Indications for the surgical excision of fibroadenomas: systematic review

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Background: The differentiation between fibroadenomas and phyllodes tumors (PTs) is often difficult to establish based on core needle biopsy (CNB) alone due to similarities on pathologic evaluation and sampling error. Lesions for which a determination cannot be made are called fibroepithelial lesions (FELs). Since the surgical management of fibroadenomas and PT differ, we sought to determine the prevalence of PT on open surgical biopsy that were initially diagnosed to be fibroadenoma or FEL on CNB.

Methods: We combined an institutional chart review over a five-year period with a systematic review of the literature (2010–2020) to determine how many breast masses were upgraded to PT or other malignancy following surgical excision. A search of Cochrane, Scopus and Medline databases was performed using the following search terms: "fibroadenoma", "fibro adenoma", "fibroepithelial lesion", "fibro-epithelial lesion", "core needle biopsy", and "CNB with ultrasound". Individual studies were assessed for bias using the ROBIS (Risk of Bias in Systematic Reviews) tool.

Results: A total of 357 articles were retrieved from the databases; 45 additional articles were identified from references of relevant papers. A total of 273 unique articles were identified and reviewed for relevance; 14 articles met all criteria for inclusion in the review. Of the 1,908 CNB diagnosed as fibroadenoma or FEL that were surgically excised, the final pathology after open biopsy was fibroadenoma (n=1,409, 73.8%), PT (n=492, 25.8%), and other malignancy (n=7, 0.37%). If the CNB showed fibroadenoma, the negative predictive value (NPV) is 98%, whereas FEL on CNB has a NPV of 65%. Of all the PT resected, 86% were benign PT.

Conclusions: Fibroadenomas diagnosed on CNB rarely harbor malignancy and most of these lesions may be clinically observed. FELs diagnosed on CNB may also undergo clinical surveillance if less than 2 cm in size due to the low risk of PT. A limitation of our study is that all the data are derived from retrospective data.

Keywords: Core needle biopsy (CNB); excision; fibroadenoma (FA); fibroepithelial lesion (FEL); phyllodes tumor (PT)

Received: 27 August 2021; Accepted: 17 January 2022; Published online: 26 January 2022.
doi: 10.21037/asj-21-87
View this article at: https://dx.doi.org/10.21037/asj-21-87

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Introduction

Fibroepithelial lesions (FELs) of the breast microscopically demonstrate biphasic morphology with proliferation of both epithelial and stromal features (1). The differential diagnosis includes fibroadenomas (FA) and phyllodes tumors (PTs). FA are the most commonly diagnosed benign solid mass (2), while PTs are relatively rare and account for only 2–3% of FELs and 0.3–1% of all primary tumors of the breast (1). Although FA may be distinguishable from PTs by core needle biopsy (CNB), FA with stromal cellularity (3) are difficult to definitively diagnose histologically due to sampling limitations on core biopsy (1,4). Upgrade rates of FEL to phyllodes on final pathology in the literature ranges between 16% and 76% (5).

The two clinical entities of FA and PT are managed and treated very differently, based on their respective differences in clinical behavior. FA are benign lesions with an incidence of occult malignancy <1% and generally regress in size with increasing age, whereas PTs are locally aggressive and require resection with wide margins (6). There is not currently a uniform consensus in the literature regarding the management of masses diagnosed as FEL on CNB. In addition, among breast pathologists, the interobserver variation distinguishing between a diagnosis of FELs, FA, and PT is high with unanimous agreement of diagnoses in only 11% of cases (7). Since not all FA or FELs mandate surgical excision, the current standard of care at our institution recommends surgical consultation for FA and FELs that are >2.5 cm (8), are enlarging over a 6-month interval at follow-up for two years (9), or are causing the patient significant pain or emotional distress (10,11). Although the overall risk of complications associated with lumpectomy is low (<2%) (12), it is well-known that FA can be clinically followed given its benign natural history (13).

In this report, among those with a CNB diagnosis of FA or FELs at our institution, we sought to determine the prevalence of PT or other malignancy in the resected surgical specimens. The literature on the rate of upgrade to PT among patients with a CNB diagnosis of FA or FEL has been limited to case reports and single institution studies. To determine factors which favor selective excisional biopsy in order to avoid overtreatment with open surgery, we conducted a systematic review of the literature. We present the following article in accordance with the PRISMA reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-21-87/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by University of Texas Medical Branch Institutional Review Board (No. 19-0159) and individual consent for this retrospective analysis was waived.

Patient selection

We collected clinicopathologic data from the electronic charts (Epic v. 2017) of patients from December 1, 2015 to February 7, 2020 with a pathologic diagnosis of "FA" or "fibroepithelial lesion" on CNB and excisional biopsy. Exclusion criteria applied to the identified cases were: (I) FA found incidentally on final pathology during resection of a known malignancy; (II) FA found incidentally following breast reduction; (III) FA removed without CNB; (IV) lesions diagnosed as FA on excisional biopsy that received a different diagnosis on CNB; (V) lesions diagnosed on CNB with general terminologies including fibrocystic changes, benign breast tissue with fibroadenomatous changes, fibroadenomatoid change, stromal fibrosis, apocrine metaplasia, and adenosis; (VI) lesions on CNB with a definitive diagnosis of PT. Information abstracted from the charts included gender, age, and family history of breast cancer. When available, information regarding the mass size, clinical palpability, interval enlargement of the breast mass, and the Breast Imaging Reporting and Data System (BI-RADS) score were also collected. The recorded lesion sizes were obtained from radiology reports taken just prior to CNB. For those cases that proceeded to excision, the reason provided for open surgical biopsy was noted. A definitive diagnosis of PT on excisional biopsy was graded as benign, borderline, or malignant in accordance with the World Health Organization criteria (14).

Statistical methods

Statistical analyses were performed using GraphPad Prism version 8.4.3 for Windows, GraphPad Software (San Diego, CA, USA). Statistical analyses used included unpaired *t*-test and one-way ANOVA for continuous variables and Fisher's exact or Chi-squared tests for categorical variables. A P value of <0.05 was considered statistically significant. The negative predictive value (NPV) was calculated using the formula: true negative/(false negative + true negative).

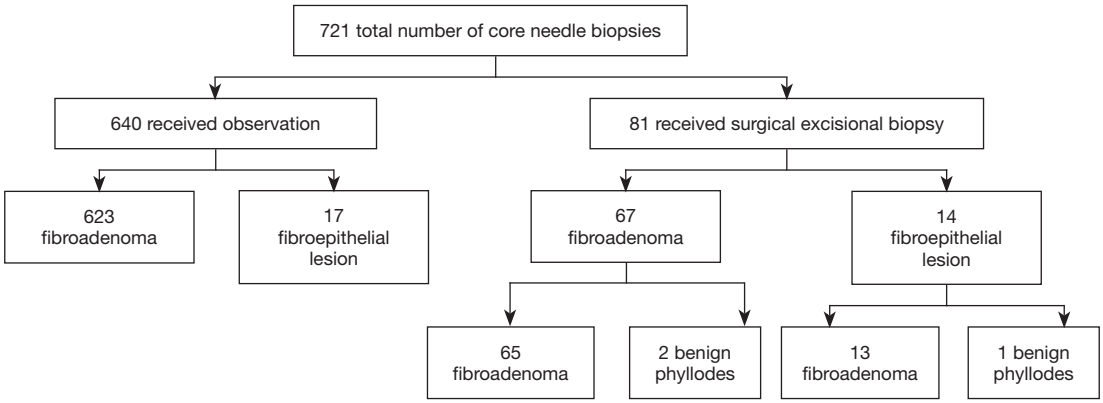

Figure 1 Distribution of core needle biopsy diagnoses and subsequent follow-up.

Systematic review

We utilized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000100) and included articles published in 2010 or later, and available in English. Additional inclusion criteria included the utilization of the triple test for breast mass evaluation and use of CNB to diagnose either FA or FEL. The information sources for this review were Cochrane, Scopus and Medline. A search of each of these databases was performed using the following search terms: "fibroadenoma", "fibro adenoma", "FEL", "fibro-epithelial lesion", "core needle biopsy", and "CNB with ultrasound". The last date of search was June 16, 2020. Two authors performed the systematic review (DP Gillette and C Chao). The references of selected articles were also subsequently searched for relevant articles. Articles identified by search terms were sorted for exclusion criteria based on title and abstract using Rayyan Qatar Computing Research Institute (Rayyan QCRI) (15). Individual studies were assessed for bias based on case selection criteria for each study using the Risk of Bias in Systematic Reviews (ROBIS) tool (16). Exclusion criteria were also developed based on the ROBIS tool. Since all papers evaluated were retrospective studies, biases due to study randomization and bias due to deviations from intended interventions did not apply to our review. Papers were evaluated for three major types of bias: bias due to missing outcome data, bias in measurement of the outcome, and bias in the selection of the reported result. Data collected from the studies included total number of FA or FEL found on CNB, number of patients monitored by observation only, number of patients treated with surgical excision and their final pathologic diagnoses. In our analysis, a CNB result of FA or FEL was grouped together as one category (FA/FEL). All PT diagnoses were grouped together for simplification. Additional data collected per paper included summaries of lesion size, patient age, family history, lesion palpability, interval size on follow-up if observed, and BI-RADS score when available. The summary measures collected were total percent of cases managed with observation versus surgical excision, and the percent of final pathologic diagnoses.

Results

Our institutional experience

A total of 721 CNBs were included in the retrospective review (*Figure 1*). These were lesions with a CNB diagnosis of FA or FEL. Among patients undergoing open biopsy for a core biopsy diagnosis of FA or FEL, the incidence of benign PT was 3/88 (3.4%; *Figure 1*); there were no cases of borderline or malignant PT. Two cases also reported atypia on initial CNB: one was excised with final pathology demonstrating FA and the other was monitored with observation (active surveillance with interval clinical breast exams and breast imaging studies) only. One case of FA on CNB displayed atypical ductal hyperplasia on final pathology. *Table 1* compares the patient and lesion characteristics between those who underwent excisional biopsy versus those who were followed clinically with observation only. Compared to patients being observed for a diagnosis of FA or FEL, those who had open biopsy were younger in age (P<0.0001), had larger lesions (P<0.0001), and were more likely to have enlarging (P<0.0001) and/or palpable masses (P<0.0001) with higher a BI-RADS score (P=0.02) on imaging. A family history of breast cancer was a

Table 1 Surgical excision versus observation among patients with core needle biopsy result of either fibroadenoma or fibroepithelial lesion

Characteristic	Intervention type		P value
	Surgical excision & CNB	CNB only	
Patients	72	602	–
Lesions	81	640	–
Age (years)			
Mean (± SEM)	29.4 (±1.5)	43.2 (±0.6)	<0.0001*
Range	14–65	14–83	–
Family history			0.686
Yes	25	162	
No	47	340	
Unknown	0	100	
Palpable			<0.0001*
Yes	65	234	
No/unknown	7	368	
Enlarging			<0.0001*
Yes	27	33	
No/unknown	45	569	
Lesion size (mm)			
Mean (± SEM)	30.6 (±1.5)	15.7 (±0.4)	<0.0001*
Median	30	13	–
Range	7.0–90.0	2.0–55.0	–
Unknown	0	20^	–
BI-RADS			
Unknown	3	1	–
≤3	4	7	0.0195*
≥4	65	594	
Follow-up (months)			
Mean (± SEM)	3.8 (±0.7)	18.2 (±0.8)	<0.0001*
Median	1	13	–

^, missing information; *, P<0.05. CNB, core needle biopsy; SEM, standard error of the mean; BI-RADS, breast imaging reporting and data system.

risk factor that was evenly distributed between patients who had conservative management (surveillance) and those who underwent open surgical biopsy (*Table 1*); most patients in either group had no family history of breast cancer.

Table 2 Clinicopathologic characteristics among patients with CNB diagnosis of fibroepithelial lesion

Characteristic	Intervention type		P value
	Surgical excision & CNB	CNB only	
Cases	14	13	–
Lesions	14	17	–
Age (years)			
Mean (± SEM)	33.9 (±4.2)	39 (±3.5)	0.360
Range	15–65	18–58	–
Family history			
Yes	6	3	0.700
No	8	8	
Unknown	0	2	–
Palpable			0.200
Yes	13	9	
No/unknown	1	4	
Enlarging			0.006*
Yes	7	0	
No/unknown	7	13	
Lesion size (mm)			
Mean (± SEM)	36.9 (±5.4)	17.6 (±1.9)	0.004*
Median	34	17	–
Range	10.0–90.0	7.0–34.0	–
BI-RADS =4	14	17	N.A.
Follow-up (months)			
Mean (± SEM)	5.9 (±2.0)	11.4 (±2.9)	0.140
Median	3	11	–

*, P<0.05. CNB, core needle biopsy; N.A., not available; SEM, standard error of the mean.

Among patients who were diagnosed with a FEL on CNB, 14 lesions (in 14 unique patients) were surgically excised, while 17 lesions (in 13 patients) were followed with observation (*Table 2*). The lesions followed with observation alone received CNB diagnoses of "FEL favoring FA" (n=14), FEL with "no definitive malignancy" (n=2), and "FEL with no in situ carcinoma or invasive carcinoma identified" (n=1). When the CNB diagnosis was a FEL, those who underwent open biopsy had larger (P=0.004) and enlarging tumors (P=0.006) compared to the observation group. The

Table 3 Reasons given for surgical excision following CNB and additional clinical characteristics

Reason for excision	Final pathology	
	Fibroadenoma (N=69 patients, 78 lesions)	Phyllodes tumor (N=3 patients, 3 lesions)
Positive family history, n (%)	7 (10.1)	0
Radiology recommendation, n (%)	4 (5.8)	0
Patient request, n (%)	21 (30.4)	0
Lesion size or lesion enlarging, n (%)	9 (13.0)	1 (33.3)
Pain, n (%)	19 (27.5)	0
Breast distortion, n (%)	2 (2.9)	0
CNB: atypical fibroadenoma, n (%)	5 (7.2)	1 (33.3)
CNB: complex fibroadenoma, phyllodes cannot be ruled out, n (%)	0	1 (33.3)
Reason not given, n (%)	2 (2.9)	0
Additional clinical characteristics		
BI-RADS ≤4, n (%)	65 (94.2)	2 (66.7)
BI-RADS 5, n (%)	0	1 (33.3)
Age (years), mean (± SEM)	29 (±1.4)	47 (±9.2)
Age ≥40 years, n (%)	16 (23.2)	2 (66.7)
Age range (years)	14–55	34–65
Tumor size (mm), mean (± SEM)	30.8 (±1.4)	59.3 (±20.7)
Tumor size (mm), range	7–90	32–100

CNB, core needle biopsy; BI-RADS, Breast Imaging Reporting and Data System; SEM, standard error of the mean.

difference between positive and negative family history of breast cancer was also not significant between these groups. Family history was unavailable for two of the patients who were clinically observed. The palpability of these lesions was also not significantly different between the excision and observation groups. All lesions diagnosed as FEL on CNB received a BI-RADS score of 4 (*Table 2*).

Table 3 summarizes the justification provided for open excisional biopsy of breast lesions diagnosed on CNB as FA (n=66) and FELs (n=14). Among patients with "FA" on final pathology, patient request (30.4%, which includes alleviation of emotional distress) and breast pain (27.5%) were the most common reasons. The reasons for open surgery in 39% of patients included large or enlarging size, positive family history, increased risk of malignancy noted by the pathologist on CNB, radiologist recommendation, or breast distortion due to mass effect. Additional comments such as "stromal fibrosis", "ductal hyperplasia", "increased cellularity", and "stromal condensation" on CNB of lesions identified as FA were associated with lesions that were surgically excised. Each of the three phyllodes cases on final pathology had a different reason for excision: (I) large or enlarging size for a FEL; (II) radiology report of "increased risk of malignancy" after CNB reported "atypical FA"; and (III) a CNB indicating "complex FA, phyllodes could not be ruled out" (*Table 3*). Radiologically, all the lesions were BI-RADS 4 or 5 preoperatively. Among the FA which were excised, 96% (75/78 tumors) were BI-RADS 4. There were two lesions deemed BI-RADS 2, one was BI-RADS 3 and no BI-RADS 5 lesions. Radiologic terms that were associated with excised lesions were "irregular margins", "asymmetry", "hypoechoic solid mass", "microlobulated margins", "circumscribed margins", "coarse calcifications", and "posterior enhancement".

Systematic review

The outcome measure for inclusion into the review is the

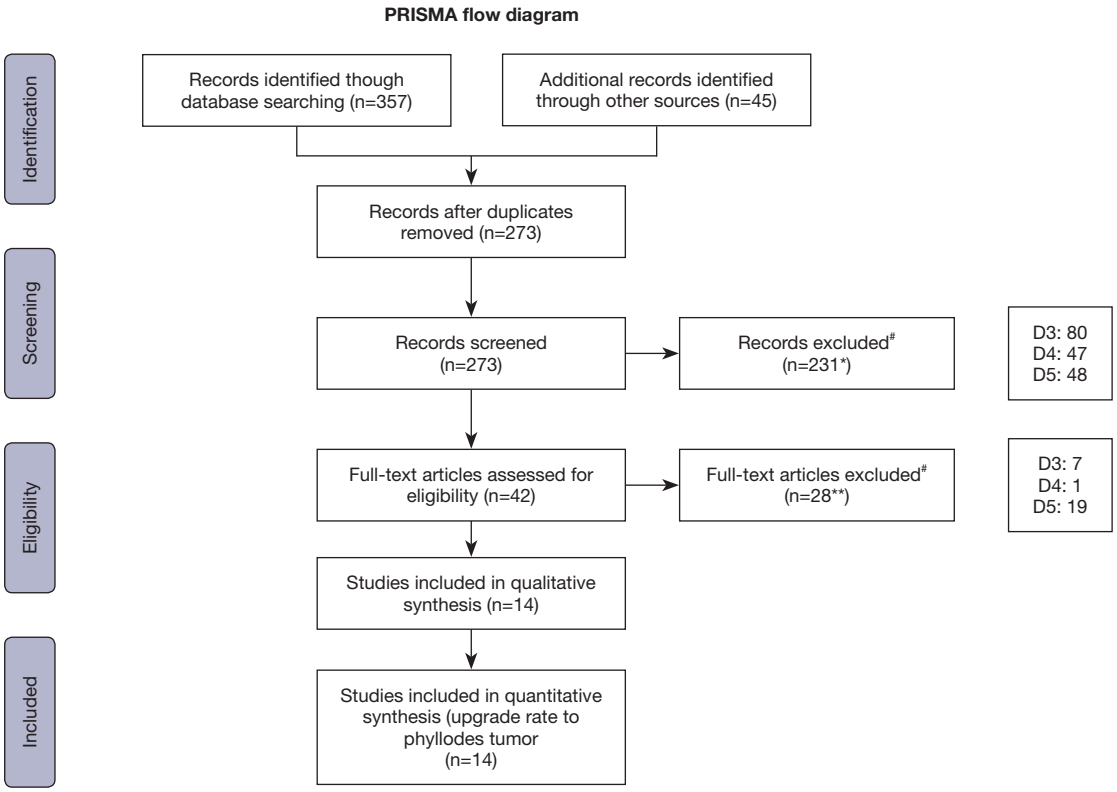

Figure 2 Systematic review article selection flow chart. *, 56 articles were excluded due to publication date older than 2010; two articles were excluded due to being available only in foreign languages; **, one article excluded due to publication date older than 2010; #, excluded articles risk of bias: domain 3 (D3), bias due to missing outcome data; domain 4 (D4), bias in measurement of the outcome; domain 5 (D5), bias in selection of the reported result.

upgrade rate to PT of all high risk (tumor size, clinical concern, pathologic notes of concern, radiology note of a discordant result), non-diagnostic core needle biopsies (FA or FEL). A total of 357 articles were retrieved from Medline (n=141), Cochrane (n=2), and Scopus (n=214). An additional 45 articles were identified from references of relevant papers. From these two searches, a total of 273 unique articles were identified and reviewed for relevance based on the title and abstract. The exclusion criteria applied were case studies, pathology other than FA or FEL on CNB, studies limited to a subset of FA types (i.e., giant FA), studies that evaluated fine-needle aspiration, studies evaluating surgical or biopsy techniques, studies evaluating only clinical outcomes (such as postoperative complications or re-excision surgery), those that did not have a surgical excision group, those that did not have an observation group, and papers which focused only on pathological or radiological differentiation of benign breast disorders. Following the application of the screening exclusion criteria, 231 articles were eliminated. The full text of 42 remaining articles were reviewed for relevance. We eliminated papers for bias if only the final pathology was used for selection of cases (n=4), only imaging criteria was used (n=1), lacked surgical excision (n=3), lacked final diagnoses or original CNB pathology (n=5), fine needle aspiration biopsy (FNA) was used as the sampling method (n=3), included patients without initial CNB (n=2), and included CNB of lesions other than FA or FEL (n=9). One paper was excluded because it was only available in Spanish. Of all articles identified, 87 were eliminated for bias due to missing data (risk of bias domain 3) such as exclusion of CNB results. We eliminated 48 papers due to bias in measurement of the outcome (domain 4); for example, papers featuring outcomes in a pediatric patient population or papers that did not report the pathology result after surgical excision. Finally, 67 studies were excluded due to bias in the selection of the reported result (domain 5), such as inclusion of CNB result of a PT. Fourteen articles met inclusion criteria for data extraction (*Figure 2*).

Table 4 Risk of Bias for papers included in the systematic review*

Paper	D3	D4	D5
Edwards *et al.* 2016, (17)	++	–	+
Neville *et al.* 2018, (18)	++	–	+
Al-Arnawoot *et al.* 2020, (19)	+	–	+
Gould *et al.* 2012, (20)	+	–	+
Jung *et al.* 2018, (21)	+	–	+
Limberg *et al.* 2020, (22)	+	–	+
Marcil *et al.* 2017, (12)	+	–	+
Mimoun *et al.* 2020, (23)	+	–	+
Resetkova *et al.* 2010, (24)	+	–	+
Van Osdol *et al.* 2014, (25)	+	–	+
Yasir *et al.* 2014, (26)	+	–	++
Wirakapun *et al.* 2014, (3)	+	–	+
Dialani *et al.* 2019, (27)	–	–	+
Durhan *et al.* 2019, (28)	–	–	++
Gillette *et al.* 2021 (current study)	–	–	+

Domains: D1, bias arising from the randomization process (N/A); D2, bias due to deviations from intended interventions (N/A); D3, bias due to missing outcome data; D4, bias in measurement of the outcome; D5, bias in selection of the reported result. *, key: (–), no identified risk of bias; (+), low risk of bias; (++), some risk of bias.

Table 4 summarizes the levels of concern for bias of papers included in the systematic review. Bias arising from the randomization process (domain 1) and bias due to deviations from intended interventions (domain 2) were not included in the table as these types of bias are not applicable to retrospective studies. For bias due to missing outcome data (domain 3), studies received a "low concern for bias" score if they excluded FA found on CNB and a "some concern for bias" score if FEL on CNB were excluded from the study. The exclusion of FEL decreases the likelihood that a PT will be found on final excision, and therefore increases risk of bias. None of the included articles were found to have risk of bias in the measurement of the outcome (domain 4) as all used the same outcome measures as our study. All included studies were determined to have a "low concern for bias" in bias in the selection of the reported result (domain 5) due to the nature of retrospective chart reviews. Papers that received "some concern for bias" included PT discovered on CNB in their analysis as these lesions were known malignancies. Of note, PT found on CNB were excluded from our analyses.

A summary of the data extracted from the selected papers is shown in *Table 5*. The paper by Edwards *et al.* (17) included all core biopsies with a pathologic description of "cellular" FA; the paper by Neville *et al.* (18) retrospectively reviewed cases that were ≥3 cm in size. Dialani *et al.* (27) patient population were those with enlarging breast FA/or FEL. Durhan *et al.* (28) paper included all FA and FEL that had concerning pathologic terms on CNB such as "complex FA", "cellular FA. As expected, when the CNB was "FA", less than 9% of patients underwent open surgical biopsy, whereas among patients with "FEL", over 42% of patients had surgical excision of the breast mass. Also, not surprisingly, only 1.6% of patients with FA on CNB revealed a final definitive diagnosis of PT and 1.3% with a diagnosis of malignancy [e.g., ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and high-risk biomarker lobular carcinoma in situ (LCIS)]. However, 35% of those diagnosed as FEL on CNB were found to have PT at open surgical biopsy and only 0.22% other breast malignancies (adenosquamous cancer and LCIS biomarker). Papers that included both diagnoses together (FA or FEL) on CNB underwent open biopsy in 21% with a definitive diagnosis of PT in 5.8% of those who underwent lumpectomy. Finally, among all PT diagnosed at lumpectomy, when pathology results were reported (n=360), 311 (86%) were benign PT and 49 (14%) borderline or malignant PT (*Table 5*).

Because the outcome measure (upgrade rate) is a diagnostic test, we calculated the NPV of a CNB result of FA or FEL. Since we excluded all CNB results of "PT", we cannot calculate true positive or false positive results. Including all core biopsies of either FA or FEL for all the studies in *Table 5*, the NPV is 74% for upgrade to PT. If the CNB is FEL, the NPV is lower at 65%; if the CNB is FA, the NPV is 98%. We were not able to calculate NPV by tumor size as that information was sporadically available among the included articles.

Discussion

Although FA and PTs generally have different clinical presentations, the radiologic findings and CNB results overlap and are not easily distinguishable to diagnose these breast lesions with sufficient accuracy (29). FA are asymptomatic in 25% of women (2). The typical symptomatic presentation occurs in 20- to 30-year-old

Table 5 Systematic review of papers with core needle biopsy showing fibroadenoma or fibroepithelial lesion with subsequent open surgical biopsy

Author	Total CNBs	Observation only, n (%)	Surgical excision, n (%)	Final diagnosis PT*, n (%)	Final diagnosis FA, n (%)	Final diagnosis other (malignant or LCIS), n (%)
Fibroadenoma on core needle biopsy						
Edwards *et al*. 2016, (17)	81	60	21	2 (9.5)	17 (81.0)	2 (9.5)
Neville *et al*. 2018, (18)	3,438	3,148	290	3 (1.0)	285 (98.3)	2 (0.7)
Total	3,519	3,208 (91.2)	311 (8.8)	5 (1.6)	302 (97.1)	4 (1.3)
# Benign *vs.* borderline or malignant phyllodes[a]				5 *vs.* 0		
Fibroepithelial lesion on core needle biopsy						
Al-Arnawoot *et al*. 2020, (19)	134[1]	0	134	45 (33.6)	89 (66.4)	0
Gould *et al*. 2012, (20)	123	18	105	40 (38.1)	65 (61.9)	0
Jung *et al*. 2018, (21)	169	17	152	92 (60.5)	60 (39.5)	0
Limberg *et al*. 2020, (22)	252	50	202	62 (30.7)	137 (67.8)	3 (1.5)
Marcil *et al*. 2017, (12)	74	26	48	18 (37.5)	30 (62.5)	0
Mimoun *et al*. 2020, (23)	1,413	1,109	304	113 (37.2)	191 (62.8)	0
Resetkova *et al*. 2010, (24)	101	58	43	13 (30.2)	30 (69.7)	0
Van Osdol *et al*. 2014, (25)	313	238	75	22 (29.3)	53 (70.7)	0
Yasir *et al*. 2014, (26)	64	0	64	27 (42.2)	37 (57.8)	0
Wiratkapun *et al*. 2014, (3)	531[2]	318	213	40 (18.8)	173 (81.2)	0
Total	3,174	1,834 (57.8)	1,340 (42.2)	472 (35.2)	865 (56.5)	3 (0.2)
# Benign *vs.* borderline or malignant phyllodes[a]				291 *vs.* 49		
Fibroadenoma or fibroepithelial lesion on core needle biopsy						
Dialani *et al*. 2019, (27)	247	201 (81.4)	44 (17.8)	1 (2.3)	43 (97.7)	0
Durhan *et al*. 2019, (28)	253	121 (47.8)	132 (52,2)	11 (8.3)	121 (91.7)	0
Gillette *et al*. (current data)	721	640 (88.8)	81 (11.2)	3 (3.7)	78 (96.3)	0
Total	1,221	962 (78.8)	257 (21.0)	15 (5.8)	242 (94.2)	0 (0.0)
# Benign *vs.* borderline or malignant phyllodes[a]				15 *vs.* 0		
Total	7,914	6,004 (75.9)	1,908 (24.1)	492 (25.8)	1,409 (73.8)	7 (0.4)
# Benign *vs.* borderline or malignant phyllodes[a]				311 *vs.* 49		

[1], 134 lesions in 131 patients; [2]531 lesions in 518 patients; *, PT includes all grades: benign, borderline, malignant. Some papers do not report the specific grade; [a], when grade reported. CNB, core needle biopsy; PT, phyllodes tumor; FA, fibroadenoma; LCIS, lobular carcinoma in situ.

females as a single, firm mobile mass (2). FA are hormonally sensitive and therefore may become symptomatic with menstrual cycle, pregnancy and lactation (2). Only 44% of FA occur in post-menopausal women, and these tend to calcify and/or involute following menopause (2). Conversely, PTs more commonly have a symptomatic presentation as a firm mass with rapid, painless growth during the first 6 months of tumor development (2). Phyllodes also characteristically presents in older females from 40 to 50 years old (2), which was also confirmed in our patient series (*Table 3*). There is a lack of universal consensus regarding removal of lesions based on size and/or pathologic

features because objective criteria for histologic grading, radiologic and clinical features to distinguish between FA and PT overlap.

FA can be clinically observed safely due to low incidence (0.1% to 0.3%) (30) with a relative risk of 1.6–2.6 (1) of carcinoma arising in FA; there is no evidence to suggest that FA undergo malignant transformation (1). PTs carry a risk of malignant, specifically sarcomatous, transformation (2). The risk of local recurrence for PTs increases with aggressive histology: 3% to 27% for benign, 18% to 42% for borderline and 13% to 53% for malignant (1). Recurrence occurs most commonly within 2 to 3 years of resection (1). Borderline and malignant PTs require at least a one-centimeter margin of resection (1,2) to reduce the risk of local recurrence. Borderline and malignant PTs also carry a small risk of metastasis (31) to lung and bone.

For our patient population, after counselling that non-operative surveillance is an appropriate option, the most common reasons for excision were patient request due to breast pain (27.5%) and patient preference (30.4%). As a tertiary care teaching hospital, we serve many patients who are under-resourced with regard to access to full medical care. However, we do have a robust breast cancer surveillance and diagnostic breast imaging program. Since close surveillance and non-operative management is less popular among our patient population, our denominator is larger and thus our upgrade rate to PT was lower at 3.7% (3/81) after open surgical biopsy, compared to other single institution studies (*Table 4*).

The systematic review of the current literature revealed a total of 7,904 lesions diagnosed as FA or FEL on CNB; 1,908 (24.1%) were surgically excised. Among all the surgically excised lesions, there were 1,409 FA (73.8%), 493 PTs (25.8%), and seven with other pathology (0.4%) including FA containing IDC, LCIS, or DCIS. Our findings of malignant pathology in a FA (<1%) is consistent with the literature (18,27). If the CNB result was described as a FEL, a final diagnosis of PT was higher at 35% (*Table 5*).

The risk of surveillance of FELs has been less well-characterized compared to surveillance of FA, but it is known that only 2–3% of all FELs are PTs (32). Limberg *et al*. (22) reported the natural history of 50 FELs on CNB which were followed for a median of 17 months. Most lesions remained stable or decreased in size; among the 35% of cases that increased in volume ≥50%, three cases were FA and one was found to be a benign PT at delayed excisional biopsy (22). Van Osdol *et al*. (25) reported on 261 patients with a CNB of FEL who were followed with active surveillance (mean of 8 years); delayed open biopsy was performed for interval size enlargement in 23 patients. Among these, three patients (1%) were diagnosed with benign PTs after excision; two patients underwent excision at 6 months follow-up and one patient had surgical excision at 18-month follow-up (25).

As shown in *Table 5*, among all the resected lesions that were upgraded to PT, 86% were benign and only 14% were borderline or malignant. Thus, the majority upgraded PTs could be clinically monitored with interval imaging, especially the smaller lesions. Gould *et al*. (20) recommended "short term radiographic follow up" for lesions <3 cm. Although Van Osdol *et al*. (25) and Resetkova *et al*. (24) do not offer size recommendations for resection, they generally recommend observation of FEL diagnosed on CNB due to the high prevalence of a benign PT finding, 95% and 100%, respectively. Based on our systematic review, if the CNB showed FA, the NPV is 98%, whereas FEL on CNB has a NPV of 65%. The combined NPV for either FA or FEL is 74%.

Together, these findings suggest that most FA and small FELs (≤2 cm) which are BI-RADS 2 lesions can be safely observed; lesions designated as BI-RADS category 3 can undergo imaging and clinical surveillance at 6, 12, and 24 months to ensure size stability. If there is a >20% size increase on repeat imaging, the BI-RADS assessment would change to category 4 and a delayed excisional biopsy would be recommended for diagnosis. The surgical treatment of FA or benign PT is resection without specific margin criteria, whereas borderline or malignant PT should undergo wide local excision to reduce the risk of recurrence.

Our study includes a systematic review which can better address the research question of the upgrade rate to PT for core needle biopsies of breast FA/FEL. However, a major limitation of our study is that all the data are derived from retrospective data. Both the radiographic and pathologic terminologies have not undergone central review and can be subject to misclassification and/or lack of uniformity of inclusion criteria. The studies included are heterogeneous in many ways: (I) radiographic features are not consistently documented; (II) follow-up data to evaluate outcome of surveillance patients are missing from many of the papers; (III) the reasons for surgical intervention are not always clearly documented or defined.

Conclusions

Educating patients on the natural history of FA when

a CNB confirms the diagnosis in conjunction with an active surveillance program will reduce unnecessary open excisional biopsies. Open excisional biopsy is indicated if (I) a core biopsy result is a "FEL" and >2 cm and has a BI-RADS category of 4; (II) there are pathologically concerning descriptors such as "atypia", stromal cellularity (15), or other comments of concern; or (III) the breast mass is enlarging on serial ultrasound or clinical exams. Lastly, patient preference is also a very important piece in the decision to offer surgical excision; some patients experience emotional distress during follow-up of a palpable mass and are risk-adverse to any aspect of histologic "uncertainty" (i.e., increasing tumor size in the future or sampling error from a CNB).

Acknowledgments

We thank Ms. Julie Trumble and Dr. Bret Howrey for their assistance with the systematic review, and Ms. Eileen Figueroa and Mr. David Chavarria for preparation of the manuscript.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-21-87/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-21-87/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by University of Texas Medical Branch Institutional Review Board (No. 19-0159) and individual consent for this retrospective analysis was waived.

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doi: 10.21037/asj-21-87

Cite this article as: Gillette DP, He J, Lee AE, Chao C. Indications for the surgical excision of fibroadenomas: systematic review. AME Surg J 2023;3:3.