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Why is LCIS Important—Pathological Review

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Abstract

Purpose of Review Lobular carcinoma in situ (LCIS) encompasses classical LCIS and other rarer and more recently recognised variants, namely pleomorphic LCIS (PLCIS) and florid LCIS. Each of those entities has characteristic histological diagnostic criteria, different rates of underestimation of malignancy and recommended management. In addition, those lesions can mimic a number of benign and malignant breast lesions and can particularly be mistaken for ductal carcinoma in situ (DCIS). Accurate diagnosis of those lesions is critical to ensuring the appropriate patient management.

Recent Findings Several international guidelines refining the pathological classification, staging and management of those lesions have recently been updated. This review will provide an up-to-date pathological overview of the current knowledge of LCIS with emphasis on the multidisciplinary management implications.

Summary Close correlation between imaging and pathology in a multidisciplinary pathway is essential in LCIS management. Classical LCIS on core biopsy/vacuum-assisted biopsy (VAB) is coded as B3 and, if without discordant imaging, should further be sampled by vacuum-assisted excision (VAE). PLCIS should be coded and managed as per high-grade DCIS. Florid LCIS is a rare entity that is thought to be more aggressive than classical LCIS. Excision with clear margin is advised.

Keywords Lobular neoplasia · Upgrade rate · Carcinoma in situ · LCIS · PLCIS · Florid LCIS

Introduction and Terminology

The lobular carcinoma in situ terminology was first coined by Foote and Stuart in 1941 [1] as a form of cancer arising in mammary lobules, although the lesion was recognised earlier by James Ewing in 1919. The term lobular neoplasia was subsequently proposed by Haagenson in 1978 [2].

In situ lobular neoplasia encompasses a spectrum of lesions including atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). Both comprise the characteristic neoplastic monomorphic cells depicting the lobular features, namely cellular discohesion and eccentric nuclei, and are commonly exhibiting intra-cytoplasmic vacuoles. The above description applied to classical LCIS that is recognised to be multifocal/

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multicentric (60–80%) [3] and bilateral (23–35%) [4, 5]. It has long been regarded as a marker of subsequent breast cancer risk (×8–10 increased risk compared with the general populations). Recent epidemiological and molecular data supports the lesion being a non-obligate precursor of breast cancer [6, 7].

More recently, other less common variants of LCIS have been recognised including pleomorphic (PLCIS) and florid LCIS. The diagnosis, core biopsy categorisation and management of those variants are different to those of classical LCIS and hence the importance of their correct classification. The diagnosis of LCIS can pose diagnostic challenges to the practising pathologist as the lesion can mimic a number of benign and malignant breast lesions or get misdiagnosed as ductal carcinoma in situ (DCIS).

This review will provide an up-to-date overview of the diagnostic features of the spectrum of lobular neoplasia lesions with emphasis on radiological–pathological correlation and management implications.

Epidemiology and Presentation

Classical LCIS is often diagnosed as an incidental microscopic finding although a small proportion calcifies and can

therefore be detected mammographically. Its precise incidence is difficult to ascertain, but the reported incidence is between 0.5 and 3.8% of all breast biopsies [2, 8]. Classical LCIS is a disease of pre-menopausal women. There is evidence, however, that PLCIS presents at a later age. A UK multicentre audit of 179 PLCIS patients showed a mean age at diagnosis of 60 years [9•].

PLCIS and florid LCIS are often associated with comedo necrosis and calcification but can also present as mass lesions. The Surveillance, Epidemiology, and End Results Program (SEER) data showed an increase in LCIS incidence over the years, likely due to mammographic screening. The largest increase was noted in women over 50 years of age [10].

Data from the SEER Program showed that subsequent breast cancer after partial mastectomy occurred almost with equal frequencies in the same (46%) and contralateral (54%) breast [4]. A retrospective follow-up series, however, showed that subsequent breast cancer development occurs three times more likely in the breast harbouring ALH compared with the contralateral breast [11].

Microscopic Features

Characteristics of the Lobular Cells

The lobular cells of in situ and invasive lobular carcinoma are generally small, uniform cells and show evidence of cellular discohesion (loss of cellular contact) due to loss of the e-cadherin protein which functions as an adhesion molecule responsible for gluing cells together. This is an important and useful feature that enables pathologists to suspect/recognise the lobular morphology even at low microscopic power. Other features that support the lobular phenotype include pagetoid spread, eccentric plasmacytoid nuclei, inconspicuous nucleoli, scant cytoplasm and intracytoplasmic vacuoles (Fig. 1a).

LCIS commonly arises within terminal duct lobular units. The dyscohesive lobular cells distend mammary lobules and can also involve large ducts in a pagetoid fashion. This pagetoid pattern refers to the proliferation of the lobular cells between an inner compressed luminal epithelial layer and an outer myoepithelial layer (Fig. 1b). While pagetoid spread is often seen with LCIS, the phenomenon is not exclusive and can also be noted in DCIS lesions.

ALH versus LCIS

The differentiation between the two entities is quantitative. LCIS is diagnosed when more than half the acini in a terminal duct lobular unit are filled, distended and distorted by the lobular cells and ALH when the same type of cells fill less than half of the acini (Fig. 1c).

Classical LCIS versus PLCIS

Both entities show the characteristic lobular cells but PLCIS exhibits high-grade (grade 3) nuclei similar to the nuclei of high-grade DCIS. These commonly are large pleomorphic nuclei (>4 times the size of a lymphocyte), with conspicuous nucleoli and moderate/ample eosinophilic cytoplasm (Fig. 1d). The cells of PLCIS can show a striking apocrine appearance and this entity is designated as pleomorphic apocrine LCIS (PAL-CIS) (Fig. 1e). Similar to DCIS, PLCIS commonly calcifies and this is reflected histologically in the association of the lesion with central necrosis and luminal calcifications. Central comedo necrosis, although commonly seen, is not a pre-requisite for the diagnosis of PLCIS (Fig. 1d).

Classical LCIS versus Florid LCIS

Florid LCIS, previously called mass forming LCIS and classical LCIS with necrosis, describes distended mammary ducts by non–high-grade lobular cell nuclei. The cells are therefore similar to classical LCIS but involve large ducts with little or no intervening stroma and/or a ductal proliferation spanning a high-power microscopic field (equivalent to 40–50 intraductal cells) [12••]. Florid LCIS can be associated with mammographic and histological calcification and/or comedo necrosis. Therefore, it can histologically mimic solid low and intermediate grade DCIS (Fig. 1f).

Florid LCIS versus PLCIS

Both show similar architecture, involve large mammary ducts, and are commonly associated with comedo necrosis and calcification. The only differentiating feature is the nuclear grade; if the nuclei are high grade, the lesion is designated as PLCIS; while if low/intermediate grade, the lesion is diagnosed as florid LCIS [13].

LCIS versus DCIS

LCIS can involve and distend large ducts resembling DCIS. Conversely, DCIS may colonise small lobules (cancerisation of lobules) and therefore mimics LCIS. DCIS lesions often show a mixture of architectural patterns such as micropapillary, cribriform and papillary. A solid atypical intraductal proliferation may therefore represent either DCIS or LCIS. Moreover, both lesions may coexist, sometimes within the same duct. The diagnosis of LCIS relies on a low index of suspicion and recognition of the lobular features within the proliferation. Loss of e-cadherin by immunohistochemistry can be used to confirm the lobular phenotype, as described below.
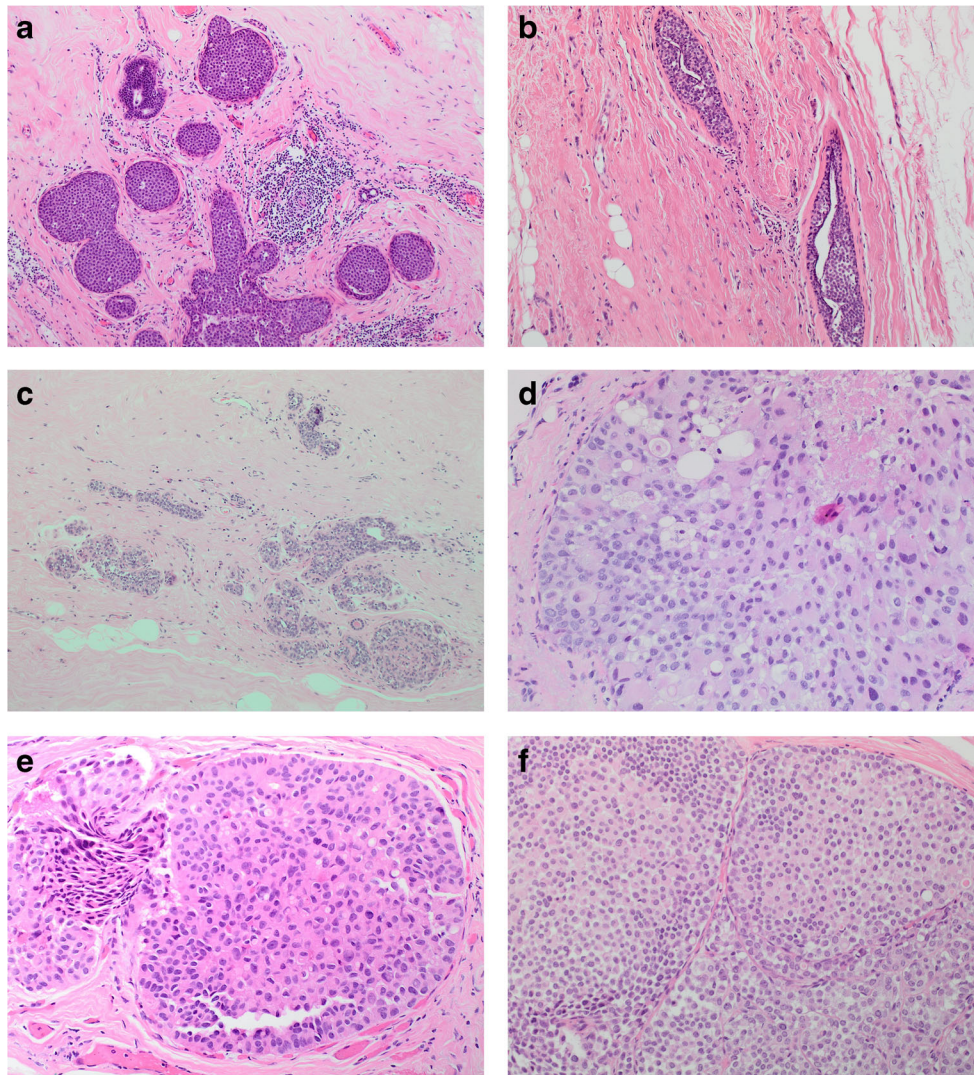
Fig. 1 Histological features of lobular neoplasia. **a** Terminal duct lobular unit distended and expanded with classical LCIS cells. The cells are uniform and dyscohesive with moderate eosinophilic cytoplasm and inconspicuous nucleoli. There are no high-grade features. **b** Pagetoid spread of lobular neoplasia cells into large ducts. The low-grade lobular cells are located between an inner compressed luminal epithelial layer and an outer myoepithelial layer. **c** Atypical lobular hyperplasia (ALH). Note the incomplete involvement of mammary lobules by the lobular cells and the associated blue luminal calcifications. **d** Pleomorphic LCIS (PLCIS): a large mammary duct contains a solid proliferation of large pleomorphic cells with dyscohesive nuclei and associated central comedo necrosis. **e** Pleomorphic apocrine LCIS (PAL-CIS): a high-grade atypical intraductal proliferation comprising pleomorphic cells with abundant eosinophilic granular cytoplasm resembling apocrine DCIS. The lobular phenotype is evident by the eccentric nuclei, intracytoplasmic vacuoles and discohesion. **f** Florid LCIS: several adjacent ducts with minimal intervening stroma distended by solid low to intermediate grade nuclei resembling solid DCIS. Note the cellular discohesion and plasmacytoid nuclei suggestive of a lobular phenotype.

Role of Immunohistochemistry

The hallmark of lobular in situ and invasive carcinoma is the loss of e-cadherin expression by immunohistochemistry due to the loss of the e-cadherin glycoprotein. The latter is encoded by the CDH gene located on chromosome 16q22.1. The gene was first cloned in 1995 [14] and is recognised to be mutated in more than 50% of lobular carcinomas [15, 16].

The e-cadherin protein is expressed in normal mammary ductal epithelial cells, myoepithelial cells, DCIS and most invasive no special type (NST) carcinomas.

The loss of e-cadherin expression is a helpful diagnostic test to confirm the lobular phenotype particularly in difficult cases and to confirm the non-classic variants' diagnosis. Classical LCIS (Fig. 2a), florid (Fig. 2b), and PLCIS (Fig. 2c) show loss of e-cadherin expression.

It is important to note that e-cadherin may not be completely lost within in situ and invasive lobular carcinoma. Heterogeneous/aberrant/attenuated expression has been reported in 10–15% of lobular carcinomas [17, 18]. This is thought to be the result of a dysfunctional e-cadherin protein.

Fig. 2 Immunohistochemistry of classical LCIS and variants. **a** Mammotome biopsy showing e-cadherin negative classical LCIS (right). Note the strong membranous e-cadherin expression in the adjacent normal mammary ductules (left) which is used as a positive internal control. **b** E-cadherin negative florid LCIS. **c** E-cadherin negative PLCIS. **d** Loss of β-catenin membranous expression by immunohistochemistry in florid LCIS with normal staining of the surrounding myoepithelium. **e** Mixed DCIS and LCIS lesion showing e-cadherin positive DCIS (right) and e-cadherin negative LCIS (left). **f** Strong ER nuclear positivity in classical LCIS and florid LCIS
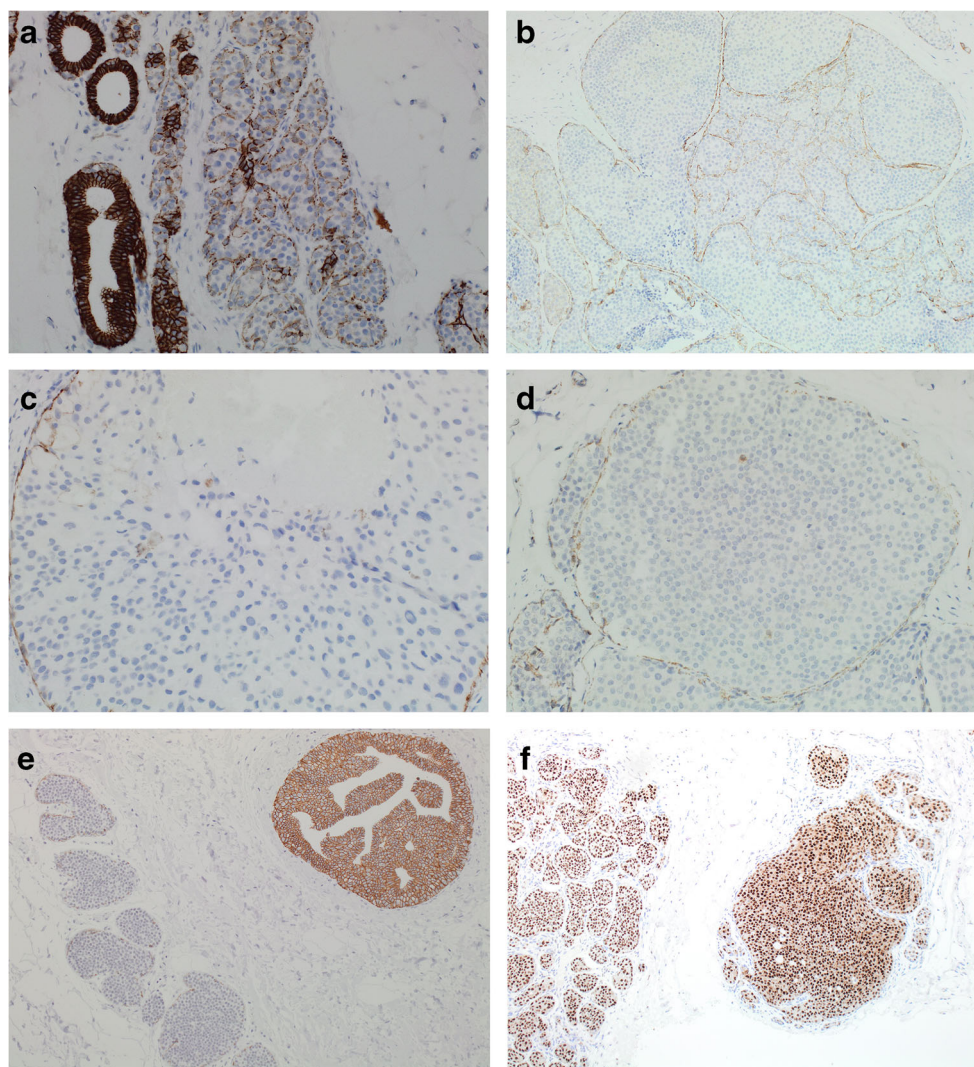
In the author's experience of second opinion practice, this phenomenon of incomplete loss of e-cadherin expression is not uncommon that can cause diagnostic difficulties for the referring pathologists as to the correct typing of the in situ and/or invasive carcinoma. In those cases, in addition to morphology, other immunohistochemistry, such as β-catenin and p120, can be used to confirm the lobular phenotype. Lobular cells show negative β-catenin (Fig. 2d) and cytoplasmic p120 expression [19, 20]. The latter is an indication of a non-functional e-cadherin protein.

As per the pathology guidelines [13, 21], the diagnosis of lobular neoplasia remains morphological with immunohistochemistry used as a supporting test particularly to differentiate variant LCIS from DCIS. The diagnosis of in situ and/or invasive lobular neoplasia should not solely be based on the e-cadherin status. Mixed lesions comprising e-cadherin positive DCIS and e-cadherin negative LCIS do exist (Fig. 2e). It is also recognised that a proportion of the poorly differentiated ductal carcinoma is e-cadherin negative and those tumours were shown to be associated with poor prognosis [22].

Molecular Profile

Molecular analysis confirmed that lobular neoplasia is clonal that shares its molecular profile with invasive lobular carcinoma supporting that it is a non-obligate precursor of breast cancer. CDH1 gene inactivation leading to the loss of e-cadherin expression/function is the hallmark of lobular neoplasia and occurs as an early event. Classical LCIS is estrogen and progesterone receptor (ER and PR) (Fig. 2f) strongly positive and HER2 negative. The lobular cells comprise a monomorphous population of luminal cells that is negative for basal cytokeratins (such as CK5, CK5/6, CK14). The combination of negative basal cytokeratin and strong and uniform ER expression can be used in the diagnostic setting to confirm the neoplastic nature of the atypical proliferation. Non high-grade DCIS shares the same expression pattern of ER and basal cytokeratins.

PLCIS is predominantly ER positive but can be ER negative and a small proportion is HER2 positive [9•]. The

apocrine variant of PLCIS, however, is often ER/PR negative (80% of cases) [23••]. The reported Her2 positivity in PLCIS ranged from 1 to 41% [24•]. Similar to classic LCIS, florid LCIS is ER/PR positive and HER2 negative [25•].

PLCIS and florid LCIS exhibit greater genetic instability when compared with classical LCIS. A recent next-generation sequencing study of PLCIS ($n = 10$) and florid LCIS ($n = 6$) and their synchronous invasive lobular carcinoma ($n = 11$) showed shared genetic mutations in the ERBB2 gene and clonal relationship between the three lesions [26•].

Associated Lesions

LCIS in Structured Benign Lesions

LCIS, and its variants, can colonise pre-existing benign lesions such as fibroadenomas (Fig. 3a), intraduct papillomas, sclerosing adenosis, radial scars and collagenous spherulosis (Fig. 3b, c). This may pose diagnostic difficulties since the complex appearances may mimic DCIS and/or invasive carcinoma. E-Cadherin immunohistochemistry can help highlight the lobular component (Fig. 3c). Smooth muscle immunohistochemistry, such as p63 and SMM, is useful to confirm the presence of surrounding myoepithelial layer thus excluding invasive carcinoma. For an overview of the useful immunohistochemistry for LCIS diagnosis and its differentiation from mimics, see Pinder and Shaaban [13].

Low Nuclear Grade Neoplasia and Rosen Triad

Classical LCIS shares similar morphological and molecular features with a range of benign, atypical, low grade in situ and invasive carcinomas. Rosen triad describes the association between lobular neoplasia, columnar cell lesions and tubular carcinoma [27].

Lobular neoplasia nuclei resemble and commonly coexist with low-grade DCIS, invasive lobular, mucinous and low-grade NST carcinoma [28]. This highlights the importance of further tissue sampling following the diagnosis of classical lobular neoplasia as the lesion may be upgraded to in situ or invasive carcinomas of those low-grade types.

The most common invasive histological type associated with lobular neoplasia is invasive lobular carcinoma (classical and pleomorphic). The largest UK-based multicentre study of PLCIS showed that the associated invasive carcinoma was lobular in 117 out of 130 cases (90%). The invasive lobular carcinoma existed either in a pure form or admixed with other invasive carcinoma types and the majority (71%) were of grade 2 differentiation. The associated carcinomas were often ER positive (92%) with only a minority (7.3%) showing HER2 positivity [9•].

Similar to classic LCIS and PLCIS, invasive lobular carcinoma grades 2 and 3 was the most common histological type associated with florid LCIS [25•, 29••]. In their series of 61
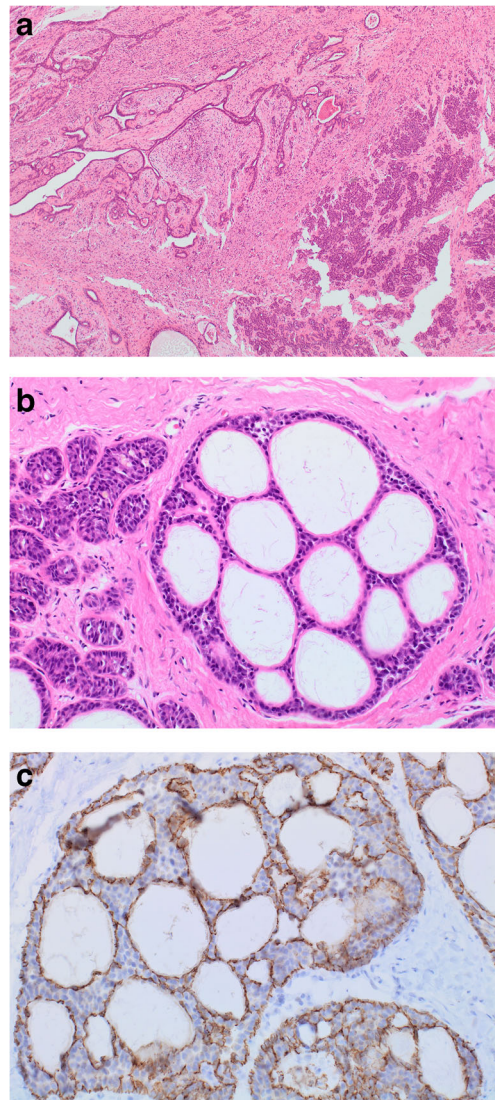
Fig. 3 LCIS involving benign lesions. **a** Classical LCIS and invasive carcinoma in a fibroadenoma. A solid low-grade lobular proliferation (right) within an intracanalicular fibroadenoma. **b** Classical LCIS in collagenous spherulosis. A dyscohesive proliferation of lobular cells colonises collagenous spherulosis. Note the eosinophilic rounded basement membrane-like structures. The appearances can lead to a mistaken diagnosis of cribriform DCIS. Lobular neoplasia is confirmed by loss of e-cadherin expression (3C)

PLCIS and 24 florid LCIS diagnosed over 20 years, Shamir et al. reported that 84% of the cancers were lobular, followed by mixed ductal/lobular carcinoma (13%) with pure invasive ductal carcinoma representing only 3% of cases [24•].

Upgrade Rate

Further sampling, by VAE or surgical excision, following the diagnosis of LCIS reveals in situ and/or invasive carcinoma in a significant proportion of lesions. A review of the literature by Hussain and Cunnick showed an average upgrade rate of 21.3% for classical LCIS [30].

In their study of 76 examples of non-classical LCIS from 75 patients, Nakhlis et al. reported an upgrade rate to in situ ($n = 10$) or invasive malignancy ($n = 17$) of 36%. No predictors of upgrade could be identified [31]. A study of 85 PLCIS and florid LCIS showed an upgrade rate to malignancy of 38% and 33%, respectively [24•]. Similarly, a multicentre UK audit of 176 PLCIS examples including data from the Glacier study reported an upgrade rate of 31.8% when PLCIS was the most significant abnormality [9•]. The upgrade rate to malignancy following the diagnosis of PLCIS, however, varied in the literature from as low as 18% [32] to as high as 65% [33] with an average of 33% [34].

Data on florid LCIS upgrade are rather limited and the few studies available generally reported on the combined florid and PLCIS outcome. A recent large multi-institutional study reported an upgrade rate of 39.7% for both lesions and a combined rate of 33.9% on reviewing the literature [29••]. The author's work of 17 florid LCIS lesions revealed an association with DCIS, PLCIS and invasive lobular carcinoma in 29.4%, 23.5% and 35.9% of cases, respectively [25•].

The variability in the reported upgrade rate of lobular neoplasia may partly be due to the differences in the terminologies and the inconsistency in the histological diagnoses due to the relative recent recognition of the rare LCIS variants. In addition, the population of patients studied (screening versus symptomatic), family history, radiological–pathological concordance, method of sampling (VAE versus surgery) and the association with other high-risk lesions are all likely to impact on the findings. The recent pathology guidelines including the WHO Blue Book for breast tumours (2019) have clarified the diagnostic features and definition of each category. Previous terminologies such as 'non classical LCIS' or 'variant LCIS' are discouraged and should no longer be used [12••].

Pathological Staging of LCIS

There has been a longstanding debate as to whether LCIS is a true in situ carcinoma or a marker of increased breast cancer risk. Unlike DCIS, it is not mandatory to excise classical LCIS with concordant imaging. PLCIS, however, is managed similar to high-grade DCIS by surgical excision with clear margin supporting its neoplastic nature [35].
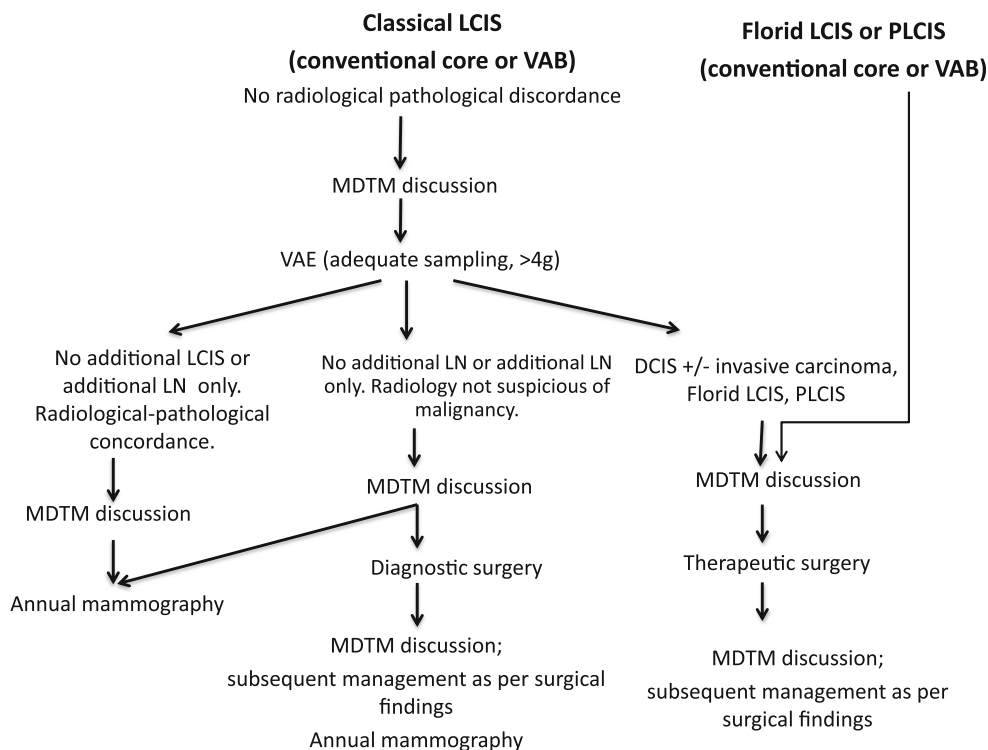
The latest 8th edition of the TNM staging by AJCC (the American Joint Committee on Cancer) does not recognise LCIS, nor its variants, as in situ carcinoma and these lesions are no longer staged as pTis [36]. The latest edition of the WHO Blue Book for breast tumours refers to the TNM AJCC staging and also recognises that PLCIS should be treated by surgical excision as per the recommendations of several international guidelines [12••].

In the UK, the current National Health Service Breast Screening Programme (NHSBSP) guidelines, and the pending update, regard LCIS and variants on surgical excisions as in situ carcinoma that are staged as pTis [21].

Management of LCIS

On the diagnostic sample, whether conventional core biopsy or vacuum-assisted biopsy (VAB), both ALH

Fig. 4 Management algorithm for LCIS and variants (modified from Pinder et al. [37•]). LN = lobular neoplasia, VAB = vacuum-assisted biopsy, VAE: vacuum-assisted excision

Classical LCIS
(conventional core or VAB)
No radiological pathological discordance
↓
MDTM discussion
↓
VAE (adequate sampling, >4g)

No additional LCIS or additional LN only. Radiological-pathological concordance.
↓
MDTM discussion
↓
Annual mammography

No additional LN or additional LN only. Radiology not suspicious of malignancy.
↓
MDTM discussion
↓
Diagnostic surgery
↓
MDTM discussion; subsequent management as per surgical findings
Annual mammography

DCIS +/- invasive carcinoma, Florid LCIS, PLCIS
↓
MDTM discussion
↓
Therapeutic surgery
↓
MDTM discussion; subsequent management as per surgical findings

Florid LCIS or PLCIS
(conventional core or VAB)

and classical LCIS are coded as B3 (lesions of uncertain malignant potential). PLCIS, on the other hand, is regarded as high-grade in situ carcinoma (similar to high-grade DCIS) and is coded as B5a. There is no international consensus on the B coding of pure florid LCIS on core biopsy. In the UK, it is recommended to code those lesions as B4 to reflect the higher likelihood of co-existent invasive carcinoma [37•].

Management of LCIS and variants should be centred on clinicopathological correlation and discussion at the multidisciplinary/tumour board meetings [38•]. Those lesions without discordance are managed by further tissue sampling to exclude co-existent lesions such as PLCIS, DCIS or invasive carcinoma. While further sampling was traditionally achieved via diagnostic excision, this has largely been replaced worldwide by vacuum-assisted excision (VAE). Adequate sampling by vacuum biopsy is the recommendation of the Swiss guidelines (the second international consensus) [39••] that endorsed the recommendations of the first national consensus [40]) and UK guidelines [37•]. A summary of the management algorithm of lobular neoplasia is provided in Fig. 4.

An adequate VAE sample, as a guide, should weigh more than 4 g (unless the lesion is radiologically small and has wholly been sampled) [37•]. Chemoprevention using endocrine therapy, such as tamoxifen or aromatase inhibitors, has been proven to reduce the risk of breast cancer by more than 50% in randomised controlled trials [41] and can be used for the chemoprevention of breast cancer following the diagnosis of LCIS [42]. A survey of chemoprevention uptake revealed a rate of only 15% [43].

It is of note that no B-coding is required for VAE diagnoses since the samples are regarded as equivalent to surgical diagnostic excisions. This highlights the need for excellent communication between radiologists and pathologists to indicate the type and indication for the biopsy taken. The specimen should ideally be weighed (either in imaging or pathology) to assess for adequacy of sampling. If this is not feasible, then the information can be extrapolated from the number of cores sampled and the gauge of needle cores. The NHSBSP B3 pathology guidelines provide a useful table of different vacuum devices and the approximate target number of core biopsies to achieve adequate sampling [37•].

Complete excision of the lesion is required following the diagnosis of PLCIS. This is also recommended for the management of florid LCIS in view of the current evidence supporting the association with more advanced lesions. PLCIS is reported as per DCIS including measurement of whole tumour size and distance to margins [21, 35].

Follow-up

There has been no international consensus on the frequency and/or duration of mammographic follow-up following the diagnosis of LCIS and collection of high-quality outcome data is important to provide evidence base guidance. The current UK and Swiss guidelines [37•, 39••] recommend an annual mammographic follow-up for 5 years for B3 lesions including LCIS. PLCIS and florid LCIS are on the other hand managed by open surgical excision followed by the standard mammographic follow-up as per DCIS.

Declarations

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Papers of particular interest, published recently, have been highlighted as:
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•• Of major importance

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