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Introduction

Lobular carcinoma in situ (LCIS), classical variant (C-LCIS), is considered a non-obligate precursor of invasive carcinoma[1]. The risk of developing an invasive carcinoma in patients affected by C-LCIS varies from 8 to 10 times relative risk compared to the general population[2]. When C-LCIS is present in pre-operative biopsies, the risk of upgrading to invasive carcinoma varies from 8 to 40%, greatly dependent on the related mammographic findings. These data suggest that surgical excision of C-LCIS may be necessary only if mammographically detected anomalies are not completely removed during the pre-operative procedures. In addition to C-LCIS, LCIS may present in variant forms, as Florid LCIS (F-LCIS) and Pleomorphic LCIS (P-LCIS), each characterized by enlarged and usually aggregated terminal ductular units (TDLUs), filled and distended with neoplastic cells. Necrosis and microcalcifications are often present. F-LCIS and P-LCIS are composed of different types of cells. In P-LCIS, neoplastic cells are larger than those of C-LCIS, show marked nuclear atypia, and bi- or multinucleated cells are a frequent finding. P-LCIS should be differentiated from high grade ductal in situ carcinoma (DCIS). E-Cadherin is markedly reduced or absent in P-LCIS and assists the differential diagnosis.

F-LCIS and P-LCIS are relatively rare and current knowledge of their biological potential is based on relatively small series. Data published to present, indicate that these LCIS variants have a close relationship with invasive carcinoma. Nevertheless, due to the scarcity of available data, the AJCC staging manual 8th Edition, does not categorise F-LCIS and P-LCIS as in situ carcinoma. Since the introduction of the AJCC cancer staging manual 8th Edition, several papers have been published focusing on the relation between F-LCIS and P-LCIS with invasive carcinoma, all producing data supporting the concept that these variants are high risk lesions.

At the present time, the management of screen detected F-LCIS and P-LCIS remains controversial.

The purpose of this study is to evaluate pre-operative biopsy accuracy and cancer underestimation in a large multi-institutional series of F- and P- LCIS diagnosed on pre-operative biopsy. Data were retrieved in order to evaluate the association between F-LCIS / P-LCIS and invasive carcinoma and to evaluate the need for surgery following the diagnosis of F-LCIS or P-LCIS on pre-operative biopsy. A literature review is also presented.

Materials and methods.

Cases were retrospectively retrieved from 15 European breast units, all involved in breast screening programs. Most of the participants are part of the European Working Group on Breast Screening Pathology (EWGBSP, http://www.ewgbsp.org/). The Ferrara, Imola and Pisa centres are not part of the EWGBSP, but share with the Bologna centre the same diagnostic protocols.

All the participants agreed on the following definitions of F-LCIS and P-LCIS, established according to previously established criteria[3,4,5]. Specifically, F-LCIS and P-LCIS presented enlarged TDLUs, filled with neoplastic cells. In all the cases, necrosis was present. F-LCIS was diagnosed when the neoplastic cells showed moderate atypia, similar to LCIS classic type. P-LCIS was diagnosed when the neoplastic cells showed marked atypia, similar to that observed in high grade DCIS. In addition,

in P-LCIS, bi- or multinucleated neoplastic cells were present. All the cases showed lack or marked reduction of E-cadherin immunostaining.

Cases were enrolled in the study when the following criteria were fulfilled: A) F-LCIS and P-LCIS presented with screen detected alterations (most often microcalcifications, distortions, dense areas). B) Diagnosis was performed on needle core biopsy or vacuum assisted biopsy. C) Pre-operative diagnosis was followed by open surgical resection and information on post-surgical histology was available.

In each case, the following parameters were collected: mammographic findings, relation with invasive carcinoma or high nuclear grade DCIS in the pre-operative biopsy and / or post-operative specimen. When invasive carcinoma was present, the histological type, TNM parameters and hormonal profile were recorded.

Pre-operative biopsy underestimation of cancer was defined as an invasive carcinoma or DCIS in the excision specimen that was not present on pre-operative biopsy according to Elsheikh and Silverman[6].

Pre-operative biopsy accuracy was defined as the ratio between the number of cancers (DCIS and or invasive carcinoma) detected on pre-operative biopsy and the total number of cancers.

Literature review

A search on PubMed was performed applying the following key words: F-LCIS, P-LCIS, LCIS with necrosis, LCIS with calcifications. Papers were retained for the present review when they reported F-LCIS and or P-LCIS diagnosed on pre-operative biopsies followed by surgical excision. Several studies included rare cases of F-LCIS and P-LCIS in large series of C-LCIS, therefore only data regarding the F-LCIS and P-LCIS cases were considered.

Statistical analyses:

All available variables were first compared between the two groups defined as pure F/P-LCIS on pre-operative biopsies and F/P-LCIS with invasive carcinoma on pre-operative biopsies.

The comparisons were made using the Chi-squared test or Fisher exact test for categorical variables and with t-test for the continuous variable Age. A significance level α equal to 0.05 was considered and the p-value reported only if this value was below this predefined level α.

Pre-operative biopsy variables were analysed using logistic regression model only considering pure F/P LCIS in biopsy. The outcome variable is represented by the pathological upgrade. As independent variable, we considered: microcalcification extent, biopsy site (quadrant) and age. Quadrants were classified in two ways: one quadrant versus two or more and external versus retroareolar or none of these two characteristics.

Ethical considerations:

The present retrospective study did not modify the patients' treatment and was conducted anonymously. The study protocol was approved by the Bologna Ethical Committee (protocol n.).

Results

A total of 117 cases were retrieved, all affecting adult female patients, aged from 31 to 83 (average 56,7). Invasive carcinoma and/or DCIS was detected in 78/117 cases.

Cases were subdivided as follows:

Group A: pure F/P-LCIS on pre-operative biopsies (n=70). Pathological upgrade in post-surgical specimens was observed in 31/70 cases presenting as pure F/P-LCIS, comprising 28 invasive carcinomas and 3 DCIS. One case of P-LCIS that remained 'pure' after open surgery, showed positive margins. At the time of surgery, no specific guidelines were available and a wait and see policy was adopted. The patient developed ILC with axillary metastasis two years after initial presentation. Therefore, it was included in the present group, among the cases with pathological upgrade.

Group B: F/P-LCIS with invasive carcinoma on pre-operative biopsies (n=47).

Table 1 summarizes and compares the clinical and pathological features of the two groups.

<u>Pre-operative biopsy accuracy</u>, defined as the ratio between the number of cancers (DCIS and/ or invasive carcinoma) detected on pre-operative biopsy and the total number of cancers, was 47/78 (60.3%).

<u>Pre-operative biopsy underestimation of cancer,</u> considered as missing an invasive carcinoma or DCIS on pre-operative biopsy (as defined by Elsheikh and Silverman[6]), was 31/70 (44.3%).

P-LCIS was frequently diagnosed in both groups, with a slight prevalence in Group B, associated with invasive carcinoma in pre-operative biopsy.

Invasive carcinoma histotype was similar in the two groups, with invasive lobular carcinoma being the most frequently diagnosed type. Most of the cases were grade 2 and 3 according to the current guidelines [7].

Cases presenting invasive carcinoma in pre-operative biopsies, showed a higher pT category. pT2/pT3 cases were 2/28 (7,1%) and 19/41 (46,3%) respectively in Group A and Group B. Similarly, lymphovascular invasion (LVI) and perineural invasion (PNI) were more common in Group B. Axillary lymph node metastases were similar in the two groups (57,1% and 45,5% in Group A and B, respectively). In both groups, most of the invasive carcinomas were positive for ER and PR; HER2 amplification was slightly more frequent in invasive carcinomas associated with Group B.

Data on mammographic presentation were available in 85 cases. Both groups presented most frequently with microcalcifications (Group A: 87,1% and Group B: 66,7%).

Microcalcifications linear extent was available in 49 cases for the Group A and in 16 cases for Group B. Microcalcifications linear extent ranged from less than 1 mm to 110 mm. Most cases in both groups showed a limited microcalcification extent (Table 2), being less than 10 mm in 45% of the cases. At multivariate analysis (table 2), microcalcification extent was the only parameter related with the risk of pathological upgrade in post-operative specimens. Specifically, as seen in table 3, all the cases presenting microcalcification linear extent higher than 20mm, had invasive carcinoma on post-operative specimens.

Differences between P-LCIS and F-LCIS (table 4).

No differences between P-LCIS and F-LCIS were noted with regard to age and type of presentation. Both conditions affected adults female patients, within the same age range and presented mainly with microcalcifications.

In Group A (pure F- or P-LCIS on pre-operative biopsy) pathological upgrade was observed in 50% of P-LCIS and in 37.5% of F-LCIS cases. Of 28 invasive carcinomas detected on excision, 18 were associated with P-LCIS and 10 with F-LCIS. In Group B, P-LCIS showed a slightly higher incidence of associated invasive carcinomas on pre-operative biopsy (43.3% versus 36%) than F-LCIS.

Histotype and grading of the associated invasive carcinoma, did not differ between P-LCIS and F-LCIS, as most of the tumours were invasive lobular carcinoma, grade 2/3. Similarly, the pT categories were similar in the two groups, with pT2/pT3 cases constituting 28.9% (13/45) and 33.3% (8/24) of the invasive carcinomas associated with P-LCIS and F-LCIS, respectively. Invasive carcinoma associated with P-LCIS showed more frequent LVI (27.9% vs 8.7%) and PNI (18.6% vs 14.3%) compared with F-LCIS. In addition axillary node involvement was more frequent in upgraded P-LCIS group (45.5% vs 30.8% in F-LCIS).

Hormone receptor profile was similar in the two groups; while HER2 amplified cases were all associated with P-LCIS.

Literature review (tables 5 and 6).

Nineteen papers met the inclusion criteria; from each paper cases presenting features of F/P LCIS only and having data on pre-operative biopsy and post-surgical resection were retained for review.

In total, 418 cases were considered. Invasive carcinoma and/or DCIS was present in 181 cases on pre-operative biopsy and in 93 (of the remaining237 cases) was detected on post-surgical specimens (75 invasive carcinomas and 21 high grade DCIS).

Therefore, pre-operative biopsy accuracy was 43.4% (181/418) while pre-operative biopsy underestimation of cancer was 39.2% (93/237).

Type and grade of invasive carcinomas were consistent with those found in the present series, being composed mainly of invasive lobular carcinoma, grade 2/3.

Discussion:

F-LCIS and P-LCIS are rare variants of LCIS, the biological nature and significance of which is still debated.

The present multi-institutional series, based on 117 cases, is, at present, the largest series reported, focusing on the pre-operative management of F-LCIS and P-LCIS.

Due to the disputed malignant potential of F-LCIS and P-LCIS (AJCC 2018), the present study examined the association with carcinoma at the time of diagnosis (pre-operative or operative).

In the present series, invasive carcinoma was present at the time of diagnosis in 78/117 cases (66.6%).

Nevertheless, pre-operative biopsy accuracy, defined as the ratio between the number of cancers (DCIS and/ or invasive carcinoma), detected on pre-operative biopsy, and the total number of cancers was 47/78 (60.3%). Pre-operative biopsy accuracy was slightly better in the literature review, where it reached 76.3%.

Pre-operative biopsy underestimation of cancer, considered as missing an invasive carcinoma or DCIS (as defined by Elsheikh and Silverman[6]), was 44.3%. Pre-operative biopsy underestimation of cancer was slightly lower in the literature, where it was limited to 39.2%.

In spite of minor differences, which are most likely related to the limited number of cases reported and to the difficulty in having uniform diagnostic criteria, all the data collected indicate that preoperative biopsy is associated with a high risk of underestimation of carcinoma in F-LCIS and P-LCIS presenting through mammographic screening programs.

In the present series, clinical data were analysed in order to identify features that may be predictive of a higher risk of associated invasive carcinoma following a diagnosis of pure F-LCIS and P-LCIS on pre-operative biopsy.

Microcalcifications linear extent and the histotype P-LCIS were associated with a higher risk of pathological upgrade to carcinoma (DCIS or invasive carcinoma) on surgical excision. Microcalcifications linear extent greater than 20 mm was always associated with the presence of invasive carcinoma in this series. Post-surgical pathological upgrade was higher for P-LCIS than for F-LCIS (50% vs 37.5%). Therefore, the risk of pathological upgrade is higher in P-LCIS and in cases with large areas of microcalcifications.

Nevertheless it should be noted that the risk of pathological upgrade is not negligible for limited microcalcifications linear extent and for F-LCIS. Carcinoma was present in 33.3% of cases showing microcalcifications linear extent less than 10 mm and pathological upgrade was observed in 37.5% of pure F-LCIS cases.

The risk of pathological upgrade observed for P-LCIS and F-LCIS here, is similar to that observed in cases of high nuclear grade DCIS[8].

The most frequent type of invasive carcinoma associated with F-LCIS and P-LCIS is invasive lobular carcinoma (ILC), both classical and pleomorphic variants. ILC is a diffusely infiltrative tumour,

which despite the increased sensitivity of modern radiological tools and advances in knowledge, may yield a false negative mammography in up to 30% of the cases[9].

Invasive lobular carcinoma may be associated with an aggressive clinical course if diagnosed at an advanced stage. It is usually hormone sensitive and prognosis is improved by early detection with survival rates of 90% for T1 and T2 tumours.[10] The pleomorphic variant of ILC (P-ILC) is a more aggressive histotype, with higher tendency to local and metastatic spread[11]. In the present series P-ILC was the second most common histotype detected and it was more frequently found in association with P-LCIS (10/12 cases of P-ILC).

The data presented here, together with those retrieved from the literature, indicate that F-LCIS and P-LCIS, when detected in pre-operative biopsies, must always be followed by open surgery.

Another question often faced during multidisciplinary evaluation of LCIS is the prognostic value of resection margin involvement. Currently available knowledge indicate that in cases of C-LCIS a wait and see policy is adequate even in cases with positive resection margins[12].

On the contrary, very limited data are available on the importance of resection margins involvement of L-LCIS and P-LCIS.

In the series published by De Brot et al[13], 4/7 patients with positive or close margins developed invasive carcinoma, on average, 54 months (range 46-67) after primary surgery. The present series did not include follow-up data collection. However, one patient, who had positive margins after open excision, developed invasive carcinoma with axillary metastases two years after primary surgery, suggesting that residual P-LCIS and F-LCIS may be associated with disease progression.

The genetic profile of LCIS has been studied in order to establish the possible relation with ILC. C-LCIS and ILC share the same genetic mutations and a clonal relation has been demonstrated[14,15], therefore supporting the concept that C-LCIS is a non-obligate precursor of ILC.

P-LCIS and F-LCIS share with C-LCIS the same genetic alterations, most commonly recurrent chromosome gains in 1q and losses at 16q[16,17].

P-LCIS and F-LCIS present a higher degree of genomic instability, a higher number of DNA copy number modifications and higher gene amplification. HER2 gene is more frequently amplified and p53 gene more frequently mutated in P-LCIS than in C-LCIS[5,15].

The molecular data on P-LCIS and F-LCIS indicate that these latter variants of LCIS constitute more advanced precursor lesions of invasive carcinoma than C-LCIS.

The pathological association between P-LCIS and F-LCIS found both in the present series and in the literature review strongly support the concept that these LCIS variants should be regarded as obligate precursor lesions of invasive carcinoma.

In conclusion:

Pre-operative biopsy accuracy in detecting carcinoma in cases of P-LCIS and F-LCIS varies from 66.6% to 76.3%, while the risk of underestimating the presence of cancer is quite high, varying from 39.2% to 44.3%.

Invasive carcinoma associated with P-LCIS and F-LCIS is usually ILC, both classical and P-ILC, an aggressive type of invasive carcinoma, often carrying a dismal prognosis.

In our opinion, no cases of F-LCIS or P-LCIS when diagnosed on pre-operative biopsy should be left untreated.

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