative margins* | | Total recurrence rate | Mean or median follow-up (range), months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Recurrences | N | Recurrences | N | Recurrences | | |
| | 7 PLCIS | 5 lumpectomies<br>2 lumpectomies with re-excision | 2 HT<br>1 RT + HT | 0 | None | 1 | 1 NCLCIS after 22.2 mo [previous HT] | 6 | None | 1/7 (14.3%) | |
| | 3 FLCIS | 2 lumpectomies<br>1 lumpectomy with 2 re-excisions | 2 HT | 1 | 1 NCLCIS after 99.2 mo | 1 | None | 1 | None | 1/3 (33.3%) | |
| | 9 PLCIS or FLCIS | 7 bilateral mastectomies<br>1 unilateral mastectomy after lumpectomy<br>3 excisional biopsies | NA | 0 | None | 1 | None | 8 | None | 0/9 (0%) | |
| Shamir et al. [46] | 5 PLCIS | Not distinguished | Not distinguished | NA | None | NA | None | NA | None | 0/5 (0%) | 32[a] (9–52) |
| | 4 FLCIS | Not distinguished | Not distinguished | NA | None | NA | None | NA | None | 0/4 (0%) | 50[a] (10–97) |
| Zhong et al. [49] | 6 APLCIS | 5 local excisions<br>1 NA | 1 HT | NA | | NA | | NA | 1 PLCIS then ILC<br>1 APLCIS then ILC + DCIS | 2/11 (18.2%) | 57[a] (4–106) |
| | 5 APLCIS + FLCIS | 3 local excisions<br>1 mastectomy after local excision<br>1 NA | 3 HT | | | | | | | | |
| Singh et al. [50] | 11 NC-LCIS | 11 wide local excisions | 7 HT<br>1 RT | NA | | NA | | NA | 1 IDC after 48 mo<br>1 ILC after 72 mo<br>1 NCLCIS after 22 mo<br>1 NCLCIS after 78 mo | 4/11 (36.4%) | 50[b] (10–96) |
| Kuba et al. [51] | 3 PLCIS | 4 lumpectomies<br>2 mastectomies | 3 HT<br>1 RT | NA | | NA | | NA | 1 FLCIS with mIC after 24 mo [no previous HT, treated with excision + SLN] | 2/6 (33.3%) | 37.5[b] (NA) |
| | 3 APLCIS | | | NA | | NA | | NA | 1 PLCIS with mIC [no previous HT, treated with excision], followed by 1 mixed IC T2 + DCIS + PLCIS [treated with excision + RT + CT] | | |
| | 14 FLCIS | 19 lumpectomies<br>1 mastectomy | 10 HT<br>1 RT | NA | | NA | | NA | | 1/20 (5%) | |
| | 6 AFLCIS | | | NA | | NA | | NA | 1 pleomorphic ILC T1b(m) + PLCIS + FLCIS after 59 mo [previous Raloxifene, treated with mastectomy + Raloxifene] | | |
| | 4 LCIS-PF | 4 lumpectomies | 1 HT | NA | | NA | | NA | | 0/4 (0%) | |
| Ferrucci et al. [54] | 20 PLCIS | 17 lumpectomies<br>1 excisional biopsy<br>2 unilateral mastectomies<br>3 re-excisions | None | 3 | 1 ILC with axillary metastasis after 43 mo<br>1 ILC + PLCIS after 34 mo | 2 | 1 PLCIS after 28 mo | 15 | None | 3/20 (15%) | 53[b] (16–115) |
| | 17 FLCIS | 9 lumpectomies<br>8 excisional biopsies<br>2 re-excisions | None | 2 | 1 ILC after 41 mo<br>1 FLCIS after 34 mo | 4 | None | 11 | None | 2/17 (11.8%) | |

(*continued on next page*)

**Table 5** (*continued*)

| Authors | Pure cases | Surgical treatment | Adjuvant treatment | Final positive margins | | Final close margins | | Final negative margins* | | Total recurrence rate | Mean or median follow-up (range), months |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | N | Recurrences | N | Recurrences | N | Recurrences | | |
| | 6 PLCIS + FLCIS | 4 lumpectomies<br>1 unilateral mastectomy<br>1 bilateral mastectomy | None | 1 | 1 ILC + FLCIS after 16 mo | 0 | None | 5 | None | 1/6 (16.7%) | |

Abbreviations: PLCIS, pleomorphic lobular carcinoma in situ; FLCIS, florid lobular carcinoma in situ; APLCIS, apocrine pleomorphic lobular carcinoma in situ; AFLCIS, apocrine lobular carcinoma in situ; PL/DLCIS, pleomorphic and ductal lobular carcinoma in situ; LCIS-PF, lobular carcinoma in situ with pleomorphic features; NC-LCIS, non-classic lobular carcinoma in situ; HT, hormone therapy; RT, radiotherapy; ILC, invasive lobular carcinoma; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ; mILC, microinvasive lobular carcinoma; NA, not available.

[a] mean.

[b] median.

a clear rationale or specified clinical indications for the selection of adjuvant therapies.

The recurrence rate was 12.1% (8/66) among patients who received ET and 7.1% (1/14) among those treated with adjuvant RT. No recurrences were documented among the 8 patients who received both ET and RT. It remains unclear whether treatment decisions were influenced by individual risk factors, such as margin status, patient age, or multifocality. In addition, key treatment details—such as the type of endocrine agent administered, radiation dose, and target volumes—were not reported in any of the studies reviewed.

## 4. Discussion

This work represents the most comprehensive review to date of the available literature on P/FLCIS, offering valuable insights into their clinical, radiologic, pathologic, and molecular features. It highlights several key challenges and unresolved issues in the clinical management of these rare LCIS variants.

A fundamental limitation of the existing literature is the significant heterogeneity in lesions classification and clinical management which hinders outcome reporting for P/FLCIS, as well as direct comparison between studies. Here we demonstrate that studies on pure LCIS variants have predominantly focused on PLCIS [17–20,22–24,26–30,32–36,38–43,49,52], while FLCIS has been exclusively addressed in only two dedicated studies [30,53] and analyzed in association with PLCIS in twelve others [21,25,31,37,44–48,50,51,54]. In addition to the studies included here, it should be noted that an additional retrospective series was published a few months after the pre-set completion date of the literature search for the present review. This study by Middleton et al. reported upgrade rates and detailed pathological, surgical, and oncological outcomes in 45 patients initially diagnosed on preoperative biopsy with PLCIS (n = 40) and/or FLCIS (n = 5) [55]. To date, the largest case series reporting detailed surgical and oncological outcomes for each of the two histologically confirmed pure variants on the final surgical specimen, have been reported by Khouri et al., in 2014 [32], which included 31 PLCIS cases, and by Kuba et al., in 2021, which analyzed 20 cases of FLCIS [51]. The study by Zhong et al. was the only one exclusively dedicated to APLCIS and comprised 11 pure cases [49]. The longest available follow-up is from DeBrot et al. [39], with a median duration of 67 months.

This lack of long-term data, combined with the small sample sizes, contributes to the absence of evidence-based recommendations for the management of P/FLCIS in current international guidelines.

### 4.1. Diagnostic challenges

All reviewed studies consistently demonstrate that PLCIS and FLCIS are clearly distinct from CLCIS in terms of morphological features, neoplastic complexity, and their associated higher risk of upgrade to IC [56–58]. Morphologically, PLCIS is characterized by marked nuclear atypia, while FLCIS shows disorganized architecture and florid distension of terminal duct-lobular units—both indicative of a more advanced proliferative alteration. Their frequent association with IC and/or atypical lobular hyperplasia (ALH) supports the hypothesis that P/FLCIS could represent a transitional stage in the neoplastic continuum of the breast lobule and should therefore be considered a non-obligate precursor lesion, with a greater potential for invasive upstaging compared to CLCIS. These distinctions were further emphasized by Brogi [59], highlighting the urgent need for a unified and standardized approach to the diagnosis and management of these rare LCIS variants. In diagnostically challenging cases, immunohistochemistry is warranted, with loss of *E*-cadherin expression supporting a lobular phenotype. β-Catenin and/or p120 catenin may also be used as adjunctive markers to further confirm lobular differentiation [22,35,37,41–43,54]; yet as detailed in this review, there remains inconsistency in use of these markers in current clinical practice.

Unfortunately, genomic analyses are still limited, with only four studies specifically addressing this aspect [7,30,47,48]. Collectively, our review highlights numerous alterations in P/FLCIS that are also reported in invasive lobular lesions. Loss or dysfunction of the cell-cell adhesion molecule *E*-cadherin, a transmembrane glycoprotein encoded by CDH1 gene, is the hallmark of lobular neoplasia. Several molecular mechanisms for loss of the functional protein have been identified, but the most common is loss-of-heterozygosity affecting the 16q chromosomal region, where the CDH1 gene is located. This is typically followed by a frameshift mutation in the remaining CDH1 gene, resulting in truncation and inactivation of the *E*-cadherin protein [60]. The combination of 1q gain and 16q loss is also the characteristic genomic signature of lobular neoplasia. The frequent mutations in ERBB2 (54.3%) reported among P/FLCIS cases deserves additional study as these are less common among cases of classic invasive lobular carcinoma. Reis-Filho et al. [61] demonstrated a substantial overlap in the genetic alterations of PLCIS and pleomorphic ILC, suggesting that PLCIS—and likely FLCIS—should be viewed not merely as risk indicators, but as non-obligate precursors of IC.

Current data on APLCIS remain limited, nevertheless, the combination of a relatively high recurrence risk, and a distinct molecular and immunohistochemistry profile—being less frequently HR-positive and more likely to exhibit HER2 overexpression—underscores the need for larger, dedicated studies to better clarify its clinical behavior and identify prognostic markers to guide management strategies [62].

### 4.2. Upgrade rates

The majority of the included studies, 28/38 (73.7%), focused on the clinical management of P/FLCIS diagnosed on core biopsy, specifically

**Table 6**
Recurrence rates according to surgical margin status in studies with available data.

| Authors | Pure cases | Recurrences among cases with positive margins[a] | Recurrences among cases with close margins[b] | Recurrences among cases with negative margins[c] |
|---|---|---|---|---|
| PLCIS | | | | |
| Sneige et al. [18] | 10 PL/DLCIS | – | 1/1 (100%) | 0/6 (0%) |
| Downs-Kelly et al. [27] | 20 PLCIS | 1/6 (16.7%) | 0/11 (0%) | 0/9 (0%) |
| | 6 PLCIS with micro invasion (≤1 mm) | | | |
| Khoury et al. [32] | 31 PLCIS[d] | 4/9 (44.4%) | – | 2/21 (9.5%) |
| Meroni et al. [33] | 2 PLCIS | – | – | 1/2 (50.0%) |
| Flanagan et al. [34] | 12 PLCIS | 0/3 (0%) | 0/4 (0%) | 0/5 (0%) |
| Fasola et al. [38] | 12 PLCIS | 0/2 (0%) | – | 0/10 (0%) |
| DeBrot et al. [39] | 11 PLCIS | 0/2 (0%) | 1/3 (33.3%) | 0/3 (0%) |
| | 5 LCIS-PF | 1/3 (33.3%) | – | 0/1 (0%) |
| Desai et al. [42] | 15 PLCIS | 1/1 (100%) | – | 1/14 (7.1%) |
| Savage et al. [43] | 16 PLCIS | 0/1 (0%) | – | 0/15 (0%) |
| Hoffman et al. [44] | 4 LCIS-PF | – | 0/2 (0%) | 0/2 (0%) |
| | 7 PLCIS | – | 1/1 (100%) | 0/6 (0%) |
| Ferrucci et al. [54] | 20 PLCIS | 2/3 (66.7%) | 1/2 (50%) | 0/15 (0%) |
| | 6 PLCIS + FLCIS | 1/1 (100%) | – | 0/5 (0%) |
| **FLCIS** | | | | |
| Hoffman et al. [44] | 3 FLCIS | 1/1 (100%) | 0/1 (0%) | 0/1 (0%) |
| Ferrucci et al. [54] | 17 FLCIS | 2/2 (100%) | 0/4 (0%) | 0/11 (0%) |

Abbreviations: PLCIS, pleomorphic lobular carcinoma in situ; PL/DLCIS, pleomorphic lobular/ductal lobular carcinoma in situ; LCIS-PF, lobular carcinoma in situ with pleomorphic features; FLCIS, florid lobular carcinoma in situ.
[a] Positive margins: on ink.
[b] Close margins: <2 mm.
[c] Negative margins: ≥2 mm.
[d] Recurrence data reported for 30/31 cases.

evaluating the risk of upgrade to IC and/or DCIS (Table 3). The overall pooled upgrade rate identified in this review reached 35.3%—specifically, 35.1% for PLCIS and 33.3% for FLCIS—which exceeds the reported upgrade rate in the recent case series by Middleton et al. (25%) [55], likely reflecting variations in case selection, diagnostic criteria, and study design across published cohorts. Several factors have been proposed as potential predictors of histologic upgrade on final pathology, most notably radiologic and histopathologic characteristics. In contrast, clinical features such as lesion palpability or personal history have not been identified as reliable predictors. Among radiological features, Foschini et al. reported that the linear extent of microcalcifications on mammography correlated with a higher risk of upgrade to IC in P/FLCIS [44, 45]. The evaluation of additional radiologic parameters—such as ultrasound margin characteristics [63,64], MRI enhancement patterns, and lesion distribution—may offer additional predictive value, yet these areas remain underexplored in the current literature.

### 4.3. Treatment and long-term oncological outcomes

All reviewed studies unanimously support therapeutic surgical excision as the current gold standard for the management of P/FLCIS diagnosed on core biopsy. Foschini et al. reported a preoperative biopsy accuracy of 60.3% for both PLCIS and FLCIS, corresponding to a 39.7% underestimation rate for associated IC [45]. This observation is consistent with the overall preoperative accuracy rate of 62.5% observed across all studies included in this review, and, therefore, in the absence of surgical excision the risk of missing an underlying IC or DCIS exceeds 30%. These findings underscore the diagnostic limitations of core needle biopsy and reinforce the crucial role of surgical excision for definitive histologic evaluation. Furthermore, this review provides the most compelling evidence to date that surgical excision, with the goal of obtaining clear margins, reduces the risk of future breast events, from 38.2% in patients with positive margins to 3.0% in those with negative margins, and notably 62.5% of identified ipsilateral breast events were invasive. Major international guidelines, including the NCCN [14], the NHS Breast Screening Programme [9], and ESMO [13], have recommended excision with negative margins as the primary surgical goal for PLCIS; however, this was primarily based on the morphologic similarities to high-grade DCIS, without clear supporting data.

The optimal margin width to define a negative margin in P/FLCIS remains an unresolved and critical issue in the management of these lesions (Table 4). Downs-Kelly et al. [27] were the first to investigate the impact of margin width in PLCIS and, despite the small cohort and limited follow-up, suggested that a 2-mm negative margin could provide effective local control. However, their study included cases with microinvasion and encompassed a heterogeneous range of treatments, limiting the strength of these findings. In the more recent retrospective cohort study from the same center, all local recurrences were invasive and occurred in patients initially diagnosed with PLCIS who had close (<2 mm) or positive margins after surgical excision, confirming margin status as a significant risk factor for local recurrence ($p = 0.01$) [55]. Larger studies with more robust cohorts are needed to establish the minimal margin required to significantly reduce recurrence risk and to guide precise surgical planning [13]. Importantly, the findings of this review do not support routine primary axillary staging.

Finally, and of particular interest, is the evaluation of the potential benefit of adjuvant treatments—ET and/or RT —in reducing the risk of local recurrence. This issue remains unclear. Once again, the very limited number of patients who received adjuvant treatments, coupled with the relatively low number of recurrences, makes it difficult to draw any generalizable conclusions. Unlike for IC and DCIS, there are no prospective data demonstrating that adjuvant therapies reduce the risk of ipsilateral breast events in patients with pure P/FLCIS. Consequently, no consensus exists regarding their adoption. With regard to RT, there is speculation that PLCIS may be radiosensitive due to its marked nuclear atypia and relatively high proliferative index [18,27], yet the risk/benefit ratio in this setting has not been demonstrated. In this context, the ESMO guidelines state that RT is not routinely warranted in patients with LCIS, with a possible exception for the pleomorphic subtype—likely due to its morphological and biological similarities with high-grade DCIS [13].

As for ET, in the prevention setting, the use of selective estrogen receptor modulators (tamoxifen, raloxifene) and aromatase inhibitors to reduce the risk of subsequent IC in patients with CLCIS has been widely discussed and supported by the literature [65,66]. However, no specific recommendations have been formulated for P/FLCIS. Given the high rate of ER positivity, which remains the strongest predictive biomarker of response to ET, it is reasonable to hypothesize a potential role for ET

in the management of patients with ER-positive P/FLCIS. The frequent concomitant detection of CLCIS at surgical excision, confirmed in >60% of case as identified in this review, would further support this hypothesis. However, as with the use of adjuvant RT, the risk/benefit ratio for ET in this population is unknown and this assumption should be validated in large, well-characterized patient cohorts.

### 4.4. Limitations

This review has several limitations. First, the overall number of reported cases is small, with extremely limited sample sizes in many of the individual studies. This issue is particularly evident for FLCIS, which remains an extremely rare entity, with only a handful of pure cases described in the literature to date. Consequently, the heterogeneity in case selection and research methodology, especially regarding individual study data collection and outcomes reporting, compromises the consistency and generalizability of the findings. Not all data points were uniformly available across studies, and outcome definitions were often non-standardized. A further limitation is the persistent lack of uniformity in histopathological classification and terminology across studies, which leads to diagnostic challenges, potential misclassification, and may affect the robustness of pooled analyses.

No formal meta-analysis was conducted due to the substantial clinical and methodological heterogeneity across the included studies. Moreover, all data were derived from retrospective cohorts, with inherent selection bias and lack of control groups. Finally, while histologic slide review with immunohistochemistry was performed in some of the studies to refine diagnosis and reduce misclassification, this was not universally applied and never centralized.

## 5. Conclusions

This review highlights the factors that have contributed to the lack of clear evidence to define a standardized management approach for pure P/FLCIS; including their rarity as pure lesions, and the challenges with uniform diagnostic classification. A fundamental step forward is ensuring that breast cancer specialists are fully aware of the existence and distinctiveness of these lesions, can accurately recognize and diagnose them, and are prepared to perform surgical excision when diagnosed on core biopsy for both complete pathologic characterization and to rule out an associated malignancy. Collectively, as demonstrated here, the available data support the pursuit of negative margins at surgical excision yet the definition of an adequate negative margin is unclear. The role of adjuvant therapies—either RT or ET—also remains controversial and undefined.

Given the scarcity of reported cases and the short duration of follow-up in most published series, future research efforts should move toward more inclusive strategies—favoring larger cohorts and longer observation periods. While randomized clinical trials are unlikely to be feasible due to the rarity of these neoplastic entities, well-designed multicenter retrospective studies, as well as the establishment of prospective international registries, may represent a pragmatic and impactful way forward. Ultimately, these findings underscore the need for multicenter studies with clearly defined diagnostic criteria and standardized outcome reporting to better clarify the biological behavior and optimal clinical management of P/FLCIS. In this context, the ongoing international MultiLCIS study is expected to provide valuable insights and generate much-needed evidence to guide treatment strategies for these rare, understudied and often overlooked lobular neoplastic lesions.

## CRediT authorship contribution statement

**Massimo Ferrucci:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Conceptualization. **Daniele Passeri:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Francesco Milardi:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Giacomo Montagna:** Writing – review & editing, Visualization, Formal analysis. **Anna C. Beck:** Writing – review & editing, Visualization. **Riccardo Audisio:** Validation, Supervision. **Fredrick Wärnberg:** Writing – review & editing, Methodology. **Gianluca Franceschini:** Writing – review & editing, Visualization, Validation. **Lucio Fortunato:** Writing – review & editing, Validation, Methodology. **Matteo Ghilli:** Visualization, Validation. **Valentina Guarneri:** Visualization, Validation, Methodology. **Alberto Marchet:** Validation, Funding acquisition, Data curation, Conceptualization. **Rocco Cappellesso:** Resources, Formal analysis, Data curation, Conceptualization. **Angelo Paolo Dei Tos:** Validation, Resources, Conceptualization. **Tari Ann King:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization.

## Declaration for studies carried out in humans

The authors followed ethical guidelines for studies carried out in humans, and the study has been carried out in accordance with the World Medical Association Declaration of Helsinki. All procedures were performed in compliance with relevant laws and institutional guidelines and Ethical approval was not necessary given the nature of the study. The privacy rights of human subjects have been observed and informed consent was not necessary given the nature of the study.

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## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Valentina Guarneri reports a relationship with Eli Lilly and Company that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with AstraZeneca that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Novartis that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Daiichi Sankyo that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Exact Sciences that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with MSD that includes: speaking and lecture fees. Valentina Guarneri reports a relationship with Pfizer that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Menarini Stemline that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Roche that includes: board membership and speaking and lecture fees. Valentina Guarneri reports a relationship with Gilead that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2026.104711.

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