Management of breast lobular carcinoma in situ: radio-pathological correlation, clinical implications, and follow-up

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Summary

Purpose of investigation: to show management of patients with breast lobular carcinoma in situ (LCIS). *Materials and Methods*: This study is the retrospective review of 65 patients, between 1996 and 2012, with isolated LCIS of the breast, evaluated through clinical examination, ultrasound, and mammography at the first examination and follow-up. *Results*: In 53 patients (81.54%), clinical examination was negative. In 14/65 (21.54%) cases, ultrasound was positive and led to biopsy. The clusters of tiny calcifications were the predominant mammographic pattern (45 cases, 69.23%). Forty-six patients (70.77%) underwent surgical biopsy after guided stereotactic placement of metallic marker (hook-wire), 12 (18.46%) by stereotactic vacuum biopsy (SVB), 5 (7.69%) by core needle biopsy (CNB) under ultrasound guidance, two (3.08%) patients CNB with clinically palpable nodules. Fourteen (21.54%) women underwent a quadrantectomy or total mastectomy after the first diagnosis; in this latter group follow-up was negative. Among the 51 patients (78.46%) who did not undergo quadrantectomy or total mastectomy, five relapses occurred, respectively, three LCIS and two infiltrating ductal carcinomas (IDC). Follow-up ranged from 12 to 144 months. *Conclusion*: LCIS is a risk factor for invasive carcinoma and should be managed with careful follow-up, but if there is a discrepancy between pathology and imaging, surgical excision is mandatory.

Key words: Lobular carcinoma in situ (LCIS); Breast cancer; Follow-up; Lobular intraepithelial neoplasia (LIN); Management.

Introduction

The management of lobular carcinoma in situ (LCIS) remains controversial: its definition is controversial, as well as biology, clinical significance, natural history and the best management in the short and long term after diagnosis.

The true incidence of LCIS in the general population is unknown, but it ranges from 0.8% to 5% of all breast cancers [1]. The LCIS is often multifocal (50% - 80%), multicentric (60-90%) and bilateral (23%-59%) [2-3].

The diagnosis is often incidental as there are no specific clinical and mammographic signs for this lesion [4-6]. Lobular neoplasia broadly defines the spectrum of changes within the lobule, ranging from atypical lobular hyperplasia (ALH) to LCIS. LCIS and ALH are associated with an increased risk of invasive breast cancer, both ipsilateral and contralateral, and more than 50% of these diagnoses occur 15 years after the first diagnosis of LCIS [7]. However, this risk of malignancy in the literature also achieves 37% [8-10].

The purpose of this manuscript was:

1. to examine the clinical, sonographic, and mammographic correlations of LCIS, the signs that have aroused suspicion and led to the diagnostic biopsy;
2. to evaluate the follow-up of patients with diagnosis of isolated LCIS at biopsy, not associated with malignant breast disease or previous breast cancer.

Materials and Methods

The authors evaluated 65 patients aged between 22 and 76 years (mean age 50 years) with a diagnosis of LCIS detected on biopsy, recruited at the 'Breast Unit of the Institute of Radiological Sciences "C. Bompiani", University of Sassari, between 1996 and 2012. The present Institutional Review Board approved the study.

Initially, the authors enrolled 162 patients, but selected only cases with the following recruitment criteria:

- Knowledge of the clinical and radiological findings relevant to the diagnosis of LCIS;
- Histological diagnosis of LCIS in the absence of other malignancies;
- Absence of previous malignancy (ipsilateral and contralateral breast diagnosed with LCIS);
- Knowledge of the course of follow-up for a minimum of 12 months.

In detail, 97 patients were excluded for the following reasons:

- 19 had history of previous malignancy;
- 45 did not undergo follow-up in our Institute and it was not possible to know their follow-up results;
- Clinical and/or radiological finding were not present for 25 patients because they were studied in other facilities before biopsy;
- Eight patients had other malignancies at specimens.

Among all patients, 36 (55.38%) were premenopausal and 29 (44.62%) postmenopausal. Family history of breast cancer was present in 28 patients (43.07%), 18 patients took the contraceptive pill for a period exceeding two years (27.69%), nine (13.85%) had performed estrogen replacement therapy for a period exceeding two years, 33 (50.77%) had their first full-term pregnancy before 35 years, and ten (15.38%) have had one abortion.

The patients were studied by clinical examination, ultrasonography (with high frequency probes: 7-15 MHz) and mammogra-

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Table 1. — *Clinical examination.*

Clinical examination	N. patients	%
Negative	53	81.54
Nipple secretion	2	3.08
Areas of thickening	3	4.61
Single nodule	2	3.08
Diffuse nodular texture	5	7.69
Total	65	100 %

Table 2. — *Ultrasound findings.*

Ultrasound findings	N. patients	%
Negative	51	78.46
Hypoechoic nodule with regulars margins	1	1.53
Hypoechoic nodule with polilobulated margins	2	3.07
Hypoechoic area with poorly defined margins	4	6.15
Dishomogenous hypoechoic area	7	10.76
Total	65	100 %

phy. Histologic examination of surgical biopsy was performed by percutaneous ultrasound-guided or stereotactic needle biopsy after placement of guided stereotactic metal marker (hook-wire), and no marker for clinically palpable nodules.

LCIS were classified by a pathologist according to LIN classification system [11]. All patients were followed-up with clinical, ultrasound, and mammographic approach for a minimum of 12 months and a maximum of 144 months. The first control was carried out at six to eight months after the surgical biopsy and afterwards every 12-18 months.

Results

In most patients (53 cases, 81.54%) the clinical examination was negative. Two patients (3.08%) had nipple discharge, serous type. In three patients (4.61%), the clinical examination revealed areas of thickening, corresponding to two cases of structural distortion and a case of irregular nodular lesion without calcifications at mammography. In two patients (3.08%), clinical examination showed a single isolated nodule. Five patients (7.69%) had diffuse nodular texture in both breasts (Table 1).

In 14/65 (21.54%) cases, ultrasound was positive and led to biopsy (Table 2); percutaneous core biopsy under ultrasound guidance in just five patients was done; the others underwent surgical biopsy (48 patients) or percutaneous guided stereotactic vacuum biopsy (12 patients). The mammographic findings that have suggested the biopsy were: minute clustered calcifications, nodular lesions with irregular contours with or without calcifications, nodules with clear margins (fibroadenoma); star lesions without calcifications; architectural distortions with calcifications. The clusters of tiny calcifications were the predominant mammographic pattern (45 cases, 69.23%) (Table 3).

LCIS was present in nodular lesions with irregular contours in 11 cases: six (9.23%) without calcifications, and five (7.69%) with calcifications. In one case (1.54%) the lesion was represented by a nodular lesion with clear limits, that histologically resulted to be a fibroadenoma with a LCIS in its contest. Similarly, in one case (1.54%) the cancer was contained in a star lesion without calcifications. Four patients (6.15%) had an area of architectural distortion of the breast, with clustered calcifications inside.

Table 3. — *Mammographic findings.*

Mammographic findings	N. patients	%
Negative	3	4.62
Calcifications	45	69.23
Irregular nodular lesions without calcifications	6	9.23
Irregular nodular lesions with calcifications	5	7.69
Nodular lesion with clear margins (fibroadenoma)	1	1.54
Star lesions without calcifications	1	1.54
Architectural distortion with calcifications	4	6.15
Total	65	100 %

Fifty-one patients (78.46%) who presented with a mammographic finding were negative at ultrasound examination. Two (3.07%) nodular lesions with irregular contours on mammogram, one with and one without calcifications, appeared as hypoechoic nodules with polilobulated margins at ultrasound. In three other cases of irregular breast lump at mammography (two with and one without calcifications), ultrasound showed a hypoechoic area with poorly defined margins. Three cases, at mammography, of irregular nodular lesion with calcifications and two cases of structural distortion with calcifications showed to be a dishomogeneous hypoechoic area at ultrasound examination. The case of fibroadenoma appeared as a hypoechoic three-cm nodule with regular shape and sharp boundaries.

Histologic examination was performed on surgical biopsy after guided stereotactic placement of metallic marker (hook-wire) in 46 patients (34 clustered calcifications, nine nodular lesions with irregular contours, one star lesion without calcifications, two structural distortions with calcifications), two patients with clinically palpable nodules (one hypoechoic nodule with regular contours and one hypoechoic nodule with polilobulated contours), percutaneous stereotactic vacuum biopsy in 12 patients (ten clustered calcifications, two architectural distortions with calcifications), percutaneous core biopsy under ultrasound guidance in five patients (one hypoechoic area with poorly defined boundaries, three dishomogeneous hypoechoic areas, and one hypoechoic nodule with polilobulated contours).

After the first biopsy diagnosis, the authors performed four quadrantectomies, respectively, for a unifocal LCIS and for three multifocal LCIS. Histological examination of the surgical specimens confirmed the first diagnosis in three cases, but in one case (LIN III) the excised quadrant contained an infiltrating lobular carcinoma (ILC) (Table 4). In ten cases the authors performed immediately complete

Table 4. — *Surgery.*

N. patients	LCIS	Surgery	Definitive histology
1	multifocal	quadrantectomy	ILC
1	unifocal	quadrantectomy	LCIS unifocal
2	multifocal	quadrantectomy	LCIS multifocal
9	multicentric	mastectomy	LCIS multicentric
1	multicentric	mastectomy	LCIS multicentric + DCIS comedo + crib
14/65 (21.54%)			

Table 5. — *Recurrences.*

Recurrences			
Quadrantectomy or mastectomy (14)	Follow-up (51)		
0	5 out of 51 (9,80%)		
	2 unifocal LCIS (3.92%)	1 multifocal LCIS (1.96%)	2 IDC + LCIS (3.92%)

mastectomy due to the presence of multicentric LCIS, and in one case of these histologic examination, they found the presence of ductal carcinoma in situ (DCIS) with comedo and cribriform type (Table 4).

The authors found that LCIS specimens were:

– in 38/63 (60.32%) cases, LIN I;
– in 24/63 (38.09%) cases, LIN II;
– in 1/63 (1.59%) case, LIN III.

The follow-up was negative in all patients undergoing quadrantectomy or mastectomy immediately after the first diagnosis (14 patients, 21.54%).

Five recurrences occurred in 51 patients (9.8%) undergoing to follow-up (Table 5). In all cases the finding that led to a new biopsy had been the presence of suspicious calcifications at mammographic examination. In two cases the authors found unifocal LCIS, occurring respectively 12 (LIN I) and 24 (LIN II) months after initial diagnosis. In one case (LIN 1), which occurred three years after initial diagnosis, histology showed the presence of a multifocal LCIS. In two cases (LIN I and II), one year after the first diagnosis, they found an infiltrating ductal carcinoma (IDC) associated with LCIS; patients then underwent mastectomy.

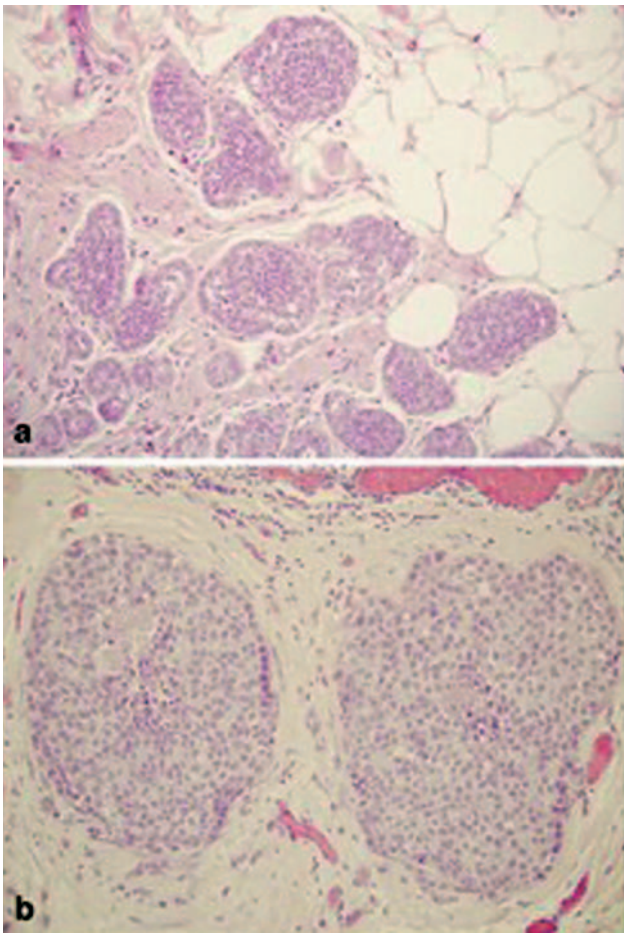

Figure 1. — Histological features of lobular intraepithelial neoplasia (LIN)
A) LIN 2: a microscopic field showing a proliferation of uniform cells which fill and distend the acini; residual lumens are still focally identifiable. B) LIN 3: a higher degree of acinar distension is easily appreciable, while neoplastic cells are significantly larger and pleomorphic; focal central necrosis is also identifiable. (Hematoxylin & Eosin, magnification x200).

Discussion

Understanding the biological evolution of LCIS and lobular neoplasia (LN) is the key to determine the most appropriate management. Although Foote and Stewart [9] have recognized a spectrum of LN, they thought that even the lightest of this process could constitute an "extreme hazard". On the contrary, Haagensen *et al.* [10] have suggested, based on data of long period follow-up, that the LCIS was an increased risk factor for cancer in both breasts, and then required close monitoring. They also proposed that similar lesions were called "lobular neoplasia (LN)" rather than carcinoma in situ. To date, this term has been accepted by WHO beside the classical distinction LCIS / atypical lobular hyperplasia (ALH) [11]. The argument that LN is a risk factor and not a true precursor of invasive disease is based on important observations [11]:

– Low risk of development of invasive cancer;
– The development of the disease in both breasts with relatively equal frequency;
– Invasive cancer after the lobular tumor is ductal or lobular with equal probability.

However, molecular studies have shown that the genetic profiles of LCIS and synchronous invasive lobular carcinoma are often similar to each other [12-14]. Therefore are there forms at higher risk of invasive transformation, which

could be considered precursor of cancer? The tumor exhibits a spectrum of lobular acinar involvement that can be divided into LCIS and ALH. The criteria for the diagnosis of LCIS include nuclear, cytological, and architectural characteristics [15] and a variability has been established in the relative risk for subsequent development of cancer between ALH (relative risk 5.5) and LCIS (relative risk between 8 and 10) [16-20]. Furthermore, a subtype of pleomorphic lobular neoplasia (pleomorphic lobular carcinoma in situ - PLCIS) is widely recognized [21-22]. The PLCIS cells may show apocrine differentiation, necrosis, and microcalcifications mimicking high-grade ductal carcinoma in situ (DCIS). The division of lobular neoplasia in three subclasses of LIN (lobular intraepithelial neoplasia) [11, 23] has been also introduced: the frequency associated with invasive carcinomas (ductal and lobular) would increase from 14% in LIN 1 to 23% for LIN 3. Figure 1 shows histological features of LIN.

In addressing the management of diagnosis of LCIS, given the recent achievements in human pathology, it is desirable to know ab initio the subtype of LCIS, for different invasive potential of non-classical forms. Actually, in the present study the authors found just one case of LIN III, and it was associated with an infiltrating lobular carcinoma.

In contrast to ductal lesions, lobular neoplasia usually has no clinical or mammographic signs. It is usually an incidental finding in a biopsy specimen which is performed for other reasons [4,5]. In the present series, approximately 82% of women were negative at physical examination, and the remaining percentage had no relevant clinical findings and were not absolutely correlated with the presence of LCIS (i.e., fibroadenoma). Equally nonspecific mammographic findings: the LCIS was contained in regular, irregular or stellate nodular lesions, or simply in areas of architectural distortion associated with calcifications. However the data shows the prevalence of calcifications associated with LCIS (70%). This association between LCIS (or more generally, lobular neoplasia) and calcification is an important key in the management of lobular neoplasia at core biopsy. The calcifications are associated with lobular neoplasia between 8% and 53% of core biopsies containing classical lobular neoplasia [24], therefore the percentage is placed above the upper limit. This discrepancy could be due to the lack of separation between pleomorphic and classical forms, the first presenting calcifications more frequently than the latter. Malignancy can be an incidental finding in a biopsy for calcifications associated only with benign disease [24-25]. Two forms of calcifications are, however, recognized in association with LCIS [11]: pleomorphic necrotic LCIS calcifications are associated with necrotic debris and resemble the calcifications of high-grade DCIS comedocarcinoma. The classic form, not necrotic, of LCIS is associated with calcifications that are similar in appearance to those of benign proliferative changes. However, the majority of these proliferative lesions does not appear as a mass and neither contains microcalcifications [11]. The ultrasound examination performed to complement mammography was negative in a high percentage of cases (78.46 %), revealing a method without a good sensitivity for the diagnosis of LCIS. The ultrasound appearance of lesions, in addition, has presented a wide variability, and this translates into a low specificity.

Women diagnosed with LCIS should undergo annual bilateral mammography; in women with dense breast an additional ultrasound should be considered [26]. Further studies are recommended to determine whether women diagnosed with LCIS should or should not undergo MRI for intensified surveillance, as has been recommended in women with increased genetic risk [11, 25].

In the present series, approximately 70% of patients underwent excisional surgical biopsy. When diagnosed at surgical biopsy, generally the LCIS does not require further investigation, even if present at the surgical margin [11], except for LIN III subtypes. Some studies [27-28] recommend surgical excision to exclude lesions that require immediate therapy. Some authors [27] have suggested that surgical excision may not be necessary when focal lobular neoplasia is diagnosed at core biopsy.

In the present series, the indication for mastectomy was greatly variable. The authors considered treatments done in a wide range of time, from 1996 to 2012, and surgical approach changed towards a more conservative surgery. Probably, patients who underwent mastectomy, nowadays, would have undergone just a quadrantectomy. Sometimes, mastectomy was a patient's choice. The authors biopsied all suspicious areas in the breast.

A diffuse lobular neoplasia may indicate an associated invasive carcinoma and should lead to excision [27-28]. The present series confirms this finding: in four cases, following an excisional biopsy, a multifocal LCIS was found and the extension has suggested to extend the excision with quadrantectomy. In one case out of four, the pathological examination revealed the presence of an infiltrating lobular carcinoma in a context of multifocal LCIS.

The surgical aspect of the problem justifies the radiodiagnostic aspect; cases where more aggressive surgical treatment is indicated should be carefully selected, while the majority of patients diagnosed with LCIS will be allocated to radiodiagnostic follow-up, keeping in mind that it is useless the excision of a classic LCIS (not pleomorphic/ not necrotic) incidentally found in a breast, when it is probable that there are other LCIS in the same breast and in the contralateral breast, given the high rate of multicentricity and bilaterality of LCIS.

Radiation therapy and chemoprevention have been considered as treatment choices for management of LCIS. Nonetheless, there is not enough literature addressing the benefits of radiation therapy, while chemoprevention is

thought to significantly reduce the percentage of progression towards invasive forms [11].

Bilateral mastectomy is to be considered an overtreatment in most cases (no genetic predisposition), as the LCIS very frequently does not evolve. Fisher *et al.* [28], in a follow-up of 12 years of patients diagnosed with LCIS, treated with local excision alone, showed the progression to invasive lesions in 5% of cases for the ipsilateral breast at first diagnosis of LCIS, and in 5.6% for the contralateral breast. Ansquer *et al.* [29] indicated a risk of 4.2% for the ipsilateral breast and 3.5% for the contralateral breast, but stressed the wide variability between studies. The present case series indicated that invasive carcinoma developed at a rate of just below 4% (two cases).

According to the literature, the authors believe that excision appears mandatory when:

- There is discordance between pathological changes at biopsy and clinical or radiographic findings, and this factor could be the cause of progression according to many studies, like those of Menon *et al.* [24] and Nagi *et al.* [30]. The findings are considered discordant when: 1) the radiological finding was a mass but pathologic diagnosis at core biopsy was lobular neoplasia or 2) X-ray shows suspicious calcifications that were not represented in the sample of core biopsy;
- Lobular neoplasia is associated with another lesion generally to excise in the core (for example, atypical ductal hyperplasia, ADH);
- There is a lobular neoplasia with atypical features (such as pleomorphic LCIS).

Hwang *et al.* [27] reported that, after excluding cases in which evolution was associated with non-classical morphology, association with invasive carcinoma was present in only 1%.

In opposite to the present results, Destounis *et al.* [31] concluded that the diagnosis of LCIS at needle core biopsy revealed that 84% of lesions either were malignant or were atypical or high risk surgery, of which 33% were found to be carcinoma; they suggested that LCIS should be excised when noted at core biopsy.

In conclusion, LCIS is certainly an important risk factor for developing invasive cancer, even after many years of diagnosis. When this finding is revealed at biopsy, the histological type should be necessarily clarified, to perform surgical excision of the area in which one type is present that is at increased risk of association with invasive carcinoma (LIN 3), or when there is a discrepancy between the report of pathological and diagnostic suspicion generated from imaging techniques. When a LCIS form is found which does not respond to these two previous conditions, if LCIS is present at the margin of surgical specimen excised, the literature does not counsel to perform additional diagnostic samples. In any case, women with this lesion should undergo a close follow-up, in order to identify as early as possible, the presence of an infiltrating carcinoma.

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