

UPDATE

CURRENT MANAGEMENT OF LOBULAR IN SITU NEOPLASIA

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Although the term of lobular neoplasia was first proposed in 1978 and the term Lobular In situ Neoplasia (LIN) has been incorporated in the current World Health Organisation (WHO) classification to cover both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS), the clinical significance and the natural history of lobular neoplasia is far from being fully understood. Furthermore problems and confusion still remain surrounding 1) the most appropriate terminology and classification for these lesions, 2) the best course of long-term management after diagnosis. This article summarizes the opinions on LCIS management of a group of Belgian experts.

Key-word: Breast neoplasms, therapy.

The term of lobular neoplasia was first proposed by Haagensen in 1978 to cover both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) (1). The term Lobular In situ Neoplasia (LIN) has been incorporated in the current World Health Organisation (WHO) book with the traditional ALH/LCIS terminology (2). However, problems and confusion remain surrounding the most appropriate terminology and classification for these lesions, and the best course of long-term management after diagnosis. The clinical significance and natural history of lobular neoplasia is far from being fully understood and most published series have relatively small numbers of cases. This article summarizes the opinions on LCIS of a group of experts who met during a meeting devoted to this topic in Brussels, Belgium, in December 2007.

The true incidence of LCIS in the general population is unknown. Lobular neoplasia is most prevalent in perimenopausal women. It is discovered in 0.5 to 3.8% of benign breast biopsies. Because of increased rates of biopsy for mammographic findings, the diagnosis of LCIS has increased in post menopausal women (3, 4). LCIS is often multifocal (from 50% to 80%) and bilateral (from 23% to 30%) (5). The risk for developing invasive cancer appears in both the ipsilateral and contralateral breasts. Unfortunately, few studies had suffi-

cient power to adequately investigate the long-term invasive breast cancer (IBC) risk associated with LCIS. In the largest population-based study of 4,853 women with LCIS with 350 IBC occurrences, the authors showed that the minimum cumulative risk of developing invasive breast cancer after LCIS was 7.1% at 10 years, with risk equally distributed between both breasts (6).

Diagnosis: Pathology

There is no consensus on the most appropriate terminology and classification (ALH/LCIS- versus Lobular In situ Neoplasia). LIN terminology includes LIN1 (atypical lobular neoplasia), LIN2 (low grade LCIS), and LIN3 (high grade or pleomorphic LCIS).

Because it encompasses a large spectrum of lesions, the term lobular neoplasia may not be adequate for risk stratification on an individual level. Furthermore inter- and intra-observer variability may complicate this issue as well as the quantitative assessment of the lesions.

In the majority of the cases, LCIS is associated with a particular immunophenotype including expression of oestrogen and progesterone receptors, lack of expression of E-cadherin, HER-2 and TP53. Differences between classic LCIS and pleomorphic variant have been described and this suggests a more aggressive profile for the pleomorphic variant (7).

Premalignant lesions are currently defined by their histologic features, and not all necessarily progress to invasive cancer. This suggests that although lesions within specific categories look alike, they must possess underlying genetic differences that cause some to remain stable and others to evolve. Recent studies indicate that cancer evolves by highly diverse genetic mechanisms, and research into these altered pathways may identify specific early defects that might be targeted to prevent progression of premalignant lesions to invasive cancer. The development of modern molecular genetic techniques may allow breast cancer researchers to clarify the multistep model of breast carcinogenesis.

A strong correlation between the lobular histological type and inactivation of E-cadherin, a protein involved in cell adhesion, has been reported. Similarly, mutations in the E-cadherin gene have been reported in invasive lobular carcinoma (ILC) and LCIS with adjacent ILC. Studies are in progress to evaluate loss of heterozygosity at chromosome 16q, E-cadherin promoter methylation. 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. The available 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, the loss of 16q material might account for a "slowed down" proliferation rate in a subgroup including well differentiated low grade DCIS, LIN1 (atypical lobular neoplasia), LIN2 (low grade lobular carcinoma in situ) in contrast to high grade DCIS.

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Although the loss of the chromosomal material at 16q (CDH1 locus) is the most frequent genetic event in invasive and in situ lobular carcinoma of the breast, recent study suggests that neighbouring novel tumour suppressor genes might be involved in the development and progression of these tumours and may, similar to CDH1, be potentially utilised as markers of predisposition in women diagnosed with LCIS. These include CCCTC-binding factor (CTCF) and Dipeptidase 1 (DPEP1) (8).

However, no single factor so far appears to be particularly powerful in predicting the development of IBC in a woman with LCIS, and panels of multiple factors will probably be more useful. The completion of these analyses will provide insight into the molecular genetic profile for lobular in situ neoplasia and will hopefully clarify their various risks potential.

Diagnosis: Imaging

In contrast to ductal lesions, lobular neoplasia generally has no clinical or mammographic manifestations. It is usually encountered incidentally at biopsy of a targeted coexistent entity. Recently, however, mammographically evident calcifications have been described in association with lobular lesions (9, 10, 11). Two forms of calcifications are recognized with LCIS. A pleomorphic, necrotic form of LCIS has been described in which the calcifications are associated with necrotic debris and closely resemble the comedocarcinoma calcifications of high-grade DCIS. The classic, non-necrotic form of LCIS is associated with calcifications that are similar in appearance to those found in benign proliferative change (clustered, punctate, variable density, and smaller than or equal to 0.5 mm). Nevertheless, the majority of these proliferative lesions does not present as a mass nor contain microcalcifications. Therefore mammography and ultrasound have no role in prospectively diagnosing LCIS. Unfortunately, once a patient is diagnosed with LCIS after biopsy, we have no data on the role of magnetic resonance imaging (MRI) in the diagnostic work up. Studies are needed in order to assess the role of imaging in evaluating multicentricity and bilaterality of these lesions.

Because LCIS is associated with the risk of developing invasive breast cancer, it is important to clarify the best imaging technique for the surveillance of these patients. In a

recent retrospective study, the authors reviewed data from 378 patients; among them 252 had LCIS on previous surgical biopsy (12). All patients underwent yearly mammography and twice yearly clinical breast examination. Additional screening MRI was performed at the discretion of the physician and patient. Cancer was detected in 6/46 (13%) MRI-generated biopsies. None of the six cancers detected on MRI were seen on recent mammogram. All six cancers were detected in five patients (one with bilateral breast cancer) with LCIS. Thus, cancer was detected in 5/135 (4%) of patients with LCIS undergoing MRI. MRI screening generated more biopsies for a large proportion of patients, and facilitated detection of cancer in only a small highly selected group of patients with LCIS, those who were younger with stronger family histories of breast cancer.

No studies so far assessed as to whether adding MRI reduces patient mortality, interval or advanced breast cancer rates, and there is no strong evidence that MRI leads to the detection of earlier stage disease (13). The extent to which high risk younger women receive the same benefits from early detection and treatment of MRI-detected cancers has not yet been established.

Recent guidelines based on experts opinion, propose 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. Current European clinical trials investigate whether or not women diagnosed with LCIS should undergo MRI for intensified surveillance, as it has been recently recommended in women with a genetically increased risk (5).

Treatment

Surgery

Most women with a diagnosis of lobular carcinoma in situ do not develop invasive breast cancer within their lifetimes. The management of LCIS depends on the setting in which it is encountered. The significance of LCIS diagnosed at core needle biopsy (CNB) is unclear, although many groups recommend surgical

excision to rule out lesions, which would require immediate, definitive therapy. In addition surgical excision may be required for definitive diagnosis because rates of histologic underestimation approach those of atypical ductal hyperplasia (ADH) especially in the case of masses or when the histological specimen reveals a pleomorphic subtype. However, the necessity of routine surgical excision remains controversial due to conflicting opinions on the biological behaviour of lobular lesions, diagnostic confusion regarding histopathology, and uncertainty of their association with high-risk lesions. In a recent review regarding this issue, Bowman and colleagues addressed the management of LIN diagnosed at CNB (14). They retrieved 19 retrospective studies that form the basis of their report including a total of 504 subjects. Nearly half of the reviewed studies were non-consecutive series, no study reported clear inclusion criteria for surgical excision versus observation, and included small number of subjects. Because of these limitations, it is difficult to reach a firm evidence-based conclusion regarding optimal management of LIN diagnosed at CNB. Associated high-risk lesions increase the risk of upgrade, but there are no mammographic predictors. The available retrospective literature suggests that some cases of LIN are associated with higher-risk lesions identified on surgical excision but does not support routine excision for all patients. Some authors have suggested that surgical excision may not be necessary when a diagnosis of only focal LN is made on core biopsy. Diffuse LN may indicate an associated invasive cancer and should prompt excision (15).

When diagnosed on surgical biopsy, LCIS generally does not require further intervention, even when present at a surgical margin. The risk for developing invasive cancer appears in both the ipsilateral and contralateral breasts. Therefore, if one has to choose surgery for lobular carcinoma in situ, the only logical approach would be a bilateral total mastectomy. This is an excessively morbid procedure for patients who have a moderate risk associated with the diagnosis of lobular carcinoma in situ. However, if the patient has other risk factors, such as a high-risk family history or evidence of genetic predisposition, prophylactic bilateral mastectomy with or without reconstruction would be a consideration.

Although this reduces risk for developing subsequent breast carcinoma by 90%, every woman should be correctly informed about the potential long term adverse effects including body image disruption, impaired sexual function, and the potential for re-operations following reconstruction (16). In this setting good cooperation between the oncological surgeon and the plastic surgeon is crucial for preoperative treatment planning and for selecting the most appropriate reconstruction technique.

Radiation Therapy

The literature on the use of radiotherapy for LCIS is limited and currently, there is little data to recommend its role in clinical management (5). Cutuli and colleagues found a 4% risk of ipsilateral breast tumor recurrence (IBTR) in 25 patients with LCIS following treatment with radiation therapy with a median follow-up of nearly 13 years (17). Because of the small number of patients in this series, it is quite possible that this failure rate is due to chance, rather than the use of radiation therapy. In addition, 12 of their patients received tamoxifen for 2 years, which may interfere with the results. The rate of subsequent contralateral breast cancer development was also low, only 1 of 23 evaluable patients. However, two patients also underwent contralateral mastectomies for cancers found at the same time as discovery of the index LCIS.

Chemoprevention

Lobular neoplasia is a risk factor for invasive breast cancer and may be a precursor lesion in unusual circumstances. Both atypical lobular hyperplasia and lobular carcinoma in situ increase the risk for the subsequent development of invasive carcinoma, by about fourfold for atypical lobular hyperplasia and tenfold for lobular carcinoma in situ. Although subsequent carcinomas can occur in either breast without a direct relationship to the previous site of biopsy, in a recent retrospective study, Page et al. reported that the development of invasive carcinoma after atypical lobular hyperplasia was three times more likely to arise in the ipsilateral breast than in the opposite breast (18). Invasive carcinomas may arise 15–20 years after diagnosis. As previously discussed, most women with LCIS can be managed without additional local therapy after

biopsy. Tamoxifen has decreased the risk of developing breast cancer in women with LCIS and should be considered in the routine management of these women. The NSABP P-1 trial of 13,388 high-risk women comparing tamoxifen to placebo demonstrated an overall 49% decrease in invasive breast cancer, with a mean follow-up of 47.7 months (19). Risk was reduced by 56% in the subset of 826 women with a history of LCIS, and the average annual hazard rate for invasive cancer fell from 12.99 per 1,000 women to 5.69 per 1,000 women. In women older than 50 years, this benefit was accompanied by an annual incidence of 1 to 2 per 1,000 women of endometrial cancer and thrombotic events (19).

A smaller reduction was noted in the International Breast Cancer Intervention Study (IBIS-I) in which a 32% risk reduction was noted after 50 months in patients with a greater than twofold relative risk of breast cancer (20). Two additional European studies, the Royal Marsden Hospital study and the Italian study, have failed to demonstrate a statistical benefit toward tamoxifen, but many believe that differences in patient selection, poor compliance, and insufficient power account for the differences (21). A further meta-analysis of these four trials produced a 38% reduction in the incidence of breast cancer and decreased ER-positive tumors by 48% (22).

Raloxifene is a second-generation SERM, with similar effects to tamoxifen on breast, bone, and liver but no agonistic effect on the uterus in contrast to tamoxifen. The NSABP STAR P-2 trial had compared 5 years of raloxifene head-to-head with 5 years of tamoxifen in high-risk, postmenopausal individuals. Raloxifene could not be administered to premenopausal women secondary to increased incidence of ovarian cyst. In approximately 20,000 randomized patients, there were no statistical differences in invasive breast cancer incidence between the two groups ($P = .83$). Compared with patients who received tamoxifen, patients randomized in the raloxifene arm had fewer uterine cancers ($P = .07$), thromboembolic events ($P = .01$), and cataracts ($P = .002$). These results support the use of raloxifene as an alternative to tamoxifen. One should note that the incidence of noninvasive cancer was slightly lower in the tamoxifen arm although this was at the limit of significance ($P = .052$) (23).

Studies of aromatase inhibitors have mainly focused on the adjuvant treatment to hormone receptor-positive breast cancer in the postmenopausal patient. In this setting, three randomized trials have demonstrated a greater reduction in contralateral cancers compared to tamoxifen (38% to 58% reduction compared to tamoxifen) (24). Furthermore, patients had an improved safety profile compared to tamoxifen with decreased incidence of uterine cancer and thromboembolic events.

With such dramatic results in the adjuvant setting, one would hypothesize similar results as a chemopreventive agent in the postmenopausal woman. Results are awaited from current randomized trials such as the National Cancer Institute of Canada Clinical Trials Group MAP3 (ExCel) trial evaluating exemestane in prevention of cancer in postmenopausal women at increased risk of developing breast cancer, the International Breast Cancer Intervention Study-II (IBIS-II) trial, and the Aromasin Prevention Study (ApreS). The IBIS-II trial compares anastrozole to placebo in high-risk women. The ExCel study will compare exemestane to placebo in patients with a Gail score of ≥ 1.66 , and the ApreS will do the same comparison in BRCA carriers (25).

Quality of life

Risk communication

Researchers have documented that patients do not have a clear understanding of breast cancer risks and that women tend to overestimate rather than underestimate their lifetime risk of breast cancer (26). Patients generally have considerable difficulty understanding and working with risk calculations and probabilities. Furthermore, decisions and behaviours about risk management are not determined by knowledge alone, there are many other powerful factors involved, including emotions, values, social pressures, environmental barriers and economic realities (27).

Effectively communicating any cancer risk information is fundamentally challenging for health care professionals as well. Not only do health care professionals have to communicate often contradictory and inconclusive information thoroughly and effectively, but they must also understand how the patient perceives the information so that

Table I. — Evidence based Clinical Management of Lobular Carcinoma In Situ (LCIS).

Management issue	Current Recommendation	Level of evidence/recommendation*
Pathology Report	LCIS on margins must be reported with extension (focal or diffuse)	V* (expert opinion)/D*
Role of imaging in diagnosis	No role in prospective diagnosis for healthy woman	IV* and V* (case series and expert opinion)/ C* and D*
Role of imaging in surveillance	Yearly mammography Breast Ultrasonography in dense breast Magnetic Resonance Imaging	II* and III* ¹ (cohort and case control studies)/ B*
LCIS on core needle biopsy	Excisional biopsy	IV* and V* (case series and expert opinion)/ C* and D*
LCIS on margins after cancer surgery	No further treatment if invasive cancer excised	V* (expert opinion)/ D*
Role of Radiation Therapy	None	II* ² and V* (cohort study and expert opinion)/ C* and D*
Role of Chemoprevention	Tamoxifen Raloxifen ³	I* (randomized controlled trials)/ A*

*Level I: Randomized Controlled Trial. *Level II: Cohort Study. *Level III: Case-control study. *Level IV: Cases series. *Level V: Expert opinion. *Level A: consistent Randomized Controlled Clinical Trial, Cohort Study, All or None, Clinical Decision Rule validated in different populations; *Level B: consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, Case-Control Study; or extrapolations from level A studies. *Level C: Case-series Study or extrapolations from level B studies. *Level D: Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles (31).

¹ High sensitivity of MRI in high risk patients in case control studies comparing MRI and Mammography.

² Only one cohort study (17).

³ Restricted to postmenopausal women.

misperceptions can be corrected (28). This difficulty is highlighted by current data from genetic counselling, which show that even with communication in one-on-one settings, there are still few perfect matches between the message communicated and the message received.

The way in which health care professionals present cancer risk information is critical to patient understanding and acceptance of the information. Because it is difficult to convert population-based estimates of cancer risk to precise statements of individual risk, it is difficult to ensure that "actual risk" is effectively communicated and accurately perceived. Currently, there is a considerable unmet need in terms of cancer risk communication research to help health care professionals utilize best practices to most effectively impart highly scientific, as well as personally relevant, information to patients. Health care professionals tend to use specialized language (or jargon) that patients find difficult to understand. Many experts use the term "risk" as a technical term that refers to a particular known probability while the general public attach-

es many different meanings to the term, such as possibility of loss or injury; level or degree of danger; and others. Specifically, people will not always respond to a given probability in the same way and 10% risk is sometimes perceived differently if it is presented as a percentage or an odds ratio or if it is presented numerically or pictorially (29).

Thus improving the communication practices by health care professionals surrounding risk of breast cancer is a fundamental and integral element of providing the best possible care for patients. This is particularly crucial given that a number of studies have demonstrated a correlation between effective physician-patient communication and improved patient health outcomes (30).

Conclusion

Lobular carcinoma in situ (LCIS) has gone from a rare form of mammary cancer to a marker of increased risk and in some cases, a true precursor. Current clinical management is heterogeneous and depends on histologic examination and individual patient factors. Available data for

decision making are limited (Table I) (31). Options for breast cancer risk reduction and prevention are available. However, we need to have better understanding of the associations between the incidence of lobular neoplasia, magnitude of cancer risk, age, mammographic density, and distributions of lesions within the breast. Furthermore, what remains to be clarified is how to better quantify and communicate risks for individual patients in order to implement most appropriate preventive strategies. High priority should be given to identifying additional prognostic factors because success in identifying and treating high-risk premalignant disease has the potential to prevent the majority of lethal invasive breast cancers.

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