Clinical guidance for the management of lobular carcinoma in situ

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This document aims to provide health professionals within a multidisciplinary team with information to assist in the management of women with lobular carcinoma in situ. In the absence of a comprehensive evidence base, the guidance in this document has been developed through a consensus process by an expert multidisciplinary Working Group convened by Cancer Australia. External consultation was sought and received from peak organisations, including Breast Cancer Network Australia, BreastScreen Australia, Breast Surgeons of Australia and New Zealand, The Cancer Nurses Society of Australia, The Medical Oncology Group of Australia, The Royal Australian and New Zealand College of Radiologists and The Royal College of Pathologists of Australasia.

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What is lobular carcinoma in situ?

Lobular carcinoma in situ (LCIS) is a non-invasive neoplastic proliferation of epithelial cells within the lobules and terminal ducts of the breast. Atypical lobular hyperplasia (ALH) is diagnosed when cells similar to those seen in LCIS only partially fill the terminal duct lobular unit (TDLU) with minimal distension and distortion of the acini. LCIS and ALH are collectively referred to as lobular neoplasia. Unlike ductal carcinoma in situ (DCIS), which is usually a segmental disease in one breast, LCIS is frequently multifocal and multicentric (85% of patients) and bilateral (30-67% of patients).[1]

Detailed descriptions of the morphological, histological and molecular pathological characteristics of lobular neoplasia and DCIS are beyond the scope of the current document. The reader is referred to the current WHO Classification: Tumours of the Breast[2] for this information. However, it should be noted that in recent years several subtypes of LCIS, in addition to the 'classic' variety, have been identified: 'pleomorphic LCIS' (PLCIS; in which cells display marked nuclear pleomorphism similar to that seen in high grade DCIS), 'classic LCIS with comedo-type necrosis', and 'florid/bulky LCIS' (classic LCIS which distends the TDLU to form confluent masses). The implications for patient management according to LCIS subtype are discussed below.

The true incidence of LCIS is unknown as the classic variant has no specific clinical or radiological features and is not seen on macroscopic examination of excisional specimens. The detection of LCIS is usually an incidental finding on core needle or excision biopsies of benign or malignant breast tissue.[1] Even then, it is an infrequent finding, with an estimated prevalence of 0.4-3.8% in women with otherwise benign breast biopsies.[3, 4]

Clinical implications of a diagnosis of LCIS

Accepting the limitations of histologically distinguishing between ALH and LCIS (i.e. a subjective assessment of the degree of involvement of the TDLU), this distinction is clinically relevant. A greater risk of subsequent invasive breast cancer is predicted by more extensive disease: women diagnosed with ALH have a relative risk 4-5 times greater than the general population, whereas women diagnosed with LCIS have a relative risk 8-10 times higher.[5] ALH is not formally considered further in this document, but given the difficulty in distinguishing between ALH and LCIS, the guidance provided for LCIS might be considered relevant to ALH.

A 2% annual incidence of breast cancer has been reported recently in women with LCIS, which is higher than earlier observations of approximately 1% per year.[6] However, previous studies were not necessarily undertaken according to the current WHO criteria[2], and were potentially diluted by the inclusion of ALH cases. While earlier studies suggested that the risk of invasive breast cancer in women with LCIS was equal for both breasts, recent evidence suggests that the risk of breast cancer is approximately 3 times higher in the ipsilateral breast.[7-9] The overall risk of invasive breast cancer associated with LCIS is similar to the risk associated with a strong family history of breast cancer. While LCIS is clearly a risk factor for the subsequent development of invasive cancer, recent molecular data show that it is also a non-obligate precursor of invasive carcinoma. There are currently no data on the natural history of the recently recognised LCIS subtypes.

Management options for women with LCIS

Limited evidence is available to determine the most appropriate management of women with LCIS. The diagnosis and management of women with LCIS should involve a multidisciplinary team who consider all relevant pathological, radiological and clinical information, and the individual patient's risk profile and preferences.

Patient involvement is a key principle of multidisciplinary care, and health professionals must ensure that women diagnosed with LCIS receive adequate information. This should include an explanation of the implications of the diagnosis in terms of risk of subsequent invasive breast cancer, and the options regarding surgical management, risk-reducing strategies and surveillance. Patients should be encouraged to be involved in the development of their individual treatment and care plan.

Biopsy and surgery

LCIS found on core needle biopsy

The appropriate management options for women with LCIS found on core needle biopsy will depend on whether LCIS is found alone, the subtype of LCIS and any associated pathological findings.

When classic LCIS is found on core needle biopsy (either conventional or vacuum-assisted) as an incidental finding, a multidisciplinary discussion is needed to determine further management. There is no strong evidence to guide whether to perform surgery (excision biopsy or other surgery) on these women. There are several studies that have attempted to correlate the results of core biopsy with subsequent excision, with widely varying upgrade rates (ranging from 2% to 26%). These variations reflect study design differences and in some cases, biases introduced due to the retrospective nature of the investigation.[10]

When classic LCIS is found on core needle biopsy, with radiological-pathological concordance and there are no other higher risk abnormalities that would impact management (e.g. DCIS or invasive carcinoma), it is the consensus of the Working Group that surveillance remains an appropriate option.

If classic LCIS is the only lesion found on core needle biopsy and it does not account for the radiological abnormality (i.e. it is not the index lesion and hence there is radiological-pathological discordance) the consensus of the Working Group is that a subsequent biopsy to obtain a larger tissue sample should be considered.

If there are other LCIS subtypes or proliferative lesions present that require investigation, the consensus of the Working Group is that an excision should be undertaken. Specific examples include:

- the presence of another lesion within the core biopsy that would itself trigger an excision (such as atypical ductal hyperplasia or DCIS)
- the LCIS is of pleomorphic subtype
- the LCIS is of the classic type with comedo-type necrosis
- the LCIS is of the florid/bulky subtype

LCIS found on excision biopsy

The appropriate management options for women with LCIS identified on excision biopsy will depend on whether LCIS is found in isolation, the subtype of LCIS and any associated pathological findings. When LCIS is found in the presence of DCIS or an invasive cancer, these will dictate further management. For LCIS found in isolation on excision biopsy, the management options for each subtype of LCIS are detailed below.

Classic LCIS

As LCIS is often a multifocal and multicentric process, the current WHO Classification: Tumours of the Breast[2] does not recommend recording size and margin status for classic LCIS. Most institutions do not attempt clear surgical margins for classic LCIS found on excision biopsy. LCIS reflects a higher risk of developing invasive

breast cancer, and surveillance will be dictated by any associated pathology, and personal or family history. Further risk-reducing strategies should be discussed, with consideration of the individual patient's preferences.

Pleomorphic LCIS

There is a lack of follow-up data to inform the natural history of this subtype. However due to the high grade morphology and molecular profile of this variant, the consensus of the Working Group is that PLCIS be managed as for DCIS. If there is PLCIS at margins in the excisional biopsy, a further surgical procedure such as re-excision, wide-local excision or mastectomy should be considered. However, in order to avoid overtreatment, it is important for pathologists to make a diagnosis of PLCIS only when the nuclear atypia is of high grade (similar to high grade DCIS).

Classic LCIS with comedo-type necrosis, and Florid/Bulky LCIS

These entities have only been described very recently. Due to their rarity and lack of robust morphological criteria for classification, and lack of follow-up data, management decisions should be made as part of the multidisciplinary team discussion. The WHO Classification: Tumours of the Breast[2] recommends that margin status should be recorded and a multidisciplinary team should plan further management, including the possibility of further excision or surgery, taking into consideration other risk factors and patient choice.

Radiotherapy

There is no evidence to support the use of radiotherapy in reducing the risk of in situ carcinoma or the development of invasive breast cancer, following a diagnosis of classic LCIS or any of the newly described LCIS subtypes. However, adjuvant radiotherapy after breast conservation surgery may be considered for women with PLCIS, given the histomorphological similarities with DCIS.

Risk-reducing medication

In women at increased risk of invasive breast cancer, risk-reducing treatment with selective oestrogen receptor modulators (SERMs), such as tamoxifen or raloxifene, reduces the risk of oestrogen receptor-positive breast cancer. Although women with LCIS comprise a relatively small proportion of subjects in the relevant clinical trials, the extent of risk reduction with SERMs is similar in women at increased risk due to LCIS compared to women at increased risk for other reasons such as family history (risk reductions of 56% and 49%, respectively).[11] Tamoxifen has been shown to reduce the risk of breast cancer for up to 20 years, even when taken for only five years.[12] In post-menopausal women at increased risk of breast cancer, risk-reducing treatment with the aromatase inhibitors (AIs) anastrozole or exemestane has been shown to reduce the risk of invasive breast cancer.[13, 14] Treatment with a SERM or an AI has been shown to halve the cumulative invasive breast cancer rate in women with LCIS.[6]

Whilst risk-reducing medication is effective at reducing invasive breast cancer incidence in women at higher risk, it is unclear if these effects impact on overall survival. Furthermore, the potential benefits of risk-reducing medication need to be weighed against potential adverse effects.[6] For pre-menopausal women, tamoxifen increases the risk of thromboembolic events such as deep vein thrombosis, although the absolute risk is low and similar to the risk associated with use of oral contraceptives.[15, 16] For post-menopausal women, tamoxifen increases the risk of thromboembolic events, endometrial cancer, and cataracts, although the additional absolute risk of serious complications is low.[17, 18] The AIs have a different side-effect profile compared to the SERMs. Anastrozole and exemestane are associated with a loss of bone mineral density and hypertension (but not thromboembolic or cardiovascular events), and are not associated with increased risk of other cancers.[13, 14, 19]

Risk-reducing medication for the prevention of invasive breast cancer is a management option for women with a diagnosis of LCIS. The decision to use medication for risk reduction should consider an individual woman's overall clinical profile.

Risk-reducing surgery

It is the consensus of the Working Group that prophylactic bilateral mastectomy is not recommended for the majority of women with LCIS. However, risk-reducing bilateral mastectomy is an option that may be chosen by some women. The potential role of risk-reducing surgery should be discussed by the multidisciplinary team with consideration of the individual patient's preferences and other risk factors.

Surveillance

All women who have been diagnosed with LCIS should have ongoing surveillance due to the increased risk of subsequent invasive breast cancer. Subject to specialist clinical judgement (e.g. considering the age of the woman), surveillance includes annual clinical examination and appropriate bilateral imaging. The type of imaging used in surveillance will depend on the woman's characteristics and how their LCIS was managed.

Summary of consensus practice points

- The diagnosis and management of women with LCIS should involve a multidisciplinary team who consider all relevant pathological, radiological and clinical data, and the individual patient's risk profile and preferences.
- Patient involvement in the choice of management options is a key aspect of care. Women should receive adequate information regarding the implications of a diagnosis of LCIS, and the risks and benefits of the different management options.
- Management options for the majority of women with LCIS include surveillance, surgical excision, and risk-reducing medication.
- Surveillance includes annual clinical examination and bilateral imaging, subject to specialist clinical judgement (e.g. considering the age of the woman).
- If LCIS of the classic variant is found in isolation or as an incidental finding (on core needle or excision biopsy), with pathological-radiological concordance, then surveillance remains an option.
- If PLCIS is found on core needle biopsy, excision should be performed.
- If other sub-types of LCIS (such as classic LCIS with comedo-type necrosis and florid/bulky LCIS) are found on core needle biopsy, excision may be considered.
- There is no evidence to support the use of radiotherapy for LCIS in general, but adjuvant radiotherapy may be considered for women with PLCIS.
- Risk-reducing medication, including aromatase inhibitors or selective oestrogen receptor modulators, is an option for preventing invasive breast cancer, subject to an individual woman's overall clinical profile.

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