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Atypical lobular hyperplasia and classic lobular carcinoma *in situ* in core biopsy specimens: routine excision is not necessary

Helena Hwang[1], Lora D Barke[2], Ellen B Mendelson[3] and Barbara Susnik[4]

[1]*Department of Pathology, Roswell Park Cancer Institute, Buffalo, NY, USA;* [2]*Radiology Imaging Associates, Sally Jobe Breast Center, Englewood, CO, USA;* [3]*Department of Radiology, Northwestern Memorial Hospital, Chicago, IL, USA and* [4]*Department of Pathology, Northwestern Memorial Hospital, Chicago, IL, USA*

Standardized recommendations for the management of lobular neoplasia in core biopsy specimens are not established. The aim of our study was to define morphologic features of lobular neoplasia in core biopsies that predict the finding of ductal carcinoma *in situ* or invasive carcinoma in the subsequent excisional specimen. We reviewed 333 cases of atypical lobular hyperplasia or lobular carcinoma *in situ* without ductal carcinoma *in situ* or invasive carcinoma diagnosed in core biopsies from 1996 to 2006. Subsequent excision was performed in 41% (136/333) of cases, including atypical lobular hyperplasia ($n=48$), lobular carcinoma *in situ* ($n=39$), and lobular neoplasia associated with atypical ductal hyperplasia ($n=49$). Upgrades were identified in 2% (1/48) of atypical lobular hyperplasia, 23% (9/39) of lobular carcinoma *in situ*, and 27% (13/49) of lobular neoplasia associated with atypical ductal hyperplasia cases. When further analyzed, the upgraded cases of lobular carcinoma *in situ* were associated with radiologic–pathologic discordance in 6/9 cases and with nonclassic pathology (two lobular carcinoma *in situ* with necrosis and one pleomorphic lobular carcinoma *in situ*) in the remaining three cases. The frequency of upgrade was 11% (3/26) in classic lobular carcinoma *in situ*, and 46% (6/13) in nonclassic types (pleomorphic or with necrosis). After excluding cases with discordant imaging/pathology, there was a 5% upgrade in our excisional specimens. After excluding cases where the upgrade was associated with nonclassic morphology, the upgrade in our study was 1%. Our results suggest that atypical lobular hyperplasia and classic lobular carcinoma *in situ* with concordant radiology and pathology can be appropriately managed with clinical follow-up without surgery.
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Lobular neoplasia refers to noninvasive proliferative lobular lesions and encompasses both atypical lobular hyperplasia and lobular carcinoma *in situ*. An alternative classification system proposed by Tavassoli[1] classifies lobular neoplasia into three grades and uses the term lobular intraepithelial neoplasia. The management of lobular neoplasia is a subject of much controversy. Lobular neoplasia is a marker of increased risk for developing invasive breast cancer; this risk is multicentric and bilateral. In addition, studies of genomic alterations support a precursor role for some lobular neoplasia lesions with the capacity to directly progress to invasive carcinoma.[2] How frequently lobular neoplasia progresses to invasive carcinoma is not known. The specific morphologic or molecular features of lobular neoplasia lesions that predict aggressive behavior are not established. Morphologically, lobular neoplasia is classically characterized by small, bland discohesive cells. Since their original description, variants of lobular carcinoma *in situ* have been recognized, aided by differential E-cadherin immunostaining.[3–5]

These variants include pleomorphic lobular carcinoma *in situ* characterized by discohesive pleomorphic cells with abundant cytoplasm.[6] Rosen described 'florid' lobular carcinoma *in situ* characterized by 'tumor cells that fill and expand the duct lumen' that 'may develop central necrosis and calcifications'.[7] Sapino *et al*[8] and Fadare *et al*[9] also have defined *in situ* lesions with morphologic features of lobular neoplasia but with necrosis as lobular carcinoma *in situ*. Not only do both pleomorphic lobular carcinoma *in situ* and lobular carcinoma *in situ* with necrosis show different

Correspondence: Dr B Susnik, Department of Pathology, Northwestern Memorial Hospital, 251 E. Huron St, Chicago, IL 60611, USA.
E-mail: b-susnik@northwestern.edu
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morphology, they can also exhibit a more aggressive biologic marker profile compared to classic lobular carcinoma *in situ*.[6,8–12] Microinvasive lobular carcinoma has been associated with pleomorphic lobular carcinoma *in situ* or lobular carcinoma *in situ* with necrosis,[6,8,9,13] although in routine practice, microinvasive carcinomas have also been observed in association with classic lobular carcinoma *in situ*. Lobular carcinoma *in situ* with nonclassic features has also been found to be more frequently associated with adjacent invasive carcinoma, especially invasive lobular carcinoma.[14] High-grade ductal carcinoma *in situ* is known to show more aggressive behavior with frequent recurrence and progression to invasive carcinoma.[15–17] Surprisingly, this basic tenet is not as accepted in lobular lesions as it is in ductal lesions.

Standardized recommendations for the management of lobular carcinoma *in situ* or atypical lobular hyperplasia diagnosed on core biopsy are not established. However, many patients currently undergo excision of the core biopsy site when lobular neoplasia is found. Previous studies have shown an upgrade to ductal carcinoma *in situ* or invasive carcinoma in 2% to over 40% of cases on subsequent excision of lobular neoplasia on core biopsy.[18–20] Possible explanations for the wide range reported in upgrades include variables in technical aspects of imaging, the degree of pathologic–radiologic correlation, and variability in pathologically defining these lesions.

The aim of our study was to review the pathologic and radiologic features of patients with atypical lobular hyperplasia or lobular carcinoma *in situ* diagnosed by core biopsy at our institution from 1996 to 2006 and to define features that predict an upgrade to ductal carcinoma *in situ* or invasive carcinoma in subsequent excisions.

Materials and methods

Patients

Following the IRB approval, we retrieved 362 consecutive core biopsies performed at our institution from 1996 to 2006 with a diagnosis of lobular neoplasia, lobular intraepithelial neoplasia, atypical lobular hyperplasia, lobular carcinoma *in situ*, or carcinoma *in situ* with mixed features (mixed carcinoma *in situ*). Cases of lobular neoplasia associated with invasive carcinoma and/or ductal carcinoma *in situ* were excluded. Lobular neoplasia cases with atypical ductal hyperplasia were analyzed separately. Follow-up surgical excision was defined as a surgical procedure (eg needle-localization and excision or mastectomy) that was performed within 3 months after the diagnostic core biopsy. Available clinical data were compiled from our patient database and included examination of variables, such as a history of breast carcinoma, synchronous breast carcinoma, and subsequent development of carcinoma.

Imaging

Images were reviewed by dedicated breast radiologists. Abnormalities were grouped into the following categories: microcalcifications, microcalcifications with masses, masses alone, and architectural distortions. The Breast Imaging Reporting and Data System (BI-RADS) was used to stratify lesions according to different levels of suspicion for carcinoma (American College of Radiology, Reston, VA, USA, 4th edn, 2003). All lesions placed in BI-RADS category 4 (suspicious for malignancy) underwent image-guided needle core biopsy. Core biopsy was performed using stereotactic, sonographic, or magnetic resonance imaging (MRI) guidance. Information regarding number of cores and gauge used for core biopsy was recorded when available. Stereotactic biopsy was performed using a directional, vacuum-assisted biopsy device with 9- to 12-gauge needles. A specimen radiograph confirmed the presence of calcifications in each sample, and a clip was used to mark the biopsy site. Sonographically guided biopsy was performed using a spring-activated device with a 14-gauge needle or a vacuum-assisted device with 9- to 12-gauge needles. MRI-guided biopsy was performed using 1.5 T MR system (Siemens) using 9-gauge needles. Radiologic findings were routinely reviewed to evaluate concordance with histopathologic diagnoses.

Pathology

The core biopsy microscopic slides reviewed included all cases with subsequent excisions and additional cases without subsequent excision. On review, lobular neoplasia cases were reclassified as either atypical lobular hyperplasia or lobular carcinoma *in situ*. Lobular carcinoma *in situ* was further categorized into classic type, pleomorphic type, or lobular carcinoma *in situ* with necrosis. Several cases in our study had an original diagnosis of 'mixed carcinoma *in situ*.' In these cases and others where the diagnosis of lobular neoplasia was equivocal (cases with nonclassic morphology), an E-cadherin immunohistochemical stain was performed for definitive classification. On review, none of the cases in this study were categorized as mixed carcinoma *in situ* as none fit our definition of it. We used the following definitions based on previously described criteria of various authors:

Classic lobular carcinoma *in situ*. An uniform population of small discohesive cells with bland nuclei with mild to absent pleomorphism. The threshold for the distinction of lobular carcinoma *in situ vs* atypical lobular hyperplasia is involvement of at least 75% of the units of a lobule[7] (Figure 1).

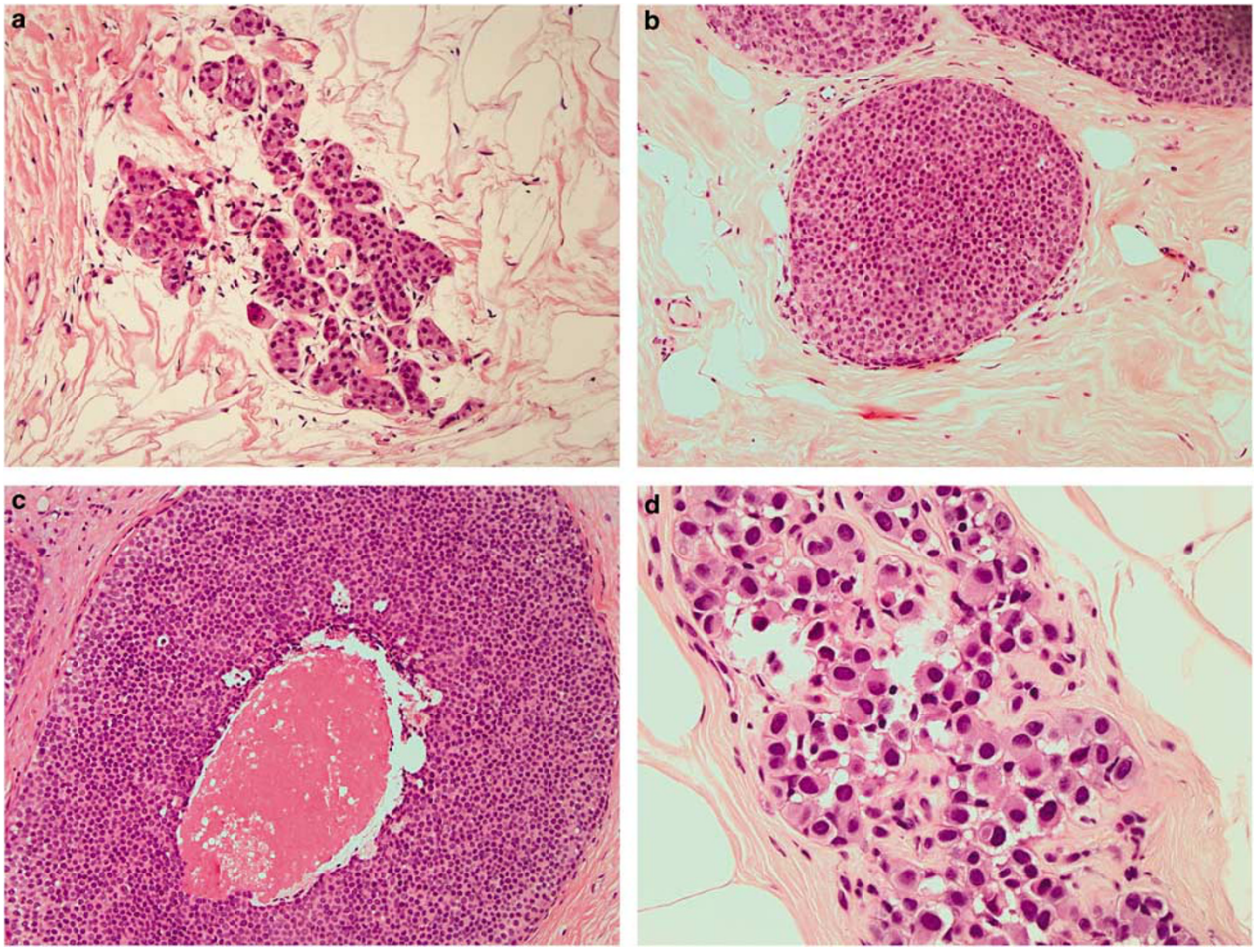

Figure 1 Atypical lobular hyperplasia and lobular carcinoma *in situ*, classic type, and variants. (**a**) Atypical lobular hyperplasia with neoplastic cells replacing normal glandular epithelium in acinar units effacing the lumens. The acini remain small, nondistended, and the borders of acinar units remain indistinct (H&E × 200). (**b**) Lobular carcinoma *in situ*, classic type, consists of a uniform population of discohesive cells with bland nuclei and intracytoplasmic mucin vacuoles (H&E × 200). (**c**) Lobular carcinoma *in situ* with necrosis, with ductules markedly distended by cells with classic morphologic features of lobular neoplasia and displaying central luminal necrosis (H&E × 200). (**d**) Lobular carcinoma *in situ*, pleomorphic type, with large discohesive cells with eccentrically placed large nuclei (> 3 × the size of lymphocyte), moderate pleomorphism, and distinct small nucleoli (H&E × 400).

Atypical lobular hyperplasia. Same neoplastic cells as described for lobular carcinoma *in situ* replacing the normal glandular epithelium in acinar units and effacing the lumens. The acini are small, nondistended, and the borders of acinar units remain indistinct.[7]

Lobular carcinoma *in situ* with necrosis. Small, bland discohesive cells with marked distention of ductules/acini, and necrosis.[7]

Pleomorphic lobular carcinoma *in situ*. Pleomorphic population of medium to large cells, with nuclei at least three times the size of a lymphocyte, eccentrically placed, and with distinct nucleoli. Cells have moderate to abundant cytoplasm and at least focal areas of loss of cohesion. Necrosis and microcalcifications may be present.[6]

Mixed carcinoma *in situ*. Proliferation of neoplastic ductal and lobular cells within the same ductule/acini, with heterogeneous expression of E-cadherin.[11]

In cases with upgrades (ie cases containing invasive carcinoma and/or ductal carcinoma *in situ* in subsequent excisional specimens), the excisional specimens were also reviewed and the findings were categorized as malignant (ductal carcinoma *in situ* or invasive carcinoma) or benign (lobular carcinoma *in situ*, atypical lobular hyperplasia, atypical ductal hyperplasia, or any other benign histologic finding). An E-cadherin immunostain was performed in excisional specimens with an equivocal diagnosis on review.

Results

Patients

From 1996 to 2006, 362 cases of lobular neoplasia on core biopsy were identified in our database. Of those, 29 cases were omitted because (1) lobular neoplasia could not be identified in the core biopsy,

Table 1 Cases with and without subsequent excision

Core biopsy diagnosis	*With excision*	*Without excision*	*Total*
LN	87 (48 ALH, 39 LCIS[a])	190 (173 ALH, 17 LCIS[b])	277
LN+ADH	49 (16 ALH, 33 LCIS[c])	7 (3 ALH, 4 LCIS[c])	56
Total	136	197	333

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*; LN, lobular neoplasia.
[a]Of the excised LCIS, classic LCIS = 26, LCIS with necrosis = 6, pleomorphic LCIS = 7.
[b]Of the nonexcised LCIS, classic LCIS = 16, LCIS with necrosis = 1.
[c]All LCIS+ADH cases, excised and nonexcised, were classic LCIS.

Table 2 Radiologic presentation and biopsy mode of core samples

	Cases with subsequent excision			*Cases without subsequent excision*	*Total (n = 333)*
	ALH (n = 48)	*LCIS (n = 39)*	*LN+ADH (n = 49)*	*LN and LN+ADH (n = 197)*	
Type of lesion					
Calcifications	37	22	48	175	282
Mass lesion	11	17	1	22	51
Biopsy mode					
Ultrasound guided	10	10	—	21	41
Stereotactic	38	27	48	175	288
MRI guided	—	2	1	1	4

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*; LN, lobular neoplasia; MRI, magnetic resonance imaging.

(2) malignancy including ductal carcinoma *in situ* or invasive carcinoma was identified in the core biopsy, or (3) on account of subsequent mastectomy performed for synchronous ipsilateral carcinoma in another part of the breast.

The total number of cases was 333. Nine patients had two different biopsies so that the total number of patients was 324. Patients ranged in age from 29 to 87 years (median of 54 years). No difference in age was observed in patients with atypical lobular hyperplasia, lobular carcinoma *in situ*, or lobular neoplasia associated with atypical ductal hyperplasia.

Pure lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma *in situ* cases without associated atypical ductal hyperplasia) was present in 277 cases, whereas atypical ductal hyperplasia was an associated finding in 56 cases. Overall, 41% (136/333) of cases had a subsequent lumpectomy or mastectomy (Table 1): atypical lobular hyperplasia + atypical ductal hyperplasia ($n = 33$), lobular carcinoma *in situ* + atypical ductal hyperplasia ($n = 16$), atypical lobular hyperplasia ($n = 48$), lobular carcinoma *in situ* ($n = 39$). Cases without subsequent excision consisted of atypical lobular hyperplasia ($n = 173$), lobular carcinoma *in situ* ($n = 17$), atypical lobular hyperplasia + atypical ductal hyperplasia ($n = 3$), and lobular carcinoma *in situ* + atypical ductal hyperplasia ($n = 4$). The majority of lobular neoplasia + atypical ductal hyperplasia cases were followed by surgical excision (49/56, 87.5%), whereas only 31% (87/277) of pure lobular neoplasia cases had an excision. 70% (39/56) of lobular carcinoma *in situ* cases and 22% (48/221) of atypical lobular hyperplasia cases had an excision. There was a significant trend to excise lobular carcinoma *in situ* rather than atypical lobular hyperplasia (χ^2-test, $P < 0.001$), reflecting a selection bias. There was also a significant trend to proceed to surgery if patients had a personal history of breast carcinoma (χ^2-test, $P = 0.001$).

Imaging

The predominant method of biopsy was stereotactic ($n = 287$), followed by ultrasound guided ($n = 40$) and MRI guided ($n = 4$). Biopsies were performed for calcifications in 85% (282/333) and mass lesions in 15% (51/333) (Table 2). A total of 38% (107/282) of cases presenting with calcifications and 57% (29/51) of cases presenting with mass lesions were excised.

Biopsies were performed with 9- to 14-gauge needles (Table 3). The number of passes performed ranged from 4 to 24 with an average of seven cores per biopsy site in lobular neoplasia cases, 4–24 with an average of nine cores in lobular neoplasia + atypical ductal hyperplasia cases, and 4–18 with an average of nine cores in cases without subsequent excision. The amount of tissue removed by core biopsy was similar in cases with and in cases without subsequent excision.

Table 3 Needle gauge used for core biopsies

Needle gauge	*Cases with excisions*		*Cases without excisions*
	LN	*LN+ADH*	*LN and LN+ADH*
9	23	11	24
10	2	2	—
11	35	30	109
12	1	—	—
14	18	—	19
Not available	8	6	45
Total	87	49	197

ADH, atypical ductal hyperplasia; LN, lobular neoplasia.

Table 4 Cases with subsequent excisions: original diagnosis and diagnosis upon review

Original diagnosis	*Review diagnosis*	
	ALH	*LCIS*
ALH	13	1
LIN 1	7	—
LIN 2 or 1–2	23	10
LIN 3 or 2–3	2	6
LCIS	—	17
MCIS	1	5
LN not specified	2	—
Total	48	39

ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*; LIN, lobular intraepithelial neoplasia; MCIS, mixed carcinoma *in situ*.

Pathology

The archival cases included in the study were previously diagnosed by various pathologists, some of them using different nomenclatures and classifications (atypical lobular hyperplasia, lobular carcinoma *in situ*, lobular neoplasia, lobular intraepithelial neoplasia 1–3, mixed carcinoma *in situ*). We reviewed cases and reclassified them into lobular carcinoma *in situ* and atypical lobular hyperplasia for uniformity (Table 4). Lobular neoplasia cases with subsequent excision were classified on review as lobular carcinoma *in situ* ($n=39$) or atypical lobular hyperplasia ($n=48$). Lobular carcinoma *in situ* cases were classified as classic type ($n=26$), associated with necrosis ($n=6$), or pleomorphic type ($n=7$). Two cases of pleomorphic lobular carcinoma *in situ* also exhibited necrosis. Lobular neoplasia cases without subsequent excision consisted of atypical lobular hyperplasia ($n=173$) and lobular carcinoma *in situ* ($n=17$). All of the nonexcised lobular carcinoma *in situ* cases were classic type, except one that was associated with necrosis.

E-cadherin immunostaining was performed in cases with an original diagnosis of mixed carcinoma *in situ* for identification of the lobular carcinoma *in situ* component. In the lobular carcinoma *in situ* group, in two cases, the excisional specimens also had an original diagnosis of mixed carcinoma *in situ*. Histologic review and E-cadherin immunostaining confirmed a diagnosis of pure lobular carcinoma *in situ* in these two excisional specimens. In another case, the original diagnosis in the excisional specimen was ductal carcinoma *in situ* and lobular carcinoma *in situ*. Upon review and with the aid of E-cadherin immunostaining, a diagnosis of pure lobular carcinoma *in situ* was confirmed. In the atypical lobular hyperplasia group, one case originally diagnosed as lobular intraepithelial neoplasia 2 with atypical ductal hyperplasia was reclassified as pure atypical lobular hyperplasia as no atypical ductal hyperplasia was identified on review. An E-cadherin immunostain on the single mixed carcinoma *in situ* case confirmed the presence of lobular neoplastic cells only and was reclassified as atypical lobular hyperplasia.

Table 5 Upgrades in lobular neoplasia cases

Type of case	*Total*	*Upgrades*	*%*
ALH	48	1	2
LCIS	39	9	23
Classic LCIS	26	3[a]	11
LCIS with necrosis	6	3[b]	50
Pleomorphic LCIS	7	3[c]	43
Total	87	10	11

ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma *in situ*.
[a]All three cases had radiologic–pathologic discordance.
[b]One case had radiologic–pathologic discordance.
[c]Two cases had radiologic–pathologic discordance.

Upgrades

When lobular neoplasia was associated with atypical ductal hyperplasia, 27% (13/49) of cases were upgraded on excision. Upgrades in this group were found in 30% (10/33) of atypical lobular hyperplasia + atypical ductal hyperplasia cases and in 19% (3/16) of lobular carcinoma *in situ* + atypical ductal hyperplasia cases. Table 5 shows the frequency of upgrades in pure lobular neoplasia (without atypical ductal hyperplasia). Upgrades were seen in 11% of lobular neoplasia cases overall (23% of lobular carcinoma *in situ*, 2% of atypical lobular hyperplasia). Lobular carcinoma *in situ* cases with an upgrade had discordant imaging and pathology in 6/9 cases: in three cases, a mass/architectural distortion/MRI enhancement could not be explained by a diagnosis of only lobular carcinoma *in situ* in core biopsy and in the remaining three cases, calcifications were not adequately sampled. The three upgraded lobular carcinoma *in situ* cases with concordant imaging and pathology included lobular carcinoma *in situ* with necrosis ($n=2$) and pleomorphic lobular carcinoma *in situ* ($n=1$) (Table 6).

In the atypical lobular hyperplasia group, four cases had an original diagnosis of mixed carcinoma *in situ* or ductal carcinoma *in situ* in the excisional

Table 6 Pathologic features and radiology/pathology correlation in upgraded cases of lobular carcinoma *in situ*

Case	*Radiologic finding*	*Core biopsy diagnosis*	*Calcifications in core biopsy*	*Radiologic–pathologic discordance*	*Excision diagnosis*
1	Mass	Classic LCIS	Yes	Yes	DCIS, LCIS, sclerosing adenosis
2	Architectural distortion	Classic LCIS	Yes, LCIS	Yes	IDC (1.0 cm), DCIS, LCIS
3	MRI enhancement	LCIS-N	Yes, LCIS	Yes	DCIS, LCIS-N
4	Indeterminate Ca^{++}	Classic LCIS	Minimal[a]	Yes[a]	IMC (0.6 cm), DCIS, LCIS
5	Pleomorphic Ca^{++}	LCIS-P	Minimal[a]	Yes[a]	DCIS
6	Pleomorphic Ca^{++}	LCIS-P	Yes, LCIS[a]	Yes[a]	DCIS, LCIS-P
7	Pleomorphic Ca^{++}	LCIS-N	Yes, LCIS	No	Microinvasive carcinoma, LCIS-N
8	Indeterminate Ca^{++}	LCIS-N	Yes, LCIS	No	ILC (0.5 cm), LCIS-N
9	Indeterminate Ca^{++}	LCIS-P	Yes, LCIS	No	DCIS, LCIS

DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; LCIS-N, LCIS with necrosis; Ca^{++}, calcifications; IMC, invasive mammary (mixed ductal and lobular) carcinoma; LCIS-P, pleomorphic LCIS; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging.
[a]Inadequate sampling of suspicious calcifications.

specimen. Two of the mixed carcinoma *in situ* upgrades were reclassified as lobular carcinoma *in situ* based on histologic review and E-cadherin immunostains. One upgrade to ductal carcinoma *in situ* was reclassified as atypical ductal hyperplasia (a less than 0.2 cm focus of cytologic atypia not satisfying the criteria for ductal carcinoma *in situ*). In the last case, a biopsy was performed for a mass. The core biopsy diagnosis was atypical lobular hyperplasia with a fibroadenoma. The excision showed a 0.4 cm focus of cribriform-type ductal carcinoma *in situ* with low nuclear grade (unfortunately, the original slide with the ductal carcinoma *in situ* was not available for review and deeper levels did not show any ductal carcinoma *in situ*).

Overall, when pure lobular neoplasia was diagnosed on core biopsy with concordant radiology/pathology, 7% (3/39) of lobular carcinoma *in situ*, and 2% (1/48) of atypical lobular hyperplasia had an upgrade corresponding to an overall upgrade of 5% (4/87). Two of these four cases were lobular carcinoma *in situ* with necrosis and one was pleomorphic lobular carcinoma *in situ*. The fourth case was biopsied for a mass, with a diagnosis of atypical lobular hyperplasia associated with a fibroadenoma on core biopsy, and an apparent incidental finding of a 0.4 cm low nuclear grade ductal carcinoma *in situ* lesion on excision.

Compared to classic lobular carcinoma *in situ* with an 11% upgrade, upgrades were more common in lobular carcinoma *in situ* with necrosis (3/6, 50%) and pleomorphic lobular carcinoma *in situ* (3/7, 43%) (Table 5). The differences in frequency of upgrade between classic and nonclassic lobular carcinoma *in situ* were significant (χ^2-test, $P = 0.016$). All cases of classic lobular carcinoma *in situ* that were upgraded had radiologic–pathologic discordance (3/26, 11%).

Previous, Synchronous, or Subsequent Carcinoma

Cases associated with atypical ductal hyperplasia were excluded in this analysis. Synchronous carcinoma was defined as carcinoma (invasive carcinoma or ductal carcinoma *in situ*) diagnosed within 3 months before or after the diagnostic core biopsy with lobular neoplasia. All cases of synchronous ipsilateral carcinoma were in another quadrant of the breast and diagnosed previous to the core biopsy showing lobular neoplasia. Overall, 30% of patients had a history of either previous or synchronous ipsilateral or contralateral carcinoma. Of all patients, 20% had a history of contralateral carcinoma (previous or synchronous). In patients with lobular neoplasia with subsequent excisions, 38% (33/87) had a history of previous or synchronous carcinoma, *vs* 26% (50/190) of those without excisions (Table 7).

Only cases with a minimum of 6 months follow-up were included. The mean follow-up time was 32 months for lobular neoplasia cases with subsequent excision ($n = 51$) and 49 months for lobular neoplasia cases without subsequent excision ($n = 148$).

In the group that had a lobular neoplasia diagnosis on core biopsy followed by a subsequent excision, 20% (2/10) of patients with an upgrade to ductal carcinoma *in situ* on excision developed recurrent ductal carcinoma *in situ*/invasive carcinoma. Both patients were originally treated with lumpectomy and tamoxifen (without radiation). One patient developed recurrent ductal carcinoma *in situ* in 3 years, whereas the second patient, who had an upgrade to micropapillary ductal carcinoma *in situ*, developed small grade 1 invasive ductal carcinoma 4 years later. A total of 41 patients without an upgrade had follow-up information and none developed subsequent carcinoma.

Of 190 cases of lobular neoplasia in core biopsy without subsequent excision, 42 had no follow-up at this institution. Follow-up of the remaining 148 cases showed three (2%) subsequent ipsilateral carcinomas and one (0.7%) subsequent contralateral invasive carcinoma. One patient presented with new calcifications in an area adjacent to the core biopsy site 2 years after her lobular neoplasia diagnosis. Biopsy of this new lesion revealed

Table 7 Patients with previous or synchronous breast carcinoma

Cases[a]	*Synchronous carcinoma*			*Total*	*Ipsilateral*	*Previous carcinoma*		*Total*
	Ipsilateral	*Contralateral*	*Bilateral*			*Contralateral*	*Bilateral*	
With excision ($n=87$)	8	14	—	22	—	11	—	11
Without excision ($n=190$)	8[b]	14	2	24	9[b]	17	—	26

[a]30% of patients had either previous or synchronous (contra- or ipsilateral) breast carcinoma. A total of 20% of all patients had a history of contralateral carcinoma (previous or synchronous). In patients with LN with subsequent excisions, 38% (33/87) had a history of previous or synchronous carcinoma, *vs* 26% (50/190) of those without excisions.
[b]One patient had both a history of, and a synchronous ipsilateral carcinoma.

tubular carcinoma. The second patient had a history of contralateral invasive carcinoma and developed invasive carcinoma 7 months after her core biopsy that showed lobular neoplasia. The invasive carcinoma manifested as a mass in the same breast at a different site from her lobular neoplasia. The third patient presented at follow-up with a palpable mass 6 months after her original core biopsy. She underwent an ultrasound guided core biopsy for a mass that demonstrated irregular hypoechogenicity and was again diagnosed with lobular carcinoma *in situ*. She subsequently had an excision that showed ductal carcinoma *in situ* in addition to lobular carcinoma *in situ* (Table 6, case 1). The last patient developed contralateral invasive ductal carcinoma 5 years after her lobular neoplasia diagnosis.

Discussion

The management of lobular neoplasia is an evolving topic. The classification of lobular neoplasia is equally problematic, complicated with increasing recognition of variants of lobular carcinoma *in situ*. In the past, without confirmatory E-cadherin staining, *in situ* lesions associated with necrosis were likely to be diagnosed as ductal carcinoma *in situ*. Although the prevalence of E-cadherin staining has confirmed the existence of lobular carcinoma *in situ* associated necrosis, some authors still classify E-cadherin negative *in situ* lesions with necrosis or with high-grade nuclei as 'mixed' *in situ* lesions with the rationale that they should be treated similarly to ductal carcinoma *in situ*.

Just as the histopathologic spectrum of lobular carcinoma *in situ* has broadened, the belief that lobular neoplasia has no detectable radiologic abnormalities has been challenged. Although lobular neoplasia is often an incidental finding on core biopsy, microcalcifications can be associated with classic lobular carcinoma *in situ*.[21] Furthermore, lobular carcinoma *in situ* with necrosis can be associated with microcalcifications and can present mammographically like comedo-type ductal carcinoma *in situ*.[1,8]

In contrast to many previous studies on lobular neoplasia, our study does not support routine excision for classic lobular carcinoma *in situ* or atypical lobular hyperplasia, but does support routine excision for nonclassic lobular carcinoma *in situ*, including pleomorphic lobular carcinoma *in situ* and lobular carcinoma *in situ* with necrosis. Concordance of radiology and pathology findings must be considered when making a decision to recommend excision. Numerous studies have examined the need for excision following a diagnosis of lobular neoplasia on core biopsy (Table 8). A common drawback of these studies, as well as our own, is the relatively small number of cases that can be identified within a single institution. The number of cases included in previously published studies (combining atypical lobular hyperplasia and lobular carcinoma *in situ*) varies from less than 10 up to 92 cases of lobular neoplasia followed by immediate excision.[22–38] In comparison, our study includes a relatively high number of cases (87 cases of lobular neoplasia followed by immediate excision). Another limitation in our study and others is that it is retrospective and may suffer from selection bias regarding the patients that underwent excision. In our institution, during the time period studied, a greater percentage of lobular carcinoma *in situ* than atypical lobular hyperplasia cases was excised. Also, patients with a personal history of breast carcinoma were more likely to undergo subsequent excision.

Although most studies have found a significant associated risk of invasive carcinoma/ductal carcinoma *in situ* on excision after a diagnosis of lobular neoplasia in core biopsy, there is a high degree of variability. One of the reasons for the low rate of upgrade on excision of lobular neoplasia in core biopsy in our study compared with other studies may be the larger volume of tissue sampled by core biopsy at our institution *vs* other institutions, ie more complete sampling. Renshaw *et al*[36] considered this to be one of the factors in the low incidence of upgrades found in their study. Another reason for the low upgrade incidence in our study may be careful radiologic–pathologic correlation. If cases with discordant imaging and pathology are included in our upgrade category, our upgrade percentage would be comparable to that published in other studies. The significance of radiologic–pathologic discordance has been demonstrated in recent studies by Menon[33] and Nagi *et al*[35] Similarly, discordance was the major cause for an upgrade in our study. Findings were considered discordant when (1) the radiologic finding was a mass and

Table 8 Literature review

Studies[a]	*LN cases*[b]	*Upgrades*	*%*	*Comments*[c]
Arpino *et al*[22]	21	3	14	1/3 Upgrade was a mass lesion
Berg *et al*[23d]	15	1	7	The upgrade was not a mass lesion
Cangiarella *et al*[24]	38	3	8	2/3 Upgrades were mass lesions
Crisi *et al*[25]	16	2	13	2/2 Upgrades were mass lesions
Elsheikh and Silverman[26]	32	8	25	1/8 Upgrades were mass lesions
Esserman *et al*[27]	26	2	8	No upgrades were mass lesions
Foster *et al*[28]	26	6	23	2/6 Upgrades were mass lesions
Karabakhtsian *et al*[29]	92	10	11	2/10 Upgrades were mass lesions
Liberman *et al*[30]	9	2	22	Both upgrades were nonclassic LCIS on core biopsy
Mahoney *et al*[31]	20	5	25	2/5 Upgrades were mass lesions
Margenthaler *et al*[32]	35	7	20	Unclear if upgrades were mass lesions
Menon *et al*[33]	47	8	17	7/8 upgrades were discordant
Middleton *et al*[34]	17	6	35	6/6 Upgrades were mass lesions
Nagi *et al*[35e]	45	1	2	The upgrade was not a mass lesion
Renshaw *et al*[36]	92	3	3	1 Upgrade was possibly pleomorphic LCIS on core biopsy; no upgrades were mass lesions
Shin and Rosen[37]	13	2	15	Unclear if upgrades were mass lesions
Yeh *et al*[38]	15	1	7	Unclear if upgrade was a mass lesion
Our study	87	10	11	6/10 Upgrades were discordant; 3/10 Upgrades were nonclassic LCIS on core biopsy
Total	646	80	12	

LCIS, lobular carcinoma *in situ*.

[a]Excludes studies with less than nine lobular neoplasia cases with subsequent excision.

[b]Includes only lobular neoplasia cases that had subsequent excision and excludes cases associated with ADH.

[c]These upgrades may not reflect all cases of radiologic–pathologic discordance as many studies did not address this issue; some studies did state which upgrades were associated with a mass lesion.

[d]The single upgrade was in a patient with synchronous carcinoma.

[e]This study cites three upgrades; however, one 'upgrade' was ADH on excision and another upgraded case showed LCIS/DCIS on the core biopsy on review.

lobular neoplasia was the pathologic diagnosis on core biopsy or (2) the radiology showed suspicious calcifications that were not represented in the core biopsy specimen. After excluding discordant cases, our study showed a 5% incidence of invasive carcinoma/ductal carcinoma *in situ* in the excision. Concordant upgraded cases had nonclassic lobular carcinoma *in situ* morphology (lobular carcinoma *in situ* with necrosis or pleomorphic lobular carcinoma *in situ*) and in one remaining upgraded case of atypical lobular hyperplasia in core biopsy, the reason for the upgrade could not be identified.

In the group of patients with lobular neoplasia in core biopsy that were not followed by a subsequent excision ($n = 148$), 2% of patients developed ipsilateral and 0.7% contralateral carcinoma (mean follow-up time = 49 months). Although in our study a low percentage of patients developed subsequent carcinoma, all patients with biopsy proven lobular neoplasia have a well-recognized long-term risk of subsequent carcinoma in either breast and should be followed carefully.

In summary, our results do not support routine excisional biopsy as the standard of care for lobular neoplasia diagnosed on core biopsy. Surgical intervention is warranted in cases of radiologic–pathologic discordance and in cases of pleomorphic lobular carcinoma *in situ* or lobular carcinoma *in situ* with necrosis. Radiologic–pathologic correlation is crucial in determining the need for excision and requires effective communication between the pathologist, radiologist, and surgeon. Although at our hospital, management of atypical lobular hyperplasia and classic lobular carcinoma *in situ* can be accomplished by follow-up without surgery, other institutions need to evaluate their own data to establish similar guidelines. With an increased understanding of lobular neoplasia, a more definitive classification system of noninvasive lobular lesions is warranted and would be useful in establishing standardized guidelines in the management of these lesions.

Disclosure/conflict of interest

The authors have no conflict of interest to disclose.

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