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ORIGINAL ARTICLE – BREAST ONCOLOGY

Lobular In-Situ Neoplasia on Breast Core Needle Biopsy: Imaging Indication and Pathologic Extent Can Identify Which Patients Require Excisional Biopsy

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ABSTRACT

Background. The surgical management of lobular in-situ neoplasia (LN) identified by core needle biopsy (CNB) is currently variable. Our institution has routinely excised LN on CNB since 2003, allowing for an unbiased assessment of upgrade rates.

Methods. Cases of LN on CNB, including atypical lobular hyperplasia (ALH) and lobular carcinoma-in-situ (LCIS), were identified in our pathology database. CNBs with concurrent pleomorphic LCIS, ductal carcinoma-in-situ (DCIS), and invasive carcinoma were excluded. Imaging indication/modality, biopsy indication, and radiologic concordance were determined. Pathology review included scoring total foci of LN in each CNB. Upgrade rates to invasive carcinoma or DCIS at excision were calculated.

Results. A total of 106 cases of LN (73 ALH and 33 LCIS) on CNB were identified. Thirty patients had concurrent atypical ductal hyperplasia (ADH) and 76 had LN alone; 93 (88%) of the patients had available surgical follow-up (25 LN + ADH and 68 LN alone). The upgrade rate at excision was 16% (4 of 25) for LN + ADH and 4.4% (3 of 68) for LN alone. Patients with LN alone and discordant imaging, imaging for high-risk indications, or extensive LCIS (>4 foci) accounted for all the upgrades. Normal-risk patients who underwent biopsy to assess calcifications found by routine mammographic screening with LN alone did not result in upgrade.

Conclusions. Women with a CNB diagnosis of LN for calcifications found on routine, normal-risk mammographic screening have a negligible risk of upgrade and may not require excisional biopsy. However, excisional biopsy should be offered to women undergoing imaging for other indications or with >4 foci of LN on CNB.

Lobular in-situ neoplasia (LN) was first described by Foote and Stewart in 1941 and later by Haagensen in 1978.[1,2] Atypical lobular hyperplasia (ALH) and lobular carcinoma-in-situ (LCIS) are considered risk factors for subsequent invasive carcinoma in either breast, with published relative risks of 4 to 5 times for ALH and up to 8 to 10 times for LCIS for both breasts.[3–6] Although more recent molecular evidence supports the role of LN as a nonobligate precursor to invasive cancer, the tendency for a multifocal and bilateral distribution, as well as an increased risk of subsequent cancers in both breasts, has resulted in treatment of LN as a risk factor, rather than as a surgically resectable disease.[7–15]

Much of the initial data on the biologic behavior of LN were based on pathologic findings in excisional specimens. It is now considered standard to use core needle biopsy (CNB) rather than excisional biopsy for initial evaluation of imaging and clinical findings. This has created the challenge of determining which risk-associated biopsy findings should be excised to rule out associated adjacent ductal carcinoma-in-situ (DCIS) or invasive carcinoma. With more sensitive imaging techniques, the incidence of finding LN on CNB is on the rise.[16–19] However, the most appropriate surgical management of LN on CNB is still a matter of debate. Although the 2011 National Comprehensive Cancer Network guidelines recommend consideration of excisional biopsy when LN is found on CNB, there are currently few

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data identifying which specific patients are most likely to benefit from excision.

Upgrade rates of LN on CNB to DCIS and invasive carcinoma range from 2 to 40%, depending on the study. The wide variability in these results has been attributed to small case numbers with relatively low excision rates resulting in case selection bias, variable radiologic correlation, and variable inclusion of cases with other high-risk lesions.[20] Furthermore, isolated LN, in which ALH or LCIS is the highest-risk lesion on CNB, is present in fewer than 2% of all CNBs, making this a difficult entity to study.[16,21,22]

Our institution has been routinely recommending excisional biopsy after diagnosis of ALH and LCIS on CNB since 2003. Consequently, we have a large collection of cases of isolated LN on CNB with routinely performed subsequent surgical excision. The purpose of this study was to determine the upgrade rate of isolated LN on CNB in this unique population with minimal selection bias. By correlating with imaging indication, imaging modality, and imaging findings as well as the pathologic extent of LN in the CNB, we were able to determine which of these characteristics could accurately identify which patients with LN on CNB were at risk of disease upgrade at excision.

METHODS

Case Selection

After institutional review board approval, we queried the University of Washington Medical Center pathology database for breast CNB reports containing a diagnosis of LN, LCIS, or ALH. Cases with invasive carcinoma, DCIS or pleomorphic LCIS in the same biopsy site were excluded. Because of its frequent association with atypical ductal hyperplasia (ADH), the presence of ADH in the same biopsy sample did not exclude a case from the study, but the presence or absence of concurrent ADH was used in the subset analysis. Patients with invasive carcinoma, DCIS, or pleomorphic LCIS in separate biopsy samples of different imaging or clinical findings were also intentionally included to determine the disease upgrade risk in patients with these risk factors. A total of 106 cases of LN on CNB were identified.

Radiology Review

Radiology reports were reviewed for all cases to establish the initial indication for imaging, the imaging modality used, and the imaging finding resulting in biopsy recommendation. The indication for imaging was categorized as one of the following: (1) routine mammographic screening, (2) diagnostic evaluation of a clinical finding, (3) extent of disease evaluation (occurred when a diagnosis of DCIS or invasive carcinoma was documented from a previous biopsy), (4) follow-up postlumpectomy/surgical procedure, and (5) routine screening (either mammogram or magnetic resonance imaging [MRI]) in a high-risk patient. High-risk patients included patients with a personal history of breast cancer, a history of a high-risk lesion found at biopsy, or strong family history of breast cancer.

The imaging modality (mammogram, MRI, or ultrasound) that contained the initial findings that led to the biopsy recommendation was recorded. If the imaging modality used to target the finding was different, the initial imaging modality identifying the finding was used. For example, a MRI finding that was targeted and biopsied under ultrasound would be considered an MRI for the purpose of imaging-modality categorization.

On the basis of the radiology report, the imaging finding leading to biopsy recommendation was categorized as calcifications on mammography, mass (on any imaging modality or at clinical examination), MRI enhancement, and architectural distortion.

The Breast Imaging Reporting and Data System (BI-RADS) was used to stratify lesions on the basis of concern for carcinoma.[23] All lesions that were suspicious for malignancy (BI-RADS category 4) underwent image-guided needle core biopsy. Biopsy was performed using sonographic, stereotactic, or MRI guidance. Imaging evaluation was performed with screen-film mammography from January 2003 through April 2004 and with full-field digital mammography from April 2004 through September 2009. From January 2003 through November 2003, procedures were performed with an 11-gauge directional vacuum-assisted breast biopsy device (Mammotome; Ethicon Endo-Surgery, Cincinnati, OH). From December 2003 through September 2009, stereotactic procedures were performed with a 9-gauge directional vacuum-assisted breast biopsy device (ATEC; Suros Surgical Systems, Indianapolis, IN). Ultrasound-guided biopsy procedures were performed with one of three 14-gauge spring-loaded CNB devices during the study dates: Manan (C. R. Bard) in 2003, MaxCore (C. R. Bard) from July 2003 through September 2009, and Achieve (Cardinal Health) from October 2003 through September 2009. The breast MRI technique performed at our institution has been described elsewhere.[24,25] In brief, MRI was performed on a 1.5-T magnetic resonance scanner (LX, GE Healthcare) using a dedicated breast coil (January 2003–January 2004, 4 Channel Breast Array, MRI Devices; February 2004–September 2005, Excite 7 Channel Breast Array, MRI Devices; October 2005–May 2009, 8 Channel Breast Biopsy Coil, GE Healthcare). All protocols included one

unenhanced and at least two contrast-enhanced T1-weighted fat-suppressed 3D fast gradient spoiled sequences. MRI-guided biopsy procedures performed before May 2003 were completed with a 14-gauge spring-loaded CNB device (Monopty Biopsy Instrument, C. R. Bard). MRI-guided biopsy procedures conducted after May 2003 were performed with a 9-gauge vacuum-assisted breast biopsy device (ATEC, Suros). Radiologic findings were rendered by dedicated breast radiologists and reviewed for concordance with subsequent histopathologic diagnoses.

Pathology Review

CNB specimens had a minimum of 3 hematoxylin and eosin-stained levels from between one and six separate tissue blocks examined. All cases were reviewed for this study by a single pathologist with a subspecialty interest in breast pathology (K.A.). The criteria used for a diagnosis of LCIS and ALH were previously published.[26,27] LCIS was further classified as classic type, pleomorphic, or LCIS with necrosis.[27] Classic-type LCIS was defined as a monotonous, discohesive proliferation of small, round cells with low to intermediate nuclear grade, evenly spaced, that both filled and distended >50% of the acini of involved lobular units. ALH was defined as the same cell population but with <50% of the acini filled and distended. Pagetoid involvement of ducts alone was classified as ALH. A diagnosis of pleomorphic LCIS was made when the nuclei were of high nuclear grade (at least three times the size of a lymphocyte with prominent nucleoli).[28] In cases where the lobular phenotype was in question, E-cadherin staining was performed.

In an effort to estimate extent of LN on CNB, the number of terminal ductal lobular units (TDLUs) involved by LN was estimated by adding up the total number of foci present in all needle cores from the same biopsy site. The H&E level with the most foci was used for each tissue block.

Pathologic findings on the subsequent surgical specimens (including excisional biopsy lumpectomy or mastectomy) performed within 6 months of the diagnostic CNB that could be correlated with the same biopsy site where LN was found were used as the follow-up diagnosis. In 13 cases, accurate follow-up was not available: 4 were lost to follow-up, 3 had concurrent carcinoma at another site and opted out of excision, 4 cases were not recommended for excision, 1 case was deemed too high a surgical risk, and 1 case had a mastectomy and the original CNB site with LN could not be identified.

Data Analysis

An upgrade from CNB to final surgical specimen was defined as a final surgical pathology diagnosis of invasive carcinoma and/or ductal carcinoma-in-situ that could be directly correlated to the site of the initial biopsy containing LN. Pleomorphic LCIS on the final surgical follow-up was not considered an upgrade for the purposes of this study (occurred in only 1 case). The imaging characteristics and pathologic extent of LN were correlated with upgrade rates in subgroup analysis.

RESULTS

From 2003 to 2009, 106 cases of LN (73 ALH and 33 LCIS) on CNB were identified in our pathology database and confirmed on pathology review (excluding all cases with invasive carcinoma, DCIS or pleomorphic LCIS at the

TABLE 1 Imaging/biopsy indication and imaging modality

Characteristic	*n* (%)
Imaging indication	
Routine mammographic screening	54 (51%)
High-risk screening	18 (17%)
Clinical finding evaluation	6 (6%)
Follow-up after lumpectomy	5 (5%)
Extent of disease evaluation	23 (21%)
Biopsy indication	
Calcification	73 (69%)
Mass	15 (14%)
MRI enhancement	17 (16%)
Architectural distortion	1 (1%)
Imaging modality	
Mammogram	79 (74%)
MRI	25 (24%)
Ultrasound	2 (2%)

TABLE 2 Upgrade rates of LN on CNB

Finding	*N*	Surgical follow-up, *n* (%)	Upgraded, *n* (%)[a]
LN + ADH	30	25 (83%)	4 (16%)
Pure LN	76	68 (89%)	3 (4.4%)
All LN	106	93 (88%)	7 (7.5%)
ALH + ADH	20	18 (90%)	2 (11%)
Pure ALH	53	48 (91%)	2 (4.1%)
Total ALH	73	66 (90%)	4 (6.0%)
LCIS + ADH	10	7 (70%)	2 (29%)
Pure LCIS	23	20 (87%)	1 (5%)
Total LCIS	33	27 (82%)	3 (11%)

[a] Upgrade refers to invasive carcinoma or ductal carcinoma found at surgical follow-up

LN lobular in-situ neoplasia (atypical lobular hyperplasia or lobular carcinoma-in-situ), *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma-in-situ, *ADH* atypical ductal hyperplasia

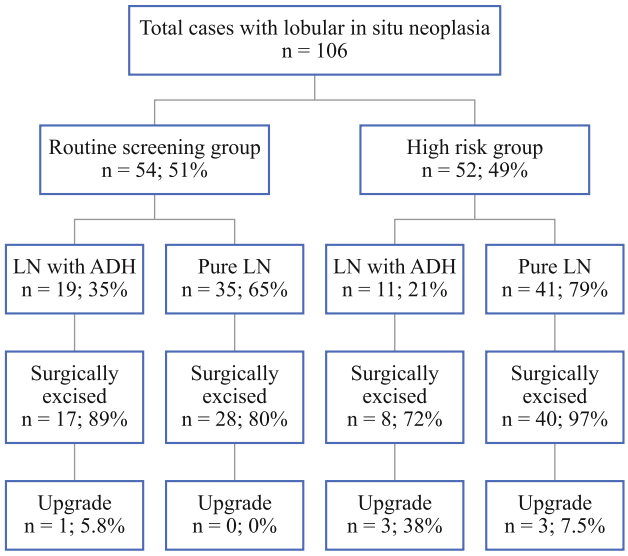

FIG. 1 Upgrade rates of LN (ALH and/or LCIS) on breast CNB separated by routine vs. high-risk imaging indication. The high-risk group includes patients with imaging performed as part of a high-risk screening program as a result of a personal or family history of breast cancer, extent of disease evaluation after a diagnosis of DCIS or invasive cancer in either breast, postlumpectomy follow-up, and evaluation of clinical findings (mass). Pure LN cases had no associated higher-risk lesion, including flat epithelial atypia, ADH, or pleomorphic LCIS. Pure LN in the routine mammographic screening group did not result in upgrade to DCIS or invasive cancer

same biopsy site, see Methods). Patients ranged in age from 35 to 86 (Median = 55). Imaging indication, imaging finding leading to biopsy and imaging modality used for cases of LN on CNB are shown in Table 1. Fifty-four (51%) were sampled as a result of findings on routine mammographic screening examination, and 52 (49%) were sampled for other imaging indications, including the following: 23 (21%) extent of disease evaluation, 18 (17%) high-risk screening, 6 (6%) evaluation of a clinical finding or mass, and 5 (5%) postlumpectomy follow-up. Mammography was the most common imaging modality that identified the findings leading to biopsy, accounting for 74% of the cases; MRI was the modality in 24% and ultrasound in 2%. The radiographic abnormalities that prompted the CNBs were most commonly calcifications (69%), followed by MRI enhancement (16%), mass (14%), and architectural distortion (1%). Radiologic–pathologic discordance was noted only in one case; a clinical mass identified on ultrasound with only ALH on the CNB (this case was upgraded to invasive lobular carcinoma at excision).

Final pathology from subsequent surgical sampling was available in 93 cases (88%). Table 2 provides surgical follow-up rates and upgrade rates by histologic diagnosis. Without accounting for imaging characteristics or extent of LN on pathology review, the overall upgrade rate for all 93 cases with LN with or without ADH on CNB and available final surgical pathology was 7.5% (7 of 93). LCIS + ADH had the highest upgrade rate of 29%, whereas pure LCIS only resulted in upgrade in 5.0%. ALH + ADH resulted in upgrade in 11%, while pure ALH resulted in upgrade in only 4.1%. Overall, LN + ADH resulted in upgrade in 16% of cases, and LN alone resulted in upgrade of 4.4% of cases.

Risks of upgrade when grouped by imaging indication are shown in Fig. 1 and the combined imaging and pathology findings of upgraded cases are shown in Table 3. Interestingly, none of the 28 cases of pure LN on CNB performed after routine screening mammography for calcifications upgraded (95% confidence interval [CI] 0.0–0.12), whereas 3 of 40 (7.5 %) of the pure LN on CNB

TABLE 3 Imaging and final pathology of cases of ALH and LCIS on CNB with upgrade at excision

Case no.	Core biopsy diagnosis	Imaging indication	Imaging findings	Excision diagnosis	Radiology concordance
1	ALH	Clinical indication	Clinical mass on ultrasound	Invasive lobular + LCIS	No
2	ALH	High-risk screening (family history)	Non-mass-like enhancement on MRI	Extensive LCIS, ADH, mastectomy with DCIS	Yes
3	LCIS	Extent of disease evaluation	Non-mass-like enhancement on MRI	DCIS and extensive LCIS	Yes
4	ALH + ADH	High-risk screening (history of cancer in other breast)	Non-mass-like enhancement on MRI	DCIS and extensive LCIS	Yes
5	ALH + ADH	High-risk screening (history of cancer in other breast)	Non-mass-like enhancement on MRI	DCIS and extensive LCIS	Yes
6	LCIS + ADH	Routine screening	Calcifications on mammography	DCIS and ADH	Yes
7	LCIS + ADH	High-risk screening (history of cancer in other breast)	Non-mass-like enhancement on MRI	Pleomorphic LCIS and DCIS	Yes

ALH atypical lobular hyperplasia, *LCIS* lobular carcinoma-in-situ, *ADH* atypical ductal hyperplasia, *DCIS* ductal carcinoma-in-situ

performed for other imaging indications upgraded (95% CI 0.016–0.2). Of the 3 cases of pure LN that upgraded, one had a clinical and ultra-sonographic mass (discordant imaging) and upgraded to invasive lobular carcinoma, whereas two cases had non-mass-like enhancement on MRI and upgraded to DCIS. LN + ADH on routine screening mammogram had a nonzero but low upgrade rate of 5.8% (upgraded to DCIS) (95% CI 0.001–0.29), whereas LN + ADH identified for any other imaging indication upgraded in 38% of cases (upgraded to DCIS) (95% CI 0.085–0.76).

Extent of LN on the CNB correlated with risk of upgrade. Six (21%) of 29 cases with ≥4 foci of LN found by biopsy resulted in upgrade, versus 1 (2.2%) of 46 cases with <4 foci ($P \leq 0.0007$). Additionally, the single case of upgrade with <4 foci of LN was determined to be discordant by imaging. This patient had ALH on CNB but underwent biopsy for a clinical mass that was subsequently found to be invasive lobular carcinoma. Consequently, in cases that were deemed concordant with the radiologic biopsy indication and that LN involved <4 TDLUs, the overall upgrade rate was 0.

DISCUSSION

Using a large cohort of patients who were routinely recommended excisional biopsy for LN on CNB, we found that patients with isolated LN on CNB for calcifications

TABLE 4 Literature review of LN on needle core biopsy

Study	Total cases of pure LN on CNB with excisions	Excision rate	Upgrade rate	P-LCIS or "mixed CIS" cases included?	Reasons identified for upgrade
Middleton et al.[29]	17	49%	6 (35%)	Not mentioned	6 of 6 upgrades were for mass on imaging
Mahoney et al.[30]	20	74%	5 (25%)	Yes	2 upgrades were for mass, 1 had P-LCIS, 1 had concurrent cancer in opposite breast
Elsheikh and Silverman [3]	33	NA	9 (27%)	Yes	P-LCIS, extensive LCIS and mass on imaging were all more likely to upgrade
Foster et al.[31]	26	74%	6 (23%)	Not mentioned	2 of 6 upgrades were for mass on imaging
Brem et al.[32]	164	59%	38 (23%)	Not mentioned	21 of 38 upgrades had discordant imaging
Liberman et al.[21]	9	74%	2 (22%)	Yes	All upgrades were in cases with mixed ductal and lobular features. No classic, pure LN upgraded.
Menon et al.[33]	25	53%	8 (32%)	Yes, two	7 of 8 cases had discordant imaging (mass or calcifications were missed), 1 of 2 P-LCIS upgraded
Shin and Rosen [34]	13	NA	2 (15%)	No	Radiologic concordance not discussed but 2 cases had a mass on imaging
Arpino et al.[17]	21	47%	3 (14%)	Not mentioned	1 of 3 upgrades had mass on imaging
Crisi et al.[35]	16	48%	2 (13%)	Yes, one case	2 of 2 upgrades had mass on imaging
Hwang et al.[36]	87	41%	10 (11%)	Yes	6 of 10 upgrades had P-LCIS or LCIS with necrosis on core biopsy. 6 of 10 upgrades had discordant imaging.
Esserman et al.[37]	32	74%	2 (8%)	Not mentioned	2 of 2 upgrades had diffuse LCIS on core biopsy
Cangiarella et al.[38]	38	NA	3 (8%)	Not mentioned	2 of 3 upgrades had mass/discordant imaging
Berg et al.[16]	15	60%	1 (7%)	Yes	All cases excised because of coexistent diagnosis of ADH, DCIS or invasive cancer at the same site
Yeh et al.[39]	15	NA	1 (7%)	Not mentioned	Radiologic concordance not discussed
Renshaw et al.[40]	92	43%	3 (3%)	Yes	1 of 3 upgrades was nonclassic LCIS
Nagi et al.[20]	45	46%	2 (4.4%)	No	Study population focused on incidental LN only based on radiology–pathology correlation
This study	68	89%	3 (4.4%)	No	All upgrades occurred in high-risk patients, those with discordant imaging, or those with extensive LCIS

LN lobular in-situ neoplasia (atypical lobular hyperplasia and/or lobular carcinoma-in-situ), *CNB* core needle biopsy, *P-LCIS* pleomorphic lobular carcinoma-in-situ, *mixed CIS* carcinoma-in-situ with mixed ductal and lobular features

present on routine mammographic screening exam did not upgrade to DCIS or invasive carcinoma on subsequent excision. However, patients with any other imaging indication (high-risk screening, determination of extent of disease, follow-up after lumpectomy, evaluation of a clinical finding) or imaging finding (mass, architectural distortion, MRI enhancement) had a nonzero risk of upgrade at excision. In addition, CNB with ≥4 TDLUs involved by LN were at a higher risk of upgrade than cases with <4 foci. Our data also confirm previous work that cases of LN with concurrent ADH should be excised regardless of the imaging indication or imaging findings.

The available literature on LN on CNB contains multiple studies from different institutions yielding upgrade rates ranging 1–35% (Table 4).[3,16,17,20,21,29–40] As a result of the relative rarity of isolated LN on CNB, many of these studies contain limited numbers of cases (majority with <30 cases/study). Selection bias, with higher-risk cases being selected for excisional biopsy, was a potential confounder of many of these studies. Our follow-up excision rate of 89% was the highest in the literature to date. Of note, in most of the studies with higher upgrade rates (rates of 11–35%), upgrades were frequently explained by either discordant imaging or inclusion of cases with mixed ductal and lobular features (or pleomorphic LCIS). One study by Esserman et al. also found, similar to our results, that more extensive LN on CNB explained upgraded cases.[37] Studies like ours, which have looked carefully at cases with radiologic concordance and separately categorized or specifically excluded cases with nonclassic histologic features (pleomorphic or mixed features, or extensive involvement) found results similar to ours, with much lower upgrade rates.

Taken together, our data suggest that the decision to excise isolated LN when found on CNB should depend on multiple factors including, the imaging indication, imaging findings, extent of LN on CNB, and the presence of concurrent ADH on CNB. We propose a treatment algorithm that allows for close follow-up of patients with calcifications on routine mammography and isolated LN on CNB that meet the following criteria: (1) normal-risk patient undergoing routine screening mammography found to have calcifications, (2) <4 foci of LN on CNB, and (3) no other high-risk lesion present. All other cases, including those imaged for higher-risk indications (high-risk screening for personal or family history of breast cancer, extent of disease evaluation, clinically detectable finding), those with isolated LN involving ≥4 TDLUs, and those with concurrent ADH or other high-risk lesion should be recommended for excisional biopsy. This proposed algorithm is detailed in Fig. 2. Although more extensive prospective validation of this treatment algorithm would be ideal, in the absence of clear guidelines in this area it may serve as a useful decision-making guide.

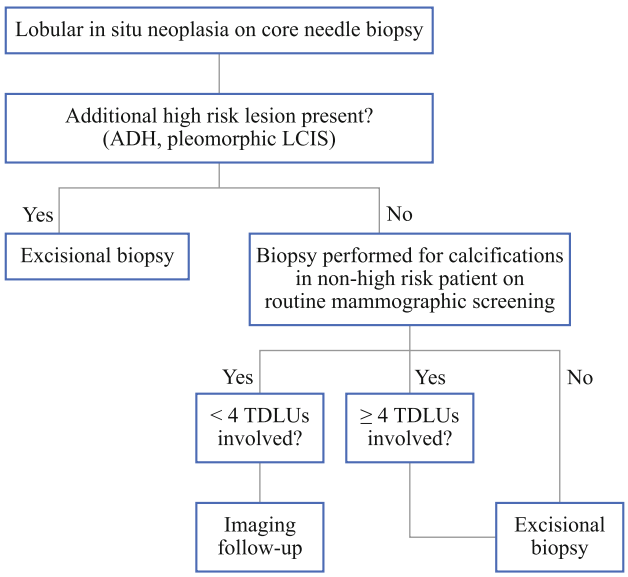

FIG. 2 Proposed algorithm for deciding which patients with LN should be recommended to undergo surgical excisional biopsy. A high-risk patient is defined as a patient with any of the following: *1* a strong family history or personal history of breast cancer, *2* imaging performed for extent of disease evaluation, and *3* a patient with a clinical finding at breast examination

As MRI becomes increasingly used to screen high-risk populations, the true incidence of upgrade of isolated LN on CNB with this screening modality needs to be further defined. Patients in our study who underwent breast MRI were either in a high-risk screening group or being evaluated for extent of disease after a diagnosis of invasive cancer or DCIS. Five of our seven upgraded cases underwent biopsy for non-mass-like enhancement on MRI. Few studies have looked specifically at upgrade rates for LN biopsy procedures performed for MRI findings. Port et al. looked at patients with a history of LCIS that enrolled in a high-risk program screened by either MRI or mammography; 13% of biopsy procedures performed in the MRI screened patients and 36% of the mammography-screened patients contained cancer, suggesting that upgrade rates are likely related to the higher-risk nature of the population rather than the specific imaging technique used.[41] We currently recommend surgical excision for LN on CNB for all patients considered high-risk on the basis of personal or family history, regardless of whether mammography or MRI is used as the screening modality.

In summary, we have determined that cases of isolated LN on CNB require subsequent surgical excision in high-risk cases as a result of a possibility of upgrade to DCIS or invasive cancer. However, we have also identified a population of women who may be spared further surgical intervention because of the unlikelihood of pathologic upgrade. Specifically, normal-risk patients presenting for routine screening with calcifications on mammography that

are explained by isolated LN involving <4 TDLUs on CNB may not require surgical excision. Given that women presenting with calcifications on routine mammographic screening represented approximately 50% of our entire case collection, these findings could have major implications on the number of women requiring surgical excision with a finding of isolated LN on CNB.

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