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Flat epithelial atypia and the risk of sampling error: Determining the value of excision after image-guided core-needle biopsy

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ABSTRACT

Background: We determined the sampling error rate of flat epithelial atypia (FEA) and evaluated current guidelines recommending excisional biopsy.
Methods: A retrospective review of consecutive excisional biopsies after image-guided core-needle biopsy identified patients with isolated FEA diagnosed between 2014 and 2018. Clinical and pathologic parameters were evaluated.
Results: Twenty-five women with 27 biopsies were included. Based on pathologic review of original core specimens, 44.4% (N = 12) were accurately diagnosed as FEA. Upon excision, lesions were upgraded to ductal carcinoma in situ (N = 2) or invasive ductal carcinoma (N = 1) in 11.1% of cases. Older age, black race, hormone replacement, and calcifications in the image-guided biopsy specimen were associated with the presence of high-risk or malignant lesions in the excisional biopsy (all $p \leq 0.05$).
Conclusions: In this study, FEA was frequently overcalled. However, lesions suspicious for FEA warrant excision due to their association with malignancy or high-risk lesions, which may necessitate further surgical management and/or risk-reducing strategies.

Introduction

Flat epithelial atypia (FEA), or columnar cell change with atypia, is a nonpalpable, asymptomatic indeterminate breast lesion that arises from the terminal duct lobular unit (TDLU). On mammogram, FEA appears as grouped amorphous calcifications, requiring image-guided biopsy for tissue diagnosis.[1] In response to the increasing recognition of this entity and need to standardize pathologic description, the World Health Organization (WHO) defined FEA as the replacement of native epithelial cells with one to five layers of low-grade atypical cells in the absence of architectural atypia.[2,3]

Although FEA is relatively rare, comprising 1%–2% of breast biopsies, it is a clinically significant "borderline" finding because of its frequent association with higher risk proliferative lesions, such as atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH).[4,5] Furthermore, while FEA is considered benign, molecular studies suggest that it is a precursor to carcinoma.[6–8] In as many as 15% of patients, FEA is associated with adjacent ductal carcinoma in situ (DCIS) or invasive cancer after excisional biopsy (Table 1).[2,6,9–21] With the potential for sampling error and limited morphologic criteria to guide recommendations of surgical excision or observation, the standard of care at most institutions is to perform an excisional biopsy in patients with FEA found on image-guided biopsy, consistent with the American Society of Breast Surgeons' consensus guidelines.[18,22] However, this practice is controversial given that upgrade rates are highly variable, raising uncertainty as to whether the risk of malignancy outweighs the emotional and physical burden of subjecting patients to possibly unwarranted procedures.

Although previously published retrospective studies have examined the rates of upgrade to malignancy after excisional biopsy, data remain unclear regarding associated pathologic or clinical risk factors. The impact of FEA extent, or terminal duct lobular unit involvement, and the presence of calcifications on the risk of malignancy are also equivocal. Thus, the objectives of this study

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Table 1
Summary of studies evaluating the rates of upgrade to ductal carcinoma in situ or invasive carcinoma among patients who underwent excisional biopsy after preoperative core needle biopsy diagnosis of pure flat epithelial atypia.

Senior author	Publication year	N	% Upgrade to DCIS	% Upgrade to carcinoma
Kleer, CG	2007	14	7.1	14.3
Engohan-Aloghe, C	2010	20	0.0	0.0
Pakzad, K	2012	95	3.2	0.0
Palli, D	2012	190	9.5*	–
Done, SJ	2013	94	4.8	4.8
Mehta, TS	2014	29	3.4	0.0
Lee, MC	2014	24	0.0	0.0
Livasy, CA	2015	73	4.0	3.0
Mancino, AT	2016	46	2.2	0.0
Peoples, GE	2016	27	11.2	0.0
Lehman, CD	2017	208	2.4	0.0
Tan, EY	2018	68	0.0	0.0
Ayala, AG	2018	43	0.0	0.0
Michenet, P	2018	20	–	15.0
Clark, BZ	2019	94	0.0	0.0

DCIS, Ductal carcinoma in situ.
* % represents DCIS and carcinoma combined.

were to determine FEA upgrade rates secondary to sampling error, and factors associated with malignancy to assess whether current recommendations are justified. We hypothesized that focal FEA, independent of higher risk lesions, would not be associated with a sampling error.

Methods

Study design and patient selection

In this single institution, retrospective study, one surgeon's operative log was reviewed to identify consecutive patients who underwent needle-localized partial mastectomy or excisional biopsy between January 2014 and December 2018 (N = 497). Corresponding image-guided biopsy pathology reports were then reviewed to identify all patients with FEA or columnar cell changes with atypia (N = 56). To isolate the impact of pure FEA on subsequent pathologic and patient outcomes, we excluded patients with concomitant atypical proliferative (N = 28) or malignant (N = 2) lesions, such as ALH, ADH, or DCIS, as well as patients without an in-house biopsy (N = 1). At our institution, all patients with FEA detected on image-guided core biopsy received an excisional biopsy in compliance with current recommendations by the American Society of Breast Surgeons,[22] amounting to 25 patients who met inclusion criteria. One patient had two biopsy sites in the same breast, and one patient had a biopsy site in each breast; these incidents were evaluated independently, amounting to 27 included lesions (Fig. 1). This study was approved by the Institutional Review Board at the University of Cincinnati (protocol number 2017–5388).

Patient variables and outcomes

Electronic medical records were reviewed to extract patient demographics and risk factors for breast cancer. These included age, race, personal and family history of breast cancer, history of breast biopsy, use of oral contraception or hormone replacement, age of menopause and menarche, and gravidity. Follow-up time was defined as the range between excisional biopsy and last known mammogram. The primary outcome was the identification of malignancy, defined as DCIS or invasive carcinoma, in the excisional biopsy specimen. Our secondary outcome was the identification of any lesion in the excision specimen that would warrant further management, including lobular carcinoma in situ (LCIS), ADH, ALH, DCIS or invasive carcinoma. Sampling error, or upgrade rate, was defined as the proportion of malignant lesions found in excisional biopsy specimens that were not previously detected by image-guided biopsy using a denominator of N = 27.

Pathologic specimen review and FEA definition

Original archived hematoxylin and eosin stained slides of breast core biopsies and excision specimens were re-reviewed by a single breast pathologist for the presence or absence of FEA, as well as for concurrent, more advanced atypical proliferative or malignant lesions. The reviewing pathologist was blinded to both the original diagnoses and patient outcomes. The purpose of the pathologic re-review was to standardize and confirm FEA diagnosis to allow for a more accurate assessment of the associated risk of malignancy.

FEA was defined using WHO criteria, and accordingly, FEA was diagnosed when TDLUs showed replacement of the native epithelial cells by either a single layer of cells with mild cytologic atypia, or by a proliferation of monotonous, cytologically atypical cuboidal to columnar cells showing stratification of up to 3 to 5 cell layers.[3] Proliferations of atypical cells with formation of micropapillae or other more complex architectural arrangements were excluded from a diagnosis of FEA, and interpreted as ADH or DCIS depending on the degree of nuclear and architectural atypia.[3,23]

Pathologic variables

The independent review conducted in the current study revealed heterogeneity amongst previously diagnosed FEA lesions, and three different morphologic patterns were recognized. *Pattern 1* included lesions that consisted of flat epithelial proliferations with epithelial monotony, but minimal to absent cytologic atypia (Fig. 2A**).** These are referred to as benign columnar cell change. *Pattern 2* included lesions that showed nuclear stratification, but also displayed prominent variation in nuclear size and shape, and accordingly, minimal cytologic monotony. These are referred to as florid columnar cell change (Fig. 2B). Lastly, *Pattern 3* consisted of lesions composed of cytologically monotonous cells with mild cytologic atypia that formed either flat, single cell layers or showed nuclear stratification of up to five cell layers thick, which we refer to as FEA (Fig. 2C).

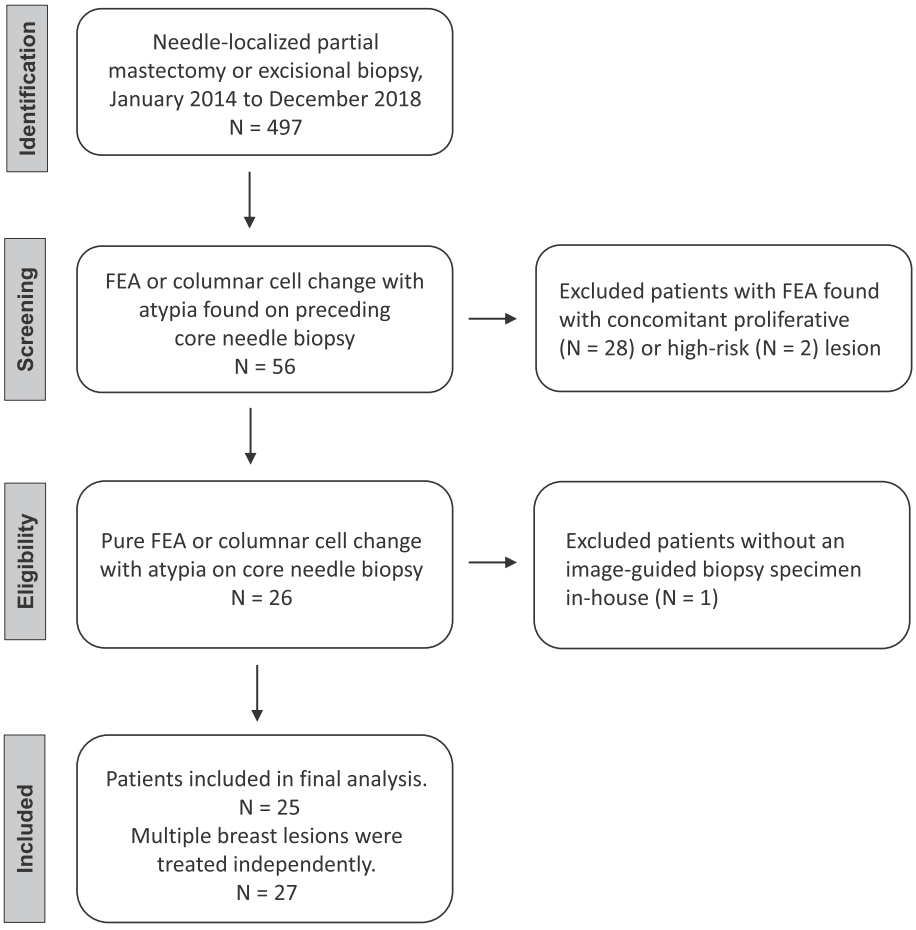

Fig. 1. Diagram of inclusion and exclusion criteria for FEA specimens.

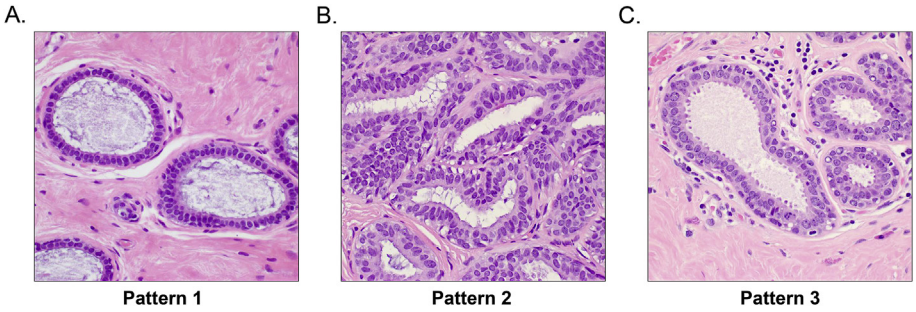

Fig. 2. These images exemplify the three different morphologic patterns of columnar cell change identified upon retrospective pathologic review of specimens. (A) *Pattern 1* lesions consisted of flat epithelial proliferations with epithelial monotony, but minimal to absent cytologic atypia. These are referred to as benign columnar cell change. (B) *Pattern 2* lesions showed nuclear stratification, but also displayed prominent variation in nuclear size and shape, and accordingly, minimal cytologic monotony. These are referred to as florid columnar cell change. (C) Lastly, *Pattern 3* lesions were composed of cytologically monotonous cells with mild cytologic atypia that formed either flat, single cell layers or showed nuclear stratification of up to five cell layers thick, which we refer to as flat epithelial atypia.

Lesion extent was assessed as a dichotomous variable, either being focal (involving two TDLUs or less, or not more than one sampled tissue core) or patchy (involving three or more TDLUs, or more than one sampled tissue core).[18] Presence or absence of calcifications was also assessed in core biopsy specimens. Lastly, given the identified morphologic heterogeneity within diagnosed FEA lesions upon retrospective review, we also recorded whether the original diagnosing pathologist received subspecialty training in breast pathology or was considered a "breast pathologist" based on primary area of clinical work and expertise.

Statistical analysis

Statistical analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC). Descriptive statistics are reported as medians and interquartile ranges or as counts and percentages. In light of the small sample size, categorical variables were compared between groups using Fisher's exact tests and Kruskal-Wallis tests, while continuous variables were compared using Wilcoxon rank-sum tests. P values ≤ 0.05 were considered statistically significant.

Results

Demographic and breast cancer risk factors are detailed in Table 2. All patients were women with a median age of 52 years (46–61 years). None of the patients were from a high-risk ethnic group, including Amish, Icelandic, or Ashkenazi Jewish ancestry, or had a tested genetic predisposition to breast cancer. Sixty percent had a family history of breast cancer, mostly through second-degree relatives. Finally, 56% (N = 14) had a history of prior breast biopsy, 13% (N = 3) had a personal history of breast cancer, and 8% (N = 2) had a current breast cancer diagnosis at the time FEA was detected. Over a median follow-up period of 12 months (6–21 months), no one was diagnosed with a breast malignancy independent of their diagnostic work-up for FEA.

The results of the retrospective review of image-guided core and excisional biopsy pathologic characteristics are listed in Table 3. The median time interval between percutaneous biopsy and excision was 47 days (27–82 days). The diagnosis of FEA (*Pattern 3*) was confirmed in 44% (N = 12) of image-guided biopsy specimens. Of the remaining specimens, 44% (N = 12) showed only the presence of florid columnar cell change (*Pattern 2*), and 11% (N = 3) demonstrated only simple columnar cell change *(Pattern 1)*. The majority of image-guided core-needle biopsies showed FEA in a patchy distribution and/or contained calcifications. Only one-third of the image-guided biopsy specimens had been originally reviewed by a breast subspecialty pathologist.

After retrospective review, 52% (N = 14) of excisional biopsy specimens were found to contain FEA (*Pattern 3)*. Although the histologic pattern was predominantly consistent between core biopsy and excision specimens, three patients with florid columnar cell change *(Pattern 2)* on core-needle biopsy had FEA *(Pattern 3)* upon excision, and a single patient showed no remaining FEA in the excision specimen. Three patients were diagnosed with malignant lesions after excision (11.1%), including two patients with DCIS and one with invasive ductal carcinoma. To better appreciate the distribution of individual patient factors in a small sample size, clinical and pathologic variables of upgraded patients are delineated in Table 4. All three women with FEA-associated malignancy were black, had no prior history of breast cancer, and had FEA (*Pattern 3*) with calcifications in their core biopsy specimens.

We observed that some surgically excised lesions were associated with not only malignancy, but also proliferative lesions with atypia (N = 6, 22%). Because these findings are themselves associated with sampling error and may warrant risk-reducing therapy, our next aim was to compare clinical and pathologic factors associated with both high-risk and malignant lesions in the excisional biopsy specimen, as detailed in Table 5. Groups were well-matched in terms of ages of menarche, menopause, and first childbirth, history of hormonal contraceptive use, and family history of breast cancer (all $p > 0.05$). There were also no differences regarding history of breast biopsy or concurrent breast cancer (both $p > 0.05$). High-risk or malignant lesions found in specimens excised for presumed FEA were associated with older age, black race, and history of hormone replacement therapy. The presence of calcifications in the core-needle image-guided biopsy specimen was the only pathologic variable associated with later detection of high-risk proliferative or malignant lesions.

Table 2
Demographics of patients diagnosed with flat epithelial atypia on original core needle biopsy, N = 25.

Patient characteristic N (%); median (IQR)	Entire cohort
Age at diagnosis (years)	52 (46–61)
Female sex	25 (100%)
Race	
White	16 (64%)
Black	9 (36%)
Age of menarche (years)	13 (12–14)
Post-menopause	14 (59%)
Age of last menstrual period (years)	48 (44–51)
Gravidity	2 (1–3)
Age of first childbirth (years)	23 (19–26)
History of hormonal contraceptive use	18 (78%)
Time hormonal contraceptive use (years)	2 (0.3–10)
History of breastfeeding	9 (43%)
History of hormone replacement	3 (13%)
Family history breast cancer	16 (60%)
1st degree relative	7 (28%)
2nd degree relative	11 (44%)
History of breast biopsy	14 (56%)
Personal history of breast cancer	3 (13%)
Concurrent breast cancer at time of FEA	2 (8%)

FEA, flat epithelial atypia; IQR, interquartile range.

Table 3
Pathologic characteristics based on retrospective review of patients diagnosed with flat epithelial atypia, N = 27.

Pathologic characteristic, N (%)	Core needle biopsy	Excisional biopsy
Laterality		
Right	16 (59%)	16 (59%)
Left	11 (41%)	11 (41%)
Pattern		
Benign	–	4 (15%)
Simple columnar cell change	3 (11%)	–
Florid columnar cell change	12 (44%)	9 (33%)
Flat epithelial atypia	12 (44%)	14 (52%)
Extent		
Focal	9 (33%)	3 (13%)
Patchy	18 (67%)	14 (52%)
Calcifications	18 (67%)	–
Original diagnosis by subspecialist	9 (33%)	–
FEA with ADH or LCIS	–	6 (22%)
FEA with malignancy		
Ductal carcinoma in situ	–	2 (7%)
Invasive ductal carcinoma	–	1 (4%)

ADH, atypical ductal hyperplasia; FEA, flat epithelial atypia; LCIS, lobular carcinoma in situ.

Discussion

We performed a retrospective, single-institution study of patients with isolated FEA to determine upgrade rates and evaluate whether they warrant excision. Upon pathologic re-review, fewer than half of included core-needle specimens were considered true FEA. However, upon excision, the rate of sampling error was a striking 11.1%, including two specimens that were upgraded to DCIS and one that was upgraded to invasive ductal carcinoma. Factors associated with identification of high-risk lesions or malignancy in excisional biopsy specimens included older age, black race, history of hormone replacement therapy, and calcifications in the core-needle biopsy.

FEA has been long recognized under a variety of designations, but the first official definition was only established by the WHO in 2003. As evidenced by the morphologic heterogeneity amongst lesions diagnosed as FEA in the current study, as well as the variability in associated rates of upgrade to high risk atypical lesions among different patterns of FEA, the diagnosis of FEA remains challenging. In one study from Samples et al., pathologists were randomly assigned to interpret slide sets containing benign non-FEA and FEA cases.[24] The authors noted enormous variability in FEA diagnosis, with the rate of agreement between participating and reference pathologists ranging from 17% to 52%. In addition, up to 66% of pathologists identified FEA on slides where none actually

Table 4
Disease and pathologic characteristics of specimens subject to sampling error, N = 3.

#	Race	H/o breast biopsy	H/o breast cancer	CNBx diagnosis	Subspecialty pathologist?	Final diagnosis	Malignancy
1	B	Yes	No	Patchy FEA	Yes	Focal FEA+	DCIS
2	B	No	No	Focal FEA	No	Patchy FEA+	DCIS
3	B	No	No	Patchy FEA	No	Patchy FEA+	Carcinoma

B, black; DCIS, ductal carcinoma in situ.
+ calcifications present.

Table 5
Clinical and pathologic differences between specimens with and without a high-risk lesion or malignancy upon excisional biopsy, N = 27.

Patient or pathologic characteristic N (%), median (IQR)	No associated lesions (N = 18)	Associated lesion (N = 9)	*P* value
Age at diagnosis (years)	49 (42–55)	61 (54–69)	*0.02*
Race			*0.04*
White	14 (78%)	3 (33%)	
Black	4 (22%)	6 (67%)	
Age of menarche (years)	13 (12–14)	13 (12–13)	0.92
Post-menopause	8 (47%)	8 (89%)	0.09
Age of last menstrual period (years)	48 (44–51)	47 (32–53)	0.72
Gravidity	2 (1–4)	2 (2–3)	0.53
Age of first childbirth (years)	22 (20–29)	23 (17–27)	0.84
History of hormonal contraceptive use	13 (81%)	7 (78%)	1.00
Hormonal contraceptive use (years)	2 (0.25–10)	4 (1–11)	0.72
History of breastfeeding	6 (43%)	4 (44%)	1.00
History of hormone replacement	0 (0%)	4 (44%)	*0.01*
Family history breast cancer	11 (61%)	6 (67%)	1.00
History of breast biopsy	11 (61%)	4 (44%)	0.45
Personal history of breast cancer	2 (12%)	1 (11%)	1.00
Concurrent breast cancer	2 (12%)	0 (0%)	0.53
Laterality			1.00
Right	11 (61%)	5 (56%)	
Left	7 (39%)	4 (44%)	
Pattern			0.08
Simple columnar cell change	3 (17%)	0 (0%)	
Florid columnar cell change	10 (56%)	2 (22%)	
Flat epithelial atypia	5 (28%)	7 (78%)	
Extent			0.42
Focal	5 (28%)	4 (44%)	
Patchy	13 (72%)	5 (56%)	
Calcifications	9 (50%)	9 (100%)	*0.01*
Original diagnosis by subspecialist	5 (28%)	4 (44%)	0.42
Time between procedures (days)	50 (30–82)	30 (25–134)	0.34

IQR, interquartile range.

existed. Similarly, in our study, blinded retrospective re-review of image-guided core-needle biopsy specimens revealed that the original FEA diagnosis was overcalled in 56% of cases. Specifically, retrospective pathologic review raised concerns about the ability to reliably discriminate FEA from columnar cell change (simple or florid) as none of the three cases with *Pattern 1* and only two of ten cases with *Pattern 2* lesions contained high risk atypical lesions after excision. Of note, we found that only one-third of image-guided biopsy specimens were initially read by a breast subspecialty pathologist, but that subspecialty interest was not associated with diagnostic accuracy (data not shown). Through further research, pathologist education, and multiple pathologist review, we may identify ways to improve diagnostic accuracy.[25,26]

Although FEA is not malignant, controversy still remains as to whether it requires excisional biopsy to rule out the diagnosis of an adjacent pathologic lesion, such as DCIS or carcinoma. The resounding contention regarding the current guidelines is that surgical excision of FEA results in overtreatment. There is abundant literature on this topic, but synthesizing previous work is problematic due to the historic lack of standardized terminology and the variety of selected pathologic specimens and outcomes. While some groups have detected no risk of upgrade to malignancy,[6,10,12,13] others have found an upgrade rate of 15% in cases where FEA is the only at-risk lesion on image-guided core-needle biopsy.[2,9,11,14–20] In the largest single-institution series to date, Lamb, et al., found that pure FEA was not associated with a risk of invasive carcinoma but was upgraded to DCIS in 2.4% of cases. In addition, FEA was associated with high-risk proliferative lesions in 36% of cases.[14] Similarly, in the largest multi-institutional study to date, Bianchi, et al. discovered an FEA upgrade rate of 9.5%.[18] However, this figure includes malignant lesions and LCIS, which is no longer considered a malignancy but a marker for increased breast cancer risk, and thus may overstate the rate of sampling error.

In our patient population, we identified an 11.1% (N = 3) rate of sampling error. This percentage was generated using the total number of original FEA diagnoses as the denominator (N = 27) in an intention-to-treat like approach, capturing how patients were initially managed based on the pathologic data available at the time of treatment. However, this may actually underestimate the true upgrade rate considering the lack of accordance between original and retrospective diagnoses. If we calculate the sampling error, or upgrade rate, based on pathologically confirmed FEA diagnoses and true disease biology (N = 12), this figure rises to 25%. Although it was outside the scope of this study, the literature suggests that the rate of sampling error only further increases when FEA is detected in the presence of another high-risk lesion by core-needle biopsy. In a prospective study from Uzoaru, et al., women with FEA plus ADH

were 6.5 times more likely to be diagnosed with carcinoma than those with FEA alone.[9] Based on these findings, current guidelines promoting the excision of FEA are justified.

In our study, one-third of excision specimens involved high-risk lesions, including LCIS and ADH, in addition to malignancy. If diagnosed by image-guided core-needle biopsy, LCIS should be narrowly excised to rule out concomitant malignancy. Management strategies include endocrine therapy, bilateral mastectomies, or continued mammographic surveillance. The algorithm for ADH and ALH found on core needle biopsy is similar; these are markers of increased risk that confer a significant risk of upgrade to malignancy upon excisional biopsy. Current National Comprehensive Cancer Network guidelines recommend risk-reduction therapy for any woman diagnosed with ALH, ADH, or LCIS, with a life expectancy greater than or equal to 10 years, who desires this option.[27] In the seminal National Surgical Adjuvant Breast and Bowel Project P-1 trial, 5 years of tamoxifen therapy reduced malignancy risk by 56% and 86% in LCIS and atypical hyperplasia, respectively.[28]

Finally, we determined that identification of malignancy or high-risk lesions in excisional biopsy specimens was associated with older age, black race, history of hormone replacement therapy, and the presence of calcifications in the image-guided biopsy. Surprisingly, the diagnosis of FEA *(Pattern 3)* based on retrospective review was not significantly correlated with high-risk findings in excision specimens, although our sample size was likely underpowered to detect this difference. This small sample size also limited our ability to further examine correlations between identified variables and primary and secondary outcomes.

There are limitations to the current study. The study design is retrospective, subjecting it to biases of referral and chart review, and preventing conclusions about causation. Although we captured granular clinical and pathologic data, our study would have been strengthened by also assessing radiologic factors, including mammography history and follow-up. In addition, our small sample size hindered our ability to perform multivariable analyses. Three factors contribute to this limitation. First, rather than review all image-guided breast pathology at our institution, we screened only patients who underwent needle-localized partial mastectomy or excisional biopsy with a preceding diagnosis of FEA. Second, to determine whether FEA was associated with sampling error, we excluded anyone with concomitant atypical lesions. Finally, we studied patients treated by a single surgeon to standardize clinical and surgical management and reduce selection bias. Future multiple surgeon, multi-institutional, or prospective studies will be beneficial in determining the safest management of FEA patients.

Conclusion

Despite efforts to standardize its definition, lesions diagnosed as FEA show substantial morphologic heterogeneity, as well as variability in upgrade rates of atypia on excision, evading diagnostic accuracy even at experienced, high-volume centers. Given its difficulty of diagnosis and the substantial rate of sampling error, lesions suspicious for FEA in core-needle biopsy warrant full excision, consistent with current guidelines. Excision offers an opportunity to triage patients and determine the best course of further management.

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Statement of author contribution

LKW, BH, JL and EAS contributed to the study design. LKW, SL, YH, and BH contributed to the acquisition of data. LKW, DH, and EAS contributed to data analysis. LKW, SL, BH, DH, CR, JL, and EAS drafted the manuscript. Each author has made final approval of the manuscript. Furthermore, each author certifies that this material has not been and will not be submitted to or published in any other publication before its appearance in the *American Journal of Surgery*.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.07.020.

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