Lobular Carcinoma In Situ

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History

Lobular carcinoma in situ (LCIS) was first described in the 1940s [1]. LCIS was first treated similarly to invasive carcinoma—with radical mastectomy—because it was often diagnosed concurrently with invasive lobular carcinoma (ILC). It was subsequently recognized that LCIS is a marker of risk for breast cancer that does not itself progress to malignancy, and treatment has thus evolved to close observation with early detection of subsequent malignancy. This management change was based in part on a 1978 review of 211 cases of women with LCIS treated by observation alone (without surgery). There was a 17% incidence of subsequent invasive carcinoma, with equivalent risk in both breasts, and only six (3%) patients died of breast cancer [2]. Close observation was associated with early breast cancer detection and high associated cure rates. However, more recently, as mammography and image-guided needle biopsies have become more widespread, the biological heterogeneity of LCIS has become more apparent, and now certain subtypes of LCIS, including the pleomorphic variant, are recognized as indolent precursors of ILC for which surgical resection with negative margins and often radiation therapy is indicated.

Epidemiology

The incidence of LCIS is difficult to estimate because it lacks specific clinical abnormalities and is always identified incidentally [3]. LCIS is generally not detectable by palpation on physical exam, by mammogram, or by gross pathological examination [4]. LCIS is identified in 0.5–3.9% of breast biopsy specimens [5, 6].

The mean age at diagnosis of LCIS is 10–15 years younger than that for invasive breast cancer. It has been described as being more common in premenopausal than in postmenopausal women [2, 7]. However, while LCIS is more often diagnosed in women between age 40 and 50, a review of the Surveillance, Epidemiology and End Results (SEER) program database from 1978 to 1998 revealed that LCIS increased during that time period in all age groups [5]. Interestingly, in women older than age 50, the incidence of LCIS increased concurrently with the incidence of ILC, whereas in women younger than 50, an increase in ILC was not observed as LCIS increased. In women aged 40–49 years old, rising LCIS diagnoses leveled off at approximately 1989, whereas the increase of LCIS in women aged 50–79 years old was the most profound and sustained. The reason for this increase in LCIS in postmenopausal women is likely multifactorial, including the increased availability of screening mammography, the implementation of MRI in breast cancer patient management, the use of hormone replacement therapy in postmenopausal women, and more accurate molecular diagnosis, to be discussed in the "Pathology" section.

Risk Assessment

Patients with LCIS have an 8- to 12-fold greater lifetime risk than the general population for developing invasive breast cancer in either breast [8, 9]. Numerous studies have documented that after the diagnosis of LCIS, if diligently sought, LCIS can be found elsewhere in the index breast and also in the contralateral breast. Approximately 50% of LCIS is multifocal, and in 30% of patients, LCIS is found within the contralateral breast [2, 9]. However, despite the bilateral risk, cancer development is skewed toward the ipsilateral breast. Furthermore, although subsequent invasive breast cancer can be either of ductal or lobular origin, 70–89% of invasive

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carcinoma after LCIS is ILC [9, 10]. The time between LCIS and invasive cancer development is approximately 15–30 years [9]. LCIS is associated with approximately 90% of ILC cases [11].

Pathology

The hallmark of LCIS is the proliferation of the epithelial cells of the terminal ductal-lobular unit, with no penetration of the basement membrane. Compared to the cells that normally line the lobular acini, LCIS cells are larger and monomorphic. There are also a loss of cellular cohesion and the presence of intracytoplasmic vacuoles. Mitoses and necrosis are infrequent, and nucleoli are inconspicuous, without prominent chromatin. The difference between LCIS and the high-risk lesion atypical lobular hyperplasia (ALH) is quantitative, with fewer abnormal cells and the preservation of residual lumen in the lobules with ALH compared to complete replacement of the lobular unit with LCIS. Many utilize the term "lobular neoplasia" to encompass both ALH and LCIS because they may represent early and later points on a spectrum of abnormal lobular proliferation [12]. LCIS is distinguished from ILC because it is contained by the basement membrane on hematoxylin- and eosin-stained sections. Cases of mixed lobular and ductal in situ lesions have also been described, with genetic aberrations of a hybrid phenotype [12].

The pleomorphic variant of LCIS (PLCIS) is architecturally similar to LCIS. However, PLCIS has substantially larger nuclei and greater nuclear polymorphisms. In contrast to classic LCIS, PLCIS has prominent nucleoli, central necrosis, and large, clustered calcifications. In some cases, PLCIS cells have eosinophilic cytoplasm, imparting an "apocrine appearance," or intracytoplasmic vacuoles, imparting a "signet ring cell appearance" [12]. Her2/neu overexpression and gene amplification have been reported in PLCIS with apocrine differentiation [13]. The combination of calcifications, necrosis, and cellular features can complicate the distinction of PLCIS from high-grade DCIS. Whereas classic LCIS is generally not associated with direct clonal progression to ILC, the pleomorphic variant lesions are. These data suggest that pleomorphic LCIS may not only be a marker for increased risk of invasive breast cancer but also a direct precursor of ILC. Classic and pleomorphic LCIS can coexist in the same lesion [14].

Molecular analyses of LCIS (as well as ALH and ILC) have revealed decreased expression or the loss of the cell surface adhesion molecule E-cadherin [15]. The loss of E-cadherin is the defining molecular event of lobular breast pathology. This contrasts with ductal lesions, in which E-cadherin expression is generally maintained. Immunohistochemistry using anti-E-cadherin antibodies can be used to distinguish ductal and lobular lesions.

E-cadherin is the protein product of the *CDH1* gene (16q22.1) and is expressed on epithelial cells [12]. The cadherins are a family of adhesion proteins that span the cell membrane and, through a calcium-dependent mechanism, form dimers with cadherins on other cells and interact with the actin cytoskeleton [12]. The portion of E-cadherin that is intracytoplasmic binds to p120-catenin [16]. In normal mammary cells, p120-catenin is present at the cell membrane. However, if the E-cadherin protein is nonfunctional or lost, p120 accumulates in the cytoplasm, where it activates cytoplasmic Rho-GTPases, resulting in increased cell motility [17]. The loss of E-cadherin and the cytoplasmic accumulation of p120-catenin are pathognomonic for lobular breast pathologies [12]. This feature can be critically important when LCIS is diagnosed concurrently with lesions, such as sclerosing adenosis or radial scars, as these together can produce patterns that mimic ILC. The lack of E-cadherin staining and cytoplasmic p120-catenin in the areas of question can differentiate LCIS and ILC [12]. Furthermore, some high-grade triple-negative DCIS may display diminished E-cadherin expression, suggesting PLCIS [12]. In addition to the loss of E-cadherin, the loss of high-molecular-weight keratins (cytokeratins 5/6, 14, and 17), which are generally present in high-grade DCIS, suggests PLCIS [12].

Some LCIS may display aberrant E-cadherin membrane expression that is not completely absent from the cell membranes, but it is fragmented, focal, or beaded. In these cases, double staining for E-cadherin and immunostaining for beta-catenin can be helpful to establish the diagnosis. The loss of beta-catenin also indicates that the E-cadherin is dysfunctional and not associated with other molecules in the cadherin-catenin complex [18, 19].

CDH1 gene mutations, deletions, and methylation have been identified in LCIS, as well as abnormal transcriptional regulation of E-cadherin [12]. Furthermore, LCIS also exhibits a loss of heterozygosity [20]. Other target genes that have been associated with the development of LCIS include fibroblast growth factor receptor 1 (*FGFR1*) and cyclin D1 (*CCND1*) [21, 22]. Pleomorphic LCIS has also been associated with *CCND1* and the oncogenes *MYC* and *HER2* [13, 23].

Diagnosis

Clinical Presentation

The clinical presentation of patients with LCIS is highly variable. LCIS is usually not detectable by physical examination and does not have pathognomonic features on mammogra-

phy. In the era of widespread mammographic screening and the shift to percutaneous breast biopsy, LCIS is most commonly diagnosed as an incidental finding on image-guided core-needle biopsy. It can also be found incidentally on surgical lumpectomy specimens removed for another indication.

Radiographically, classical LCIS is associated with small punctate calcifications in 42% of cases, whereas the pleomorphic variant of LCIS is more likely to have large and clustered calcifications related to the presence of comedo-type necrosis [4]. Pathological diagnosis is described above. Occasionally, even in the presence of E-cadherin, p120-catenin, beta-catenin, and cytokeratin staining, the diagnosis of LCIS is ambiguous and difficult to distinguish from DCIS. In this case, diagnosis should employ a multidisciplinary approach. However, when a definitive diagnosis cannot be rendered even after a multidisciplinary discussion or in the case of mixed LCIS and DCIS, the lesion should be managed as DCIS.

Treatment

Surgery

After an incidental diagnosis of LCIS by percutaneous image-guided core-needle biopsy, surgical excisional biopsy should be performed to rule out synchronous invasive cancer and DCIS. Percutaneous biopsy is limited by sampling error, and it can present difficulty in making a definitive histological diagnosis [24]. Upgrading to invasive cancer when the biopsy site is surgically excised can occur [25]. The goal of surgical excisional biopsy is to remove the biopsy site and any residual imaging abnormalities.

Excisional biopsy demonstrates a 0–10% risk of synchronous invasive breast cancer and a 0–50% risk of synchronous DCIS [6, 26, 27]. Surgical excisional biopsy is most commonly performed using a technique to localize a titanium marker clip placed radiographically during percutaneous biopsy. Two such localization techniques are wire or radioactive seed localization. To document the removal of the LCIS on excisional biopsy, mammography of the surgical specimen after excision should reveal the presence of the clip. Furthermore, the surgical pathology report should describe residual biopsy site changes due to the percutaneous core-needle biopsy. Contralateral mirror-image breast biopsy, a procedure described in the past for patients with LCIS, is no longer performed. Instead, close observation of all remaining breast tissue is recommended.

The management of microscopic margin status in LCIS is guided by the results of several studies described below. In a study of 180 patients who underwent observation alone after margin-negative surgical excision of LCIS, the overall ipsilateral and contralateral breast cancer event rates at 12 years of follow-up were 14.4% and 7.8%, respectively [10]. The rate of invasive breast cancer was 5.6%. This rate was similar whether ipsilateral or contralateral, although contralateral cancers occurred later. Nearly 85% of subsequent ipsilateral breast tumors were detected mammographically. More than 96% of all ipsilateral tumors occurred in the same quadrant as the original LCIS. Breast cancer-specific mortality was 1.1% at 12 years [10]. In another study of 100 patients with LCIS in which margin status was not documented, the ipsilateral and overall breast cancer event rates were 13% and 16%, respectively [28]. Finally, in a retrospective analysis of 2894 patients who underwent breast-conserving surgery for DCIS or early breast cancer between 1980 and 2007, 10% had LCIS within the lumpectomy specimen, and of those, approximately one-third had LCIS at the margin [29]. The difference in crude local recurrence rate between the patients with LCIS within the specimen (4.5%) and in those with no LCIS (3.8%) was not statistically significant [29]. Furthermore, there was also no significant difference in actuarial 5- and 10-year local recurrence rates if LCIS was present at the margin (6% and 6%), if LCIS was present but not at the margin (1% and 15%), or if no LCIS was present at all (2% and 6%). The results of these studies suggest that re-excision to achieve negative margins for classical LCIS is not warranted. However, for the pleomorphic PLCIS subtype, re-excision to achieve negative margins is indicated. In addition, identification of LCIS in a lumpectomy specimen resected for the diagnosis of DCIS or invasive cancer should not alter surgical management of the primary breast because the presence of LCIS does not increase the rate of in-breast recurrence in patients undergoing breast conservation [29].

Once a diagnosis of LCIS has been rendered and concurrent malignancy excluded, patients with LCIS should be counseled regarding their increased lifetime risk of breast cancer development. The surgical management of LCIS is generally conservative, and only a small minority pursue bilateral risk-reducing mastectomy, although this number has recently been increasing [30]. This approach is usually reserved for patients who have additional risk factors for breast cancer development or who experience significant anxiety regarding observation and/or chemoprevention options. It is important that patients considering this option are aware that bilateral mastectomy does not completely eliminate the risk of breast cancer development [31]. Because LCIS poses no risk of regional metastasis, sentinel lymph node biopsy or axillary node dissection is not required. Immediate breast reconstruction should be offered for patients who undergo risk-reducing mastectomy for LCIS. Women should be informed about the impact of this treatment approach on quality of life, particularly body image and sexual function [32]. Nipple-areola complex-sparing mastectomy may be a viable option in carefully selected women pursuing surgical risk reduction [33].

Risk-Reducing Endocrine Therapy

Risk-reducing therapy, often called "chemoprevention," is an important treatment option for patients with LCIS. In the NSABP P-1 breast cancer prevention trial, the incidence of invasive breast cancers was reduced by 56% in women with LCIS who received tamoxifen compared to observation alone [34]. Women with LCIS represented 6.2% of the patients in that trial. The annual hazard rate of invasive cancer was 5.69 per 1000 women who received tamoxifen compared with 12.99 per 1000 women who did not. In the NSABP P-2 trial, postmenopausal women with LCIS were randomized to tamoxifen or raloxifene [35]. Women with LCIS comprised 9.2% of the patients on the trial. There was no difference in risk reduction for invasive breast cancer between the two agents (incidence 4.30 per 1000 vs. 4.41 per 1000 for tamoxifen and raloxifene, respectively). Patients receiving raloxifene had a lower incidence of thromboembolic events and cataracts. There was no significant difference in the risk of other cancers, fractures, ischemic heart disease, or stroke for the two drugs. At 81 months of median follow-up, raloxifene was 78% as effective as tamoxifen at preventing invasive disease but had fewer toxicities, with significantly fewer endometrial cancers [36]. Raloxifene may be of particular benefit to postmenopausal women with an intact uterus and a risk of osteoporosis; tamoxifen would be an appropriate choice for high-risk postmenopausal women.

Radiation Therapy

Adjuvant radiation therapy is not recommended for the treatment of LCIS. If synchronous DCIS or invasive breast cancer is found in an excised LCIS specimen, the patient should be treated according to the guidelines for DCIS or invasive breast cancer and may benefit from radiation.

Surveillance

Following excisional biopsy demonstrating LCIS, patients should undergo annual bilateral breast physical examinations and diagnostic mammography. Screening ultrasound in patients with high breast cancer risk, including LCIS, is associated with high false-positive results [37]. A recent single-institution analysis revealed that with either annual mammograms or MRI, the cancer detection rate was 13% [38]. MRI was not associated with diagnosing breast cancer at earlier stage, smaller size, or node negativity. For this reason, the routine use of MRI for screening patients with a diagnosis of LCIS is not recommended. Patients with LCIS who undergo a bilateral mastectomy with or without reconstruction should also undergo an annual physical examination, but routine imaging is not indicated. Any suspicious lesions should be evaluated with ultrasound and biopsy analysis.

Conclusion

LCIS is a histological finding characterized by an intact basement membrane with a loss of E-cadherin leading to a dysfunctional E-cadherin/catenin complex. LCIS confers increased long-term risk of breast cancer that may affect either breast. The pleomorphic subtype is also a non-obligate precursor to invasive cancer. Patients found to have LCIS on core-needle biopsy are evaluated with bilateral diagnostic imaging, and additional suspicious lesions are further evaluated. Marker clips should routinely be placed at the time of percutaneous image-guided biopsy. Patients diagnosed with LCIS should undergo surgical excisional biopsy with localization of the percutaneous biopsy cavity to increase accuracy. If synchronous DCIS or invasive breast cancer is diagnosed, subsequent treatment is administered according to the guidelines for these tumors. Re-excision to attain negative margins is not performed in patients with classical LCIS unless pleomorphic LCIS is identified, in which case negative margins should be achieved. Bilateral risk-reducing mastectomy is generally reserved for patients with additional risk factors for breast cancer or with extreme anxiety regarding observation and/or chemoprevention options but does not completely eradicate the risk of subsequent breast cancer development. Patients with LCIS should receive systemic risk reduction with antiestrogen therapy, namely, tamoxifen or raloxifene. Follow-up includes clinical and imaging surveillance. All patients with LCIS should be considered for clinical trials.

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