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Histologic work-up of non-palpable breast lesions classified as probably benign at initial mammography and/or ultrasound (BI-RADS category 3)

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This paper is dedicated to Silvia Jaromi who passed away far too young and tragically.

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ABSTRACT

Purpose: To determine the accuracy of a probably benign assessment of non-palpable breast lesions (BI-RADS category 3) at mammography and/or ultrasound with immediate histological work-up.
Materials and methods: Stereotactic or ultrasound guided core needle breast biopsy (NBB) was performed to evaluate 288 lesions, which were prospectively assessed as BI-RADS category 3. Imaging findings included 195 masses, 73 calcification cases, 16 focal asymmetries, and four architectural distortion cases. After NBB, patients underwent either open surgical biopsy (OSB) ($n = 204$) or mammographic follow-up ($n = 84$) for at least 24 months. Histological results of NBB were compared with those of OSB.
Results: Three of the 288 lesions (1.0%) proved to be malignant at histological work-up, two of them were ductal carcinoma *in situ* (DCIS) and one of them was an invasive carcinoma. NBB revealed invasive carcinoma in 1/288 (0.35%) and atypical ductal hyperplasia (ADH) in 13/288 (4.5%) lesions. OSB revealed DCIS in 2/204 (1%) and invasive carcinoma in 1/204 (0.5%) lesions. The two DCIS were underestimated as ADH by NBB. The remaining 285 (99%) lesions proved to be benign at OSB or remained stable during follow-up.
Conclusion: Confirmed by tissue diagnosis, the low likelihood of malignancy of prospectively assessed probably benign lesions is below the 2% threshold established for BI-RADS category 3. Imaging follow-up is a safe and effective alternative to immediate histological work-up for such lesions.

1. Introduction

Many studies have established the validity of short-term imaging surveillance for probably benign breast lesions (BI-RADS category 3) detected at screening mammography [1–17]. Data from various institutions in several countries showed a very small likelihood of malignancy for circumscribed breast masses, calcifications with specific morphologic features, and focal asymmetries, ranging from 0.3% to 1.7% [1–24]. Moreover, malignant breast lesions that are initially assessed as probably benign are reliably and promptly identified by interval change at short-term imaging follow-up when they are still early in stage, with favourable prognosis [6,14–16]. This approach should lead to a reduction in biopsies that yield a benign result, whilst maintaining a high detection rate of early stage cancers. The proper use of the BI-RADS category 3 helps to reduce cost, morbidity and patient anxiety associated with breast cancer screening, and increases the cost effectiveness of screening [7,25–29].

However, this management strategy is not universally accepted. In some institutions immediate percutaneous core needle breast biopsy (NBB) or even open surgical biopsy (OSB) is often used and deemed safer [8,23]. In addition, the national screening programmes in some European countries (*e.g.* United Kingdom, Sweden) use programme-specific assessment categories that do not include the 'probably benign' category, instead recommending either immediate tissue diagnosis or routine (rather than short-interval) follow-up for such lesions [9,30].

The lack of histological proof of benignity for BI-RADS category 3 lesions with specific morphologic imaging features has been cited by some as an argument against periodic imaging surveillance [7,8,23,31,32]. To our knowledge, no previous studies have involved tissue sampling of lesions classified as probably benign upon initial assessment. The purpose of this retrospective study is to determine the likelihood of malignancy for probably benign (BI-RADS 3) assessments at mammography and/or ultrasound and to

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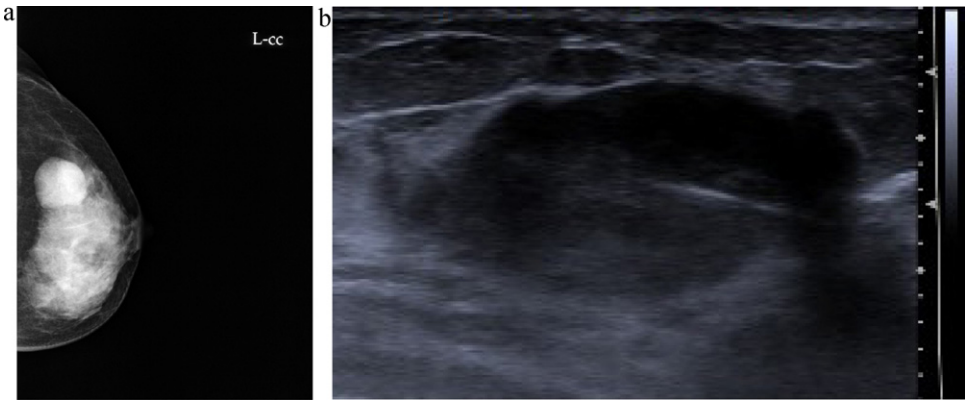

Fig. 1. (a and b) BI-RADS category 3. Baseline screening mammogram (left cranio-caudal) (a) and ultrasound (b) of a 51 year old female patient showing a circumscribed, oval, 23 mm in diameter measuring mass, which was prospectively classified as BIRADS III. Ultrasound NBB revealed fibroadenoma, which was confirmed by OSB.

validate previous studies based primarily on long-term lesion stability by demonstrating immediate histological proof of the benign nature of almost all these lesions.

2. Materials and methods

2.1. Case selection

Our database was searched for women with non-palpable breast lesions that were classified as probably benign at mammography and/or ultrasound (BI-RADS category 3) and in which percutaneous NBB was subsequently performed. The identification and analysis of cases was based on final written reports. In case of any discrepancy (imaging characteristics/NBB histopathology, NBB histopathology/OSB histopathology) the images were reviewed by one senior breast radiologist. The retrospective nature of this study was approved by the ethics committee of our University. The need for written informed consent was waived by the ethics committee.

During a 4 year period 5051 image-guided interventional breast procedures were performed at our institution, of which four-hundred cases met the criteria of being 'probably benign' at imaging (BI-RADS category 3). Of these 400 women, 112 were excluded, because either they underwent needle localization and OSB or fine-needle aspiration biopsy only, or because imaging follow-up after biopsy was less than 24 months. Thus, our study population consisted of 288 women (age, 24–88 years; median age, 51 years) who underwent prompt percutaneous NBB for probably benign lesions.

Women with benign findings at mammography and/or ultrasound (BI-RADS 2), or with findings suspicious for malignancy (BI-RADS 4 or 5), as well as those with palpable abnormalities irrespective of the imaging findings, were not included in this study [2,33,34].

2.2. Imaging

Mammography was performed with dedicated equipment (Senographe 2000 or Senographe 2000D, General Electric Medical Systems, Milwaukee, Wisconsin). All women had cranio-caudal and mediolateral oblique screen-film mammograms, followed by full diagnostic work-up, including 90° lateral views, spot-compression magnification views and/or ultrasound (US) [1,4,6,7,13–16,35–37].

Ultrasound was performed with a hand-held 7.5–12-MHz linear phase array transducer and high-resolution ultrasound equipment (Ultramark 9-HDI or HDI 5000; Advanced Technology Laboratories, Bothell, WA). US was used to determine the nature of a circumscribed mass detected at mammography, to define its contour and characteristics, and to ascertain the absence of a mass associated with a focal asymmetry. Mammographic and US findings were determined to represent the same lesion if the size, shape, and location of a mass, focal asymmetry, or architectural distortion were consistent.

The assessment of probably benign (BI-RADS 3) lesions followed the standard descriptive criteria in previous published studies and in the BI-RADS lexicon [2–16,18–24,33,34,38].

Mammographic findings of masses that were interpreted as probably benign included well-defined circumscribed masses that were not palpable and were not calcified. They had a round, oval, or slightly lobular contour that was completely visible, with or without halo sign. Circumscribed masses with contours less than 25% obscured (due to superimposed or adjacent normal breast tissue) were also assessed as probably benign findings. Masses could either be isodense or could have a higher or lower density than fibroglandular breast tissue, but were not fat-containing. US diagnostic criteria for masses included margins, shape, height-width ratio, echogenicity, echotexture, posterior echoes, and echogenic pseudocapsule. Lesions classified as probably benign at US had circumscribed margins, were round, oval or slightly lobulated, wider than tall (parallel orientation to the skin surface), with a homogenous echotexture that was iso- or slightly hypoechoic as compared to subcutaneous fat and with normal through transmission of sound. Lesion size did not represent a criterion for exclusion [8,14,20,38] (Fig. 1a and b). Other findings at US that were considered to be probably benign included a hypoechoic oval mass with homogenous low-level internal echoes (consistent with complicated cyst) and clustered microcysts [13,33,34,36].

Mammographic findings of focal asymmetry involved noncalcified opacities similar in size and shape on orthogonal-view images, occupying less than a quadrant of the breast. They represented discrete opacities with concave-outward margins, usually interspersed with fat, with no counterpart in the opposite breast and a complete lack of the conspicuity of a true mass.

Mammographic findings of architectural distortion were represented by subtle changes in tissue geometry with no definite mass visible, but only when occurring at known biopsy sites. This included spiculations radiating from a point without central increased fibroglandular density, and focal retraction or distortion of the edge of the parenchyma.

Calcifications assessed as probably benign (BI-RADS category 3) were grouped calcifications that occupied less than 2 cm^3 of tissue, multiple discrete clusters of calcifications, or numerous bilateral scattered and randomly clustered calcifications (Fig. 2). Probably benign calcifications contained particles with well-defined margins and consisted of more than five elements that could exhibit minor size and density differences. These calcifications were smaller than 1 mm in diameter and oval or round in shape, or they were smaller than 0.5 mm in diameter and punctate in morphology.

Fig. 2. BI-RADS category 3. Spot-compression magnification mammogram of a 54 year old female patient showing round and punctuate scattered microcalcifications.

Multiple masses or calcifications that were similar in morphology and distribution, which were individually classified as probably benign, were also assessed collectively as BI-RADS category 3.

The median lesion size assessed at mammography was 12.2 mm (range, 3–50 mm). Of the 288 lesions 195 (67.7%) were masses, calcifications were found in 73 (25.3%), focal asymmetry in 16 (5.6%), and discrete architectural distortion (when occurring at known biopsy sites) in four (1.4%) cases. NBB was performed under stereotactic ($n = 212$) or ultrasound guidance ($n = 76$).

The readers analyzed the mammographic and ultrasound findings according to the BI-RADS lexicon [33,34,39]. The final assessment of a probably benign lesion (BI-RADS category 3) was approved by one of two senior breast radiologists at our institution.

2.3. Patient management and tissue diagnosis

In accordance with international guidelines, it was not our policy to recommend NBB or OSB in non-palpable, probably benign breast lesions; rather, we recommended periodic imaging surveillance [39]. However, in the 288 reported cases women underwent NBB on the basis of the patient's or the attending physician's preference. Following NBB, histological results were correlated with imaging findings, and specific recommendations were made to the patient and the referring physician.

After having obtained written informed consent from each patient, percutaneous NBB was performed using stereotactic guidance in 212 cases (73.6%) and US guidance in 76 cases (26.4%) The choice of guidance technique depended on a number of factors including lesion location, lesion visibility, imaging characteristics, and individual radiologist's preference. All biopsies were performed by one of two attending radiologists specialised in breast imaging. Of the 288 patients included in this study, stereotactic 14-gauge large core breast biopsy was performed in 37 lesions, stereotactic 14-gauge vacuum-assisted biopsy was performed in 85 lesions, and stereotactic 11-gauge vacuum-assisted breast biopsy was performed in 90 lesions. All stereotactic biopsies were performed after disinfection and local anaesthesia with patients prone on a dedicated examination table (Fischer Imaging Mammotest, Denver, Colorado). A minimum number of 5 specimens were obtained with 14-gauge large-core needles [40,41]. A minimum number of 12 specimens were obtained with a 14-gauge or an 11-gauge vacuum-assisted biopsy device (Mammotome; Ethicon Endo-Surgery, Cincinnati, OH) [40,41]. In case of microcalcifications, specimen radiography was performed to document removal of targeted calcifications. Ultrasound-guided 14-gauge large-core breast biopsies were performed with patients in supine or supine-oblique position following disinfection and local anaesthesia using an automated spring-loaded gun (Magnum, BARD, Covington, GA). The correct needle placement was verified in two orthogonal imaging planes. A minimum number of five specimens were obtained at each biopsy procedure [40,41].

Surgery was recommended in cases in which NBB results were discordant with the imaging features, or if surgical excision was suggested by the pathologist. OSB was also performed in cases in which histological results of NBB yielded a high risk lesion (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma *in situ*, radial scar, phylloides tumour, and atypical papilloma) because of the risk of histological underestimation of malignancy [31,42–48]. If cancer was found at NBB, the patient was referred for definitive surgery. Additional reasons to perform surgery in cases of a benign and concordant histological result after NBB were due to preference of the patient or the referring surgeon. At the beginning of the study period, surgeons at our institution preferred to use NBB as a preoperative procedure that was performed in addition to and not in lieu of OSB. For women with probably benign breast lesions, the use of OSB in addition to NBB resulted in more procedures and higher costs, but that was the preference of our clinicians. Women were aware of that before undergoing the OSB procedures. This was the case in 204 (70.8%) of 288 NBB patients.

Imaging surveillance was recommended if benign histological results of NBB were concordant with the imaging findings, except when subsequent surgical excision was performed. Mammographic follow-up information was available for 84 of 288 patients (29.2%). Follow-up examinations were performed at our own institution in 48 of the 84 cases (57.1%). In the remaining 36 cases (42.9%), follow-up mammograms were performed at outside facilities. Our short-interval follow-up protocol consisted of a unilateral mammogram or ultrasound at 6 months after NBB, followed by a bilateral diagnostic mammographic and/or ultrasound examination at 12 and 24 months [6,7,9,10,14–16,25]. If the full set of follow-up examinations documented stability, the patient was advised to resume routine yearly screening and the histological result of NBB was regarded as benign for statistical analysis. Any increase in size of a mass, focal asymmetry, or architectural distortion or in the number of calcifications and/or changes in morphology of the imaging finding was regarded as a substantial change in lesion appearance and thus was assessed as suspicious and re-biopsy or OSB was recommended [1,4,6,9,14–16,35,37].

2.4. Data analysis

A malignancy (carcinoma) was defined as a lesion that yielded invasive carcinoma or DCIS at NBB, OSB, or both, confirmed at subsequent pathology review. We determined the likelihood of malignancy (positive predictive value [PPV]) of probably benign findings by dividing the number of malignant lesions by the number of lesions undergoing NBB [31,42–48].

Data were entered into a computerized spread-sheet (Excel: Microsoft, Redmond, WA). Statistical analyses were performed with statistical software (SPSS Inc., Chicago, Illinois). Descriptive statistical metrics were calculated, including mean value and standard deviation. In order to demonstrate that the number of study cases was sufficient to prove the assumption of a less than 2% PPV, exact 95% confidence intervals were given (Wilson Method) [49] (see Table 1).

Table 1
Cancer rate in non-palpable, probably benign BI-RADS category 3 lesions according to the literature.

	No. of probably benign lesions	Total No. of cancers	Cancer rate (%)[a]
Sickles et al. [7]	3184	17	0.5
Helvie et al. [1]	144	1	0.7
Varas et al. [14]	535	9	1.7
Vizcaino et al. [16]	795	2	0.3
Varas et al. [15]	511	2	0.4
Yasmeen et al. [17]	1138	12	1.1
Graf et al. [20]	157	0	0
Graf et al. [38]	80	0	0
Graf et al.[a,b] [50]	445	1	0.2
Current study	288	3	1.0
Total	7277	47	0.59

[a] Cancer rate = No. of cancers divided by No. of probably benign lesions times 100.
[b] Nos. including [20] and [38].

3. Results

NBB yielded benign findings in 274 (95.1%) cases, ADH in 13 (4.5%) cases, and invasive carcinoma in one (0.4%) case (Fig. 3). Two of the 13 ADH lesions were underestimated at NBB because OSB revealed ductal carcinoma *in situ* (DCIS) in these cases. Of the remaining 11 ADH lesions, OSB confirmed the diagnosis of ADH in five cases and led to a different benign diagnosis in six cases. In seven cases with non-hyperplastic benign findings at NBB, surgery revealed ADH. Correlations between histological findings at NBB and OSB are shown in Table 2.

The final histological diagnosis of all lesions ($n = 288$), based on subsequent surgical excision or follow-up after NBB, is shown in Table 3. In this study, 285 out of 288 (99%) were prospectively correctly assessed as probably benign, based upon the histological results after NBB and subsequent imaging follow-up ($n = 84$) or OSB ($n = 204$). Malignancy was found in 3/288 cases (1%). Two of the carcinomas were DCIS, one was an invasive carcinoma. The median size of these three lesions was 12 mm (range, 10–14 mm). Mammographic findings in these cases were a circumscribed mass in one case and grouped microcalcifications in two cases. NBB in these three cases was performed under stereotactic guidance using a 14-gauge needle for the mass and using an 11-gauge needle for the calcification cases. The median number of specimens obtained for these three lesions was 16 (range, 12–20). NBB histological results in these three cancers was invasive carcinoma in one and ADH in two. Review of images of the two cases that were underestimated as ADH at NBB showed that the lesions were properly targeted. Histologic review of these two cases confirmed the absence of malignancy in the stereotactic biopsy material.

Follow-up imaging was performed in 84 out of 288 patients (median follow-up 45 months; range, 26–93). In 81 cases the imaging findings remained stable. In three cases, two of which were masses and one was calcifications, the lesion increased in size

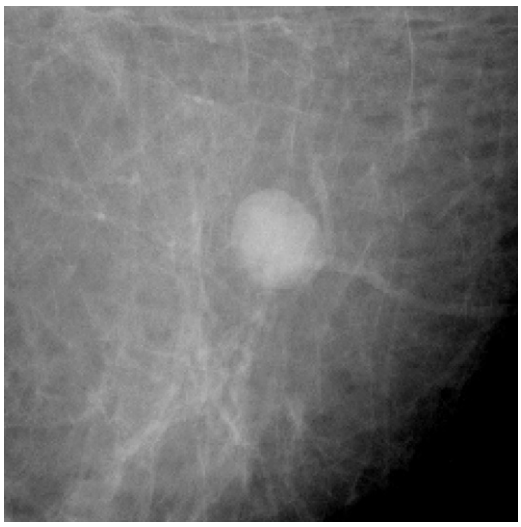

Fig. 3. BI-RADS category 3. Mammogram (Scout view) of a 68 year old female patient showing a circumscribed, round, 11 mm in diameter measuring mass, which was prospectively classified as BIRADS III. Stereotactic NBB revealed invasive carcinoma, which was confirmed by OSB (Histology: invasive ductal carcinoma not otherwise specified Grade 3).

Table 2
Correlation between histological findings of needle breast biopsy and open surgical biopsy in 204 BI-RADS category 3 lesions.

NBB	OSB			
	Benign	ADH[a]	DCIS[b]	Invasive carcinoma
Calcifications				
Benign	42	2	0	0
ADH[a]	0	2	2	0
DCIS[b]	0	0	0	0
Masses				
Benign	128	5	0	0
ADH[a]	6	3	0	0
DCIS[b]	0	0	0	0
Invasive carcinoma	0	0	0	1
Asymmetric densities				
Benign	12	0	0	0
ADH[a]	0	0	0	0
DCIS[b]	0	0	0	0
Architectural distortions				
Benign	1	0	0	0
ADH[a]	0	0	0	0
DCIS[b]	0	0	0	0
All lesions				
Benign	183	7	0	0
ADH[a]	6	5	2	0
DCIS[b]	0	0	0	0
Invasive carcinoma	0	0	0	1

[a] ADH, atypical ductal hyperplasia.
[b] DCIS, ductal cancer *in situ*.

Table 3
Histological results of 288 BI-RADS category 3 lesions undergoing core needle breast biopsy, verified by open surgical biopsy or follow-up.

Histological diagnosis	No. of findings[a]
Benign lesions	
Fibroadenoma	108 (28) 37.5%
Fibrocystic changes	78 (20) 27.1%
Fibrosis	18 (4) 6.3%
Benign breast parenchyma	23 (15) 8.0%
Scar tissue	6 (2) 2.1%
Mastitis	3 (2) 1.0%
Duct hyperplasia	5 (2) 1.8%
Sclerosing adenosis	11 (5) 3.8%
Fatty tissue	1 (0) 0.3%
Lymph node	7 (3) 2.4%
Microcalcification	2 (2) 0.7%
Cyst	2 (1) 0.7%
Hamartoma	7 (0) 2.4%
Papilloma	2 (0) 0.7%
High-risk lesions	
Atypical ductal hyperplasia	9 (0) 3.1%
Phylloides tumour	2 (0) 0.7%
Papilloma with atypia	1 (0) 0.3%
Malignant lesions	
Ductal carcinoma *in situ*	2 (0) 0.7%
Invasive carcinoma	1 (0) 0.3%
Total	288 (84) 100.0%

[a] Numbers in parentheses represent the subset of lesions validated by imaging follow-up.

during the follow-up period and showed benign findings at subsequent OSB.

Of the 195 mass lesions, 186 had a benign histological result, eight were ADH, and one was an invasive carcinoma. Of the 73 calcification cases, 66 were found to be benign, five were found to be ADH, and two were DCIS. Of the 16 focal asymmetries and the four cases of architectural distortion, all cases were confirmed to be benign at OSB.

We have observed 3 carcinomas in 288 lesions that were classified as probably benign. Consequently, the exact one-sided confidence interval for this number of patients is 0.026.

4. Discussion

BI-RADS category 3 assessment is used for findings whose morphologic characteristics suggest that a breast lesion is probably benign and the likelihood of malignancy is less than 2% [2,33,34]. Previous studies have shown that these lesions can be followed safely with periodic imaging surveillance instead of immediate histological work-up, and that stability for at least 2 years strongly indicates benignity (2–16, 18–24).

Benignity in these studies was presumed by showing stability at surveillance imaging; histological proof was available in only a small number of the cases, comprising 0.9–7.7% (mean 4.7%) of lesions [1–16,50]. Tissue diagnosis was obtained only if lesions showed progression during the surveillance period or because of patient or physician.

The strength of our study is that it offers histological proof of a <2% cancer rate for lesions classified as probably benign according to the BI-RADS lexicon. Only three out of 288 lesions (1%) proved to be malignant at initial imaging and subsequent histological evaluation.

Two hundred and four out of 288 lesions (70.8%) underwent confirmatory OSB following NBB; the remaining concordantly benign lesions at NBB (84/288, 29.2%) had follow-up of at least 24 months to verify benignity [7–10,14–16,25,31]. In one lesion, NBB correctly revealed invasive carcinoma, in two cases NBB showed underestimation of ADH lesions that turned out to be DCIS after OSB. All three carcinomas were small in size and early stage, indicating a favourable prognosis. The low frequency of cancer in this study does not support the concept of immediate histological work-up instead of short-term follow-up for lesions with probably benign morphologic features. Thus, the results of our study in addition to previously published robust data should help to convince opponents of the BI-RADS category 3 approach of the safety and efficacy of substituting periodic imaging surveillance for tissue diagnosis.

It is important to strictly apply the morphologic criteria listed in the BI-RADS lexicon for probably benign findings. Inappropriately broadening the imaging criteria for rendering probably benign assessments may raise the frequency of malignancy, because some otherwise biopsied cancers may be recommended for follow-up instead [3,4,14,21,37,51,52]. As it is important not to miss early stage breast cancer in mammography screening, it is equally important not to overuse BI-RADS category 3 in typically benign lesions, such as calcified fibroadenomas, secretory calcifications and simple cysts to maintain the cost-effectiveness and acceptance of the probably benign approach.

In every case of interval change during mammographic and/or ultrasound surveillance, tissue diagnosis is necessary [1,4,6,9,14–16,35,37]. In this study, three (1%) out of the 288 lesions that were initially assessed as BI-RADS category 3 proved to be malignant at histological work-up. Imaging review in these three cases showed that the cancer mimicked a probably benign lesion at initial imaging. However, due to the early stage of these three carcinomas, the likelihood that a delayed diagnosis would have led to a reduction in the overall survival rate is low as well. This is in accordance to the literature, in which lesions that were initially considered to be probably benign but were then identified as cancer during the surveillance period showed a good prognosis, equivalent to the prognosis of screening-detected cancers [6,14–16]. Thus, based on all published results the recommended management of BI-RADS category 3 with periodic imaging surveillance is justified [2–16,18–24].

Some reasons may explain the high number of BI-RADS category 3 lesions that underwent NBB and OSB at our institution. In the beginning of the study period, both the BI-RADS classification and NBB had only recently been introduced in our country, thus there was a lack of confidence between radiologists and surgeons. Almost two thirds of study patients underwent OSB despite a definitive benign histological result at NBB. This has since changed due to tumour board meetings, publications and oral presentations. Now, the NBB rate of BI-RADS category 3 lesions has decreased substantially at our institution. However, there are still physicians who tend to recommend immediate tissue diagnosis for different reasons.

One of them is patient anxiety. In our opinion, prompt tissue diagnosis should only be performed in cases with extreme patient anxiety over the inherent uncertainty about presumed benignity. The vast majority of women are, in fact, anxiety free when the imaging surveillance option is presented to them both competently and confidently. As reported by Lindfors et al., the anxiety of patients after diagnosis of a BI-RADS category 3 lesion who underwent imaging follow-up was lower than that of patients who underwent NBB [24].

Some critics say that missed carcinomas in BI-RADS category 3 lesions have a similar size and nodal extension to those found in lesions in BI-RADS categories 4 and 5 [6,11,14–16]. During the course of mammographic surveillance, the vast majority of BI-RADS category 3 lesions that actually are malignant will be identified by means of imaging change rather than the interval development of a palpable mass or other signs or symptoms of breast cancer. Furthermore, lesions initially considered being probably benign but then identified as cancer during the surveillance period are reported to have an excellent prognosis, equivalent to that of screening-detected cancers [6,14–16].

Another criticism of short-term imaging follow-up is the lack of patient's compliance to return to surveillance examinations. It is essential that the patient and the referring physician are aware of the fact that the lesion may be malignant despite its benign morphology. We told our patients that less than 2% of non-palpable probably benign breast lesions prove to be malignant at biopsy and that standard practice is to follow the lesion. The decision to proceed with imaging surveillance should be made only if the patient accepts follow-up as an alternative to NBB. As demonstrated in this study, NBB can be safely used as an alternative to OSB in these cases.

One of the limitations of our study is that the identification and analysis of cases was based on final written reports. During the study time the BI-RADS lexicon was already implemented in our department thus our breast radiologists were confident with the use of the BI-RADS lexicon. In case of any discrepancy images were reviewed by one senior breast radiologist. Consequently, the inclusion of cases based on final written reports should not be seen as a limitation.

In conclusion, mammographic and/or ultrasound short-term imaging follow-up is the method of choice to deal with probably benign lesions detected at breast cancer screening. The low number of malignancies seen in our study does not favour NBB as an alternative to short-term follow-up in the probably benign assessment.

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