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The 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 Nakhliis, 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, MD^{9,*}, and Tari A. King, MD^{10,*}

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 (ALH) and lobular carcinoma in situ (LCIS). 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 following excision for pure LN on CB.

Methods—Patients with a CB diagnosis of pure LN were prospectively identified and consented for excision. Cases with discordant imaging and those with additional lesions requiring excision

Address correspondence and reprint requests to: Tari A. King, MD, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 300 East 66th Street, New York, NY 10065, (T) 646 888 5352, (F) 646 888 4921, tking7@partners.org.
*Dr. Stuart J. Schnitt and Dr. Tari A. King share senior authorship of this article

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were excluded. Upgrade rates to cancer were quantified based on local and central pathology review. Confidence intervals (CI) and sample size were based on exact binomial calculations.

Results—77 of 79 registered patients underwent excision (median age 51 years, range 27–82). 2 (3%, 95%CI 0.3%–9%) cases were upgraded to cancer (1 tubular carcinoma, 1 DCIS) 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 second case, LN was not identified, yielding an upgrade rate of 1 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 core biopsy and concordant imaging findings.

Synopsis

We conducted TBCRC 20 to determine the rate of upgrade to cancer following excision for a core biopsy diagnosis of pure lobular neoplasia. We find that routine excision is not indicated for patients with pure lobular neoplasia on core biopsy.

Keywords

lobular neoplasia; atypical lobular hyperplasia; lobular carcinoma in situ

INTRODUCTION

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 mastectomy¹; 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 4–5-fold higher than the general population, and patients with LCIS have a relative risk as high as 8–10-fold.

LN lacks a distinct radiographic correlate⁵ and, as such, it is frequently diagnosed as an incidental finding in otherwise benign breast biopsies, with a reported incidence ranging from 0.3 % to 4%.^{3,6–9} In the era of image-guided core biopsy, a diagnosis of LN led to concern that the imaging abnormality in question was potentially under-sampled^{9,10}, and numerous studies have evaluated the upgrade rate to ductal carcinoma in situ (DCIS) or invasive breast cancer following surgical excision of LN. These rates vary widely, with some studies reporting no upgrades¹¹ and others reporting upgrades in up to 50% of patients.^{12,13} 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 core biopsy was accompanied by another lesion which by itself would warrant excision (such as atypical ductal hyperplasia^{8,14}), and in some reports, cases with pleomorphic LCIS (P-LCIS)¹⁹ or radiographic-pathologic discordance (e.g., ALH or LCIS on core biopsy but a highly

suspicious mass on imaging studies) were included. With the exception of a study by Irfan et al¹⁶, many of the earlier studies also failed to report the Breast Imaging-Reporting and Data System (BI-RADS) classification of the initial imaging lesion.^{6–8,11–15,17–21}

Given the limitations of the available literature, current National Comprehensive Cancer Network (NCCN) guidelines remain conservative and recommend excision following a core biopsy diagnosis of LCIS²², yet amongst providers, this issue remains a matter of debate. The purpose of this study was to determine the upgrade rate to DCIS or invasive cancer following a core biopsy diagnosis of pure LN in a single-arm multicenter prospective study.

MATERIALS AND METHODS

The protocol received IRB approval at the Dana Farber/Harvard Cancer Center in November 2004 and was expanded in 2012 to included 5 additional sites in the Translational Breast Cancer Research Consortium (TBCRC) (Table 1). Eligibility criteria are listed in Figure 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 2 breast pathologists (LG, SJS).

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% vs. 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 (CIs) 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, thus the accrual of the 79th patient was permitted. An additional patient cancelled surgery and rescheduled to a date long after her core biopsy, 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 described in Table 2. Median patient age was 51 years (range 27–82 years), and median time between core biopsy and surgical excision was 2 months (0.5–15 months). Per local pathology interpretation, the core biopsy diagnosis was ALH in 49 (64%) patients, LCIS in 17 (22%), and both ALH and LCIS in 11 (14%) patients (Table 3).

Primary Endpoint

On the basis of local pathology review, 2 of 77 patients were upgraded following surgical excision: one patient was found to have a grade I invasive tubular carcinoma (Case No. 6) and another patient was found to have intermediate nuclear grade DCIS (Case No. 59). Therefore, the upgrade rate based on the local pathology diagnosis was 2 of 77, or 3% (95% CI 0.3%–9%). The case upgraded to tubular carcinoma (Case No. 6) represented an MRI-guided core biopsy diagnosis of LCIS. The biopsy was performed for an area of abnormal enhancement in a 49-year-old patient undergoing MRI screening due to 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 core biopsy 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 core biopsy site changes.

Central Pathology Review

Core biopsy slides were available for central pathology review in 76 of 77 cases, and LN was confirmed in 74 (96%) cases. In one case (Case No. 16), the local pathology report diagnosed LCIS in the core biopsy; however, no LCIS (or ALH) was identified on central pathology review, and Case No. 6 (upgraded to tubular carcinoma at excision per local pathology) was found to harbor a focus of tubular carcinoma in the core biopsy 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 of cancer in the core biopsy 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 following excision of LN, various methodological 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^{7,14,19–21,23–31} 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%. 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

demonstrate that routine excision for a concordant core biopsy diagnosis of pure LN is not warranted.

Lewis et al²⁶ 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. Niell et al²⁸ reported an upgrade rate of 11% in 63 concordant LN lesions, while Shah-Khan et al³⁰ reported an upgrade rate of 2% among 101 LN lesions, 90% of which were concordant with imaging findings. Rendi et al²⁹ reported 3 (4%) upgrades among 68 BI-RADS 4 lesions, without specific concordance information provided. Forty of these patients were designated as “high risk” on the basis of their family history, and all 3 upgrades were in “high-risk” patients. While pathologic-radiographic concordance is likely more important than pure BIRADS classification, studies reporting both have consistently reported the lowest upgrade rates. Atkins et al²³ reported no upgrades among 38 concordant lesions, Chaudhary et al²⁵ reported an upgrade rate of 3% among 87 concordant lesions, and, similar to our study, Murray et al³² conducted a prospective study of 80 excisions following a core biopsy diagnosis of pure LN and reported 2 upgrades (3%) among 72 concordant cases. In contrast, in the discordant group, the upgrade rate was 3/8 (38%). Among the 3 upgraded discordant cases, two were felt to have had insufficient sampling of the target lesion by core biopsy, both of which were upgraded to DCIS, and one represented a spiculated mass, classified as BIRADS 5, which was upgraded to invasive carcinoma.

As demonstrated here and in other studies of LN, there is a degree of inter-observer variability for a diagnosis of ALH vs. 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 of 17 (47%) cases and an agreement for a diagnosis of LCIS in 31 of 45 (69%) cases.³³ In our series of core biopsy specimens, among 49 cases diagnosed as ALH by the local pathologist, there was agreement by central pathology review in 46 (94%) cases, and among 28 cases diagnosed as LCIS, with or without ALH, there was agreement in 14 (50%) cases. 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 2 lesions on core biopsy 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

Our study, with its unique prospective design, predetermined statistical endpoints, strict eligibility criteria, and central pathology review, represents the most comprehensive evaluation of this subject to date. Although the CIs for the upgrade rates in our study range from 0–9%, the predetermined statistical endpoints 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 diagnosis³⁵, our findings suggest that a concordant core biopsy diagnosis of LN is amenable to follow-up imaging at 6 months rather than excision, as the upgrade rates are similar. Prospective data to document the yield of 6-month follow-up imaging in patients with concordant diagnosis of pure LN on

core biopsy 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 BIRADS 4 or lower concordant lesions with LN on core biopsy, we found a very low upgrade rate to invasive cancer or DCIS on excision. These results indicate that routine excision following a diagnosis of LN on core biopsy is not indicated. Patients with a concordant core biopsy 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), and the risks and benefits of chemoprevention.

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- Females, age ≥ 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
- Signed, dated informed consent
- The patient has been given a copy of the signed informed consent
- The patient has been registered in QACT# before beginning of treatment
- All information is documented in the medical record

*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.

#QACT – DF/HCC's Quality Assurance Office for Clinical Trials.

Fig. 1.

Eligibility criteria

ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ

Table 1

Accrual by Translational Breast Cancer Research Consortium (TBCRC) site

Institution	Registered patients (%)	Cancelled 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

Table 2

Characteristics of the study cohort (n=77)

Characteristic	Category	Number of Patients (%)
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	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	1 st degree	25 (32%)
	Any	44 (57%)
Postmenopausal (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; BI-RADS, Breast Imaging-Reporting and Data System

Table 3

Summary of local pathology and central pathology interpretation of the initial core biopsy results

	Local Pathology Review (%)	Central Pathology Review
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 *	76 **

ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ

* Total number of registered patients who underwent surgery

** Total number of registered patients who underwent surgery and whose core biopsy was available for central pathology review

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

Table 4

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