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Update on Lobular Lesions of the Breast

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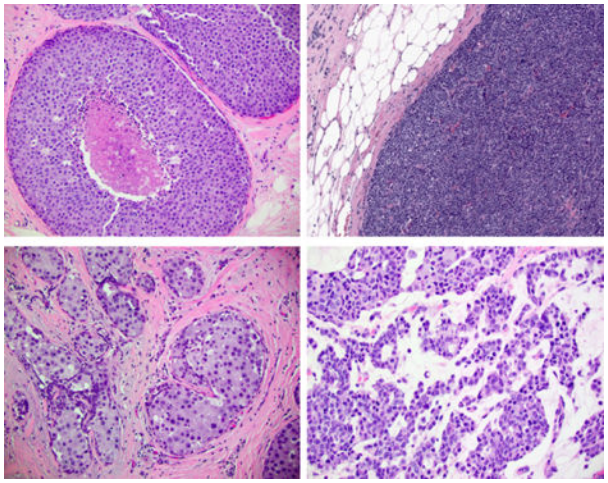
Abstract

The current histologic classification of *in situ* and invasive lobular carcinomas (ILCs) includes different morphologic variants, some of which have been recently described. In this review, we will focus on: 1) the diagnostic criteria of non-invasive lobular neoplasia and treatment implications across different countries; 2) utility and limitations of immunohistochemistry; 3) recently described variants of invasive lobular carcinoma; and 4) the significance of lobular differentiation in invasive carcinoma for clinical management.

Graphical Abstract



This review will focus on current diagnostic criteria, new entities, and management implications of lobular lesions of the breast

Keywords

Breast; lobular carcinoma in situ; invasive lobular carcinoma; e-cadherin

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Introduction

The spectrum of non-invasive and invasive lobular carcinoma has broadened since the initial descriptions by Foote and Stewart in 1941, who introduced the term lobular carcinoma[1]. In their landmark study, they described a rare form of carcinoma in situ which involved the lobules and small lobular ducts (compared to the most common “noninfiltrative comedo-carcinoma, which involved the larger ducts) composed of non-cohesive cells with an infiltrative counterpart that would qualify as what we currently recognize as classic lobular carcinoma in situ (LCIS) and the classic pattern of invasive lobular carcinoma (ILC), respectively. Since then, several morphologic variants of ILC have been recognized, as well as different subtypes of LCIS.

In the early 1990s, loss of E-cadherin, a transmembrane protein with a key role in cell-to-cell adhesion, was identified by immunohistochemistry (IHC) as a defining feature in lobular carcinoma[2–4]. Biallelic inactivation of *CDH1* gene, which encodes E-cadherin, was later recognized as a critical step in the pathogenesis ILC and LCIS[5, 6].

This review will focus on: 1) diagnosis and current classification of non-invasive lobular neoplasia (atypical lobular hyperplasia (ALH) and LCIS), and implications for management; 2) role of immunohistochemistry; 3) newly described morphologic variants of ILC; 4) clinicopathologic features and nomenclature of invasive carcinomas with mixed ductal and lobular features; and 4) diagnosis of lobular phenotype in invasive carcinoma and its clinical significance.

Non-invasive lobular neoplasia

Non-invasive lobular neoplasia is a proliferation of non-cohesive epithelial cells of the terminal duct lobular units (TDLUs) but can also involve terminal ducts in a pagetoid pattern. The neoplastic cells can be classified into 3 types: type A and type B cells, and cells with lobular phenotype (non-cohesive) and pleomorphic nuclei at least 4 times the size of a lymphocyte nuclei[7, 8]. Type A cells are small with round to oval nuclei, inconspicuous nucleoli, and scant cytoplasm. Type B cells are slightly larger with some variation in size and shape, more abundant cytoplasm and may display prominent nucleoli. These proliferations vary in the degree and extent of involvement of TDLUs, as well as the cytologic features and receptor profile, and are categorized by the current WHO classification into ALH and LCIS, which includes classic LCIS (CLCIS), florid LCIS (FLCIS) and pleomorphic LCIS (PLCIS)(Figure 1)[8–14]. The morphologic criteria of these lesions are detailed in Table 1. ALH and classic LCIS represent a morphologic spectrum and are often referred as lobular neoplasia (LN)[7, 15].

It should be noted that FLCIS is now considered a unique entity, and the term “florid” should not the used to describe extensive CLCIS. The WHO classification does not specify if there is a minimum number of involved spaces or extent required for the diagnosis of FLCIS and at present it remains unclear if FLCIS should be diagnosed when a single acinar structure is involved. Diagnosis of FLCIS would be recommended if the proliferation causes massive acinar expansion that could correlate with a radiologic mass, is associated

with calcifications when these are the radiologic target or show central necrosis. The clinical significance of a single space involved by proliferation of type A or B cells (of approximately 40 cells in diameter) found incidentally on CNB is uncertain.

Distinction between the different types of non-invasive lobular neoplasia may not always be straightforward. Occasionally, in situ lesions with classic lobular cytology may show distention of the acini borderline between CLCIS and FLCIS. In these cases the WHO recommends classification as classic LCIS, regardless of how many acini are involved[8]. In rare cases, a lesion with predominantly ALH or CLCIS morphology may show occasional larger cells with mild to moderate nuclear pleomorphism. The current recommendation is to classify these as CLCIS with type B cells. The biologic and clinical significance of these borderline findings is unclear.

The main differential diagnosis of LCIS is with ductal carcinoma in situ (DCIS). Solid DCIS with low or intermediate grade nuclei may mimic CLIS or FLCIS (Figures 2a–b). Similarly, PLCIS may resemble high grade DCIS. The presence of secondary lumens and cribriform architecture favor ductal differentiation, however, it should be noted that glandular spaces from residual benign epithelium in association with lobular neoplasia can mimic an atypical ductal proliferation. Moreover, LCIS and DCIS may coexist in the same acini (Figures 2c–d). If comedo necrosis is present in an *in situ* carcinoma with mixed features, a helpful clue is the appearance of the interface between the necrotic debris and the adjacent cells. In LCIS, the cells adjacent to the necrosis are round to oval and appear discohesive, whereas in DCIS the cells are more cohesive and the apical membrane adjacent to the necrotic debris has a defined linear appearance (Figures 2e–f)[16].

ALH and CLCIS are more commonly diagnosed in premenopausal women. These lesions are usually clinically and radiologically occult and considered incidental findings. ALH and CLCIS are frequently bilateral and multicentric, but their true incidence is difficult to determine. While ALH and CLCIS are often combined into LN, the relative risk to develop breast cancer (BC) is 4–5 times for ALH and 8–10 times for classic LCIS compared to the general population, thus distinction between the two may be useful for risk assessment[13, 17].

In contrast, FLCIS and PLCIS are mainly diagnosed in postmenopausal women and are usually associated with ILC[11, 18, 19]. Finding FLCIS and PLCIS without an associated infiltrative tumor is extremely rare, and these cases are mostly detected as mammographic calcifications and occasionally as a mass or architectural distortion[11, 12, 18, 20–22].

CLCIS is almost exclusively oestrogen receptor (ER) positive and HER2 negative[10–12, 23]. Similarly, FLCIS is frequently ER positive (94–100%) but can demonstrate HER2 overexpression in 5 to 18% of cases[10, 11, 20]. FLCIS with apocrine morphology is less frequently ER positive (33%)[20]. Compared to CLCIS and FLCIS, PLCIS is ER negative in 14 to 34% of cases, particularly apocrine PLCIS (18–100% ER negative), and shows HER2 overexpression in 13–43% of cases[10–12, 20, 22]. Androgen receptor is almost always positive in LCIS, regardless of the subtype[12, 20].

In addition to biallelic inactivation of the *CDH1* gene, the hallmark of lobular neoplasia, targeted next-generation sequencing studies have identified recurrent *ERBB2* and/or *ERBB3*

alterations in FLCIS and PLCIS[24, 25]. In another study using array-based comparative genomic hybridization FLCIS displayed more genomic alterations than CLCIS and, interestingly, showed similar genomic complexity as apocrine PLCIS.[10]. These studies demonstrate that FLCIS and PLCIS are biologically different from CLCIS, indicating a more aggressive behaviour.

Management of lobular neoplasia diagnosed on core needle biopsy

Management of non-invasive lobular neoplasia varies depending on the type of lesion and different practices across the globe (Table 2). Yet, there is unanimous consensus that lesions with discordant pathologic and radiologic findings should be excised[26–32]

Currently, most guidelines do not endorse surgical excision of ALH and LCIS diagnosed on core needle biopsy (CNB). Management in the US favors conservative management and patients are usually followed up in high risk clinics and offered chemoprevention with endocrine therapy[28, 29]. In the 2019 guidelines for management of early BC, the European Society of Medical Oncology mentions that lobular neoplasia “unlike DCIS, is considered a non-obligate precursor to invasive carcinoma. It is regarded as a risk factor for future development of invasive cancer in both breasts [relative risk: 5.4–12] and does not require active treatment”[27]. In the same year, a consensus recommendation published by a multidisciplinary panel of European experts endorsed excision of ALH and LCIS (classified as B3 lesions), if visible on imaging, with a vacuum assisted device. Similar management is recommended by the United Kingdom National Health Service[31]. The Breast Committee of the German Gynecological Oncology Group (Arbeitsgemeinschaft Gynäkologische Onkologie, AGO) does not recommend surgical excision if ALH or CLCIS involves less than 4 TDLUs in a vacuum assisted biopsy[33]. Excision with a vacuum assisted device is a minimally invasive procedure that is performed under local anesthesia. This is routinely performed in European countries but is uncommon in North America.

In contrast, management of PLCIS diagnosed on CNB requires follow-up excision. Surgical excision for FLCIS is also endorsed in the US, Australia and in most European countries (where FLCIS is classified as a B5a lesion -malignant in situ), except in the United Kingdom, where FLCIS is classified as a B4 lesion and managed with repeat core biopsy with 14-gauge needle or vacuum assisted biopsy.

The 8th edition of the AJCC Cancer Staging Manual does not include LCIS in the Tis category[34]. However, LCIS is still classified as Tis (LCIS) in the 8th edition of the UICC Classification of Malignant Tumours, as it was in the 7th edition of the AJCC staging[35, 36]. LCIS is considered a benign entity in the current AJCC classification but there is no mention of PLCIS and FLCIS.

Lobular neoplasia in surgical specimens

Classic LN present at surgical margin does not require re-excision and margin status should not be reported, regardless if it is the highest risk finding or associated with non-classic LCIS, DCIS or invasive carcinoma. Management of PLCIS and FLCIS requires complete excision, however, there are currently no guidelines on adequate margin clearance for

these lesions (Table 3). In addition, there is a lack of data on the role of radiation and chemoprevention in these patients[27–30, 32]. The European Society of Medical Oncology (ESMO) considers PLCIS as high grade DCIS from a treatment perspective, which includes adjuvant radiation therapy in patients undergoing breast conservation surgery.

In the 2016 guidelines for pathology reporting of excision specimens, the Royal College of Pathologists in the UK recommended documentation of extent of disease and margin clearance for PLCIS and FLCIS (referred as LCIS with classical cytology, central necrosis and distended acini)[37]. The current guidelines of the College of American Pathologists in the US do not include FLCIS and PLCIS in the cancer reporting templates.

In an effort to standardize reporting criteria for PLCIS and FLCIS in excision specimens, the International Collaboration on Cancer Reporting (ICCR) recently published their recommendations with input from 10 breast pathologists from 8 different countries, 1 breast surgeon and 1 breast radiation oncologist[38]. The dataset (which was also developed for the reporting of DCIS and other low-grade lesions such as encapsulated papillary carcinoma, solid papillary carcinoma in situ and Paget disease) includes required and recommended fields (Table 4). Importantly for PLCIS and FLCIS, they recommend documentation of extent of disease and margin status given that these lesions appear to behave more like DCIS than CLCIS. Nuclear grade is not required for non-classic LCIS (mandatory for DCIS) as PLCIS should be high grade by definition and FLCIS low or intermediate nuclear grade. The guideline mentions assessment of microcalcifications in surgical specimens for DCIS (if this was the biopsy indication). While this is not specified for FLCIS and PLCIS, these lesions are most often detected in biopsies for suspicious calcifications and therefore, pathologic evaluation as well as concordance with specimen radiograph should also be performed. Similarly, the dataset includes ER assessment as a required ancillary study for DCIS. This should also be included in the reporting of FLCIS and PLCIS. Standardized reporting of these lesions will allow better clinico-pathologic assessment and outcome comparison between different studies of these lesions, hopefully leading to uniform strategies in the management of FLCIS and PLCIS.

Immunohistochemistry

Loss of E-cadherin expression is considered the hallmark of lobular lesions, however, retained or aberrant expression has been described in both ILC and LCIS in up to 24% of cases[39–41]. Aberrant E-cadherin expression can have different patterns, such as reduced (compared to staining in normal lobules) or incomplete membranous expression, a dot-like perinuclear Golgi-type pattern, and diffuse cytoplasmic staining[42, 43]. Strong, complete membranous staining has also been described in a small subset of ILCs. However, lobular lesions with retained E-cadherin expression display cytoplasmic p120 or lack membranous β-catenin, indicating disfunction of the cadherin-catenin complex, characteristic of ILC and LCIS[42, 44]. Initial staining with E-cadherin is recommended to help in the classification of carcinomas with ambiguous morphology, and p120 as well as β-catenin can further assist in the characterization of tumours with discordant morphology and E-cadherin staining. It should be noted that E-cadherin staining is not required for the diagnosis of ILC and it is

the opinion of breast pathology experts that E-cadherin should not be performed in *in situ* or invasive carcinomas that display clear lobular morphology[8, 42, 44].

When examining *in situ* lesions, interpretation of E-cadherin staining pattern should always be correlated with the morphology given that residual benign ductal epithelium and intermingled myoepithelial cells display membranous E-cadherin expression, which should not be mistaken for retained expression in the neoplastic cells[16, 42]. In addition, myoepithelial cells may show decreased E-cadherin staining compared to the benign ductal epithelium, which could be misinterpreted as lobular neoplasia.

Updates on invasive lobular carcinoma

The 5th edition of the WHO classification of breast tumours includes different variants of ILC, some based on growth pattern (i.e. solid, alveolar, and tubulo-lobular) and others based on cytomorphology (i.e. pleomorphic, histiocytoid/apocrine). Other histologic variants have been described in the literature, such as trabecular ILC, first reported in 1979 by Martinez and Azzopardi[45]. This pattern is composed of trabeculae mainly two or three-cell thick; the original description also included one-cell thick trabeculae which were described as more compact compared to the single cell files[46, 47]. ILC with a trabecular growth pattern appears to have a similar prognosis to classic ILC, and likely this is classified as such by most pathologists if IHC supports lobular differentiation[47]. Osteoclast-like giant cells have been described in association with ILC in a few case reports[48–52]. These tumours had areas of hemorrhage and increased vascularity as those seen in other histologic types of BC associated with osteoclast-like giant cells, such as cribriform carcinoma.

In the following sections we will describe recently recognized variants, namely invasive ILC with extracellular mucin (ILCEM), ILC with solid papillary growth pattern and discuss the diagnostic dilemmas in invasive carcinomas with mixed ductal and lobular components.

Invasive lobular carcinoma with extracellular mucin

An unusual form of ILC associated with pools of extracellular mucin was first reported by Rosa et al in 2009[53]. Previously, mucin in ILC had exclusively been described in the intracellular compartment, and extracellular localization was recognized as a sign of ductal differentiation[54, 55]. To date, 39 cases of ILCEM have been reported in the literature[53, 56–67]. These tumours were more frequently diagnosed in post-menopausal women (median age 62; range 31–87), primarily presenting with palpable masses. Multifocally was not uncommon, and most of the tumours (69%) were ≥2 cm (range 0.7 to 10 cm).

The amount of extracellular mucin ranged from 5% to 95%, with 61% of cases featuring at least 25% of mucinous areas. The foci associated with extracellular mucin were present as scattered tumour cells within pools of mucin, solid nests and in some areas a pseudoglandular or pseudocribriform pattern was noted[60, 62]. Almost half of the tumours displayed grade 3 nuclei. Areas with the conventional infiltrative pattern with single cells and single files were seen in all cases, and signet ring cells were identified in most tumours (79%) upon excision. Alveolar or solid growth pattern were not infrequent. Most

of the tumours were associated with LCIS. In 3 cases, LCIS also displayed extracellular mucin[60, 66]. An example of ILCEM is shown in Figure 3.

E-cadherin was negative or aberrant in all cases. These tumours were HER2 positive in 10% of cases (4/39) and ER positive in all cases.

The majority of cases presented with lymph node metastasis. There were local or distant recurrences in 52% of cases and almost one third of patients died of disease, suggesting that these tumours are associated with a worse prognosis compared to classic ILC. Genomic alterations involving *TP53*, *ERBB3*, *ERBB2*, *POLQ*, and *CCND1* have been described in cases that relapsed[66].

Diagnosis of ILCEM on CNB can be difficult because 1) the pseudoglandular or pseudocribriform pattern ILCEM may resemble ductal carcinoma, 2) the tumour may feature large solid areas with no mucin, which may be confused with either solid ILC or even IBC-NSTs on CNB 3) extracellular mucin has historically been associated with ductal phenotype. While these cases are rare, it is likely that this entity is underrecognized. The diagnosis of ILCEM may not be possible on limited CNB material, however, extracellular mucin with tumour clusters showing loss of cellular cohesion, presence of signet ring cells and/or associated LCIS should raise the possibility of lobular differentiation.

Invasive lobular carcinoma with solid papillary growth pattern

Papillary architecture in invasive carcinoma has historically been associated with a ductal phenotype. However, recent case studies have described a variant of ILC characterized by a growth pattern resembling solid papillary carcinoma (SPC) and encapsulated papillary carcinoma (EPC)[68–72]. This entity was first described in 2016 by Rakha et al in a series of 3 cases. To date, only 6 cases have been reported, all diagnosed in elderly women (range 73–86 years) presenting with masses. The diagnoses on CNB ranged from LCIS to ILC, IBC-NST with lobular features, and SPC or EPC. These tumours presented as a single or multiple well-circumscribed masses comprised of a solid proliferation of cells with fibrovascular cores, as those seen in SPC with some tumours also featuring cystic areas with a fibrous thick capsule, resembling EPC. Areas with classic ILC were seen in all cases, usually extending from the papillary carcinoma or in close association. The nuclear grade ranged from low to high grade. Lobular phenotype was confirmed in all cases with loss of membranous e-cadherin expression. Myoepithelial markers (smooth muscle myosin, smooth muscle actin, or p63) were negative in all cases in the papillary masses and none showed expression of neuroendocrine markers (synaptophysin and chromogranin). All tumours were ER positive and HER2 negative. No lymph node metastases were reported. All patients were alive with no recurrences documented during a relatively short follow-up period (median follow up ranging from 8 to 13 months).

We have recently encountered a case in our practice of a 53-year-old woman with no history of BC who presented with a palpable mass. A CNB biopsy performed at an outside institution was reported as ILC with neuroendocrine differentiation. The mastectomy specimen showed a 2.1 cm ill-defined tumour, composed of multiple well-circumscribed

solid nodules with fibrovascular cores admixed with a conventional infiltrative component (Figure 4). Interestingly, this tumour focally featured extracellular mucin. Cytologically, the tumour cells were discohesive with scant cytoplasm and intermediate grade nuclei. E-cadherin and p120 confirmed lobular differentiation. The tumour cells were diffusely positive for synaptophysin and chromogranin, similar to the pattern seen in SPC[73]. There was associated LCIS but no DCIS. The invasive carcinoma was ER positive (99% strong), PR positive (20%, strong), and HER2 negative (1+). All sentinel lymph nodes were negative. The Oncotype Dx recurrence score was 29 and the patient is currently on adjuvant chemotherapy.

The differential diagnosis of ILC with solid papillary pattern includes solid variant of ILC, non-invasive PC (SPC in situ and EPC) and lobular neoplasia extensively involving a papillary lesion. The solid pattern of ILC is also comprised of a solid growth of tumour cells, however, these are arranged in sheets rather than circumscribed nodules and lack fibrovascular cores or a fibrous capsule. The clinical relevance of distinguishing these two subtypes is unclear given limited data.

The distinction with SPC is more challenging without IHC, as the tumour cells in SPC are usually of low nuclear grade and may display plasmacytoid features, intracytoplasmic vacuoles, and prominent signet ring cells. SPC frequently expresses neuroendocrine markers, which may be seen in ILC with SP pattern, as demonstrated in our case. In addition, loss of cohesion in tumour cells may not be prominent in ILC with solid papillary pattern, as reported in one the cases by Rakha et al. leading to a diagnosis of EPC on CNB[68]. The presence of classic ILC and LCIS associated with the papillary carcinoma should raise the possibility that the papillary tumour is of lobular differentiation and additional workup with E-cadherin, as well as p120 or β-catenin is recommended.

Rarely, lobular neoplasia may extensively involve a papilloma or papillary lesion. In this case, IHC may reveal the presence of residual ductal epithelium and myoepithelial cells, as well as any evidence of (micro)invasion.

These reports, and our case described herein, suggest that EPC and SPC represent growth patterns of breast carcinoma rather than unique entities[68]. All the cases studies were associated with classic or solid ILC. Therefore, it is unclear if lobular carcinoma with an exclusively solid papillary growth pattern behaves and should be managed similarly to SPC and EPC, which are currently staged as Tis (DCIS)[34]. Awareness within the pathology community of this entity will hopefully lead to identification of these lesions and better understanding of its clinical behaviour.

Invasive carcinomas with mixed morphologic features

In the current WHO classification, tumours with dual (IBC-NST and lobular) histopathologic features can be grouped into *mixed IBC-NST and ILC* if the lobular component makes up 10–90% of the invasive carcinoma, the *tubulolobular pattern of ILC*, which by definition is “composed of the admixture of a tubular growth pattern and small uniform cells arranged in a linear pattern”, and IBC-NST with lobular growth pattern[8].

These definitions are based on morphologic assessment and E-cadherin is not required for diagnosis. Recently, the clinicopathologic features of ILC with gland/tubule formation have been described under the proposed term of “ILC with tubular elements”[74].

Mixed IBC-NST and ILC

The definition of mixed invasive carcinomas has changed over time and likely its interpretation. The 4th Ed (2012) of the WHO classification defined them as “having an ILC pattern in at least 50% of the tumour and an invasive ductal carcinoma pattern in between 10 and 49%”[75]. However, this definition did not account for tumours with a small amount of lobular component. Thus, the current WHO classification defines mixed IBC-NST and ILC (or other special subtypes) as having a lobular component comprising 10 to 90% the tumour (Figures 5a–b). The WHO expert panel recommends that the percentage of the ILC component should be reported (i.e. mixed IBC-NST and ILC [40% lobular component]), and that those invasive carcinomas with <10% ILC, should be classified as IBC-NST with a focal ILC component[8]. While E-cadherin is not required for this diagnosis, studies have shown that the IBC-NST/ductal component is E-cadherin positive with aberrant staining in the lobular areas. Some of these invasive carcinomas may represent collision tumours, while others may develop dual phenotype via clonal divergence from the ductal to the lobular phenotype with acquisition of *CDH1* mutations[43]. Although in some studies mixed IBC-NST and ILC were more frequently diagnosed with more advanced disease, the prognosis was not significantly different from pure ILC or IBC-NST[76, 77]. In a study by Rakha et al, mixed tumours were shown to have a recurrence rate in between pure ILC (lowest) and IBC-NST (highest), however, these differences appeared to be related to tumour grade on multivariate analysis[78]. Another study by Metzger-Filho et al showed that histologic grade is prognostic in mixed IBC-NST but not in pure ILC, and that these tumours are associated with better prognosis compared to ILC in postmenopausal women[79].

Tubulolobular carcinoma

Tubulolobular carcinoma was originally described by Fisher et al in 1977 as a tumour composed of cells arranged in infiltrative cords and targetoid pattern admixed with small tubules, with morphologic features resembling both ILC and tubular carcinoma[80]. They favored classification as ILC based of worse outcome compared to tubular carcinoma. However, subsequent studies have demonstrated that both tubules and single files show strong membranous E-cadherin expression, favoring ductal phenotype[81, 82]. Moreover, 3-D modelling studies using serial sections stained with cytokeratin have shown that in tubulolobular carcinomas the single files of tumour cells seen on H&E slides represented connected tubules on different plane of sectioning[83]. The tail of the tear-drop shaped tubules appeared as solid cords of cells. On the other hand, ILC can display membranous E-cadherin in at least 10% of cases, and focal tubule formation is a recognized finding in ILC, therefore, some pathologists consider these tumours as a variant of ILC (Figures 2c–d)[42, 45, 84].

Invasive lobular carcinoma with tubular elements

Rare gland or tubule formation can be found in tumours that have otherwise the histopathologic features of ILC (discohesive cells, single files, targetoid pattern) and are E-cadherin negative. The term “invasive lobular carcinoma with tubular elements” has been

recently proposed by Christgen et al for this subset of tumours[74]. They studied 13 ILCs in which the tubular elements showed similar cytomorphology with loss of E-cadherin expression but with preserved cell adhesion. Tubules comprised 5 to 60% of the tumour areas and displayed variable sizes and shapes. While all tumours showed lost or reduced membranous expression of E-cadherin, the tubular elements retained β-catenin expression indicating preserved cell-to-cell-adhesion. The authors demonstrated P-cadherin positivity by IHC in the tubular elements but not in the areas of conventional ILC, arguing that rescue of cell-to-cell adhesion was due to E-cadherin to P-cadherin switching. P-cadherin, as E-cadherin, is a transmembrane protein that provides cell-to-cell adhesion by interacting with other components of the adherens junction (p120, γ-catenin and β-catenin)[85]. All cases were ER positive and HER2 negative. Eleven of 13 cases harbored *CDH1* mutations and 9 of 11 cases showed 16q loss. Interestingly, the foci with tubular elements showed lower Ki67 proliferation index than the conventional ILC pattern (median 8.3% vs 13.2%). An example of this tumour is depicted in Figure 6.

Invasive breast carcinoma of no special type with lobular growth pattern

It is not uncommon to find areas with single file infiltration and targetoid pattern in IBC-NST which are E-cadherin positive and lack the cytomorphology seen in lobular carcinomas. Usually these areas are focal and rarely the entire tumour display this infiltration pattern. The presence of cohesive clusters of tumour cells, nuclear pleomorphism and associated DCIS (with absence of LCIS) should raise the possibility of IBC-NST. E-cadherin IHC can help in the classification of these tumours, as they retain membranous expression.

These studies suggest that invasive carcinomas with mixed appearing morphology can be grouped into different categories based on pathogenesis and immunoprofile (Table 5). Mixed IBC-NST and ILC are E-cadherin positive in the glandular/tubular component while negative in the single file infiltrative areas. Some of these may represent collision tumours, while others IBC-NST with E-cadherin negative subclones harboring *CDH1* mutations[43]. Classification of tubulolobular carcinoma as either of “ductal” or “lobular” phenotype is controversial. Lastly, ILC with focal gland/tubule formation are diffusely E-cadherin negative but express P-cadherin in the tubular areas, suggesting cadherin switching as a rescue mechanism in cell-to-cell adhesion, and the term ILC with tubular elements has been proposed for these tumours. Focal E-cadherin negative tubules in in otherwise classic ILC are a well-recognized finding and whether ILC with tubular elements represents a distinct clinicopathologic entity remains unclear.

Diagnosis of lobular carcinoma and clinical implications

Diagnosis of ILC and LCIS has historically been based solely on morphology. Since the initial characterization of ILC and LCIS by Foote and Stewart in 1941, different morphologic patterns of lobular carcinoma, both invasive and in situ, have been described[1, 8]. Subsequently, biallelic inactivation of *CDH1* with loss of E-cadherin expression by IHC were described as the hallmark features of lobular lesions, which distinguished them from “ductal” carcinomas[2–5]. Use of E-cadherin, as well as related catenins (β-catenin and p120) by pathologists in daily practice in non-invasive epithelial

proliferative lesions and invasive carcinomas would raise additional issues regarding best classification of lesions with ambiguous morphology and/or IHC patterns.

The implications of a diagnosis of lobular phenotype in an *in situ* lesion have been described in previous sections. Briefly, regardless if patients with ALH or LCIS undergo excision, these patients are usually offered endocrine therapy for chemoprevention, which reduces their risk of subsequent invasive carcinoma and DCIS[86, 87]. Evidence shows that FLCIS and PCLIS are more aggressive variants and are usually completely excised to negative margins, similar to DCIS[16, 27–30, 32, 37]. However, unlike DCIS, appropriate margin clearance, as well as the role of radiation therapy and chemoprevention in non-classic LCIS is unclear.

Currently, standard treatment for ILC is similar to IBC/NST of same clinical stage and receptor profile[27, 88]. However, studies have shown that ILC has different clinical presentation, prognosis, and recurrence pattern with predilection for bone and atypical sites for breast metastasis such as the gastrointestinal tract, peritoneum, and gynaecologic tract[89–92]. ILC appears to have a survival advantage compared to IBC/NST in the first 10–15 years after surgery, however, prognosis is worse for patients with ILC after this period[90, 92]. In addition, patients with ILC are more likely to undergo mastectomy and have positive margins at surgical excision[93]. Large scale studies have reported lower rates of pathologic complete response to neoadjuvant therapy in ILC compared to IBC/NST, however, this difference was no longer seen when cases were adjusted for tumour size, grade, and ER/HER status in some series[94–97]. While MRI is not routinely used for BC screening, this is the recommended modality in patients with ILC, as these tumours are more likely to be occult, or poorly defined, on mammogram and ultrasound[27, 28].

Despite the increasing evidence that ILC portrays a distinct BC subtype in terms of presentation and clinical behaviour there is currently no gold standard for the histopathologic diagnosis of lobular differentiation in BC. The emergence of IHC markers differentially, but sometimes aberrantly expressed in lobular lesions (E-cadherin, β-catenin, and p120) likely added to the complexity of the pathologic interpretation.

A recent study including 35 pathologists (28 with a special interest in breast pathology and 7 general pathologists) from 9 countries evaluated the interobserver agreement in the diagnosis of ILC[98]. The participants independently evaluated 2 sets of hormone receptor (HR) positive BCs, each set with similar number of IBC/NSTs and ILCs, and similar tumour characteristics. Only H&E slides were provided for set A (n=61), while H&E and E-cadherin slides were available for set B (n=62). Tumour classification for each case had been originally set by central pathology review within the ADAPT trial by 2–4 expert breast pathologists based on H&E sections and E-cadherin IHC. Cases were reviewed with digital slides and classified by participants as ILC, non-lobular BC, and mixed BC. Pairwise interobserver agreement was moderate when only H&E slides were reviewed (median κ=0.58, interquartile range 0.48–0.66) and substantial when E-cadherin was also evaluated (median κ=0.75, interquartile range 0.56–0.86). Cases with discordant subtype calls by the participants were less common when E-cadherin was provided (set B 15/62 vs set A 30/61). The majority of discordant cases in both sets included IBD/NST composed of tumour cells arranged in slender trabeculae with weak E-cadherin positivity. Additional

staining for p120 and β-catenin showed membranous positivity in all cases, none of which carried *CDH1* mutations. Another subset of discordant cases included E-cadherin positive ILC (by reference standard) with missense *CDH1* mutations These tumours showed classic ILC morphology and were more frequently misdiagnosed when E-cadherin was reviewed (3/15 discordant calls in set B vs 1/30 in set A). The last group of discordant cases consisted of E-cadherin negative invasive carcinoma with single files of tumour cells and focal tubules, with associated LCIS. The tubules showed expression of P-cadherin (ILC [with tubular elements] by reference standard). Cases with E-cadherin to P-cadherin switching in the tubular component of ILC accounted for 1/30 discordant cases in set A and 3/15 in set B.

The findings of study support previous recommendations, as those of the WHO, that when an invasive carcinoma shows clear ILC morphology the tumour should be classified as such, regardless of E-cadherin results,[8, 41, 44]. Tumours with non-classic morphology would likely benefit from IHC for final classification.

However, use of IHC to diagnose ILC appears to vary across different practices. To assess what criteria is currently used for diagnosis of ILC, De Schepper et al recently published the results from a worldwide survey of 92 participants from 34 countries addressing this issue. The survey results show that more than half of the participants (52%) routinely performed IHC to diagnose ILC, while 45% only resorted to IHC in case of doubt. When a tumour with lobular pattern was E-cadherin positive, about half of the pathologists performed additional IHC. It is worth noting that 2 respondents commented (not part of the survey questions) that if a case had lobular morphology but was E-cadherin positive, they would still diagnose ILC. There was great variation in the types of antibody clones and protocols used. In addition, the participants were also asked to mention which subtypes of ILC they report. Besides the recognized patterns by the WHO (solid, alveolar, pleomorphic, histiocytoid/apocrine), other subtypes included trabecular and ILC with tubular elements.

Summary

The spectrum of lobular lesions, both in situ and invasive, has broadened in recent years and pathologists should be aware of these variants and their differential diagnoses for appropriate patient management. Aberrant expression E-cadherin (and other catenin related proteins such as p120 and β-catenin) is characteristic of these lesions, however, IHC should be interpreted as an adjunct to morphology, as lesions with classic lobular morphology may retain E-cadherin expression and lack *CDH1* gene mutations. Current studies show variability in the histopathologic criteria used for diagnosis of ILC, and particularly tumours with mixed morphology. Histologic tumour classification should be based on clinical behaviour for better patient stratification and management. Consensus guidelines for the histopathologic diagnosis of ILC and the different subtypes are needed.

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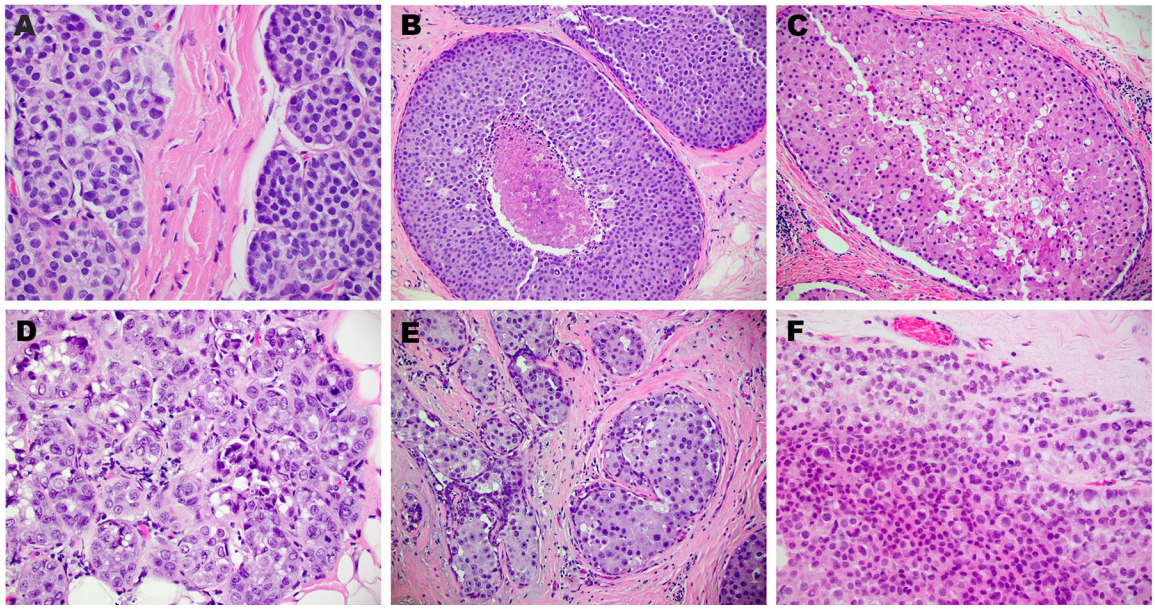

Figure 1.

Non-invasive lobular neoplasia. A. Classic LCIS with type A (right) and B cells (left). B. Florid LCIS with necrosis. C. Florid LCIS with apocrine cytology. Marked acinar expansion by lobular cells without significant nuclear pleomorphism and ample eosinophilic cytoplasm D. Pleomorphic LCIS involving lobules without significant expansion E. Pleomorphic LCIS with apocrine cytology. F LCIS, predominantly classic with scattered pleomorphic cells.

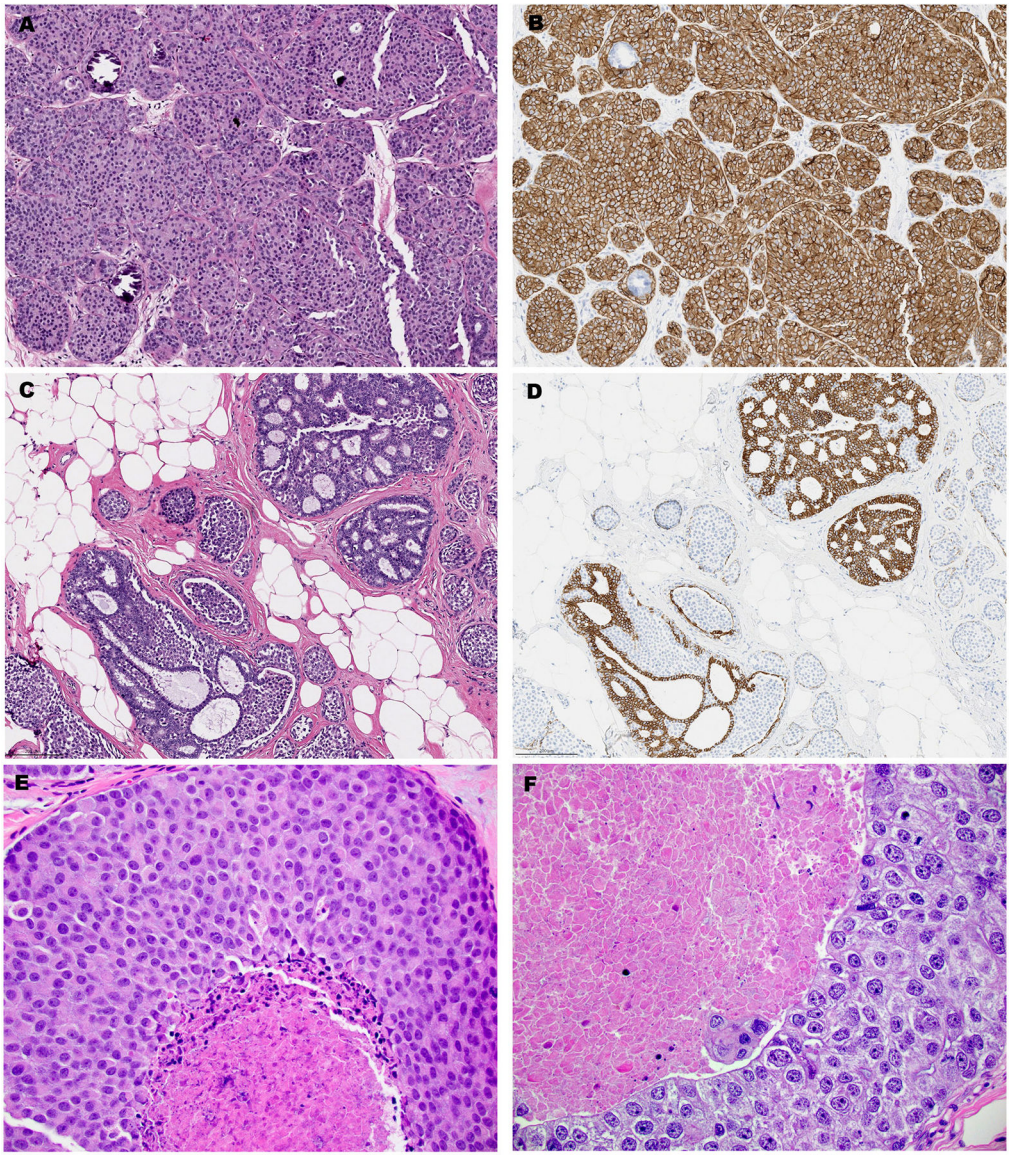

Figure 2.

Morphologic overlap and differences between LCIS and DCIS. A. Low grade DCIS mimicking LCIS. The presence of discrete cell membranes and occasional secondary lumens surrounded by cells with similar morphology as those in the solid component should raise the possibility of DCIS, which is confirmed by E-cadherin (B). C Low grade DCIS with cribriform pattern and LCIS involving the same ducts. The dual cell population is highlighted by E-cadherin IHC (D). The appearance of the interphase between the neoplastic cells and the necrotic debris can help in distinguishing LCIS (E), which shows a more ragged appearance, compared to DCIS (F) where there appears to be a clear line formed by the apical membranes of the neoplastic cells.

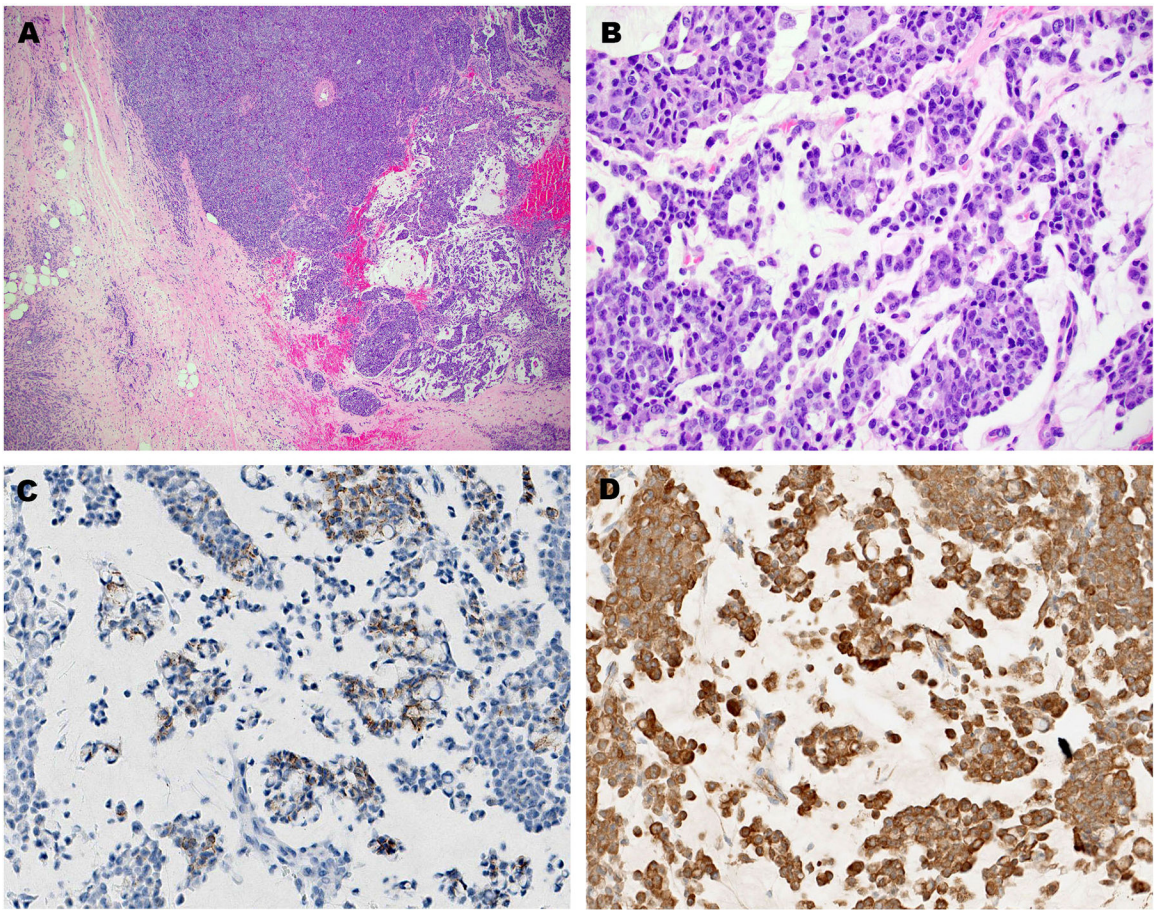

Figure 3.

Invasive lobular carcinoma with extracellular mucin (ILCEM). A. The tumor is focally associated with mucin pools adjacent to ILC with solid and classic infiltrative patterns. B. The neoplastic cells display nuclear pleomorphism and occasional signet ring morphology. C. The is absent or aberrant E-cadherin expression and cytoplasmic p120 positivity (D), confirming lobular differentiation.

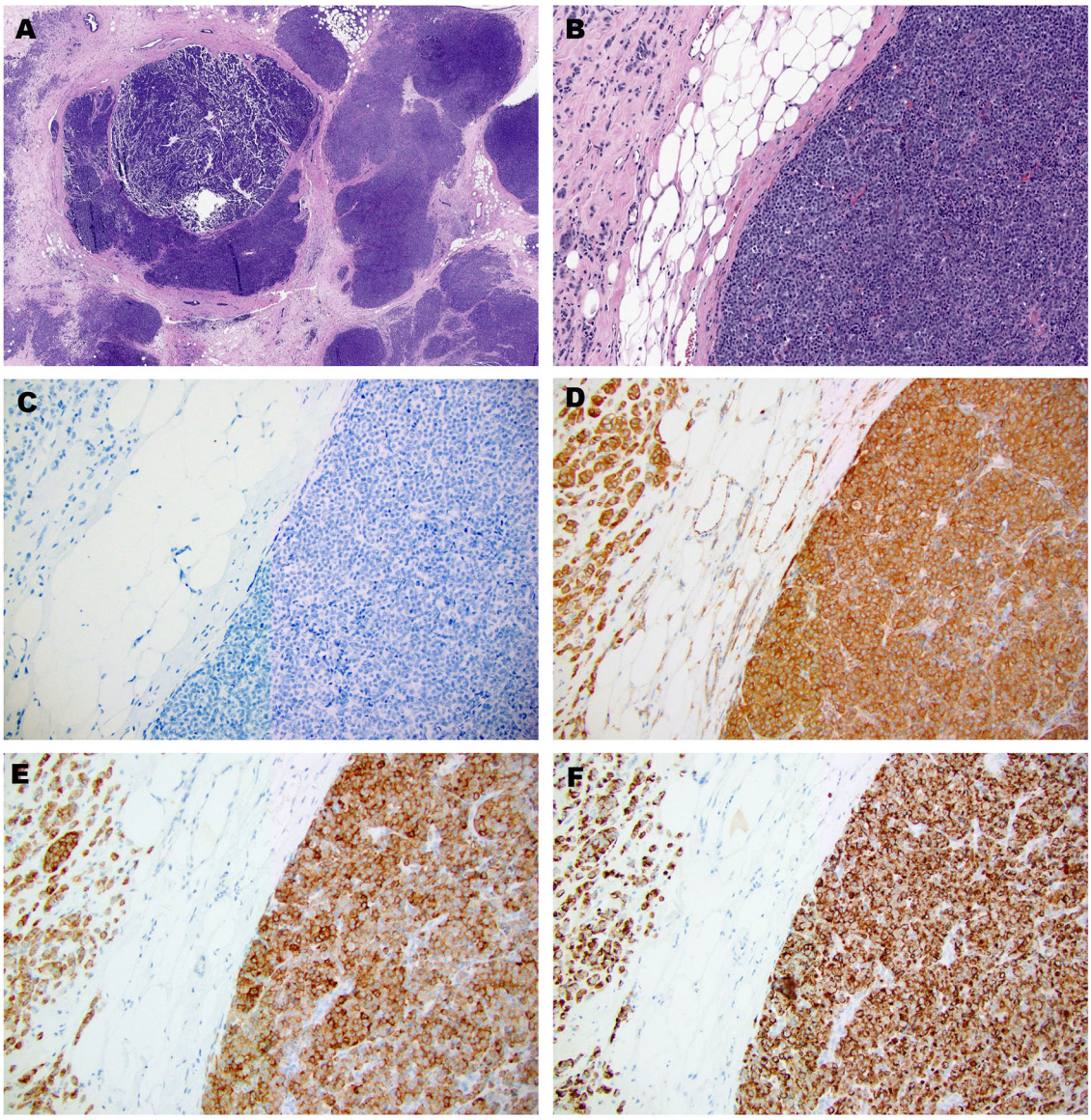

Figure 4.

Invasive lobular carcinoma with solid papillary growth pattern. A. The tumor is composed of expansile solid nodules with fibrovascular cores with areas of ILC with conventional growth seen at the periphery (left). B. The solid nodules are composed of tumor cells with lobular cytomorphology surrounded by a fibrous capsule. The tumor cells are E-cadherin negative (C) and show cytoplasmic expression of p120 (D). There is diffuse positivity of synaptophysin (E) and chromogranin (F).

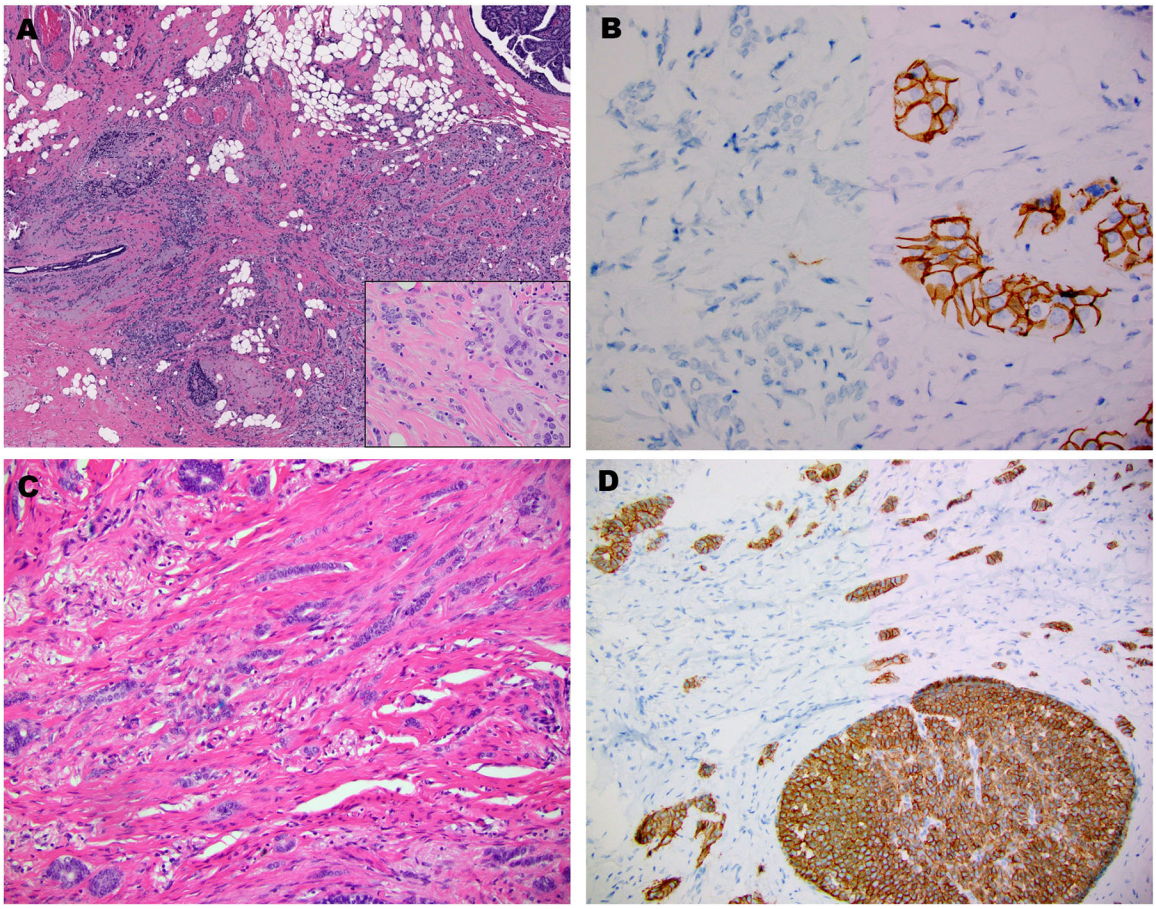

Figure 5.

Invasive carcinomas with mixed ductal and lobular features. A. Mixed IBC-NST and ILC. The 2 components form a single mass and show distinct morphology (see A insert), which is highlighted with E-cadherin IHC (B, negative in ILC component, left, and positive in the NBC-NST component in the right). C. Tubulolobular carcinoma is a low grade tumor composed of infiltrative small, round tubules and single files, both showing E-cadherin membranous expression.

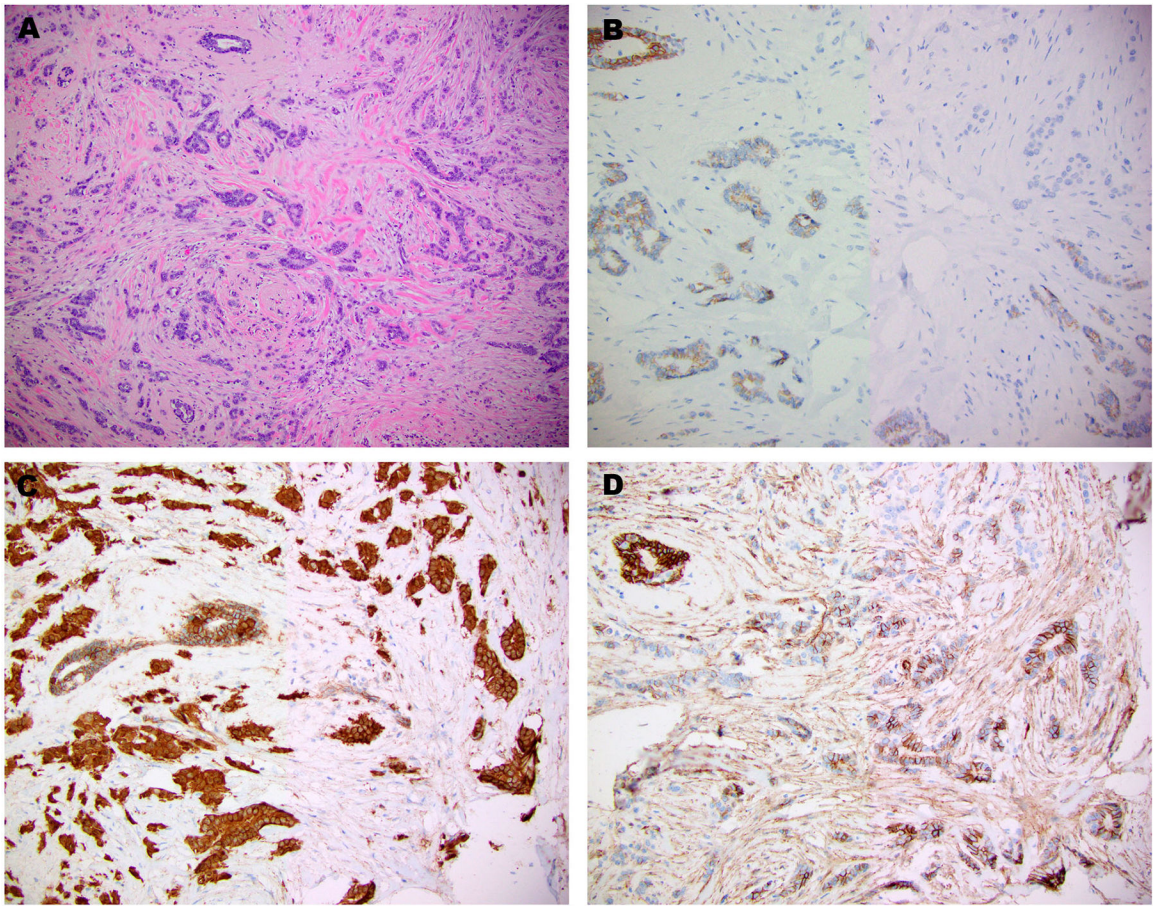

Figure 6.

Invasive lobular carcinoma with tubular elements. A. The ILC shows areas with gland/tubule formation, which shows aberrant E-cadherin staining (B). Both single files and tubules demonstrate cytoplasmic p120 expression (C), while only the tubules show retained β-catenin membranous staining, suggesting functional adherens junctions via E to P-cadherin switching.

Table 1.

Morphologic features of ALH and LCIS

	ALH	Classic LCIS (CLCIS)	Florid LCIS (FLCIS)	Pleomorphic LCIS (PLCIS)
Cytologic features	Non-cohesive proliferation of epithelial cells involving TDLUs May involve ducts in a pagetoid pattern			
	Type A cells (small with uniform hyperchromatic nuclei) or type B cells (slightly larger vesicular nuclei with mild variability in size/shape and small nucleoli), or mixture of both		Similar to ALH and CLCIS. May show apocrine features	Marked nuclear pleomorphism; >4x size of lymphocyte nucleus (similar to high grade DCIS). May show apocrine features
Architectural features	Proliferation slightly expands and involves <50% of acini in TDLU	Proliferation fills and expands >50% of acini in TDLU	a) Little to no intervening stroma between markedly distended acini, and/or b) expanded acinus or duct dilated with ~40–50 cells in diameter	None
Necrosis	Single cell apoptosis or minute foci of necrosis. No comedonecrosis		Comedonecrosis may be present	
Calcifications	May be present, but rare or minute		Coarse calcifications may be present	

Table 2.

Regional guidelines on management of lobular carcinoma in situ diagnosed on core needle biopsy

	Classic lobular neoplasia (ALH/Classic LCIS)	Pleomorphic LCIS	Florid LCIS
NCCN[a], 2022 (US)[28]	Surgical excision not required if radiologic pathologic concordant	Surgical excision	Not mentioned
American Society of Breast Surgeons, 2016 (US)[29]	Surgical excision not required if radiologic pathologic concordant	Surgical excision	Surgical excision
Second International Consensus Conference on B3 lesions, 2018 (Europe)[26]	(Category B3, lesion of uncertain malignant potential) Excision with vacuum-assisted biopsy; if findings are pathologic radiologic concordant and no residual lesion then surveillance is appropriate	(Category B5a, malignant in situ) Surgical excision	(Category B5a, malignant in situ) Surgical excision
ESMO[b], 2019 (Europe)[27]	Surgical excision not required	Surgical excision	Not mentioned
AGO[c], 2019 (Germany)[30,33]	Surgical excision not required if ALH/CLCIS involves ≤3 TDLUs in vacuum assisted biopsy and radiologic pathologic concordant	Open biopsy and preferably complete excision	Open biopsy and preferably complete excision
NHS[d],2018 (UK)[31]	(Category B3, lesion of uncertain malignant potential) Surgical excision not required if diagnosed on 14g core or vacuum-assisted biopsy and if radiologic-pathologic concordant	(Category B5a, malignant in situ) Surgical excision	Only referred as non-pleomorphic LCIS with necrosis or mass forming (Category 4, suspicious) Repeat sampling with 14g core or vacuum assisted biopsy
Cancer Australia, 2016 (Australia)[32]	Surgical excision not required if radiologic pathologic concordant	Surgical excision	Surgical excision

[a]National Comprehensive Cancer Network

[b]European Society for Medical Oncology

[c]Breast Committee of the German Gynecological Oncology Group/Arbeitsgemeinschaft Gynäkologische Onkologie

[d]National Health Service

Table 3.

Regional guidelines on management of non-invasive lobular neoplasia in surgical excisions

	Classic lobular neoplasia (ALH/Classic LCIS)	Pleomorphic LCIS	Florid LCIS
NCCN[a], 2022 (US)[28]	Size and margin status not reported	Negative margins should be considered	
American Society of Breast Surgeons, 2016 (US)[29]		Margin adequacy not mentioned	Margin adequacy not mentioned
ESMO[b], 2019 (Europe)[27]		Negative margins and radiation therapy should be considered	
AGO[c], 2019 (Germany)[30,33]		Complete excision recommended	Complete excision recommended
NHS[d]/The Royal College of Pathologists, 2016, (UK)[31,37]		Extent of disease should be recorded Negative margins recommended	Margin adequacy not mentioned
Cancer Australia, 2016 (Australia)[32]		Margin status should be recorded Re-excision should be considered if positive margin	Margin status should be recorded Re-excision considered on a case-by-case basis after multidisciplinary discussion

[a]National Comprehensive Cancer Network

[b]European Society for Medical Oncology

[c]Breast Committee of the German Gynecological Oncology Group/Arbeitsgemeinschaft Gynäkologische Onkologie

[d]National Health Service

Table 4.

International Collaboration on Cancer Reporting (ICCR) recommended dataset for reporting FLCIS and PLCIS in surgical specimens. Adapted from Fox et al[38]

Data element	
Required	**Recommended**
Clinical information	
Type of surgical procedure	
Specimen laterality	Specimen dimensions
	Specimen weight
Tumour site	
Tumour dimension	Additional tumor dimensions
Diagnostic classification (PLCIS or FLCIS)	
Nuclear grade[a]	
Necrosis	
Central (“comedo”): central necrosis easily identified at low magnification (≥10% duct diameter)	
Focal (“punctate”): small foci, or single cell necrosis (<10% duct diameter) that are indinstinct at low magnification	
Not identified	
Margin status	Margins status Linear extent of involvement a margin: • unifocal (single duct) • multifocal (2 or more foci) • extensive (broad front >5 mm) Distance from closest margin (if <5 mm) Cannot be determined, specify
Biopsy site	Coexistent pathology
Microcalcifications[b]	
Ancillary studies[b]	
Oestrogen receptor (ER)	Progesterone receptor (PR)
Pathological staging[c] (UICC 8th Edition TNM classification)	

[a]By definition, PLCIS should be high nuclear grade and FLCIS low or intermediate nuclear grade

[b]The guidelines do not specifically mention FLCIS or PLCIS in these sections

[c]The AJCC 8th Edition TNM classification does not include LCIS in Tis category. UICC 8th Edition still includes LCIS as Tis (LCIS)

Table 5.

Invasive carcinomas with mixed morphologic features

	Tumor cells in single files and targetoid pattern	Tubules	Note
Mixed IBC-NST and ILC	E-cadherin negative	E-cadherin positive	Despite different morphology and immunoprofile, both components should be measured as a single tumor for staging purposes
Tubulolobular carcinoma	E-cadherin positive	E-cadherin positive	Some pathologists consider this tumor a variant of tubular carcinoma or IBC-NST while others diagnosed them as a variant of ILC
ILC "with tubular elements"	E-cadherin negative	E-cadherin negative	Tubules are β-catenin and P-cadherin positive
IBC-NST "with lobular growth pattern"	E-cadherin positive	E-cadherin positive	Similar cytomorphology throughout the tumor