Core Breast Biopsies Showing Lobular Carcinoma In Situ Should Be Excised and Surveillance Is Reasonable for Atypical Lobular Hyperplasia

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OBJECTIVE. The purpose of this article is to determine the upgrade rate to ductal carcinoma in situ (DCIS) or invasive carcinoma at excision at the same site after percutaneous breast biopsy findings of atypical lobular hyperplasia (ALH) or lobular carcinoma in situ (LCIS) using current imaging and strict pathologic criteria.

MATERIALS AND METHODS. From January 2006 through September 2013, 32,960 breast core biopsies were performed; 1084 (3.3%) core biopsies found ALH or classic LCIS. For 447 lesions in 433 women, this was the only high-risk lesion at that site, with no ipsilateral malignancy, and results of excision were available.

RESULTS. Among the 447 lesions, 22 (4.9%) were malignant at excision, including 10 invasive carcinomas (two grade 2 and eight grade 1; all node negative) and 12 DCIS. The upgrade rate of LCIS was 9.3% (10/108; 95% CI, 5.1–16.2%) and that of ALH was 3.5% (12/339; 95% CI, 2.0–6.1%; $p = 0.02$). After excluding five cases with radiologic-pathologic discordance and reclassifying one core from ALH to LCIS at review, the upgrade rate for LCIS remained higher (8.4%; 9/107; 95% CI, 4.5–15.2%) than that for ALH (2.4%; 8/335; 95% CI, 1.2–4.6%; $p = 0.01$).

CONCLUSION. Excision is recommended for LCIS on core biopsy because of its 8.4–9.3% upgrade rate. Excluding discordant cases, patients with other high-risk lesions or concurrent malignancy, the risk of upgrade of ALH was 2.4%. Surveillance at 6, 12, and 24 months can be performed in lieu of excision because a short delay in diagnosis of the few malignancies is not expected to cause harm.

Keywords: atypical lobular hyperplasia, lobular carcinoma in situ, lobular neoplasia, radiologic-pathologic discordance

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Lobular carcinoma in situ (LCIS) was first described by Foote and Stewart [1] in 1941, and the term "lobular neoplasia" (LN), encompassing both atypical lobular hyperplasia (ALH) and LCIS, was introduced by Haagensen et al. [2] in 1978. LCIS comprises a population of neoplastic cells replacing the normal epithelium of acini and intralobular ductules, thus causing expansion and enlargement of the lobules [3, 4]. The distinction between ALH and LCIS is controversial, on the basis of quantitative differences in extent of lobular involvement and distention of the acini [4, 5]. LN is associated with increased risk of developing invasive cancer or ductal carcinoma in situ (DCIS) in either breast [6], though subsequent cancers are noted to occur more frequently in the ipsilateral breast by some investigators [7–9], which may suggest that LN is a nonobligate precursor rather than merely a risk indicator [8, 9]. The notion of LN as a nonobligate precursor of invasive carcinoma has also been supported by genetic evidence [10]. Across the literature, the upgrade rate of LN on core biopsy to invasive cancer or DCIS at surgical excision ranges from 0% to 50% [11–57] (Table 1).

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TABLE 1: Summary of Observed Rates of Upgrade at Excision to Malignancy After Core Breast Biopsy Diagnosis of Lobular Neoplasia (LN), Atypical Lobular Hyperplasia (ALH), or Lobular Carcinoma in Situ (LCIS)

Study, Year	LN, No. Upgraded at Excision/Total No. Excised (%)	ALH, No. Upgraded at Excision/Total No. Excised (%)	LCIS, No. Upgraded at Excision/Total No. Excised (%)	PLCIS Grouped With LCIS	Discordant Lesions Included	E-Cadherin Testing Performed
Meroni et al. [11], 2014	7/64 (10.9)	1/14 (7.1)	6/50 (12)	No	NR	NR
Menes et al. [12], 2014	16/68 (23.5)	NR	NR	NR	NR	NR
Atkins et al. [13], 2013	0/38 (0)	NR	NR	Yes	No	NR
Chaudhary et al. [14], 2013	3/87 (3.4)	0/22 (0)	3/65 (4.6)	No	No	Some cases
Murray et al. [15], 2013	2/72 (2.8)	2/30 (6.7)	0/42 (0)	NR	No	Some cases
Bianchi et al. [16], 2013	22/149 (14.8)[a]	NR/90	NR/59	No	NR	NR
Ibrahim et al. [17], 2012	28/84 (33.3)	11/40 (27.5)	17/44 (38.6)	No	NR	NR
Lewis et al. [18], 2012	27/199 (13.6)[b,c]	6/72 (8.3)	15/79 (19.0)	No	NR	NR
Polat et al. [19], 2012	7/86 (8.1)	7/86 (8.1)	NR	NA	NR	NR
Shah-Khan et al. [20], 2012	1/91 (1.1)	0/73 (0)	1/18 (5.6)	No	No	NR
Niell et al. [21], 2012	4/47 (8.5)	1/16 (6.3)	3/31 (9.7)	No	No	Some cases
Rendi et al. [22], 2012	3/68 (4.4)	2/48 (4.2)	1/20 (5.0)	No	Yes[c]	Some cases
Rakha et al. [23], 2011	0/7 (0)	NR	NR	NR	NR	NR
Flegg et al. [24], 2010	2/9 (22.2)	0/4 (0)	2/5 (40)	NR	NR	NR
Gao et al. [25], 2010	8/49 (16.3)	NA/0	8/49 (16.3)	No	NR	Some cases
Purdie et al. [26], 2010	8/45 (17.8)	NR	NR	No	No	All cases
O'Neil et al. [27], 2010	5/27 (18.5)	1/13 (7.7)	4/14 (28.6)	NR	NR	NR
Subhawong et al. [28], 2010	5/68 (7.4)	0/56 (0)	5/12 (41.7)	NR	NR	Some cases
Graesslin et al. [29], 2010	0/32 (0)	0/30 (0)	0/2 (0)	NR	NR	All cases
Mulheron et al. [30], 2009	0/12 (0)	NA/0	0/12 (0)	NR	NR	NR
Polom et al. [31], 2009	10/20 (50)	5/11 (45.5)	5/9 (55.6)	NR	NR	NR
Brem et al. [32], 2008	38/164 (23)	21/97 (21.6)	17/67 (25.3)	NR	Yes	NR
Cangiarella et al. [33], 2008	3/38 (7.9)	1/18 (5.6)	2/20 (10.0)	NR	NR	None
Londero et al. [34], 2008	13/28 (46.4)	1/8 (12.5)	12/20 (60.0)	NR	NR	NR
Sohn et al. [35], 2008	0/21 (0)	0/19 (0)	0/2 (0)	NR	NR	NR
Menon et al. [36], 2008	9/25 (36.0)	NR	NR	No	NR	Some cases
Nagi et al. [37], 2008	2/45 (4.4)	NR	NR	No	Yes	NR
Hwang et al. [38], 2008	1/71 (1.4)	1/48 (2.1)	0/23 (0)	No	No	Some cases
Karabakhtsian et al. [39], 2007	10/92 (10.9)	5/63 (7.9)	5/29 (17.2)	No	NR	NR
Lavoué et al. [40], 2007	7/42 (16.7)	NR	NR	No	NR	All cases
Margenthaler et al. [41], 2006	7/35 (20.0)	3/19 (15.8)	4/16 (25.0)	NR	NR	NR
Mahoney et al. [42], 2006	4/18 (22.2)	1/10 (10.0)	3/8 (37.5)	No	NR	NR
Renshaw et al. [43], 2006	6/91 (6.6)[d]	NR/40	NR/51	Yes	Yes	Some cases
Elsheikh and Silverman [44], 2005	7/30 (23.3)	4/19 (21.1)	3/11 (27.3)	No	No	Some cases
Arpino et al. [45], 2004	3/21 (14.3)	1/17 (5.8)	2/4 (50)	NR	NR	NR
Foster et al. [46], 2004	6/26 (23.1)	2/14 (14.3)	4/12 (33.3)	NR	NR	NR
Bauer et al. [47], 2003	1/7 (14.3)	NR	NR	NR	NR	NR
Crisi et al. [48], 2003	2/16 (12.5)	NR	NR	No	NR	NR
Dmytrasz et al. [49], 2003	3/7 (42.9)	3/7 (42.9)	NA/0	NA	NR	NR
Middleton et al. [50], 2003	6/17 (35.3)[e]	4/6 (66.7)	2/9 (22.2)	No	No	NR
Irfan and Brem [51], 2002	1/7 (14.3)	1/7 (14.3)	NA/0	NA	NR	NR
Renshaw et al. [52], 2002	0/15 (0)	0/6 (0)	0/9 (0)	NR	NR	NR

(Table 1 continues on next page)

TABLE 1: Summary of Observed Rates of Upgrade at Excision to Malignancy After Core Breast Biopsy Diagnosis of Lobular Neoplasia (LN), Atypical Lobular Hyperplasia (ALH), or Lobular Carcinoma in Situ (LCIS) (continued)

Study, Year	LN, No. Upgraded at Excision/Total No. Excised (%)	ALH, No. Upgraded at Excision/Total No. Excised (%)	LCIS, No. Upgraded at Excision/Total No. Excised (%)	PLCIS Grouped With LCIS	Discordant Lesions Included	E-Cadherin Testing Performed
Shin and Rosen [53], 2002	2/13 (15.4)	0/5 (0)	2/8 (25)	NR	NR	NR
Berg et al. [54], 2001	1/15 (6.7)	1/7 (14.3)	0/8 (0)	NR	NR	NR
O'Driscoll et al. [55], 2001	3/7 (42.9)	NR	3/7 (42.9)	NR	NR	NR
Philpotts et al. [56], 2000	1/4 (25)	0/NA	1/4 (25)	NR	NR	NR
Liberman et al. [57], 1999	3/18 (16.7)	0/4 (0)	3/14 (21.4)	NR	NR	NR

Note—Pure LN lesions with subsequent follow-up surgical excisions were included. Hence, if patients subsequently developed carcinoma during the follow-up period, those lesions were not included in the table. If the study clearly stated the number of other coexisting high-risk lesions (e.g., flat epithelial atypia or atypical ductal hyperplasia), those cases were excluded. If a lesion was reclassified, the number after the reclassification was used. If the lesions were subdivided into classic LCIS and pleomorphic LCIS (PLCIS), PLCIS was excluded. If the authors calculated the upgrade rates for concordant and discordant lesions separately, only the concordant lesions were included. If the authors listed mixed LCIS and ALH, they were classified under LCIS. The overlapping series from Zhao et al. [65] is not included in this table. NR = not reported, NA = not applicable.

[a]There were 25 upgraded cases, including three PLCIS at excision. The three cases of PLCIS found at excision were excluded from the upgraded cases. However, it is unclear whether those three cases were ALH or LCIS at core biopsies. Hence, NR is listed under upgrade of ALH or LCIS.

[b]One hundred ninety-nine LNs include 48 LN (not specifying LCIS or ALH). The total numbers of upgraded cases include six ALH, 15 LCIS, and six LN.

[c]One of three upgraded cases was discordant.

[d]The study had 92 pure LNs, but one core biopsy (LCIS) was later classified as either PLCIS or ADH by different observers in the pathology department. Of the remaining six upgraded lesions, two were in sites away from the biopsy site, two were in the same sites as the biopsy site, and two were in women with previous excision of the biopsy site without finding of cancer. Hence, if only the two invasive carcinomas found at excision of the biopsy site are considered as upgraded, the total upgrade rate is 2.2% (2/91), 2.5% (1/40) for ALH, and 2.0% (1/51) for LCIS.

[e]Includes LN; total of ALH plus LCIS plus LN is 17; upgrade rate of ALH plus LCIS is 40.0% (6/15).

Pleomorphic LCIS (PLCIS) is cytologically different from classic LCIS [58]. Although there is no consensus for management of surgical margins and adjuvant therapy, it is generally accepted that PLCIS should be excised [59–62]. Low and intermediate nuclear grade LCIS are now considered classic LCIS [25]. A finding of classic LCIS at core biopsy has traditionally prompted a recommendation for excision. However, the management of LN found at core biopsy remains controversial, and some authors advocate observation rather than excision, particularly after a core biopsy diagnosis of ALH [11, 13, 14, 20, 28, 35, 37, 38, 63, 64].

The purpose of this study was to determine the rate of upgrade to DCIS or invasive carcinoma at excision at the same site after a percutaneous breast biopsy finding of ALH or classic LCIS using current radiologic imaging and strict pathologic criteria. In particular, we sought to identify a subset of lesion or patient characteristics associated with a low upgrade rate, where surveillance would be reasonable in lieu of excision.

Materials and Methods

Literature Search

For review of the existing literature, the PubMed database was searched for the following terms: "lobular neoplasia," "atypical lobular hyperplasia," and "lobular carcinoma in situ." Studies published before 1999 were not included. We excluded review articles, case reports, meta-analyses, and non-English articles. A publication by Middleton et al. [64] was excluded because it was based on cases submitted to multidisciplinary conference, and only a small percentage of cases (20/124; 16.1%) was recommended for excision. This resulted in 47 articles analyzing the upgrade rate of LN on excision (Table 1).

Patient Selection

The study was approved by the institutional review boards of both the University of Pittsburgh and Yale University School of Medicine and was compliant with HIPAA. The need for informed consent was waived.

A retrospective pathology database review was performed at the University of Pittsburgh Medical Center from January 1, 2006, through September 30, 2013. Of 32,960 breast core biopsies, 1084 (3.3%) had ALH or classic LCIS diagnosed at histopathologic examination. We excluded patients who did not undergo excision (n = 162); women with ipsilateral DCIS or invasive carcinoma, PLCIS, or incidental DCIS (found elsewhere at prophylactic mastectomy); and those with another high-risk lesion at the initial core biopsy site, including atypical ductal hyperplasia (ADH), flat epithelial atypia, apocrine atypia, papilloma, microscopic papilloma, radial scar, or microscopic radial scar, leaving 447 biopsies (433 women) in the analysis set. During the study period, all patients with ALH or LCIS found at core biopsy were referred to surgeons. The decision for some patients to not have surgery was affected by expected low upgrade rate, patient comorbidities, and surgeon preferences.

In a subset series performed at our institution, Zhao et al. [65] reported the upgrade rate at excision for 237 patients with radiologic findings of calcifications and LN at core biopsy, with 233 of those stereotactically guided (three by ultrasound and one by MRI). Our series encompasses a longer study period and lesions with and without calcifications. In addition, unlike the series by Zhao et al., we now distinguish whether the LN was associated with the targeted calcifications or was an incidental finding, and histopathologic-radiologic review is now performed for upgraded lesions. In this study, we reviewed and analyzed the detailed imaging features of all LN lesions, when the imaging studies were available, which was not performed in the series by Zhao et al.

Pathologic Analysis

ALH and LCIS form a continuum; distinguishing LCIS from ALH can be challenging. Page et al. [5, 66] use a threshold of expansion of at least 50% of the acini with characteristic monomorphic cells, below which ALH rather than LCIS is defined. Classic LN lesions consist of small rounded monomorphic dyshesive cells with an increased nuclear-to-cytoplasmic ratio. Intracytoplasmic vacuoles are a common finding and can be a prominent feature. In PLCIS, the cells appear dyshesive as in classic LCIS; however, they exhibit nuclear pleomorphism and enlargement (four times the size of a lymphocyte). Occasionally, there is abundant eosinophilic cytoplasm, giving the cells an apocrine appearance (apocrine PLCIS). Comedo or punctate necrosis and calcifications may be as-

sociated with PLCIS, which can be confused with comedo-type DCIS [67, 68]. At our institution, a lack or aberrant expression of E-cadherin and cytoplasmic staining on P120 catenin immunohistochemistry tests are and have been used routinely to support the lobular phenotype of all LN lesions. As previously stated, PLCIS was excluded from this analysis. When invasive cancer was found on excision and was multifocal, the size of the largest focus was reported.

Data Collection

Clinical data, including age at LN diagnosis, biopsy date, follow-up excision histopathology, signs and symptoms, and personal and family histories of breast cancer, were collected from the medical records. Images were reviewed and findings were recorded, including breast density; mammographic, ultrasound, or MRI BI-RADS lesion type (calcification morphologic features and distribution, mass shape and margins, asymmetry, architectural distortion, or MRI enhancement pattern); and size. Biopsy guidance method, device used, and number of specimens obtained were retrieved from the procedure reports. Percutaneous biopsy results and surgical excision histopathologic results were retrieved from histopathology reports.

All cases upgraded to malignancy at excision underwent imaging and histopathologic review together by a dedicated breast pathologist with 30 years' experience and two radiologists with 24 and 22 years' experience in breast imaging. We determined whether the LN was incidental on the core biopsy (i.e., adjacent to the targeted lesion or the actual targeted lesion). Although radiologic-pathologic concordance or discordance had been assessed for all cases at the time of biopsy, we reassessed this for all malignant cases. Concordance was defined as present if a suspicious group of calcifications was targeted and confirmed at specimen radiography and histopathologic examination, or if histopathologic findings otherwise provided an acceptable explanation of imaging features.

Biopsy Methods

Of 317 stereotactically guided biopsies, 281 were performed using 7-, 8-, 9-, 10-, 11-, or 12-gauge vacuum-assisted devices (mean, 9 passes; range, 3–31 passes; 25 cases were missing the number of passes), and 36 were performed with devices of unknown gauge (19 of which had unknown gauge and number of passes). Of 103 ultrasound-guided biopsies, 22 were performed using 8-, 11-, or 12-gauge vacuum-assisted devices (mean, 4 passes; range, 2–6 passes; five were missing the number of passes); 60 used 13- or 14-gauge automated core biopsy devices (mean, 4 passes; range, 2–15 passes); and details of 21 ultrasound-guided procedures were not available. Of 27 MRI-guided biopsies, all were performed using 9-gauge vacuum-assisted technique (mean, 7 passes; range, 6–16 passes; two cases were missing the number of passes) on a 1.5-T unit.

Statistical Analysis

Fisher exact tests were used to examine differences in the upgrade variable for demographics, lesion type, and biopsy guidance method (stereotactic, ultrasound, or MRI). For qualitative data, frequency and percentages were reported. For quantitative data, range and median were reported. The corresponding 95% CIs were computed by the Wilson method, and a p value of 0.05 was used as the threshold for significance. Subset analyses were also performed on upgrade rates for ALH and LCIS subgroups, without adjustment for multiple comparisons.

Validation Study

To validate our results, using the same inclusion and exclusion criteria, the histopathology database at Yale University School of Medicine was also reviewed from January 1, 2007, through December 31, 2013, yielding 10,988 core breast biop-

TABLE 2: Imaging Findings for 447 Lesions Determined to be Lobular Neoplasia (LN), Including Atypical Lobular Hyperplasia (ALH) and Lobular Carcinoma In Situ (LCIS) Subsets, at Core Biopsy

Lesion Type	LN	ALH	LCIS
Calcifications on mammography, morphologic features	307	238 (77.5)	69 (22.5)
Amorphous	124	92	32
Pleomorphic	87	74	13
Coarse heterogeneous	52	33	19
Punctate	27	25	2
Fine linear	4	4	0
Unknown[a]	13	10	3
Mass	119[b]	87 (73.1)	32 (26.8)
Shape			
Oval	59	47	12[c]
Round	9	7	2
Irregular	46	31[d]	15[c]
Unknown[a]	5	2	3
Margins			
Circumscribed	31	28	3
Indistinct	46	36[d]	10
Angulated	18	12	6
Irregular	14	5	9
Microlobulated	3	2	1
Obscured	2	2	0
Unknown[a]	5	2	3
Nonmass enhancement on MRI	7	5 (71.4)	2 (28.6)
Asymmetry	6	5 (83.3)	1 (16.7)
Architectural distortion	5	3 (60.0)	2 (40.0)
Unknown[a]	3	1 (33.3)	2 (66.7)

Note—Data are number of lesions or number (%) of lesions.

[a]Initial core biopsy was performed at an outside hospital and pathologic specimen was sent to Magee-Womens Hospital of University of Pittsburgh Medical Center for second opinion. For 21 lesions (13 calcifications, five masses, and three unknown type), the lesion types were obtained from the outside hospital reports (imaging or pathology reports), but imaging studies were not available for review.

[b]Thirty-nine were seen on both ultrasound and mammography, 38 were seen on ultrasound only, 18 were seen on MRI only, nine were seen on mammography only, nine were seen on ultrasound and MRI, and one was seen on mammography and MRI (five unknown).

[c]One each oval and irregular masses were intraductal.

[d]One irregular mass with indistinct margin was intraductal.

TABLE 3: Details of 22 Cases of Lobular Neoplasia (12 Atypical Lobular Hyperplasia [ALH] and 10 Lobular Carcinoma in Situ [LCIS]) on Core Biopsy Upgraded to Malignancy at Excision

Type of Malignancy, Case No.	Age (y)	Breast Density	Imaging Finding	Size on Imaging (cm)	Guidance	Excision Finding	Grade	Invasive Tumor Size (cm)	Radiologic-Pathologic Concordance	Family History of Breast or Ovarian Cancer (Age at Diagnosis [y])	Comment
ALH											
1	64	Scattered	Grouped amorphous calcifications	2.3	Stereotactic	DCIS; ER and PR positive	2		Concordant, calcifications in fibrocystic changes	Sister (60s), 3 paternal aunts (70s), 2 maternal aunts (unknown), first cousin (58)	ALH incidental; DCIS immediately adjacent to biopsy site
2	69	Heterogeneous	Grouped fine linear calcifications	0.8	Stereotactic	DCIS; ER and PR positive	2		Concordant, calcifications in fibrocystic changes with apocrine metaplasia	Mother, ovarian cancer (75)	Very little ALH on CNB; DCIS 6 mm from biopsy site
3	68	Scattered	Grouped amorphous calcifications	0.2	Stereotactic	DCIS; ER and PR positive	1		Concordant, calcifications in fibrocystic changes	None	Miniscule ALH on CNB; DCIS is incidental
4	45	Heterogeneous	Grouped coarse heterogeneous calcifications	0.3	Stereotactic	Invasive tubular carcinoma; ER and PR positive; HER2/neu negative	1	0.3	Concordant, benign epithelial calcifications	None	3-mm spiculated mass at surgery without calcifications
5	70	Heterogeneous	Grouped pleomorphic calcifications	2.0	Stereotactic	DCIS; ER positive; PR negative	3		Concordant, calcifications in columnar cell changes and hyperplasia	Sister (50)	DCIS is incidental
6	72	Scattered	Irregular mass with a microlobulated margin	0.8	Stereotactic	DCIS; ER not tested; PR positive	1		Concordant, calcifications in fibrocystic changes	Mother, maternal and paternal grandmothers (unknown); maternal aunt (ovarian cancer)	DCIS is incidental
7	61	Scattered	Oval hypoechoic mass with an angulated margin	1.1	Ultrasound	DCIS; ER and PR positive	1		Concordant, mass likely due to fibroepithelial lesion	Mother bilateral (59); maternal aunt (diagnosed at 55, died of metastatic disease at 61)	ALH incidental; LCIS at excision (closer to DCIS)
8	57	Scattered	Grouped amorphous calcifications	0.7	Stereotactic	Multifocal ILC; ER positive; PR weakly positive; HER2/neu negative	2	1.3, 0.3, and 0.2	Concordant, calcifications in fibrocystic changes	Aunt ovarian cancer (49), cousin ovarian cancer (40), cousin breast cancer (42)	Patient has *BRCA* variant (Y1749C); ADH elsewhere same breast upgraded to ILC

(Table 3 continues on next page)

TABLE 3: Details of 22 Cases of Lobular Neoplasia (12 Atypical Lobular Hyperplasia [ALH] and 10 Lobular Carcinoma in Situ [LCIS]) on Core Biopsy Upgraded to Malignancy at Excision (continued)

Type of Malignancy, Case No.	Age (y)	Breast Density	Imaging Finding	Size on Imaging (cm)	Guidance	Excision Finding	Grade	Invasive Tumor size (cm)	Radiologic-Pathologic Concordance	Family History of Breast or Ovarian Cancer (Age at Diagnosis [y])	Comment
9	63	Heterogeneous	Grouped coarse heterogeneous calcifications	1.2	Stereotactic	Microinvasive ILC; ER and PR positive; too small for HER2/neu evaluation	1	0.03	Discordant	Aunt (75)	CNB missed calcifications
10	63	Scattered	Fine linear calcifications, linear distribution	2.3	Stereotactic	DCIS; ER positive, PR negative	2–3		Discordant	Mother (65), aunt (77)	Most suspicious linear calcifications were not biopsied on CNB
11	41	Heterogeneous	Focal asymmetry on mammography; round mass with a slightly irregular margin on MRI	0.4	MRI	DCIS; ER and PR positive	2–3		Discordant	Mother (48)	Mass due to DCIS 8 mm from biopsy site; CNB missed the lesion
12	59	Scattered	Segmental amorphous calcifications	1.4	Stereotactic	DCIS; ER and PR positive	3		Concordant	Aunt (unknown)	Mastectomy showed DCIS 2–3 mm from biopsy site and remotely; review of CNB slides found LCIS
LCIS											
1	51	Heterogeneous	Grouped amorphous calcifications	0.4	Stereotactic	Invasive tubular carcinoma; ER and PR positive; HER2/neu negative	1	0.2	Concordant, calcifications associated with LCIS	None	IDC immediately adjacent to ALH and LCIS
2	52	Heterogeneous	Outside hospital imaging; NA; indeterminate calcifications per report	NA	Stereotactic	Multifocal ILC; ER and PR positive; HER2/neu negative	1	1.3 and 0.25	Concordant, calcifications associated with LCIS and fibrocystic changes	Maternal cousin (54)	One tumor focus is 5 mm from CNB site
3	63	Heterogeneous	Grouped amorphous calcifications in a circumscribed mass	0.8	Stereotactic	DCIS; ER and PR testing cannot be performed	1		Concordant, benign epithelial calcifications	None	DCIS 4 mm from LCIS

(Table 3 continues on next page)

TABLE 3: Details of 22 Cases of Lobular Neoplasia (12 Atypical Lobular Hyperplasia [ALH] and 10 Lobular Carcinoma in Situ [LCIS]) on Core Biopsy Upgraded to Malignancy at Excision (continued)

Type of Malignancy, Case No.	Age (y)	Breast Density	Imaging Finding	Size on Imaging (cm)	Guidance	Excision Finding	Grade	Invasive Tumor size (cm)	Radiologic-Pathologic Concordance	Family History of Breast or Ovarian Cancer (Age at Diagnosis [y])	Comment
4	49	Heterogeneous	Asymmetry with a few calcifications	1.6	Stereotactic	DCIS; ER and PR positive	1		Concordant, calcifications in fibrocystic changes and fibroadenomatoid nodule	Mother (50s), aunt (60s), both sisters (40s)	DCIS about 3–4 mm from biopsy site
5	39	Heterogeneous	Oval mass on mammography; intraductal mass on ultrasound	0.8 on mammogram; 1.3 on ultrasound	Ultrasound	ILC; ER and PR positive; too few cells to test HER2/neu	1	0.12	Concordant, mass was in part due to LN and in part due to fibrocystic changes	Two maternal aunts (50s) and (62)	ILC was immediately adjacent to the mass
6	36	Heterogeneous	Enhancing oval mass with an indistinct margin and washout kinetics	0.5	MRI	Microinvasive ILC; ER and PR positive; too few cells to test HER2/neu	1	0.1	Concordant	Great aunt (≥ 70)	CNB site is ≈ 8 mm away from ILC
7	43	Heterogeneous	Grouped pleomorphic calcifications	1.0	Stereotactic	Multifocal ILC; ER and PR positive; HER2/neu negative	1	0.12 and 0.01	Concordant, LCIS with calcifications	None	Florid LCIS with calcification
8	39	Heterogeneous	Irregular hypoechoic mass	0.9	Ultrasound	Microinvasive ILC; ER and PR positive; HER2/neu negative	2	0.09	Concordant	Distant cousin (unknown)	Excision performed at outside hospital
9	55	Scattered	Regional amorphous calcifications	1.6	Stereotactic	DCIS; ER and PR positive	1		Discordant	Paternal aunt (40s), cousin (28), the aunt's daughter	Calcifications were targeted, but none seen on specimen radiograph
10	62	Scattered	Dilated ducts on mammography; intraductal irregular mass on ultrasound; linear non-mass enhancement on MRI	NA	Ultrasound	IDC; ER and PR positive; HER2/neu negative	1	0.35	Discordant	Maternal cousin (unknown)	Atypical papilloma on excision adjacent malignancy likely accounts for the intraductal mass

Note—All invasive cancers were node negative. Nuclear grade is reported for ductal carcinoma in situ (DCIS) or LCIS and Nottingham grade for invasive tumors. ER = estrogen receptor, PR = progesterone receptor, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma, CNB = core needle biopsy, LN = lobular neoplasia, NA = not applicable, ADH = atypical ductal hyperplasia.

TABLE 4: Upgrade Rates at Excision as a Function of Patient Age

Patient Age (y)	No. of Lobular Neoplasias Upgraded/Total (%)
< 40	3/11 (27.3)
40–49	4/139 (2.9)
50–59	5/182 (2.7)
60–69	8/74 (10.8)
≥ 70	2/27 (7.4)

Note—$p = 0.002$ for Fisher exact test for comparison across five groups.

sies, of which 68 (0.62%) showed LN as the highest risk lesion. At Yale University School of Medicine, pathologists do not routinely distinguish ALH from LCIS: upstaged cases were reviewed and classified as either ALH or LCIS on core biopsy. Pathologic findings were reviewed by a dedicated breast pathologist with 7 years' experience, together with the breast imaging findings by a breast imaging radiologist with 19 years' experience.

Results

A total of 447 biopsies were performed in 433 women, ranging in age from 28 to 86 years (median, 52 years). Lesion types included 307 mammographically identified calcifications, 119 masses (seven masses containing calcifications), seven lesions with nonmass MRI enhancement, six asymmetries, five architectural distortions, and three unknown lesions (Table 2).

Of the 447 biopsy findings, 339 (75.8%) were ALH and 108 (24.2%) were classic LCIS. All 447 lesions underwent surgical excision, revealing 22 (4.9%) malignancies, including 10 invasive cancers (two grade 2 and eight grade 1; mean size, 0.4 cm; range, 0.03–1.3 cm; all node negative) and 12 DCIS (Table 3). The upgrade rate to malignancy at excision was greater after a diagnosis of classic LCIS on initial core biopsy than ALH (10/108 [9.3%; 95% CI, 5.1–16.2%] vs 12/339 [3.5%; 95% CI, 2.0–6.1%]; $p = 0.02$). Of 433 women, 10 women's family history was unknown. Of the remaining 423 women, 204 (48.2%) had a positive family history of breast or ovarian cancer, with 17 of 204 (8.3%) lesions upgraded, versus 219 of 423 (51.8%) women without family history, with five of 219 (2.3%) lesions upgraded ($p = 0.01$). However, when we only evaluated the women with calcifications, there were 293 women with 307 lesions seen as calcifications. Of the 293 women, 134 (45.7%) had a positive family history versus 159 (54.3%) without. Nine of 134 (6.7%) women with a positive family had upgraded lesions versus five of 159 (3.1%) without a family history ($p = 0.17$).

Of 433 women, 11 were younger than 40 years, 139 were 40–49 years old, 182 were 50–59 years old, 74 were 60–69 years old, and 27 were 70 years old or older. In our study group, women between 40 and 59 years old had particularly low upgrade rates (Table 4). Of the 11 women younger than 40 years, five had a palpable mass, three were recalled from

TABLE 5: Upgrade Rates at Excision of Lobular Neoplasia (LN) as a Function of Breast Density, Biopsy Guidance, Lesion Type, and Location of Calcifications

Characteristic	LN ($n = 447$)	p[a]	Atypical Lobular Hyperplasia ($n = 339$)	p[a]	Lobular Carcinoma In Situ ($n = 108$)	p[a]
Overall	22/447 (4.9)		12/339 (3.5)		10/108 (9.3)	0.02
Breast density[b]		0.44		0.08		1.0
Scattered	9/120 (7.5)		7/95 (7.4)		2/25 (8.0)	
Heterogeneously dense	13/294 (4.4)		5/219 (2.3)		8/75 (10.7)	
Extremely dense	0/26 (0)		0/21 (0)		0/5 (0)	
Unknown density[c]	0/7 (0)		0/4 (0)		0/3 (0)	
Biopsy guidance		0.74		0.36		0.88
Stereotactic	16/317 (5.0)		10/246 (4.1)		6/71 (8.5)	
Ultrasound	4/103 (3.9)		1/77 (1.3)		3/26 (11.5)	
MRI	2/27 (7.4)		1/16 (6.3)		1/11 (9.1)	
Lesion type		0.47		1.0		0.15
Calcifications	14/307 (4.6)		9/238 (3.8)		5/69 (7.2)	
Mass	7/119 (5.9)		3/87 (3.4)		4/32 (12.5)	
Architectural distortion	0/5 (0)		0/3 (0)		0/2 (0)	
Nonmass enhancement	0/7 (0)		0/5 (0)		0/2 (0)	
Asymmetry	1/6 (16.7)		0/5 (0)		1/1 (100)	
Unknown[d]	0/3 (0)		0/1 (0)		0/2 (0)	
Calcifications present at pathologic examination		0.77		0.21		1.0
Calcifications in LN	3/85 (3.5)		0/53 (0)		3/32 (9.4)	
LN incidental[c]	13/273 (4.8)		9/222 (4.1)		4/51 (7.8)	
No calcifications present at pathologic examination	6/89 (6.7)		3/64 (4.7)		3/25 (12.0)	0.34

Note—Except for p values, data are number of lesions upgraded at excision/total (%).
[a]When imaging features are unknown, those lesions are not included in the p value calculation.
[b]Based on mammographic reports.
[c]Calcifications are not associated with LN.
[d]Seven lesions had no outside imaging studies or report. Four of seven lesion types were obtained from pathology reports.

screening mammograms (two women with high risk and one before breast augmentation), two had lesions detected on high-risk breast MRI, and one woman presented with pain.

Subanalyses by breast density, guidance method, lesion type, and calcifications within LN or that were incidental on histopathologic analysis showed no statistically significant differences (Table 5).

Of 119 masses, 85 were identified in asymptomatic women, with six upgraded (7.1%); 19 masses were in women who presented with a palpable abnormality, with none upgraded; seven masses were in women who had concurrent contralateral malignancy, with none upgraded; five masses were in women with pain, with none upgraded; and three masses were in women with nipple retraction or nipple discharge, with one upgraded (33.3%; the patient with an upgraded lesion had bloody nipple discharge without nipple retraction; $p = 0.27$).

For lesions biopsied with stereotactic or ultrasound guidance, neither biopsy device gauge nor number of passes affected the upgrade rate. For more information, see the data supplement to this article (available at www.ajronline.org).

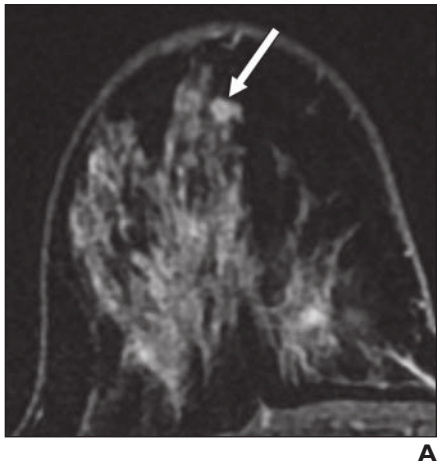
Atypical Lobular Hyperplasia Upgrades

Twelve of 339 (3.5%) ALH lesions were upgraded to malignancy. Three of 12 upgraded cases were invasive carcinomas, with one multifocal grade 2 invasive lobular carcinoma (ILC) (largest 1.3 cm) in a patient with a strong family history of both breast and ovarian cancer, one microinvasive ILC (discordant with imaging due to failure to retrieve calcifications), and one invasive tubular carcinoma (all node negative; size, 0.03–1.3 cm; mean, 0.5 cm). The remaining nine upgrades were six grade 2–3 DCIS (including one discordant finding with mass biopsied under MRI guidance and another discordant finding where the most suspicious calcifications were not sampled on stereotactically guided biopsy) and three grade 1 DCIS.

Nine upgraded ALH lesions were calcifications (four amorphous, two fine linear, two coarse heterogeneous, and one pleomorphic). Three upgraded lesions were masses (one irregular mass with a microlobulated margin, one oval mass with an angular margin, and one round mass with a slightly irregular margin).

Of 238 lesions seen as calcifications, 92 (38.7%) were amorphous, 74 (31.1%) were pleomorphic, 33 (13.9%) were coarse heterogeneous, 25 (10.5%) were punctate, four (1.7%) were fine linear, and 10 (4.2%) were unknown (Table 2) (percentages do not total 100% because of rounding). Upgrades were observed for five of 92 (5.4%) amorphous, one of 74 (1.4%) pleomorphic, one of 33 (3.0%) coarse heterogeneous, two of four (50%) fine linear, and zero of 25 (0%) punctate calcifications ($p = 0.01$). We also investigated the upgrade rate by distribution of calcifications: seven of 186 (3.8%) grouped, zero of 22 (0%) regional, zero of 13 (0%) linear, and two of seven (28.6%) in segmental distribution were upgraded ($p = 0.06$). For lesions seen as calcifications on imaging and as ALH on core biopsies, there was statistical significance when stratifying the data by calcification morphologic characteristics ($p = 0.01$). This is related to the higher upgrade rate of fine linear calcifications at 50% (2/4). Although there was a mild increase in upgrade rates of amorphous (5.4%; 5/92) and coarse heterogeneous (3.0%; 1/33) calcifications versus pleomorphic calcifications (1.4%; 1/74), this difference was not statistically significant once fine linear calcifications were excluded from the calculation ($p = 0.43$).

A total of 87 ALH lesions were seen as masses (no imaging was available for two lesions). One of 47 (2.1%) oval masses, one of 31 (3.2%) irregular masses, and one of seven (14.3%) round masses were upgraded ($p =$



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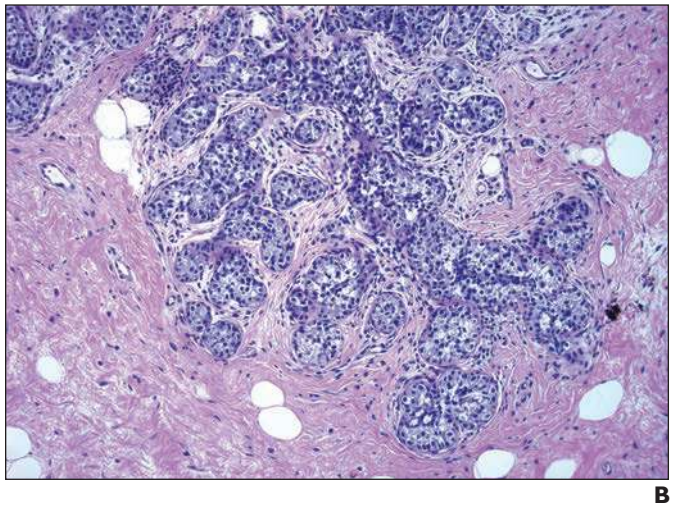

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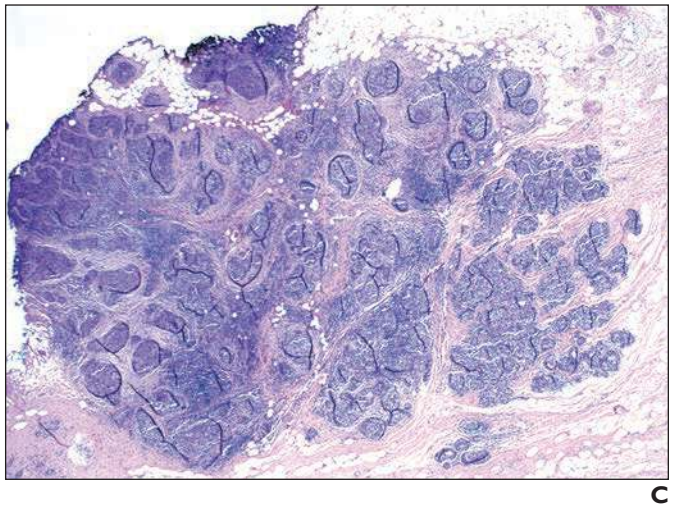

C

Fig. 1—41-year-old woman with atypical lobular hyperplasia (ALH) found at MRI-guided biopsy (targeted lesion was missed at MRI-guided biopsy) that was upgraded to ductal carcinoma in situ (DCIS) at follow-up excision. Asymmetry was noted on craniocaudal mammogram (not shown).
A, Because of extensive shadowing on ultrasound, breast MRI was performed, which showed 4-mm enhancing mass (*arrow*).
B, MRI-guided core needle biopsy rendered diagnosis of ALH on histopathologic examination. Photomicrograph (H and E, ×40) shows that lobules are distended, with small rounded monomorphic dyshesive cells with increased nuclear-to-cytoplasmic ratio.
C, On subsequent excision, 3-mm DCIS nuclear grade 2–3 was identified. On close inspection of histopathologic specimen (H and E, ×10), lesion closely matches MRI finding, which was not recognized prospectively. Hence, MRI-guided biopsy missed lesion.

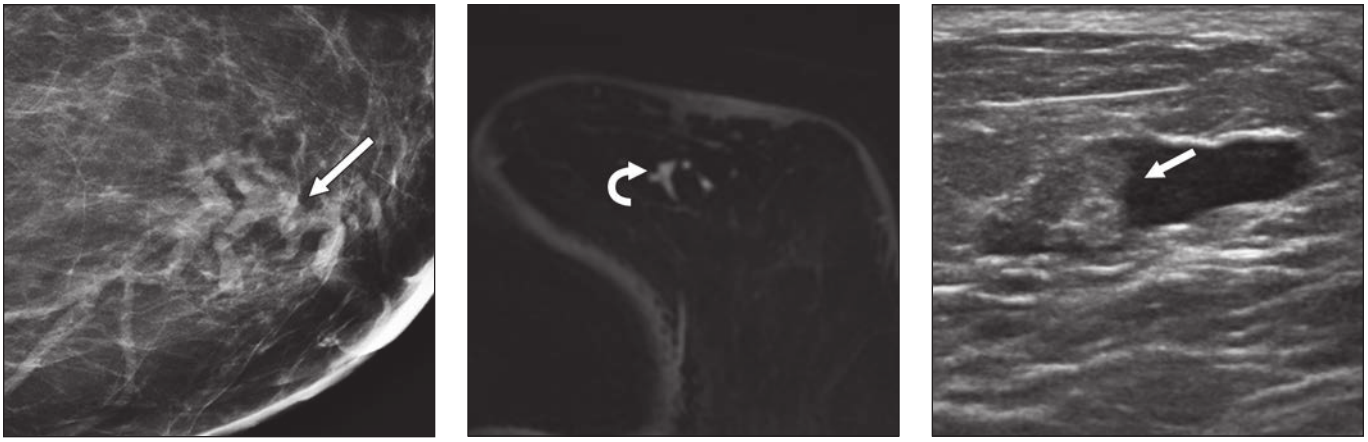

Fig. 2—62-year-old woman with lobular carcinoma in situ (LCIS) found at ultrasound-guided core needle biopsy that was upgraded to invasive ductal carcinoma (IDC) not otherwise specified (NOS) at excision. She initially presented with left bloody nipple discharge for 6 weeks.
A, Spot-compression lateral view mammogram shows dilated ducts (*arrow*). Ductogram (not shown) showed dilated ducts without definite filling defects.
B, Subsequent T1-weighted contrast-enhanced MR image shows linear non-mass enhancement in 7-o'clock position (*arrow*).
C, On second-look ultrasound, there was isoechoic heterogeneous intraductal mass (*arrow*). Ultrasound-guided core needle biopsy revealed LCIS, discordant with intraductal mass, and this discordance was not recognized prospectively. Excision showed 3.5-mm IDC NOS, atypical ductal hyperplasia, and LCIS. Additionally, atypical intraductal papilloma was identified, which likely accounted for lesion seen on MRI and ultrasound.

0.28). One MRI-depicted round mass with washout kinetics was upgraded to grade 2–3 DCIS at excision and was later recognized as having been missed at initial core biopsy (Fig. 1). Upgrade rates by largest lesion diameter or span of calcifications were six of 211 (2.8%) between 0 and less than 1 cm, three of 76 (4.0%) between 1 and less than 2 cm, three of 19 (15.8%) between 2 and less than 3 cm, and zero of 21 (0%) between 3 and 8 cm (with no imaging available for 12 lesions) ($p = 0.07$).

Lobular Carcinoma In Situ Upgrades

Of 108 LCIS lesions, 10 (9.3%) were upgraded to malignancy. Seven of 10 upgrades showed invasive carcinoma (Table 3), including two grade 1 multifocal ILCs, one grade 1 ILC, one grade 1 invasive ductal carcinoma (IDC) (with initial LCIS discordant with an intraductal mass on imaging), one grade 1 microinvasive ILC, one grade 2 microinvasive ILC, and one invasive tubular carcinoma (all node negative; size, 0.09–1.3 cm; mean, 0.3 cm). The remaining three upgrades were low nuclear grade DCIS (one discordant with imaging due to failure to retrieve calcifications).

Five upgraded LCIS lesions were calcifications (three amorphous, one pleomorphic, and one unknown details because of outside imaging unavailable). One group of amorphous calcifications was within a circumscribed mass on mammography. Four upgraded lesions were masses (two intraductal masses, one oval mass with an indistinct margin, and one irregular mass). One upgraded lesion was seen as an asymmetry with a few calcifications.

Of 69 lesions that were seen as calcifications, 32 (46.4%) were amorphous, 13 (18.8%) were pleomorphic, 19 (27.5%) were coarse heterogeneous, two (2.9%) were punctate, and three (4.3%) were unknown (Table 2) (percentages do not total 100% because of rounding). Three of 32 (9.4%) amorphous, one of 13 (7.7%) pleomorphic, zero of 19 (0%) coarse heterogeneous, and zero of two (0%) punctate calcifications were upgraded ($p = 0.48$) (no imaging was available for one upgraded lesion). For lesions seen as calcifications on imaging and as LCIS on core biopsies, there was a mild increase in the upgrade rate of amorphous (9.4%; 3/32) versus pleomorphic (7.7%; 1/13) calcifications that was not statistically significant. The slight increase is related to chance. We also investigated the upgrade rate for distribution of calcifications: three of 54 (5.6%) grouped, one of 10 (10%) regional, and zero of two (0%) linear calcifications were upgraded ($p = 0.56$) (no imaging was available for one upgraded lesion).

A total of 32 LCIS lesions were manifest as masses (no imaging was available for three masses). Two of 12 (16.7%) oval masses (one was intraductal), two of 15 (13.3%) irregular masses (one was intraductal), and zero of two (0%) round masses were upgraded ($p = 1.0$). Upgrade rates by largest lesion diameter or span of calcifications were five of 68 (7.4%) between 0 and less than 1 cm, four of 19 (21.1%) between 1 and less than 2 cm, zero of eight (0%) between 2 and less than 3 cm, and zero of five (0%) between 3 and 5 cm (no imaging was available for eight lesions, including three calcifications, three masses, and two unknown type. One of the three lesions seen as calcifications was upgraded) ($p = 0.27$).

Histopathologic-Radiologic Review of Upgraded Cases

Among the 22 upgraded lesions, five (22.7%) showed radiologic-pathologic discordance (Table 3). One was the mass missed at MRI-guided biopsy already described (Fig. 1). For three discordant cases later upgraded, the most suspicious calcifications were not successfully targeted stereotactically. The fifth patient with radiologic-histopathologic discordance had bloody nipple discharge, and dilated ducts were seen on mammography and galactography (Fig. 2). MRI-directed ultrasound showed an irregular intraductal mass, with ultrasound-guided core biopsy revealing LCIS, which is discordant with an intraductal mass. Excision showed a 0.4-cm grade 1 IDC and atypical papilloma, with the latter likely accounting for the intraductal mass. In usual practice at Magee-Womens Hospital of University of Pittsburgh Medical Center, any discordant cases were rebiopsied or excised. Of the five discordant cases, only one was recognized at the time of pathology addendum, for which rebiopsy or excision with bracketing was recommended. The other four cases were not recognized prospectively.

A sixth patient had ALH found at core needle biopsy and subsequently underwent

mastectomy at an outside hospital. The mastectomy slides showed that DCIS was at the initial ALH biopsy site. A review of the core biopsy slides showed that the initial histopathologic specimen should have been classified as LCIS rather than ALH.

After excluding the five cases with radiologic-pathologic discordance and reclassifying the latter case as LCIS and not ALH at core biopsy, the overall upgrade rate would be 3.8% (17/442). The upgrade rate for LCIS (8.4%; 9/107; 95% CI, 4.5–15.2%) remained statistically significantly higher than the upgrade rate for ALH (2.4%; 8/335; 95% CI, 1.2–4.6%; $p = 0.01$).

To assess the generalizability of our results, specifically the low upgrade rate, a validation study was conducted at Yale University School of Medicine, as detailed in Table S1 in the data supplement. We incidentally discovered that at that institution, distinction between ALH and LCIS is not routinely performed.

Discussion

In this study, we sought to identify a subset of lesions or patients with a percutaneous biopsy result of ALH or LCIS who might be candidates for surveillance in lieu of excision. As expected, the upgrade rate to malignancy after excision was statistically significantly higher for LCIS (9.3%; 10/108) than for ALH (3.5%; 12/339) ($p = 0.02$). After excluding five cases with radiologic-pathologic discordance and reclassifying one case from ALH to LCIS, the upgrade rate for LCIS remained statistically significantly higher (8.4%; 9/107) than that for ALH (2.4%; 8/335) ($p = 0.01$). Women between 40 and 59 years old have particularly low upgrade rates. Women with a family history of breast or ovarian cancer are more likely to have their lesions upgraded versus those without such a history ($p = 0.01$). However, in the subset of women presenting with calcifications, there was no statistically significant difference between women with or without a family history.

A recent study by Khoury et al. [69] showed an upgrade rate of 29% (9/31) on excision of pure LN (excluding PLCIS) after MRI-guided core biopsies, which was much higher than our finding of 7.4% (2/27). Additionally, in our study, no statistical significance was shown for upgrade rates as a function of differing biopsy guidance.

Data extracted from the Surveillance, Epidemiology, and End Results cancer registry by Li and colleagues [70] showed that the frequency of LCIS increased by 2.6-fold (95% CI, 2.3–2.9) from 1980 to 2001. However, the management of LN found at core needle biopsy remains controversial. Across the literature, the range of ALH upgrade rates is wide (0–66.7%; Table 1). Multiple studies have concluded that patients with radiologic-pathologic concordant pure ALH may be safely observed rather than undergo surgery [13, 14, 20, 35, 37, 38, 64]. Less is reported on the outcome of surveillance. Provencher et al. [63] showed that among 275 women with pure LN and conservative management, only three women (1.1%) received a diagnosis of cancer in the same breast quadrant as the site of original core biopsy after a mean (± SD) follow-up of 3.9 ± 2.6 years; as a result, they too suggested that ALH and even classic LCIS with radiologic-histopathologic concordance do not require excision in the absence of suspicious changes on imaging or clinical follow-up.

Unlike ADH, subsequent carcinomas after LN are often not at the same site. Chuba and colleagues [6] used the Surveillance, Epidemiology, and End Results Cancer Incidence Public-Use Database from 1973–1998 and identified 350 women with invasive breast cancer 1 year or longer after a diagnosis of LCIS (4853 women with a diagnosis of LCIS). Frequencies of ipsilateral and contralateral invasive breast cancer were nearly the same 5–25 years after LCIS followed by partial mastectomy, ranging from 0.7% each at 5 years to 30.5% in the ipsilateral breast and 26.2% in the contralateral breast at 25 years [6]. Even for patients who undergo initial excision of LCIS, the subsequent cancer risk may not be reduced. In a study by Meroni et al. [11], although the upgrade rate was 7.1% (1/14) for ALH and 12% (6/50) for LCIS, it was noted that the rate of developing an ipsilateral malignancy was similar among the groups treated by surgery (6/11; 54.5%) and those clinically monitored (5/11; 45.5%); hence, the authors advocated that patients with ALH and LCIS found at core needle biopsy should be monitored by clinical and radiologic surveillance rather than immediate excision. Middleton and colleagues [64] found that with a median follow-up of 3.4 years, five of 104 patients with LN received a diagnosis of malignancy, but three of these five malignancies were remote from the site of initial core biopsy; those authors concluded that clinical management of low-volume LNs (i.e., less than three terminal duct lobular units involved by ALH, LCIS, or LN) in a multidisciplinary setting could be a viable alternative to excision. In a study by Mulheron et al. [30], with a mean follow-up of 66 months after core biopsy diagnosis of LN, five of 25 patients (20%) developed DCIS or invasive cancer; the frequency of carcinoma among patients who underwent initial excision was 25% versus 15% of those who did not undergo excision ($p = 0.57$) and none of the patients without initial excision developed carcinoma in the same quadrant [30]. However, Page and colleagues [7] did observe that invasive carcinoma is three times more likely to arise ipsilaterally in the breast with initial diagnosis of ALH than in the contralateral breast.

Variability in Pathologic Profiles

On reviewing the 22 upgraded cases, we found variability in classification of the initial core biopsy histopathologic profile for one (4.5%) case. The case initially reported as ALH was thought to have marked distention of more than 50% of the lobule with monomorphic cells (i.e., LCIS).

In addition to variability distinguishing ALH from LCIS on core biopsy, or PLCIS from classic LCIS, there can be challenges distinguishing DCIS with cancerization of the lobules from LCIS. LCIS can show pagetoid spread in ducts mimicking DCIS. The cell adhesion molecule E-cadherin can be helpful in differentiating morphologically similar low-grade DCIS with a solid growth pattern from classic LCIS [71]. E-cadherin expression is retained in DCIS and lost in LCIS. P120-catenin is also a useful marker of LN [72, 73], with cytoplasmic staining in lobular lesions and membranous staining in ductal lesions. In earlier literature, such immunostains were not routinely used, and, thus, rates of upgrade may have been overestimated. For example, Liberman et al. [57] reported that LN lesions with ductal extension were more likely upgraded, and some of those could have been DCIS initially. At our institution, E-cadherin and P120-catenin are routinely used to distinguish ductal from lobular origin.

Recommended Management

At Magee-Womens Hospital of University of Pittsburgh Medical Center, our usual practice has been to recommend excision to patients with a diagnosis of LN at percutaneous breast biopsy. A nonoverlapping earlier series from our institution (Karabakhtsian et al. [39]) showed a 10.9% (10/92) upgrade rate of LN at core biopsy (5/63 [8%] for ALH; 1/10 [10%] for ALH and LCIS; and 4/19 [21%] for LCIS).

In the current report, the upgrade rate remained greater than the 2% threshold used

for probably benign assessments in BI-RADS [74] for all subsets, though for concordant ALH, the rate was only 2.4% (8/335; 95% CI, 1.2–4.6%). All upgraded invasive cancers were stage I with negative nodes. Indeed, eight of 10 invasive cancers were smaller than 5 mm (T1a tumors). Importantly, the observed 9.3% upgrade to malignancy rate for LCIS in this series remains substantially greater than the 2% target accepted for imaging surveillance. As such, regardless of concordance, we continue to recommend excision after a core biopsy result of LCIS.

In general, when surveillance is offered to the patient in lieu of biopsy or excision, delay in diagnosis of the few cancers present should not be harmful to the patient. Delay in diagnosis of small low-grade invasive cancers or DCIS is not likely to put the patient at risk for advanced breast cancer. Considering only ALH, after excluding discordant lesions, the upgrade rate in this series was 2.4% (8/335), with one tubular carcinoma, one multifocal ILC, and six grade 1 or grade 2 DCIS (all estrogen receptor positive, except one lesion that could not be evaluated because of the loss of DCIS in deeper sections). Invasive tubular carcinoma generally carries an excellent prognosis with a low frequency of lymph node metastasis and low rate of local recurrence [75]. Regarding the patient with multifocal ILC, she had ADH in the same quadrant (different biopsy site). Hence, she would have undergone excision for ADH, which itself showed ILC at excision; she tested positive for a *BRCA* variant and also had a strong family history of both breast and ovarian cancers. Surveillance may not be appropriate or acceptable to women at high risk for breast cancer according to family history, though for the subset of women presenting with suspicious calcifications, no statistical significance was observed in women with or without a family history. A 2–4% malignancy threshold may be reasonable when the alternative is surgical excision, especially when all cancers followed would be expected to remain node negative with good prognosis if and when later detected on imaging surveillance.

On the basis of results of this analysis, we have modified Magee-Womens Hospital of University of Pittsburgh Medical Center policy. First, we ensure that the most suspicious calcifications have been sampled. If calcifications have been well sampled with concordant benign results, and the most severe histopathologic finding is ALH, without other high-risk lesions or concurrent malignancy, we now perform imaging surveillance at 6, 12, and 24 months. We are currently validating this approach, which should reduce unnecessary surgery. In this series, this approach could have obviated excision of 238 of 447 (53.2%) lesions with LN found at core biopsy. Importantly, in the validation study of 68 LN lesions at Yale University School of Medicine (detailed in the online data supplement), all four cases upgraded at excision were LCIS at core biopsy. No malignancies would have gone undetected.

Because ALH is not expected to produce a mass or distortion on imaging, we still recommend excision of noncalcified lesions shown to represent ALH unless the ALH is clearly unrelated to the imaging finding, such as a mass due to fibroadenoma that was targeted, with incidental adjacent ALH. All women with LN at core biopsy are ultimately referred to our high-risk program to discuss risk reduction strategies, possibly including tamoxifen therapy [76].

There are limitations to our study. Because the study is retrospective, potential biases in patients not undergoing excision are unknown; however, we would expect the malignancy rate to be higher, if anything, among (presumably more suspicious) lesions going to excision on which we base this report. Additionally, the needle gauge and number of biopsy specimens are also nonuniform, as in usual practice. We did not investigate the effect of complete removal of all imaging evidence of the lesion on upgrade rates. Four of 22 (18.2%) malignancies were only recognized as discordant at detailed retrospective pathologic review. Our results suggest a need to be more critical when clinically assessing radiologic-pathologic concordance. Finally, distinct management of ALH versus LCIS relies on accurate distinction of these entities on core biopsy, and these lesions represent a continuum. As we found in the validation study, not all institutions distinguish ALH from LCIS when reporting core biopsy histopathology; having distinct management recommendations necessitates such distinctions. Because pathologic distinction between ALH and LCIS can be subtle, excision is prudent when there is uncertainty, given the higher upgrade rate of LCIS.

Conclusion

In conclusion, the upgrade rate to malignancy at excision was statistically significantly higher after a concordant core biopsy diagnosis of LCIS (8.4%; 9/107; 95% CI, 4.5–15.2) than of ALH (2.4%; 8/335; 95% CI, 1.2–4.6). Women between 40 and 59 years old have particularly low upgrade rates. LN lesions in women with a family history of breast or ovarian cancer were more likely to be upgraded, but the upgrade rate was not statistically significant in the subset of women with suspicious calcifications. Upgrade rates were not statistically significantly lower for calcifications than for masses or for any particular biopsy guidance type. Reduced breast density did not predict lower rates of upgrade. Malignancies found were all stage 0 or stage I disease. On the basis of our results, we recommend excision for LCIS found at core biopsy, with surveillance of ALH at 6, 12, and 24 months after biopsy of calcifications well sampled with concordant benign results, excluding patients with other high-risk lesions or concurrent malignancy. We continue to recommend excision after a finding of ALH at biopsy of noncalcified lesions because ALH is not expected to produce such a finding on imaging.

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