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ORIGINAL LABORATORY INVESTIGATION

Immediate and delayed risk of breast cancer associated with classic lobular carcinoma in situ and its variants

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Abstract

Objective To determine the risk of breast cancer due to lobular carcinoma in situ (LCIS).

Methods This retrospective IRB-approved study identified cases of LCIS after percutaneous breast biopsy from 7/2005 to 7/2022. Excluded were cases with less than 2 years of imaging surveillance or a concurrent ipsilateral breast cancer diagnosis within 6 months of the LCIS diagnosis. Final outcomes of cancer versus no cancer were determined by pathology at surgical excision or the absence of cancer on imaging surveillance.

Results A total of 116 LCIS lesions were identified. The primary imaging findings targeted for percutaneous biopsy included calcifications (50.0%, 58/116), MR enhancing lesions (25.0%, 29/116), noncalcified mammographic architectural distortions (10.3%, 12/116), or masses (14.7%, 17/116). Surgical excision was performed in 49.1% (57/116) and imaging surveillance was performed in 50.9% (59/116) of LCIS cases. There were 22 cancers of which 11 cancers were discovered at immediate excision [19.3% (11/57) immediate upgrade] and 11 cancers developed later while on imaging surveillance [18.6% (11/59) delayed risk for cancer]. Among all 22 cancers, 63.6% (14/22) occurred at the site of LCIS (11 at immediate excision and 3 at surveillance) and 36.4% (8/22) occurred at a location away from the site of LCIS (6 in a different quadrant and 2 in the contralateral breast).

Conclusion LCIS has both an immediate risk (19.3%) and a delayed risk (18.6%) for cancer with 90.9% occurring in the ipsilateral breast (63.6% at and 27.3% away from the site of LCIS) and 9.1% occurring in the contralateral breast.

Keywords Lobular carcinoma in situ · Cancer · Variant · Pleomorphic · Florid

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Abbreviations

TDLU	Terminal duct lobular unit
LCIS	Lobular carcinoma in situ
ALH	Atypical lobular hyperplasia
BWUP	Benign with upgrade potential
EHR	Electronic health records
VAB	Vacuum-assisted biopsy
ILC	Invasive lobular carcinoma
DCIS	Ductal carcinoma in situ

Introduction

Lobular neoplasia is an atypical proliferation of monotonous discohesive epithelial cells within the terminal duct lobular unit (TDLU). The term lobular neoplasia encompasses both lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH). The natural history of LCIS and hence its clinical significance have been debated over time. In some instances, surgical excision may be indicated; however,

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alternative management strategies, including medical chemoprophylaxis and surveillance, have been used in lieu of surgery. Current recommendations of the American Society of Breast Surgeons aim to reduce unnecessary surgeries and ensure appropriate follow-up of LCIS and other benign with upgrade potential (BWUP) lesions [1]. As a result, there has been a trend toward conservative management, rather than surgical excision [2], especially as current concepts suggest that LCIS is a high-risk marker, rather than being an obligatory precursor lesion such as DCIS. Despite this, a 2019 report of major academic institutions in the United States reported that surgical excision remains the most frequent recommendation for all BWUP lesions, including LCIS. The surgical excision recommendation rate for lobular neoplasias ranges from 61 to 71% [3]. Engagement of a consistent and timely multidisciplinary conference to review individual cases has been suggested to make appropriate personalized recommendations of excision versus no excision [4]. The goals of this study were to: (1) determine the inherent cancer risk associated with LCIS; (2) determine the geographic location of the cancer relative to the site of LCIS; and (3) determine if the variables used to make recommendations for excision versus no excision are valid.

Materials and methods

Patient selection and institution

This was an institutional review board (IRB) approved, Health Insurance Portability and Accountability Act (HIPAA) compliant retrospective study from a single academic center. The need for informed consent was waived. Electronic health records (EHR) (EPIC, Verona, WI, USA) were queried for keywords and associated ICD9 and ICD10 codes for LCIS between the dates of July 2005 and July 2022. This identified 160 cases of LCIS. Included were all adults over the age of 18 years with percutaneous needle biopsy results of LCIS with either surgical excision or greater than 2 years of imaging follow-up. Excluded were 21 cases of LCIS with an ipsilateral breast cancer diagnosis within 6 months of the LCIS diagnosis and 23 cases of LCIS due to either lack of surgical excision or insufficient follow-up less than 2 years. The final study cohort consisted of 116 cases of LCIS.

The academic center is a National Cancer Institute designated cancer center that also serves as a tertiary referral center. Patients with a percutaneous needle biopsy diagnosis of LCIS and other BWUP lesions are reviewed at a weekly multidisciplinary clinical management conference (CMC) to determine further management. At the CMC, patient-related clinical factors, imaging, and pathology are reviewed by a team of rotating specialists in the fields of breast imaging, breast pathology, breast surgical oncology, and primary care providers with a special interest in high-risk patients.

Imaging, biopsy, and pathology

Breast imaging studies were reviewed and recorded for the imaging finding type (calcifications, MRI enhancing lesions, mammographic architectural distortions, or masses), biopsy technique, and imaging-pathologic assessment of concordance or discordance. Calcifications, MRI enhancing lesions, and architectural distortions were percutaneously sampled with a 9-gauge Eviva or ATEC (Hologic, Marlborough, MA, USA) vacuum-assisted biopsy (VAB) device. Mass lesions visualized at ultrasound imaging were percutaneously sampled by a 14–18 gauge spring-loaded core biopsy or a 9–12 gauge ultrasound handheld VAB, based on the procedure radiologists' preference. The size of imaging abnormality before biopsy was recorded. When available, the number of samples was recorded and the percentage of residual imaging finding remaining after percutaneous needle biopsy was recorded. Imaging considerations included the size of the imaging finding, and the percentage of the lesion removed after percutaneous needle biopsy, with the goal of assessing the adequacy of sampling. Although complete excision of the imaging finding leaves no question about the adequacy of sampling, removal of $\geq 50\%$ of the targeted imaging finding was accepted as sufficient sampling.

Pathologic considerations included whether the LCIS was seen incidentally at pathology or in association with the imaging target. The degree of TDLU involvement with the atypical cells was used to differentiate ALH from LCIS, with LCIS involvement demonstrating greater than 50% TDLU involvement. Breast pathologists assessed the nuclear grade and presence or absence of necrosis to categorize LCIS into classic (grade 1, no necrosis) versus non-classic variant forms (grade 2 or 3, presence of necrosis). Furthermore, breast pathologists assessed for multifocality and the extent (size) of LCIS involvement.

Reasons for surgical excision versus imaging surveillance

The specific reason why surgical excision versus no excision was recommended after the CMC was queried from the EHR. In cases when there was not a clear documentation of the reason for discordance or in cases when the reason for surgical excision was due to a patient preference, the principal investigator reviewed the clinical notes, imaging report and/or images, and pathology to determine the most probable reason. For example, if the CMC note indicated surgical excision was recommended due to discordance and there was a mass finding, the discordance was attributed to the presence of a mass. If the mass had a corresponding

MRI enhancement, the discordance was attributed to MRI enhancement. Similarly, if the patient chose surgical excision, the EHR was queried for the CMC note or the pre-surgical note indicating the reason for the patient's preference for surgery.

Data analysis

Truth was determined by either surgical excisional pathology results or the absence of malignancy on imaging surveillance. Upgrade to cancer was defined by the presence of DCIS or invasive cancer at the site of LCIS after immediate surgical excision. Cancers that developed among patients undergoing imaging surveillance, rather than immediate excision, comprised the group with a delayed risk of cancer. In this latter group, the location of the cancer, relative to the site of LCIS biopsy, was assessed as either at the site of LCIS if the cancer developed within 1 cm of the LCIS biopsy site or away from the site of LCIS if the cancer developed in the same breast but in a different quadrant or in the contralateral breast. Patient demographics, imaging findings, and biopsy details were summarized using frequencies, means, medians, ranges, and standard deviations (SD). Age and the final outcomes of cancer versus no cancer were compared using the Wilcoxon rank sum test and Fisher's exact test. All tests were two-sided and p-values of 0.05 or less were considered statistically significant. Statistical analysis was carried out using R (version 3.6.3, R Development Core Team).

Results

Between July 2005 and July 2022, there were a total of 7391 percutaneous needle breast biopsies performed at the institution. Pure LCIS, without other high-risk pathology, was diagnosed in 160 cases, yielding an overall incidence of 2.2%. After applying the exclusion criteria of those without surgical excision or with less than 2 years of follow-up, the final study cohort consisted of 116 cases of LCIS. After multidisciplinary CMC review, 41.4% (48/116) were recommended surgical excision, 50.0% (58/116) were recommended imaging surveillance without excision, and 8.6% (10/116) were offered a choice of surgery, repeat biopsy, or imaging surveillance.

Among the 10 cases where a choice of surgery, repeat biopsy, or imaging surveillance was offered to the patient, 1 patient elected to have surveillance and developed a cancer (grade 1, invasive lobular carcinoma (ILC)) 12 years and 7 months later, within 8 mm of the original LCIS biopsy site. In a second case where the patient was offered a choice, the patient elected to have surgery in the form of a prophylactic mastectomy due to a concurrent contralateral breast cancer diagnosis and was found to have a grade 2, ductal carcinoma in situ (DCIS) at the site of LCIS. In the remaining 8 patients offered a choice, all 8 patients elected for surgical excision and were found without evidence of cancer at immediate surgery. Thus, the cancer risk among those offered a choice was 20.0% (2/10).

There were a total of 57 cases that had surgical excision; 48 patients that had been recommended immediate excision after multidisciplinary review at clinical management conference and 9 patients that had been given a choice. The reasons for surgical excision recommendation and/or patient choice for excision were as follows: a corresponding MRI enhancement ($n=15$), florid or pleomorphic variant form of LCIS ($n=11$), patient choice ($n=9$), concern for insufficient sampling ($n=6$), mass finding without MRI correlate ($n=5$), another pathologic lesion requiring surgery ($n=5$), radial scar or complex sclerosing lesion with LCIS ($n=3$), and unknown ($n=3$).

There were 22 cancers, 11 diagnosed at immediate excision and 11 diagnosed later while undergoing imaging surveillance. Of the 11 cancers that developed later, 9 occurred in the ipsilateral breast (3 at the site of LCIS and 6 at a different quadrant) and 2 occurred in the contralateral breast at a median follow-up of 60.5 months or 5 years (range 2–13 years). In summary, 63.6% (14/22) of cancers occurred at the site of LCIS (11 at immediate excision and 3 at imaging surveillance) and 36.4% (8/22) of cancers occurred at a location away from the site of LCIS (Fig. 1). Patient demographics, imaging features, and biopsy characteristics are summarized in Table 1. The imaging findings which yielded LCIS on percutaneous core needle biopsy were calcifications (50.0%, 58/116), MR enhancing lesions (25.0%, 29/116), architectural distortions (10.3%, 12/116), or masses (14.7%, 17/116).

The cancerous and noncancerous LCIS groups showed no difference in age, racial background, imaging finding type or size, biopsy modality, vacuum versus nonvacuum technique, or in the recommendation to excise or not after multidisciplinary review. Specifically, there was no difference in the final outcome of cancer versus no cancer based on the type of imaging finding. LCIS lesions manifesting as MRI enhancing lesions comprised 25.0% (29/116) of all LCIS lesions. MRI enhancement was seen more frequently among those without cancer (26.6%, 25/94) than in those with cancer (18.2%, 4/22). Additionally, there were 11 cancers that had a breast MRI examination; however, in 2 of 11 cancers, the MRI examination was false negative yielding a false-negative rate of 18.2%. Mass presentation of LCIS occurred in 18.2% (4/22) of the cancers compared to mass presentation of LCIS among 13.8% (13/94) of benign cases ($p=0.856$), not statistically significant. Similarly, LCIS lesions undergoing ultrasound-guided biopsy were slightly more likely to represent a cancer [22.7% (5/22) versus 16.0%

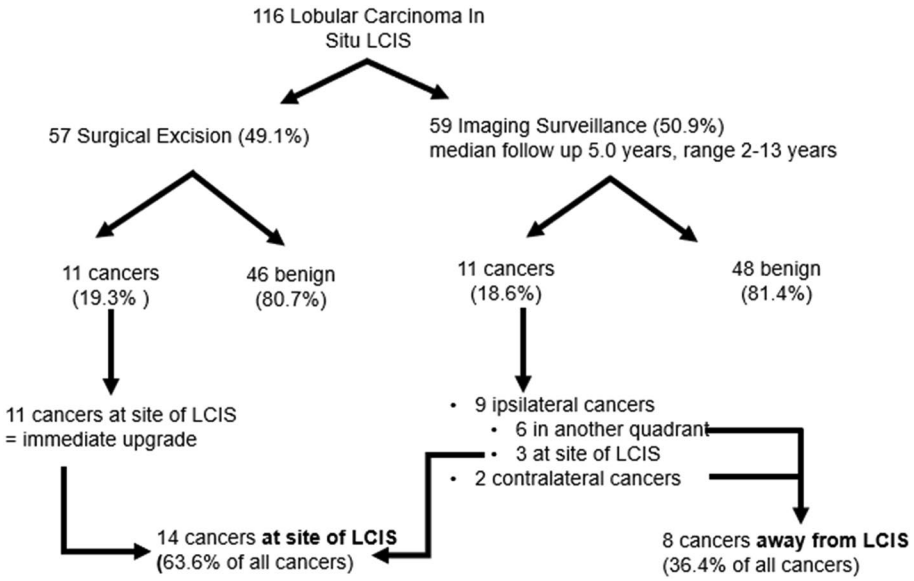


Fig. 1 Outcomes of LCIS based on surgical excision versus imaging surveillance

Table 1 Patient demographics, imaging finding, biopsy

	Benign ($N=94$)	Cancer ($N=22$)	Total ($N=116$)	p value
Age				0.276
Mean (SD)	54.63 (10.32)	57.36 (11.80)	55.15 (10.62)	
Median (Range)	51.50 (37, 81)	56.00 (39, 80)	52.50 (37, 81)	
Race				0.199
Asian	5 (5.3%)	1 (4.5%)	6 (5.2%)	
Black	10 (10.6%)	4 (18.2%)	14 (12.1%)	
Hispanic	13 (13.8%)	0 (0.0%)	13 (11.2%)	
White	66 (70.2%)	17 (77.3%)	83 (71.6%)	
Imaging finding				0.856
Calcifications	46 (48.9%)	12 (54.5%)	58 (50.0%)	
MR Enhancing Lesion	25 (26.6%)	4 (18.2%)	29 (25.0%)	
Architectural Distortion	10 (10.6%)	2 (9.1%)	12 (10.3%)	
Mass	13 (13.8%)	4 (18.2%)	17 (14.7%)	
Size of lesion				0.856
<1 cm	28 (29.8%)	8 (36.4%)	36 (31.0%)	
1–4 cm	53 (56.4%)	12 (54.5%)	65 (56.0%)	
>4 cm	13 (13.8%)	2 (9.1%)	15 (12.9%)	
Biopsy modality				0.681
MRI	24 (25.5%)	4 (18.2%)	28 (24.1%)	
Stereotactic	55 (58.5%)	13 (59.1%)	68 (58.6%)	
Ultrasound	15 (16.0%)	5 (22.7%)	20 (17.2%)	
Vacuum versus nonvacuum				0.480
Non-vacuum core	11 (11.7%)	4 (18.2%)	15 (12.9%)	
Vacuum core	83 (88.3%)	18 (81.8%)	101 (87.1%)	

(15/94) that were benign, $p=0.681$)], but not at statistically significant levels (Fig. 2).

Among the 116 LCIS lesions, 89 (76.7%) had classic LCIS and 27 (23.3%) had either florid or pleomorphic LCIS. Thus, classic LCIS was 3.3 times more prevalent than the non-classic variant forms. Among the variant forms of LCIS, 25.9% (7/27) were ultimately diagnosed with cancer at excision. In comparison, only 16.9% (15/89) of classic LCIS were diagnosed with cancer at excision. The relative risk of cancer conferred by having a variant form of LCIS was 1.53. Finally, nearly one third

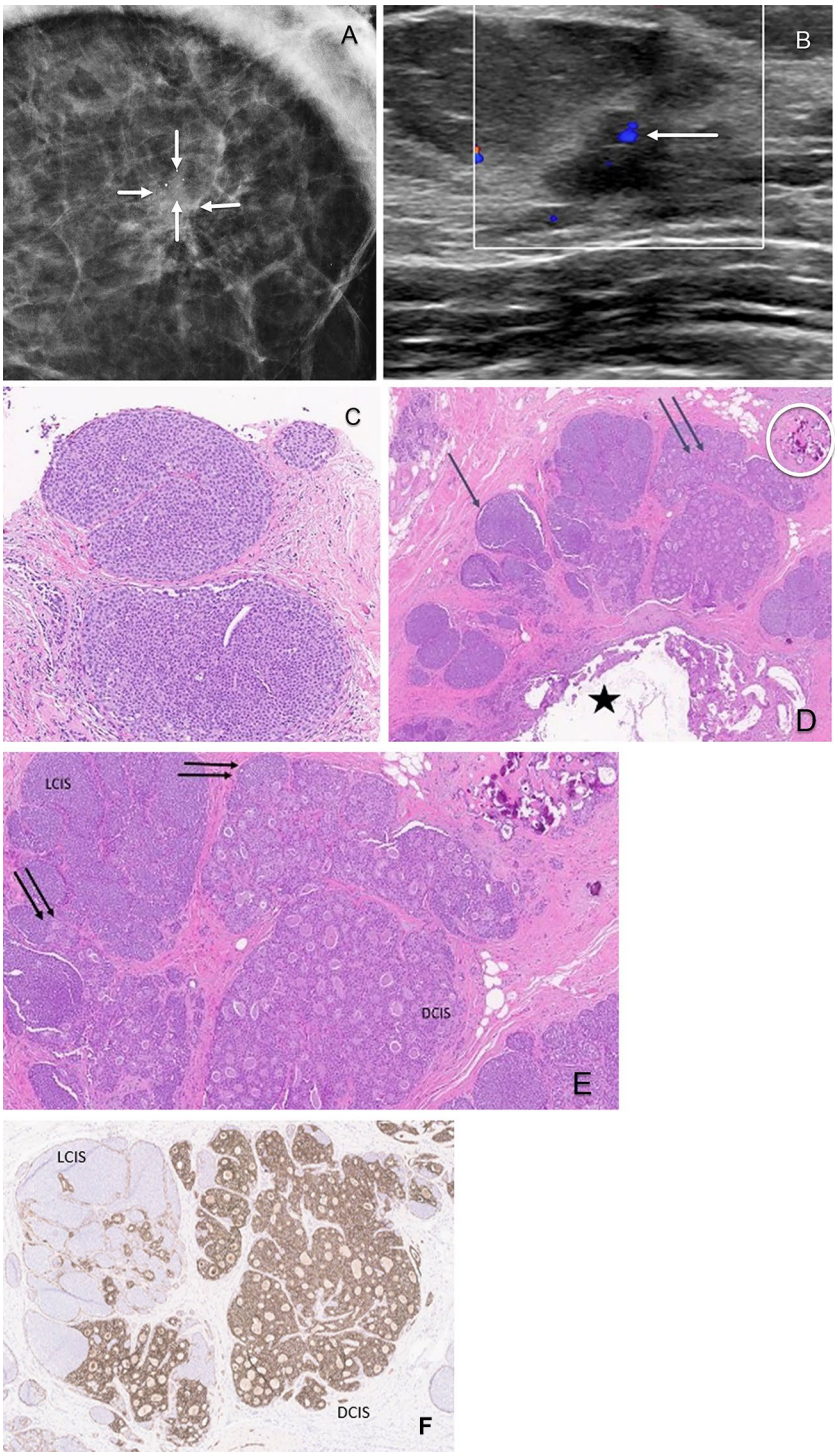
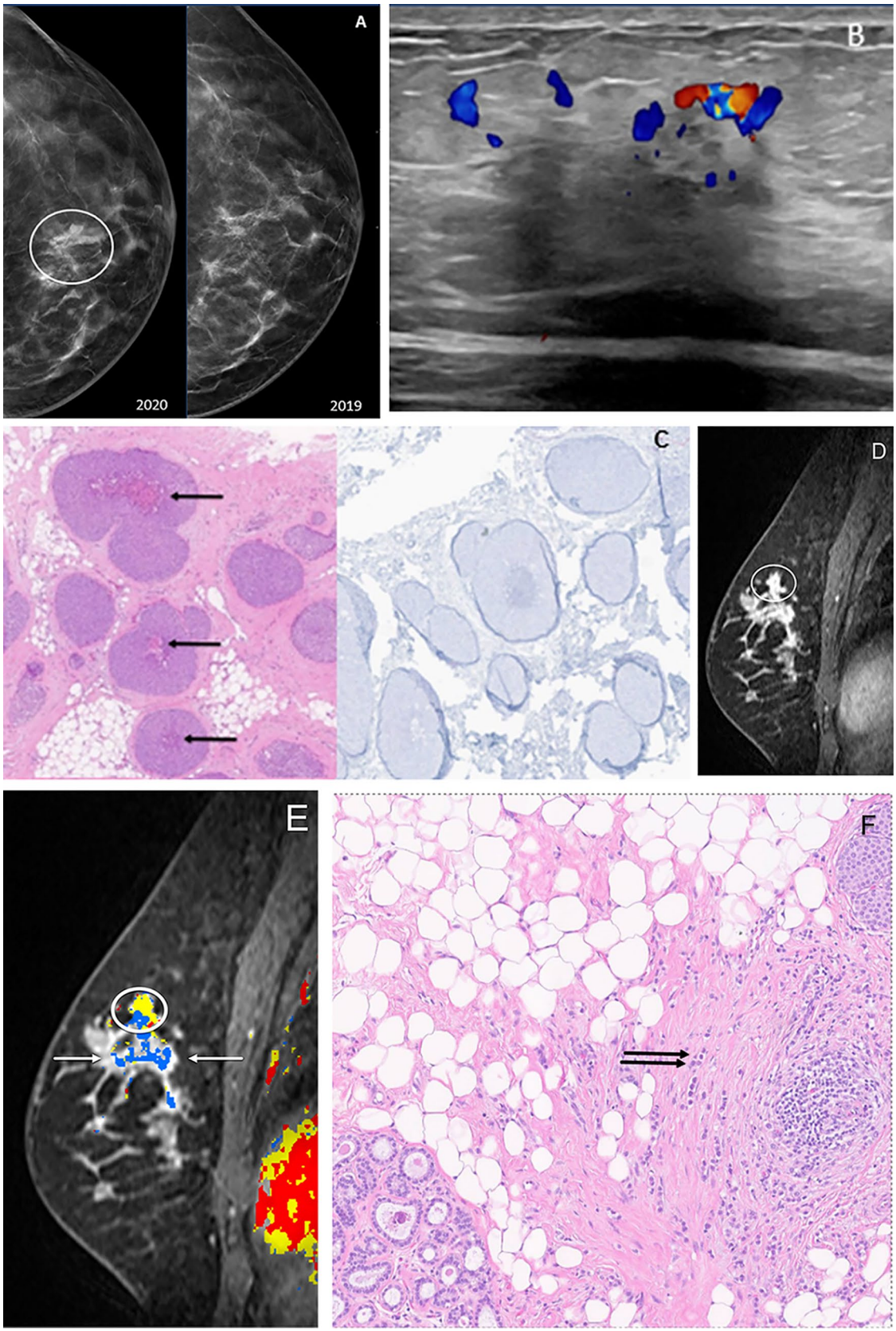


Fig. 2 54-year-old with imaging findings of a mass. At ultrasound core needle biopsy, both classic and florid LCIS were diagnosed. Surgical excision was recommended which revealed an upgrade to cancer with both DCIS and LCIS identified at surgery. **a**: Magnification craniocaudal (CC) view mammogram shows asymmetry with calcifications (arrows). **b**: Longitudinal color Doppler ultrasound shows a hypoechoic lobulated mass at left breast 9 o'clock with internal vascularity (arrow). **c**: High-power hematoxylin and eosin (H&E) of the ultrasound-guided core biopsy shows terminal ductal lobular unit expansion by a monotonous proliferation of cells without secondary lumen formation, consistent with LCIS. Both classic and florid LCIS were seen in association with microcalcifications. **d**: Low-power hematoxylin and eosin (H&E) of the surgical excision shows biopsy tract (black star), LCIS (single black arrow) and DCIS (double black arrows). Note the secondary lumen formation within the DCIS. Calcium oxalate calcifications are noted in the periphery of the image (circle). **e**: High power of the surgical excision shows LCIS, without lumen formation and DCIS, with lumen formation, involving the same ducts (double arrows). **f**: Immunohistochemical stain of the surgical excision highlights the intact membranous E-cadherin on the cell surface of DCIS (brown areas) on the right side of image. On the left side of image, note the majority of the duct shows the absence of E-cadherin, indicative of LCIS


A
2020
2019
B
C
D
E
F

◂**Fig. 3** 50-year-old with florid and pleomorphic LCIS on core needle biopsy initially confused for DCIS. Surgical excision showed. **a**: A craniocaudal (CC) view digital breast tomosynthesis mammograms with comparison from one year prior shows developing asymmetry (circle) in the left medial breast. **b**: On the date of scheduled tomosynthesis-guided biopsy, a repeat longitudinal color Doppler ultrasound image shows an irregular heterogeneous nonmass lesion measuring 2.5×1.8×0.9 cm with surrounding vascularity felt to correlate with the developing asymmetry in the left breast at 11 o'clock. The patient underwent ultrasound-guided core biopsy with a 9-gauge vacuum-assisted ATEC device with initial diagnosis of DCIS. **c**: Low-power H&E (left) and immunohistochemical stain (right) of the core biopsy show monotonous cells without secondary lumen formation. There are the areas of central comedonecrosis (arrows) with intermediate and high-grade nuclei which lack E-cadherin staining, indicating that the lesion is florid and pleomorphic LCIS. **d**: Sagittal T1W + gadolinium image shows an irregular mass enhancement (circle) at left 11 o'clock, 7 cm from nipple. **e**: Sagittal T1W + gadolinium with color overlay image at a 100% threshold demonstrates both mass (circle) and non-mass enhancement (arrows) with heterogeneous persistent and plateau kinetics. **f**: High-power magnification H&E of the surgical excision shows multifocal invasive lobular carcinoma infiltrating in a single file (double arrows) in a background of florid and pleomorphic LCIS extending over 6 cm

(31.8%, 7/22) of the cancer group ultimately diagnosed with breast cancer had either florid or pleomorphic LCIS.

Discussion

LCIS is characterized by a proliferation of monotonous atypical epithelial cells that distend at least 50% of the TDLU without secondary lumen formation [5]. As with invasive lobular carcinomas, LCIS proliferations lack E-cadherin, a cell surface adhesion molecule. The use of immunohistochemical stains highlights E-cadherin on the cell surface of DCIS, while LCIS lacks E-cadherin, thereby differentiating the two entities (Fig. 3). Whereas DCIS is considered a precursor lesion to an invasive carcinoma, usually invasive ductal carcinoma, LCIS has been considered an indicator of increased risk in either breast, with a cumulative annual risk of 1–2% per year [6]. Depending on the age of the women diagnosed with LCIS and assuming a life expectancy to age 80 years, the estimated lifetime risk is inversely related to the patient's age. For example, a 60-year-old may have a 30% lifetime risk of cancer while a 50-year-old may have a higher 40% lifetime risk.

The management of LCIS has been the topic of debate for decades, but many of the earlier studies lacked clinical and imaging correlation. The rationale for surgical excision has been based on reported immediate risk of upgrade of at least 14% [7]. In many cases, however, surgical excision may not be necessary, especially after a comprehensive multidisciplinary review [8]. In this study, both the immediate and delayed risk of cancer of approximately 19% (19.3% immediate upgrade risk and 18.6% delayed risk) suggest management decisions to recommend excision versus observation may be more complex, necessitating consideration of multiple factors. Furthermore, knowing specifically the location of the cancer in relation to the site of LCIS is clinically important to help determine if surgical excision confers any health benefit. Page et al. had previously reported invasive cancers after ALH was three times more likely to arise in the same or ipsilateral breast than in the contralateral breast [9]. In this study, a cancer diagnosis was ten times more likely to arise in the same breast. 90.9% of cancers (20/22) occurred in the same breast as the LCIS diagnosis, compared to 9.1% (2/22) which occurred in the opposite or contralateral breast. Furthermore, the cancer risk was greatest at the site of LCIS (63.6%, 14/22), followed by the same breast but in a different quadrant (27.3%, 6/22), and was least likely to occur in the opposite breast (9.1%, 2/22).

Significance of the imaging target

LCIS may be identified on pathology after a biopsy targeting suspicious calcifications, MRI-enhancing lesions [10, 11], architectural distortions, or masses [12]. Of these imaging findings, calcifications were the most common and comprised 50.0% of all LCIS lesions. The calcifications were sometimes associated with the LCIS but often were associated with columnar cell changes adjacent to the LCIS. Both LCIS and columnar cell changes are estrogen-dependent proliferations that tend to develop concurrently in the breast [13]. Radiologists are likely to determine imaging-pathologic concordance when LCIS is obtained after biopsy of calcifications.

One quarter of all LCIS lesions manifested as a MRI enhancing lesion, likely reflecting the current prevalent use of MRI for screening high-risk women. Some controversy exists on the significance of MRI enhancement in high risk or BWUP lesions. For example, Speer et al. [14] reported a low upgrade rate of 6% for MRI enhancing lobular neoplasia lesions compared to Okamoto et al. [15] who reported a 29% upgrade rate. Kuhl et al. [16] stated that noncalcified lesions such as MRI enhancing lesions have a higher likelihood of being malignant. Findings of this study, however, did not validate this notion that MRI enhancement was associated with a higher likelihood of cancer as MRI enhancement was seen more frequently among those without cancer than in those with cancer. At least two studies have inferred that surgical excision may still be warranted in cases of lobular neoplasia and atypical ductal hyperplasia [17, 18]. Likewise, this study supports the need for surgical excision based on the parameters of adequacy of sampling and pathologic determinants, rather than reliance on a negative MRI to exclude cancer. Rather, surgical excision immediately identified 50% of all cases that ultimately were diagnosed with cancer.

In noncalcified lesions of either architectural distortions or masses, radiologists are more likely to determine imaging-pathologic discordance and subsequently recommend excision of the LCIS. Interestingly, despite a higher likelihood to recommend surgical excision, there was no statistically significant difference in the occurrence of architectural distortions or masses between the cancer and the noncancer groups. In cases of architectural distortion without a mass, radial scar is the expected pathologic entity. Martaindale et al. [19] previously reported a 17% upgrade rate among radial scars with associated atypia compared to a 0% upgrade rate among radial scars without atypia. Thus, if percutaneous needle biopsy yields results a radial scar with LCIS, which by definition has atypical proliferations, it is no surprise that surgical excision was usually recommended. In 12 cases of radial scar with LCIS, 9 were recommended for surgical excision; however, none of these upgraded to a cancer. Three cases were recommended for imaging surveillance as notes from the CMC indicated that the radial scar explained the architectural distortion and the LCIS was seen as an incidental finding occurring in a location separate from the architectural distortion. Of the 3 radial scars with LCIS that were recommended imaging surveillance, 2 had no evidence of cancer at follow-up [one at 84 months (7 years) and the other at 90 months (7.5 years) follow-up], while 1 developed DCIS 85 months (7.1 years) later, within 1 cm of the LCIS biopsy site. In summary, only 8.3% (1/12) of radial scars with LCIS proved to be associated with an eventual delayed cancer, a cancer rate lower than the 12.5% (1 in 8) observed among all women. Finally, several authors have reported that mass lesions are more likely to be associated with cancer [8, 20]. In our study, while mass lesions were more commonly seen among cancers (18.2%, 4/22), compared to noncancerous mass lesions (13.8%, 13/94), this did not meet statistical significance. The lack of validation that a mass correlated with a cancer may be due to the overall small number of total cancers encountered among all LCIS lesions.

Pathologic determinants of LCIS

The pathologist plays a key role in determining whether the LCIS is seen incidentally versus directly correlating with the targeted lesion. The determination of whether LCIS is diagnosed incidentally versus targeted on core needle biopsy has important clinical importance. LCIS lesions diagnosed incidentally have been reported less likely to upgrade on excision (5% vs 39%) [21]. As a result, when LCIS was noted to be an incidental finding, surgical excision was not usually recommended.

The pathologist also plays an important role in subcategorizing LCIS as classic versus florid or pleomorphic, as the outcomes have been reported to be disparate based on this distinction [22, 23]. Pleomorphic LCIS is a relatively recently described pathological lesion that is distinguished from classic LCIS by the presence of large pleomorphic nuclei [24, 25]. The reported upgrade rates are estimated to be 31.8%–39.7% among pleomorphic LCIS [26], compared to the 16.4%–19% upgrade rates observed among classic LCIS [27, 28]. Thus, pleomorphic LCIS has a twofold increased risk for cancer, compared to classic LCIS. This study also reports a higher relative risk for cancer among the variant forms, albeit our smaller 1.53 relative risk may reflect the inclusion of both florid and pleomorphic LCIS as variant forms. It has been reported that 73.9% of pleomorphic LCIS cases are associated with an invasive cancer, usually estrogen receptor-positive, human epidermal growth receptor-2 negative invasive lobular cancers [29]. Another study reported the variant forms of florid and pleomorphic LCIS coexist in 45% of cases with comedonecrosis and similar molecular aberrations, and up to 77% of variant LCIS cases were associated with invasive cancers [30]. Based on these observations, some believe that variant forms of LCIS should be treated in a manner like DCIS and mandate surgical excision, regardless of imaging-pathologic concordance [29, 31]. At the study's institution, surgical excision is recommended for florid and pleomorphic LCIS variants and the distinction of the classic versus non-classic variants is a key variable that breast pathologists specifically remark upon.

Limitations

There are several limitations of this study. The single institution, retrospective design of this study has the potential for selection biases and data collection errors. To minimize data collection errors, the principal investigator collected and reviewed the data for accuracy. Due to a number of cases with missing data regarding the gauge of needle used for sampling, number of cores obtained during sampling, and number of cores with the imaging target, the significance and contribution of these data points could not be assessed. In some cases, the CMC note indicated that the consensus recommendation was for surgical excision but the specific reason for the surgical recommendation was not stated. Similarly, in some cases of discordance, the reason for discordance was not specifically given. In these cases, the clinical judgment of the principal investigator was used determine the reason why surgical excision was performed.

Despite the 15-year retrospective database of more than 7,000 ($n = 7391$) percutaneous needle biopsies, after applying the exclusion criteria to include only cases of LCIS without other high-risk lesions or a concurrent or a recent breast cancer diagnosis with either surgical excision or > than 2 years follow-up, the number of subjects was reduced to 116. Additionally, as the variant forms are far less common than classic LCIS, there were only 27 florid or pleomorphic

LCIS cases. Due to the small number, florid and pleomorphic LCIS were purposefully grouped together for analysis; however, it is uncertain if this arbitrary grouping is truly valid or if florid and pleomorphic LCIS should in fact be considered as separate entities. A larger pooled meta-analysis may be necessary to be able to remark on the true significance of each of the variant forms.

Even among subspecialists in breast imaging and breast pathology, variations exist in the assessment of imaging suspicion, determinants of discordance, and the use of the terminologies "multifocal" and "extensive." For the radiologist, multifocal LCIS represents a discontiguous imaging finding that is pathologically proven to be LCIS at more than one site of biopsy. For the pathologist, multifocal LCIS may represent smoldering disease that involves multiple TDLUs which may be obtained at a single biopsy site. This needs to be differentiated from the term of "extensive" LCIS, which some pathologists may use to describe LCIS that involves a single TDLU which may be amenable to surgical excision and more appropriately termed florid LCIS, while other pathologists correctly utilize "extensive" to describe the size of LCIS involvement. Additionally, there is inherent subjectivity in the interpretation of atypia, which presents as a morphological continuum reflecting a biological spectrum [32]. The lack of standardization in defining degrees of atypia and pathologists' nonuniformly in the description of variant forms of LCIS may contribute to disagreement in breast pathology interpretations and subsequent management recommendations [33]. While these variations among radiologists and pathologists may be viewed as a limiting factor, we believe the institution's use of rotating specialists to the multidisciplinary conference helped to bring additional and potentially differing opinions from within the same disciplines, which can in turn allow for additional insight and perhaps validate a more conservative management of a controversial entity such as LCIS.

Conclusion

LCIS has an overall cancer risk of 19.0% (22/116), with an immediate upgrade risk of 19.3% (11/57) and a delayed risk of 18.6% (11/59). The risk of cancer is 90.9% (20/22) to the same breast, with the greatest risk at the site of LCIS (63.6%, 14/22), followed by in the same breast but in a different quadrant (27.3%, 6/22), and is less common in the contralateral breast (9.1%, 2/22). Finally, though classic LCIS is 3.3 times more prevalent than the variant forms of florid or pleomorphic LCIS, almost a third (31.8%, 7/22) of the LCIS lesions ultimately diagnosed with cancer at excision had a variant form, reflecting the significance of this pathologic differences and its impact on the management of LCIS.

Author contributions HLC, GJW, and LPM contributed to the study conception and design. Material preparation, data collection, and analysis were performed by HLC. JS performed the data analysis. The first draft of the manuscript was written by HLC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest GJW is a consultant for Siemens and an editor for UpToDate. The remaining authors have no relevant financial or non-financial interests to disclose.

Consent to publish The authors affirm that human research participants provided informed consent for publication of the images in Figs. 2 and 3.

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