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## The management of lobular carcinoma in situ (LCIS). Is LCIS the same as ductal carcinoma in situ (DCIS)?

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### ABSTRACT

Lobular carcinoma in situ was first described over 60 years ago. Despite the long history, it continues to pose significant difficulties in screening, diagnosis, management and treatment. This is partly due its multi-focal and bilateral presentation, an incomplete understanding of its biology and natural history and perpetuation of misconceptions gathered over the last decades. In this review, the working group on behalf of EUSOMA has attempted to summarise the current thinking and management of this interesting lesion.

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## 1. Historical perspective

The proliferative lesion referred to as lobular carcinoma in situ (LCIS) has been depicted by a number of authors including Ewing in 1919.<sup>1</sup> However, the first clear description using the term LCIS was by Foote and Stewart in

1941.<sup>2</sup> LCIS has been extensively characterized in the literature since. However, despite this long time span, problems and confusion surrounding the most appropriate terminology and classification for these lesions and the best course of long-term management after diagnosis remains a problem.

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Foote and Stewart<sup>2</sup> chose the name to emphasise the morphologic similarities between the cells of LCIS and those of frankly invasive lobular carcinoma (ILC). In this respect, there are parallels with ductal carcinoma in situ (DCIS): cells with the morphology of invasive cancer still contained within a basement membrane. They hypothesised that LCIS, in a manner akin to DCIS, may represent an established step along the pathway to development of invasive cancer. Mastectomy was recommended as the standard form of treatment, a management plan that was adopted for many years. More recently, the term atypical lobular hyperplasia (ALH) has been introduced to describe morphologically similar but less well-developed lesions. An all-encompassing term, lobular neoplasia (LN) was introduced by Haagensen et al. in 1978<sup>3</sup> to cover both ALH and LCIS. The current World Health Organisation (WHO) book does incorporate this term side by side with the traditional ALH/LCIS terminology.<sup>4</sup>

## 2. Morphologic aspects

Morphologically LN is defined as ‘a proliferation of generally small and often loosely cohesive cells originating in the terminal duct-lobular unit, with or without pagetoid involvement of terminal ducts’.<sup>5</sup>

LN encompasses a group of entities with distinctive histologic features. The most common type, so-called classic LCIS, is composed of acini filled with a monomorphic population of small, round, polygonal or cuboidal cells, with a thin rim of clear cytoplasm and a high nuclear-to-cytoplasmic ratio.<sup>2,6</sup> The nuclei are uniform and the chromatin fine and evenly dispersed. A characteristic cytologic feature is the presence of cells containing intracytoplasmic lumina or magenta bodies. The cells are loosely cohesive and regularly spaced, and fill and distend the acini; however, overall lobular architecture is maintained.<sup>2,6</sup> Glandular lumina are not seen and mitoses, calcification, and necrosis are uncommon. Pagetoid spread, where the neoplastic cells extend along adjacent ducts between intact overlying epithelium and underlying basement membrane, is also frequently seen.

The term ALH<sup>7</sup> is used when involved terminal duct-lobular units are not completely distended, or when residual lumens are present while LCIS is used for fully developed lesions. Clearly, the differentiation between ALH and LCIS on these criteria is rather arbitrary, and prone to inter- and intra-observer variability. LN replaces these terms and encompasses the whole spectrum of lobular epithelial proliferations although it has not been widely accepted by pathologists.

The cells contained in classic ALH/LCIS, as described above, are also referred to as type A cells. A well-recognized subtype of LCIS is an architecturally similar lesion containing cells with mild to moderately large nuclei, some increase in pleomorphism, and more abundant cytoplasm. These cells are known as type B cells.<sup>8</sup>

Several subtypes of LN have been described. These include endocrine, amphicrine, apocrine, histiocytoid, rhabdoid, signet ring and pleomorphic variants.<sup>9–11</sup> Mostly, the variants have been designated on the basis of cyto-nuclear features. However, subclassification based on extent (extensive versus non-extensive/focal) has also been suggested.<sup>12</sup>

There is indirect evidence to suggest that pleomorphic LN has a worse prognosis compared to classic LCIS; however, there are no firm prospective data at present.<sup>11,13</sup> The data for extent of LCIS as a predictive factor for recurrence after breast conserving treatment for invasive carcinoma are also conflicting at present.<sup>14,15</sup>

On occasions a regular, evenly-spaced monotonous population is seen within both ducts and lobules; in these circumstances it may be difficult to classify the lesion. If only scanty terminal ducts are involved and the proliferation is almost entirely lobular, the lesion is classified as LCIS. However, distinguishing DCIS from LCIS may indeed be impossible if both an organoid lobular and ductal component are identified. If both ducts and lobules contain epithelial proliferation of this type, categorisation as both LCIS and DCIS is recommended at the present time to infer the precursor risk of DCIS and the bilateral cancer risk of LCIS. E-Cadherin staining may be helpful in classifying the lesion (see later). It is not within the scope of this article to describe in full the classification of DCIS and the reader is referred to the review by Pinder and Ellis.<sup>16</sup>

## 3. Immunophenotype

All subtypes of LCIS are associated with oestrogen (ER) and progesterone receptor (PgR) expression (60–90% of cases positive).<sup>17,18</sup> The cells of LN also characteristically lack expression of E-cadherin, an epithelial cell membrane molecule involved in cell-cell adhesion.<sup>19,20</sup> The cells of classic LCIS do not usually show amplification or expression of HER-2 and expression of TP53 is uncommon.<sup>17,18,21</sup> A number of authors have shown differences between classic LCIS and pleomorphic variant (PLCIS),<sup>22</sup> including a higher Ki67 (proliferation) index and more frequent expression of p53 and Her-2 in PLCIS, all of which may indicate a more aggressive profile. PLCIS can also express GCDPF-15 (gross cystic disease fluid protein-15), a marker of apocrine differentiation.<sup>22,23</sup>

## 4. Risks associated with LCIS

It is generally stated in the literature that the diagnosis of LCIS is most frequent in women aged 40 to 50 years, a decade earlier than DCIS. However, it is apparent from recent literature that the incidence in post-menopausal women is increasing.<sup>24</sup> Calculating the true incidence of LCIS has always proved difficult as there are no specific clinical abnormalities, in particular, absence of a palpable lump, and, because most (but not all) LCIS is not associated with microcalcifications, it is often undetectable by mammography.<sup>25,26</sup> When examining a pathologic specimen, there is no macroscopic features characteristic of LCIS to guide tissue sampling. The diagnosis of LCIS is therefore often made as an incidental, microscopic finding in breast biopsy performed for other indications. For these reasons, the true incidence of LCIS in the general population is unknown, and many asymptomatic women presumably go undiagnosed. In studies, the incidence of LCIS in otherwise benign breast biopsy is documented as between 0.5% and 3.8%.<sup>3,27</sup>

Characteristically, LCIS is both multifocal and bilateral in a large percentage of cases. Over 50% of patients diagnosed

with LCIS show multiple foci in the ipsilateral breast, and roughly 30% of patients have further LCIS in the contralateral breast.<sup>28–30</sup> Such multifocality in a clinically non-detectable lesion is one of the reasons why planning subsequent management has proven problematic and contentious.

LCIS has generally been considered a risk indicator, conferring an increased rate of development of invasive carcinoma of about 1–2% per year, with a lifetime risk of 30–40%.<sup>3,31,32</sup> There is a suggestion that the risk for invasive carcinoma is greater for PLCIS than classic LCIS.<sup>11</sup>

Page et al.<sup>7,27</sup> documented that the relative risk for development of subsequent breast cancer was different in women diagnosed with ALH compared with LCIS. Patients diagnosed with ALH have a fourfold to fivefold higher risk than the general population (i.e. women, of comparable age, who have had a breast biopsy performed with no atypical proliferative disease diagnosed).<sup>7,33</sup> This relative risk appears doubled to 8 to 10x for LCIS.<sup>27</sup> Thus, although LN is a helpful term for collectively describing this group of lesions, specific classification into ALH and LCIS may still be justified or preferable in terms of risk stratification and management decisions.

In a meta-analysis of nine separate studies evaluating the outcome of a new diagnosis of LCIS, 228 patients were identified. Of these, a proportion underwent either unilateral or bilateral mastectomy. On follow-up, 15% of 172 patients (who did not undergo unilateral mastectomy as primary treatment) had invasive carcinoma in the ipsilateral breast and 9.3% of 204 patients had invasive carcinoma in the contralateral breast.<sup>34</sup> The development of contralateral breast cancer is three times more likely in patients diagnosed with LCIS than in those without LCIS.<sup>35</sup> The risk for development of breast cancer is therefore bilateral,<sup>28</sup> and it used to be a common belief that this risk was equal for both breasts. However, more recent studies demonstrate carcinoma is three times more likely to develop in the ipsilateral compared with the contralateral breast,<sup>7,36,37</sup> supporting the view that ALH and LCIS act both as precursor lesions and as risk indicators.

The time to the development of invasive cancer in an individual patient after a diagnosis of LCIS is difficult to predict. Page et al.<sup>27</sup> documented that in two thirds of women in whom invasive cancer developed, it did so within 15 years of biopsy. In a separate study, in over 50% of patients in whom cancer developed, it did so between 15 and 30 years after biopsy, with an average interval of 20.4 years.<sup>29</sup> This extended time span may have significant implications for planning patient follow-up.

Both invasive ductal carcinoma (IDC) and ILC occur with LCIS, a fact that some have used to suggest that LCIS is not a true precursor lesion. However, the incidence of ILC occurring with LCIS is significantly greater than without.<sup>38</sup> The coexistence of DCIS and LCIS may explain the IDC component observed, whereby DCIS and not LCIS is the likely precursor lesion.<sup>39,40</sup> Evidence for the role of LCIS as a precursor for ILC is supported by the epidemiologic data outlined previously, the morphologic similarity between cells of ALH/LCIS and lobular carcinoma, and the development of tumours in regions localised to ALH/LCIS. Work on molecular aspects of lobular lesions, in particular, that focusing on the marker E-cadherin, adds to this view<sup>41</sup> (see below).

It has been suggested for more than 50 years that LCIS and ILC show an association with a positive family history of

breast cancer. To date, the predisposition gene(s) have not been identified and the current literature does not support a significant role for germline mutations in BRCA1, BRCA2 or E-Cadherin in its pathogenesis.<sup>42–44</sup>

## 5. Molecular genetics

There has been an explosion of new and innovative techniques for molecular genetic analysis. This is resulting in the generation of new data on the molecular alterations present in both preinvasive and invasive lesions. In breast cancer, it is hoped that this new information will help elucidate pathogenesis in terms of precise chromosomal events. In addition, in cases such as ALH and LCIS where morphologic and immunohistochemical classification remains controversial, molecular analysis may clarify the uncertainties.

Comparative genomic hybridisation (CGH) analysis is a technique where “test” DNA is compared with normal DNA on metaphase chromosome spreads to assess DNA copy number changes. Computer-aided analysis can identify chromosome loci that differ from normal. These loci are potential sites of, for example, amplifications of oncogenes or losses of tumour suppressor genes. This method can be applied to paraffin-embedded tissue, and with the use of laser capture microdissection, allows for precise analysis of even small lesions such as ALH/LCIS. Loss of heterozygosity (LOH) studies refer to identification of loci in test DNA that have “lost” one copy of a gene, presumably through DNA deletion. This event is often associated with loss of a tumour suppressor gene.

CGH analysis of LCIS and ALH<sup>45</sup> has demonstrated loss of material from chromosomes 16p, 16q, 17p, and 22q and gain of material from 6q at a similar high frequency in both lesions. Losses at 1q, 16q, and 17p are also seen in ILCs.<sup>46,47</sup> LOH data in LCIS are limited but do demonstrate a similarity between LCIS and ILC.<sup>48,49</sup> E-cadherin is a candidate tumour suppressor gene on 16q22.1 that is involved in cell–cell adhesion and in cell cycle regulation through the catenin/Wnt pathway.<sup>50</sup> Most IDCs of no special type (NST) have been shown to exhibit positive staining by immunohistochemistry, whereas most ILCs are negative.<sup>19,20</sup> Bex et al.<sup>51,52</sup> consistently identified protein-truncating mutations in ILCs but failed to demonstrate mutations in other subtypes. Roylance et al.<sup>53</sup> also failed to find any pathogenic mutation in low-grade IDCs. The LOH at 16q (the locus of the E-cadherin gene) found in lobular carcinomas is usually accompanied by truncating mutations or gene promoter methylation, and absent staining by immunohistochemistry.<sup>41,53</sup>

E-cadherin staining has also been identified in DCIS, and although the molecule is expressed in normal epithelium, staining is rarely seen in LCIS. Recently, some authors have advocated the use of E-cadherin as an adjunct antibody in the differentiation of LCIS from DCIS.<sup>22,23,39,54</sup> In addition, Vos et al.<sup>41</sup> have demonstrated the same truncating mutation in the E-cadherin gene in LCIS and the adjacent ILC. The data provide strong evidence for the role of E-cadherin gene in the pathogenesis of lobular lesions and support the hypothesis for a precursor role for LCIS.

In addition to lobular breast carcinoma, E-cadherin mutation has been linked to the pathogenesis of diffuse

gastric carcinoma. In cases of familial predisposition to diffuse gastric cancer, a germline mutation of E-cadherin has also been demonstrated in up to one third of the cases. In contrast, apart from anecdotal cases,<sup>55</sup> no such germline mutations have been identified in cases of familial LCIS and ILC, despite the clear pathogenetic role of E-cadherin mutation in these lesions.

## 6. Diagnosis and management

### 6.1. Radiology

Since most LCIS do not present as a mass nor contain microcalcification, mammography and ultrasound do not appear to have a role in prospectively diagnosing LCIS. LCIS may be associated with contrast enhancement in magnetic resonance imaging (MRI) and may therefore be visible, but this is usually masked by enhancement secondary to concomitant fibrocystic change, hence reliable diagnosis may not be possible even with MRI. However, PLCIS, which more often show microcalcification will be picked up because of similarities in presentation with DCIS.<sup>25,26</sup>

Radiology, however, may have a role in subsequent surveillance of patients following a diagnosis of LCIS, either to identify other preinvasive lesions such as DCIS or the invasive carcinoma that the patient would be at risk of. In particular, this may be important in high-risk women with a positive family history of breast cancer.

Although there are no data available on systematic randomised clinical trials regarding the efficacy of radiologic follow-up in women diagnosed with LCIS, and although we do not know whether it will improve outcome of women who develop invasive breast cancer, it seems reasonable to suggest at least the same degree of surveillance as is recommended in women at average risk. Accordingly, women who are diagnosed with LCIS should undergo annual two-view mammography of the affected and of the contralateral breast; in women with dense breasts (defined as mammograms rated as ACR II or higher) additional screening breast ultrasound should be considered. Whether or not women diagnosed with LCIS should undergo MRI for intensified surveillance as has been recently recommended in women with a genetically increased risk, is subject to current European clinical trials (e.g. MARIBS).<sup>56</sup>

### 6.2. Pathology/surgical

A number of pre-surgical techniques are used in routine clinical practice to make a diagnosis. Fine Needle Aspiration (FNA) cytology is an easy and rapid technique that has gained a role in mammographically detected lesions. It is not possible to distinguish ALH, LCIS and even ILC reliably on FNA smears alone. The cells are similar or identical in morphology. The difference between LCIS and ALH is one of extent of lobule involvement seen in histological sections and is not based on the cytological appearances of the cell.<sup>8</sup>

The cytological features of LN have been well described. Cytologically dissociated small epithelial cells with rounded or squared-off nuclei are seen. These are present singly or in small groups with nuclear moulding. The cells may con-

tain intracytoplasmic lumina (private acini) seen best on mucin staining where they appear like a 'bull's-eye' with an alcian blue stained microvillous membrane and a periodic acid Schiff (PAS) stained mucin droplet in the centre. However, aspirates from LN may be difficult to interpret. The cellularity of these specimens is usually less than that seen in 'ductal' lesions. A number of patterns can be observed, ranging in cytological appearance from benign looking uniform cells to atypical cells. The presence of small three-dimensional collections of cells with only slightly enlarged nuclei is helpful. A large number of cells with intracytoplasmic lumina (private acini) in association with the above features are an indication of LN, although not specific. Nuclear irregularities and small protrusions from the nucleus ('noses') may also be seen.

Needle Core biopsies are increasingly replacing FNA in many screening centres. A small cell regular epithelial proliferation within lobules which is considered by the pathologist to represent intra-lobular neoplasia (ALH/LCIS) should be classified as B3 LN. Separation between ALH and LCIS is not necessary on core biopsy samples as the management is similar and the histological criteria for distinction are based on assessment of larger tissue volumes. On occasions it may be impossible to classify a small cell epithelial proliferation in lobules and/or ducts as either LN or low grade DCIS and in these circumstances a numerically higher category (B4 or B5) is prudent and should be considered.

Occasionally LN may be mammographically visible due to associated calcification<sup>25</sup> but in general it is identified as a chance finding following identification of a coexisting symptomatic or mammographically visible lesion. LN is most frequently a co-incidental finding in a core biopsy and therefore multidisciplinary discussion is essential to determine the management of the LN and to determine whether the abnormality identified radiologically has been adequately represented. These cases must be managed cautiously. The data in the literature are confusing and contradictory as most studies comparing the pathology of further excision with a core biopsy diagnosis of LCIS have been retrospective and have rarely specified the reason for the further excision. In view of this uncertainty different units currently adopt differing approaches. Some units proceed on all cases to diagnostic surgical excision while others adopt a more cautious approach involving multidisciplinary team discussion to determine whether the imaging abnormalities have been adequately explained, and whether to action further assessment or diagnostic surgical excision.<sup>57–63</sup>

Nevertheless, if the data reported by Elsheikh and Siverman<sup>57</sup> of underestimation of cancer in 28% of their prospectively studied patients are confirmed, then it may become difficult to refrain from a wide excision after a diagnosis of LN. However, even in this situation, multidisciplinary team approach to assess why the core biopsy was performed and whether there is radiological-pathological correlation will remain the most important step to further management.

The use of core biopsy allows identification of architecture, hence an ability to distinguish in situ from invasive lesions and also provides material for ancillary techniques such as

E-Cadherin staining in cases where there is doubt about LCIS versus DCIS.

Where a diagnosis of LCIS in core biopsy is with other high-grade lesion, mass lesion on radiology or radiological-pathological discordance, it will clearly lead to further excision. If LCIS is a true incidental finding, it is imperative that a discussion with colleagues in a multi-disciplinary team meeting takes place so that any suspicious circumstance or discordance lead to further excision (This will involve the majority of patients.)

Pathological reporting and management based on excisional specimens is also controversial. LCIS at margins should be reported. However, the further management will depend on the associated pathology. If LCIS only is seen in an excision biopsy then no further excision is required. If LCIS is seen in association with an invasive cancer and is at margins no further excision is required if the invasive cancer is excised. It is of course important that the multidisciplinary team and clinicians involved in the case understand the implications of such findings and do not overinterpret this information in terms of requirement for further excision, which is not indicated in the majority of cases.

### 6.3. Radiotherapy

The literature on the use of radiotherapy for LCIS are limited<sup>64</sup> and currently, there is little data to recommend its role in clinical management.

### 6.4. Endocrine therapy

There is very interesting data from the National Surgical Adjuvant Breast Project (NSABP) which shows a 50% reduction in invasive cancer for *in situ* proliferations.<sup>65,66</sup> Currently, duration of treatment and long term outcome data are pending, hence patients with LCIS should be encouraged to participate in clinical trials such as IBIS-2.

### 6.5. Quality objective

If LCIS only is seen:

- a. in an excisional biopsy, no further excision is required
- b. A diagnosis of LCIS in core biopsy with other high grade lesion will lead to further surgery
- c. LCIS at margins should be reported by pathologists
- d. If LCIS in association with an invasive carcinoma (IC) is at margins, no further excision is required if the IC is completely excised
- e. Radiotherapy is not recommended in case of LCIS

### 6.6. Outcome measure

- a. Patients with pure LCIS following wide excisional biopsy shouldn't undergo further surgery
- b. Patients with associated lesions and/or mass lesion on radiology and/or radiological-pathological discordance should undergo further surgery

- c. Pathological report should include description of margins involvement by LCIS
- d. Further excision of involved margins by LCIS shouldn't be performed
- e. A close radiological follow-up of women diagnosed with LCIS is probably indicated due to the increased risk of ipsilateral (and contralateral) invasive breast cancer

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### Conflict of interest statement

None declared.

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