Fibroadenoma: Can fine needle aspiration biopsy avoid short term follow-up?

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Abstract

Objective: To confirm whether fine needle aspiration biopsy (FNAB) can avoid close monitoring, a source of worry for women patients with a suspected fibroadenoma found by ultrasound, and requiring their compliance.

Patients and methods: Over 39 months, 427 nodules with a diagnosis of fibroadenoma were sampled in 372 patients using ultrasound-guided FNAB. The sonographic appearance of all the nodules suggested BI-RADS category 3 fibroadenomas. The mean size of the fibroadenomas was 9 mm. The mean duration of follow-up was 29.7 months.

Results: Seven nodules had atypical cytology: a microbiopsy and/or excision found a simple fibroadenoma (n = 3), mastitis (n = 1), a fibroadenoma associated with a papilloma (n = 1), fibrosis (n = 1) and normal tissue (n = 1). Seven other nodules were resected during treatment for synchronous cancer, and were diagnosed as fibroadenomas. Two hundred and seventy-six nodules were followed-up (121 patients were lost to follow-up [n = 132]) and the appearance of 263 nodules (95.2%) was stable. Seven nodules, which had increased in size, underwent another FNAB or microbiopsy or surgery. Five nodules were not found again. The borders of one nodule showed modifications.

Conclusion: The use of fine needle aspiration biopsy, interpreted by an experienced cytologist, means that short term follow-up of fibroadenomas can be avoided.
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A fibroadenoma is a frequent, benign, fibroepithelial tumour, representing 20% of all breast masses in premenopausal women and 10% in women after the menopause [1], with incidence peaking during the 2nd and 3rd decades. It usually presents as a palpable, firm, painless, mobile mass. It usually occurs in isolation, but in 15% of cases there may be several [2]. Its size generally varies from 0.5 to 5 cm for the adult type and may exceed 15 cm in the case of juvenile and giant fibroadenomas. A slight increase in size may occur during follow-up, but this must remain less or equal to 20% over 6 months [3].

The evolution of fibroadenomas is affected by hormonal levels and they usually involute after the menopause. Simple adult fibroadenomas are generally found in young women, and contain stromal and epithelial components in varying proportions. Cytological examination reveals the association of bare nuclei, corresponding to the stroma, and map-like epithelial plaques with myoepithelial cells. There are two special cases: sclerotic fibroadenomas and complex fibroadenomas. The best imaging technique for detecting and characterising fibroadenomas is ultrasonography.

Mammography is indeed not very specific except for sclerotic fibroadenomas with ‘popcorn’ calcifications. With ultrasound, a simple fibroadenoma appears as a circumscribed hypo- or isoechoic, homogeneous mass with a long axis parallel to the skin. It may contain hyperechoic linear internal septa. Adjacent breast tissue may be compressed and form a hyperechoic pseudocapsule. There is variable posterior acoustic enhancement (Fig. 1).

Most simple fibroadenomas are classified as BI-RADS 3 and are closely monitored, even if they are palpable [4]. Some are removed depending on the patient’s risk factors, their size (>3 cm) and the patient’s wishes. This close ultrasound monitoring is a source of worry for the patients. It also poses the problem of compliance. Ultrasound-guided fine needle aspiration biopsy is a simple, rapid procedure with little discomfort, performed directly during the consultation. With an experienced cytologist the results are available within 24 hours or even within minutes if there is a cytologist immediately available. It also means that biopsies and the resulting stress can be avoided. The objective of this study was to verify whether an ultrasound-guided FNAB can avoid the need for short term ultrasound follow-up in patients with a simple fibroadenoma suspected using ultrasound.

Patients and methods

This retrospective study was performed based on histological data consisting of a list of cytological results of fibroadenomas over 39 months. The study included 427 nodules in 372 patients (median: 41 years old, extremes: 15 to 86 years old) seen in our breast clinic. The patients consulted either in the context of a screening programme or of monitoring after treated breast cancer or after having themselves felt a breast nodule. After recording their history and a clinical examination, all patients underwent breast ultrasound. In the clinical examination, where there was a palpable nodule, it was considered benign if it was mobile, regular and soft. Certain patients (on average over 40 years of age) also had a mammogram. All the patients had one or more breast nodules visualised by ultrasound. FNAB was performed on single nodules. Where there were several nodules, only those that had newly appeared, were large in size, had increased in size (>20% within 6 months) or which had criteria favouring malignancy were subjected to FNAB. Only nodules given a BI-RADS 3 classification were included in the study. In all, FNAB was performed on 427 nodules of benign appearance.

The ultrasound examinations were performed by radiologists with more than 10 years’ experience of breast imaging (IL, LF, MS) and by assistants in training, on a Philips iU22 ultrasound system (Philips Ultrasound, Bothell, WA, USA) using a 17-5 MHz linear probe, or possibly a 12–5 MHz linear probe where the lesion was deep and/or the breasts voluminous. All the examinations were performed with direct visualisation (PACS) of previous ultrasound images when they were available. Compound imaging, allowing definition of the borders and the internal echostructure to be increased, was applied by default. The nodules were considered to be benign if they had the following ultrasound characteristics:

- oval in shape with the long axis parallel to the skin;
- homogeneous hypo- or isoechoic parenchyma;
- thin echoic ‘pseudocapsule’;
- the borders were regular in appearance with at most little marked bi- or trilobulation;
- ± septa.

The nodules were classified according to the ultrasonic criteria of the BI-RADS lexicon. Simple or complex cysts were not included in the study, nor were suspect nodules.

If the nodule was located in a fatty environment, harmonic imaging was systematically used to increase contrast. Doppler was systematically applied. The location, the number and the size of the nodules in the three axes were noted. After ultrasound location of the nodule, the FNAB was performed using a 22G fine needle fitted to a 10 mL syringe, in turn fixed to a metal syringe pistol (Camco® Medical Ltd., London), allowing aspiration. Cytological analysis looked for bare nuclei (corresponding to stromal cells) and map-like epithelial plaques with myoepithelial cells, the latter indicating that the lesion was benign [5,6]. The abundance of

Figure 1. Simple fibroadenoma: hypoechoic, homogeneous, oval nodule, parallel to the skin, with a pseudocapsule and septa.
the material was assessed by the cellularity ‘+’ score and graded as ‘0, ±, ++ and +++’.

Results

The results are summarised in Tables 1 and 2. Fine needle aspiration was performed on a total of 427 nodules and produced a cytological diagnosis of fibroadenoma (with at least one ‘+’ for cellularity) in 372 patients aged 15 to 86 years old (median: 41 years old). A diagnosis of simple fibroadenoma had been suggested from the ultrasound for all the nodules. The aspirated nodules had a large axis of 3 to 43 mm, i.e. a mean length of 9 mm (SD: 6.7). Multiple nodules were present in 84 patients (22.58%). The length of patient follow-up varied from 6 to 60 months, with a mean of 29.7 months (SD: 13.8). Follow-up was possible for 276 nodules (64.64%), with evolution as follows:

- stable size for 263 of these nodules (95.29%);
- disappearance of five nodules (1.81%), which initially measured between 5 and 13 mm;
- increase in size of seven nodules (+20% in each of the three axes) (2.54%);
- modification of the margins (irregular) for one nodule (0.36%).

Of the nodules where the size increased:

- three underwent repeat FNA, with a cytological diagnosis of fibroadenoma (n = 2) and fibrocystic disease (n = 1);
- two were monitored using ultrasound and remained stable;
- one underwent surgery directly, with a histological diagnosis of fibroadenoma;
- one had a microbiopsy with resection, with a histological diagnosis of fibroadenoma.

Microbiopsy was performed on one nodule with modified margins, and it was resected, with a histological diagnosis of grade II invasive lobular carcinoma (Fig. 2). Seven nodules had atypical cytology (2.37%) and were therefore subjected to ultrasound-guided microbiopsy, in some cases followed by surgical resection (n = 2), with a histological diagnosis of:

- fibroadenoma: (n = 3), 1 of which was resected;
- fibroadenoma and papilloma (n = 1), with resection;
- mastitis (n = 1);
- fibrosis (n = 1);
- normal tissue (n = 1).

Nineteen nodules (4.4%) underwent surgical resection directly and seven (2.37%) were operated because of the synchronous development of an ipsilateral neoplastic lesion, with fibroadenoma diagnosed from the histology. Twelve nodules (4.07%) were treated surgically at the patients’ request. In this case, they were mainly voluminous lesions measuring from 3 to 43 mm (median: 29 mm) in young patients from 15 to 54 years old (median: 22 years old). In one of these patients aged 17, histological examination of a 31 mm nodule produced a diagnosis of a benign phylloides tumour (Fig. 3). During monitoring, 121 patients (32.53%) were lost to follow-up after the first examination, accounting for 132 nodules (30.91%). The mean age of these patients was 37.8 years, with extremes of 15 and 86 years. Five patients (1.34%) did not come for the ultrasound check-up at 6 months, but returned after 12 or 24 months. They were patients aged between 38 and 45 years old (median: 42). Eighteen patients (4.84%) came solely to the first ultrasound check-up at 6 months (median age of 34.6, with extremes of 18 and 61 years).

One hundred and forty-four patients in all (38.71%) had problems, therefore, with compliance.

Discussion

Mammary ultrasonography is the standard examination for diagnosis and monitoring of fibroadenomas. The growing use of ultrasonography for screening and identifying breast abnormalities has resulted in an increase in the detection of benign nodules. These nodules, classified as BI-RADS 3, would normally be subject to short term follow-up every 6 months for 2 years. In certain cases, where there are risk factors, the patient or the clinician wishes it, or the size is more than 3 cm, biopsy or resection is performed immediately. Both of these approaches, biopsy and short term follow-up, cause stress for the patients (which is
nevertheless greater for a biopsy than for follow-up) [7–9], and a problem with compliance.

In our establishment, with the agreement of the gynaecologists and general practitioners, a fine needle aspiration biopsy is performed during a breast examination. Unlike biopsy, this procedure is quick to perform and minimally invasive, with very rapid results (<24 h), and is reliable with sensitivity of 97.1% and specificity of 99.1% for nonpalpable lesions [10]. The aim of this study was thus to reduce patients' stress, by 'replacing' biopsy by a less invasive procedure and eliminating short-term monitoring.

Our results show that in the vast majority of cases (95.29%) simple fibroadenomas are stable at follow-up of more than 2 years (a mean of 29.7 months). This is in line with the literature, which reports a level of stable lesions at 24 months of between 97% and 99% [11,12]. Graf et al. showed stability at 39 months for 99.3% of the lesions [13].

Five nodules (1.81%) were not found again. Several explanations can be suggested: difficulty of visualisation in a fatty environment (n = 2) hence the usefulness of harmonic imaging (Fig. 4a, b), menopause without hormone substitution therapy (n = 2), previous ultrasound images not available (n = 1). There was an increase in size more than 20% in each of the three axes in seven nodules (2.54%), in line with the literature [12]. The size of fibroadenomas varies depending on the hormonal level (increasing in the luteal phase, during pregnancy and breast-feeding and involuting at the menopause). An increase less or equal to 20% in the mean diameter in 6 months is tolerated [3]. Of these seven nodules, two were followed-up and remained stable afterwards. Of the nodules that were subjected to another FNAB, to biopsy or surgery, there were four fibroadenomas and one case of fibrocystic disease. Fibrocystic disease nodules correspond to an intermediate stage in the formation of cysts. Ductal spaces are sometimes completely filled with debris and macrophages and in this case, the nodule appeared to be solid. It could be confused with a fibroadenoma at ultrasound (Fig. 5).

Modification of the margins was observed in 1 nodule that was a 9 mm invasive lobular carcinoma. Re-reading the images showed that the border was already angular in the previous examination (Fig. 2). This nodule was therefore wrongly classified as BI-RADS 3 and should have been classified as BI-RADS 4. On cytological examination, seven nodules (2.37%) showed cytonuclear atypia. Definitive histology (following microbiopsy or surgery) concluded that four were fibroadenomas, including one with a papilloma, one indicated mastitis, one fibrosis and one normal tissue. Cytonuclear atypia are sometimes seen in fibroadenomas but are not found in the histology. These cellular modifications are related to the hormonal cycle (proliferation phase, cyclic pill) and pregnancy (hyperplastic fibroadenomas) [5,6].

As for the three other histological diagnoses (mastitis, fibrosis and normal tissue), the most likely explanation is
In addition, the results of this study show a problem with compliance. Indeed, 32.53% of the patients were lost to follow-up. These were mainly patients under 40 years old, the age advised in our establishment for first screening. Similar results, with 64% compliance, have been described in the literature [18]. Five patients between 38 and 45 years old did not attend the 6 months control but returned at 12 or 24 months. Eighteen patients, also mostly less than 40 years old, attended only the control at 6 months. This inadequate level of compliance is an additional argument for performing an FNAB at the outset. A reliable cytological result reassures the patient and the clinician, particularly if patients do not come to the check-ups offered. Young patients of less than 25 years of age can however be considered separately. In the absence of risk factors, the risk of cancer is 0.03% [19]. Maxwell et al. reported that if there is a palpable nodule in patients less than 25 years old, a FNAB is not necessary if the precise clinical and ultrasound criteria are present to assert its benign nature. Clinical monitoring may be proposed while informing patients of the possible variation in size of the fibroadenoma and of the need to consult if there is a non-reversible increase in size.

Another special situation to mention concerning this population of young women is pregnancy (and breast-feeding). During pregnancy, the echogenicity of the breast parenchyma decreases and the contrast between possible fibroadenomas and the surrounding mammary tissue becomes very weak. In addition, the size of a fibroadenoma known before pregnancy may be modified, with dilatation of intratumoral ducts [20]. In the absence of malignancy criteria, such as irregular margins, a control can be performed after breast-feeding has finished (Fig. 6). It is nevertheless best to be extremely cautious, since cancers discovered during pregnancy are usually high grade because they are in young women, with in addition an inherent delay in diagnosis due to the pregnancy [21,22]. To conclude, the case should be discussed of women at high risk of breast cancer. These are notably women with BRCA1 and 2 mutations. Hamilton et al. have reported the pseudobenign appearance of cancers in the BRCA1 population [23]. However, these authors did not take into account the strict ultrasound criteria for a benign nature, since the cancers considered as benign in their study were round rather than oval in shape [24]. Caution remains the watchword in these at-risk populations, which include women who have already undergone surgery for breast cancer.

Our study has several limitations.

First of all, this was a retrospective study with selection bias, risk factors not having been taken into account. In addition, patients coming for screening (>40 years of age
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Figure 6. Fibroadenoma: a: before breast-feeding; b: during breast-feeding; c: after breast-feeding.

Figure 7. Guidelines for fibroadenomas in women with no high risk factors for breast cancer.

in our establishment) were not separated from the others (young patients, those coming for breast cancer monitoring, those having found a nodule by self-palpation). Patient follow-up time was sometimes insufficient (6 months for 18 patients [4.84%]). Ultrasound examinations were undertaken by radiologists with differing experience (seniors and juniors), which might have resulted in different interpretation of the images. The 6-month controls were not always performed by the same radiologist. Ultrasonography is an operator-dependent examination and requires specific training and high-performance equipment. Introduction of the BI-RADS lexicon has however standardised interpretation and action to be taken, and the intra- and interobserver correlation for BI-RADS classification is excellent [25]. In the same way, fine needle aspiration biopsy requires a learning curve. To improve ultrasound performance, recent technological developments such as elastography have been developed. Elastography is particularly useful for lesions classed in the BI-RADS 3 and BI-RADS 4 categories. Its use often means that lesions can be reclassified, usually into BI-RADS 2, and unnecessary biopsies and close monitoring avoided [26–29]. Fleury et al. in particular reported good correlation between the elastographic score and the histology of fibroadenomas, resulting in refining the diagnosis [30].

Given the results of this study, a guideline for fibroadenomas can be proposed in women who have no high risk factors for breast cancer (Fig. 7).

Conclusion

It seems reasonable to propose routine surveillance and not short term follow-up if cytological results indicate fibroadenoma, given the high level of stability over time of fibroadenomas and the very low level of false negatives reported in this study. Of course, this is only true when the ultrasound criteria used are the criteria for a fibroadenoma. A reliable cytological result also reassures the clinician and the patient and overcomes non-compliance, common in women under the age of 40. The management model suggested is obviously only possible with the cooperation of a specialist breast cytopathologist. Nevertheless, caution
is required in women with a high risk of breast cancer, particularly women with a BRCA1 and 2 mutations and women who have had surgery for breast cancer, in whom a biopsy is recommended.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References