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Classic lobular neoplasia on core biopsy: a clinical and radio-pathologic correlation study with follow-up excision biopsy

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There are no consensus guidelines for the management of lobular neoplasia diagnosed on core biopsy as the highest risk factor for cancer. This study aimed to assess the risk of upgrade (invasive carcinoma or ductal carcinoma *in situ*) at the site of the lobular neoplasia and any clinical, radiological or pathologic factors associated with the upgrade. We reviewed all cases with a diagnosis of lobular neoplasia on core biopsy from June 2006 to June 2011. Any cases with radio-pathologic discordance, coexistent lesion that required excision (atypical ductal hyperplasia, flat epithelial atypia, duct papilloma or radial scar) or non-classic variant of lobular carcinoma *in situ* (pleomorphic, mixed ductal and lobular, lobular carcinoma *in situ* with necrosis) were excluded from the study. Core biopsy indications included calcification in 35 (40%), non-mass like enhancement in 19 (22%), mass lesion in 31 (36%) and mass as well as calcification in two cases (2%). Follow-up excisions were studied for the presence of upgrade. The study cohort included 87 cases and showed an upgrade of 3.4% (95% confidence interval: 1–10%). Three cases showed an upgrade (one ductal carcinoma *in situ* and two invasive cancers). All upgraded cases were breast imaging-reporting and data system score ≥ 4 and associated with atypical duct hyperplasia or *in situ* or invasive cancer in prior or concurrent biopsies in either breast. The number of cores and lobules involved, pagetoid duct involvement, presence of microcalcification in lobular neoplasia, needle gauge and number of cores obtained showed no correlation with the upgrade. Our results suggest that with radio-pathologic concordance and no prior biopsy proven risk for breast cancer, core biopsy finding of lobular neoplasia as the highest risk lesion can be appropriately and safely managed with clinical and radiologic follow-up as an alternative to surgical excision.
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Lobular neoplasia that includes atypical lobular hyperplasia and lobular carcinoma *in situ* was first described by Foote and Stewart in 1941 and later by Haagensen in 1978.[1,2] Lobular neoplasia are considered risk factors for subsequent invasive carcinoma in either breast with relative risk of 4 to 5 times for atypical lobular hyperplasia and up to 8 to 10 times for lobular carcinoma *in situ*.[3–5] The majority of breast cancers that subsequently developed were invasive ductal carcinoma.[3–5] Classic type lobular carcinoma *in situ* is defined as a monotonous, discohesive proliferation of small, round cells with low to intermediate nuclear grade, evenly spaced, that both fill and distend $>50\%$ of the acini of the involved lobular units.[6,7] Atypical lobular hyperplasia is defined as the same cell population but with $<50\%$ of the acini filled and distended.[6,7] Since classic atypical lobular hyperplasia and lobular carcinoma *in situ* are multicentric and bilateral and considered a marker

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of generalized increase in cancer risk in either breast,[4,8] surgical excision is unnecessary, just as further surgery is not recommended for patients with lobular neoplasia diagnosed on excision biopsy.

Lobular neoplasia is not associated with any specific clinical abnormality and lacks any diagnostic mammographic features.[9] Lobular neoplasia may be identified in breast core biopsies as an incidental finding associated with microcalcifications, mass lesion or indeterminate enhancement on imaging. With the advances in breast imaging and increasing use of MRI, the use of core biopsy has greatly increased and is the preferred method for the initial evaluation of most lesions. The diagnosis on core biopsy determines further management. However, there are no consensus guidelines for follow-up management of patients where lobular neoplasia is the highest risk factor lesion. A great variability exists in the management of lobular neoplasia diagnosed on core biopsy. Prior studies have shown upgrade rates ranging from 0 to 35%.[5,10–33] However, the majority of these studies are limited by one or more of the following factors (a) small number of cases, (b) selection bias when only selected patients underwent excision for this diagnosis, (c) radiologic studies lacking review of pathology slides, (d) inclusion of lobular neoplasia cases with other coexistent high risk lesions such as atypical ductal hyperplasia, (e) inclusion of cases with radio-pathologic discordant core biopsy findings, (f) inclusion of high-risk variants of lobular carcinoma *in situ* (pleomorphic, mixed lobular and ductal *in situ* variant and variants with necrosis), (g) inclusion of cases with a second diagnosis such as papilloma, radial scar or flat epithelial atypia warranting an excision. At our institution, excision is routinely performed on all cases with a diagnosis of lobular neoplasia on core biopsy. The aim of our study was to assess the risk of a higher-grade lesion (invasive carcinoma/ductal carcinoma *in situ*) at the site of the lobular neoplasia diagnosis on core needle biopsy and to assess any clinical, radiological or pathologic factors associated with this upgrade.

Materials and methods

Case Selection

After obtaining IRB approval, the surgical pathology data base of the North Shore University Hospital and Long Island Jewish Medical Center was reviewed for all core needle biopsies from June 2006 to June 2011 with a diagnosis of lobular neoplasia, atypical lobular hyperplasia and/or lobular carcinoma *in situ*. Cases with coexistent invasive carcinoma or ductal carcinoma *in situ* in the core biopsy specimen were excluded. Cases lacking radiologic studies or biopsy slides were excluded. A total of 113 cases with a diagnosis of lobular neoplasia on core biopsy were identified. Follow-up surgical excision was defined as a surgical procedure (excision biopsy using needle localization or mastectomy) that was performed subsequent to the core biopsy. All but two cases had an excision biopsy or mastectomy performed within 6 days to 4 months after the core biopsy results. One patient status post-bilateral malignant lumpectomy had the excision biopsy after 8 months and other patient status post-contralateral breast cancer and chemotherapy had excision biopsy after 24 months. Patients with a diagnosis of invasive carcinoma (ipsilateral or contralateral), ductal carcinoma *in situ* or pleomorphic lobular carcinoma *in situ* in prior or concurrent biopsy samples from either breast were intentionally included to determine the disease upgrade in patients with these risk factor for cancer development and had a subset analysis.

Radiologic Review

The imaging modality that led to a core biopsy (mammogram, ultrasound or MRI) was noted for each case. All core biopsies were performed using ultrasound, stereotactic or MRI guidance. Ultrasound guided biopsies were performed using a 12- or 14-gauge needle. Stereotactic guidance using a vacuum suction probe predominantly used 9-gauge and sometimes 11-gauge needle. MRI guided core biopsies were performed using mostly 9 and sometimes 10 gauge needles. The past history of any breast disease, breast cancer or family history of breast cancer was recorded. Prior breast biopsy findings, if any were recorded. The radiologic findings were categorized as calcifications on mammogram, mass on mammogram, ultrasound or MRI and enhancing lesions on MRI. The breast imaging reporting and data system (BIRADS)[34] was used to stratify lesions according to different levels of suspicion for carcinoma and was recorded for all cases. The follow-up surgical excision was performed in patients with BIRADS ranging from three to six with the majority of the excised lesions being category 4 and above. The radiologic findings were correlated with core needle biopsy diagnosis for each case. One case was excluded because of radio-pathologic discordance, an 8-mm stellate enhancing lesion on MRI diagnosed as lobular carcinoma *in situ* and proliferative fibrocystic disease on core biopsy while excision biopsy showed ductal carcinoma *in situ* and 2 mm infiltrating tubular and lobular carcinoma with adjacent fat necrosis.

Pathology Review

Core biopsy specimens varied from 3–16 cores under MRI guidance, 2–15 cores under stereotactic guidance and 2–10 cores under ultrasound

guidance. Core biopsy tissue specimens were fixed in 10% formalin, embedded in paraffin and stained with hematoxylin and eosin. Up to three cores were submitted in one cassette. The tissue was sectioned at 4-μm intervals. For most of the cases, two slides with sections at two different levels from all blocks (varying from 1 to 6) were studied with the exception of nine cases where only one level was studied and two cases where up to 16 levels were studied to ascertain the presence of calcification. The core biopsy for all cases was reviewed using Page's criteria.[6] Lobular carcinoma *in situ* was further classified as classic type, pleomorphic, or lobular carcinoma *in situ* with necrosis. Since E-cadherin has a role in categorization of ambiguous *in situ* carcinomas,[35] it was performed in cases with an equivocal ductal/lobular morphology or in cases of pleomorphic lobular carcinoma *in situ*. In the study cohort, E-cadherin was performed on 14/87 (16%) cases with negative results confirming lobular origin of the lesion. All core biopsy slides were reviewed for the number of cores and lobules involved by lobular neoplasia, pagetoid duct involvement, lobular carcinoma *in situ* variant (type A/B), presence of necrosis, presence and distribution of microcalcification and coexistent benign findings accounting for radiologic concordance. Five cases were excluded following review of core biopsy slides as they did not fulfilled criteria for a diagnosis of lobular neoplasia. Five cases with pleomorphic lobular carcinoma *in situ* component were excluded. Fifteen cases with concurrent findings considered as risk factors that would necessitate an excision biopsy (one case with atypical ductal hyperplasia, seven cases with flat epithelial atypia, four cases of intraductal papilloma, two cases of radial scar, and one case with intraductal papilloma and radial scar) were excluded from the study. In all, 87 cases qualified for inclusion in the study. Follow-up resection specimens included 76 excision biopsy using needle localization, 1 partial mastectomy and 10 modified radical mastectomies). Appropriate follow-up excision biopsy was confirmed by radiologic correlation of clip removal and documentation of biopsy site changes on excision specimens. In all, 48/76 (63%) of the excision biopsy specimens were submitted entirely for microscopic examination. In all, 28/76 (37%) cases were partially submitted with submission of the entire area of interest with adjacent tissue, extensive sampling of any fibrous tissue beyond this area and representative sampling of remaining fatty breast tissue. Mostly this protocol lead to extensive sampling and accounted for $>90\%$ specimen submission for microscopy. Follow-up excision specimen were reviewed for the presence of biopsy site changes, number of slides involved by residual lobular neoplasia and presence of any upgrade lesions (ductal carcinoma *in situ*, invasive lobular carcinoma, invasive ductal carcinoma).

Data Analysis

The presence of an invasive carcinoma and/or ductal carcinoma *in situ* located in the region of the initial biopsy site containing lobular neoplasia defined the lesion upgrade. The number of cases with diagnosis of lobular neoplasia on core biopsy specimens that upgraded on excision biopsy was determined. 95% confidence interval (CI) was calculated. Data were analyzed for any clinical, radiologic and histopathologic factors predicting the upstage of isolated lobular neoplasia on the core biopsy. Patients with prior history of carcinoma and prior biopsy proven risk factor for cancer were analyzed as a subset. The upgrade rates in the excluded cases were assessed and compared with the study cohort.

Results

Our study population consisted of 83 females and 87 core biopsies with four of our patients having two biopsies each. The age ranged from 37 to 88 years with a mean age of 55 years. Fifty cases were from the left breast and 37 cases were from the right breast. The core biopsy indication included calcification in 35 (40%), non-mass like enhancement in 19 (22%), mass lesion in 31 (36%) and mass as well as calcification in 2 cases (2%). Core biopsy was performed using US guidance in 19 (21.8%), MRI guidance in 32 (36.7%) and stereotactic guidance in 36 (41.4%) cases. The needle gauge varied from 9 to 14 with 9 gauge used for 57 cases (66%), 10 gauge for 2 cases (2%), 11 gauge for 9 cases (10%), 12 gauge for 9 cases (10%), 14 gauge for 10 cases (12%). Of our study cohort, 13 patients had a family history of breast cancer, 28 a history of breast cancer (2 bilateral, 16 contralateral and 10 ipsilateral), 5 a history of benign breast disease, 4 a history of prior LCIS and 1 a history of prior multifocal atypical duct hyperplasia associated with lobular carcinoma *in situ* in the ipsilateral breast. The number of cores varied from 2–16 cores but averaged approximately 9 for MRI, 8 for stereotactic and 4.5 for ultrasound guided biopsies.

The imaging indications for core biopsy and benign lesions associated with lobular neoplasia found on core biopsy are enumerated (Table 1). The majority of cases were 'type A' lobular carcinoma *in situ* except two cases of 'type B' variant, both of which were negative for E-cadherin on immunostaining. None of the 87 case of lobular neoplasia was associated with necrosis/ comedonecrosis on core biopsy.

In all, 11 cases showed pagetoid duct involvement by classic lobular neoplasia but none of the upgraded lesion showed pagetoid duct involvement. In all, 8/11 cases with pagetoid duct involvement had >4 lobules and more than half of all cores involved. In three cases, pagetoid involvement was

associated with <2 lobules involved by lobular neoplasia in a single core. Pagetoid duct involvement by lobular neoplasia showed neither specific association with extent of involvement by lobular carcinoma *in situ* nor any correlation with lesion upgrade.

In all, 11/36 (30%) of core biopsies performed for mammographic calcification showed focal microcalcification within the lobular neoplasia. Of all lobular neoplasia cases, 19/ 87 cases (21.8%) showed focal microcalcification within the lobular neoplasia component (17 type 'A' and two Type 'B' lobular carcinoma *in situ*). Eleven of these 19 cases (58%) were performed for mammographic calcification. Additionally, all of these cases had prominent microcalcifications in other benign breast components such as columnar cell change, columnar cell hyperplasia, proliferative fibrocystic change and sclerosing adenosis. Both cases of type B lobular carcinoma *in situ* were biopsied for microcalcification detected on mammogram and both had columnar cell hyperplasia with microcalcifications. The remaining eight cases had no calcification detectable on radiology, suggesting that the calcification associated with lobular carcinoma *in situ* is usually incidental and may not be detectable radiographically. Only two cases with microcalcifications in lobular neoplasia had lesion upgrade in follow-up biopsy whereas 17 cases with microcalcification showed no lesion upgrade on follow-up surgical excision.

The number of cores and terminal duct lobular units involved by lobular neoplasia on core biopsy showed no correlation with lesion upgrade but was associated with the volume of lobular neoplasia on follow-up surgical excision (Table 2).

In all, 87 core biopsies with lobular neoplasia as the highest risk lesion were comprised of 22 atypical lobular hyperplasia, 44 lobular carcinoma *in situ* and 21 with both atypical lobular hyperplasia and lobular carcinoma *in situ*. Follow-up excision biopsies showed an upgrade rate of 3.4% (95% CI: 0–10%). All the upgrades were seen in association with lobular carcinoma *in situ* (Figure 1; Table 3). For atypical lobular hyperplasia alone as the highest risk factor, none of the case showed upgrade. The needle gauge used or the number of cores obtained showed no correlation with the lesion upgrade. Two of the upgraded cases with invasive cancer on the excision had BIRADS of 6 and a history of bilateral cancer and contralateral DCIS, respectively. The third case had a history of multifocal ADH that showed an upgrade to DCIS and also showed focal pleomorphic lobular carcinoma *in situ* on excision (Table 4). Excluding the patients with synchronous and prior breast cancer/ductal carcinoma *in situ*, only a single case showed an upgrade 1.7% (1/59).

Also, two of our lobular neoplasia cases showed extensive pleomorphic lobular carcinoma *in situ* and single focus of atypical ductal hyperplasia on excision. Both of these lesion were in elderly

Table 1 Lesions associated with lobular neoplasia on core needle biopsies

	Number of cases
Lesion with mammographic calcifications	
Columnar cell change and hyperplasia	17
Proliferative fibrocystsic change	7
Benign breast and ducts	6
Non-proliferative fibrocystic change	2
Sclerosing adenosis	2
Fibroadenoma	1
Mass lesion associated with lobular neoplasia	
Fibroadenoma	12
Proliferative Fibrocystic change	8
Sclerosing adenosis	7
Nodular stromal fibrosis	2
Fat necrosis	1
Nodular LCIS	1
Enhancing lesion on MRI[a]	
Nodular adenosis	7
Non-proliferative fibrocystic change	6
Proliferative fibrocystsic change	3
Columnar cell hyperplasia	1
Fibroadenomatoid nodule with lobular carcinoma *in situ*	1
Pseudoangiomatous stromal hyperplasia	1
Lesion presenting as mass and calcification	
Fibrocystic change	1
Sclerosing adenosis	1

[a]Magnetic resonance imaging.

Table 2 Upgrade and extent of lobular involvement in various categories

	>4 Lobules	*>1 Lobule/core*	*Upgrade*
Benign beast disease	3/5	0/5	None
Bilateral breast cancer	2/2	1/2	1 Upgrade
Ipsilateral breast cancer	7/9	1/9	None
Ipsilateral ductal carcinoma *in situ*	1/1	0/1	None
Contralateral breast cancer	2/14	0/14	None
Contralateral ductal carcinoma *in situ*	0/2	0/2	1 Upgrade
Routine screening	11/36	1/36	None
Prior lobular carcinoma *in situ*	2/4	0/4	None
Multifocal atypical duct hyperplasia	1/1	0/1	1 Upgrade
Family history of breast cancer	4/13	1/13	None

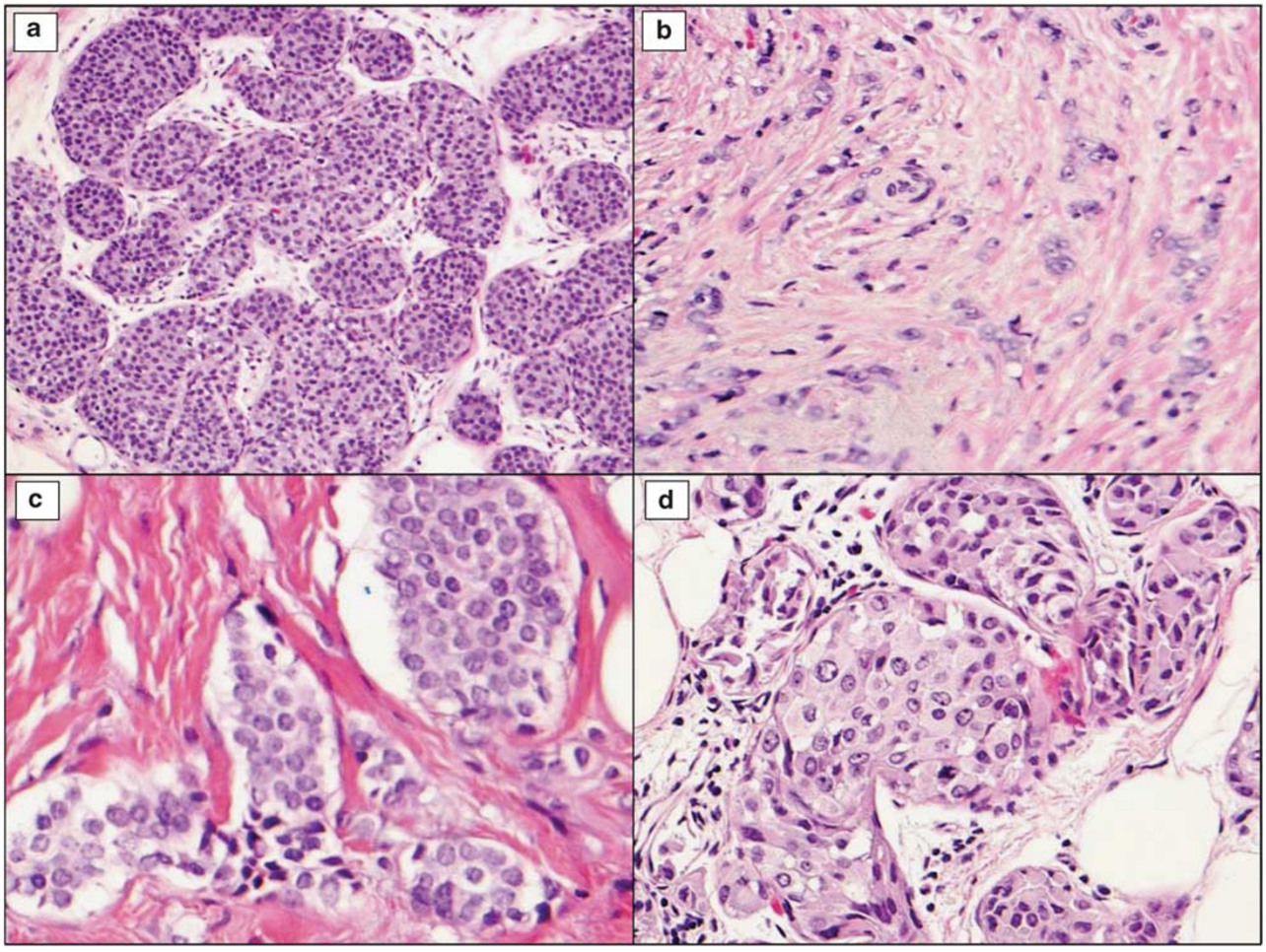

Figure 1 Lobular carcinoma *in situ* on core needle biopsy and the excision of upgraded cases. (**a**) Classic lobular carcinoma *in situ* on core biopsy (H&E ×100). (**b**) Upgrade to invasive lobular cancer on excision (×200). (**c**) Upgrade to invasive cancer on excision (×200). (**d**) Upgrade to ductal carcinoma *in situ* on excision (×200).

Table 3 Comparison of upgrade rates on study cohort and excluded cases

	Study cohort	*Excluded case cohort*
Lobular neoplasia on core biopsy	3.4% (3/87)	19.0% (4/21)
Atypical lobular hyperplasia on core biopsy	None (0/22)	25% (1/4)
Lobular carcinoma *in situ* on core biopsy	4.6% (3/65)	17.6% (3/17)

patients (>80 years) and performed for mammographic calcifications.

Subset analysis performed in patients with various risk factors showed an upgrade rate of 7.1% (2/28) for patients with synchronous ipsilateral or contralateral breast cancer or ductal carcinoma *in situ* and 0% for patients undergoing screening mammogram (0/13) or prior history of benign breast disease (0/5) or prior lobular carcinoma *in situ* as the highest risk lesion (0/4). One upgrade was seen in a patient with a prior biopsy diagnosis of multifocal atypical duct hyperplasia in the ipsilateral breast (Table 5).

The cohort of excluded cases showed an upgrade rate of 19% for lobular neoplasia. The upgrade was seen in one case with radio-pathologic discordance, two cases with pleomorphic lobular carcinoma *in situ* and one case with flat epithelial atypia and mucocele like lesion (Table 6). All upgraded cases in the excluded case cohort showed the upgraded lesion to be at a distant site from the site of classic lobular carcinoma *in situ* and near the coexistent risk lesion in all cases, suggesting that lobular carcinoma *in situ* is purely an incidental finding in these cases.

Discussion

Lobular neoplasia are often multifocal and not uncommonly present in the contralateral breast.[5,8,36–39] Up to 50% of patients with lobular carcinoma *in situ* have multifocal disease in the ipsilateral breast and up to one third in the contralateral breast.[39,40]

Table 4 Clinical and histologic features of the cases in study cohort with upgrade on excision

	Age	*Clinical history*	*Radiology (MRI)*	*Needle gauge*	*Core biopsy findings*	*BIRADS*	*No. of cores involved*	*Upgrade lesion*
1	47	Bilateral IDC	5 mm nodular indeterminate enhancement 7 mm from tumor satellite nodule	10	CCC, PFCC	6	5/8	Invasive mammary carcinoma (ductal and lobular features), 6 mm
2	68	Contra lateral DCIS	Lobulated enhancing mass (6 mm)	9	PFCC with microcalcifications, Apocrine metaplasia	6	1/8	Invasive lobular carcinoma (4 mm)
3	57	Multifocal ADH, LCIS	5 mm rim enhancing nodule	9	CCC, PFCC	4a	4/7	DCIS, P-LCIS

ADH, atypical ductal hyperplasia; CCC, columnar cell change; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma *in situ*; PFCC, proliferative fibrocystic change; P-LCIS, pleomorphic lobular carcinoma *in situ*.

Table 5 Upgrades in different clinical groups in study cohort

Clinical group	*Number of upgrades*
Ipsilateral or contralateral breast cancer or ductal carcinoma *in situ*	2/28
Prior biopsy with atypical duct hyperplasia	1/1
Screening for family history of breast cancer	0/13
Prior biopsy with lobular carcinoma *in situ* as the highest risk factor	0/4
Benign breast disease	0/5
Routine mammographic screening, no risk factor or prior history	0/36

Table 6 Etiology of upgrades in the excluded case cohort

Exclusion criteria	*Number of upgrade*
Radio-pathologic discordance	1/1
Pleomorphic lobular carcinoma *in situ*	2/5
Other coexistent lesions which may warrant excision (ADH, FEA, IDP, RS)	1/15

ADH, atypical ductal hyperplasia; FEA, flat epithelial atypia; IDP, intraductal papilloma; RS, radial scar.

Determining the incidence of lobular neoplasia is difficult as there is no radiologic correlate.[25] The incidence of lobular neoplasia has increased fourfold over the last 20 years, a consequence of the increase in the frequency of core biopsies and the greater amount of tissue acquired through the larger bore vacuum suction needles.[41]

Lobular neoplasia is rare as an isolated lesion and is usually found coexisting with other lesions that may pose some risk for cancer development and would therefore be subject to a follow-up excision biopsy. The inclusion of such cases is a cause of bias in multiple previous studies and makes the explicit studies for upgrade difficult. Numerous studies have evaluated the need for excision following a diagnosis of lobular neoplasia on core biopsy (Table 7). Our study had no selection bias as all patients at our hospital diagnosed with lobular neoplasia on core biopsy undergo routine excision. The case selection criteria were stringent including only unambiguous cases of classic variant of lobular carcinoma *in situ* as the highest risk factor lesion without coexisting lesions associated with risk for cancer development.

Only 30% of cases performed for microcalcification on imaging showed focal calcification in the lobular carcinoma *in situ* component with the predominant calcifications seen in columnar cell change and hyperplasia, sclerosing adenosis, proliferative and non-proliferative fibrocystic change, fibroadenoma and unremarkable breast tissue. Zhao *et al*[33] also focused on lobular neoplasia presenting with microcalcification on imaging and reported the presence of calcium mainly in fibrocystic changes, columnar cell changes and unremarkable breast tissue and stroma.

Radiopathologic concordance is essential in the follow-up evaluation as discordant correlation may lead to a false positive lesion upgrade demonstrated in recent studies by Hwang *et al*,[17] Menon *et al*,[23] and Nagi *et al*.[25] Discordant radio-pathologic correlation includes the presence of a mass lesion, indeterminate enhancement or suspicious calcifications on imaging that cannot be explained by the presence of lobular neoplasia or other coexisting lesion on the needle biopsy. Rarely, lobular carcinoma *in situ* can produce a nodular mass and present as a nodular lesion or enhancement on MRI. One of the cases in our study presented as an 8-mm nodular enhancement on MRI and core biopsy revealed nodular lobular carcinoma *in situ* measuring 6 mm. Zhang *et al*[42] recently reported a case of lobular carcinoma *in situ* presenting as a 20-mm solid mass.

Table 7 Literature review

Study	*LN with follow-up excision*	*Excision rate*	*# Upgrade (%)*	*P-LCIS excluded*	*Slides reviewed*	*Radiologic discordance excluded*	*Comments*
Arpino *et al*[10]	21	47%	3(14%)	NM	Yes	NM	One upgrade was a mass lesion and other two were calcification associated
Berg *et al*[11]	15	60%	1 (7%)	No	NM	NA	All cases excised because of coexistent diagnosis of ADH, DCIS or invasive cancer
Brem *et al*[12]	164	59%	38 (23%)	NM	No	NA[a]	21 Upgrades mass lesion, higher BIRADS, core biopsy, fewer specimen
Cangiarella *et al*[13]	38	NA[b]	3 (8%)	NM	NM	No	2 Upgrades had discordant radiology
Crisi *et al*[14]	16	46%	2 (13%)	No	Yes	No	Both upgrades had mass on imaging
Elsheikh and Silverman[5]	33	NA	9 (27%)	No	Yes	No	Upgrade with *P*-LCIS, synchronous C/L DCIS, mass on imaging missed by core biopsy
Esserman *et al*[15]	35	74%	3 (9%)	NM	Yes	No	Diffuse LCIS (>1 lobule/core) and one case with residual calcification
Foster *et al*[16]	26	74%	6 (23%)	NM	No	NM	2 Upgrades were mass on imaging
Hwang *et al*[17]	87	31%	10 (11%)	No	Yes	No	6 Discordant imaging, 2 *P*- LCIS or 1 LCIS with necrosis, 1 slide not reviewed
Karabakhtsian *et al*[18]	92	91%	10 (11%)	Yes	Yes	No	2 Upgrades were mass lesion and 4 cases with neoplastic epithelium associated microcalcification
Lewis *et al*[19]	201	71%	26 (13%)	No	No	NM	No mention of the radio-pathologic concordance of upgrade cases
Liberman *et al*[20]	9	81%	2 (22%)	No	Yes	No	Mixed ductal LCIS upgraded, no classic pure LN upgraded
Mahoney *et al*[21]	20	74%	5 (25%)	No	Yes	No	1 Upgrade for mass lesion, 1 *P*-LCIS and 1 had concurrent C/L breast cancer
Margenthaler *et al*[22]	35	85%	7 (20%)	NM	NM	No	Presence of mammographic mass was associated with increased upgrade rate
Menon *et al*[23]	25	53%	8 (32%)	No	Yes[e]	No	7 Discordant imaging (biopsy missed mass in 5 and calcification in 2 cases
Middleton *et al*[24]	17	49%	6 (35%)	Yes	Yes	No	6/6 Upgrades were for mass on imaging which were missed on core biopsy
Nagi *et al*[25]	45	46%	2 (4.4%)	Yes	Yes	Yes	One NB classified as DCIS on review and second case had minute focus of ILC away from the lesion (incidental finding)
O' Neil *et al*[26]	27	60%	5 (19%)	NM	Yes	No	—
Rendi *et al*[27]	68	89%	3 (4.4%)	Yes	Yes	No	Discordant imaging, extensive LCIS (>4 TDLUs involved), high-risk patients
Renshaw *et al*[28]	15	21%	3 (3%)	No	NM	No	1 Upgrade non-classic LCIS, 2 carcinomas were away from biopsy site
Shah- Khan *et al*[29]	101	55%	2 (2%)	Yes	Yes	No[d]	One upgrade radio-pathologically discordant
Shin and Rosen[30]	13	NA[c]	2 (15%)	Yes	Yes	No	Radiologic concordance not discussed
Subhawong *et al*[31]	56	48%	0 (0%)	NA	Yes	Yes	Focused on minimal ALH (≤3 foci) only
Yeh *et al*[32]	15	NA	1 (7%)	NM	Yes	No	Radiologic concordance not discussed
Zhao *et al*[33]	237	70%	11 (4.6%)	Yes	Yes (the upgraded cases)	Yes	Study focused only on LN associated with calcification
Present study	87	100%	3 (3.4%)	Yes	Yes	Yes	Upgrades in synchronous cancer, C/L DCIS and prior biopsy proven multifocal ADH in ipsilateral breast

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BIRADS, breast imaging reporting and data system; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; LN, lobular neoplasia; NA, not applicable; NM, not mentioned; P-LCIS, pleomrophic lobular carcinoma *in situ*; TDLU, terminal duct lobular unit.
[a]No standardization between participating institutions.
[b]The cases without surgical excision follow-up were excluded.
[c]Included 20 non-consecutive biopsies with follow-up excision.
[d]93% Radiologic pathologic concordance.
[e]Six core biopsies were not available, hence not reviewed.

Studies by Hwang *et al*,[17] Fadare *et al*,[43] and Liberman *et al*[20] suggested that pleomorphic and classic lobular carcinoma *in situ* associated with necrosis show a high upgrade rate and recommended excision for all such cases. Many of the studies performed on lobular neoplasia have higher upgrades because of inclusion of pleomorphic lobular carcinoma *in situ* or mixed ductal lobular carcinoma *in situ* or lobular carcinoma *in situ* with comedonecrosis.

Other studies are compromised because of inclusion of risk factors for cancer such as atypical duct hyperplasia, radial scar lesions, duct papilloma for which an excision biopsy is usually performed. Karabakhtsian *et al*[18] excluded cases with atypical duct hyperplasia, intraductal papilloma and radial scar. Rendi *et al*[27] excluded cases of atypical duct hyperplasia but not mention excluding other lesions such as duct papilloma, radial scar and flat epithelial atypia.

Details of prior history and biopsies are also required to exclude cases with a prior history of synchronous ipsilateral/contralateral breast cancer or ductal carcinoma *in situ*. Cangiarella *et al*[13] did not mention if their upgraded cases had such a past history.

Excluding patients with synchronous and prior invasive breast cancer and ductal carcinoma *in situ*, the upgrade rate in our study was 1.7% (1/59) similar to study by Hwang *et al*[17] of 1% after exclusion of cases with discordant radio-pathologic findings and non-classic lobular carcinoma *in situ* morphology. They concluded that classic lobular carcinoma *in situ* with concordant radiology and pathology can be appropriately managed by clinical follow-up without surgery. In all, 32% (28/87) of our study cohort had a history of either previous or synchronous ipsilateral, contralateral or bilateral invasive cancer/DCIS similar to the findings in the study by Hwang *et al.*[17]

In the present study where excision was routinely performed for all lobular neoplasia diagnosed on core biopsy, the upgrade rate was 3.4%. However, all the upgraded cases had a biopsy proven history of a risk factor (multifocal atypical duct hyperplasia, invasive ductal cancer, and ductal carcinoma *in situ*). Therefore, we suggest that classic lobular neoplasia as the highest risk lesion with radiopathologic concordance and no other biopsy proven risk factors for breast cancer development can be appropriately and safely managed with clinical and radiologic follow-up. This study provides an accurate assessment and unbiased upgrade rates with a good sample size and constitutes a useful reference for patient management.

Rendi *et al*[27] in their study found that extensive lobular carcinoma *in situ*>4 terminal duct lobular unit's involvement accounted for lesion upgrade and recommend excision. Esserman *et al*[15] suggested that diffuse lobular neoplasia (involvement of>1 lobule per core) may indicate an associated invasive cancer and should prompt excision. We did not find any correlation between the extent of lobular neoplasia or pagetoid involvement and lesion upgrade. Middleton *et al* in their study concluded that lobular carcinoma *in situ* involving adenosis and with pagetoid spread on core biopsy did not show a more significant lesion on excision.[23]

In all, 21.8% of our lobular neoplasia cases showed lobular carcinoma *in situ* associated calcification but the presence of calcification does not correlate with lesion upgrade. Middleton *et al* also reported that lobular carcinoma *in situ* associated calcification does not portend any higher-grade lesion in the excision biopsy.[23]

In one of the cases with synchronous prior biopsy proven ductal carcinoma *in situ* in the ipsilateral breast, the core biopsy showed lobular carcinoma *in situ* along with proliferative fibrocystic change and 5 mm nodular stromal fibrosis for a 6-mm indeterminate enhancement and BIRADs of 4b on MRI. Mastectomy performed later showed multifocal extensive ductal carcinoma *in situ* and no lobular carcinoma *in situ*. Clearly ductal carcinoma *in situ* does not represent an upgrade as it is not directly related to the site of lobular carcinoma *in situ* and had no association with the lobular carcinoma *in situ* in the resection specimen. The prior biopsy proven ductal carcinoma *in situ* in same breast was a major risk factor for development of cancer and the presence of lobular carcinoma *in situ* was an incidental finding.

Another of our cases showed extensive pleomorphic lobular carcinoma *in situ* on excision. Core biopsy performed for calcification with a BIRADS of 4a showed predominant calcification in benign breast tissue and focal classic lobular carcinoma *in situ* with microcalcifications. The excision biopsy showed extensive pleomorphic lobular carcinoma *in situ* with comedonecrosis. This case emphasizes the fact that calcification with a BIRADS of 4 cannot be explained by classic lobular neoplasia and benign breast tissue calcification and should be treated with excision.

A third case of needle biopsy performed for indeterminate calcification on mammogram and BIRADS of 4 showed fibroadenomatoid change with nodular fibrosis and calcification in proliferative fibrocystic disease and focal atypical lobular hyperplasia. The follow-up resection showed lobular carcinoma *in situ* (8/15 slides), atypical lobular hyperplasia, flat epithelial atypia and single adjacent focus of atypical duct hyperplasia, suggesting that the presence of flat epithelial atypia and atypical duct hyperplasia are confounding risk factors.[44]

In conclusion, with a good sample size, appropriate radiologic pathologic correlation, optimal sampling and exclusion of other coexistent risk factors lesions in core biopsy, our study showed a 3.4% (95% CI, 1–10%) upgrade on follow-up excision for classic lobular neoplasia on core biopsy. However, all three upgrades had biopsy proven risk factor for cancer development. A BIRADS score of 4 or above may be associated with a lesion upgrade. The number of cores and lobules involved, pagetoid duct involvement, presence of microcalcification in lobular neoplasia, classic lobular carcinoma *in situ* (type A or B), needle gauge and number of cores are not associated with an upgrade on excision. This study highlights the benign outcome for classic lobular neoplasia as the highest risk factor lesion on core biopsy and suggests that non-surgical management with clinical and radiologic follow-up is an appropriate and safe alternative to surgical excision in these patients.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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