ANTICANCER RESEARCH *40*: 939-950 (2020)
doi:10.21873/anticanres.14027

Reducing the Number of Unnecessary Percutaneous Biopsies: The Role of Second Opinion by Expert Breast Center Radiologists

CHIARA ADRIANA PISTOLESE[1], FELICIANA LAMACCHIA[1], DANIELA TOSTI[1], LUCIA ANEMONA[2], FRANCESCA RICCI[1], MICHELA CENSI[1], MARCO MATERAZZO[3], GIANLUCA VANNI[3], ALBERTO COLLURA[1], FRANCESCA DI GIULIANO[1], TOMMASO PERRETTA[1] and ORESTE CLAUDIO BUONOMO[3]

[1]*Department of Diagnostic Imaging and Interventional Radiology, Molecular Imaging and Radiotherapy, Policlinico Tor Vergata (PTV) University, Rome, Italy;*
[2]*Anatomic Pathology, Department of Experimental Medicine, Policlinico Tor Vergata (PTV) University, Rome, Italy;*
[3]*Breast Unit - Department of Surgical Science, Policlinico Tor Vergata (PTV) University, Rome, Italy*

Abstract. *Background/Aim: The research objectives of this study were the estimation of the number of misdiagnosed breast lesions by non-expert-center-breast-radiologists (NEBR) and the investigation of the discordant rate (DR) calculated between initial and second opinion. Moreover, this study evaluated the impact of second opinion and the factors associated with DR. Materials and Methods: A total of 399 patients were sent to our Tertiary Breast Cancer (BC) Center to perform fine needle aspiration/core needle biopsy (FNAC/CNB) after external examination. Lesions were reclassified according to Breast Imaging-Reporting and Data System (BI-RADS). External examinations were classified as breast-expert, not-breast-expert and physicians as expert-center-breast-radiologists (EBR), NEBR, and non-radiologists (NR). Personal/family history of breast cancer (BC), breast-density and presence of prior imaging were collected. Results: DR was 74.3%. After second opinion, FNAC/CNB was proposed in 25.7% of cases and 2 additional cancers were detected. About 59.5% of unnecessary FNAC/CNB were avoided. Dense breast, no prior imaging examination and BC family-history were associated with higher DR (p-value<0.001); personal BC-history was associated in NEBR evaluations (p-value=0.0383). Conclusion: Second opinion review of outside examinations at expert BC Center may decrease unneeded biopsy, reducing health-care costs.*

Correspondence to: Materazzo Marco, Breast Unit - Department of Surgical Science, Policlinico Tor Vergata (PTV) University, Viale Oxford 81, 00133 Rome, Italy. Tel: +39 3395685883, e-mail: mrcmaterazzo@gmail.com

Key Words: Fine needle aspiration cytology, Tru-Cut needle biopsy, breast lesions, breast cancer, breast imaging reporting and data system, tertiary care center, cancer, multidisciplinary team.

Breast cancer (BC) is the most commonly diagnosed cancer and the second cause of cancer death among women (1). The radiological diagnosis of BC involves several modalities including mammography (MMG), ultrasound (US) and magnetic resonance imaging (MRI) (2). Inter- and intra-observer variabilities affect the interpretation of the different examinations, mainly due to the experience of operators or equipment's different technologies (3-6). Therefore, the availability of wide range of different diagnostic techniques increases the risk of incorrect and inappropriate clinical application (7). Screening mammography programs led to detection of early breast cancer (EBC) and improvement in survival (8, 9). Although an accurate interpretation is fundamental in EBC, interpretation of MMG varies greatly among radiologists (10-12).

Moreover, knowledge of BC type has allowed the development of target therapy (13, 14) and has provided information to assess the oncological risk of distant relapse and local node invasion (15, 16). The paradigmatic shift of breast treatment leads to a change in clinical presentation, local recurrence and mortality, with an increased rate of conservative breast treatment (17-19) and awake surgical approach (20, 21). Regarding systemic treatment, novel molecular biomarkers and radiomics may optimize the selection of effective BC therapies, reducing treatment cost and side effects in BC and in oncology treatment in general (22-25).

The breast and axilla US are a complementary modality to mammography and a complementary tool for BC screening, particularly for women with dense breasts. Moreover, US is essential when there is doubt about the diagnosis or the nature of lesions (liquid and/or solid) detected during mammography has to be defined (26-29). Nevertheless, US examination is an operator-dependent

Table I. *Malignancy rate and management for each BI-RADS category according to the American College of Radiology's BI-RADS Atlas [modified from (35)].*

BIRADS Category	% of malignity	Clinical management
BI-RADS 0	Impossible to expect	Need to review prior examinations and/or complete additional imaging
BI-RADS 1	Essentially 0% (Negative)	Continue routine screening
BI-RADS 2	Essentially 0% (Benign)	Continue routine screening
BI-RADS 3	≤2% (Probably benign)	Short-term follow-up at 6 months, then every 6-12 months for 2 years
BI-RADS 4	2-94% (Suspicious)	Perform biopsy, preferably needle biopsy
BI-RADS 5	≥95% (Highly suggestive of malignancy)	Perform biopsy and treatment, as necessary
BI-RADS 6	100% (Proven malignancy)	Assure that treatment is completed

technique and the training and experience of the operator is very important. A number of studies have found that, radiologists, who have been subspecialized in breast imaging [expert-center-breast-radiologists (EBR)], detect more cancers than general radiologists [non-expert-center-breast-radiologists (NEBR)] (30, 31). However, US examination can be performed also by non-radiologist physicians (NR) that cannot perform the different breast imaging methods (mammography, tomosynthesis, magnetic resonance). Due to the inter-observer variability in breast imaging interpretations, a certain number of women with newly diagnosed breast findings need a second opinion at tertiary BC centers (32). As a result of the aforementioned limitations in breast imaging interpretations and the fear of medico-legal disputes, an increased number of unnecessary fine needle aspiration cytology (FNAC) or biopsies like core needle biopsy (CNB) and vacuum assisted biopsy (VAB) have been noticed, which cause patient anxiety and worry and, additionally, rise considerably health care costs (7).

The American College of Radiology (ACR) has developed a descriptor system for breast lesions, the Breast Imaging Reporting and Data System (BI-RADS), to standardize terms for the description and management of lesions. According to this system, each lesion matches a category of suspicion that corresponds to subsequent diagnostic and therapeutic choices (Table I) (33). At our Tertiary BC Center, before breast interventional procedures, all patients with external imaging are given a second opinion on the interpretation by subspecialized breast imaging radiologists.

The present study aimed to estimate how many breast lesions sent by an external center to our institute should undergo US-guided FNAC or CNB according to our EBR. Our estimation was based on the discrepancies rate between the initial and second opinion breast imaging recommendations [discrepancy rate (DR)]. In addition, this study calls into question the impact of Tertiary BC Centers' second opinion on patient management and determines the factors associated with increased need for second opinion.

Materials and Methods

This monocentric study was carried out at the Breast Radiology Unit of the Policlinico Tor Vergata Hospital (tertiary BC Center) in Rome, Italy between December 2015 and March 2017. The Institutional Review Board of Policlinico Tor Vergata Foundation waived the need for a formal approval because of the clinical nature of the study with no evidence of detrimental effect or clinical risk. All patients signed written-informed consent for participating in the study.

Study population. We examined 401 recent-onset BC findings of 399 patients. The inclusion criteria were the following: breast abnormalities detected by US, radiological examination performed in outside facilities and prescription by external physician to perform US-guided FNAC or CNB. Patients may undergo MMG and/or MRI evaluation if they were prescribed by outside facilities physicians according to anamnestic, clinical and personal data.

Exclusion criteria were: male sex, patients without image and/or reports from outside facilities, women who had already undergone additional or repeated examinations due to inadequacy of external ones; patients who did not underwent FNAC/CNB if suggested after our second opinion or did not complete the suggested close follow-up at our Institute.

Preoperative review and percutaneous procedure. We collected anamnestic data (including age, family history or personal history of BC) and information about symptoms (nipple discharge, skin retraction, palpable nodule) for each patient. Outside facility US image and reports were evaluated to understand the lesions' features. External MMGs and MRIs were reviewed and included into our study. External BI-RADS category was collected with the indication given by the external physician. When BI-RADS category was missing in the outside facility reports, a BI-RADS assessment category was assigned based on the recommendation in the external reports. If US-guided FNAC/CNB was recommended, a BI-RADS category greater or equal to 4 (suspicious) was assigned. Findings without a FNAC/CNB indication, were considered BI-RADS smaller or equal to 3. Further information

collected included external institute name, identity of the physician and his/her specialization.

Outside health care providers have been classified into breast-expert and not-breast-expert Centers, according to EUSOMA guidelines for Breast Center (34). Physicians who had performed outside breast imaging evaluation were classified according to their specialization and the characteristics of the facility they work into NR, EBR and NEBR.

Before undergoing FNAC or CNB, all the patients received a second opinion review at our Tertiary BC Center. In addition, two separate US examinations with a high-resolution ultrasound equipment (My Lab Twice, Esaote, Genoa, Italy) and a high-frequency linear-array probe (10-13 MHz) were performed by two radiologists with more than 10 years of experience in breast image interpretations.

After our evaluation, we characterized breast composition according to four categories: extreme fibro glandular, heterogeneous fibro glandular, scattered fibro glandular, and almost entirely fatty. Then, a new BI-RADS category was assigned to each lesion. Therefore, cases that were re-classified as BI-RADS category 1, 2 and 3, were addressed to follow-ups (6-12-24 months). According to the ACR, BI-RADS categories 1 and 2 require only a continuous routine screenings (35). Nevertheless, we recommended a tailored close instrumental follow-up considering age, family and personal history, and features of the breast finding due to the incongruence of opinions provided by outside facility physicians and our center. If downgrading BI-RADS 2 or 3 caused discomfort or anxiety to the patients, a FNAC or CNB was performed to reduce stress due to short follow up after interview with patients.

BI-RADS categories 4 or 5 were subjected to US-guided FNAC or CNB. FNAC was performed for retroareolar lesions or lesions with diameter smaller than 7 mm; in other cases, CNB was performed. If BI-RADS 5 lesion with a maximum diameter larger than 2.5 cm was observed or the patients had been addressed to neo-adjuvant chemotherapy due to high suspicion of locally advanced breast cancer diagnosis (LABC), metallic clip was released at the end of CNB. With the patient in a supine position, and after a careful disinfection, the lesion was identified with the US probe and the FNAC (21-25 gauge) or CNB was performed. In the last case, a 13-gauge Tru-Cut (PRECISA™) and one frustule was taken at a time, and up to 5 frustules were prescribed after local anesthetic administration (10 ml Lidocaine hydrochloride) and a 5 mm skin incision (with a scalpel to guarantee appropriate access for a needle insertion).

Cytological and histological examinations were performed at the Anatomic Pathology Department of the Policlinico Tor Vergata Hospital (Rome, Italy). The cytological and histological results were classified into five diagnostic categories according to the fourth edition of "European guidelines for quality assurance in breast cancer screening and diagnosis" and then were matched with the ultrasound characteristics of the lesions (36).

Furthermore, FNAC reports were classified into five categories: inadequate/insufficient for diagnosis (C1), benign epithelial cells (C2), atypia probably benign (C3), suspicious for malignancy (C4) and malignant (C5). Respectively, histology results from CNB were classified into five categories: unsatisfactory/normal breast tissue (B1), benign (B2), benign but with uncertain malignant potential (B3), suspicious of malignancy (B4), malignant (B5) (37). In cases of lesions evaluated as malignant at percutaneous biopsy (B4-B5), definitive surgeries were performed. If benign histological or cytological results at percutaneous procedure (respectively, B2 or C2) corresponded to the iconographic characteristics, 6 months US follow-up was recommended. C3 lesions underwent CNB or, when it was requested by the patient, surgery was performed. Surgical biopsy was required for B3 lesions (uncertain malignant potential) because of the risk of histologic underestimation of malignancy (38, 39). Lesions classified as C1 or B1 that had suspicious features on imaging evaluation underwent surgical biopsies.

BI-RADS categories were assigned based on the first facility interpretation and then were compared to our subspecialized breast imaging radiologist interpretations. Therefore, DR, agreement rate (AR), downgrading rate (DWR), upgrading rate (UPR), additional biopsy rate (ABR) and additional cancer rate (ACR) were evaluated. When the second opinion interpretation confirmed the outside BI-RADS category assessment and lesion management, opinions were considered as concordant. On the contrary, if there was a change in BIRADS category or lesions management, the opinions were considered as discordant.

AR and DR were calculated as the ratio of the number of concordant cases *versus* the total number of subjects and the ratio of the number of discordant cases *versus* the total number of subjects, respectively.

The DWR and the UPR were obtained by the ratio of the number of BI-RADS more or equal to 4 downgraded to BI-RADS ≤3 *versus* the total number of women and by the ratio of the number of BI-RADS ≤3 upgraded to BI-RADS ≥4 *versus* the total number of patients, after our radiologists' second opinion, respectively. The ABR was the ratio of the number of repeated FNAC/CNB requested by our radiologists, and not after outside breast evaluation, *versus* the total number of cases. The ACR was calculated as percentage of detected cancer after additional biopsies *versus* the total number of subjects. Information regarding personal and family history of breast cancer, breast density, and availability of prior imaging were statistically analyzed for detecting an association with discordant interpretation.

Statistical analysis. As the first step, descriptive and comparative statistics were performed. Summary statistics were performed for general analysis of the population frequencies and percentages were calculated for categorical variables; for continuous variables mean, median and interquartile range (IQR) were assessed. Statistical analysis was performed with the Fisher exact test. *p*-Values smaller than 0.05 were considered to indicate statistically significant differences. All statistical analyses were carried out using the SPSS platform (V.23; IBM, Armonk, NY, USA).

Results

Study population description. Our database included 401 recent-onset US-detectable breast findings in 399 women. The mean of age was 49.7 years with a range between 10 and 82 years. Patients were addressed to undergo FNAC/CNB at our Institute, as it was indicated in the report after a breast instrumental examination received at an external center. Among 401 lesions, 399 were detected at an outside facility and two additional contralateral lesions in two different cases were identified at our evaluation.

Out of 399 patients, 138 had a family history of BC and 49 had experienced mastectomy or breast conservative treatment

Table II. *Prevalence of findings, classified according to the Breast Imaging Reporting and Data System (BI-RADS) category by our subspecialized breast imaging radiologist evaluation. Women were addressed to our center for cytological/histological verification of suspicious lesions after outside breast imaging studies conducted by non-radiologist physicians, breast expert center radiologists and not breast expert center radiologists.*

	Non-radiologists	Radiologists	
		Breast expert center	Not breast expert center
BI-RADS 1 (n=49)	40/49 (81.6%)	0	9/49 (18.4%)
BI-RADS 2 (n=63)	42/63 (66.7%)	0	21/63 (33.3%)
BI-RADS 3 (n=184)	35/184 (19.0%)	0	149/184 (81.0%)
BI-RADS 4 (n=47)*	15/47 (33.3%)	7/47 (14.9%)	24/47 (51.1%)
BI-RADS 5 (n=58)*	16/58 (27.6%)	9/58 (15.5%)	32/58 (51.2%)

*Two lesions, assigned respectively to BI-RADS category 4 and 5 after our subspecialized breast imaging radiologists second opinion, were not reported as suspicious after non-radiologist physician evaluation, and for these reasons they do not appear in any of the three columns (Non-radiologists, Breast expert center, Not breast expert center). These lesions underwent further biopsy, after our breast expert radiologist study.

(BCT) for previous BC. Moreover, heterogeneous or extremely dense breast was observed in 181 cases, 220 breasts were classified as scattered fibroglandular or fatty breasts. No patients had BRCA1/2 mutation. No prior imaging examinations were available for 222 women at the time of breast evaluation in an outside facility. According to the personal and anamnestic data, US was performed only in 170 cases. For 209 patients, US examination was integrated with MMG and for 20 patients MMG plus MRI were performed.

Outside facilities BI-RADS category assessment. Among 399 findings identified at outside facilities, BI-RADS categories were assigned only in 8.5% (34 cases): 16 BI-RADS 4 by EBR, nine BI-RADS 3 and nine BI-RADS 4 by NEBR were identified. All lesions evaluated by EBR were assigned a certain BI-RADS category; NEBR gave a BI-RADS category only in 7.1% of cases (18 cases out of 255) with a statistically significant difference ($p<0.001$). NR never assigned a BI-RADS category. In the remaining 365 cases (91.5%) a BI-RADS category was not given but they were considered if BI-RADS was equal or greater than 4, due to the requirement of a cytological/histological verification if was clearly written in the physician's report.

Second opinion evaluation and management. After our Tertiary Care Center radiologist examinations, 25.7% of 401 breast findings (103 cases) were assigned to the BI-RADS category greater or equal to 4 (46 cases of BI-RADS 4 and 57 cases of BI-RADS 5). These groups included 20 lesions assigned to BI-RADS category 4 according to outside facility reports and considered concordant with our second opinion. The previous score was assigned in 16 cases by EBR and in four cases by NEBR. BI-RADS greater or equal to 4 was detected in 29.5% (31 cases out of 105) by NR, in 15.2% (16 cases out of 105) by EBR and in 53.3% (56 cases out of 105) by NEBR (Table II). Moreover, in the BI-RADS ≥4 score population we found two additional contralateral recent-onset abnormalities in two different patients. They were assessed as not suspicious after NR evaluation and not addressed for FNAC/CNB (likely as BI-RADS category smaller than 3). Both cases were reassigned to BI-RADS category ≥4 (1 BI-RADS 4 and 1 BI-RADS 5) and were considered as discordant with our review of these cases. All 105 (103+2 additional diagnosis) BI-RADS categories greater or equal to 4 underwent US-guided FNAC and/or CNB as shown in Table III. All the cytological or histological results are displayed in Figure 1. In addition, the two above-mentioned additional contralateral recent-onset highly suspicious findings turned out to be malignant [two ductal carcinomas *in situ* (DCIS)]. BI-RADS 5 lesions (58 cases) after CNB were classified as 2 unsatisfactory/normal breast tissue (B1 category), with a subsequent definitive histological diagnosis after surgery of fibrous mastopathy, and 56 as malignant (B5 category) [five invasive ductal carcinomas (IDC), nine invasive lobular carcinomas (ILC) and 12 DCIS after surgery]. The malignancy rate was 57.4% (27 cases out of 47) for BI-RADS 4 and 96.6% (56 cases out of 58) for BI-RADS 5 (Table III).

Out of 401 cases, 287 were reclassified as BI-RADS less or equal to 3 (unnecessary biopsy) including five lesions that were identified as BI-RADS 4 by NEBR and then downgraded after reevaluation by our radiologists and were considered discordant with our analysis. In nine cases, breast abnormalities were assigned to BI-RADS 3 by NEBR which corresponded to our second opinion, but they were considered discordant due to different management (FNAC/CNB suggested by NEBR vs follow up according to our opinion). 296 cases of BI-RADS ≤3 discordant lesions were grouped into 49 BI-RADS 1, 63 BI-RADS 2 and 184 BI-RADS 3 (Table III). BI-RADS ≤3 lesions defined in external facilities 39.5% (117/296) were detected by NR, 60.5% (179/296) by NEBR, and none by BER (Table II). According to our observations, NR showed the higher tendency to mark breast findings classified as BI-RADS 1 BI-RADS 2 as suspicious

Table III. *Breast Imaging Reporting and Data System (BI-RADS) category assigned in our tertiary care center to findings identified in an outside facility, with malignancy and benignity rate. BI-RADS 1 and BI-RADS 2 category lesions showed no malignancy after follow-up (F.U.) or after fine needle aspiration cytology (FNAC) or ultrasound-guided automated Tru-cut needle biopsy (CNB). BI-RADS 3, BI-RADS 4 and BI-RADS 5 lesions showed respectively a malignancy rate of 0.5%, 57.4% and 96.7% and a benignity rate of 99.5%, 42.6% and 3.3%.*

	Total cases n=401 (100%)						
BI-RADS category	BI-RADS 1 (n=49; 12.2%)	BI-RADS 2 (n=63; 15.7%)		BI-RADS 3 (n=184; 45.9%)		BI-RADS 4 (n=47; 11.2%)	BI-RADS 5 (n=58; 15.0%)
Management	F.U. n=49	F.U. n=40	CNB/FNAC n=23	F.U. n=89	CNB/FNAC n=97	CNB/FNAC n=47	CNB/FNAC n=58
Malignancy rate	0	0	0	0	1/184 (0.5%)	27/47 (57.4%)	56/58 (96.6%)
Benignity rate	49/49 (100%)	63/63 (100%)		183/184 (99.5%)		20/47 (42.6%)	2/58 (3.4%)

in comparison to NEBR (p-value<0.001). Nevertheless, not breast expert radiologists indicated more BI-RADS 3 lesions as suspicious than non-radiologists (p-value<0.001).

After revision of breast findings' classifications by our radiologists, 176 breast abnormalities (49 out of 49 BI-RADS 1, 40 out of 63 BI-RADS 2 and 87 out of 184 BI-RADS 3) were addressed to follow-up, reducing by 59.5% the unnecessary percutaneous procedures. No BI-RADS 1 findings showed malignancy and/or lesion evidence after follow-up; for BI-RADS 2 lesions the benign nature was confirmed in all cases. No BI-RADS 3 lesions showed malignancy during follow-up. However, following patient requests, 36.5% (23 cases out of 63) BI-RADS 2 and 52.7% (97 out of 184) BI-RADS 3 lumps underwent histological or cytological examination, resulting in seven benign findings (B2) after CNB and 16 benign epithelial cells (C2) in FNAC, BI-RADS 2 lesions (Figure 2). Among BI-RADS 3, which underwent percutaneous procedures (Figure 3), 62 FNAC, and 35 CNB were performed. Only one lesion characterized by FNAC as C3, turned out to be an invasive papillary carcinoma after surgery (Figure 4). The remaining BI-RADS 3 findings which were examined by FNAC were 46 benign epithelial cells (C2) and 15 atypia probably benign (C3), showing no malignancy. One C3 lesion underwent surgical excision with a definitive histological outcome of fibroadenoma; 14 C3 lesions underwent CNB and turned out to be 12 B2 and two B3. Besides, 35 BI-RADS 3 were subjected to CNB as first option: 31 B2 and 4 B3. All six B3 lesions underwent surgical excision and none was subsequently upgraded to malignancy. The malignancy rate of BI-RADS 3 category lesions was 0.5% (one case out of 184), and the benign rate was 95.5% (183 cases out 184) (Table III).

Evaluating all the 401 breast findings AR was 25.7% and only in these cases there was a real indication to perform FNAC/CNB, according to our subspecialized breast imaging radiologists. DR was 74.3%. DNR was 71.6%, the UPR, the ABR and the ACR were all 0.5%.

BI-RADS ≤3 and BI-RADS ≥4 mean age was 43.4 years old (range=19-62) and 67.8 years old (range=31-82), respectively.

Analysis of variables associated with interpretation discrepancy at outside facilities. Analyzing US reports, no discordance between examinations performed at outside EBR and our radiologists' evaluation was found. Statistically significant difference was found in DR after imaging, by NR (117/148, 79.1%; p-value<0.001) and NEBR (179/235, 76.2%; p-value<0.001).

Comparing DR between NEBRs' and NRs' reports, no statistically significant differences were observed (p-value=0.5338). This result shows no difference between NEBR and NR regarding DR.

Considering all examinations performed at outside facilities, statistically significant factors associated with interpretation discrepancy were dense breasts (p-value<0.00001), absence of prior examinations for comparison (p-value<0.00001) and a family history of breast cancer (<0.00001). Analysis according to each physician, revealed that none of the confounding factors previously described reached statistical significance in the study carried out by BER and history of prior treated breast cancer showed a statistically significant difference only in examinations performed by NBER (p-value=0.0383) (Table IV).

Discussion

Interpretation of imaging results can be affected by inter- and intra-observer variabilities, due to operators' experience and application of different technologies (3-6). Different diagnostic techniques increase the risk of incorrect and inappropriate clinical assessment and application (7). In this study, we examined 401 lesions at our Tertiary Care Center for second opinion and according to our final report, there

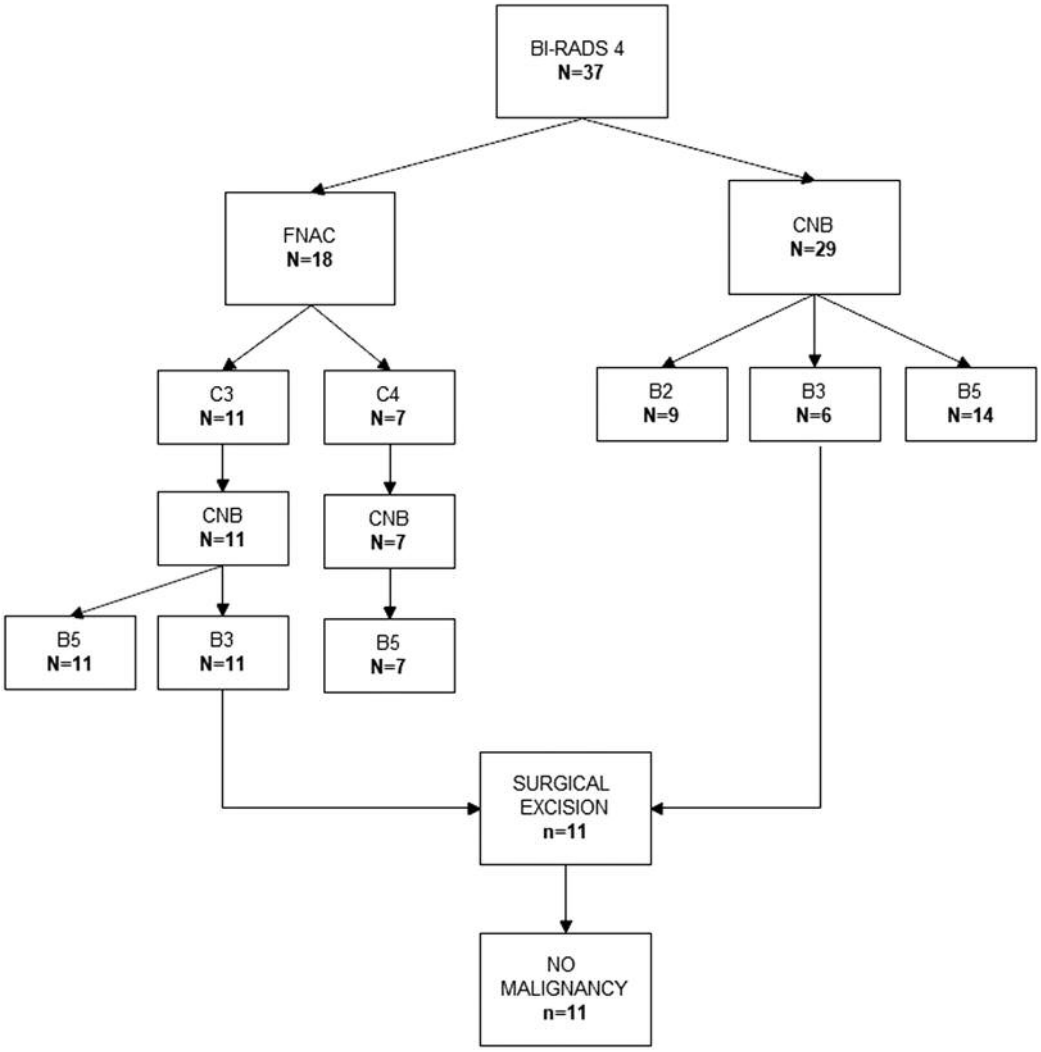

Figure 1. *Chart shows results of fine needle aspiration cytology (FNAC), ultrasound-guided automated Tru-cut needle biopsy (CNB) and follow-up of BI-RADS 4 lesions.*

were reasonable indications to perform FNAC/CNB only in 25.7% of cases (AR).

DWR from BI-RADS equal or greater than 4-5 for BI-RADS 1, 2, or 3 was 74.3% with a high prevalence among recent onset BI-RADS 3 lesions. BI-RADS 3 findings turned out to be the most frequent lesion sent for FNAC/CNB, followed by BI-RADS 2, BI-RADS 5, BI-RADS 1 and BI-RADS 4 lesions (Table III). This is a relevant result considering that BI-RADS 1 and 2 findings require only routine screening and not cytological/histological verification. BI-RADS category 3 findings are probably benign lesions, with a malignancy likelihood of less than 2%, and for this reason they do not require biopsy but short-term imaging surveillance (after 6, 12 and 24 months). The stability of the lesions during follow-up is a benign index; in contrast, their modifications represent an indication for biopsy (40).

When a patient sent by an external center comes to our Institute to be submitted to US-guided FNAC/CNB, after collecting anamnestic information, we assess whether the instrumental examinations performed before that moment were sufficient. If so, new US evaluation before the procedure was carried out to exclude different findings. Our breast expert radiologists personally discussed all initial BI-RADS 3 assessments with patients at the moment of diagnostic evaluation, explaining the meaning of a BI-RADS category 3 finding, the malignancy rate and preference given to close instrumental follow-up, rather than to cytological/histological verification. However, after giving our second opinion, out of 184 patients with a BI-RADS

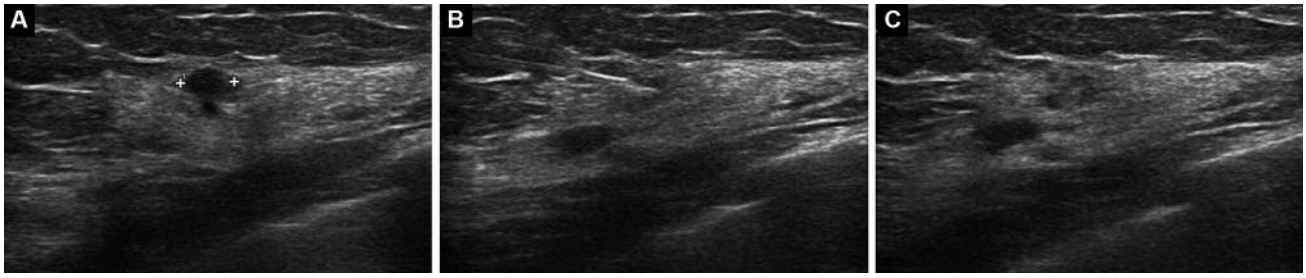

Figure 2. *Clinical Case I: Cyst. (A) Ultrasound evaluation (anechoic, oval breast lump with circumscribed margins) indicated a breast cyst, with a maximum diameter of 6 mm and, therefore, classified as Breast Imaging Reporting and Data System (BI-RADS) category 2, in a 33 year old woman; (B) Fine needle aspiration cytology (FNAC) was performed; (C) at the end of the procedure the lesion was aspirated. The cytological diagnosis revealed a very low number of epithelial cell clusters with abundant scattered macrophages and proteinaceous material, in accordance with the US diagnosis of cyst.*

category 3 lesion, less than half of the patients (46.3%) accepted to undergo close instrumental follow-up. The majority (52.7%) preferred to undergo FNAC/CNB, because of the anxiety and worrying caused by the presence of two different medical opinions about lesion management, asking for the best and safest choice for a correct diagnosis. In addition, due to anxiety, 36.5% of patients with BI-RADS 2 lesions chose histological/cytological verification, even after discussing with our radiologists. On the one hand, second opinion at our Tertiary Care Center modified the diagnostic-therapeutic management, helping to avoid unnecessary biopsies in 59.5% of patients, which were submitted to close instrumental follow-ups with no evidence of malignancy.

Only one case was diagnosed as malignant (invasive papillary carcinoma) among eight BI-RADS 3 findings (six lesions diagnosed as B3 and two lesions as C3) in our series who performed surgical biopsy. Our results underline once again the significantly low malignancy rate for BI-RADS category 3 lesions (0.5% in our study), which corresponds to the ACR assessment (35). All BI-RADS 3 lesions who did not undergo FNAC/CNB underwent close follow up (mean 2 years) with no evidence of modification, new findings or tumor, supporting our first evaluation.

As we found out in our study, NR and NEBR have a significantly higher tendency to prescribe unnecessary biopsies: we reported an extremely significant (p-value<0.00001) high DR of 79.1% and 76.2% for interpretations coming from NR and NBER respectively when compared EBR. No DR was found between EBR and opinion according our evaluation.

Moreover, our data pointed out a high tendency of NR in comparison with NBER in marking BI-RADS 1 and BI-RADS 2 lesions as suspicious ones. This may be partially explained by: NR performing breast ultrasound examinations cannot integrate the different breast imaging methods (mammography, tomosynthesis, magnetic resonance) and they rely only on the ultrasound interpretation of breast findings. US is a highly operator-dependent imaging technique and the lack of experience of radiologists who interpret the results increase the rate of false positive results (41). Chae *et al*. demonstrated the radiologist's difficulty in assessing BI-RADS 3 category using breast US. In their experience, 14.6% of breast ultrasounds are classified as BI-RADS 3. However, when they reinterpreted the ultrasound findings using the American College of Radiology Imaging Network (ACRIN) 6666 criteria, 19.3% of cases had an assessment change and 213 cases out of 225 were changed to BI-RADS 2 (42).

Nowadays, the increasing use of imaging methods, the radiological examinations with poor quality and the lack of experience of operators, lead to a high rate of false positive results and unnecessary biopsies being performed (43-45). Multiple examinations implemented by inexperienced units that do not perform breast radiology lead to unnecessary costs, waste of time and increase patients' anxiety (32). Nevertheless, NBER indicated more BI-RADS 3 lesions as suspicious than non-radiologists. BI-RADS 3 findings create a wide variety of actions and reactions. They cause patient anxiety and some unneeded biopsies and are often ignored by patients and referring clinicians. Radiologists who are uncertain about the required actions for specific findings often overuse BI-RADS 3 (46). It should be emphasized that our radiologist's evaluations led to 0.5% of additional biopsies and cancer detection, too. Therefore, the present study stresses out the usefulness of a second opinion from a Tertiary Care Center with subspecialized breast imaging radiologists. According to the European Society of Breast Cancer Specialists (EUSOMA), to ensure quality in the diagnostic pathway of breast cancer, a Breast cancer Unit should ensure sufficient quality control in place, employ experienced personnel and be able to keep proper records (47). In this regard, a recent study by Horvat *et al*. showed that the US examination performed in real-time, during the second opinion evaluation in a dedicated breast center, led

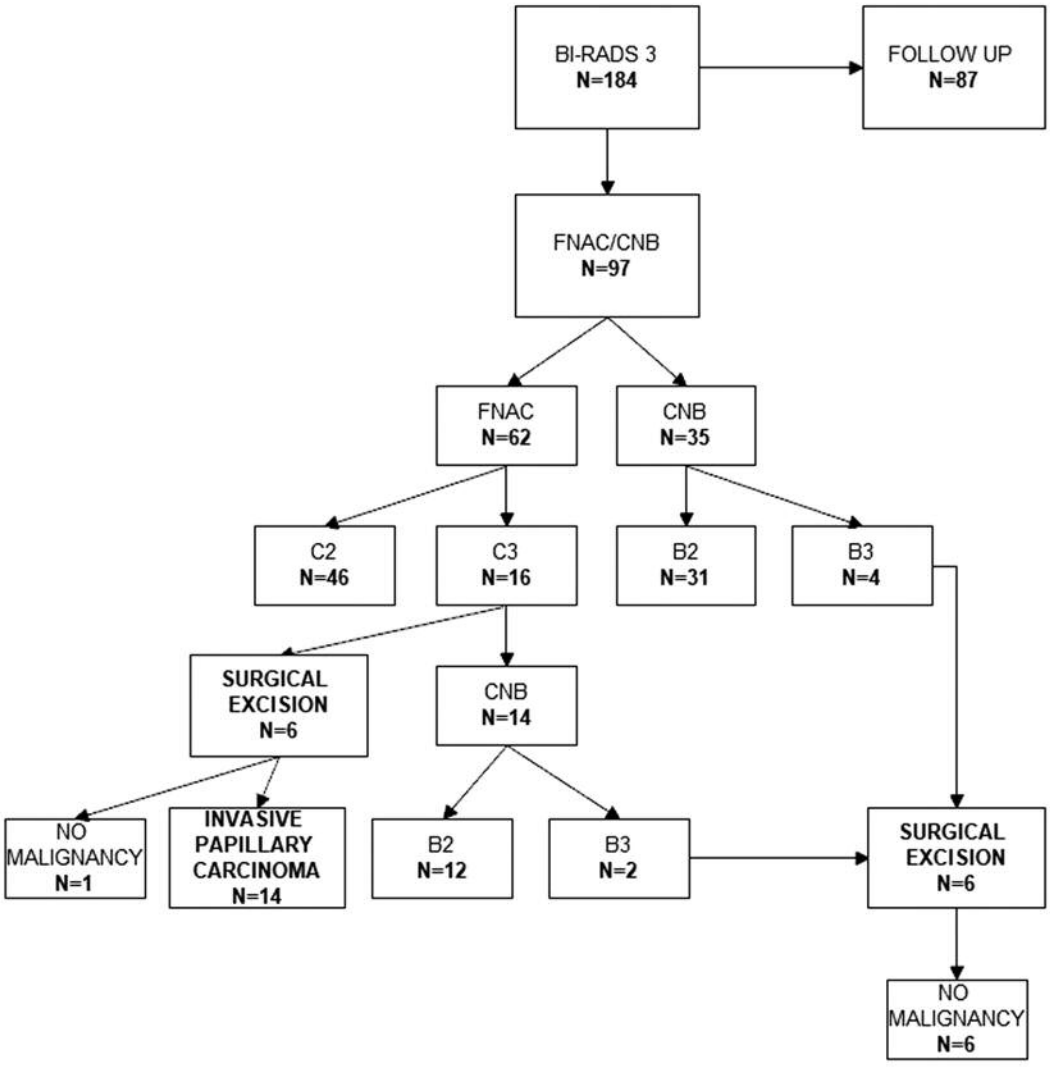

Figure 3. *Chart shows results of fine needle aspiration cytology (FNAC), ultrasound-guided automated Tru-cut needle biopsy (CNB) and follow-up of BI-RADS 3 lesions.*

to 20.6% of additional biopsies, 14.8% of avoided biopsies, noting a further number of cancers in 24.5% of biopsies performed and in 5.3% of the total number of subjects included in the study (48). Coffey *et al*. have provided second opinions with different imaging methods (mammography, ultrasound and magnetic resonance), demonstrating a change in the interpretation of images in about 28% of patients, with a significant change in their management in 13% of cases, including further cancer diagnosis in 5% of cases (6). Spivey *et al*. reported a change in patient management due to providing second opinions in 53.3% of cases, including the recommendations for additional imaging or biopsy methods (32). In a recent study by Chang Sen *et al*., the evaluation of breast imaging by second opinion resulted in a 12.3% downgrading of BI-RADS 4-5 cases (with indication to biopsy) to BI-RADS 1, 2 or 3, and an upgrading in 8.5% of BI-RADS 1, 2, or 3 cases to BI-RADS 4 or 5, reducing the number of patients with a biopsy indication to 3.9% (11).

Our experience highlighted that the use of the BI-RADS classification is not widespread among NEBRs and NERs. In fact, only 8.5% of the findings were assigned to a BI-RADS category. However, according to our subspecialized breast imaging radiologists, they were correct in all cases assigned by EBR and only in 22.2% cases provided by not-breast expert-center-radiologists. A correct use of BI-RADS assessment, a universal system of iconographic descriptors, has paramount importance for establishing patient management in a standardized way, avoiding unnecessary biopsies and reducing health care costs and waiting lists for

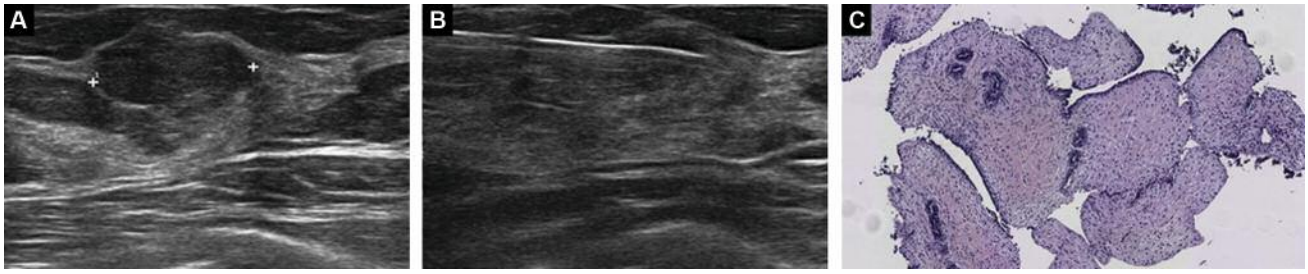

Figure 4. *Clinical Case II: Benign phyllodes tumor. (A) Ultrasound evaluation showed an hypoechoic, oval breast lump (maximum diameter: 18 mm), with regular shape, circumscribed margins and parallel orientation, not vascularized at color-Doppler evaluation, classified as Breast Imaging Reporting and Data System (BI-RADS) category 3 in a 36-year-old woman; (B) Ultrasound-guided automated Tru-cut needle biopsy (CNB) was performed; (C) Hematoxylin-Eosin stain (4×) showed leaflike projections of mildly increased stromal cellularity in a fragmentated core biopsy. The final diagnosis was benign phyllodes tumor.*

Table IV. *Analyzed variables associated with interpretation discrepancy in all studies performed at outside facilities and in examinations carried out, respectively, by non-radiologists and not breast expert radiologists. A p-value<0.05 was considered statistically significant.*

	Total		Non-radiologists		Not-breast-expert radiologists	
Interpretation variables	Discrepant second interpretation, n/N (%)	*p*-Value	Discrepant second interpretation, n/N (%)	*p*-Value	Discrepant second interpretation, n/N (%)	*p*-Value
Personal history of breast cancer	39/49 (79.6)	0.4851	1/1 (100%)	1	38/48 (79.2)	0.2176
No personal history of breast cancer	259/352 (73.4)		116/147 (78.9)		143/205 (69.8)	
Heterogeneously or extremely dense breasts	161/181 (89.9)	<0.00001	79/86 (91.9)	<0.00001	82/95 (86.3)	<0.001
Scattered or fatty breasts	137/220 (62.3)		38/62 (61.3)		99/158 (62.7)	
No prior imaging studies available	179/222 (80.6)	0.0018	96/116 (82.8)	0.0487	83/106 (78.3)	0.0486
Prior imaging studies available	119/179 (66.5)		21/32 (65.6)		98/147 (66.7)	
Family history of breast cancer	123/138 (89.1)	<0.00001	39/40 (97.5)	0.0004	84/98 (85.7)	0.0001
No family history of breast cancer	175/263 (66.5)		78/108 (72.2)		97/155 (62.6)	

breast interventional procedures. All the patients that underwent a breast biopsy claimed that they have experienced biopsy-related stress even though the results were benign. Once the decision for biopsy is made, the time between the procedure and pathology report raises the stress levels of patients (49). False positive study results and increasing number of benign breast biopsies are not associated with the stress experienced by patients, but also with the rising healthcare expenditures for unnecessary procedures. Coupled by the existing technical incapacities, the lack of experience of radiologists and the worry about providing false negative results caused by malpractice laws, the rates of performing additional studies alongside mammography are rising (40).

In our study, we have described and analyzed for each group of interpreters (NR, NEBR, EBR) variables associated with increased discrepancy including a personal history of breast cancer, a family history of breast cancer, dense breasts, and unavailable prior imaging. The different discrepancy rate for patients with an existing history of breast cancer evaluated by NEBR would suggest that this is a strong bias. In our opinion, a not significantly different discrepancy rate and an extremely low number of women examined by NR who have a personal history of breast cancer, could be partially explained. These women rely on personal experience and are more likely to go to radiologists for follow-ups, as they are aware that they can integrate the

different imaging methods for a correct diagnostic and therapeutic planning. Moreover, a family history of breast cancer could represent a bias for NR and NEBR. The significant discrepancy rate in patients without prior imaging suggests that every effort should be made to obtain prior imaging examinations before a new evaluation is performed.

There are some limitations to our study. It was a retrospective single-institution study at a Tertiary Cancer Center. When BI-RADS assessment categories were not assigned at an outside-facility, a BI-RADS category was assigned based on the management recommendation of the outside-facility's written report. The data regarding the usage of the BI-RADS classification was obtained from the reports of examinations performed at outside centers which, however, do not represent the totality of the existing centers. Since there is a wide variability in breast imaging experience of radiologists and non-radiologists at outside facilities, the results should not be generalized. Nevertheless, our data could be a starting point for multicentric studies with a greater number of cases.

Based on our experience, we point out that in daily practice there is a real indication to perform FNAC/CNB only for a small number of patients reaching our facility (25.7% in our study). False positivity in studies performed at unexperienced centers and carried out by NR are extremely high. Our data also underlined that BI-RADS category 3 lesions (requiring close instrumental follow-up) are most frequently sent for cytological/histological verification at our Institute. The rate of lesions' overestimation in studies performed by non-radiologists or not expert centers radiologists is significantly higher compared to expert center radiologists. A personal history of breast cancer, a family history of breast cancer, dense breasts, and unavailable prior imaging are associated with increased discrepancy of examinations performed by non-radiologists and not breast expert center radiologists.

The BI-RADS classification is not widely used among NR and NEBR. A correct use of BI-RADS categorization with a multidisciplinary approach involving other subspecialized breast specialists is essential for successful patient management.

To conclude, second opinion review from outside breast imaging examinations provided from our breast expert cancer center resulted in a change in the patients' recommendation. Our study stressed out the importance of Tertiary Care Centers' second opinion interpretations in order to reduce patient anxiety and worry. Shift in patients' management could cause a reduction of unneeded procedures and a shortening of waiting list. Moreover, further evaluation could lead to additional cancer detection in misdiagnosed breast findings.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to this study.

Authors' Contributions

Study conception and design: Chiara Adriana Pistolese, Buonomo Oreste Claudio, Feliciana Lamacchia; Acquisition of data: Daniela Tosti, Lucia Anemona; Analysis of data: Francesca Di Giuliano, Tommaso Perretta; Interpretation of data: Francesca Ricci, Alberto Collura; Drafting of article: Materazzo Marco, Gianluca Vanni, Michela Censi; Critical revision: Chiara Adriana Pistolese, Michela Censi.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin *69*: 7-34, 2019. PMID: 30620402. DOI: 10.3322/caac.21551

2 Weinfurtner RJ, Niell B, Mekhail Y, Aguila E and Kamat L: Specialized Second Opinion Interpretations of Breast Imaging: Impact on Additional Workup and Management. Clin Breast Cancer *18*: e1031-e1036, 2018. PMID: 29625911. DOI: 10.1016/j.clbc.2018.03.009

3 Berg WA, Campassi C, Langenberg P and Sexton MJ: Breast imaging reporting and data system: Inter- and intraobserver variability in feature analysis and final assessment. Am J Roentgenol *174*: 1769-1777, 2000. PMID: 10845521. DOI: 10.2214/ajr.174.6.1741769

4 Kerlikowske K, Grady D, Barclay J, Frankel SD, Ominsky SH, Sickles EA and Ernster V: Variability and accuracy in mammographic interpretation using the american college of radiology breast imaging reporting and data system. J Natl Cancer Inst *90*: 1801-1809, 1998. PMID: 9839520. DOI: 10.1093/jnci/90.23.1801

5 Lee HJ, Kim EK, Kim MJ, Youk JH, Lee JY, Kang DR and Oh KK: Observer variability of Breast Imaging Reporting and Data System (BI-RADS) for breast ultrasound. Eur J Radiol *65*: 293-298, 2008. PMID: 17531417. DOI: 10.1016/j.ejrad.2007.04.008

6 Coffey K, D'Alessio D, Keating DM and Morris EA: Second-opinion review of breast imaging at a cancer center: Is it worthwhile? Am J Roentgenol *208*: 1386-1391, 2017. PMID: 28301207. DOI: 10.2214/AJR.16.16871

7 Pistolese CA, Ciarrapico AM, della Gatta F and Simonetti G: Inappropriateness of breast imaging: cost analysis. Radiol Med *118*: 984-994, 2013. PMID: 23801396. DOI: 10.1007/s11547-013-0948-5

8 Youlden DR, Cramb SM, Dunn NAM, Muller JM, Pyke CM and Baade PD: The descriptive epidemiology of female breast cancer: An international comparison of screening, incidence, survival and mortality. Cancer Epidemiol *36*: 237-248, 2012. PMID: 22459198. DOI: 10.1016/j.canep.2012.02.007

9 Bonfiglio R, Scimeca M, Toschi N, Pistolese CA, Giannini E, Antonacci C, Ciuffa S, Tancredi V, Tarantino U, Albonici L and Bonanno E: Radiological, histological and chemical analysis of breast microcalcifications: diagnostic value and biological significance. J Mammary Gland Biol Neoplasia *23*: 89-99, 2018. PMID: 29744755. DOI: 10.1007/s10911-018-9396-0

10 Ciatto S, Houssami N, Apruzzese A, Bassetti E, Brancato B, Carozzi F, Catarzi S, Lamberini MP, Marcelli G, Pellizzoni R, Pesce B, Risso G, Russo F and Scorsolini A: Reader variability in reporting breast imaging according to BI-RADS® assessment categories (the Florence experience). Breast *15*: 44-51, 2006. PMID: 16076556. DOI: 10.1016/j.breast.2005.04.019

11 Chang Sen LQ, Mayo RC, Lesslie MD, Yang WT and Leung JWT: Impact of second-opinion interpretation of breast imaging studies in patients not currently diagnosed with breast cancer. J Am Coll Radiol *15*: 980-987.e1, 2018. PMID: 29789230. DOI: 10.1016/j.jacr.2018.03.055

12 Elmore JG, Jackson SL, Abraham L, Miglioretti DL, Carney PA, Geller BM, Yankaskas BC, Kerlikowske K, Onega T, Rosenberg RD, Sickles EA and Buist DSM: Variability in interpretive performance at screening mammography and radiologists' characteristics associated with accuracy. Radiology *253*: 641-651, 2009. PMID: 19864507. DOI: 10.1148/radiol.2533082308

13 Løberg M, Lousdal ML, Bretthauer M and Kalager M: Benefits and harms of mammography screening. Breast Cancer Res *17*, 2015. PMID: 25928287. DOI: 10.1186/s13058-015-0525-z

14 Tot T, Gere M, Hofmeyer S, Bauer A and Pellas U: The clinical value of detecting microcalcifications on a mammogram. Semin Cancer Biol *301*: 127065, 2019. PMID: 31733292. DOI: 10.1016/j.semcancer.2019.10.024

15 Orsaria P, Caredda E, Genova F, Materazzo M, Capuano I, Vanni G, Granai AV, de Majo A, Portarena I, Sileri P, Petrella G, Palombi L and Buonomo OC: Additional nodal disease prediction in breast cancer with sentinel lymph node metastasis based on clinicopathological features. Anticancer Res *38*: 2109-2117, 2018. PMID: 29599329. DOI: 10.21873/anticanres.12451

16 Buonomo OC, Caredda E, Portarena I, Vanni G, Orlandi A, Bagni C, Petrella G, Palombi L and Orsaria P: New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. PLoS One *12*: e0184680, 2017. PMID: 28922402. DOI: 10.1371/journal.pone.0184680

17 Buonomo O, Granai A V, Felici A, Piccirillo R, De Liguori Carino N, Guadagni F, Polzoni M, Mariotti S, Cipriani C, Simonetti G, Cossu E, Schiaroli S, Altomare V, Cabassi A, Pernazza E, Casciani CU and Roselli M: Day-surgical management of ductal carcinoma *in situ* (DCIS) of the breast using wide local excision with sentinel node biopsy. Tumori *88*: S48-9, 2002. PMID: 12365390. DOI: 10.1177/030089160208800342

18 Buonomo O, Cabassi A, Guadagni F, Piazza A, Felici A, Piccirillo R, Atzei G, Cipriani C, Schiaroli S, Mariotti S, Guazzaroni M, Cossu E, Simonetti G, Pernazza E, Casciani C and Roselli M: Radioguided-surgery of early breast lesions. Anticancer Res *21*: 2091-2097, 2001. PMID: 11501831.

19 Calì Cassi L, Vanni G, Petrella G, Orsaria P, Pistolese C, Lo Russo G, Innocenti M and Buonomo O: Comparative study of oncoplastic *versus* non-oncoplastic breast conserving surgery in a group of 211 breast cancer patients. Eur Rev Med Pharmacol Sci *20*: 2950-2954, 2016. PMID: 27460720.

20 Calì Cassi L, Biffoli F, Francesconi D, Petrella G and Buonomo O: Anesthesia and analgesia in breast surgery: the benefits of peripheral nerve block. Eur Rev Med Pharmacol Sci *21*: 1341-1345, 2017. PMID: 28387892.

21 Vanni G, Materazzo M, Perretta T, Meucci R, Anemona L, Buonomo C, Dauri M, Granai AV, Rho M, Ingallinella S, Tacconi F, Ambrogi V, Chiaravalloti A, Schillaci O, Petrella G and Buonomo OC: Impact of awake breast cancer surgery on postoperative lymphocyte responses. *In Vivo* (Brooklyn) *33*: 1879-1884, 2019. PMID: 31662515. DOI: 10.21873/invivo.11681

22 Ferroni P, Roselli M, Spila A, D'Alessandro R, Portarena I, Mariotti S, Palmirotta R, Buonomo O, Petrella G and Guadagni F: Serum sE-selectin levels and carcinoembryonic antigen mRNA-expressing cells in peripheral blood as prognostic factors in colorectal cancer patients. Cancer *116*: 2913-2921, 2010. PMID: 20336782 DOI: 10.1002/cncr.25094

23 Ferroni P, Palmirotta R, Spila A, Martini F, Formica V, Portarena I, Del Monte G, Buonomo O, Roselli M and Guadagni F: Prognostic value of carcinoembryonic antigen and vascular endothelial growth factor tumor tissue content in colorectal cancer. Oncology *71*: 176-184, 2007. PMID: 17652942. DOI: 10.1159/000106072

24 Roselli M, Guadagni F, Buonomo O, Belardi A, Ferroni P, Diodati A, Anselmi D, Cipriani C, Casciani CU, Greiner J and Schlom J: Tumor markers as targets for selective diagnostic and therapeutic procedures. Anticancer Res *16*: 2187-2192, 1996. PMID: 8694541.

25 Valdora F, Houssami N, Rossi F, Calabrese M and Tagliafico AS: Rapid review: radiomics and breast cancer. Breast Cancer Res Treat *169*: 217-229, 2018. PMID: 29396665. DOI: 10.1007/s10549-018-4675-4

26 Hatfield GP and Hogan MT: The role of ultrasound in breast imaging. W V Med J *105 Spec No*: 64-6, 2009. PMID: 19999269.

27 Flobbe K, Bosch AM, Kessels AGH, Beets GL, Nelemans PJ, von Meyenfeldt MF and van Engelshoven JMA: The additional diagnostic value of ultrasonography in the diagnosis of breast cancer. Arch Intern Med *163*: 1194-1199, 2003. PMID: 12767956. DOI: 10.1001/archinte.163.10.1194

28 Pistolese CA, Perretta T, Cossu E, della Gatta F, Giura S and Simonetti G: Value of the correct diagnostic pathway through conventional imaging (mammography and ultrasound) in evaluating breast disease. Radiol Med *116*: 584-594, 2011. PMID: 21431300. DOI: 10.1007/s11547-011-0657-x

29 Scimeca M, Giannini E, Antonacci C, Pistolese CA, Spagnoli LG and Bonanno E: Microcalcifications in breast cancer: an active phenomenon mediated by epithelial cells with mesenchymal characteristics. BMC Cancer *14*: 286, 2014. PMID: 24758513. DOI: 10.1186/1471-2407-14-286

30 Sickles EA, Wolverton DE and Dee KE: Performance parameters for screening and diagnostic mammography: Specialist and general radiologists. Radiology *224*: 861-869, 2002. PMID: 12202726. DOI: 10.1148/radiol.2243011482

31 Leung JWT, Margolin FR, Dee KE, Jacobs RP, Denny SR and Schrumpf JD: Performance parameters for screening and diagnostic mammography in a community practice: Are there differences between specialists and general radiologists? Am J Roentgenol *188*: 236-241, 2007. PMID: 17179372. DOI: 10.2214/AJR.05.1581

32 Spivey TL, Carlson KA, Janssen I, Witt TR, Jokich P and Madrigrano A: Breast Imaging second opinions impact surgical management. Ann Surg Oncol *22*: 2359-2364, 2015. PMID: 25608767. DOI: 10.1245/s10434-014-4205-5

33 Costantini M, Belli P, Lombardi R, Franceschini G, Mulè A and Bonomo L: Characterization of solid breast masses. J Ultrasound Med *25*: 649-659, 2006. PMID: 16632790. DOI: 10.7863/jum.2006.25.5.649

34 Biganzoli L, Marotti L, Hart CD, Cataliotti L, Cutuli B, Kühn T, Mansel RE, Ponti A, Poortmans P, Regitnig P, van der Hage JA, Wengström Y and Rosselli Del Turco M: Quality indicators in breast cancer care: An update from the EUSOMA working group. Eur J Cancer *86*: 59-81, 2017. PMID: 28963914. DOI: 10.1016/j.ejca.2017.08.017

35 American College of Radiology. BI-RADS Committee: ACR BI-RADS atlas: breast imaging reporting and data system. American College of Radiology, 2013.

36 Perry N, Broeders M, de Wolf C, Tornberg S, Holland R and von Karsa L: European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition-summary document. Ann Oncol *19*: 614-622, 2007. PMID: 18024988. DOI: 10.1093/annonc/mdm481

37 Wang M, He X, Chang Y, Sun G and Thabane L: A sensitivity and specificity comparison of fine needle aspiration cytology and core needle biopsy in evaluation of suspicious breast lesions: A systematic review and meta-analysis. Breast *31*: 157-166, 2017. PMID: 27866091. DOI: 10.1016/j.breast.2016.11.009

38 Orsaria P, Grasso A, Carino R, Caredda E, Sammarra M, Altomare C, Rabitti C, Gullotta G, Perrone G, Pantano F, Buonomo OC and Altomare V: Heterogeneous risk profiles among B3 breast lesions of uncertain malignant potential. Tumori J: 030089161986830, 2019. PMID: 31451072. DOI: 10.1177/0300891619868301

39 Pistolese CA, Tosti D, Citraro D, Ricci F, Di Stefano C, Lamacchia F, Ferrari D and Floris R: Probably Benign Breast Nodular Lesions (BI-RADS 3): Correlation between ultrasound features and histologic findings. Ultrasound Med Biol *45*: 78-84, 2019. PMID: 30340921. DOI: 10.1016/j.ultrasmedbio.2018.09.004

40 Fiaschetti V, Salimbeni C, Gaspari E, Dembele GK, Bolacchi F, Cossu E, Pistolese CA, Perretta T and Simonetti G: The role of second-look ultrasound of BIRADS-3 mammary lesions detected by breast MR imaging. Eur J Radiol *81*: 3178-3184, 2012. PMID: 22417393. DOI: 10.1016/j.ejrad.2012.01.027

41 Demircioglu O, Uluer M and Aribal E: How many of the biopsy decisions taken at inexperienced breast radiology units were correct? J Breast Heal *13*: 23-26, 2017. PMID: 28331764. DOI: 10.5152/tjbh.2016.2962

42 Chae EY, Cha JH, Shin HJ, Choi WJ and Kim HH: Reassessment and follow-up results of BI-RADS category 3 lesions detected on screening breast ultrasound. Am J Roentgenol *206*: 666-672, 2016. PMID: 26901026. DOI: 10.2214/AJR.15.14785.

43 Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med *151*: 716, 2009. PMID: 19920272. DOI: 10.7326/0003-4819-151-10-200911170-00008

44 Taplin SH, Rutter CM, Finder C, Mandelson MT, Houn F and White E: Screening mammography: Clinical image quality and the risk of interval breast cancer. Am J Roentgenol *178*: 797-803, 2002. PMID: 11906848. DOI: 10.2214/ajr.178.4.1780797

45 Kerlikowske K and Barclay J: Outcomes of modern screening mammography. J Natl Cancer Inst Monogr *(22)*: 105-111, 1997. PMID: 9709285. DOI: 10.1093/jncimono/1997.22.105

46 Lee KA, Talati N, Oudsema R, Steinberger S and Margolies LR: BI-RADS 3: Current and future use of probably benign. Curr Radiol Rep *6*: 5, 2018. PMID: 29399419. DOI: 10.1007/s40134-018-0266-8

47 Wilson ARM, Marotti L, Bianchi S, Biganzoli L, Claassen S, Decker T, Frigerio A, Goldhirsch A, Gustafsson EG, Mansel RE, Orecchia R, Ponti A, Poortmans P, Regitnig P, Rosselli Del Turco M, Rutgers EJT, Van Asperen C, Wells CA, Wengström Y and Cataliotti L: The requirements of a specialist Breast Centre. Eur J Cancer *49*: 3579-3587, 2013. PMID: 23968730. DOI: 10.1016/j.ejca.2013.07.017

48 Horvat J V., D'Alessio DD, Bernard-Davila B, Martinez DF and Morris EA: Second opinion interpretation of breast ultrasound images-Is it worth another look? Clin Imaging *52*: 79-87, 2018. PMID: 30005207. DOI: 10.1016/j.clinimag.2018.06.012

49 Steffens RF, Wright HR, Hester MY and Andrykowski MA: Clinical, demographic, and situational factors linked to distress associated with benign breast biopsy. J Psychosoc Oncol *29*: 35-50, 2011. PMID: 21240724. DOI: 10.1080/07347332.2011.534024

Received December 9, 2019
Revised December 20, 2019
Accepted December 23, 2019