Recommendations for Women With Lobular Carcinoma In Situ (LCIS)

By Bridget A. Oppong, MD and Tari A. King, MD

This article will review current management trends for women with classical lobular carcinoma in situ (LCIS).

Introduction

Atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) represent a spectrum of breast disease referred to as "lobular neoplasia" (LN). Although LN occurs relatively infrequently, it is associated with an increased risk of breast cancer, ranging from a three- to four-fold increased risk with ALH up to an eight- to ten-fold increased risk with LCIS.[1-3]

What we now refer to as LCIS was first described by James Ewing in 1919 as a noninvasive proliferation of the lobules and terminal ducts of the breast. This lesion was not named, however, until 1941, when Foote and Stewart coined the term "lobular carcinoma in situ."[4] Initially regarded as a direct precursor to invasive lobular carcinoma, LCIS used to be treated by mastectomy. Subsequent studies demonstrating that the risk of invasive disease was conferred bilaterally and that subsequent cancers were of both the ductal and lobular phenotype led to the acceptance of LCIS as a marker of increased risk rather than a true precursor.

As additional histopathologic information on LCIS emerged in the 1970s, the proliferative changes within the breast lobule were recognized as a spectrum of changes including both atypical lobular hyperplasia (ALH) and LCIS, and efforts were made to reclassify these two lesions as LN.[2] This nomenclature was not universally adopted, however, and some authors continue to report on these two lesions independently, while others do not, resulting in some difficulty in making comparisons across series. More recently, advances in immunohistochemistry and molecular biology have led to an appreciation of greater diversity within the spectrum of LN, and there is considerable speculation that the pleomorphic variant of LCIS will prove to have a different clinical behavior than the "classical" LCIS subtype.[5] This article will review current management trends for women with classical LCIS.

Incidence

LCIS is typically an incidental finding in a breast biopsy performed for another reason. As such, the true incidence of LCIS in the population has been difficult to ascertain. Several approaches to determining the true incidence, including autopsy series, individual institution biopsy series, and population-based studies, have been undertaken. The results achieved with these various approaches have been somewhat different, yet they all suggest that LCIS is likely a rare lesion among women in the general population.[6] Two classic studies by Haagensen[7] and Page[8] reported LCIS in 3.7% and 0.5% of otherwise benign breast biopsies performed at their respective institutions. Other studies report LCIS in 0.8% to 3.8% of open surgical biopsies and in 0.02% to 3.30% of image-guided core needle biopsies.[9] Population-based data reported to Surveillance, Epidemiology, and End Results (SEER) from 1978 to 1998 demonstrate a much lower incidence—3.19 per 100,000 women[6]—yet during this time there was an observed four-fold increase in the number of LCIS cases reported among women over 40 years of age, with the highest...
incidence rate (11.47 per 100,000 person-years) occurring in 1998 among women aged 50 to 59 years. While this trend may reflect the increasing use of mammography and image-guided biopsies during this period, the impact of other factors, such as the increased use of combination hormone replacement therapy during this time, remains uncertain.

**Presentation and Diagnosis**

Historically, LCIS has been considered a clinically occult lesion not associated with changes on physical examination or mammographic imaging; when identified, it was frequently found to be multicentric and bilateral.[2,4,7] In the era of widespread screening mammography, more recent data suggest that LCIS is associated with calcifications in 21% to 67% of cases.[10] LCIS has also been reported to enhance on MRI,[11] although these data remain relatively limited. In their original description, Foote and Stewart described LCIS as a proliferation of small, uniform, discohesive cells that fill and often distend the acinar units within a lobule.[4] Criteria for diagnosis, later outlined by Page and Anderson, are as follows:

1. The characteristic and uniform cells must comprise the entire population of cells within the lobular unit.
2. All of the lobule must be filled with these cells (ie, no intercellular empty spaces between cells).
3. There must be distension and expansion of at least half of the acini in the lobular unit.[12]

A diagnosis of LCIS made by surgical excision does not require further surgical intervention, and there is no indication to document margin status in a specimen that contains only LN.[13] Similarly, the finding of LCIS in the surrounding breast parenchyma of a lumpectomy specimen containing DCIS or invasive carcinoma does not alter surgical management of the breast primary and does not increase the rate of in-breast recurrence in patients undergoing breast conservation.[14-16] The scenario that often results in controversy regarding management is that of LCIS diagnosed on core biopsy. The most recent National Comprehensive Cancer Network (NCCN) guidelines state that a core biopsy diagnosis of LCIS should always be followed by surgical excision to rule out an associated malignancy, with subsequent management decisions to be made based on the final pathologic diagnosis (Figure).[17]

**The Management of LCIS on Core Biopsy**

**TABLE**

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<th>Incidence of Breast Cancer After Excisional Biopsy for Lobular Carcinoma on Situ (LCIS) Found on Core Biopsy</th>
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While routine surgical excision following a core biopsy diagnosis of LCIS is employed by many clinicians, a review of the reported rates of upstaging to malignancy demonstrates a wide range of findings, making it difficult to define the true rate of cancer at excision (Table).[18-35] These series also demonstrate that not all patients with LCIS on core biopsy go on to excision, raising the possibility of an inherent selection bias for excision in certain cases, such as those with radiographic-pathologic discordance, thereby increasing the likelihood of finding an associated malignancy. In a pooled analysis of studies published from 1999 to 2008, Hussain et al identified 1229 reported cases of LN on core biopsy, of which only 789 (64%) underwent surgical excision. Among those who proceeded to excision, 241 cases (31%) were further classified as LCIS. Following surgical excision, 32% of LCIS cases were upstaged to either ductal carcinoma in situ (DCIS) or invasive cancer, compared with 19% and 29% of cases defined as either ALH (280 cases) and/or unspecified LN (246 cases), respectively.[9] Information about outcomes for patients not undergoing excision are rarely reported; however, for women who are not found to have an associated
malignancy at immediate surgical excision yet go on to develop breast cancer during surveillance, there is often little relation between the site of the original core biopsy and the subsequent cancer diagnosis.

At Memorial Sloan-Kettering Cancer Center (MSKCC), the breast surgical service adopted the practice of routine surgical excision for a core biopsy diagnosis of LN in early 2004. A recent retrospective review of pathology reports by Luedtke et al from June 2004 to May 2009 identified 80 patients (82 core biopsies) with LN as the only indication for surgical excision following core biopsy.[36] A single radiologist reviewed the pre-biopsy imaging studies for radiographic-pathologic correlation and excluded 11 patients, leaving 69 patients with 71 core biopsies for analysis. Among these, 29 (41%) were ALH and 42 (59%) were LCIS. Overall, 2 of 71 cases (3%) were upstaged to cancer after surgical excision: 1 patient was found to have a 2-mm focus of low-grade DCIS and the other a 2.3-mm tubular cancer. Both cases occurred in the ALH subgroup. While the retrospective nature of this report remains a limitation, and while it is possible that there were additional patients with LN who did not undergo surgical excision during this time period, the adoption of a standard policy makes it unlikely that a large number of cases were missed. In contrast to other series, these data—by eliminating cases with synchronous lesions, such as atypia requiring excision, as well as those with radiographic—pathologic discordance—suggest that the likelihood of upstaging to cancer following a core biopsy diagnosis of LCIS is actually quite low and that routine excision may not be warranted. Although we have not yet changed our practice and continue to recommend surgical excision following a core biopsy diagnosis of LCIS, efforts to document the rate of upstaging in a prospective manner are underway.[37]

Subsequent Cancer Risk

A diagnosis of LCIS is one of the greatest identifiable risk factors for the subsequent development of breast cancer. Compared to the general population, women with LCIS have an eight-fold to ten-fold increased risk of breast cancer.[8] In the series with the longest follow-up, the probability of developing carcinoma in situ or invasive cancer was 13% in the first 10 years after diagnosis, 26% after 20 years, and 35% by 35 years, or roughly 1% per year.[38] When counseling women about their risk, it is important to stress that the risk remains steady over their lifetime, and that the absolute risk of breast cancer for a given individual is therefore impacted by her age at LCIS diagnosis. Still, most women with LCIS will not develop breast cancer.

Parallel to the increasing incidence of LCIS, recent studies have also reported that the incidence of invasive lobular carcinoma increased from the late 1980s to the mid-1990s among women 50 years of age and older.[39] Recent studies have also highlighted the high proportion of infiltrating lobular carcinomas that occur following a diagnosis of LCIS.[40] These observations, combined with emerging laboratory evidence, have generated renewed interest in the biology of LCIS and have reopened the debate over its clinical significance as a "risk factor or precursor lesion." The presence of shared molecular alterations in LCIS and co-existing invasive lobular carcinoma[41-43] have led some investigators to suggest that LN is a nonobligate precursor of low-grade invasive breast cancer.[44] Increasingly, these observations are resulting in confusion regarding the proper management of LCIS, highlighting the need for an improved understanding of the risk imparted by this lesion.

Surveillance

Surveillance is the minimum necessary action for women in whom LCIS is diagnosed. Recommendations from the NCCN Breast Cancer Screening and Diagnosis Clinical Practice Guidelines include annual mammography and clinical breast exam every 6 to 12 months.[45] Although the lifetime risk for an individual woman with LCIS may exceed 20% (depending on age at diagnosis), the American Cancer Society guidelines for MRI screening do not support routine use of MRI in this setting, stating that there is not enough evidence to recommend for or against MRI screening in women at increased risk from LCIS.[46] The increased sensitivity of MRI in women at high risk because of an inherited predisposition or strong family history of breast cancer may be related to the biology of the particular breast cancers that develop in those settings, whereas it is unknown whether MRI screening significantly increases the cancer identification rate in women at increased risk because of LCIS.

Port et al performed a retrospective review of women with atypia and/or LCIS who participated in the MSKCC high-risk screening program from 1999 to 2005. A total of 378 women, including 126 with atypical hyperplasia (either ductal or lobular) and 252 women with LCIS were identified. All patients
were offered yearly mammography and twice-yearly clinical breast examination, and during the study period, MRI screening was performed in 182 patients (48%) at the discretion of the physician and patient.[47] Patients who had MRI screening were younger ($P < .001$) and more likely to have one or more first-degree relatives with breast cancer ($P = .02$). While the frequency of MRI screening varied, a total of 478 screening MRIs were performed, and 55 biopsies were recommended in 46 of the 182 patients (25%) during the study period; 46 of the 55 biopsies (84%) were recommended based on MRI findings alone. Cancer was detected in 6 out of 46 MRI-generated biopsies (13%), which represented 5 out of 182 patients (3%) and 5 out of 478 MRIs (1% of all MRIs performed). All 6 cancers were mammographically occult and were detected in patients with LCIS; thus, cancer was detected in 5 out of 135 patients with LCIS who underwent MRI screening (4%). Among those who did not have MRI screening, 22 biopsies were performed in 21 out of 196 patients (11%), and cancer was found in 8 of 22 biopsies (36%) in 7 patients, 5 of whom had LCIS. The overall cancer detection rate in patients with LCIS who did not undergo MRI screening (5/117, [4%]) was equal to that in patients who had MRI screening, with only a trend toward earlier diagnosis in those screened with MRI.

More recently, King et al presented updated results from the MSKCC high-risk surveillance program,[48] which now includes more than 900 women with a diagnosis of LCIS. Limiting the analysis to the 646 patients diagnosed with LCIS after 1999 when MRI screening became available at our institution, we identified 339 women (52%) who were participating in MRI screening. Similar to the earlier findings, women having MRI were younger ($P < .0001$), more likely to have at least one first-degree relative with breast cancer ($P = .005$), and more likely to undergo at least one biopsy during surveillance ($P < .001$). There was no difference between the two groups in Breast Imaging Reporting and Data System breast density or in the presence of concurrent atypia. At a median follow-up of 41.5 months (range, 0 to 139 months), 95 screen-detected cancers have been diagnosed in 89 of 646 patients (13.7%). The crude cancer detection rate remained similar between the two groups: 54 out of 339 (16%) in the MRI group vs 41 out of 307 (13%) in the no-MRI group. However, in this data set with a larger number of cancers detected, there was not a trend toward smaller tumor size or earlier stage at diagnosis with MRI screening. Further analysis of this data set to explore the relationship between patient age and length of follow-up are underway; however, at this time, the use of MRI screening in patients with LCIS remains controversial.

### Chemoprevention

In September 1998 the National Surgical Adjuvant Breast and Bowel Project (NSABP) released results from the Breast Cancer Prevention Trial (BCPT, P-1) demonstrating that among high-risk women, tamoxifen decreased the risk of developing invasive breast cancer by 49%.[49] Eligible patients included women over 60 years of age, those with a personal history of atypical ductal hyperplasia or LCIS, and women over 35 years of age with a 5-year predicted probability for developing breast cancer of ≥ 1.66% according to a modified Gail model.[50] Of 13,338 participants, 826 (6.2%) had LCIS. In this subset, tamoxifen reduced the risk of developing breast cancer by 56%. The following year, the Multiple Outcomes of Raloxifene Evaluation (MORE) study concluded that raloxifene was not only effective at preventing and treating osteoporosis in postmenopausal women, but also decreased the risk of developing breast cancer by 76%,[51] and in 2006 the NSABP Study of Tamoxifen and Raloxifene (STAR, P-2) trial demonstrated that raloxifene was just as effective as tamoxifen at reducing the risk of breast cancer in high-risk postmenopausal women.[52] Women with LCIS comprised 9.2% of 19,747 participants in the STAR trial. Collectively, these data led to a statement from the American Society of Clinical Oncology (ASCO) recommending 5 years of tamoxifen for high-risk premenopausal women to reduce the risk of estrogen receptor (ER)-positive invasive breast cancer, and raloxifene to reduce risk for postmenopausal women. Other agents, including aromatase inhibitors, are not currently recommended outside of a trial.[53] Despite these recommendations, neither tamoxifen nor raloxifene has been widely embraced, and studies addressing patient and physician attitudes toward chemoprevention are limited. Port et al found that among 43 high-risk patients offered tamoxifen, 41 declined because of perceived risks.[54] Tchou et al[55] reported a higher acceptance rate—42%—among 137 high-risk women offered tamoxifen, and they specifically noted that older age and a history of atypical hyperplasia or LCIS were significant predictors of patient acceptance of tamoxifen at their institution.
Anastrozole (Arimidex)

Raloxifene

Tamoxifen

In a recent review of chemoprevention use among our high-risk LCIS surveillance population at MSKCC, we identified 163 women (16%) with a history of tamoxifen, raloxifene, or anastrozole (Arimidex) use of greater than 6 months.[48] Compared with 835 women in our LCIS population who did not choose chemoprevention, there was no difference in patient age, race, menopausal status, family history of breast cancer, concurrent diagnosis of atypia, or breast density between the two groups. Among patients pursuing chemoprevention, 120 (74%) used tamoxifen, 55 (34%) used raloxifene, and 3 patients used anastrozole (a small number of patients used more than 1 agent). At a median follow-up of 84 months, 59 patients (36%) had completed 5 years of therapy, 57 patients (35%) remained on therapy at the time of last follow-up, 20 patients had discontinued treatment early due to concerns over side effects or the development of unrelated medical problems, and therapy status was unknown for the remaining 13 patients.

Although only a minority of our population used chemoprevention, it resulted in a highly significant reduction in the cancer rate for this cohort ($P < .0001$). Only 6 out of 163 patients who chose chemoprevention (3.6%) developed breast cancer, compared with 121 out of 835 patients not taking chemoprevention (14.5%). The retrospective nature of this data set limits our ability to further explore factors contributing to patient acceptance and compliance; however, these data strongly support the need to improve our efforts to educate patients about the risks and benefits of chemoprevention.

**Risk-Reducing Surgery**

When LCIS was first described, it was treated as a malignancy necessitating mastectomy, like all breast carcinomas at the time. This remained the standard approach until studies demonstrated that the actual risk of breast cancer was lower than expected and that women with LCIS were equally likely to be diagnosed with contralateral as with ipsilateral breast cancer, leading to the conclusion that bilateral total mastectomy would be the only logical operation that could truly reduce risk.[13] In parallel with the trend toward more conservative therapy for the treatment of invasive breast cancer, aggressive surgical therapy for LCIS fell out of favor, and in our experience, only a minority of women with LCIS (5%) will pursue bilateral prophylactic mastectomy (BPM). Nevertheless, BPM may be a reasonable option for a subset of women with LCIS and other risk factors, such as a strong family history or extremely dense breasts.

Historically, we have cited data indicating that BPM results in an approximately 90% risk reduction for the development of subsequent cancer.[56] This figure was based on a retrospective analysis of 639 women with a family history of breast cancer undergoing BPMs between 1960 and 1993. While it is important to inform patients that prophylactic mastectomy does not completely eliminate cancer risk, many women in this series underwent subcutaneous mastectomy, an operation that has fallen out of favor because of the amount of breast tissue frequently left behind. The current standard of care for prophylactic mastectomy is total mastectomy (with or without reconstruction), with the goal of removing the entire mammary gland as would be done during therapeutic mastectomy. The desire for nipple preservation in this setting and others is becoming increasingly common, and while this may result in improved cosmesis and patient satisfaction, prospective data supporting this contention and/or the long-term oncologic safety of this approach are not yet available.

Patients considering surgery for risk reduction need to be fully aware of all the risks and benefits of this approach, and they should be encouraged to consider the impact that prophylactic surgery may have on their quality of life with respect to body image and sexual functioning. If reconstruction is to
be pursued, they should also have a reasonable expectation of the most likely cosmetic outcome. The decision to undergo BPM is highly individual and should not be undertaken without ample time to consider all of the available options for risk management.

Summary

Since the original description of LCIS, there has been confusion regarding its management. Epidemiologic data suggest that LCIS is not an obligate precursor to invasive disease, and until relatively recently, LCIS has been widely accepted as a risk factor for the development of invasive breast carcinoma in both the affected and nonaffected breast. The diagnostic management is influenced by the type of biopsy performed, and NCCN guidelines support surgical excision following a core biopsy diagnosis of LCIS. Once diagnosed, conservative management predominates, yet only a minority of women pursue chemoprevention, highlighting the need for improved patient education and counseling. Increasing incidence rates of LCIS and emerging laboratory findings supporting a precursor role for LCIS in the development of invasive breast cancer support the need for an improved understanding of the risk imparted by this lesion.

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