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NON-INVASIVE BREAST CANCER DIAGNOSIS AND TREATMENT (ES HWANG, SECTION EDITOR)

Lobular Neoplasia

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Abstract

Purpose of Review Today, the term lobular neoplasia (LN) incorporates atypical lobular hyperplasia (ALH), classical lobular carcinoma in situ (C-LCIS) and nonclassical lobular carcinoma in situ (NC-LCIS). These neoplastic lesions are thought of as risk indicators and non-obligate precursors of invasive breast cancer. This review highlights the current literature and up-to-date treatment recommendations for ALH, C-LCIS, and NC-LCIS.

Recent Findings Currently, NC-LCIS requires surgical excision to rule out a concurrent carcinoma; but a core biopsy diagnosis of ALH or C-LCIS can be safely managed with close clinical and imaging observation, elevated future breast cancer risk counseling and consideration for chemoprevention. Controversy regarding categorizing NC-LCIS remains with respect to its histologic features and terminology.

Summary The treatment and surveillance recommendations for LN continue to evolve. Overall, the treatment of LN requires a multidisciplinary approach to ensure appropriate screening and comprehensive counseling about the elevated lifetime breast cancer risk and about standard and investigational breast cancer risk-reducing options in this patient population.

Keywords Lobular neoplasia · Lobular carcinoma in situ · Atypical lobular neoplasia · Nonclassical lobular carcinoma in situ · Pleomorphic LCIS

Introduction

The term lobular neoplasia (LN) encompasses atypical lobular hyperplasia (ALH), classical lobular carcinoma in situ (C-LCIS), and nonclassical lobular carcinoma in situ (NC-LCIS). LN was first described in 1919 by James Ewing when he described a lesion comprised of an "atypical proliferation of acinar cells" [1]. In 1941, Foote and Stewart further described this lesion and coined the term "lobular carcinoma in situ"(LCIS) [2] as a rare neoplasia arising from the lobular units of the breast. They described the lesion as grossly normal but microscopically showing enlarged cells with large nuclei, opaque cytoplasm, disorganized epithelial arrangement and rare mitosis. They hypothesized that this "explosive liberation of cell growth" would lead to mammary cancer and recommended treatment with mastectomy. Foote and Stewart also described a more general pattern of lobular epithelial hypertrophy, which would later be termed ALH.

In 1978, Haagensen et al examined the natural history of LCIS and found that, over a median follow-up period of 14 years, only 17% of women with LCIS who did not undergo mastectomy went on to develop carcinoma [3]. Collectively, these data and others demonstrating the long-term breast cancer risk conferred equally to both breasts and the fact that 50% of the cancers were of the ductal phenotype contributed to a change in the treatment paradigm whereby the recommendation for mastectomy was replaced with a conversation regarding risk reduction and surveillance.

The concept of NC-LCIS, previously termed "pleomorphic LCIS," is a lobulocentric proliferation of cells which are

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significantly pleomorphic and large compared to C-LCIS. The term NC-LCIS was introduced into the literature in the 1990 [4–7], and in 2012, the World Health Organization acknowledged the prognostic importance of distinguishing ALH, C-LCIS, and NC-LCIS within the spectrum of LN.

LN is both a risk indicator and non-obligate precursor of invasive breast cancer [7, 8]. Abdel-Fateh et al found that 91% of invasive lobular carcinoma (ILC) cases have associated LN [8]. Similarly to most ILC, LN is commonly estrogen receptor (ER) positive, progesterone receptor (PR) positive, and HER2 negative [9]. The hallmark feature of LN is the loss E-cadherin staining, although aberrant E-cadherin staining patterns are seen in up to 15% of cases [10].

As our knowledge progresses, several central questions remain: which lobular neoplasia lesions require excision, how do we manage disease at the surgical margins and what are the long-term clinical implications of these lesions?

Genetics

A loss of function mutation in CDH1, the gene encoding E-cadherin, is attributed to the loss of E-cadherin immunohistochemistry staining in the majority of these lesions [11, 12]. Loss of CDH1 expression leads to loss of cell-cell adhesion that characterizes the cellular growth pattern observed in lobular proliferative lesions. In addition to CDH1, the most frequently mutated genes seen in LCIS are PIK3CA and CBFB [13]. Similar genetic mutations have been observed in both LCIS and ILC [13]. A previous microarray analysis identified a total of 169 candidate genes involved in the progression of normal epithelium to LCIS and eventually to ILC [13]. Many of these candidate genes are involved in cell motility as well as in tumor growth and proliferation. ALH, C-LCIS, and NC-LCIS show similar genetic alterations, but NC-LCIS has an increased frequency of genetic alterations [14, 15]. The greater frequency of concurrent invasive carcinoma seen with NC-LCIS is potentially attributable to the increased genetic complexity of the latter lesions [14, 15]. Of the known high to moderate penetrance breast cancer predisposition genes, CHEK2 is the only gene that shows an association with LN [16•].

Imaging and Diagnosis

LN lesions have been reported in 0.3–4% of breast core biopsies [3, 7]. Because LN does not form a palpable mass, nor does it have any characteristic imaging features, it is thought to be an incidental finding whose true incidence is not well known. The incidence of LN has increased over the last few decades, and this is possibly related to the more wide-spread use of screening mammography potentially leading to more image-guided biopsies [17].

LN is most commonly found on an image-guided core needle biopsy of mammographic calcifications (50–75% of all LN diagnoses) [18] but the sensitivity and specificity of microcalcifications for LN, being an incidental lesion, is low [18, 19, 20•, 21•].Histologically, calcifications are often found in foci adjacent to LN but not associated with it [18, 21•].

Non-mass-like enhancement on magnetic resonance imaging (MRI), another common imaging presentation of LN, and mammographic calcifications are often considered concordant imaging findings of LN diagnosed on breast core-needle biopsy [21•]. At the same time, radiographic–pathologic concordance for LN has different implications for ALH and C-LCIS from those for P-LCIS, the latter requiring a follow-up excisional biopsy, as described below.

Atypical Lobular Hyperplasia (ALH)

ALH (Fig. 1a) is described as small monomorphic cells that fill < 50% of acinar units or fill no more than 1 complete lobule without lobular distension [22]. ALH is ER positive, PR positive, HER2 negative, and E-cadherin negative. Foci are usually found incidentally on biopsy or excision of a breast imaging abnormality, with only 9% of ALH found directly at the site of radiographic lesion [23].

The upgrade rate of isolated ALH found on core biopsy, deemed concordant, has been reported to be as low at 3.4% [24•, 32]. However, ALH is associated with an increased risk of developing future invasive carcinoma. The relative risk of subsequent carcinoma development, compared to age-matched controls, is 3.2–6.5 [7,25,26]. In other words, patients with ALH have a 1% annual risk of developing invasive carcinoma, and the risk appears to be higher in women under 45 years of age [25, 26]. Furthermore, a cohort study from the Mayo Clinic looking at the natural history of ALH showed that the breast cancer risk remains elevated over 20 years, and the cumulative incidence approaches 35% at 30 years [26]. The study also found that multi-focality but not family history increases the risk of carcinoma development. Muller et al. found that 13% of patients diagnosed with isolated ALH developed breast cancer within an average follow-up time of 58 months, and over 80% of these breast cancer events occurred in the contralateral breast [24•].

The current National Comprehensive Cancer Network (NCCN) guidelines recommend that ALH with concordant imaging be surgically excised or followed closely with physical exams and imaging [27••]. The guidelines recommend only surgical excision for patients with ALH and discordant imaging. Muller et al. suggested that surgical excision might not be warranted for pure ALH diagnosed on core biopsy given the low risk of developing invasive carcinoma [24•]. In contrast, Speer et al., in the same year, determined that ALH combined with LCIS on MRI-guided vacuum-assisted biopsy had an upgrade of 6% and recommended surgical

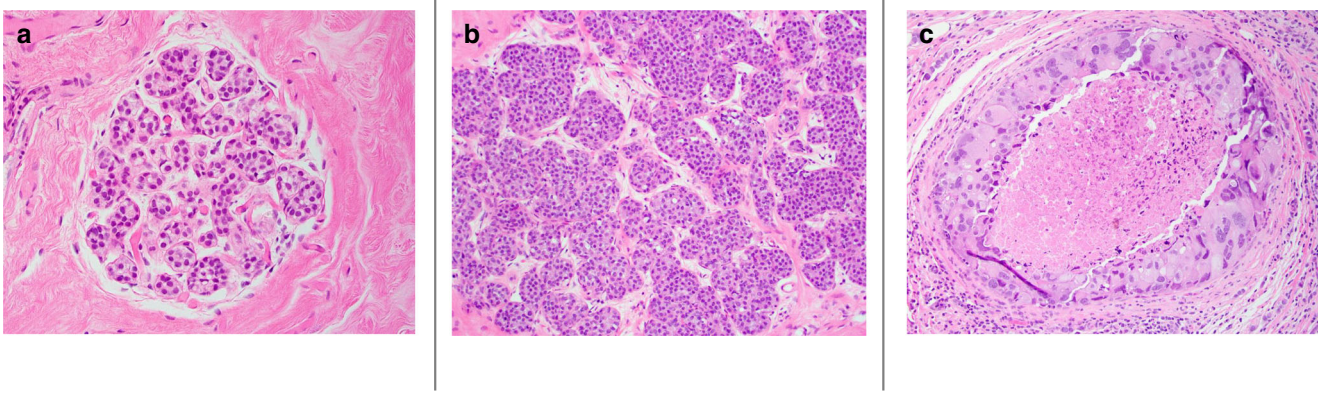

Fig. 1 (**A**) ALH involving a lobule without acinar distention. (**B**) C-LCIS composed of low-grade monomorphic cells filling and distending the acini of the lobule. (**C**) Pleomorphic LCIS with striking nuclear pleomorphism and comedonecrosis. Reprinted by permission from Spinger Nature: [Springer] [Current Surgery Reports] [Non-classic LCIS Versus Classic LCIS Versus Atypical Hyperplasia: Should Management be the Same?, Faina Nakhlis, Beth T. Harrison, Tari A. King, [2018]

excision [28•]. At academic institutions across the USA surveyed in 2017, ALH is recommended for excision only 61% of the time, highlighting the treatment discrepancies for this risk indictor lesion [29•].

In practice, margins involved with ALH do not need to be re-excised, and ALH does not require adjuvant chemotherapy or radiation. The role of chemoprevention for ALH will be discussed later in the review. The upgrade risk, relative risk of developing carcinoma, and treatment recommendations for lobular neoplasia are summarized in Table 1.

Classical Lobular Carcinoma in Situ (C-LCIS)

Similarly to ALH, C-LCIS (Fig. 1b) consists of small monomorphic discohesive cells with small nucleoli; however, in contrast with ALH, C-LCIS cells fill greater than 50% of the acinar units, sufficiently enough to cause lobular distension [22]. C-LCIS shares a number of other similarities to ALH, such as typically being ER positive, PR positive, HER2 negative, and E-cadherin negative, as well as being found incidentally on core biopsy or excisional biopsy of a breast imaging abnormality. Multi-centric C-LCIS is present in up to 85% of patients, and bilateral C-LCIS is seen in up to 50% of patients with this diagnosis [30–32].

Patients with C-LCIS found on core biopsy who have concordant imaging have an upgrade rate of 3% or less [33•, 34–36]. The risk of subsequent carcinoma is higher for C-LCIS compared with ALH, with a relative risk of developing a future breast cancer being increased eight to tenfold compared to the general population [7, 37•]. This translates into a ~2% annual incidence of breast cancer associated with C-LCIS [37•], with a cumulative incidence of breast cancer having been reported to be 11.3% and 19.8% at 10 and 20 years, respectively [38]. Fifty-five percent of these subsequent breast cancers are diagnosed in the ipsilateral breast.

Historically, the treatment for C-LCIS found on core biopsy was excision. Recently, published low upgrade rates to carcinoma found at excision of C-LCIS diagnosed on core biopsy have made close observation a reasonable alternative for patients with a C-LCIS diagnosis and concordant imaging [29•, 33•, 34, 35]. Additionally, close observation compared to surgical excision of C-LCIS does not appear to adversely affect long-term survival [37•]. It is important to note, however, that patients with C-LCIS on core biopsy and discordant imaging should continue to undergo excision as the upgrade rate

Table 1 Natural history and management of ALH, C-LCIS and NC-LCIS

	RR*	Upgrade rate on excision	Treatment Recommendations	Adjuvant therapy	Chemo-prevention
ALH	3.2–6.5	Up to 3%	Close imaging and clinical follow-up without excision if concordant; excision if discordant	None	Yes
C-LCIS	8–10	Up to 3%	Close imaging and clinical follow-up without excision if concordant; excision if discordant	None	Yes
NC-LCIS	Unknown	25–80%	Excision to clear margins	Consideration for radiation therapy	Yes

*Relative risk of developing subsequent ipsilateral or contralateral carcinoma

ALH – atypical lobular hyperplasia, C-LCIS – classic LCIS, NC-LCIS – non-classic LCIS

to malignancy in this patient population ranges from 5% to 38% [36, 39•]. The presence of C-LCIS at margin does not increase the local recurrence risk in patients undergoing breast conservation [40]. The most recent Society of Surgical Oncology-American Society for Radiation Oncology (SSO-ASTRO) margin guidelines do not recommend re-excision if C-LCIS is found at a surgical margin [41]. C-LCIS does not require adjuvant chemotherapy or radiation, but patients should be offered chemoprevention as discussed below.

Nonclassical Lobular Carcinoma In Situ (NC-LCIS)

NC-LCIS consists of large pleomorphic cells with significant dyshesion, pleomorphism, and prominent nucleoli (Fig. 1c). The lesions can also present with mitosis, apoptosis, necrosis, calcifications, and apocrine features [22]. Khoury et al found that 28% of NC-LCIS cases were ER negative, 36% of cases were PR negative, and 20% were both ER and PR negative [42]. They also found that 42% of case were HER2 positive. Chen et al found that only 13% of NC-LCIS cases were HER2 positive [15]. Overall, ER and PR positivity is lower in NC-LCIS compared to C-LCIS [6, 15, 42].

NC-LCIS is a relatively new histologic entity as it was not described until the 1990s [4–6]. This was largely due to the availability of immunostains for E-cadherin allowing the ability to distinguish NC-LCIS from ductal carcinoma in situ (DCIS). It is likely that studies published before 2000 studied almost exclusively C-LCIS. Complicating the study of the natural history of NC-LCIS is the fact that these lesions have been referred to by multiple terms in the literature. These terms have included LCIS with comedo necrosis, pleomorphic LCIS, carcinoma in situ with mixed ductal and lobular features, clear cell variant, signet ring cell variant, and variant LCIS.

When NC-LCIS diagnosed on core biopsy is followed by surgical excision, upgrade rates range from 25% to 80%, which is much higher than the upgrade rates reported for ALH or C-LCIS, therefore surgical excision of NC-LCIS is recommended [43•, 44, 45•, 46•, 47•]. For those patients whose diagnosis is upgraded, the long-term outcomes are not well documented, although the majority of the concurrent cancers appear to be early-stage disease [41]. Hoffman et al. recently showed that patients with pure NC-LCIS excised had no evidence of invasive disease at 4.5 years of mean follow-up [48•]. Metachronous NC-LCIS is not uncommon; Khoury et al found that 6 of 31 patients diagnosed with pure NC-LCIS were diagnosed with metachronous ipsilateral disease at a median follow-up of 55.6 months [42].

There are very limited data on the risk of local recurrence when NC-LCIS is found at the margin in cases of pure NC-LCIS [49] and no data in cases of DCIS/invasive cancer with NC-LCIS at the margin. Therefore, unlike C-LCIS in which margin reexcision is not recommended, there is no consensus on the management of NC-LCIS when it is found at the margins. Given the paucity of data, reasonable attempts should be made to achieve clear margins and multidisciplinary management, incorporating a patient's overall risk and personal preferences for breast conservation should be considered [49]. The 2009 French Breast Carcinoma in Situ guidelines (https://www.e-cancer.fr) suggest that whole breast radiation should be discussed in patients with "aggressive" LCIS, such as NC-LCIS, "very extensive" LCIS (with over ten involved acini) or LCIS with necroses. In practice, most patients undergo an excision alone.

Chemoprevention

The use of pharmacologic interventions to reduce the risk of breast cancer has been studied for over two decades. The US Food and Drug Administration approved the first agent, tamoxifen, for breast cancer chemoprevention in 1999.

The National Surgical Adjuvant Breast and Bowel Project Prevention-1 (NSABP P-1) trial showed that patients diagnosed with ALH and C-LCIS who completed a 5-year course of tamoxifen had a reduction in the incidence of a subsequent ER-positive breast cancer. Specifically, patients with C-LCIS and ALH had a breast cancer risk reduction of 56% and 86%, respectively [50]. However, the study also found that tamoxifen use was associated with a small increase in the risk of endometrial cancer and thromboembolic events. The International Breast Cancer Intervention Study I (IBIS-I) trial showed that the risk reduction benefits persist for at least another 10–15 years after treatment cessation [51]. The NSABP Study of Tamoxifen and Raloxifene (STAR) compared the efficacy of raloxifene to tamoxifen [52]. The STAR trial found that the cumulative incidence of invasive breast cancer was 25.1/1000 and 24.8/1000 for the tamoxifen and raloxifene treatment groups, respectively. The cumulative incidence for noninvasive breast cancer over the 6 years was 8.1/1000 in the tamoxifen group and 11.6/1000 in the raloxifene group. When compared with tamoxifen, raloxifene's side effect profile appears to be more favorable, with fewer endometrial cancers and thromboembolic complications [52]. Based on these results, raloxifene was formally approved in 2007 for the use of chemoprevention in post-menopausal women.

More recently, aromatase inhibitors (AIs) have also been shown to reduce the risk of breast cancer in high risk post-menopausal women with potentially fewer side effects compared to tamoxifen [53, 54]. Goss et al. showed a 65% relative reduction in the annual incidence of invasive breast cancer in patients with ALH or C-LCIS taking exemestane versus placebo [53]. The International Breast Cancer Intervention Study II (IBIS-II) trial showed that, after a median follow-up of 5 years, 2% of women in the anastrozole group and 4% in the placebo group developed breast cancer

[54]. In 2015, King et al. reported that in patients diagnosed with C-LCIS and who did not undergo risk-reducing mastectomies, the risk of a subsequent breast cancer was significantly reduced in women taking chemoprevention, with a 10-year cumulative risk of 7% with chemoprevention and 21% with no chemoprevention [38].

Despite these proven benefits, only 29.3% of patients with ALH and 23.3% with C-LCIS have been reported to use chemoprevention [55•]. When compared to women with atypical hyperplasia, the diagnosis of C-LCIS and a referral to medical oncology are significantly associated with chemoprevention uptake, while younger women are less likely to take chemoprevention [55•].

The US Preventive Services Task Force has recommended that physicians discuss chemoprevention options with their high-risk patients [56]. The most recent American Society of Clinical Oncology (ASCO) guidelines published in 2019 recommend a 5-year course of tamoxifen 20 mg (for women 35 years and older, regardless of menopausal status), raloxifene 60 mg, exemestane 25 mg, or anastrozole 1 mg daily (the latter 3 drugs for post-menopausal women only) in patients diagnosed with C-LCIS or ALH [57••]. There is scant evidence regarding the role of chemoprevention in patients with NC-LCIS. Clinicians should discuss the risk and benefits of chemoprevention with their patient and consider side effect profiles carefully when choosing a chemoprevention agent.

Surveillance

Lifelong clinical follow-up of patients with ALH and C-LCIS is recommended because of the risk of late-occurring carcinomas. The NCCN Breast Cancer Screening and Diagnosis guidelines recommend a clinical breast exam every 6–12 months and annual mammography starting at age 30 until age 75 (Table 2) [27••]. These NCCN guidelines apply to patients diagnosed with C-LCIS and patients with ALH who have a greater than 20% risk of invasive breast cancer. These guidelines also suggest consideration of annual breast MRI but without a formal recommendation. Similarly, the American Cancer Society's guidelines state that there is currently insufficient evidence to recommend for or against breast MRI surveillance [58]. It is important to keep in mind that breast MRI is not associated with improved clinical outcomes in C-LCIS, and MRI imaging is not associated with early detection or increased sensitivity in this patient population. Therefore, MRI for surveillance is not routinely used [58, 59].

Table 2 Surveillance recommendations for lobular neoplasia

Lobular neoplasia surveillance recommendations
• Clinical breast exam every 6–12 months
• Annual mammography starting at age 30 until age 75
• Consideration of annual breast MRI

Conclusion

LN is an indicator of future breast cancer risk as well as a non-obligate precursor lesion of invasive breast cancer. As our knowledge about LN lesions expands, the treatment and surveillance recommendations will continue to evolve. This review helps to summarize the current literature and treatment recommendations for patients diagnosed with ALH, C-LCIS, and NC-LCIS. Overall, the treatment of LN requires a multidisciplinary approach to ensure appropriate screening and comprehensive counseling about existing and evolving breast cancer risk-reducing options in this patient population.

Compliance with Ethical Standards

Conflict of Interest Ashley DiPasquale and Faina Nakhlis declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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