

Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In-situ in Patients with Lobular Neoplasia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 020)

Faina Nakhlis, MD^{1,8}, Lauren Gilmore, MD², Rebecca Gelman, PhD¹, Isabelle Bedrosian, MD⁴, Kandice Ludwig, MD⁵, E. Shelley Hwang, MD⁶, Shawna Willey, MD⁷, Clifford Hudis, MD³, J. Dirk Iglehart, MD^{1,8}, Elizabeth Lawler, BA¹, Nicole Y. Ryabin, BS¹, Mehra Golshan, MD^{1,8}, Stuart J. Schnitt, MD⁹, and Tari A. King, MD¹⁰

¹Dana-Farber/Harvard Cancer Center, Boston, MA; ²Mount Auburn Hospital, Cambridge, MA; ³Breast Medicine Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; ⁴University of Texas MD Anderson Cancer Center, Houston, TX; ⁵Indiana University Cancer Center, Indianapolis, IN; ⁶Duke University Medical Center, Durham, NC; ⁷Georgetown University Cancer Center, Washington, DC; ⁸Dana-Farber/Brigham and Women's Cancer Center, Boston, MA; ⁹Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; ¹⁰Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

ABSTRACT

Background. Lobular neoplasia (LN) represents a spectrum of atypical proliferative lesions, including atypical lobular hyperplasia and lobular carcinoma-in-situ. The need for excision for LN found on core biopsy (CB) is controversial. We conducted a prospective multi-institutional trial (TBCRC 20) to determine the rate of upgrade to cancer after excision for pure LN on CB.

Methods. Patients with a CB diagnosis of pure LN were prospectively identified and consented to excision. Cases with discordant imaging and those with additional lesions requiring excision were excluded. Upgrade rates to cancer were quantified on the basis of local and central pathology review. Confidence intervals and sample size were based on exact binomial calculations.

Results. A total of 77 of 79 registered patients underwent excision (median age 51 years, range 27–82 years). Two cases (3 %; 95 % confidence interval 0.3–9) were upgraded to cancer (one tubular carcinoma, one ductal carcinoma-in-situ) at excision per local pathology. Central pathology review of 76 cases confirmed pure LN in the CB in all but two cases. In one case, the tubular carcinoma identified at excision was also found in the CB specimen, and in the other, LN was not identified, yielding an upgrade rate of one case (1 %; 95 % CI 0.01–7) by central pathology review.

Conclusions. In this prospective study of 77 patients with pure LN on CB, the upgrade rate was 3 % by local pathology and 1 % by central pathology review, demonstrating that routine excision is not indicated for patients with pure LN on CB and concordant imaging findings.

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Dr. Stuart J. Schnitt and Dr. Tari A. King share senior authorship of this article.

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T. A. King, MD

e-mail: tking7@partners.org

Lobular neoplasia (LN) is a term used to encompass a spectrum of atypical proliferative lesions that includes atypical lobular hyperplasia (ALH) and lobular carcinoma-in-situ (LCIS). LCIS was initially considered to be a form of mammary carcinoma and as such was treated with mastectomy.¹ However, long-term results of clinical follow-up studies suggested that LCIS and ALH represented markers of generalized increased breast cancer risk, not true precursor lesions, and surgery fell out of favor.^{2–4} Patients with ALH have a relative risk of breast cancer that is 4- to 5-fold

higher than the general population, and patients with LCIS have a relative risk as high as 8- to 10-fold.

LN lacks a distinct radiographic correlate, and thus it is frequently diagnosed as an incidental finding in otherwise benign breast biopsy specimens, with a reported incidence ranging from 0.3 to 4 %.^{3,5-9} In the era of image-guided core biopsy (CB), a diagnosis of LN led to concern that the imaging abnormality in question was potentially under-sampled, and numerous studies have evaluated the upgrade rate to ductal carcinoma-in-situ (DCIS) or invasive breast cancer after surgical excision of LN.^{9,10} These rates vary widely, with some studies reporting no upgrades and others reporting upgrades in up to 50 % of patients.¹¹⁻¹³ Unfortunately, most early studies were retrospective and described small numbers of patients, not all of whom underwent excision.^{6,8,11-18} In some studies, LN in the CB was accompanied by another lesion, which by itself would warrant excision (such as atypical ductal hyperplasia), and in some reports, cases with pleomorphic LCIS or radiographic-pathologic discordance (e.g., ALH or LCIS on CB but a highly suspicious mass on imaging studies) were included.^{8,14,19} With the exception of a study by Irfan and Brem, many of the earlier studies also failed to report the Breast Imaging Reporting and Data System (BI-RADS) classification of the initial imaging lesion.^{6-8,11-21}

Given the limitations of the available literature, current National Comprehensive Cancer Network guidelines remain conservative and recommend excision after a CB diagnosis of LCIS.²² However, among providers, this issue remains a matter of debate. The purpose of this study was to determine the upgrade rate to DCIS or invasive cancer after a CB diagnosis of pure LN in a single-arm multicenter prospective study.

MATERIALS AND METHODS

The protocol received institutional review board approval at the Dana Farber/Harvard Cancer Center in November 2004 and was expanded in 2012 to include five additional sites in the Translational Breast Cancer Research Consortium (TBCRC) (Table 1). Eligibility criteria are listed in Fig. 1. In all cases, the breast imaging-detected lesion had a BI-RADS score of 4 or lower, and all pathologic diagnoses of LN were deemed concordant with imaging findings. Image-guided core biopsies were performed as per institutional standards; neither device type nor gauge were standardized for the study. Eligible patients signed informed consent, completed registration, and underwent surgical excision. Hematoxylin and eosin-stained sections (and in some cases immunostains for E-cadherin) were evaluated by the local pathologist to establish the diagnosis and subsequently underwent central pathology review by two breast pathologists (L.G., S.J.S.).

TABLE 1 Accrual by translational breast cancer research consortium site

Institution	Registered patients, <i>n</i> (%)	Canceled patients
Dana-Farber/Harvard Cancer Center	51 (65 %)	2
Memorial Sloan Kettering Cancer Center	20 (25 %)	0
Indiana University Cancer Center	3 (4 %)	0
University of Texas MD Anderson Cancer Center	3 (4 %)	0
Georgetown University Cancer Center	1 (1 %)	0
Duke University Cancer Center	1 (1 %)	0
Total	79 (100 %)	2

Statistical Considerations

The primary objective was to estimate the frequency with which LN found on core needle biopsy (by local pathology report) was upgraded to invasive breast cancer or DCIS on surgical excision. We aimed to accrue 78 patients based on the desire to use a decision rule with the power to differentiate between a true upgrade rate of 5 versus 15 %. The protocol-specified decision rule stated that if ≤ 7 of 78 patients were upgraded, we would conclude that the chance of upgrade on excision was too low to continue research on this subject (and that we would not recommend surgical excision for LN). Conversely if ≥ 8 patients were upgraded, we would continue to investigate which patients required surgical excision. With this design, if the true probability of upgrade was 5 %, there would be a 4 % chance that we would continue research on this issue, and if the true probability of an upgrade was 15 %, there would be a 91 % chance that we would continue to do research on this issue. This decision rule and the calculation of 95 % confidence intervals were based on the exact binomial distribution.

RESULTS

In total, 79 patients were registered on the study. At the time the 78th patient was registered, it was known that one of the previously registered patients was unable to undergo surgical excision due to concomitant illness; the accrual of the 79th patient was thus permitted. An additional patient cancelled surgery and rescheduled to a date long after her CB, prompting her treating physician to remove her from the study. Thus, 77 of 79 patients who underwent surgical excision per protocol guidelines were included in this analysis. Patient characteristics of the 77 eligible participants are listed in Table 2. Median patient age was 51 years (range 27–82 years), and median time between CB and surgical excision was 2 months (range 0.5–15 months).

FIG. 1 Eligibility criteria. *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma-in-situ

- Females, age \geq 20 years
- Must have an imaging abnormality necessitating a core needle biopsy
- Core biopsy must reveal ALH and/or LCIS
- Subject may have a personal history of fibroadenoma and/or proliferative lesions with or without atypia
- No personal history and/or concomitant diagnosis of invasive breast cancer or DCIS
- No palpable abnormality diagnosed by core needle biopsy to be ALH or LCIS
- No previous tamoxifen or raloxifene use*
- No pleomorphic LCIS on core biopsy

*The study commenced when tamoxifen was the only FDA-approved chemopreventive agent. The eligibility criteria were amended to include prior raloxifene use as an exclusion criterion after this medication was FDA-approved for chemoprevention in 2007. The FDA approval of exemestane and anastrozole for chemoprevention occurred close to or after accrual completion of the current study.

TABLE 2 Characteristics of study cohort ($n = 77$)

Characteristic	Category	n (%)
Race	Unknown	7 (9)
	White	64 (83)
	Black	5 (6)
	Asian	1 (1)
Ethnicity	Unknown	10 (13)
	Hispanic	3 (4)
	Not Hispanic	64 (83)
Age (year)	27–40	5 (6)
	41–50	32 (42)
	51–60	25 (32)
	61–82	15 (19)
Age at menarche	Unknown	4 (5)
	10–11	15 (19)
	12–13	39 (51)
	14–15	15 (19)
	16–17	4 (4)
Family history of breast cancer	First degree	25 (32)
	Any	44 (57)
Postmenopausal (\geq 1 year since menses)	Unknown	1 (1)
	No	41 (53)
	Yes	35 (45)
Prior HRT	Unknown	1 (1)
	No	61 (79)
	Yes	15 (19)
Imaging abnormality	MRI enhancement	3 (4)
	Calcifications	57 (74)
	Mammographic density	13 (17)
	Calcifications and mammographic density	3 (4)
	Architectural distortion	1 (1)
BI-RADS	1	1 (1)
	3	5 (7)
	4	71 (92)

HRT hormone replacement therapy, *MRI* magnetic resonance imaging, *BI-RADS* breast imaging reporting and data system

Per local pathology interpretation, the CB diagnosis was ALH in 49 patients (64 %), LCIS in 17 (22 %), and both ALH and LCIS in 11 (14 %) (Table 3).

Primary End Point

On the basis of local pathology review, the diagnosis of 2 of 77 patients was upgraded after surgical excision: one patient was found to have a grade I invasive tubular carcinoma (patient 6), and another patient was found to have intermediate nuclear grade DCIS (patient 59). Therefore, the upgrade rate based on the local pathology diagnosis was 2 (3 %) of 77 (95 % CI 0.3–9). The case upgraded to tubular carcinoma (patient 6) represented an magnetic resonance imaging–guided CB diagnosis of LCIS. The biopsy was performed for an area of abnormal enhancement in a 49-year-old patient undergoing magnetic resonance imaging screening because of a strong family history of breast cancer. In the case upgraded to DCIS, the original mammographic abnormality represented an area of calcifications spanning 8 mm in a 49-year-old woman with distant family history of postmenopausal breast cancer. The CB revealed LCIS, and the subsequent excision demonstrated solid, cribriform, and micropapillary DCIS of intermediate nuclear grade. Of the 18 excision slides, DCIS was present in 3 slides, one of which had CB site changes.

Central Pathology Review

CB slides were available for central pathology review in 76 of 77 cases, and LN was confirmed in 74 cases (96 %). In one case (patient 16), the local pathology report diagnosed LCIS in the CB; however, no LCIS (or ALH) was identified on central pathology review, and patient 6 (whose disease was upgraded to tubular carcinoma at excision per local pathology) was found to harbor a focus of tubular carcinoma in the CB specimen that was similar to that identified in the surgical excision. In a post hoc analysis, based on the 74 cases for which LN and absence

TABLE 3 Summary of local pathology and central pathology interpretation of initial CB results

Biopsy result	Local pathology review, <i>n</i> (%)	Central pathology review, <i>n</i> (%)
ALH	49 (64)	60 (79)
LCIS	17 (22)	1 (1)
ALH and LCIS	11 (14)	14 (18)
Any LCIS (alone or with ALH)	28 (36)	15 (20)
Neither	0	1 (1)
Total	77 ^a	76 ^b

ALH atypical lobular hyperplasia, LCIS lobular carcinoma-in-situ, CB core biopsy

^a Total number of registered patients who underwent surgery

^b Total number of registered patients who underwent surgery and whose CB was available for central pathology review

of cancer in the CB could be confirmed by central pathology review, there was only 1 upgraded case (1 %, 95 % CI 0.01–7).

DISCUSSION

Although many studies have looked at upgrade rates to carcinoma after excision of LN, various methodologic issues, including their retrospective design with inherent selection bias, failure to describe the BI-RADS classification and/or radiographic-pathologic concordance, and inclusion of pleomorphic LCIS, have made it difficult to interpret the findings. Table 4 summarizes the findings of the more contemporary, larger (comprising more than 20 cases) series on this subject and demonstrates that upgrade rates remain highly variable, ranging from 0 to 27 %.^{7, 14, 19–21, 23–31} In our prospective study with strict eligibility criteria and central pathology review, we found an upgrade rate for concordant, BI-RADS 4 or lower, pure LN lesions to be 3 % based on the local pathology diagnosis and 1 % based on central pathology review. These findings are in agreement with more recent studies reporting the presence of concordance for the LN lesions in question, and they demonstrate that routine excision for a concordant CB diagnosis of pure LN is not warranted.

Lewis et al. reviewed 201 cases of LN and reported an upgrade rate of 13 %; however, BI-RADS and/or pathologic-radiographic concordance information for these cases was not available.²⁶ Niell et al. reported an upgrade rate of 11 % in 63 concordant LN lesions.²⁸ Shah-Khan et al., however, reported an upgrade rate of 2 % among 101 LN lesions, 90 % of which were concordant with imaging findings.³⁰ Rendi et al. reported three upgrades (4 %) among 68 BI-RADS 4 lesions, without specific concordance information provided.²⁹ Forty of these patients were designated as high risk on the basis of their family history, and all three upgrades were in high-risk patients. Although pathologic-radiographic concordance is likely more

important than pure BI-RADS classification, studies reporting both have consistently reported the lowest upgrade rates. Atkins et al. reported no upgrades among 38 concordant lesions.²³ Chaudhary et al. reported an upgrade rate of 3 % among 87 concordant lesions.²⁵ Finally, similar to our study, Murray et al. conducted a prospective study of 80 excisions after a CB diagnosis of pure LN and reported two upgrades (3 %) among 72 concordant cases.³² In contrast, in the discordant group, the upgrade rate was 3 (38 %) of 8. Among the three upgraded discordant cases, two were thought to have had insufficient sampling of the target lesion by CB, both of which were upgraded to DCIS, and one represented a spiculated mass, classified as BI-RADS 5, which was upgraded to invasive carcinoma.

As demonstrated here and in other studies of LN, there is a degree of interobserver variability for a diagnosis of ALH versus LCIS, and the distinction is to some degree subjective and dependent on the amount of submitted material. In a series of breast specimens sent for formal consultation at the Universidade Federal de Minas Gerais School of Medicine in Brazil, Gomes et al. reported agreement for a diagnosis of ALH in 8 (47 %) of 17 cases and an agreement for a diagnosis of LCIS in 31 (69 %) of 45 cases.³³ In our series of CB specimens, among 49 cases diagnosed as ALH by the local pathologist, there was agreement by central pathology review in 46 cases (94 %), and among 28 cases diagnosed as LCIS, with or without ALH, there was agreement in 14 cases (50 %). Although clinical follow-up studies demonstrate a greater magnitude of subsequent breast cancer risk associated with LCIS than with ALH, clinical management algorithms remain the same; therefore, the clinical significance of the distinction between these two lesions on CB may be less relevant. Patients with ALH and LCIS should be counseled regarding their cumulative increased risk of subsequent breast cancer, which is conferred equally to both breasts and significantly reduced with the use of chemoprevention.³⁴

TABLE 4 Summary of existing literature on upgrade rates found on excision of lobular neoplasia diagnosed on core biopsy

Study	Study design	No. of excisions	BI-RADS	Radiographic-pathologic concordance, %	Upgrade, n (%)	Comments
Bonnett (2003) ²⁰	Retrospective	24	Not reported	Not reported	2 (8)	
Arpino (2004) ¹⁴	Retrospective	21	4	Not reported	3 (14)	
Foster (2004) ⁷	Retrospective	26	Not reported	Not reported	6 (23)	
El-Sheikh (2005) ²¹	Prospective and retrospective	33	3, 4	Not reported	9 (27)	Upgraded 5 (27 %) of 18 prospective and 4 (27 %) of 15 retrospective cases
Cangiarella (2008) ²⁴	Retrospective	38	Not reported	11 (29 %)	3 (8)	Unknown how many upgraded cases were discordant
Hwang (2008) ¹⁹	Retrospective	87	4	Mentioned, not quantified	4 (5)	
Nagi (2008) ²⁷	Retrospective	45	Not reported	Not reported	2 (4)	
Lewis (2012) ²⁶	Retrospective	201	Not reported	Not reported	26 (13)	4 % of all cases had palpable masses, unclear if any of them were upgraded
Niell (2012) ²⁸	Retrospective	63	Not reported	100 %	7 (11)	
Rendi (2012) ²⁹	Retrospective	68	4	Mentioned, not quantified	3 (4)	All upgrades were among 40 "high-risk" patients based on family history
Shah-Khan (2012) ³⁰	Retrospective	101	Not reported	90 %	2 (2)	
Zhao (2012) ³¹	Retrospective	237	Not reported	Not reported	11 (5)	
Atkins (2013) ²³	Retrospective	38	3, 4, 5	100 %	0 (0)	
Chaudhary (2013) ²⁵	Retrospective	87	4,5,6	100 %	3 (3)	
Murray (2013) ³²	Prospective	80	4, 5	90 %	5 (6)	Upgraded 2 (3 %) of 72 concordant and 3 (38 %) of eight discordant cases
Current study	Prospective	76	4 or lower	100 %	2 (3)	1 % upgrade rate by central pathology review

BI-RADS Breast Imaging Reporting and Data System

Our study, with its unique prospective design, predetermined statistical end points, strict eligibility criteria, and central pathology review, represents the most comprehensive evaluation of this subject to date. Although the confidence intervals for the upgrade rates in our study range from 0 to 9 %, the predetermined statistical end points were clear, and our goal was to differentiate between a true upgrade rate of 5 versus 15 %. Considering that a BI-RADS 3 designation implies a less than 2 % risk of upgrade to a cancer diagnosis, our findings suggest that a concordant CB diagnosis of LN is amenable to follow-up imaging at 6 months rather than excision, as the upgrade rates are similar.³⁵ Prospective data to document the yield of 6-month follow-up imaging in patients with concordant diagnosis of pure LN on CB are not available, yet it is our opinion that this practice should be considered in the management algorithms for patients with pure LN who do not undergo excision to allow multidisciplinary groups to collect this information and report their outcomes.

In conclusion, in this prospective multi-institutional study of patients with BI-RADS 4 or lower concordant lesions with LN on CB, we found a very low upgrade rate to invasive cancer or DCIS on excision. These results indicate that routine excision after a diagnosis of LN on CB is not indicated. Patients with a concordant CB diagnosis of pure LN should be counseled regarding their increased lifetime risk of breast cancer and offered participation in high-risk surveillance programs, including a full discussion of lifestyle interventions (diet, exercise) as well as the risks and benefits of chemoprevention.

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