Contemporary management of atypical breast lesions identified on percutaneous biopsy: a narrative review

Amanda L. Amin^, Jamie L. Wagner^

Department of Surgery, The University of Kansas Health System, Kansas City, KS, USA

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Correspondence to: Amanda L. Amin, MD, MS, FACS. The University of Kansas Health System, 4000 Cambridge St, MS 2005, Kansas City, KS 66160, USA. Email: aamin5@kumc.edu.

Abstract: The management of atypical breast lesions identified on core needle biopsy (CNB) for a breast imaging abnormality is a topic of controversy. While all these atypical lesions have routinely been excised in the past, contemporary management requires a multidisciplinary approach that does not have a one-size-fits-all option. Rigorous multidisciplinary review from the breast radiologist and the pathologist should confirm concordance. All discordant biopsies require surgical excision or additional sampling with more aggressive CNB. Concordant biopsies demonstrating pure flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), and classic type lobular carcinoma in situ (LCIS) should not routinely undergo surgical excision. Of all the atypical breast lesions, atypical ductal hyperplasia (ADH) has the highest risk of upgrade to underlying malignancy and may still be considered for excision, though opportunities for observation for low volume disease may exist. Presentation and extent of atypia, as well as the specific type of atypia should determine the need for excision to rule out underlying malignancy. With the exception of FEA, regardless of whether the site of atypia is excised or not, the patient is also at increased risk of future breast cancer in both breasts. The highest lifetime risk is in women with LCIS. Lifestyle modification, high-risk screening, discussion of chemoprevention, and even bilateral risk-reducing mastectomy may be appropriate for those at a lifetime risk >50%.

Keywords: Atypical ductal hyperplasia (ADH); atypical lobular hyperplasia (ALH); lobular carcinoma in situ (LCIS); flat epithelial atypia (FEA); benign breast biopsy

Introduction

Percutaneous biopsy is commonly performed to evaluate a mammographic abnormality, resulting in more than 1 million benign breast biopsies performed annually in the United States (1). Benign breast biopsies that have histologic epithelial abnormalities associated with increased risk of breast cancer are characterized as high-risk lesions or atypia, which represents >10% of all benign breast biopsies (2,3). The finding of a high-risk breast lesion on pathology from a percutaneous biopsy may be from under-sampling by core needle biopsy (CNB) with malignancy identified at the time of surgical excision. Alternatively, in the absence of malignancy upon excision, it represents an increased future risk of breast cancer (2). Continued improvement in the

^ ORCID: Amanda L. Amin: 0000-0002-9784-6226; Jamie L. Wagner: 0000-0002-3710-7798.

Table 1 Contemporary studies investigating pure flat epithelial atypia upgrade rate to breast cancer

Flat epithelial atypia studies	N	Upgrade rate (%)
Lamb 2017, *J Am Coll Surg* (33)	200	2.4
Chan 2018, *Breast* (34)	68	0
McCroskey 2018, *Mod Pathol* (35)	43	0
Lamb 2018, *J Am Coll Surg* (36)	62	1.6
Alencherry 2019, *Clin Imaging* (37)	72	2.8
Hugar 2019, *Am J Clin Pathol* (38)	111	1

quality of breast cancer screening modalities necessitates a better understanding of the implications of these pathologic findings and development of appropriate management strategies that includes selection criteria for surgical excision, high risk screening, chemoprevention for risk reduction, and a more accurate assessment of future risk of breast cancer.

In this review, we will tackle the topic of atypical lesions of the breast identified on percutaneous biopsy. There is no clear consensus for who benefits from excision and who may be considered for observation. We will look into the unique aspects of each entity and how that may determine the benefit of excision. The question of how this diagnosis of atypia affects future breast cancer lifetime risk will also be addressed. Finally, potential interventions to mitigate future breast cancer will be discussed.

Flat epithelial atypia (FEA)

FEA was defined in 2003 by the World Health Organization (WHO) as a presumably neoplastic intraductal alteration characterized by enlarged acini and terminal ducts lined by layer(s) of monotonous epithelial cells with low-grade cytologic atypia, but lacking architectural atypia required for the diagnosis of atypical hyperplasia (AH) (4,5). FEA was thought to be a precursor lesion in the pathway for the development of breast cancer based on molecular data (6,7), and as it often occurs simultaneously with other high-risk lesions such as atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and lobular carcinoma in situ (LCIS) (8). FEA is identified in anywhere from 0.7–12.2% of benign breast biopsies, usually presenting as screen-detected calcifications on mammogram (4,9-12). There is no current consensus on whether FEA identified on CNB without the presence of additional high-risk lesions

warrants surgical excision (13).

When CNB identifies FEA, National Comprehensive Cancer Center (NCCN) recommendations suggest select patients may be suitable for monitoring in the absence of surgical excision, but does not provide guidance as to patient specifics (14). Historically, there has been a wide range in upgrade rate to underlying malignancy from 0–42% (4,10-12,15-30). In a meta-analysis of studies evaluating pure FEA on CNB by Rudin and colleagues, there was significant heterogeneity across studies; however, when restricting to higher-quality studies with stricter criteria, upgrade to malignancy was 7.5% (13). For those that did not have an underlying malignancy, excision for pure FEA identified ADH in 18.6% of surgical specimens. While not a malignancy itself, ADH carries an increased risk for future malignancy and may warrant more frequent screening and discussion of chemoprevention with the benefits of risk reduction discussed below, the information of which may be useful for the patient and her provider. Overall, the excision of pure FEA upgrades to malignancy or higher-risk atypia in up to 25% of patients, which may alter treatment recommendations. Therefore, the general recommendation would be that patients be considered for excision while also taking into account preferences and patient co-morbidities (13). However, more recent studies citing lower malignancy upgrade rates of <3% describe better lesion sampling with larger gauge needles (9–11 G), vacuum-assistance, and radiographic-pathologic concordance (31-38). This rate is on par with the Breast Imaging-Reporting and Data System (BIRADS) 3 lesions, which are typically recommended for surveillance over excision (39). With such a low rate of upgrade in contemporary studies (*Table 1*), observation over excision should be favored in most cases.

Future risk of malignancy does not appear to be significantly affected by the presence of FEA. In Said and colleagues' study of 282 women with FEA with a median follow-up of 17 years, nearly half of women had coexisting AH with FEA. When comparing the future risk of breast cancer for those with FEA alone to those with FEA+AH, the risk with FEA alone was comparable with women with proliferative breast disease, and those with FEA+AH had elevated risk similar to women with AH alone (5). As the presence of FEA does not appear to be an independent risk factor for future breast cancer beyond that of any proliferative lesion, increased surveillance and chemoprevention may not be necessary.

Table 2 Contemporary studies investigating atypical lobular hyperplasia upgrade rate to breast cancer

Atypical lobular hyperplasia studies	N	Upgrade rate (%)
Shah-Khan 2012, *Ann Surg Oncol* (41)	81	1
Sen 2016, AJR *Am J Roentgenol* (42)	339	4
Nakhlis 2016, *Ann Surg Oncol* (54)	48	0
Lamb 2018, *J Am Coll Surg* (36)	143	2.8
Schmidt 2018, *Breast Cancer Res Treat* (55)	68	2.9
Muller 2018, *Arch Pathol Lab Med* (56)	87	3
Genco 2020, *Virchows Archiv* (43)	172	1.7

Lobular neoplasia

The term "lobular neoplasia" (LN) was coined in 1978 by Haagensen to include both ALH and LCIS (40). LN account for approximately 3% of all breast biopsies (41-43), and are defined by monomorphic epithelial cell populations with minimal nuclear atypia that lacks cellular cohesion and contains frequent intracytoplasmic vacuoles, negative for E-cadherin because of somatic alterations of the CDH1 gene on the long arm of chromosome 16 (44-46). ALH and classic type LCIS are subclassifications of LN based on the quantity of atypia, with ALH defined as filling and distention of <50% of the acini in the terminal duct lobular unit and LCIS as >50% (47-49). LN is associated with underlying malignancy at the time of diagnosis on CNB, with upgrade rates ranging from 0–67%, as well as an elevated risk of future malignancy (50).

ALH

Page and colleagues established criteria for the diagnosis of ALH as a distinct entity in 1985 (45), which is frequently identified as an incidental finding on CNB (24,51). There is large variability in the studies attempting to define upgrade rate, many with small sample size, and ALH is often being grouped with LCIS (50). Many of these studies also did not exclude additional high-risk lesions such as intraductal papilloma, radial sclerosing lesion, or discordant lesions, which would presumably contribute to the higher upgrade rate. In contemporary studies that have controlled for all of those factors, the upgrade rate is <3% (36,41-43,52-56) (*Table 2*). Because of the low incidence of malignancy at a site of pure ALH, routine surgical excision is not recommended for ALH as an incidental finding with concordance between radiology and pathology (14,55,57,58).

There are many factors that affect breast cancer risk, including lifetime estrogen exposure (age at menarche and menopause, parity, breastfeeding, hormone replacement therapy use), family history genetics, chest wall radiation at a young age, obesity, alcohol consumption, physical activity, in addition to breast specific features such as mammographic density and benign breast disease. Multiple large cohort studies have been performed investigating benign biopsies as a source of future risk [Nashville Breast Cohort, Partners Cohort, Nurses' Health Study, Breast Cancer Surveillance Consortium, and Mayo Clinic Benign Breast Disease (BBD) Cohort]. Future breast cancer risk with a biopsy of ALH is 4-fold higher than the general population, which translates into an absolute risk of approximately 1–2%/year (50,59,60). Hartmann and colleagues using the Mayo BBD Cohort have gone even further by stratifying women by the number of atypical foci, demonstrating that increasing foci of atypia increases the future risk of breast cancer, with women ≥3 foci having a 25-year risk of malignancy close to 50% (50).

LCIS

Foote and Stewart first described LCIS in 1941 (61). LCIS, as with ALH, is typically an incidental finding on percutaneous biopsy performed for another imaging abnormality, but may occasionally be associated with microcalcifications on screening mammogram (9,24,51,53,62). Reports in the literature of upgrade rate after surgical excision for LCIS have been 15–33% (9,36,42,54).

It is important to recognize that there are several histologic subtypes of LCIS, the most common being classic type, which typically has an incidental presentation. Additional subtypes such as pleomorphic LCIS and LCIS with comedo-necrosis are typically associated with calcifications and may even be misclassified as DCIS. Less is known about these non-classic variants as most reports are single institution with small numbers, but reported upgrade rates to underlying malignancy are up to 70% (63-71). Therefore, surgical excision should be discussed for all non-classic type LCIS (24,66,72-74). However, more contemporary studies of classic type LCIS with radiographic-pathologic correlation has an upgrade rate of only 1–3% (24,55). Therefore, observation without excision should be considered for this entity (58). To further illustrate the low risk of upgrade upon excision of

LCIS, Taylor and colleagues used the National Cancer Database (NCDB) to investigate the surgical practices for patients with LCIS. Nearly 85% of the 30,105 women with LCIS underwent excision, including 4% with unilateral mastectomy and 5.1% with bilateral mastectomy, representing a portion of women undergoing overtreatment for this entity (75).

Women with LCIS have an 8-fold relative risk of developing a future breast cancer, translating into an absolute risk of approximately 2%/year (51). Other contributing factors are age at diagnosis and number of atypical foci (58). Based on a large SEER study, it appears that race and ethnicity also play a role in future breast cancer risk, with Black women with LCIS having a 1.3× higher risk of future breast cancer than white women with LCIS (76). It is important that risk stratification be performed considering these factors allowing high-risk screening and offering chemoprevention to be considered when appropriate.

ADH

ADH, like DCIS, frequently presents as calcifications on screening mammogram and is identified in 8–17% of breast biopsies (31,53,77). Unfortunately, ADH and DCIS are histologically virtually identical, with the distinction being quantity of atypia and nuclear grade. A lesion is characterized as ADH if low-grade cytologic atypia and monomorphism combined with epithelial architectural complexity is involving less than two contiguous membrane-bound spaces and measures less than 2 mm in linear extent (51). Because the amount of sampling of the lesion can be the distinction between ADH and DCIS, surgical excision is typically recommended for ADH to rule out an underlying malignancy (14,53,78). An additional difficulty with ADH is the interobserver variability between pathologists to distinguish ADH from DCIS or usual ductal hyperplasia, as these diagnoses are made on morphology alone, without the aid of specific immunohistochemical stains. One study cites a concordance rate between pathologists for atypia to be as low as 48% (79). Clinicians and patients should not hesitate to seek a second opinion or at least request another pathology review before proceeding with excision or surveillance under these circumstances to confirm the diagnosis.

Recent studies report an overall upgrade rate of ADH to malignancy of 15–25% and approximately 3% risk of invasive breast cancer alone (3,9,36,62,77,80-92) (*Table 3*). This then translates to 75–85% not having any malignancy

and nearly 97% not having invasive breast cancer. This has resulted in many studies trying to identify those patients at the lowest risk of having a current malignancy, which could be successfully managed with observation over surgical excision.

The earliest study investigating the feasibility of selecting a low-risk for upgrade group for observation incorporated patient factors, including younger age (<50 years), screen-detected lesions (no palpable masses or nipple discharge), radiographic features such as small lesion size (<1.5 cm), imaging presentation of calcifications without a mass, and pathologic features including low burden of atypical foci (only 1 focus). When patients meeting those restrictions underwent excision, this resulted in an upgrade rate of 5.6% (93). Subsequent studies identified their lowest-risk populations to consider for observation to be those with radiographic calcifications without mass, and also incorporating pathologic features of no individual cell necrosis and the extent of the radiographic lesion removal by biopsy (>95%). This low-risk group had an upgrade rate of 6% (91). This is further refined to allow observation when there is no necrosis, and using a combination of volume of atypia with the degree of sampling (only 1 focus and >50% removed or ≤3 foci and >90% removed), with a resulting upgrade rate of 4.9% (77). In general, the lowest risk for upgrade is in concordant lesions without a mass, small lesions, and well-sampled lesions with complete or near complete removal (32). When these criteria are not met, surgical excision should be performed (78,94,95).

As mentioned above, if ADH does upgrade to malignancy, most upgrades are to DCIS. Outside of a clinical trial, the standard of care for the management of DCIS is surgical excision followed by whole breast irradiation after lumpectomy and endocrine therapy. However, the standard management of DCIS is being called into question, with several international trials currently accruing offering observation over excision for grade 1–2 hormone-positive DCIS. Thus, the routine surgical excision of ADH should also be questioned. If the site of ADH is not excised, patients do not appear to be at increased risk of malignancy specifically at that location. Menen and colleagues demonstrated patients with ADH meeting the above low-risk criteria can be safely offered observation over excision, with the subsequent breast cancer rate of 5.6% over a median three year follow up and the majority not being at the ADH biopsy site (96).

Whether or not the ADH site is excised, future breast cancer risk persists and is a global risk, not isolated to

Table 3 Contemporary studies investigating atypical ductal hyperplasia upgrade to breast cancer, specifically invasive breast cancer

Atypical ductal hyperplasia studies	N	Overall upgrade rate (%)	Upgrade to invasive breast cancer (%)
Eby 2008, *Ann Surg Oncol* (87)	105	17	3.8
Forgeard 2008, *Am J Surg* (88)	116	25	2.6
Wagoner 2009, *Am J Clin Pathol* (89)	123	18	0
Kohr 2010, *Radiology* (90)	101	20	3
Nguyen 2011, *Ann Surg Oncol* (91)	121	13	1
McGhan 2012, *Ann Surg Oncol* (92)	114	18	5.3
McLaughlin 2014, *AJR Am J Roentgenol* (80)	101	13	2
Menes 2014, *Am J Surg* (62)	685	18	3.2
Khoury 2015, *Histopathology* (81)	203	28	4.9
Mooney 2016, *Mod Pathol* (9)	192	18	3.1
Peña 2017, *Breast Cancer Res Treat* (77)	399	16	2.3
Lamb 2018, *Am J Coll Surg* (36)	337	18	3
Linsk 2018, *Breast J* (82)	96	20	NR
Sutton 2019, *Am J Surg* (83)	84	19	3.5
Rageth 2019, *Breast Cancer* (84)	63	16.5	1.5
Weiss 2019, *Am J Surg* (85)	61	16	0
Sergesketter 2019, *J Surg Res* (3)	398	13.3	NR
Williams 2019, *Acad Radiol* (86)	124	17.7	4
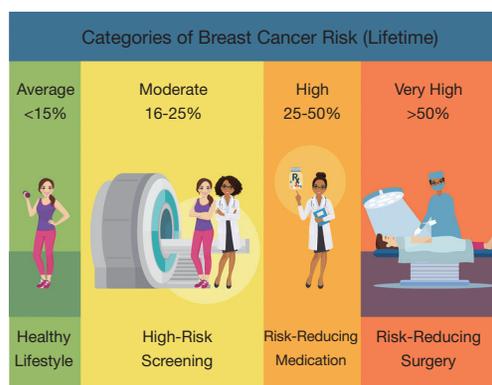
Figure 1 Categories of lifetime breast cancer risk and appropriate interventions for surveillance and risk reduction.

the site of ADH diagnosis, with 40% of diagnoses being contralateral (50,59,60,62). Similar to ALH, having a diagnosis of ADH carries a four-fold risk of future breast cancer, translating into 1–2%/year absolute risk, with no plateau seen with extensive follow up (60,97).

High risk screening and chemoprevention

For all women who have LN or ADH, future breast cancer risk is elevated to varying degrees. NCCN management recommendations for patients diagnosed with atypia include clinical encounter every six to twelve months, annual MMG after age 30, consider annual MRI after age 25, risk reduction strategies, and breast awareness (*Figure 1*) (14). This recommendation is regardless of if the site of atypia undergoes excision. American Society of Clinical Oncology (ASCO) guidelines recommend chemoprevention be discussed with women with a 5-year absolute risk of breast cancer of 1.7% or higher (98,99). Chemoprevention with tamoxifen, raloxifene, anastrozole, or exemestane results in a 50% reduction in future malignancy risk (100-102). This risk reduction is even more significant in women with LN and ADH ranging from 65–70%, when compared to those with a family history of breast cancer without an atypia diagnosis (50,59).

Chemoprevention acceptance has been historically low even for the treatment of DCIS, let alone for women

with a family history or history of LH/ADH (103-106). Reasons for this low rate include clinicians and women underestimating their future risk of breast cancer, as well as women's fear of adverse effects from this therapy. Tamoxifen is associated with elevated rates of endometrial cancer (RR 2.25), cataracts (RR 1.22), and thromboembolic events (RR 1.93), while anastrozole and exemestane are associated with bone loss. Future directions for prevention include low dose tamoxifen of 5 mg daily have much fewer side effects compared to the traditional dosage of 20 mg daily with a 52% reduction of ipsilateral breast cancer events, and a 76% reduction in contralateral breast cancer events (107). Because the systemic side effects of oral medication are a large reason for the lack of adherence or acceptance for chemoprevention, a topical formulation of tamoxifen (4-OHT) that can be applied to breast skin is currently under investigation (108,109).

Conclusions

Many women present with screen detected calcifications that undergo percutaneous biopsy that results in a diagnosis of atypia. However, the presence of atypia on CNB should no longer be an automatic indication for surgical excision. Emphasis should be placed on assessing radiographic and pathologic concordance, and further consideration for observation over excision for well-sampled, concordant lesions, particularly for FEA and LN. Surgical excision should be reserved for discordant lesions, large lesions that are under-sampled, and for ADH in many cases. Recognition that future breast cancer risk persists even after atypia excision is vital, and appropriate counseling about lifestyle modification, increased intensity of breast screening, and discussion of chemoprevention should be offered.

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Footnote

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