Clinical Imaging 57 (2019) 35–39

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Breast Imaging

Enlarging biopsy-proven fibroadenoma: Is surgical excision necessary?

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ARTICLE INFO

Keywords:
Fibroadenoma
Enlarging
Biopsy proven

ABSTRACT

Purpose: Core biopsy-proven fibroadenomas that enlarge on clinical or imaging follow-up are often surgically excised to exclude an associated malignancy. The purpose of this study was to assess how often malignancy is detected upon excision, and to determine whether excision of enlarging, biopsy-proven, uncomplicated fibroadenomas is still warranted.

Materials and methods: Review of our institutional pathology database from 2000 to 2010 identified 1117 cases of fibroadenoma, and retrospective chart review, including review of pathology and imaging findings of all these records, was performed.

Results: 1117 cases of fibroadenoma were identified in a population of women ranging from ages 17 to 78. Of these, 378 (33.8%) were diagnosed by ultrasound core needle biopsy and formed the study population. Of the 378 cases, 24 (6.3%) had co-existent atypia and were immediately excised; these cases were excluded. An additional 107 (28%) were lost to follow-up. Of the remaining 247 cases, 201 (81%) showed stability on follow-up imaging (mean 31.5 months), and 46 (18.6%) enlarged on follow-up. Of the 46 biopsy proven fibroadenomas that enlarged, 19 had a biopsy at initial presentation and 27 underwent biopsy after they enlarged. Seventeen of the 19 were excised after enlargement, and pathology confirmed fibroadenoma in all cases (100%); two enlarged on initial follow-up imaging but remained stable for at least three years on continued follow-up. Of the 27 cases which were biopsied after enlargement, 23 revealed fibroadenoma on core biopsy, 3 had fibroadenoma with associated atypia with subsequent surgery revealing fibroadenoma and no associated malignancy, and one showed fibroadenoma with smooth muscle with subsequent surgery showing phyllodes tumor.

Conclusion: Based on this study, enlarging biopsy proven fibroadenomas are not associated with malignancy; therefore, surgical excision does not seem warranted. For presumed enlarging fibroadenomas on imaging, core biopsy should be performed to exclude associated atypia or phyllodes tumor. Finally, surgical excision is indicated for lesions with associated atypia or suspected phyllodes and for symptomatic lesions or cosmetic reasons.

1. Introduction

Fibroadenoma, a benign proliferative tumor of the breast comprised of stromal and epithelial elements, has a reported incidence of 7–13% in the general population [1,2]. More commonly seen in premenopausal and perimenopausal women, up to 20% present with multiple and bilateral fibroadenomas [3,4]. Multiple studies of the natural history of fibroadenomas suggest that these tumors often undergo self-limited

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https://doi.org/10.1016/j.clinimag.2019.03.014
Received 28 August 2018; Received in revised form 8 March 2019; Accepted 26 March 2019
0899-7071/

growth during the second and third decades due to exogenous hormones, pregnancy, or other hormonal fluctuations, usually stabilizing in size between 1 and 3 cm over the course of several years [3–5], thereby suggesting that not all women ought to be treated surgically [6]. However, when there is a fibroepithelial lesion with increased stromal elements on core biopsy, phyllodes tumor remains in the differential, and in these circumstances, surgical excision is advised [7,8].

Given that a minority of biopsy-proven fibroadenomas enlarge, they pose a management dilemma given concerns of malignancy or misdiagnosis of phyllodes tumor [2,3,6]. Recent literature now suggests that fibroadenomas with associated atypia and even complex fibroadenomas – those with associated sclerosing adenosis, papillary apocrine metaplasia, cystic changes greater than 0.3 cm or epithelial calcification – may not need excision [8–11] as the incidence of malignancy is very low, estimated to be around 0.002–0.00125% [6,12–15].

Some practices still recommend excision for an enlarging, biopsy-proven, benign mass out of concern for malignancy. However, this recommendation has come into question as a recent study of 83 enlarging fibroadenomas failed to reveal malignancy and suggests that repeat core biopsy may be sufficient [11]. However, this study had a majority of its patients lost to follow-up limiting its applicability to practice. Another study recently suggested that less than 20% mean change in size over six months is not worrisome and is consistent with hormonally-induced size fluctuations [16].

Therefore, given that our practice serves a compliant patient population, we undertook this study to assess how often malignancy is detected upon excision for enlarging core biopsy-proven fibroadenomas and to determine whether excision of enlarging biopsy-proven uncomplicated fibroadenomas is actually warranted.

2. Materials and methods

Through an online search of the institution's pathology records, this retrospective IRB-approved, HIPAA-compliant study identified 1117 benign breast biopsies revealing fibroadenoma diagnosed at our Institution from January 2000 through December 2010. From this dataset, the online radiology records were cross-referenced, identifying 378 cases of biopsy-proven fibroadenomas that were diagnosed by ultrasound-guided percutaneous core biopsy. For these 378 cases, clinical, radiological, and pathological data were recorded. Specific parameters included: patient age; risk factors for breast cancer including personal history of prior breast cancer, family history of breast cancer, age at menarche, age of first full-term pregnancy (if applicable), and history of exposure to exogenous hormones; modality-specific imaging features including size on presentation and on follow-up (range 2–10 years); mode of biopsy, device and number of biopsies; and available pathology (including initial core biopsy diagnosis and surgical pathology, if available). For lesions with interval enlargement, lesion volumes and percentage change were recorded. In addition, blinded to final surgical pathology, co-investigators reviewed the imaging and core pathology to ensure that the diagnosis of fibroadenoma was concordant with the initial imaging finding. Findings were then correlated with final pathology for those that underwent surgical excision. Women who had associated atypia or malignancy at initial biopsy or who did not undergo clinical or imaging follow-up at our institution were excluded from the final analysis.

2.1. Definitions

2.1.1. Classic imaging features of a fibroadenoma

Well circumscribed, round or oval, homogenously hypoechoic or isoechoic solid mass, parallel to the chest wall with smooth margins and no posterior shadowing.

2.1.2. Cellular fibroadenoma

Fibroadenomas with increased stromal cellularity described as such on the pathology report. Cellular fibroadenomas were excised subsequent to enlargement at our institution, given difficulty to distinguish these from phyllodes tumor.

2.1.3. Complex fibroadenoma

Fibroadenomas associated with sclerosing adenosis, papillary apocrine metaplasia, cystic changes greater than 0.3 cm or epithelial calcification.

2.1.4. Uncomplicated fibroadenomas

Fibroadenomas with no association of atypia, smooth muscle, fibroepithelial lesion or phyllodes tumor on core biopsy.

2.1.5. Upgrade

Presence of malignancy, atypia, smooth muscle, fibroepithelial lesion or phyllodes tumor on core biopsy after enlargement or surgical excision, was considered as an “upgrade”.

2.2. Imaging parameters

Imaging was performed on dedicated breast ultrasound units (Philips IU-22, Amsterdam, Netherlands) using 12.5 MHz or 17 MHz linear array transducers by one of ten MQSA-certified fellowship-trained breast radiologists with over five years of clinical experience. Lesions were scanned in orthogonal planes and three dimensions were recorded from which lesion volume was calculated. Patients undergoing follow-up imaging, whether initially or subsequent to core biopsy were imaged at 6, 12, and 24 months. In order to assess for growth, comparison of three-dimensional measurements and percentage of change was calculated for all lesions.

2.3. Biopsy methods and tissue processing

All ultrasound-guided core biopsies were performed by board-certified fellowship-trained breast radiologists (range 1–15 years of experience) using either a 14-guage co-axial spring-loaded device (n = 372) or an 11-gauge vacuum device (n = 6). The median number of core specimens was 5 (range 3–6). The tissue specimens were formalin-fixed and processed according to the 2007 CAP/ASCO guidelines. Three 5 μm thick sections were examined for each paraffin-embedded tissue block as per the standard microtomy protocol for breast needle core biopsies at institution.

2.4. Statistical analysis

Statistical analysis was performed using statistical software (Stata and MATLAB) and Microsoft Excel. P-values for growth rate vs. other variables were calculated using Mann–Whitney test. P-values for upgraded cases vs. other variables were calculated using Fisher exact test. The volume growth rate was determined as $(V2 - V1)/t$, where $V1$ is the volume at the previous visit (cm^3), $V2$ is the volume at the subsequent visit (cm^3), and t is time in years.

3. Results

The 1117 cases of fibroadenoma were identified in women aged 17 to 78 years (mean = 34 years: median = 42 years). Of these, 378 (33.8%) were diagnosed by ultrasound-guided core needle biopsy, and formed the study population. 201 of 378 (53.2%) had a biopsy at initial imaging, and follow-up imaging showed stability in size for a mean period of 31.5 months. 107/378 (28.3%) were not followed or were lost to follow-up after the initial biopsy. 24/378 (6.3%) demonstrated atypia at initial biopsy, and 18/24 (75%) underwent excisional biopsy with the following results: DCIS (3), LCIS/ALH (6), ADH (5), phyllodes

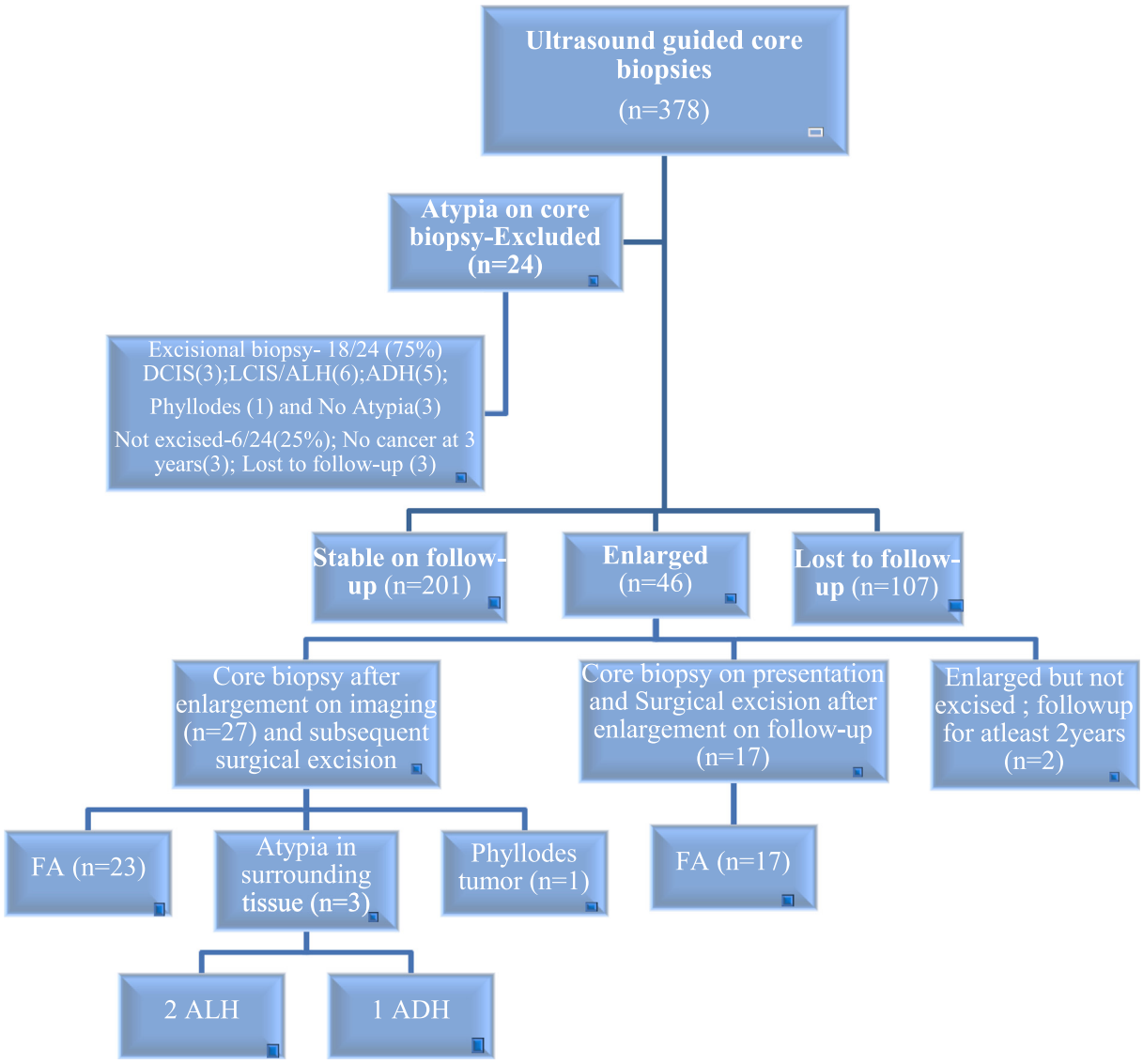

Fig. 1. Study population.

tumor (1), and no atypia (3). 6/24(25%) were not excised; 3/6 were lost to follow-up and 3/6 showed no cancer at 3 year follow-up. The remaining 46/378 (12.2%) cases were enlarging fibroadenomas and were studied in detail. These 46 cases (mean age: 37 ± 11.5), fell into two groups based on the timing of the core biopsy: biopsy performed immediately after initial imaging and biopsy performed based on documented growth on follow-up and formed the study population (Fig. 1).

Of the 46 enlarging fibroadenomas, 19/46 (41.3%) had a core biopsy confirming fibroadenoma immediately following initial imaging, and then enlarged on clinical/imaging follow-up. 17 of these 19 were excised with pathology confirming fibroadenoma in all 17/17 (100%) cases. 2/19 were not excised despite their initial growth, but demonstrated stability in size during subsequent continued follow-up periods of 36 and 47 months; to date, neither patient has been diagnosed with an associated malignancy. The remaining 27/46 (58.7%) were presumed fibroadenomas based on classic initial imaging features, but were biopsied when enlargement was documented on clinical/imaging follow-up and subsequently excised given enlargement, to rule out malignancy. Upon subsequent biopsy, 1/27(3.7%) of these lesions revealed "Fibroepithelial lesion with increased stromal cellularity" on core biopsy, and excision revealed benign phyllodes tumor (Fig. 2). 3/27 (14.8%) showed fibroadenoma on core biopsy with associated atypia upon excision (2 ADH/1 ALH). 23/27 (81.4%) were benign fibroadenomas on both core biopsy and excision (Fig. 2). 2/23 (8.6%) were cellular fibroadenomas on core biopsy and did not show an "upgrade" on excision.

Majority of the masses were hypoechoic (43/46; 93.5%), well circumscribed (42/46; 91.3%), oval (37/46; 80.4%), avascular (31/35, 88.6%) with posterior acoustic enhancement (39/40, 96%).

Growth rate was not significantly different between upgraded and not upgraded cases (median 2.7 cm3/year [IQR 0.4–5.0] for upgraded vs. 0.76 [IQR 0.23–4.32] for no upgrade, P = 0.45). Upgrade was dependent on margins (P = 0.0007) and menopausal status (P = 0.05). Post-menopausal status and not well circumscribed (microlobulated and indistinct) margins were associated with an upgrade (Table 1). There was no significant relation of growth rate to menopausal status, shape, vascularity, presence or absence of calcifications (Table 2).

4. Discussion

Pathology-proven fibroadenomas that remain unchanged in size, or that decrease in size over time, typically do not require any surgical intervention; however, fibroadenomas, more commonly in younger

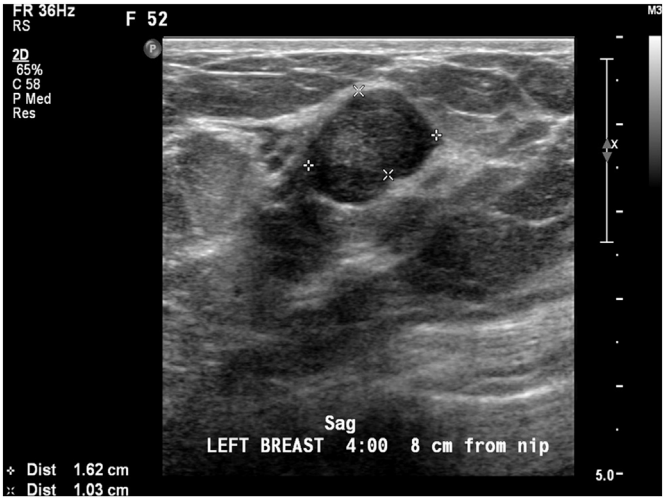

Fig. 2. 52 year old women presented with a palpable mass showing a well circumscribed, oval, lobulated hypoechoic mass, measuring 2.2 × 1 × 1.6 cms. Ultrasound guided core biopsy showed a "Fibroadenoma". Subsequently three years later the patient presented with enlargement of the biopsy proven fibroadenoma. Ultrasound showed the mass to now measure 2.9 × 2.5 × 2.5 cms. Ultrasound guided core biopsy subsequently showed "Fibroepithelial lesion with increased stromal cellularity" and excision was recommended. Surgical excision showed a "Benign phyllodes tumor".

women, can sometimes grow over time, with estimates of upwards of 18% demonstrating increase in size on follow-up [16,17]. Enlarging fibroadenomas at some institutions are routinely surgically excised if they enlarge on clinical or imaging follow-up in order to exclude the presence of associated malignancy [2,6]. In our study of 378 women with biopsy-proven fibroadenomas, 46 (13.3%) enlarged over time with an average growth of 2.03 cm^3/year. At our institution, a majority of the enlarging biopsy proven fibroadenomas were ultimately surgically excised revealing no malignancies, although one benign phyllodes tumor was discovered. However, in this case, the core biopsy after enlargement showed the presence of smooth muscle, which is an unusual finding for a fibroadenoma, and prompted surgical excision given the atypical features. Although relatively rare, the only circumstances where malignancy was uncovered within or in the adjacent tissue to the biopsy-proven fibroadenoma were in cases where atypia was also found at initial core biopsy. Therefore, if atypia is present on core biopsy of a fibroadenoma, immediate surgical excision should be performed rather than imaging or clinical follow up so as to enable appropriate patient management.

Table 2
Median growth rate vs. ultrasound features. P-values calculated using Mann-Whitney test.

Features		Count	Median growth rate	P-value
Margin	Not well circumscribed, microlobulated	3	2.69	0.58
	Well circumscribed	42	0.75	
	Indistinct	1	4.24	
Pattern	Heterogeneous	3	0.53	0.41
	Hypoechoic	43	0.81	
Shape	Irregular	6	0.91	0.91
	Oval	37	0.74	
	Round	3	1.16	
Calcifications	Absent	43	0.76	0.74
	Coarse	3	1.38	
Vascularity	No	31	0.88	0.45
	Central	1	3.67	
	Peripheral	3	0.19	
Menopausal status	Premenopausal	42	0.64	0.26
	Postmenopausal	4	2.84	

Conservatism is generally the acceptable rule in women under the age of 25 years if a fibroadenoma is not increasing in size or not cosmetically problematic [18]; however, the literature suggests that it is prudent to regard all enlarging fibroadenomas of the breast occurring in patients over 40 years of age as potentially malignant. These studies most often recommend that these lesions be examined histologically with care, particularly since sarcomatous change may be present in one part only and therefore could be easily overlooked. In a systematic review of seven studies by El-Wakkel, the author concluded that core biopsy may be a better option than surgical excision for diagnosis of fibroadenomas [19]. Our study showed that about 11% of growing fibroadenomas are associated with atypia or phyllodes tumor and 6.3% showed atypia at the initial diagnosis. Therefore, core biopsy of a presumed fibroadenoma especially if they are enlarging in a women over 40 seems a wise decision [20].

The surgical literature over the past 20 years suggests the relative risk of a fibroadenoma is 1.48–1.7 without hyperplasia, 3.47–3.7 with hyperplasia, and 6.9–7.29 with hyperplasia and atypia [21–27]. Though some authors have recommended excision of enlarging fibroadenomas without delay [2], core biopsy may be a better option in diagnosis of an enlarging biopsy-proven or enlarging presumed fibroadenoma. As shown in this study, immediate surgical excision should only be performed if the core biopsy shows associated atypia or

Table 1
Summary statistics of ultrasound features for upgraded versus not upgraded subgroups. P-values calculated using Fisher exact test.

Features	Upgrade	Counts			P-value
Margin		Not well circumscribed, microlobulated	Well circumscribed	Indistinct	0.00066
	Upgrade	3	2	0	
	No upgrade	0	40	1	
Pattern		Heterogeneous	Hypoechoic		0.3
	Upgrade	1	4		
	No upgrade	2	39		
Shape		Irregular	Oval	Round	0.15
	Upgrade	2	3	0	
	No upgrade	4	34	3	
Calcifications		Absent	Coarse		1
	Upgrade	5	0		
	No upgrade	38	3		
Vascularity		No	Central	Peripheral	1
	Upgrade	3	0	0	
	No upgrade	28	1	3	
Menopausal status		Premenopausal	Postmenopausal		0.053
	Upgrade	3	2		
	No upgrade	39	2		

atypical features given that the relative risk is highest when atypia is present. Additionally, some studies have determined excision only based on clinical growth and have shown an association with phyllodes tumor [28]. However, in our study, growth rate was not associated with the presence of phyllodes tumor.

In a recent study at the Mayo Clinic, in an analysis stratified by involution status and proliferative disease without atypia, complex fibroadenoma was not an independent risk marker for breast cancer [29]. Based on our study and others [30], excision of cellular fibroadenomas may not be necessary, once radiological pathological concordance is achieved, as there is no upgrade to cancer.

There were a few limitations to our study. The small sample size is one of the limitations of the study. Secondly, as the study was retrospective and given ultrasound operator dependency, any increase in volume from the initial ultrasound was considered an enlarging fibroadenoma at the discretion of the reporting radiologist. Some institutions already do not recommend surgical excision of fibroadenomas with growth or even a short interval follow-up once a diagnosis of benign fibroadenoma is established. Lastly 28% of the patients were lost to follow-up so we recognize that there could be patients who had excision based on clinical growth without a follow-up exam at our institution. However, it is felt that the loss to follow-up was random and therefore likely did not substantially affect the results.

So in conclusion, based on this study and a recent study by Sanders et al. [11], enlarging biopsy proven fibroadenomas are not associated with malignancy; therefore, surgical excision does not seem warranted. For enlarging presumed fibroadenomas on imaging, core biopsy should be performed to exclude associated atypia or phyllodes tumor, as these findings would warrant surgical intervention. Finally, surgical excision remains indicated for lesions with associated atypia, unusual pathologic features on core biopsy, or suspected phyllodes and for symptomatic lesions or cosmetic reasons.

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