BIRADS 3 Breast Lesions: Can Follow-up Replace Biopsy

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Abstract

Objective: To compare the two years follow-up versus biopsy in probably benign breastlesions (BIRADS3 category) with assessment of the malignancy potential in both conditions.

Patients and Methods: This is a comparative descriptive record survey where records of all BIRADS 3 patients (number=575) who were admitted to the Women and Fetal Imaging (WAFI) center in Cairo-Egypt during the period from January 2007 to December 2010 were traced, however, only 464 were finally included and divided into: Group A (number = 395), those who were subjected to follow up protocol and Group B (number = 69), who underwent biopsy.

Results: 85.1%of the cases underwent the two years follow up by mammography and ultrasonography through periodic imaging surveillance (group A), while 14.9% underwent biopsy and were allocated as (group B). Among the follow up cases 98.48%weretrue negative (benign cases) and six cases (1.52%) were upgraded in their follow up visits and were confirmed malignant by histopathology. In group (B) 97.1% were true negative while 2 cases (2.9%) were confirmed malignant (false negative).No significant difference between both groups as regards false negative results (p=0.339). When we investigated all false negative cases (cases proved malignant) in both groups, positive family history was the only variable that counts and favoring the malignant suspicion in all cases but other parameters like irregular lesions, subtle asymmetry, calcified masses, focal distortion and parenchymal disruption may direct the radiologists and physicians, to proceed to biopsy.

Conclusion: In BIRADS 3 breast lesions interpreted by experienced radiologists and surgeons especially in absence of the parameters favoring malignancy, short term follow up can confidently replace biopsy.

Keywords*:* BIRADS; breast lesions; breast ultrasound; mammography.

Introduction

Breast cancer is one of the well-known causes of death among women worldwide. There are number of investigations used for diagnosing this disease: mammography, sonography, and biopsy, among others. Each of these has illustrious advantages and disadvantages [1].When a non-palpable breast lesion, discovered accidently on screening mammography, classified as probably benign, BIRADS category 3, after a full diagnostic imaging workup, the authoritative practice is to implement a six-month-interval follow-up mammography for 2 years[2]. Moreover, the data in this category have a very good probability (greater than 98%) of being benign (not cancer). The benign findings are not expected to change over time. But since it could not be documented in BIRADS 3 lesions to be benign, it's wise to see if these suspicious lesions do change over time or not. Follow-up with repeated imaging is usually done as authenticated above. The follow up strategy helps to avoid unnecessary biopsies, but if the area does change over time, this necessitates early diagnosis. Moreover, the strategy of follow up increases the positive predictive value of the biopsy, thereby lowering potential patient morbidity[3].On the other hand, it has been noticed that in another practices, when a palpable breast mass is detected, a biopsy is usually done even if the mass authenticates probably benign morphologic criteria on imaging, as there is somewhat little data reporting the outcome of such breast masses[4].The aim of the current study was to compare the two years follow-up versus biopsy in probably benign breast lesions (BIRADS3 category) with assessment of the malignancy potential in both conditions. Moreover, another objective is to study the

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factors that could affect follow up prognosis of the BIRADS 3cases downgraded to BIRADS 2.

Patients and Methods

This is a comparative descriptive record survey where records of all BIRADS3 patients (number=575) who were admitted to the Women and Fetal Imaging (WAFI) center in Cairo-Egypt during the period from January 2007 to December 2010 were traced. All mammography and breast ultrasound examinations for breast lesions of Breast Imaging and Reporting Data System BIRADS category 3, either coming for screening or diagnostic examinations and with final recommendations of short-interval follow-up or biopsy were selected from the database. Informed consents were taken from the patients and the local breast imaging board approved the study.

During the study period, Out of 3971 women attended the breast imaging unit, 575 patients' breast imaging examinations revealed lesions assessed as BIRADS category 3. One hundred and eleven women were recommended to have short-interval follow up but were excluded because they did not continue their 2 year follow up protocol, resulting in a study population of 464 patients. These 464 patients were then classified into group A (number = 395): those who were subjected to follow up protocol and group B (number = 69) who underwent biopsy .These cases were classified according to the treatment plan taken by the referring surgeon and the patient and this explains the difference in the number of patients in both groups in this comparative record survey.

Medical records were reviewed including the patient' personal, past, family and drug history, clinical breast examination, mammography and ultrasonography reports, and the pathological examination endings. The final outcome of the BIRADS 3 lesions whether proved to be benign or malignant was based on the pathology report or two years or more follow up results. The inclusion criteria included all women diagnosed with a breast lesion of BIRADS 3 category (probably benign) and underwent either biopsy or completed 2 year follow up protocol. Lesions followed up for 2 years and kept as BIRADS 3 or downgraded to BIRADS 2 or lesions having benign pathological results are considered benign. Lesions that have positive pathology results are considered malignant. Patients who did not undergo at least 2 years of follow-up and those who did not undergo biopsy; were excluded from study and those who were diagnosed with BIRADS categories 0, 1,2,4,5 [5,6] were also excluded.

Mammography and breast ultrasound techniques

Standard mammograms were performed in mediolateral oblique and craniocaudal projections by using a dedicated mammography unit (Selenia, Hologic 2D Digital Mammography, USA). Mammograms were interpreted by one of two radiologists with 10–15 years of experience in breast imaging. Routine interpretation of a mammogram includes assessment of breast density and reporting the BIRADS categories according to the American College of Radiology categories 1-5 [6]. In the case of a circumscribed mass that was partly enigmatic by breast tissue on standard projections, a mediolateral whole-breast view and spot-compression magnification views in two other projections were requested by the radiologist to authenticate the findings with greater preciseness[6]. Ultrasound was then done to detect the cystic or solid nature, border criteria, and internal features of masses. Ultrasound was performed by using 11–14MHz transducers (GE Voluson 730 pro, GE Healthcare, USA) and findings were registered on laser film hard-copy prints (Kodak, Rochester, NY, USA). Lesions appropriately placed in category 3, probably benign assessment according to the American College of Radiology[5,6], included oval, macrolobulated, circumscribed mass on a baseline visit with more width than height (unless it can be shown to be a cyst, an intramammary lymph node, or another benign finding), or a lesion showing focal asymmetry which partially thins on spot compression, and a cluster of punctate calcifications. The initial short term follow up was usually a unilateral mammogram at 6 months after the time of the initial screening examination with or without complementary ultrasound .If the finding was stable, the recommendation was then for a bilateral follow up examination in another 6 months (corresponding to 12 month after the initial visit). If the findings remained stable the next visit is recommended after one year (two years from the initial visit)[5,6].The primary outcome measure was to compare the two years follow-up versus biopsy in probably benign breast lesions (BIRADS3 category) and

to assess the malignancy potential in both conditions. The secondary outcome measure was the assessment of BIRADS 3 lesions which were downgraded to BIRADS 2 during their follow up visit and compare them to BIRADS 3 lesions which were then proved to be malignant.

Statistical analysis

The statistical analysis was performed using the SPSS software (16.0 version, SPSS Inc., Chicago, IL). The description of qualitative (categorical) data was performed in the form of number of cases and percentage. The analysis of categorical variables was performed by using Chi-square test and Fisher's Exact test. The statistical analysis was mostly exploratory and involved a descriptive assessment of the use of the BIRADS 3 category by WAFI center radiologists and the database that reported radiological findings among women with BI-RADS 3 results and description of criteria of the malignant cases too. Cross-tabulation tests were also used to correlate between the cases downgraded from BIRADS 3 to BIRADS 2 during their follow up, and the cases upgraded to proven malignancy. P value of less than 0.05 was considered to indicate a statistically significant difference and less than 0.01 indicated highly significant results.

Results

In group A, 389 (98.48%) were true negative (benign) while false negative cases (malignant) were 6 (1.52%). In group B, 67 (97.1%) were true negative while the remaining2 (2.9%) cases were false negative cases (figure-1).

There was no significant statistical difference between the two groups as regards the false negative results with the P value = (0.339).

The patients' characteristics were compared between group A and group B in (Table 1). All results as regards the age, body mass index, menopausal status, history of contraceptive pills' intake, positive family history and breast feeding were non-significant.

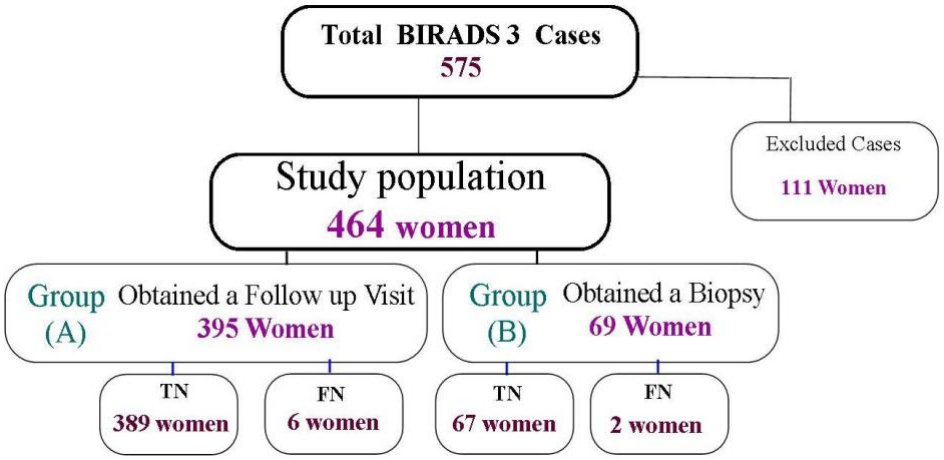
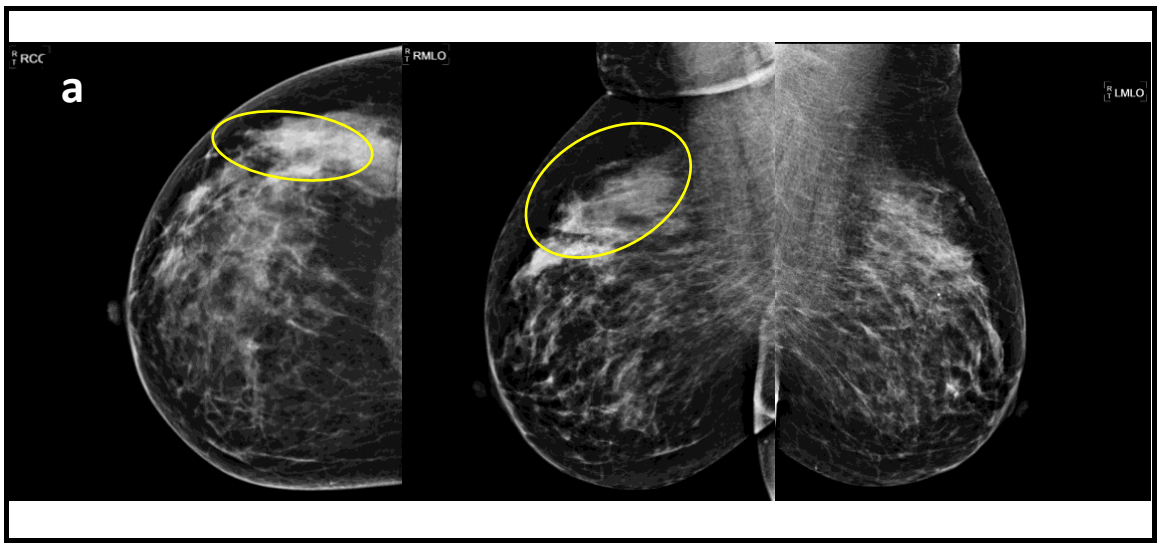


Figure 1. Participants' flow chart. **TN**; True negative, **FN**; False negative

Table (1): The Patients' characteristics

Patients characteristics		Group A Cases obtained Follow-up (number=395)	Group B Cases obtained Biopsy (number=69)	P value†
Age (years)¥		44±5	46±6	0.31†
BMI (kg/m^2)¥		28 ±4	27±3	0.29†
Menopausal Status n (%)	Pre-menopausal	250 (63.3%)	23 (33.3%)	0. 1 ‡
	Post-menopausal	145 (36.7%)	46 (66.7%)	
Positive family History of breast cancer		53 (13.4%)	34 (49.3%)	0.06‡
CCP n (%)		48(12.2%)	12 (17.4%)	0.6 ‡
Breast feeding n (%)		94(23.8%)	18 (26.1%)	0.3 ‡

¥ Mean ±SD, BMI: body mass index; CCP: contraceptive Pills
┼Analysis using independent Student t-test; ‡analysis using chi square or Fisher's exact tests.
N.B.: P value is considered of statistical significance if <0.05, therefore none of the P values in this table is significant.



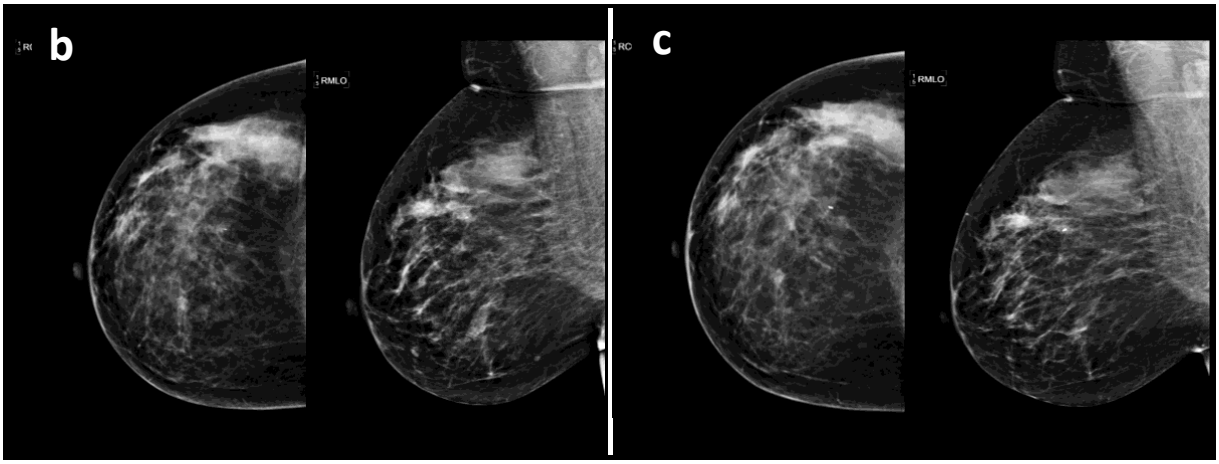


Figure 2: A Right breast craniocaudal and bilateral mediolateral oblique mammogram views showing a non palpable non calcified asymmetry noted at upper outer quadrant (yellow circle) of the right breast (a). Complementary ultrasound demonstrated coarse parenchyma only (not shown). A follow up mammogram obtained after 6 months (b), and another one after 12 months (c), no significant changes depicted.

Figures 2, 3, 4 illustrate BIRADS 3 lesions that they were stable during their follow up visits with no significant changes encountered.

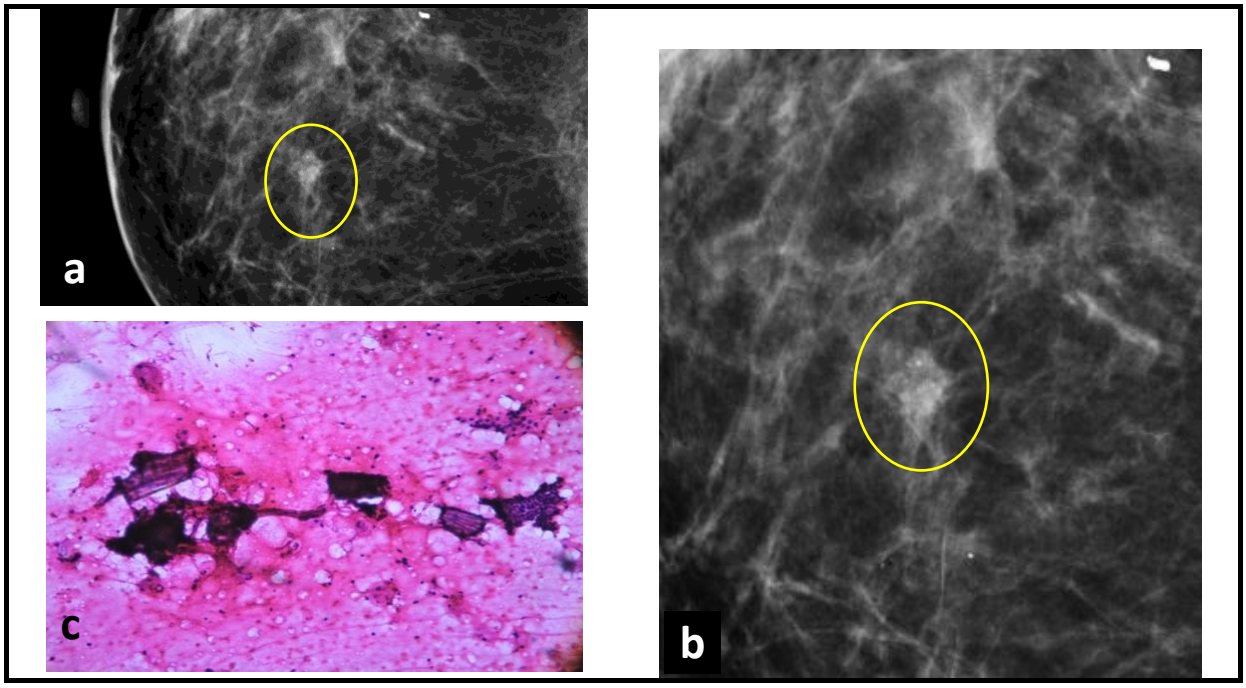


Figure 3: A small asymmetry with tiny calcific foci unchanged in craniocaudal view (a) and the magnification view (b) inside the yellow circle. Despite there were no significant changes on the 6 months follow up visit, a wire localization and excision biopsy has been requested by the surgeon and carried out for this patient. Benign microcalcification with fibroadenosis (c).

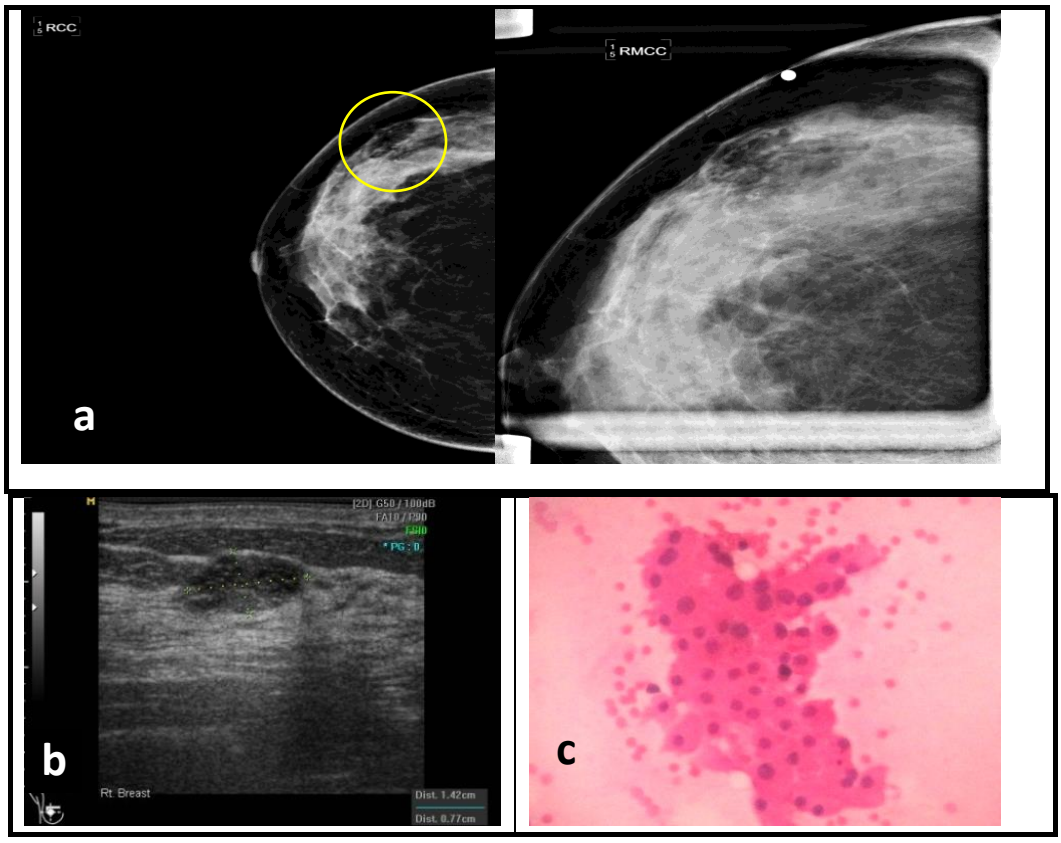


Figure 4: A focal area of asymmetry is noted with few clusters of calcific foci at upper outer quadrant of the right breast in the craniocaudal and right magnification craniocauadal views (a). Ultrasonography demonstrated a small septated cystic lesion at upper outer quadrant of the right breast measures 1.4 cm x 0.7 cm (b). The pathology report revealed tightly cohesive cluster of bland looking ductal epithelial cells with prominent apocrine metaplasia (c).

The 8 malignant (false negative) lesions depicted were further assessed and described in both groups as regards the type and the histopathology grading of cancer, positive lymph nodes for malignancy by mammography and or ultrasonography, the size of the lesion, the month at which cancer is detected, palpability, survival years, history of oral contraceptive pills intake, Breast density rating by ACR [6], age at diagnosis of malignancy, family history of breast cancer, and visit type whether diagnostic or screening. This was to point out the important variables which may direct us to know which patients we should start with biopsy when we further encounter BIRADS 3 lesions. Surprisingly, higher percentage of malignant cases were encountered in screening visits(62.5%) compared to diagnostic visits (37.5%).The only remarkable common finding in all malignancy cases (number=8) was the positive family history (table 2) otherwise there were no differences as regards the forementioned variables between malignancy in the two groups.

Table 2: Descriptive assessment of the 8 malignant lesions in both groups

Diagnosed by	Type of Cancer	Pathology Grading	LN	Lesion Size (cm)	Malignancy Detected at	Clinically Palpable mass	Survival years	OCP	Breast Density	Age at Diagnosis	Family History of BC	Visit Type
Follow up (Group A) n=6	DCIS	II	x	2.5x2.4	6 months	✓	5	x	3	36	+ve	Diagnostic
	IDC	II	x	0.8x0.5	6 months	x	3	x	2	57	+ve	Screening
	IDC	II	x	0.7 x 0.6	12 months	x	3.5	✓	3	50	+ve	Screening
	IDC	I	x	1.1x0.9	6 months	x	5	✓	2	35	+ve	Diagnostic
	IDC	I	x	0.8 x 0.8	6 months	x	2	✓	4	40	+ve	Screening
	Granular cell tumor with DIN	1B	x	2.4 x 1.7	6 months	✓	5	x	2	54	+ve	Screening
Biopsy (Group B) n=2	IDC	II	x	1.5x1.7	1 st visit	✓	2.5	x	2	63	+ve	Screening
	LCIS	I	✓	2.2 x 1.5	1 st visit	✓	5	✓	4	40	+ve	Diagnostic

DCIS Ductal carcinoma in situ
IDC Intraductal carcinoma
DIN Ductal intraepithelial neoplasia
LCIS Lobular carcinoma in situ
LN Lymph node
OCP Oral contraceptive pills
BC Breast Cancer

In the follow up visits, some BIRADS 3 lesions were reevaluated as BIRADS 2 (number=96) and they were then correlated with lesions initially diagnosed as BIRADS 3 and then proved to be malignant (having false negative results), (number=8). The analysis included history, complaint, and clinical breast examination, mammographic and sonographic features. Significant results were found with positive family history and type of visit whether screening or diagnostic, and as regards the mammographic features , irregular mass, subtle asymmetry, calcified mass and focal distortion were all significant and the only significant sonographic feature found was the parenchymal disruption (table-3).

Table 3: History, clinical and sono-mammographic features of the cases downgraded from BIRADS 3 to BIRADS 2 (n=96) during their follow up in correlation to the cases upgraded to proven malignancy (n=8)

	Cases downgraded to BIRADS 2 on their follow up (n= 96)	%	Cases with FN (malignant) results on their follow up/biopsy (n=8)	%	Total	P value
History and Examination						
History of previous conservative breast surgery	10	10.1	2	25	12	0.2
History of previous mastectomy	6	6.3	0	-	6	1.0
Pre Menopausal status	64	66.7	3	37.5	67	0.1
Post Menopausal status	32	33.3	5	62.5	37	
Positive family history	33	34.4	8	100	41	**0.005***
Screening visit	33	34.4	6	75	39	**0.04***
Diagnostic visit	63	65.6	2	25	65	
Palpable mass	43	44.8	2	25	45	0.2
Pain	15	15.6	0	-	15	0.3
Skin changes	3	3.1	0	-	3	0.8
Nipple Discharge	8	8.3	0	-	8	0.5
Axillary swelling	3	3.1	0	-	3	0.8
Mammographic features	**n =71**	**%**	**n =8**	**%**	Total	P value
Breast Density ACR1	2	2.8	0	-	2	
ACR2	40	56.4	3	37.5	43	0.1
ACR3	22	31	4	50	26	
ACR4	6	8.5	1	12.5	7	
well defined soft tissue density	30	42.3	4	50	34	0.2
irregular mass	1	1.04	2	25	3	**0.01***
Subtle asymmetry	6	8.5	4	50	10	**0.003****
Microcalcification	11	15.5	2	25	13	0.3
Dilated ducts	8	11.3	0	-	8	0.5
calcified mass	2	2.8	2	25	4	**0.03***
focal distortion	7	9.9	3	37.5	10	**0.02***
Sonographic features	**n = 96**	**%**	**n = 8**	**%**	**Total**	**P value**
Fibroadenoma (single or multiple)	31	32.3	0	-	31	0.1
Cystic mass	43	44.8	2	25	45	0.5
Solid mass	42	43.8	6	75	48	0.09
Suppurative infection. Abscess	7	7.3	0	-	7	0.7
Inflammation/ Mastitis	1	1.04	0	-	1	0.8
Intra mammary lymph node	1	1.04	0	-	1	0.9
Lipoma	1	1.04	0	-	1	0.9
Papillomata	5	5.2	0	-	5	0.7
Parenchymal disruption	1	1.04	2	25	3	**0.01***
Retroareoler dilated ducts	28	29.2	1	12.5	29	0.3
Complex lesions	23	23.9	2	25	25	0.6
Duct ectasia	12	12.5	0	-	12	0.4
calcific focus	20	20.8	0	-	20	0.2

*statistically significant ** highly statistically significant
FN False negative

Fig 5 and 6 illustrates an example of BIRADS 3 cases that were downgraded to BIRADS 2 or upgraded to malignancy during the follow up visits.

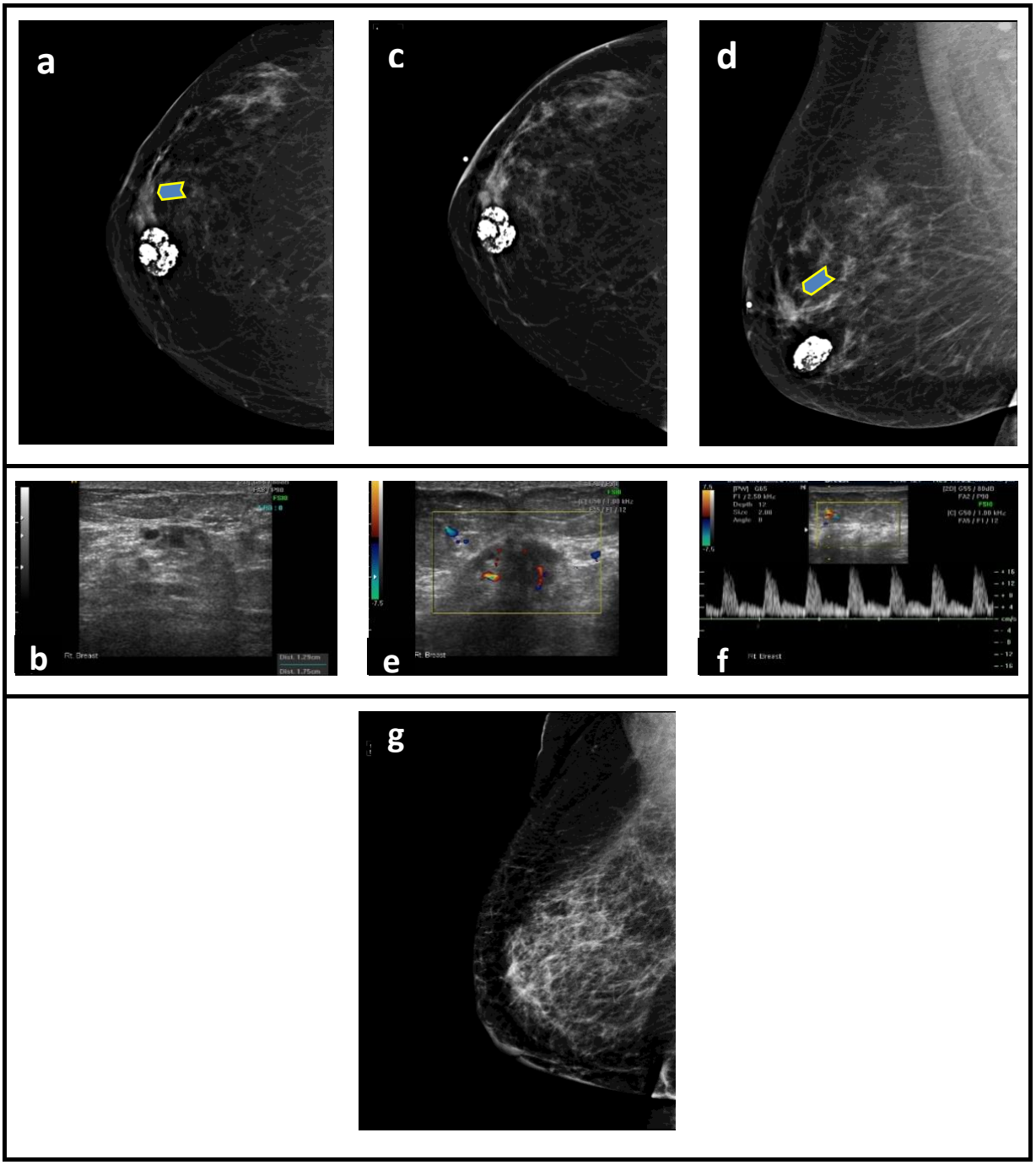


Figure 5: Digital mammography craniocaudal (CC) view showing non palpable non calcified retro areolar mammographic asymmetry (arrow heads) noted in right breast in 52-year-old women adjacent to a popcorn calcification pathognomonic for degenerated fibroadenoma (a), the asymmetry was seen only in one view as the mediolateral oblique (MLO) view was negative (not shown). Complementary ultrasound showed small retroareolar hypoechoic area (b), interpreted as BIRADS 3 (probably benign). At 6 months follow up, a palpable lesion was felt adjacent to the right nipple, a metallic marker were placed and CC (c) & MLO (d) of the right breast showed a suspicious irregularly bordered retroareolar mass. US demonstrated suspicious irregular mass (e), with abnormal color Doppler (f). FNAC guided by US revealed cellular smears positive for invasive mammary duct carcinoma C5 cytology category, Core biopsy reveled intraductal carcinoma grade II. Post-operative follow up mammography MLO view (g)

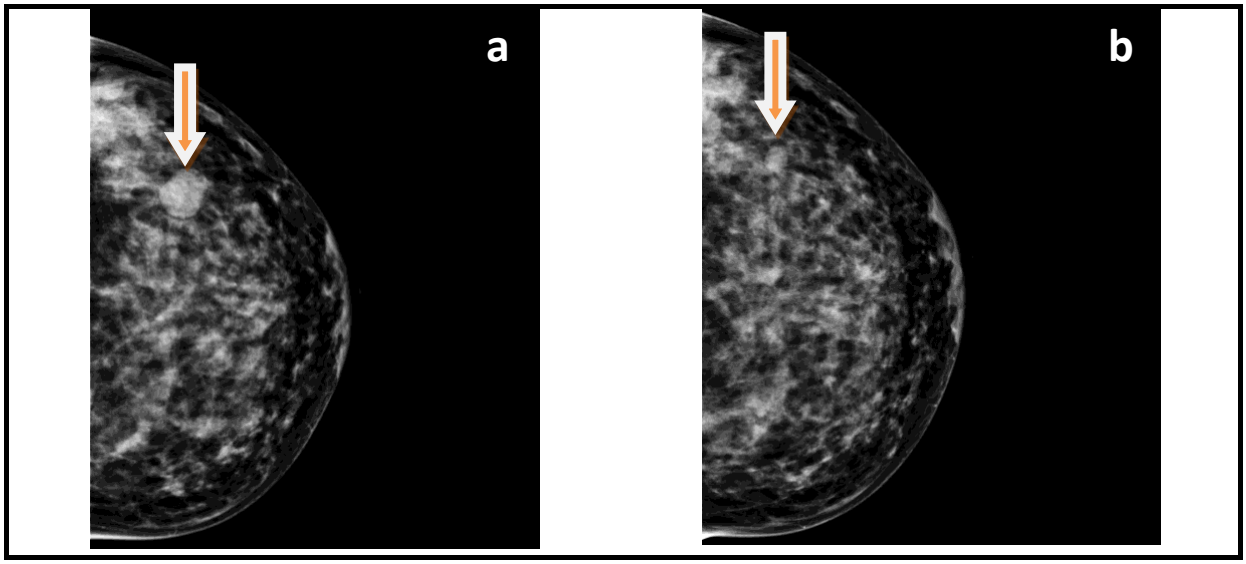


Figure 6:A Palpable well defined oval shaped lesion (arrow) in a heterogeosly dense Rt breast, CC mammographic view (a), Ultrasonography showed a cyst with internal echoes (not shown). A 6 months follow up mammography (b) demonstrated a noted decrease in size (arrow).

Discussion

To the best of our knowledge, no other studies compared BIRADS 3 cases which were downgraded to BIRADS 2, with malignant cases. In this study, we tried to know significant parameters that may help us to predict upgrading or downgrading of BIRADS3 cases. The current study demonstrated also that follow up by imaging is recommended rather than biopsy as all malignant cases were discovered in early visits in their short term follow up and at an early stage too with no difference in the survival years. In addition, there was considerably low percentage of the false negative cases (1.52%) in the follow up group, in spite that we were working on the palpable and non-palpable lesions, and this improves the level of confidence in the follow up protocol. Moreover, the results were nonsignificant when we compared the false negative results in the follow up and in the biopsy groups. Previous studies demonstrated that malignant breast lesions that are originally diagnosed as probably benign are accurately and immediately identified with periodic mammographic follow up. Depiction of these probably benign lesions is a valuable and commonly used weapon by the breast radiologist to avoid low-yield biopsies, which increase both the morbidity and the cost affiliated with breast cancer screening[6, 7, 8]. However, classical teaching and practice have demonstrated that biopsy is frequently done in solid palpable masses, often regardless the recognized benign imaging criteria [9]. The current study concluded that, both palpable and nonpalpable BIRADS 3 lesions were nearly equal in malignancy risk (less than 2 %), therefore we can direct palpable BIRADS 3 masses to follow up rather than biopsy as well as the nonpalpable masses. In accordance with our results, Graf et al. [7] authenticated that BIRADS 3 category has classically been applied to nonpalpable lesions, as only nonpalpable lesions have been demonstrated to have such a low probability of malignancy during periodic imaging surveillance and can be considered as a safe and convincing alternative to biopsy. They recommended that palpable masses that display the same probably benign features at mammography and US can be managed in a similar way and that biopsy could be averted [7].

In this study, the 19% dropped out cases were considered to be a good percentage when comparing patient compliance to the other countries but this means that there is still a lack of awareness about the risk of malignancy and the importance of follow up. Improvement of the patients' retention plans to maintain their adherence to follow up and improve their awareness is required and good patient counseling and education are necessary. Raza et al. [10] assigned the discrepancy in the compliance may be due to the fact that with biopsy, an answer has been

afford to the patient, whereas with imaging follow-up, there is continued ambiguity, pushing the patient to return for the recommended interval imaging. No universal interval has been established for follow up of palpable probably benign lesions. However, a minimum of 2 years of follow-up has been widely approved as a barometer of benignity of the nonpalpable masses [9, 10].

Biopsy for breast lesions is approximately simple, safe, and commonly performed. However, it is troublesome for patients to undergo biopsy of all palpable masses; moreover, it is an invasive procedure that may also increase the patient's stress level and may result in drawbacks as hematoma, infection, parenchymal distortion, and scarring. Aforementioned complications as parenchymal distortion, skin thickening, and raised focal density, can increase the false-positive diagnoses in follow-up screening mammograms [4].The current study demonstrated that family history was the only common risk in the 8 malignant cases; therefore, we may consider biopsy in BIRADS 3 cases with positive family history rather than follow up.

This report had limitations as we did not correlate dense breast tissue with BIRADS 3 lesions and we did not also study the cost effectiveness of the follow up protocol in relation to the performance of biopsy. In addition, we recommend further analysis based on large scale multi-institutional studies to find out more data that will help to establish the clinical acceptability of periodic surveillance for palpable probably benign masses. The strengths of this study lies in including palpable with the non-palpable BIRADS 3 lesions in the assessment, and this has not been studied before except in a single institution, besides this study included all BIRADS 3 lesions and not only masses which we have not encountered in previous studies.

Conclusion

In BIRADS 3 breast lesions interpreted by experienced radiologists and surgeons especially in absence of the parameters favoring malignancy, short term follow up can confidently replace biopsy.

Acknowledgment

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References:

1. **Nicandro CR, Efrén MM, MaríaYaneli AA, Enrique MD, Héctor Gabriel AM, Nancy PC, Alejandro GH, Guillermo de Jesús HR, RocíoErandi BM (2013)**: Evaluation of the diagnostic power of thermography in breast cancer using bayesian network classifiers. Comput Math Methods Med., 2013:264246.
2. **Fiaschetti V, Salimbeni C, Gaspari E, Dembele GK, Bolacchi F, Cossu E, Pistolese CA, Perretta T, Simonetti G(2012):** The role of second-look ultrasound of BIRADS3 mammary lesions detected by breast MR imaging. Eur J Radiol., 81(11):3178-3184.
3. **Puliti D, Duffey SW, Miccinesi G(2012) :** Over diagnosis in mammographic screening for breast cancer in Europe: a literature review. J Med Screen, 19 (1):42-56.
4. **Park YM, Kim EK, Lee JH, Ryu JH, Han SS, Choi SJ, Lee SJ, Yoon HK(2008):** Palpable breast masses with probably benign morphology at sonography: can biopsy be deferred? ActaRadiol., 49(10):1104-1111.
5. **American College of Radiology (2003):** Illustrated Breast Imaging Reporting and Data System (BI-RADS): ultrasound. Reston, Va: American College of Radiology.
6. **American College of Radiology (2003):** Illustrated Breast Imaging Reporting and Data System (BI-RADS): Mammography. Reston, Va: American College of Radiology.
7. **Graf O, Helbich TH, Hopf G, Graf C, Sickles EA(2007):**Probably benign breast masses at US: is follow-up an acceptable alternative to biopsy? Radiology,244(1):87-93.
8. **Kopans DB, Monsees B, Feig SA(2003):** Screening for cancer: when is it valid? Lessons from the mammography experience. Radiology , 229:319–327.
9. **Kopans DB(2004):**Sonography should not be used for breast cancer screening until its efficacy has been proven scientifically. Am J Roentgenol ., 182:489–491.
10. **Raza S, Goldkamp AL, Chikarmane SA, Birdwell RL(2010):** US of breast masses categorized as BIRADS 3, 4, and 5: Pictorial review of factors influencing clinical management. Radiographics ;30(5):1199-1213.