Breast Cancer in Patients Initially Assigned as BI-RADS Category 3

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Objectives: *To determine the Positive Predictive Value (PPV) for malignancy and characteristics of breast cancer found in patients who were initially categorized as having Breast Imaging Reporting and Data System (BI-RADS) 3.*
Material and Method: *Medical records of patients assigned to BI-RADS 3 from January, 1st to December, 31st 2002 at the Breast diagnostic center, Ramathibodi Hospital who had imaging follow-up for at least 2 years or had biopsy performed were retrospectively reviewed.*
Results: *Of 949 patients, 23 were found to have malignancy, i.e., 2.4% PPV. The most common imaging findings of breast cancer were calcifications on mammogram and mass on sonogram. Mean interval from first imaging to biopsy was 13.1 months. Only 78% of malignancies were diagnosed within 2 years. Less than 50% of these were ductal carcinoma in situ or stage I invasive ductal carcinoma.*
Conclusion: *PPV for malignancy in the present study was comparable to the previous studies. However, longer time to diagnosis and more advanced stage of breast cancer at diagnosis were found. Periodically short-interval mammogram and sonogram, at not less than 2 year-intervals, were recommended.*

Keywords: *BI-RADS, BI-RADS category 3, Probably benign lesion, Short-interval follow-up, Breast cancer*

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Mammogram is accepted to be the most appropriate tool for screening breast cancer[1]. Ultrasonogram is a useful adjunctive diagnostic tool in cases of dense breasts, which decrease sensitivity of the mammogram[2]. Their wide uses have resulted in the detection of many small nonpalpable lesions. However, the low specificity of mammogram and sonogram has also resulted in many unnecessary biopsies[3]. These biopsies raise the cost of mammographic screening and results in emotional and physical disturbance to patients[3]. The American College of Radiology (ACR) has developed the Breast Imaging reporting and Data System (BI-RADS) that is intended to standardize the terminology in mammogram and sonographic report, the assessment of the findings, and the recommendation of the action to be taken[3-5]. BI-RADS category 3 is defined as a lesion with low probability of malignancy[4-15]. The frequency of malignancy among lesions in this category should be less than 2%[6-15]. For these almost certainly benign lesions, periodic mammographic surveillance may be recommended, principally to avoid morbidity and to reduce cost[6-15]. The follow-up protocol purposed by ACR is 6-month-interval follow-up for at least 2 or 3 years[7].

The purpose of the present study was to determine the Positive Predictive Value (PPV) for malignancy and characteristics of breast cancer found in the patients who initially were categorized in BI-RADS category 3 in our center.

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Material and Method

From January, 1st to December, 31st 2002, 12,695 women underwent mammography at the Breast Diagnostic Center, Faculty of Medicine, Ramathibodi

Hospital. Mammography was performed using two mammographic machines (Lorad M-IV, Danbury, CT, USA and Senographe DMR, GE, Milwaukee, WI, USA). Sonography (HDI 5000, Philips ultrasound, Bothell, WA, USA), used as a complementary investigation, followed mammography in the same visit in nearly all of the women, except those with almost entirely fatty breasts. Thirteen radiologists, including three radiologists specialized in breast imaging, interpreted the mammograms and sonograms. Final assessment was based on BI-RADS category. In this period, 2,175 patients (17.1%) were assigned to BI-RADS category 3. Patients who had follow-up imaging within at least 2 years or had undergone biopsies for histopathologic diagnosis were included in the present study. Using these criteria, 949 patients were enrolled. Among the 1,226 excluded patients, 699 patients either had no follow-up mammography or continued to be categorized as BI-RADS category 3 on their last mammograms. The remaining 527 patients had BI-RADS category 1 or 2 on their follow-up mammogram, which did not extend to the 2 year-interval.

Age, personal history of breast cancer, mammographic and sonographic findings, size of mass or complicated cyst, date of first and last images, intervention procedure, reason for intervention, type of intervention, frequency, type and stage of malignancy and status of lesions at last imaging in non-biopsy group were retrospectively reviewed.

Size of mass or complicated cyst was estimated from the records of mammographic or sonographic findings that were available. Status of lesion on last follow-up image in the non-biopsy group was classified as "stable", "regression", "disappear", or "progression". "Stable" was defined as lesions that did not change in size and morphology. "Regression" was defined as lesions that became smaller, decreased in number or the previously seen solid nodule or complicated cysts present as simple cyst in the subsequent study. "Disappear" was defined as lesions that were no longer seen. "Progression" was defined as lesion that became larger, increased in number, had more irregular shape or ill-defined border, or de novo interval-detected BI-RADS category 3,4 or 5 lesions that were independent from the initial category 3 lesion or stable lesions that another radiologist categorized as BI-RADS category 4.

Malignancy was defined as any type of breast cancer including ductal carcinoma in situ diagnosed from histopathology during the 2-year observation. Patients without demonstrated malignancy in the observation period were assumed to have truly benign lesions.

Medical records, mammography and sonography of all malignant cases were retrospectively reviewed by the principle investigator. Size was measured on the initial image, which was categorized as BI-RADS category 3. Cancer was staged according to the American Joint Committee on Cancer Staging System[16].

Data were entered into a computerized spreadsheet for analysis with statistical software SPSS (Statistical Package for Social Sciences) version 11.5. The frequency and percentage distribution with descriptive of statistics, monography and sonography were presented. Diagnostic test was preformed for malignancy in BI-RADS category 3.

Results

There were 949 patients in the present study. The mean age was 49.3 years (SD 7.6 years, range; 24 to 82 years). One hundred patients (10.5%) had a personal history of breast cancer. The mean size of mass or complicated cyst was 1 cm. (range; 0.2-5 cm). Details of mammographic and sonographic findings are listed in Table 1.

Most cases were managed with imaging surveillance only. There were 803 patients (85%) in this non-biopsy group. The mean follow-up period was 28.9 months (SD 5 months, range; 0 to 39 months). On the last follow-up imaging, 422 lesions (44.5%) were stable. Regression was found in 169 lesions (17.8%). One hundred and fifty seven lesions (16.5%) disappeared. Progression was found in 55 lesions (5.8%).

Overall, 146 biopsy procedures were performed (15.4%), after a mean follow-up period of 10 months (SD 10.2 months, range; 0-38 months). Core needle biopsy was performed in 62.3% of patients and 37.7% by surgical biopsy. The reasons for intervention and results of biopsies are shown in Table 2.

There were 23 malignant cases in the present study (2.4% PPV for malignancy). The mean follow-up period was 13.1 months (SD 11.4 months, range; 0-38 months). The mean size of the lesion was 1.5 cm (SD 2 cm, range; 0.3-10 cm). In the present study 39.1%, 60.9%, 69.6%, 78.3% and 100% of malignancies were identified at the 6, 12, 18, 24 and 38-month follow-up examination, respectively.

Only 44% of breast cancers were detected at their early course of disease; DCIS in 7 cases (30.4%) and stage I invasive ductal carcinoma (IDC) in 3 cases (13%). Five patients had stage IIA, 3 cases had stage

Table 1. Characteristics of 949 BI-RADS category 3 lesions seen on mammography and sonography

Characteristics	Mammography			Sonography		
	Total	Pathology		Total	Pathology	
		Benign	Malignant		Benign	Malignant
Mass	216 (22.8)	212 (22.9)	4 (17.4)	471 (49.6)	459 (49.6)	12 (52.2)
Calcifications	179 (18.9)	171 (18.5)	8 (34.8)	1 (0.1)	1 (0.1)	0
Mass with calcifications	18 (1.9)	17 (1.8)	1 (4.3)	11 (1.2)	11 (1.2)	0
Complicated cyst	NA	NA	NA	189 (19.9)	188 (20.3)	1 (4.3)
Architectural distortion	45 (4.7)	43 (4.6)	2 (8.7)	12 (1.3)	12 (1.3)	0
Asymmetric density	99 (10.4)	95 (10.3)	4 (17.4)	NA	NA	NA
Others	7 (0.7)	7 (0.8)	0	9 (0.9)	8 (0.9)	1* (4.3)
Negative finding**	385 (40.6)	381 (41.1)	4 (17.4)	256 (27.0)	247 (26.7)	9 (39.1)
Total	949 (100)	926 (100)	23 (100)	949 (100)	926 (100)	23 (100)

* Focal duct dilatation
** Negative finding refers to negative finding on Mammography (middle column) or Sonography (last column), but not both
Note. Number in parentheses was percentage
Abbreviation: NA = Not applicable

Table 2. Reason for intervention and pathologic results

Reason for biopsy	Number of lesions biopsied	Results		PPV (%)
		Benign	Malignant	
Interval progression	62 (42.5)	47 (38.2)	15 (65.2)	24.2
Surgeon's preference	59 (40.4)	55 (44.7)	4 (17.4)	6.8
Patient's preference	15 (10.3)	14 (11.4)	1 (4.3)	6.7
De novo lesions	10 (6.8)	7 (5.7)	3 (13.0)	30.0
Total	146 (100)	123 (100)	23 (100)	15.8

Note. Number in parentheses was percentage
Abbreviations: PPV= Positive predictive value

IIB, 1 case had stage IIIB and one patient had stage IV IDC. Stage of cancer could not be determined in 3 cases.

Discussion

The BI-RADS category 3 is associated with lesions with less than 2% likelihood for malignancy. The benign nature of such lesions can be confirmed by demonstrating stability on short interval follow-up mammograms after 2 years[4-15]. Initially, BI-RADS category has been used only for nonpalpable lesions[8-10]. A recent study suggests that palpable noncalcified solid breast masses with benign morphology on mammography and sonography can be managed similar to nonpalpable BI-RADS category 3 lesions[11].

The scientific evidence establishing the safety of periodic mammographic surveillance of lesions in this category is based primarily on large well-conducted, longitudinal prospective studies from Sickles in 1991[8], 1994[9] and Varas et al in 1992[10] that found the prevalence of the malignancies to be 0.5, 1.4 and 1.7%, respectively. More recent studies also reported low probability of malignancy, ranging from 0.3-2%[4,12-14]. In the present study, the authors found 2.4% PPV for malignancy (23 from 949 patients), which was comparable to the previous studies.

A variety of mammographic and sonographic findings are interpreted as BI-RADS category 3 lesions. The three most common mammographic findings are

(a) noncalcified solid masses with a round, oval, or gently lobular contour and margins that are predominantly circumscribed, (b) clustered tiny round calcifications and (c) focal asymmetric density which resembles breast tissue on spot compression[6,7,15]. For sonography, common category 3 findings include a solid mass with circumscribed margins, oval shape and horizontal orientation, most likely a fibroadenoma[7,11]. Nonpalpable complicated cysts and clustered microcysts are also assigned to be sonographic finding of category 3 lesion[7].

The most commonly encountered BI-RADS category 3 lesions in the present study was a breast mass in either mammography or sonography. In the malignant group, calcifications were the most frequent mammographic findings (8 from 23 cases or 34.8%). A mass was also the most common sonographic lesion found to be malignant (12 from 23 cases or 52.2%). Interestingly, four malignant lesions were invisible on the mammogram. Fortunately, most of these could be seen as a mass on the sonogram. On the other hand, nine lesions were not apparent on sonogram. The majority of these lesions were calcifications, which were hardly visible on the sonogram. These findings strongly suggested that the combination of mammography and sonography as either a screening or diagnostic procedure increased sensitivity in detecting abnormal lesions.

Positive predictive value for malignancy in BI-RADS category 3 patients who underwent biopsy in the present study was 15.8% (23 from 146 biopsies). These data were different from previous studies from Sickles[8] and Rosen et al[15], who reported 10.6% (17 from 161 biopsies) and 28.7% (51 from 178 biopsies), respectively.

The main reason to perform a biopsy in the initial category 3 lesions was interval progression (42.5%), followed by surgeon's preference (40.4%). Interval progression is also the main reason that prompted a biopsy recommendation in several published studies[6,8,9,15]. However, de novo lesion was the finding with the highest PPV for breast cancer (30%) in the present study. This indicated that a meticulous examination of whole breasts bilaterally in patients who were assigned to BI-RADS category 3 was important, and not to evaluate only the initial lesions.

Some surgeons prefer to biopsy BI-RADS category 3 lesions, which may be ambiguous on physical examination. This reason was a common indication for biopsies in the present study. According to the presented data, this indication was associated with only 6.8% PPV for cancer (4 out of 59 lesions). This information might reassure the surgeon to withhold a biopsy in cases of mammographic and sonographic findings that fulfilled the criteria of being BI-RADS category 3.

Management, with periodic surveillance of BI-RADS category 3 lesions, is based on three principles[6-15]. First, the category 3 lesion has very low likelihood of malignancy. Second, if this lesion is malignant, its growth or so called interval progression can be identified usually within 6-12- months. Finally, the malignant lesion initially categorized in BI-RADS category 3 is likely to be an early stage cancer with prognosis similar to that of other malignancies identified on routine screening mammography.

The follow-up protocol for patients with BI-RADS category 3 purposed by ACR[7], primarily based on studies of Sickles[6,8,9], consisted of a unilateral mammogram obtained at 6 months and bilateral mammogram obtained 6 months later, when routine screening of the contralateral breast would be scheduled. The length of follow up should be at least 2-3 years.

Lesions assigned to BI-RADS category 3 in our center did not display features which required a short time to intervene or features of early stage malignancies as demonstrated in the published literature[8-10]. Only 60.9% of malignancies were diagnosed within the first 12-month interval follow-up. If the follow-up period extended to 24 months, only 78.3% of cancers were detected. Moreover, 5 lesions (21.7%) proved to be cancerous at a period beyond 24 months with the longest interval of 38 months.

Less than 50% of malignancies found in the present study were DCIS and stage I invasive ductal carcinoma. One case of stage IV invasive ductal carcinoma was also noted. Different natural histories might be able to explain this finding. But there was also a lack of standardization in the reading of mammograms as well as sonograms. There were many radiologists interpreting mammograms and sonograms in the authors' center. Each radiologist applied standards based on their individual training, experience[15] and judgment. Sometimes the lesion was not improperly categorized. However, the aspect of false negative rate of BI-RADS category 3 lesions was beyond the scope of this present study. A meticulous, retrospective review of images of those malignant cases might be the authors' next investigation.

The attending physician also plays an important role in the early detection of breast cancer by sending patients for surveillance regularly. Finally,

the patients themselves should cooperate with the doctor's instructions.

There were a few limitations in the present study. Firstly, a large proportion of the patients were lost to follow-up. Thirty-two percent of patients were lost to follow-up despite the assignment as BI-RADS category 3. Secondly, retrospectively reviewed features of the lesions were based on official reports interpreted by thirteen radiologists. Thus, there should have been a lack of standardization.

Conclusion

Positive predictive value for malignancy in BI-RADS category 3 of the present study was comparable to the previous studies. This shows that the interpretation of BI-RADS category 3 lesion is reliable. However, longer time to diagnosis and more advanced stage at diagnosis of breast cancer were found. Interval progression was the main reason for biopsy. De novo lesion had the highest PPV for malignancy. Maintaining regularly periodic surveillance imaging for at least 2 years in conjunction with meticulously evaluating whole breasts bilaterally were strongly recommended according to the authors' findings.

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มะเร็งเต้านมที่พบใน BI-RADS category 3

ชลทิพย์ วิรัตกพันธ์, บุษณี วิบุลผลประเสริฐ, ภาณุวัฒน์ เลิศสิทธิชัย

บทนำ: *ความผิดปกติที่ตรวจพบในแมมโมแกรมและอัลตราซาวด์ที่สามารถจัดอยู่ใน Breast Imaging Reporting and Data System (BI-RADS) category 3 ควรมีความเสี่ยงที่จะเป็นมะเร็งเต้านมน้อยมาก กล่าวคือ น้อยกว่าร้อยละ 2 ซึ่งสามารถติดตามการเปลี่ยนแปลงทุก 6 เดือน เป็นเวลา 2-3 ปี*

วัตถุประสงค์: *เพื่อศึกษาโอกาสที่จะเป็นมะเร็งเต้านมในผู้ป่วยที่ได้รับการจัดอยู่ใน BI-RADS category 3 และศึกษารายละเอียดของมะเร็งเต้านมที่พบ*

วัสดุและวิธีการ: *ศึกษาข้อมูลย้อนหลังของผู้ป่วยที่มารับการตรวจที่ศูนย์ตรวจวินิจฉัยเต้านม คณะแพทยศาสตร์โรงพยาบาลรามาธิบดีในปี พ.ศ. 2545 และได้รับการติดตามผลด้วยแมมโมแกรมและ / หรืออัลตราซาวด์เป็นเวลาอย่างน้อย 2 ปี หรือได้รับการตรวจชิ้นเนื้อ*

ผลการศึกษา: *จากจำนวนผู้ป่วย 949 ราย พบมะเร็งเต้านม 23 ราย (ร้อยละ2.4) ระยะเวลาเฉลี่ย ตั้งแต่วันแรกที่ตรวจพบถึงวันที่ทำการตรวจชิ้นเนื้อพบมะเร็งคือ 13 เดือน 1 วัน เมื่อติดตามถึง 2 ปี วินิจฉัยมะเร็งได้ร้อยละ 78.3 มะเร็งที่พบน้อยกว่าร้อยละ 50 เป็นมะเร็งระยะต้น (Ductal carcinoma in situ และ Invasive ductal carcinoma stage I)*

สรุป: *การศึกษานี้พบโอกาสเป็นมะเร็งเต้านมใกล้เคียงกับการศึกษาอื่นๆ ที่ผ่านมา แต่พบระยะเวลาที่สามารถตรวจพบมะเร็งนานกว่า และพบมะเร็งระยะสูงกว่า ผู้ป่วยที่ได้รับการจัดอยู่ใน BI-RADS category 3 ควรมีการติดตามผลอย่างสม่ำเสมอเป็นเวลาไม่น้อยกว่า 2 ปี*