Pathologic Findings of Follow-up Surgical Excision for Lobular Neoplasia on Breast Core Biopsy Performed for Calcification

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Key Words: Lobular carcinoma in situ; Atypical lobular hyperplasia; Breast core biopsy; Calcifications; Upstaging

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Abstract

This study aimed to ascertain pathologic findings of surgical follow-up excision (FUE) on patients who had radiologic finding of calcifications and lobular neoplasia on core biopsy. Breast core biopsy specimens from 2006-2011 with a diagnosis of pure classic-type LN (lobular carcinoma in situ [LCIS] and atypical lobular hyperplasia [ALH]) with no history of invasive carcinoma (IC) or ductal carcinoma in situ (DCIS) were studied. Two hundred thirty-seven patients with the diagnosis of calcium on radiologic studies had FUE and were included in the study. Cases were divided into group 1 (pure ALH, n = 163) and group 2 (pure LCIS, n = 74). The interval between the core biopsy and FUE ranged from 0.2 to 7 months (mean, 1.5 ± 1.1 months). The risk of upstaging on FUE (DCIS or IC) is as follows: LCIS, 8.1% (6/74) and ALH, 3.1% (5/163). The data indicate that there is a low risk of upstaging to DCIS/IC from a core biopsy diagnosis of lobular neoplasia.

Lobular neoplasia (LN) both in the form of atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) is regarded as a definitive risk indicator for the development of invasive ductal or lobular carcinoma in both breasts. This association was first reported by Foote and Stewart1 in 1941, by demonstrating the coexistence of LCIS and invasive lobular carcinoma in 60% of their cases. Compared with the general population, the risk of breast cancer development is elevated up to 5-fold after a diagnosis of ALH and up to 10-fold after a diagnosis of LCIS.2-6 The term lobular neoplasia was introduced by Haagensen et al7 to discriminate it from ductal neoplasia, and they recommended a conservative approach in dealing with these lesions.

Currently, there are no well-established guidelines for the treatment of patients who receive a diagnosis of LN based on core-needle biopsy (CNB). Instead, the significance of these lesions on core biopsy is controversial, with relatively small samples described in existing literature. The most common treatment options are careful observation along with mammographic and clinical follow-up, and more recently, endocrine chemoprophylaxis for high-risk patients. The usefulness of surgical follow-up excision (FUE) is still debatable.8-14

Lobular neoplasia is typically asymptomatic and often lacks discriminating mammographic findings.15 Several imaging studies have found an association between microcalcifications and LN in significant numbers of cases.16-18 In addition to microcalcifications, LN may display radiographic findings of masses or architectural distortion.19,20

The goals of our study are to review a relatively large number of cases diagnosed as pure LN, without invasive...
Materials and Methods

This study was approved by the University of Pittsburgh School of Medicine institutional review board. A pathology database search at Magee-Women’s Hospital of the University of Pittsburgh Medical Center (UPMC) was performed for a study period of 66 months (January 2006 to July 2011). The biopsy specimens were received in separate formalin containers labeled “with calcification” and “without calcification” in most cases. Tissue cores were embedded in paraffin, sectioned, and leveled, and 5 slides were stained with H&E. Surgical excision specimens were fixed in 10% formalin, submitted entirely, and stained with H&E.

ALH was defined by uniform small cells filling and distending fewer than 50% of the terminal duct units of a lobule. The cells were discohesive and evenly spaced, with round nuclei and minimal pleomorphism. LCIS was diagnosed when the entire lobule was involved and more than 50% of the acini in the terminal duct units were distended. In this article, we use the term lobular neoplasia to include ALH and LCIS. Pathologic findings were divided into 2 groups: group 1 (pure ALH) and group 2 (pure LCIS with or without ALH).

A total of 807 cases of LN were identified out of 20,260 breast core biopsies (4%). Of these, 243 (30.1%) cases were excluded because of history or synchronous IC or DCIS, 96 (11.9%) because of radiologic diagnosis of mass or lesion other than calcifications, 123 (15.2%) because of the presence of ADH or flat epithelial atypia (FEA), and 7 (0.9%) because of the presence of pleomorphic component of LCIS. Those cases were excluded because the surgeon intended to excise the lesions. Among the remaining 338 cases of classic type LN, 237 (70.1%) had FUE. All cases had a screening mammogram with calcifications. The breast core biopsies were stereotactic, ultrasound, or magnetic resonance imaging–guided in 233 (98.3%), 3 (1.3%), and 1 (0.4%), respectively. Patients’ clinical information, history, biopsy, and excisional results were extracted from the pathology reports. The slides of both CNB and FUE for the cases upstaged to DCIS or IC were reviewed by 2 authors (C.Z. and M.M.D.).

At our institution, stereotactic and magnetic resonance imaging–guided biopsies are usually performed with 9-gauge vacuum-assisted needles with a 12-mm-long trough; ultrasound-guided biopsies are usually performed with 14-gauge non–vacuum-assisted needles. The radiographic Breast Imaging Reporting and Data System (BI-RADS) scores (from 1-6) were recorded from the imaging data files. Cases were considered to be upstaged if FUE showed IC or DCIS.

Statistical Analysis

Data were entered and analyzed using SPSS 16 (SPSS for Windows, SPSS, Chicago, IL); for qualitative data, frequency and percentages were used, and for quantitative data, range, median, mean, and standard deviation were used. χ², Fisher exact, and independent t test were used to test significance between groups, and the cutoff point to detect significance (P value) was less than or equal to .05.

Results

Table 1 illustrates the clinicopathologic and radiologic characteristics of LN cases with FUE biopsy that were included in the study. The mean and median ages of patients were 54 and 52 years, respectively (range, 28-79 years). The radiologic abnormalities reported for all cases and confirmed on biopsy showed calcium present mainly in fibrocystic changes, columnar cell changes, and benign breast ducts and stroma in most cases.

Upstaging of cases was not statistically significant between the 2 groups, with a higher frequency seen in the LCIS than in the ALH group (P = .102). No cases from the pure ALH cases were upstaged to ILC. Two cases of LCIS were upstaged to invasive lobular carcinoma (ILC) (2.7%). One (0.6%) of 163 ALH cases and 1 (1.4%) of 74 LCIS cases were upstaged to invasive ductal carcinoma, and 4 (2.5%) of 163 ALH cases and 3 (4.1%) of 74 LCIS cases were upstaged to DCIS. Collectively, 5 (3.1%) of 163 pure ALH cases and 6 (8.1%) of 74 pure LCIS cases were upstaged to DCIS with or without IC.
Cases upstaged to invasive carcinomas were (1) multifocal ILC, nuclear grade 2, largest focus measuring 1.3 cm, no lymphovascular invasion (LVI), with associated calcification in benign ducts and biopsy site changes; (2) small focus of ILC, 0.12 cm, Nottingham grade 1, no LVI, and biopsy site changes in 230 (99.1%) of 232 cases, with no significant difference rendered a BI-RADS score of 4. The BI-RADS score was 4 in 33 (20.2%) of 163 cases of pure ALH and 21 (28.4%) of 74 cases of FEA and FEA in the absence of ADH were identified in FUE.

The DCIS phenotypes were cribriform (5 cases) and solid (2 cases), and nuclear grades were grade 1 (4 cases), grade 2 (2 cases), and grade 3 (1 case). Comedonecrosis was focally present in the 2 cases (Table 3).

In cases upstaged to IC or DCIS specifically, specimens were obtained by 9-gauge Suros vacuum-assisted device (Suros Surgical Systems, Indianapolis, IN) (7 cases), 11-gauge vacuum-assisted core biopsy device (2 cases), 9-gauge Kopans needle (1 case) or 14-gauge biopsy device (1 case). The calcifications detected on mammography varied in description between clusters of pleomorphic to fine calcifications, some of which appear linear and uniform in shape with appearance of benign milk-of-calcium, and all calcifications were indeterminate (Table 3).

Interestingly, high-risk lesions, eg, ADH with or without FEA and FEA in the absence of ADH were identified in FUE in 33 (20.2%) of 163 cases of pure ALH and 21 (28.4%) of 74 cases of pure LCIS with core biopsy diagnoses.

No statistically significant difference was found in the BI-RADS score reported on core biopsy with upstaging of cases on FUE (P = .9). This may be because most cases were rendered a BI-RADS score of 4. The BI-RADS score was 4 in 230 (99.1%) of 232 cases, with no significant difference between the 2 groups or in relation to upstaging. The interval between the core biopsy and FUE ranges from 0.2 to 7 months (mean ± SD, 1.5 ± 1.1) (Table 1).

The mean age of the 11 patients upstaged to DCIS or IC was 56.8 years (8 [72.7%] of 11 patients >50 years) compared with 53.8 years in all other cases (n = 226) not upstage to DCIS or IC (156 [69.0%] of 226 patients ≥50 years).

### Discussion

ALH and LCIS are often multifocal and not uncommonly present in the contralateral breast. They have generally been considered to be risk factors for the development of bilateral breast carcinoma, with relative risk rates for ALH being 4 to 5 times and for LCIS up to 8 to 10 times those reported in the literature. This is in contrast to ADH and DCIS, which are considered by most as direct precursors to the development of malignancies.

Management of isolated lobular neoplasia found on core biopsy is a controversial topic. Many studies have examined the need for excision biopsy for LN diagnosed on breast core biopsy. The data in the literature reflect mixed recommendations, divided between reexcision or solid (2 cases), and nuclear grades were grade 1 (4 cases), grade 2 (2 cases), and grade 3 (1 case). Comedonecrosis was focally present in the 2 cases (Table 3).

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### Figure 1

A summary flow chart with the number and percentage of cases upstaged to DCIS with or without IC in relation to clinicopathologic and radiologic findings.
Representative cases diagnosed as lobular carcinoma in situ (A and C) or atypical lobular hyperplasia (E) on breast core biopsy with upstaging to infiltrating lobular carcinoma (B), tubular carcinoma (D) or cribriform ductal carcinoma in situ (F). Notice negative to weak positive membranous immunohistochemical stain for the dual E-cadherin/P120 with cytoplasmic expression of P120 (inset in A), negative to weak positive membranous immunohistochemical stain for E-cadherin (inset in C and E), and negative P63 myoepithelial marker around tubular carcinoma (inset in D). Arrows point to determinate calcifications associated with lobular carcinoma in situ.

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Table 3

Histopathologic Characteristics of Lobular Neoplasia Cases Upstaged to Invasive Carcinoma or DCIS on FUE Biopsy (n=11)

<table>
<thead>
<tr>
<th>Case No.</th>
<th>LN</th>
<th>Core Biopsy LN in Cores With and Without Calcium</th>
<th>Calcium Localization</th>
<th>Needle Gauge and Device</th>
<th>Calcium Description on Mammogram</th>
<th>Upstaging on FUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LCIS</td>
<td>In both cores</td>
<td>Outside LCIS</td>
<td>9-gauge Kopans needle</td>
<td>Indeterminate calcifications</td>
<td>ILC, multifocal, 1.3 cm, NG2 (6/9), no LVSI; ILC is close to biopsy site</td>
</tr>
<tr>
<td>2</td>
<td>LCIS</td>
<td>In first cores</td>
<td>In LCIS</td>
<td>14-gauge biopsy device</td>
<td>Three groups of indeterminate calcifications</td>
<td>ILC, 0.12 cm, NG1 (5/9), no LVSI; ILC is close to biopsy site</td>
</tr>
<tr>
<td>3</td>
<td>ALH</td>
<td>In both cores</td>
<td>Outside ALH</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Cluster of indeterminate calcifications</td>
<td>Tubular Ca, 0.3 cm, NG1 (4/9), no LVSI; Ca is close to biopsy site</td>
</tr>
<tr>
<td>4</td>
<td>LCIS</td>
<td>In both cores</td>
<td>In LCIS</td>
<td>11-gauge vacuum-assisted device</td>
<td>2 cm area of indeterminate calcifications</td>
<td>Tubular Ca, 2x1 cm, NG1 (3/9), no LVSI; Ca is close to biopsy site</td>
</tr>
<tr>
<td>5</td>
<td>ALH</td>
<td>In both cores</td>
<td>Outside ALH</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Tiny lonely pleomorphic microcalcifications</td>
<td>DCIS, 0.4 cm, NG2, solid with necrosis and calcifications; DCIS is close to biopsy site</td>
</tr>
<tr>
<td>6</td>
<td>ALH</td>
<td>In both cores</td>
<td>Outside ALH</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Fine calcifications of which appear linear</td>
<td>DCIS, 0.2 cm, NG2, cribriform; DCIS is close to biopsy site</td>
</tr>
<tr>
<td>7</td>
<td>ALH</td>
<td>In cores with calcium</td>
<td>Outside ALH</td>
<td>11-gauge vacuum-assisted device</td>
<td>Tiny mildly pleomorphic calcifications</td>
<td>DCIS, 0.4 cm, NG1, solid; DCIS is close to biopsy site</td>
</tr>
<tr>
<td>8</td>
<td>ALH</td>
<td>In both cores</td>
<td>Outside ALH</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Extensive calcifications in subareolar region</td>
<td>DCIS, 2 cm, NG3, cribriform, with comedo, and calcifications; DCIS is close and away from biopsy site</td>
</tr>
<tr>
<td>9</td>
<td>LCIS</td>
<td>LCIS: with ALH: w/o calcium</td>
<td>Outside LCIS</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Multiple clusters of indeterminate calcifications</td>
<td>DCIS, 0.2 cm, NG1, cribriform, with calcifications; DCIS is close to biopsy site</td>
</tr>
<tr>
<td>10</td>
<td>LCIS</td>
<td>In both cores</td>
<td>Outside LCIS</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Numerous calcifications relatively uniform in shape with some degree of pleomorphism</td>
<td>DCIS, 0.3 cm, NG1, cribriform; DCIS is close to biopsy site</td>
</tr>
<tr>
<td>11</td>
<td>LCIS</td>
<td>In both cores</td>
<td>Outside LCIS</td>
<td>9-gauge Suros vacuum-assisted device</td>
<td>Cluster of calcifications some of which had appearance of benign milk-of-calcium but others are nondescript</td>
<td>DCIS, 0.25 cm, NG1, cribriform; DCIS is close to biopsy site</td>
</tr>
</tbody>
</table>

ALH, atypical lobular hyperplasia; Ca, carcinoma; DCIS, ductal carcinoma in situ; FUE, follow-up excision; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; LN, lobular neoplasia; LVSI, lymphovascular space invasion; NG, Nottingham grade.

Table 4

High Risk Lesions in Cases of Lobular Neoplasia in Surgical FUE

<table>
<thead>
<tr>
<th>Grading of FUE</th>
<th>ALH (%) (n = 163)</th>
<th>LCIS (%) (n = 74)</th>
<th>Total (%) (n = 237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH ± FEA</td>
<td>31 (19)</td>
<td>16 (21.6)</td>
<td>47 (19.8)</td>
</tr>
<tr>
<td>FEA</td>
<td>2 (1.3)</td>
<td>5 (6.8)</td>
<td>7 (3.0)</td>
</tr>
<tr>
<td>Total (%)</td>
<td>33 (20.2)</td>
<td>21 (28.4)</td>
<td>54 (22.8)</td>
</tr>
</tbody>
</table>

ALH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; FEA, flat epithelial atypia; FUE, follow-up excision; LCIS, lobular carcinoma in situ.

Figure 1

Upstaging of lobular neoplasia on breast core biopsy to ductal carcinoma in situ or invasive carcinoma on follow-up excision biopsy according to clinicopathologic and epidemiologic data. ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ.

Figure 11

Upstaging of lobular neoplasia on breast core biopsy to ductal carcinoma in situ or invasive carcinoma on follow-up excision biopsy according to clinicopathologic and epidemiologic data. ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ.

Additional drawbacks of these studies are the small number of cases studied and the lack of complete FUE in every case. Another drawback in the studies, including the current study, is that all studies are retrospective, which may suffer from selection bias by including those patients who underwent excision. However, 237 (70.1%) of 338 of our study patients had FUE, which minimizes selection bias. Another flaw in most of the studies, including the current study, is the lack of identification of the nature of the calcifications found on core biopsy. In most cases, it is likely that the calcifications on core biopsy were not “determinate” for LN—rather they were more likely to be associated with benign tissue elements.

To our knowledge, this is the largest retrospective study of the outcomes of follow-up surgical excision of LN found on breast core biopsy. The risk for DCIS and IC on FUE was 4.6%. The overall risk may be considered to be low to moderate and stratification of patients for excision should be considered on an individual basis. Age, for example, is a risk factor in upstaging with a higher rate of upstaging seen in women older than 50 years. Although the current study...
did not address whether calcifications on core biopsy were determinant for LN, further studies should address this issue to determine if complete removal of calcifications may obviate the need for FUE.

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