Clinical Data as an Adjunct to Ultrasound Reduces the False-Negative Malignancy Rate in BI-RADS 3 Breast Lesions

Authors S. Ackermann[1], C.-A. Schoenenberger[2], R. Zanetti-Dällenbach[3]

Affiliations
[1] Gynecology & Obstetrics, Hôpital de Morges, Morges, Switzerland
[2] Department of Chemistry, University of Basel, Basel, Switzerland
[3] Gynecology & Obstetrics, University Hospital Basel, Basel, Switzerland

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- breast ultrasound
- BI-RADS
- breast cancer
- false-negative
- cancer rate

Abstract

Purpose: Ultrasound (US) is a well-established diagnostic procedure for breast examination. We investigated the malignancy rate in solid breast lesions according to their BI-RADS classification with a particular focus on false-negative BI-RADS 3 lesions. We examined whether patient history and clinical findings could provide additional information that would help determine further diagnostic steps in breast lesions.

Materials and Methods: We conducted a retrospective study by exploring US BI-RADS in 1469 breast lesions of 1201 patients who underwent minimally invasive breast biopsy (MIBB) from January 2002 to December 2011.

Results: The overall sensitivity and specificity of BI-RADS classification was 97.4% and 66.4%, respectively, with a positive (PPV) and negative predictive value (NPV) of 65% and 98%, respectively. In 506 BI-RADS 3 lesions, histology revealed 15 malignancies (2.4% malignancy rate), which corresponds to a false-negative rate (FNR) of 2.6%. Clinical evaluation and patient requests critically influenced the further diagnostic procedure, thereby prevailing over the recommendation given by the BI-RADS 3 classification.

Conclusion: Clinical criteria including age, family and personal history, clinical examination, mammography and patient choice ensure adequate diagnostic procedures such as short-term follow-up or MIBB in patients with lesions classified as US-BI-RADS 3.

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Correspondence
Dr. R. Zanetti-Dällenbach, PD Dr.
University Hospital Basel
Gynecology & Obstetrics
Spitalstrasse 21
4031 Basel
Switzerland
Tel.: +41/61/328 73 31
Rosanna.Zanetti@unibas.ch

Introduction

Ultrasound (US) is a well-established diagnostic tool for breast examinations. It is commonly used to evaluate breast abnormalities that are detected by physicians during clinical breast exams, by mammography (MG) or by magnetic resonance imaging (MRI) [1]. Moreover, US is used in initial examinations of young women [2], as a screening method in women at high risk [3,4], and as an adjunct to breast cancer screening in women with dense breast tissue because the sensitivity of MG is low for these patients [1,4]. US is also performed to evaluate problems associated with breast implants [5,6], and it is recommended as the primary imaging modality to guide minimally invasive breast biopsies (MIBB) [1]. Although it is known that detecting, describing, and interpreting breast lesions depends on the examiner [7], breast US in outpatients is carried out in teaching hospitals not only by experienced operators but also by trainees.

Classifying sonographic features, as described by the Breast Imaging Reporting and Data System (BI-RADS) [8], provides the basis for assessing breast lesions by US. Solid breast lesions are characterized according to several features: their form (oval, round, irregular); their orientation (horizontal, vertical); their margins (circumscribed, angular, microlobulated, spiculated, non-circumscribed); their echogenicity (anechoic, hyperechoic, hypoechoic, complex); their posterior acoustic features; and the surrounding tissue reaction. Benign masses are round or oval, and they are more wide than tall, with smooth, defined margins. In contrast, malignant masses tend to be irregular, with ill-defined to spiculated margins, and they are taller than wide. In addition, BI-RADS represents solid breast lesion classification according to their malignancy risk. A solid breast lesion without any suspicious features is considered to be BI-RADS 3, i.e., probably benign, whereas BI-RADS 4 indicates a suspicious finding, and BI-RADS 5 is most likely malignant.

In MG studies, BI-RADS 3, BI-RADS 4, and BI-RADS 5 lesions have a likelihood of malignancy of ≤2%, 3–89%, and ≥95%, respectively. In diagnostic US series, BI-RADS 3 lesions have been reported to have cancer rates from 0.2% [9] to 11.4% [10]. Cancer rates in BI-RADS 4 lesions range from 8.6% [11] to 47.8% [12], and in BI-RADS 5 they range from 57.1% [10] to 96.8% [12]. On the one hand, these variations demonstrate that breast US is highly user-dependent. On the other hand, the considerable overlap between benign and malignant US features contributes to the variations. In general, breast US studies report results from examinations performed by experts. There are only a few reports of results from US conducted by technicians [1, 13] or by private practice physicians [14].

Here we present results from a study on the malignancy rates of solid breast lesions that were classified in different BI-RADS categories according to breast US performed either by experienced examiners or by trainees which reflects the daily clinical practice in a teaching hospital. As the US BI-RADS 3 category represents breast lesions that are 'probably benign' and thus require close follow-up rather than biopsy, we scrutinized the false-negative cases in this specific category. In particular, we studied the extent to which a patient's history and other clinical findings minimized false-negative results obtained from sonographic evaluation of the breast lesion.

Materials and Methods

We conducted a single-center, retrospective study exploring 1469 sonographic solid breast lesions in 1201 patients. The study was approved by the local ethics committee. Women with a solid breast lesion who were scheduled for minimally invasive breast biopsy (MIBB) at our breast clinic between January 2002 and December 2011 were included. Only patients who were at least 18 years old and had lesions classified as BI-RADS 3, 4 or 5 were considered. Patients with BI-RADS 2 lesions were not included because MIBB is not generally indicated. Patients who underwent skin biopsy, lymph node biopsy or fine needle aspiration (FNA) in case of symptomatic cysts (BI-RADS 2) were also excluded. Before MIBB was carried out, patients were asked about their personal and family history. All women had a bilateral clinical breast examination and a bilateral whole breast US. Breast US and MIBB were performed either by experienced examiners or by trainees who were supervised by an experienced examiner, as is common in teaching hospitals. Sonographic examinations were conducted using either a Philips HDI 5000 Sono CT© (Philips, Zürich, Switzerland) (2002–2008) or a Hitachi EUB-7500 V© US system (Hitachi Medical System Europe Holding AG, Zug, Switzerland) (2008–2011).

In cases in which an MG was performed, the examiner was aware of the results at the time of US. Each lesion was scanned in a transverse and a sagittal plane. The dimensions were recorded along 3 orthogonal planes. US features were described and categorized according to ACR® BI-RADS ultrasound [15, 16]. In cases in which the US examinations were performed before the implementation of the US BI-RADS lexicon in 2003, the US diagnosis and the final probability of malignancy was scored on a 5-point scale, based on the BI-RADS score under development for US [17]. MIBB was performed using either a core instrument (Magnum© core high speed, Bard Medica S.A., Switzerland) or a vacuum biopsy tool (Mammotome hand held©, Johnson & Johnson AG, Switzerland). The core had a 14-gauge needle, while the vacuum had an 8 or 11-gauge needle. Biopsy specimens were processed for histopathology by standard procedures and evaluated by an experienced pathologist. Data on patient and lesion characteristics were retrieved from electronic medical records (View Point©, Bildverarbeitung, Wessling, Germany) before being recorded in an Excel database.

Statistical methods

Metric or ordinal data were summarized using the mean, median, minimum, maximum, and SD as appropriate. Categorical variables were summarized using counts and percentages. Comparisons between study groups were done with T-tests, Mann-Whitney U-tests, or Fishers' exact tests, as appropriate. A p-value < 0.05 was considered to be significant. In order to assess the US BI-RADS accuracy of predicting cancer, we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with a 95% confidence interval. All evaluations were done using the statistical software R v. 3.1.3. [18].

Results

We identified 1232 patients with 1504 breast lesions who underwent MIBB between January 2002 and December 2011. 31 patients with 35 breast lesions had to be excluded due to male gender (n = 18), age under 18 years (n = 10), missing histology (n = 2), or skin lesion (n = 1). Thus, 1201 female patients with 1469 breast lesions were included in the final analysis. Some of the patients had more than one breast lesion. Accordingly, 2 biopsies were performed in 155 patients, 3 in 39 patients, and more than 3 in 15 patients. In 80 cases, a bilateral biopsy was necessary.

In 74.6% (n = 896) of 1201 breast US examinations, the examinations were performed by experienced examiners while 25.4% (n = 305) were carried out by trainees under supervision. Patient ages ranged from 18 to 98 years, with a mean of 53.2 years. Patient and lesion characteristics are summarized in **Table 1**. 42.1% (n = 506) of all patients had BI-RADS 3 lesions, 31.0% (n = 373) had BI-RADS 4 lesions, and 26.9% (n = 323) had BI-RADS 5 lesions. The patients with BI-RADS 3 lesions were significantly younger than those with either BI-RADS 4 or 5 lesions. In addition, patients with BI-RADS 4 lesions were significantly younger than patients with BI-RADS 5 lesions. 600 women (50%) were <52 years old or premenopausal and 601 women (50%) were ≥52 years of age, i.e., postmenopausal, if the mean age of menopause in our population was considered to be 52. In the distribution of BI-RADS 3 to 5 lesions according to age, BI-RADS 3 lesions were most prominent in premenopausal women.

While the majority of all patients had no personal history of breast disease, 7% (n = 84) reported a personal history of breast cancer, 11.2% (n = 134) a personal history of MIBB or open breast biopsy, and 1.5% (n = 18) a history of mastitis. Of the 84 women with a personal history of breast cancer, 16.7% (n = 14) had BI-RADS 3 lesions, 42.8% (n = 36) had BI-RADS 4 lesions, and 40.5% (n = 34) had BI-RADS 5 lesions. Patients with BI-RADS 3 lesions had a positive personal history significantly more often than those with BI-RADS 4 or 5 lesions. In addition, patients with BI-RADS 4 lesions had a positive personal history significantly more often than patients with BI-RADS 5 lesions. Of those women whose family history was known, 303 women had a positive family history, while 609 had a negative family history.

Table 1 Patient and lesion characteristics; percentages in the gray shaded area of the table are calculated based on the number of the respective subgroup as opposed to percentages of the total number of patients or lesions.

Category	Total	BI-RADS 3	BI-RADS 4	BI-RADS 5	p-value	p-value	p-value	p-value
Number of patients	**1201 (100 %)**	**506 (42.1 %)**	**373 (31.0 %)**	**323 (26.9 %)**	**BI-RADS 3 vs. 4**	**BI-RADS 3 vs. 5**	**BI-RADS 4 vs. 5**	**overall**
Mean age in years ± SD	53.2 ± 18.0	42.1 ± 13.7	55.6 ± 15.8	68.0 ± 14.2	0.000	0.000	0.000	< 0.001
Age range (min–max, years)	(18–98)	(18–90)	(19–93)	(29–98)				
Maximal age					< 0.001	< 0.001	< 0.001	< 0.001
Age < 52 years	600 (50.0 %)	398 (66.3 %)	161 (26.9 %)	41 (6.8 %)				
Age ≥ 52 years	601 (50.0 %)	108 (18.0 %)	211 (35.1 %)	282 (46.9 %)				
Personal history					< 0.001	< 0.001	0.003	< 0.001
Negative	965 (80.3 %)	418 (43.3 %)	279 (28.9 %)	268 (27.8 %)				
MIBB or open biopsy	134 (11.2 %)	67 (50.0 %)	48 (35.8 %)	19 (14.2 %)				
Mastitis	18 (1.5 %)	7 (38.9 %)	9 (50.0 %)	2 (11.1 %)				
Breast cancer	84 (7.0 %)	14 (16.7 %)	36 (42.8 %)	34 (40.5 %)				
Family history					0.335	0.001	0.003	< 0.001
Positive	303 (25.2 %)	148 (48.8 %)	95 (31.4 %)	60 (19.8 %)				
Negative	609 (50.7 %)	248 (40.7 %)	201 (33.0 %)	160 (26.3 %)				
Unknown	289 (24.1 %)	109 (37.7 %)	77 (26.6 %)	103 (35.7 %)				
Number of lesions	**1 469 (100 %)**	**614 (41.8 %)**	**474 (32.3 %)**	**381 (25.9 %)**				
Mean max. lesion ø (mm) ± SD	17.6 ± 14.0	15.0 ± 9.2	15.1 ± 10.7	24.7 ± 20.2	0.999	0.000	0.000	< 0.001
Range of ø (min–max, mm)	(0.71–190)	(0.71–90.0)	(0.91–82.0)	(1.20–190)				
Maximal lesion diameter					0.538	< 0.001	< 0.001	< 0.001
< 20 mm	1 008 (71.9 %)	459 (45.5 %)	366 (36.3 %)	183 (18.2 %)				
≥ 20 mm	394 (28.1 %)	123 (31.2 %)	88 (22.3 %)	183 (46.5 %)				
Histopathology					< 0.001	< 0.001	< 0.001	< 0.001
Benign	835 (56.9 %)	574 (68.7 %)	239 (28.6 %)	22 (2.7 %)				
High-risk lesion	67 (4.5 %)	25 (37.3 %)	37 (55.2 %)	5 (7.5 %)				
Malignant	567 (38.6 %)	15 (2.6 %)	198 (34.9 %)	354 (62.5 %)				

Table 2 Malignancy rate.

	Total	BI-RADS 3	BI-RADS 4	BI-RADS 5
Number of breast lesions	1469	614	474	381
Number of malignancies	567	15	198	354
Malignancy rate	38.6%	2.4%	41.8%	92.9%

Table 3 Age-dependent and lesion size-dependent sensitivity, specificity, PPV, NPV.

	All	≥ 52 years	< 52 years	≥ 2 cm	< 2 cm
Sensitivity	97 %	99 %	92 %	99 %	97 %
Specificity	66 %	46 %	76 %	69 %	65 %
PPV	65 %	74 %	43 %	80 %	57 %
NPV	98 %	96 %	98 %	98 %	98 %

Women with BI-RADS 3, 4 and 5 lesions had a positive family history in 48.8 % (n = 148), 31.4 % (n = 95) and 19.8 % (n = 60), respectively. Significantly fewer women with a positive family history had a BI-RADS 5 lesion compared to a BI-RADS 4 lesion (p = 0.001) or a BI-RADS 3 (p = 0.003) lesion.

With respect to the total number of breast lesions, the retrospective review found that the lesions were classified as BI-RADS 3 in 41.8 % of cases (n = 614), BI-RADS 4 in 32.3 % of cases (n = 474), and BI-RADS 5 in 25.9 % of cases (n = 381). As summarized in **Table 2**, the malignancy rate was 2.4 % (n = 15) for BI-RADS 3 lesions, 41.8 % (n = 198) for BI-RADS 4 lesions, and 92.9 % (n = 354) for BI-RADS 5 lesions.

The histopathologic examination of the 1469 biopsies revealed 835 (56.9 %) benign lesions, 67 (4.5 %) high-risk lesions, and 567 (38.6 %) malignant lesions. In the 835 benign lesions, 35.4 % were fibroadenomas (n = 295); 15.7 % were fibroses (n = 131); 12.8 % were fibrocystic changes (n = 107); 3.8 % were inflammations (n = 32); and 32.3 % had other benign histologies (n = 270). Papillary lesions (n = 43) accounted for 64.2 % of the high-risk lesions. In the 567 malignancies, there were 388 ductal cancers (68.4 %); 76 lobular cancers (13.4 %); 17 ductal-lobular cancers (3.0 %); 23 ductal carcinomas in situ (4.0 %); 8 mucinous cancers (1.4 %); 1 medullary cancer (0.2 %); 40 other rare histologies of breast cancer (7.0 %); 4 lymphomas and 3 infiltrations from leukemia (1.2 %); 2 sarcomas and 2 malignant fibrous histiocytomas (0.8 %); and 1 malignant phyllodes tumor (0.2 %).

The mean volume of all lesions was 3.37 ml (0.01–168 ml). The mean volume was 1.69 ml (0.01–39.0 ml) for BI-RADS 3 lesions, 2.08 ml (0.01–173 ml) for BI-RADS 4 lesions, and 7.64 ml (0.03–168 ml) for BI-RADS 5 lesions. There was hardly a difference in volume between BI-RADS 3 and 4. The volumes of BI-RADS 3 (p = 0.000) and 4 lesions (p = < 0.001) were significantly smaller than those of BI-RADS 5 lesions. The mean of the largest lesion diameter was 17.6 mm (0.71–190 mm). In 71.9 % of cases (n = 1008), the lesion size was smaller than 2 cm, and 2 cm is reportedly the size at which a lesion becomes palpable [19].

Our results show an overall sensitivity and specificity of BI-RADS classification of 97 % and 66 %, respectively. The PPV and NPV are 65 % and 98 %, respectively. The age-dependent and lesion size-dependent sensitivity, specificity, PPV, and NPV are listed in **Table 3**. When analyzed according to age, our data show that US is less sensitive but more specific in premenopausal women compared to postmenopausal women.

In 12 patients, 15 lesions were categorized as BI-RADS 3, but the histology revealed a malignancy, yielding a false-negative rate (FNR) of 2.5 % in patients or in 2.6 % of breast malignancies. Among the 15 malignancies, 10 were breast cancers, yielding an

Table 4 False-negative and true-positive cancers.

		False-neg. rate	False-neg.	True-pos. rate	True-pos.	p-value
Number of patients with cancer	n = 479	2.51 %	n = 12	97.49 %	n = 467	
Mean age	65.2		52.2		65.5	0.001
(min–max, years)	(19–98)		(33–68)		(19–98)	
age < 52 years	97	7.21 %	7	92.79 %	90	0.004
age ≥ 52 years	382	1.30 %	5	98.70 %	377	
Number of cancer lesions	n = 567	2.65 %	n = 15	97.35 %	N = 552	
Mean max. lesion ø mm	21.9		20.9		22	0.838
(min–max, mm)	(1.2–190)		(7.00–70)		(1.20–190)	
Maximal lesion diameter						0.231
< 20 mm	323	3.41 %	11 (3.4 %)	96.59 %	312	
≥ 20 mm	220	1.37 %	3 (1.4 %)	98.63 %	217	

FNR of 1.67 % in breast cancer patients or in 1.76 % of breast cancers. The other 5 malignancies included a histiocytoma, a malignant phyllodes tumor, 2 leukemia lesions, and 1 lymphoma. The characteristics of all malignancies (false-negative in BI-RADS 3 and true-positive, i. e., BI-RADS 4 and 5) are listed in **Table 4**. The patients with a true-positive lesion had a mean age of 65.5 years (19–98 years), and they were significantly older (p = 0.001) than the patients with false-negative lesions, who had a mean age of 52.2 years (33–68 years). Other patient and lesion characteristics, such as personal history and lesion size, showed no significant difference between the false-negative and true-positive lesions. Furthermore, the data indicate a higher FNR for premenopausal women (7.21 %) compared to postmenopausal women (1.3 %), and also for small lesions (3.4 %) compared to large lesions (1.4 %).

None of the patients with false-negative lesions had a history of breast cancer or a previous MIBB or open biopsy. Other characteristics are listed in **Table 5**.

All but one patient (no. 1; **Fig. 1**) were older than 45 years. 2 postmenopausal patients (no. 2 and no. 7) had non-palpable lesions, refused immediate MIBB, and were followed up for 6 and 12 months. Because an increase in lesion size was observed, biopsy was performed. In one patient (no. 9; **Fig. 2**), in whom stem cell transplantation was planned due to leukemia, physical examination revealed a breast lump. In US, multiple bilateral breast lesions were seen and one lesion in each breast was biopsied. 2 patients either had a mother (no. 2) or a sister (no. 4; **Fig. 3**) with premenopausal breast cancer. Overall, 5 of the 12 women were premenopausal, 1 of them with a non-palpable lesion, while 6 of them were postmenopausal, 4 of them with non-palpable lesions. This does not include the one patient with leukemia (no. 9).

Discussion

US examinations are important clinical procedures for diagnosing breast lesions. However, there is significant overlap between benign and malignant US features so that a precise scanning technique, correlation to MG, and clinical examination are essential.

Previous studies of US BI-RADS classification report a sensitivity of 81.7 % [2] to 98 % [20], a specificity of 32.9 % [20] to 89 % [11], a PPV of 13.2 % [11] to 67.8 % [20], and an NPV of 92.3 % [20] to 99.9 % [11]. Our data corroborate the high sensitivity (97 %) and high NPV (98 %) as well as the low specificity (66 %) and low PPV (65 %).

In MG studies, BI-RADS 3 breast lesions have a risk of malignancy ≤ 2 %, while results from US studies vary considerably. Our data reveal a malignancy rate of 2.4 % and a breast cancer rate of 1.6 %. Those rates are in line with other reports that indicate cancer rates of less than 2 % (0.2–1.2 %) [9, 21]. However, higher rates (2.4–11.4 %) [10, 22] have been published. MG BI-RADS 4 and BI-RADS 5 lesions have cancer rates from 3–89 % and ≥ 95 %, respectively. Similar rates have been reported for US BI-RADS 4 (8.6–47.8 %) [10, 11] and 5 lesions (90.0–96.8 %) [11, 12]. Although a cancer rate of ≥ 90 % for US BI-RADS 5 lesions may be expected, lower cancer rates of 57.1 % [10] and 87.35 % [20] have been published. We found cancer rates of 41.8 % for BI-RADS 4 lesions and 92.9 % for BI-RADS 5 lesions, which closely aligns with published rates. MG reports were not included in our database as not all patients received an MG. Therefore, it was not possible to compare BI-RADS categories derived from MG with those derived from US.

BI-RADS provides standardized terms for US mass features, their assessment, and recommendations for how to proceed. While BI-RADS 4 and 5 lesions clearly demand clarification with MIBB, the ambiguities associated with BI-RADS 3 lesions make it the most difficult category to handle. The difference in BI-RADS 3 cancer rates reflects the observer dependence of real-time US. The difference also emphasizes the fact that additional parameters have to be included when deciding how to proceed with a patient, e. g., short-term follow-up or tissue sampling. Moreover, the FNRs indicate decreasing accuracy of the US BI-RADS system for predicting malignancy in younger patients or in those with decreasing lesion size.

Short-term US follow-up of BI-RADS 3 lesions is a reasonable alternative to MIBB provided that the lesions remain stable, in which case, a benign nature can be presumed [6, 9, 23]. Graf et al. [9] reported that 99.3 % of all lesions were stable during a follow-up over a mean duration of 3.3 years, with an FNR of 0.2 %. Considering the low risk of malignancy, monitoring BI-RADS 3 lesions is particularly recommended in young patients [6, 23, 24]. If the mass gets larger or if a change in US features is observed at follow-up, the classification changes to BI-RADS 4 and MIBB is indicated [20]. An increase in lesion size was observed in 2 of our patients, and in one of them an additional change in US features was detected. Because changes in size and/or US features often indicate malignancy, MIBB was subsequently carried out, which revealed an invasive ductal cancer in one case and a malignant phyllodes tumor in the other (**Fig. 4**).

Table 5 Patient and lesion characteristics of false-negative cases.

Patient (no.)	Lesion (no.)	Age (years)	Hormone therapy	Family history	Personal history	Max. diameter (mm)	Palpable lesion	Histopathology	ER	PR	Her-2/neu	BI-RADS MG
1	1	33	Premenopausal	–	–	9.0	–	Ductal cancer	Ne.	Neg.	Neg.	2
2	2	51	Current user	+ * *	–	10.8	–	Ductal cancer	Pos.	Pos.	Neg.	2
3	3	68	Past user	–	–	35.8	+	Ductal cancer	Neg.	Neg.	Neg.	5
4	4a	46	Premenopausal	+ * *	–	13.0	+(*)	Ductal cancer	Pos.	Pos.	Neg.	5
	4b*					10.0	+(*)	Ductal cancer	Pos.	Pos.	Neg.	5
5	5	58	Current user	–	–	50.5	+	Histiocytoma				–
6	6	62	Unknown	Unknown	–	7.0	–	DCIS				4
7	7	65	Current user	–	–	16.5	–	Malignant phyllodes				3
8	8	53	Never user	–	–	10.4	–	Ductal cancer	Neg.	Neg.	Pos.	4
9	9a	49	–	+	Leukemia	17.3	–	Leukemia				–
	9b #					18.1	+	Leukemia				–
10	10	46	Premenopausal	+	–	52	+	Lymphoma				0
11	11a	47	Premenopausal	–	–	16.2	+(*)	Ductal cancer	Pos.	Pos.	Pos.	4
	11b*					7.7	+(*)	Ductal cancer	Pos.	Pos.	Pos.	4
12		49	Premenopausal	–	–	15.4	+	Ductal cancer	Neg.	Neg.	Neg.	4

* Ipsilateral breast lesion; # Contralateral breast lesion; * * Mother or sister with premenopausal breast cancer; (*) 2 sonographic, one palpable lesion

Fig. 1 Patient no. 1 with triple negative, invasive ductal breast cancer.

Fig. 2 Patient no. 9 with leukemia.

Fig. 3 Patient no. 4 with invasive ductal cancer, sister with premenopausal breast cancer.

In our series of 506 BI-RADS 3 breast lesions (**Table 1**), there was only one false-negative lesion that occurred in a young patient (33 years). In this patient, BI-RADS classification, age, negative family history, and an inconspicuous MG suggested short-term follow-up by US. However, on patient request, MIBB

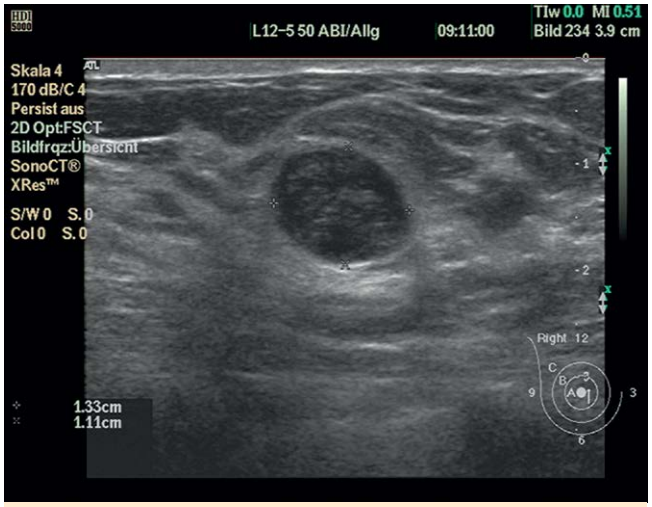

Fig. 4 Patient no. 7 with malignant phylloides tumor.

was performed and revealed an invasive ductal, triple-negative breast cancer. All other patients with BI-RADS 3 lesions were older than 45 years. In this age group, biopsy rather than follow-up is recommended in newly diagnosed breast lesions. This is because increasing age is a risk factor for developing breast cancer, as others have suggested [25,26].

Our data indicate that significantly fewer women with BI-RADS 5 lesions had a positive family history compared to women with BI-RADS 3 lesions. This finding reflects the fact that a positive family history was taken into account when deciding whether to follow-up a lesion or to perform MIBB. Because of the higher incidence of breast cancer in women with a positive family history, family history is an important parameter for breast cancer risk assessment. Particularly, in cancers occurring in individuals with a family history of BRCA mutation [27], lesions may lack suspicious sonographic features which then result in a false BI-RADS 3 classification. Our series of false negatives included 4 patients with a positive family history, 2 of them with first degree relatives who were diagnosed with premenopausal breast cancer.

Focused clinical examination and correlation with clinical history are important steps in evaluating breast lesions [6]. Consistent with this notion, breast lesions that were detected by clinical examination turned out to be cancer in 7 out of 12 patients, despite the US BI-RADS 3 classification of their lesions. Because of a previously diagnosed leukemia in one of the symptomatic patients with BI-RADS 3, MIBB was performed. In another case, patient concerns resulted in MIBB, which histology revealed to be a lymphoma.

Although MG was not available for all study subjects, MG showed BI-RADS 4 or 5 lesions in 8 of the patients with false-negative BI-RADS 3 lesions. Therefore, MIBB was carried out regardless of the US BI-RADS classification.

It has been reported that between 5.5% and 15.8% of all triple-negative breast cancers are misinterpreted as being probably benign based on the sonographic appearance which lacks malignant features [22,28,29]. Consistent with this notion, our series of false-negative BI-RAD 3 lesions also included 3 triple-negative breast cancers.

In our study, 74.6% of breast US examinations were performed by experts, and 25.4% were performed by trainees under supervision, as is common in daily clinical practice in a teaching hospital. Only 1 out of 12 patients that were classified as having a false-negative lesion was examined by a trainee. This finding is consistent with the conclusion of Berg et al. [3,7] who found that consistent US exam performance and interpretation is possible with minimal training. In their study, examinations that that were performed by experienced and less experienced sonographers showed substantial agreement in the key features of lesion description, but only moderate agreement in the BI-RADS final assessment for larger lesions. In addition, Bosch et al. [30] reported a high degree of interrater reliability in detection and classification across 3 sonographers, one of whom was inexperienced.

One limitation of our study is that it represents a retrospective analysis of data from a single institution with a selected population, namely patients referred for MIBB. Furthermore, elastography as a modality to further characterize breast lesions [31] was not part of the study protocol.

In summary, the sensitivity and specificity of US BI-RADS classification were 97.4% and 66.4%, respectively, with a positive (PPV) and negative predictive value (NPV) of 65% and 98%, respectively. In 506 BI-RADS 3 lesions, histology revealed 15 malignancies (2.4% malignancy rate), which corresponds to a false-negative rate (FNR) of 2.6%. Furthermore, our data indicate that breast US performed by supervised trainees is as reliable as breast US performed by experts. Most significantly, our study demonstrates the importance of not only focusing on US when deciding whether to follow-up a BI-RADS 3 breast lesion or to perform MIBB, but to include the patient's history and clinical findings as well as the patient's choice. Nevertheless, strictly adhering to BI-RADS criteria and classification is essential to minimize the false-negative cancer rate.

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References

1 *Hooley RJ, Greenberg KL, Stackhouse RM et al.* Screening US in patients with mammographically dense breasts: initial experience with Connecticut Public Act 09-41. Radiology 2012; 265: 59–69
2 *Houssami N, Irwig L, Simpson JM et al.* Sydney Breast Imaging Accuracy Study: Comparative sensitivity and specificity of mammography and sonography in young women with symptoms. AJR American journal of roentgenology 2003; 180: 935–940
3 *Berg WA, Blume JD, Cormack JB et al.* Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. Jama 2008; 299: 2151–2163
4 *Berg WA, Zhang Z, Lehrer D et al.* Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. Jama 2012; 307: 1394–1404
5 *Shin JH, Han BK, Ko EY et al.* Probably benign breast masses diagnosed by sonography: is there a difference in the cancer rate according to palpability? AJR American journal of roentgenology 2009; 192: W187–W191
6 *Harvey JA, Nicholson BT, Lorusso AP et al.* Short-term follow-up of palpable breast lesions with benign imaging features: evaluation of 375 lesions in 320 women. AJR American journal of roentgenology 2009; 193: 1723–1730
7 *Berg WA, Blume JD, Cormack JB et al.* Operator dependence of physician-performed whole-breast US: lesion detection and characterization. Radiology 2006; 241: 355–365
8 *ACoRACR ACR BI-RADS® Atlas.* Breast Imaging Reporting and Data System. 5rd ed. Reston, VA: American College of Radiology; ed. 2013

9 *Graf O*, *Helbich TH*, *Hopf G et al.* Probably benign breast masses at US: is follow-up an acceptable alternative to biopsy? Radiology 2007; 244: 87–93
10 *Kim SJ*, *Ko EY*, *Shin JH et al.* Application of sonographic BI-RADS to synchronous breast nodules detected in patients with breast cancer. AJR American journal of roentgenology 2008; 191: 653–658
11 *Lehman CD*, *Lee CI*, *Loving VA et al.* Accuracy and value of breast ultrasound for primary imaging evaluation of symptomatic women 30–39 years of age. AJR American journal of roentgenology 2012; 199: 1169–1177
12 *Hille H*, *Vetter M*, *Hackeloer BJ*. The accuracy of BI-RADS classification of breast ultrasound as a first-line imaging method. Ultraschall in der Medizin 2012; 33: 160–163
13 *Foxcroft LM*, *Evans EB*, *Porter AJ*. The diagnosis of breast cancer in women younger than 40. Breast 2004; 13: 297–306
14 *Madjar H*, *Becker S*, *Doubek K et al.* Impact of breast ultrasound screening in gynecological practice. Ultraschall in der Medizin 2010; 31: 289–295
15 ACR ACoR. ACR BI-RADS® Ultrasound Atlas. Breast Imaging Reporting and Data System. 2003;
16 *Madjar H*, *Ohlinger R*, *Mundinger A et al.* BI-RADS-analogue DEGUM criteria for findings in breast ultrasound – consensus of the DEGUM Committee on Breast Ultrasound. Ultraschall in der Medizin 2006; 27: 374–379
17 *Mendelson EB*, *Berg WA*, *Merritt CR*. Toward a standardized breast ultrasound lexicon, BI-RADS: ultrasound. Seminars in roentgenology 2001; 36: 217–225
18 *Team RC*. R: A language and environment for statistical computing. 2014
19 *Guth U*, *Huang DJ*, *Huber M et al.* Tumor size and detection in breast cancer: Self-examination and clinical breast examination are at their limit. Cancer detection and prevention 2008; 32: 224–228
20 *Costantini M*, *Belli P*, *Lombardi R et al.* Characterization of solid breast masses: use of the sonographic breast imaging reporting and data system lexicon. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2006; 25: 649–59 quiz 61
21 *Heinig J*, *Witteler R*, *Schmitz R et al.* Accuracy of classification of breast ultrasound findings based on criteria used for BI-RADS. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2008; 32: 573–578
22 *Bullier B*, *MacGrogan G*, *Bonnefoi H et al.* Imaging features of sporadic breast cancer in women under 40 years old: 97 cases. European radiology 2013; 23: 3237–3245
23 *Ha R*, *Kim H*, *Mango V et al.* Ultrasonographic features and clinical implications of benign palpable breast lesions in young women. Ultrasonography 2015; 34: 66–70
24 *Maxwell AJ*, *Pearson JM.* Criteria for the safe avoidance of needle sampling in young women with solid breast masses. Clinical radiology 2010; 65: 218–222
25 *Patterson SK*, *Neal CH*, *Jeffries DO et al.* Outcomes of solid palpable masses assessed as BI-RADS 3 or 4A: a retrospective review. Breast cancer research and treatment 2014; 147: 311–316
26 *Giess CS*, *Smeglin LZ*, *Meyer JE et al.* Risk of malignancy in palpable solid breast masses considered probably benign or low suspicion: implications for management. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2012; 31: 1943–1949
27 *Rhiem K*, *Flucke U*, *Schmutzler RK*. BRCA1-associated breast carcinomas frequently present with benign sonographic features. AJR American journal of roentgenology 2006; 186: E11–E12 author reply E2–E3
28 *Boisserie-Lacroix M*, *Mac Grogan G*, *Debled M et al.* Radiological features of triple-negative breast cancers (73 cases). Diagnostic and interventional imaging 2012; 93: 183–190
29 *Dogan BE*, *Gonzalez-Angulo AM*, *Gilcrease M et al.* Multimodality imaging of triple receptor-negative tumors with mammography, ultrasound, and MRI. AJR American journal of roentgenology 2010; 194: 1160–1166
30 *Bosch AM*, *Kessels AG*, *Beets GL et al.* Interexamination variation of whole breast ultrasound. The British journal of radiology 2003; 76: 328–331
31 *Fleury EF*. The importance of breast elastography added to the BI-RADS (5th edition) lexicon classification. Revista da Associação Médica Brasileira 2015; 61: 313–316