Evolving Concepts in the Management of Lobular Neoplasia

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Lobular neoplasia represents the spectrum of changes within the lobule, ranging from atypical lobular hyperplasia (ALH) to lobular carcinoma in situ (LCIS), and is associated with increased risk for developing subsequent invasive breast carcinoma (Figure 1). When LCIS was first described, it was assumed to be premalignant because it was found in association with invasive carcinoma and was therefore believed to be best managed with mastectomy. Subsequent data suggested that LCIS was an indolent lesion with low malignant potential, but one that conveyed bilaterally symmetric breast cancer risk for both invasive ductal and lobular cancers. This led most experts to conclude that LCIS is primarily a risk factor for breast cancer rather than a precursor to invasive cancer. The logical assumption, therefore, is that surgery is not indicated for LCIS.

Although the conclusion remains unchanged that LCIS generally does not warrant operative therapy, the question of its malignant potential has resurfaced. Experts wonder if a definable subset of LCIS cases has premalignant properties analogous to those for ductal carcinoma in situ (DCIS). LCIS could encompass a spectrum of biologic activity ranging from indolent to aggressive, as is the case with DCIS and invasive breast cancer. Aggressive subtypes of LCIS, if they exist, could confer an increased likelihood of developing into invasive lobular carcinoma (ILC), thereby warranting a different or more aggressive therapeutic approach than is currently used for LCIS in general. In particular, experts have suggested that pleomorphic LCIS may have more aggressive biologic behavior than classic LCIS, raising the question of whether some subsets of LCIS should be managed the same as low-grade DCIS.

The diagnostic management of lobular neoplasia is also evolving, particularly related to core needle and vacuum-assisted biopsy. Because ALH and LCIS have been considered benign lesions not warranting surgical therapy, observation alone was recommended when core

Abstract
Lobular neoplasia broadly defines the spectrum of changes within the lobule, ranging from atypical lobular hyperplasia (ALH) to lobular carcinoma in situ (LCIS). This continuum of lesions is associated with an increased risk for developing subsequent invasive breast cancer, with the magnitude of that risk corresponding to the degree of proliferative change. The associated risk for developing invasive breast cancer after a diagnosis of lobular neoplasia is multicentric, bilateral, and equal in both breasts. Lobular neoplasia itself may transform into invasive carcinoma, although the frequency of this occurrence is unknown. Thus, lobular neoplasia is a risk factor for invasive breast cancer and may be a precursor lesion in unusual circumstances. The management of ALH and LCIS depends on the setting in which they are encountered. When ALH and LCIS are diagnosed after core needle breast biopsy, wire localization for surgical excision is required for definitive diagnosis because rates of histologic underestimation approach those of atypical ductal hyperplasia (ADH). When diagnosed on surgical biopsy, ALH and LCIS generally do not require further intervention, even when present at a surgical margin. However, bilateral breast cancer risk must be considered, especially when patients have a family history of breast cancer. In selected situations, bilateral prophylactic mastectomy with or without reconstruction may be considered when atypical hyperplasia or LCIS is diagnosed. Although this reduces risk for developing subsequent breast carcinoma by 90%, patients selected for prophylactic mastectomy represent a small subgroup of lobular neoplasia patients and generally have other risk factors, such as strong family history or evidence of genetic predisposition. (JNCCN 2006;4:511–522)
needle biopsy showed these findings. In contrast, when ADH is seen on needle sampling, surgical biopsy is recommended because a significant fraction of these patients are found to have DCIS or invasive carcinoma when surgical excision is performed after core needle biopsy. Recent data suggest that the same is true with lobular neoplasia, causing the National Comprehensive Cancer Network (NCCN) to change its recommendations to include these lesions with ADH among those that warrant surgical biopsy when initially diagnosed on core needle biopsy.

This overview 1) defines the historical background that led to the current understanding of lobular neoplasia biology; 2) delineates histopathologic features of the spectrum of lesions categorized as lobular neoplasia; 3) describes the clinical presentation and natural history of these lesions; 4) reviews the role for chemoprevention in management; 5) examines the role of surgical biopsy when lobular neoplasia is seen on needle sampling; and 6) discusses the role of surgical prophylaxis for LCIS in the small subgroup of patients in whom it may be appropriate.

Historical Background

Concepts have evolved regarding the underlying biologic behavior of LCIS (Table 1). In 1941, Foote and Stewart described LCIS as a noninvasive lesion arising from the lobules and terminal ducts. Assuming it had a premalignant behavior, they recommended mastectomy for treatment, even when no invasive cancer was present. In 1952, Godwin published a case report in which he formally suggested that LCIS evolves into ILC, cementing the earlier idea. The mastectomy was the dominant clinical treatment for LCIS over the next 3 decades.

In 1978, Haagensen et al. and Rosen et al. independently challenged this dominant belief that LCIS requires mastectomy. Haagensen et al. argued that LCIS, like ALH, is a fundamentally benign process. Among 211 patients with pure LCIS treated with excision alone, 10% were later diagnosed with another cancer in the same breast and 9% were diagnosed with a cancer in the opposite breast. Haagensen et al. coined the inclusive term lobular neoplasia to discourage surgeons from performing mastectomies in this setting. They reasoned that avoidance of mastectomy was appropriate because of the low incidence of subsequent breast cancer and that a unilateral mastectomy would not address the nearly equal hazard of contralateral breast cancer. In a 21-year
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The medical community gradually came to accept this conceptual model of lobular neoplasia, concomitantly recognizing that surgical treatment for the disorder is generally not required or indicated. By the 1990s, Haagensen et al.'s position that LCIS (or lobular neoplasia) is neither a malignant nor a premalignant lesion had become the dominant thinking.

Several professional groups continue to use the term LCIS and to distinguish it from ALH, rather than applying the all-encompassing lobular neoplasia term. The Surveillance, Epidemiologic, and End Results (SEER) Program, the National Surgical Adjuvant Breast and Bowel Program (NSABP), and the American Joint Committee on Cancer (AJCC) each continue to classify LCIS as a stage 0 noninvasive histopathologic entity in the same category as DCIS. Reluctance to redefine LCIS as a purely nonmalignant lesion is based on data suggesting that 1) LCIS is associated with greater risk for subsequent invasive cancer than is ALH and 2) LCIS may occasionally be a direct precursor of ILC in selected circumstances. However, this nomenclature question (risk factor vs. preinvasive malignancy) has not changed the recommendation that LCIS should generally not be treated with surgery. NCCN continues to discuss LCIS in the context of breast cancer treatment, although observation remains the preferred treatment (Figure 2).

**Histopathology**

In their original 1941 description, Foote and Stewart described LCIS as a proliferation of small, uniform, discohesive cells filling and often distending the acinar units within a lobule. This classic LCIS contains type A cells, which are small, are relatively uniform in size, have round to oval nuclei with scanty cytoplasm, lack prominent nucleoli, and frequently contain intracytoplasmic lumina. Some cases of LCIS contain type B cells that are cytologically reminiscent of intermediate- or high-grade DCIS, suggesting a potentially more aggressive cellular bioactivity. Whether these LCIS variants manifest different biologic behavior from classic LCIS is currently unclear. Type B cells are larger and more pleomorphic, have more cytoplasm, and frequently contain prominent nucleoli. Both types of LCIS can exhibit pagetoid spread in which the disease, beginning in the lobules, can extend up into the most peripheral microscopic ducts, splitting the ductal epithelial layer off from the surrounding...

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**Table 1** Historical Evolution of Concepts Regarding LCIS and Lobular Neoplasia

<table>
<thead>
<tr>
<th>Year</th>
<th>Investigator(s)</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>1865</td>
<td>Cornil</td>
<td>Described intraepithelial breast carcinoma in lobules</td>
</tr>
<tr>
<td>1919</td>
<td>Ewing</td>
<td>Published photomicrographs of LCIS</td>
</tr>
<tr>
<td>1931</td>
<td>Cheatle and Cutler</td>
<td>Challenged the concept that malignant-appearing cells confined to the lobules and ducts were merely precancerous</td>
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<tr>
<td>1941</td>
<td>Foote and Stewart</td>
<td>Coined term lobular carcinoma in situ</td>
</tr>
<tr>
<td>1940s</td>
<td>Broders</td>
<td>In situ carcinoma can exist within the duct or lobule and progressively infiltrate into the native glandular structure to form invasive malignancy</td>
</tr>
<tr>
<td>1950s</td>
<td>Haagensen et al.</td>
<td>LCIS generally seen together with invasive cancer, assumed to be premalignant hazard</td>
</tr>
<tr>
<td>1952</td>
<td>Godwin</td>
<td>Case report suggesting that LCIS evolves into ILC; mastectomy recommended as treatment</td>
</tr>
<tr>
<td>1978</td>
<td>Haagensen et al.</td>
<td>Defined lobular neoplasia (ALH and LCIS) as fundamentally benign</td>
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<tr>
<td>1980s</td>
<td>Lakhani et al.</td>
<td>LCIS seen as risk factor for, rather than precursor of, invasive cancer</td>
</tr>
<tr>
<td>1995</td>
<td>Berx et al.</td>
<td>Same chromosomal loss of heterozygosity seen in ILC and adjacent LCIS, suggesting that LCIS is likely to be a direct precursor of ILC</td>
</tr>
<tr>
<td>1996</td>
<td>Frost et al.</td>
<td>Describes pleomorphic LCIS</td>
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<tr>
<td>2000</td>
<td>Middleton et al.</td>
<td>Proposes relationship between pleomorphic LCIS and pleomorphic ILC</td>
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Abbreviations: ALH, atypical lobular hyperplasia; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ.
myoepithelial layer. LCIS with pagetoid spread can sometimes be challenging to distinguish from some forms of DCIS, particularly when the DCIS extends in an analogous fashion back into the lobules (so-called “cancerization of the lobules”). The cells of all types of LCIS can manifest different cytologic changes, including intracellular mucin, signet ring cell formation, clear cell change, and apocrine differentiation.

**Pleomorphic LCIS**

LCIS with the classic lobular pattern of growth but with more pleomorphic cytology has been described in many ways. Such lesions have been variably called pleomorphic LCIS or type B LCIS. In almost all of these, the cells in question grow in the pattern of classic LCIS with acinar distention, discohesiveness, and pagetoid extension along terminal ducts. However, in contrast with the monomorphic cells of classic LCIS, the cytology is more pleomorphic, the cells contain more cytoplasm, the nuclei are larger and more irregular, nucleoli can be prominent, and central necrosis is often identified. Although it is relatively rare in classic LCIS, Tavassoli noted that necrosis itself does not rule out that diagnosis. This histopathologic pattern is visually reminiscent of DCIS, but the loss of E-cadherin staining suggests that the lesion is lobular rather than ductal in origin.

Because the therapies for classic LCIS and DCIS differ significantly, experts must determine whether the prognosis of this large cell type of LCIS is more similar to classic LCIS or to DCIS. Some speculate that pleomorphic LCIS could have an increased likelihood of association with ILC and, in particular, the pleomorphic form of ILC. Several cytologic features of pleomorphic LCIS are more similar to those of DCIS and are vastly different from the small, uniform, round cells of classic LCIS. However, long-term follow-up data on pleomorphic LCIS have not yet been reported.

**Immunohistologic and Molecular Genetic Features of LCIS**

LCIS has consistently favorable tumor marker expression. In the NSABP B-17 trial, 182 women with LCIS were treated only with lumpectomy. All LCIS samples tested had favorable prognostic tumor markers, including estrogen receptor-positive, progesterone receptor-positive, Her-2/neu-negative, and flow cytometry showing universally diploid cells with normoproliferative DNA content.

E-cadherin is a transmembrane glycoprotein involved in calcium-dependent cell–cell adhesion whose expression has been shown to be lost in both LCIS and ILC of the breast but is not altered in DCIS or invasive ductal carcinoma (IDC). E-cadherin immunostaining is useful for distinguishing LCIS from DCIS in cases in which borderline histologic features are seen. As with classic LCIS, pleomorphic LCIS lacks E-cadherin membrane staining, despite the appearance of larger, more cytologically atypical cells akin to those seen in DCIS. Pleomorphic LCIS tends to have less-favorable tumor marker expression than classic LCIS, can be estrogen receptor- and progesterone receptor-negative, and can overexpress Her-2/neu.

Molecular evidence suggests that LCIS and ILC are related at a genetic level. Lishman and Lakhani studied loss of heterozygosity (LOH) among cases of LCIS with associated adjacent invasive carcinoma. LOH at chromosomal arms exhibiting imbalance at high frequency in invasive carcinoma can also be found with LCIS associated with invasive carcinoma, and also with pure LCIS. The investigators interpreted these data to confirm the neoplastic nature of LCIS. Suspecting that LCIS is a likely direct precursor of ILC, Vos et al. studied E-cadherin gene mutations in ILC, IDC, DCIS, and LCIS associated with ILC. Using mutation analysis, they showed the same truncating mutations and LOH of the wild-type E-cadherin in the LCIS component as in the adjacent ILC. These data not only indicate that these LCIS cells are
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markers of increased risk for breast cancer but also seem to confirm that they are direct precursors of ILC.

Clinical Presentation, Natural History, and Biologic Significance

Changing Incidence of Lobular Neoplasia
Although lobular neoplasia is a relatively uncommon diagnosis, its incidence has been increasing, especially among postmenopausal women. Overall, the age-adjusted, age-specific LCIS rates increased fourfold in the United States from 0.90 per 100,000 person-years in 1978 to 1980 to 3.19 per 100,000 person-years in 1996 to 1998, based on data from the Surveillance, Epidemiology, and End Results (SEER) Program. Among women 50 to 79 years of age, LCIS incidence rates increased continuously between 1978 and 1998. By 1998, women aged 50 to 59 had the highest incidence rate (11.47 per 100,000 person-years) and experienced the greatest absolute increase in incidence over the prior 20 years (9.48 per 100,000 person-years). This rising incidence was not observed in women 30 to 49 years old or in those older than 70. The increasing incidence of LCIS among postmenopausal women is not fully understood, but it may relate to increased use of combination hormone replacement therapy (estrogen + progestin) during this period.

Clinical Features of Lobular Neoplasia
Generally, LCIS and ALH are asymptomatic and clinically occult. Unlike invasive breast cancer, LCIS rarely (if ever) forms palpable masses. This is the primary reason that LCIS and ALH are most commonly diagnosed as incidental findings among women undergoing breast biopsy for another reason, such as a benign palpable mass or an indeterminate mammographic finding. Some evidence shows that a subset of LCIS is not completely incidental but is associated with mammographic calcifications, particularly with pleomorphic LCIS. However, this represents a small group of patients. Thus overall, a significant number of women with no indications for breast biopsy may have undiagnosed LCIS.

Multifocality, Multicentricity, and Bilaterality
Multifocality and multicentricity are often-confused but conceptually distinct terms. Multifocality refers to how disease is grossly distributed in the breast in multiple distinct regions or quadrants of the breast. LCIS exhibits both of these features and also bilaterality, although all of these features are not necessarily present in every case. The original publications by Foote and Stewart and Muir describe the multifocal nature of LCIS. These investigators observed that when patients underwent mastectomy after surgical biopsy showing LCIS, the mastectomy specimen commonly had residual disease in areas outside the biopsy cavity, tending to show a speckled, microscopic distribution in multiple lobules of a given breast region. In contrast, multicentricity with LCIS is more difficult to prove. Rosen et al. provided the most convincing data, observing LCIS in multiple quadrants of the breast in 24 of 50 (48%) mastectomy specimens.

Regarding the bilaterality of LCIS, Swain’s review of 15 studies shows bilaterality rates varying from 9% to 69%. Beute et al. reviewed mammography and pathology of 104 patients with LCIS identified from biopsies and mastectomy specimens. Among these patients, 82 underwent sampling of both breasts either through mirror-image biopsy or contralateral mastectomy. LCIS was found to be bilateral in half of these patients (41/82).

Natural History
Women diagnosed with LCIS are at increased risk for developing breast cancer in both the ipsilateral and contralateral breast. The absolute risk for ipsilateral breast cancer after LCIS is 17% at 15 years and the relative risk is 8.0 in the first 15 years of follow-up compared with the general population. Mathematic modeling suggests that during the first 15 years after biopsy, women with LCIS have 10.8 times the risk for breast cancer compared with women of comparable age without proliferative changes on breast biopsy. Definitive information regarding the types of breast cancers (invasive vs. non-invasive, ductal vs. lobular) that can be expected to develop after an LCIS diagnosis is difficult to provide because most series are relatively small and used different diagnostic tools and therapies from those used now. The reported incidence of invasive cancer in patients with LCIS has ranged from 2% to 38%. In reported series of patients diagnosed with LCIS through surgical biopsy and then followed up without further intervention, 2% to 20% of patients developed ipsilateral invasive cancer and 1% to 18% developed contralateral invasive cancer.
percentage of all subsequent carcinomas with lobular histology ranges from 0% to 100% depending on the series, but clusters between 20% and 60%.

In general, the risk for cancer in the ipsilateral and contralateral breasts is approximately equal (Table 2). These studies illustrate the primary reason that LCIS is not treated surgically: the only logical operation would be a bilateral mastectomy, which would be unnecessary approximately 80% of the time.

**Pleomorphic LCIS May Represent Biologically Aggressive Disease**

Pleomorphic LCIS and pleomorphic invasive lobular carcinoma (PLC) have received little attention in the past. These diagnoses are seldom made, partly because some cases are diagnosed as ductal because of the pleomorphic cytology. In 1991, Page et al. wrote about cancer risk implications among different patterns of the LCIS spectrum. In this study, 39 patients diagnosed with isolated LCIS underwent surgical biopsy but not mastectomy and were followed-up for an average of 19 years. The absolute risk for invasive cancer was 17% at 15 years. The histologic pattern of 10 invasive carcinomas developing in 9 patients was predominantly of the lobular type, with 3 pure and 4 variant types representing 70% of the developed carcinomas. Three women with invasive breast cancer died at an average interval of 5.3 years, and all had a histologic pattern of PLC. Although the investigators pointed out that this represents a much stronger association with the tubular and lobular types of invasive cancer than Haagensen et al. or Rosen et al., reported, they stated that, “The reason for this may be our selection of more completely developed examples of lobular neoplasia.”

PLC with associated LCIS portends a poorer outcome. In a 1992 report from Italy, Eusebi et al. described 10 cases of PLC, 6 of which included LCIS. Six of 10 patients died within 42 months of diagnosis and 3 patients developed recurrence or distant metastases at short intervals. The authors concluded that PLC is a highly lethal variant of invasive carcinoma. Also in 1992, Weidner and Semple in San Francisco compared the clinical course of 25 cases of classic ILC with 16 cases of PLC. Survival until recurrence was significantly worse in patients with PLC. Patients with positive nodes and pleomorphic histology were 30 times more likely to experience breast cancer recurrence than were patients with classic ILC histology. A more recent article by Bentz et al. in Utah evaluated 12 patients with PLC, 11 of whom underwent long-term clinical follow-up. Of the 12 cases, 7 had coexisting pleomorphic LCIS. Among the 11 cases, 9 developed fatal metastatic disease with a median survival of 2.1 years. Middleton et al., from the National Cancer Institute identified 38 cases of PLC. Pleomorphic LCIS was associated with PLC in 45% of cases. Of the 19 patients available for follow-up, 7 had no evidence of disease at last examination (range, 1–15 years), 3 were alive with disease (range, 2–14 years), and 9 patients were dead of disease (range, 2 months–9 years). Six patients had subsequent diagnoses of tumor in the contralateral breast. Analysis showed that PLC tends to appear in older postmenopausal women who present with locally advanced disease.

These findings suggest that PLC may be as aggressive as most forms of IDC, and that pleomorphic LCIS could be a harbinger for that aggressive underlying biology. This part of the spectrum of LCIS warrants different management from classic LCIS, although what that management should be is yet to be determined.

**Endocrine Chemoprevention for Lobular Neoplasia with Tamoxifen**

Tamoxifen is a selective estrogen receptor modulator with both agonist and antagonist properties. Initially approved by the Food and Drug Administration (FDA) in 1978 for treating metastatic breast cancer, tamoxifen has been widely studied in clinical trials and its safety and efficacy are well established. In addition to treating known hormone receptor-positive invasive breast cancers in the adjuvant and metastatic setting,
tamoxifen has also been shown to decrease the risk for contralateral breast cancer. For this reason, tamoxifen was initially chosen for breast cancer prevention trials. Of the 3 worldwide tamoxifen prevention trials published, only NSABP P-01 specifically evaluated participants with LCIS. The NSABP study is also the only study that shows a statistically significant benefit from tamoxifen in the prevention setting, although the patient populations enrolled in each trial have important differences.

The NSABP P-01 trial is a randomized, double-blind trial initiated in 1992 that enrolled 13,388 women at increased risk for breast cancer by virtue of an elevated Gail model score (≥ 1.66% 5-year risk for developing breast cancer), age older than 60 years, or a history of biopsy-proven LCIS or ADH. Participants in this trial were randomized to tamoxifen, 20 mg daily, versus a placebo for a planned duration of 5 years. Of the women with a history of LCIS, 411 were randomized to the placebo arm and 415 to the tamoxifen arm. The results showed that 18 cases of invasive breast cancer occurred in the placebo arm and 8 cases occurred in the tamoxifen arm. These numbers translated to a 56% (95% CI, 84%-6%) reduction in risk for invasive breast cancer among patients with LCIS who used tamoxifen.

Overall, this study reported a 49% risk reduction between the 2 arms for all women enrolled, and an 86% reduction for patients with atypical hyperplasia. Thus, tamoxifen's benefits were seen whether subjects had pre-existing LCIS or atypical hyperplasia. The absolute reduction in invasive breast cancer at 5 years for all participants was 1.3%. Also, this risk reduction was seen for the occurrence of estrogen receptor-positive tumors, but not for estrogen receptor-negative tumors. In addition, no difference in survival was observed or expected between the 2 arms, primarily because only short-term follow-up was conducted. Based on these results, the trial was terminated early at the recommendation of an independent monitoring committee. The FDA has now approved tamoxifen for breast cancer prevention.

The average annual rate of invasive breast cancer for patients with LCIS was 12.99 cases per 1000 women, compared with 5.69 cases per 1000 women among those with no history of LCIS. Although these data are based on a limited number of events, they are the only evidence in the literature that specifically addresses LCIS as a breast cancer risk factor.

Surgical Intervention for LCIS

Surgical Excisional Biopsy Showing LCIS
Because classic LCIS generally does not require surgical treatment, surgical biopsy showing LCIS should not demand further intervention. Like ADH, the implication is that surgical margins for LCIS are not clinically relevant. Therefore, surgical removal of more breast tissue simply because the excised tissue had LCIS at the edge is not necessary. A possible exception to this is in patients with pleomorphic LCIS, although the long-term follow-up data are not adequate to make definitive recommendations.

Surgical Excision of Core Needle Samples Showing Lobular Neoplasia

When ADH is seen on core needle biopsy, an excisional procedure is performed because a percentage of these needle-diagnosed cases will contain DCIS or even invasive cancer. Until recently, experts questioned whether the same principle applies to the management of ALH and LCIS.

Some investigators recommend routine surgical excision of all needle sampling showing LCIS. In the Cambridge and Huntingdon breast screening programs, 749 patients underwent core needle biopsy for mammographic abnormalities but only 7 were found to have isolated LCIS. All 7 patients subsequently underwent surgical excision, which showed 1 case of LCIS with ILC, 2 cases of LCIS with DCIS, and 1 case of a probable focus of IDC. LCIS was the only abnormality on both core needle and surgical biopsy in only 3 of 7 cases.

Other investigators have taken a more selective approach. Liberman et al. retrospectively reviewed the Memorial Sloan-Kettering experience of 1315 consecutive stereotactic biopsies, of which 16 were found to have LCIS on percutaneous core needle biopsies (1.2%). Of these, 14 lesions from 13 women were surgically excised. Five of the 14 stereotactic biopsies showed LCIS together with a high-risk lesion (radial scar in 3 and ADH in 2). Of these 5, 1 (20%) was found to have DCIS on subsequent surgical excision. In 4 of 14 lesions, LCIS in the percutaneous biopsy had histologic features overlapping with those of DCIS. Of these 4, 1 had DCIS and 1 had infiltrating lobular carcinoma on subsequent surgical excision. Based on these findings, the authors identified 3 scenarios in which LCIS on core needle biopsy should be considered for further surgical excision:
Breast Conservation in Patients Who Have LCIS Coincident with Invasive Cancer

In general, LCIS is not a contraindication for breast-conserving surgery. Most studies have not shown an increased risk for ipsilateral breast cancer recurrence after breast conservation for invasive breast cancer coincident with LCIS. However, a more recent study had different results, suggesting that patients with invasive breast cancer and coincident LCIS (IBC+LCIS) may be at markedly increased risk for ipsilateral breast tumor recurrence (IBTR). The 10-year cumulative incidence rate of IBTR was 6% in women without LCIS versus 29% in women with LCIS ($P = .0003$). Risk factors for IBTR included age younger than 50 years, small invasive tumor size (< 2 cm), negative lymph node status, and the absence of any adjuvant systemic treatment ($P < .001$). The authors did not recommend mastectomy for these patients. They noted that among women with IBC+LCIS who underwent treatment with tamoxifen, IBTR was markedly lower at only 8%. The authors recommend that treatment with tamoxifen be considered to decrease IBTR risk in these women when they elect to undergo breast conservation.

Does Surgical Prophylaxis with LCIS Have a Defined Role?

In general, LCIS is not a pathologic entity that warrants surgery. Although patients with LCIS have a...
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significantly higher risk for developing invasive breast cancer compared with the general population, most will not develop invasive disease within their lifetimes. For those who do get breast cancer, the relative risk seems to be similar for both breasts. Thus, the only logical operation would be a bilateral total mastectomy, and such a procedure seems excessive for the moderate risk associated with LCIS.

At a minimum, LCIS and ALH warrant careful follow-up studies with screening mammography and clinical breast examination every 6 to 12 months (Figure 4). The use of magnetic resonance breast imaging for intensive surveillance among women at high risk is being investigated and seems very promising. In a recent international study of 367 women at genetically high risk, Lehman et al. showed that screening magnetic resonance imaging (MRI) can detect mammographically and clinically occult breast cancers. On the basis of screening MRI findings, 22 of 367 women (6%) who had negative mammogram and negative clinical breast examinations underwent additional biopsy, leading to the diagnosis of 3 additional cancers. MRI also resulted in 19 (5%) false-positive outcomes, resulting in additional benign biopsies for these patients. No studies specific to LCIS are currently available that weigh the efficacy of MRI for showing radiographically occult cancers against the high false-positive rate of the study. Further investigations are underway.

Nonetheless, prophylactic mastectomy remains a reasonable option for a subset of women with LCIS. Bilateral prophylactic mastectomy (with or without reconstruction) confers an approximately 90% risk reduction for the development of subsequent cancer.

An LCIS diagnosis might contribute to the decision to use this procedure, for example, in a patient who is otherwise a reasonable candidate for prophylactic surgery, such as a woman from a high-risk family for whom genetic testing is noninformative who is then found to have LCIS. Because of the paucity of data on this topic and the huge personal impact that such a procedure will have on the patient’s life, any use of prophylactic surgery for breast cancer must be highly individualized and selected, and generalized recommendations are virtually impossible. Counseling for both medical and psychologic issues is mandatory, and the patient must have ample time (measured in months) to make an appropriate personal decision.

The proper treatment for higher-grade pleomorphic LCIS is currently unclear. This lesion has many cytologic characteristics that resemble DCIS, but it expresses the immunocytologic profile of LCIS as measured by E-cadherin immunostaining. Experts are unsure whether this lesion is best treated through observation as with classic LCIS or if surgical intervention should be highly considered as with DCIS. Pleomorphic ILC represents biologically aggressive high-grade disease. If pleomorphic LCIS specifically predisposes patients to the development of pleomorphic ILC, then the risk increases for leaving untreated pleomorphic LCIS in the breast. Treatment with tamoxifen with or without surgery could also be particularly protective for women diagnosed with pleomorphic LCIS. Unfortunately, current long-term follow-up data are not available on pleomorphic LCIS because the reported numbers of cases are relatively few. Only recently has this form of LCIS received significant attention in the literature. Further study and subset analyses are needed.

Pleomorphic LCIS can be handled with 1) no additional treatment, 2) breast-conserving surgery (such as DCIS), or 3) tamoxifen. If pleomorphic LCIS is extensive and present at surgical margins, the pathological finding is difficult to ignore, given the lesion’s cytologically aggressive pattern. Historically, many pathologists have simply labeled pleomorphic LCIS as DCIS because they believed it should be removed despite its lobular architecture. Although this approach may seem rational, it has confused the epidemiologic investigation and contributed to the therapeutic quandary that exists today. No data support the use of post-lumpectomy radiation for pleomorphic LCIS, so local management after complete excision is problematic. Furthermore, treating pleomorphic LCIS as a localized lesion such as DCIS does not address the bilateral risk for subsequent cancers associated with lobular neoplasia.

One evidence-based approach for pleomorphic LCIS management is the use of tamoxifen, which addresses both the bilateral breast cancer risk for LCIS
and the local risk for pleomorphic disease recurrence. As mentioned, the NSABP B-01 trial found a 56% reduction in the risk for invasive breast cancer in either breast (4.4% vs. 1.9%) among patients with LCIS who used tamoxifen. The NSABP B-24 trial, in which women treated for DCIS through lumpectomy and radiation were given either tamoxifen or a placebo, showed a 31% reduction in ipsilateral breast tumor events among those treated with tamoxifen (2.0% vs. 1.4% at 7 years, \( P = .02 \)).

Although subset analysis of patients with pleomorphic LCIS from these landmark trials is not possible, tamoxifen use in this setting seems well justified.

In our institution, we consider patients with pleomorphic LCIS individually, evaluating the size and extent of the lesion, degree of pleomorphism, and margin involvement. Other risk factors, especially family history, are weighed. Breast MRI is generally recommended to evaluate clinically and radiographically occult disease after patients are advised about the associated significant false-positive rate. Patients are presented with the limited data on management of this unique lesion and are strongly encouraged to consider tamoxifen. We then carefully follow-up to monitor for evidence of subsequent disease.

References
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