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Original article

Accuracy of ultrasound-guided vacuum-assisted fine-needle aspiration for diagnosis and management of BI-RADS 4 lesion

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Background: Breast imaging-reporting and data system (BI-RADS) 4 lesions are in the category of suspicion for malignancy which has to be managed with core needle biopsy as specified in the standard guidelines. Nonetheless, at King Chulalongkorn Memorial Hospital, an ultrasound-guided vacuum-assisted fine-needle aspiration (FNA) is performed in some cases of BI-RADS 4 lesions because it has been considered a simple and cost-effective tool for managing breast lesions in a previous study.

Objectives: This study aimed to evaluate the accuracy of an ultrasound-guided vacuum-assisted fine-needle aspiration in the diagnosis and management of BI-RADS 4 lesions.

Methods: A retrospective review was conducted on 251 female patients with BI-RADS 4 lesions who underwent an ultrasound-guided vacuum-assisted FNA, together with a subsequent procedure of either surgical biopsy or follow-up imaging for at least 2 years at King Chulalongkorn Memorial Hospital from January 2011 to December 2013. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the study data were evaluated. Also, the underestimation rate of unsatisfactory samples (C1) was calculated.

Results: The sensitivity, specificity, PPV, and NPV for ultrasound-guided vacuum-assisted FNA were 72.73% (95% CI:67.22 - 78.24%), 98.07% (95% CI:96.36 - 99.77%), 88.89% (95% CI:85.0 - 92.78%) and 94.42% (95% CI: 91.58 - 97.26%) respectively. Sixteen patients with discordant lesions between FNA cytology and surgical pathology were found; 4 of them (1.9%) were false positives and 12 (27.3%) were false negatives. Among 71 patients with unsatisfactory samples (C1), 67 cases (94.4%) showed benign results, while 4 cases (5.6%) showed malignant results.

Conclusion: An ultrasound-guided vacuum-assisted FNA is a reliable diagnostic tool for BI-RADS 4 lesions. However, there are some limitations that may cause false negatives, especially in the case of a very small lesions, such as an inexperienced performer along with other uncontrollable factors e.g. the heterogeneity type of a tumor. Therefore, subjects should be properly selected to prevent an error.

Keywords: Fine-needle aspiration, BI-RADS 4, accuracy.

Breast cancer is a major health burden with the highest prevalence among women worldwide causes the greatest number of deaths of women in Thailand, Southeast Asia, and worldwide.

Since a regular breast cancer screening program has been set up, the mortality rate from breast cancer has been reducing. The American College of Radiology (ACR) has created the Breast Imaging Reporting and Data System (BI-RADS)[1] to categorize radiographic findings into 5 classifications which illustrate the likelihood of cancer and guidelines for further management (Table 1).

BI-RADS 4 lesions are in the category of suspicion for malignancy which can be classified into 4A, 4B, and 4C subcategories, depending on radiographic findings and needs for tissue diagnosis (Table 2).

According to the standard guidelines of the NCCN version 1. 2017[2], BI-RADS 4 lesions have to be managed with core needle biopsy. Nevertheless, at King Chulalongkorn Memorial Hospital, the guidelines for screening/diagnostic mammogram was established with an additional ultrasound (Figure 1) adapted from the standard guideline. If the patient is diagnosed with a BI-RADS 4 lesion after the screening/ diagnostic mammogram, she will be examined by the ultrasound-guided fine-needle aspiration (FNA) with vacuum assistance or a core needle biopsy.

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Table 1. BI-RADS assessment categories.

Category	Management	Likelihood of cancer
0 Need additional imaging and/or await prior examination	Recall for additional imaging and/or await prior examination	Not available
1 Negative	Routine screening	Essentially 0%
2 Benign	Routine screening	Essentially 0%
3 Probably benign	Short interval-follow-up (6 month) or continued	> 0% but ≤ 2%
4 Suspicious	Tissue diagnosis	4A: low suspicion for malignancy (> 2% to 10%) 4B: moderate suspicion for malignancy (>10% to < 50%)4C: high suspicion foe malignancy (> 50% to < 95%)
5 Highly suggestive of malignancy	Tissue diagnosis	≥ 95%
6 Known biopsy proven	Surgical excision when clinically appropriate	Not available

Table 2. BI-RADS 4 Classification system.

Category	Likelihood of cancer	Findings
4A	Low suspicion for malignancy (> 2% to ≤ 10%)	- Partially circumscribed solid mass with US features suggestive of fibroadenoma - Palpable solitary complicated cyst - Probable abscess
4B	Moderate suspicion for malignancy (> 10% to ≤ 50%)	- A group of amorphous or fine pleomorphic calcifications - Non descript solid mass with indistinct margins
4C	Highly suspicious, but not classic for malignancy (> 50% to < 95%)	- New group of fine linear calcifications - New indistinct, irregular solid mass

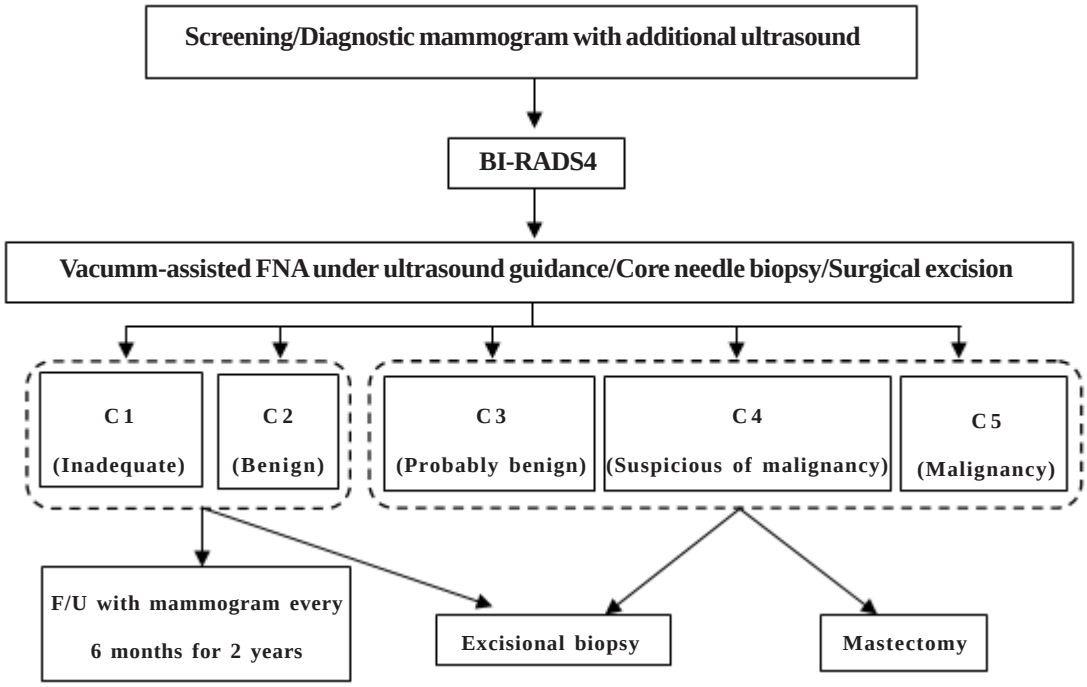

Figure 1. Guideline for breast cancer screening at King Chulalongkorn Memorial Hospital.

As previous studies have shown that a fine-needle aspiration can be considered a simple and cost-effective tool for the diagnosis and management of a palpable breast mass with high accuracy,[3 - 5] the purpose of this study was to evaluate the accuracy of an ultrasound-guided vacuum-assisted FNA in the diagnosis and management of BI-RADS 4 lesions at King Chulalongkorn Memorial Hospital.

Materials and methods

A retrospective review through a computer database was performed on 312 patients who had both screening and diagnostic mammograms from January 2011 to December 2013 at the Outpatient Unit of King Chulalongkorn Memorial Hospital, and who were diagnosed with BI-RADS 4 lesions. The patients who underwent an ultrasound-guided vacuum-assisted FNA, together with a subsequent procedure of either surgical biopsy or follow-up imaging for at least 2 years were included in this study. On the contrary, the patients whose lesions were diagnosed as a benign cystic fluid by FNA, could not be seen on the ultrasound, those with inconclusive pathological results, or lost to follow-up were excluded.

The data of cytological results from FNA and a surgical pathological result must have been available in the Hospital Information System (HIS). Radiographic data had to have been available in the Picture Archiving and Communicating System (PACS). In this regard, age, location of the lesion, size, shape and margin of the lesion, the subcategory of BI-RADS 4 (4A, 4B and 4C), and cytological and surgical histopathological results of each patient were all recorded.

Fine-needle aspiration was performed twice for each lesion with a 10 mL syringe and a 22G spinal needle under ultrasound guidance (GE 2013) by a breast radiologist at the Outpatient Department. The skin was prepared with a povidone-iodine solution and anesthetized with 2% lidocaine. The lesion was punctured and aspirated under negative pressure. If the fluid was obtained, the lesion would be aspirated until it disappeared. If the mass was partially solid or entirely solid, the needle would be advanced and would maintain negative pressure in various directions until it could yield an approximate volume of content. After that, the contents was sprayed and smeared on the glass slide and immediately fixed in 95% alcohol. All slides were submitted to the Department of Pathology on the same day. The cytological results were categorized into 5 grades according to the recommendations of the National Cancer Institute (NCI) for the diagnosis of a breast aspiration cytology, ranging from insufficient materials (C1), benign (C2), atypical (C3), suspicious of malignancy (C4) to exactly malignant (C5) (Table 3). The results of FNA cytology were classified as positive (C3 - C5) and negative (C1 -C2), adapted from Kanchanabat B.[3] and Pisano ED.[6] In this respect, a mass with an indeterminate cytological nature (C3) required other diagnostic procedures to minimize the underestimation.

The cytological specimens were evaluated by one pathologist. Descriptive statistics were used in this study. The histopathological results from surgical biopsies were set as the criterion standard. As for the lesions which did not undergo surgical excision, its benign state was inferred by the stability on the follow-up radiographic imaging for at least 2 years.

The cytological and histopathological data were applied in two by two tables and the test accuracy was evaluated by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The discordant findings between cytological data and the criterion standard (false-positive and false-negative data) were mentioned and discussed later. With regard to the unsatisfactory samples (C1), they were analyzed in the form of binary data as the percentage of benignancy or malignancy.

Results

Two hundred and fifty-one patients who matched the criteria were studied. They were in the age range of 23 – 76 with a mean age of 49 years. Concerning BI-RADS 4 subcategories, 192 (76.5%) were BI-RADS 4A; 46 (18.3%) were BI-RADS 4B; and, 13 (5.2%) were BI-RADS 4C.

The cytological results from FNA showed that 215 patients (85.6%) had negative FNA results (C1 and C2), whereas 36 patients (14.4%) had positive or suspicious aspiration (C4 and C5). On this point, 203 cases had negative cytology with benign surgical pathology (true negative), while 32 cases had positive cytology with malignant surgical pathology (true positive). Thus, the accuracy of FNA for BI-RADS 4 lesions is 93.6% (Table 4).

From analysis for the criterion standard, there were 45 patients (18%) with malignant surgical pathology, 70 patients (28%) with benign surgical pathology, and 136 patients (54%) with inferred benign lesions by the stability on the follow-up radiographic imaging for at least 2 years i.e. no progression was found in the radiographic findings during the 2-year follow-up study.

Table 3. Cytological category according to NCI.

Category	Cytology results	Findings
C1	Unsatisfactory/Inadequate	- Less than 6 epithelial group of 5 - 10 cell each - Broken slide, wrong labeled slide - Poorly prepared (Too thick - too vigorous smearing, prolonged air-drying, no fixation for pap stain; Poor staining-weak diluted staining solution - Too bloody obscuring diagnostic cells - Completely necrotic - Poorly cellular - Contaminants: Ultrasound gel
C2	Cells present all benign, no suspicious features	- Non-specific pattern - Specific : Mastitis/Abscess - Numerous neutrophils and histiocytes, granular background, scanty reactive ductal cell (open chromatin vesicular/central nuclei) Breast cyst - Background of amorphous material, degenerate cells and debris, foamy macrophages, ductal epithelial cell (often apocrine and balling-up), myoepithelial cell may not be seen (do not overcall aspirate as malignant) Fibroadenoma- Moderate to high cellularity, tight cohesive branching antler-horn or finger-like projections of epithelial cells, stromal fragments (metachromatic fibrillary matrix material), need both and stromal components to be diagnostic, numerous bare bipolar nuclei, bordering and within epithelial clusters, may see few foam cells or apocrine cells, often mild nuclear atypia with prominent nucleoli, particularly in younger patients. Fat Necrosis - usually not very cellular, fragments of degenerate necrotic adipocytes with loss of nuclear staining, ductal cells are generally scant, dirty background, foamy macrophages with multinucleated giant cells, calcium may be seen
C3	Cell suspicious but probably benign	- Loss of cohesion/dyscohesive ductal cell - High cellularity - No/ rarely seen myoepithelial cells (bipolar naked nuclei) - Single atypical cells or loosely sheets of atypical cells - Enlarged, pleomorphism
C4	Cells suspicious but probably malignant	- Ductal cells with nuclear enlargement and prominent nucleoli but are in large sheets with no single cells - Only a few malignant cells are present - Malignant cell intermixed with bare bipolar nuclei
C5	Definite malignancy	- Unequivocal evidence of malignancy is present - Need to type whether carcinoma, lymphoma, sarcoma or melanoma

Table 4. Two-by-two table of the accuracy of FNA cytology.

	Gold standard (Surgical histopathology/2-year imaging stable)	
	Malignant	**Benign**
Malignant (C3 - C5)	32 (A)	4 (B)
Benign (C1-C2)	12 (C)	203 (D)

A = True malignant lesion, B = False positive, C = False negative, D = True benign lesion

The diagnosis of malignant lesions by the ultrasound-guided vacuum-assisted FNA showed a 72.73% sensitivity (95% CI:67.22 - 78.24%), 98.07% specificity (95% CI:96.36 - 99.77%), 88.89% positive predictive value (95% CI:85.00 - 92.78%), and 94.42% negative predictive value (95% CI:91.58 - 97.26%).

There were 16 patients with discordant lesions between FNA cytology and surgical pathology, 4 of whom were positive for cytology with benign surgical pathology (false positive), and 12 of whom were negative for cytology with malignant surgical pathology (false negative). In brief, the false-positive and false-negative rates were 1.9% and 27.3%, respectively.

Seventy-one patients (28.3%) had inadequate cytology (C1), 67 of them (94.4%) showed benign results from the surgical histology or the stability on the radiographic imaging for at least 2 years, whereas 4 of those (5.6%) showed malignant results from the surgical histology. Out of the 4 patients with malignant surgical histology, 2 had atypical ductal hyperplasia and the others had invasive mammary carcinoma.

Discussion

Although current standard guidelines for BI-RADS 4 lesion management is to perform a core needle biopsy, recent studies have proved that FNA is a high-accuracy tool in managing a palpable breast mass with simplicity and cost-effectiveness. For this reason, it may be suitable for developing countries.

This study has shown that ultrasound-guided vacuum-assisted FNA is a reliable diagnostic tool for BI-RADS 4 lesions as it has high accuracy, NPV, and PPV. The fine-needle aspiration biopsy (FNAB) could detect 32 true malignant lesions from 36 suspected malignant lesions, or 88.9% PPV, and could detect 203 true benign lesions from 215 suspected benign lesions, or 94.4% NPV.

From 16 patients with discordant lesions between FNA cytology and surgical pathology (Table 5), 4 false positives, i.e., case no. 3, 14, 15 and 16 were found with details as follows. Firstly, the patient in case no. 3 had the result of suggestive ductal carcinoma in situ (DCIS) or papillary neoplasm from FNA cytology, but the surgical pathology showed fibroadenomatous hyperplasia and adenosis. Secondly, the one in case no. 14 had a result suggestive of low-grade ductal carcinoma from FNA cytology, but the surgical pathology showed fibroadenoma. Regarding the last 2 cases, they had results of the C3 category showing suspicion for malignancy and presence of atypical ductal cells from FNA cytology, but the surgical pathology showed foreign body granuloma and fibrocystic change, respectively. Mendoza P, *et al*. demonstrated that false-positive findings were commonly found in ductal hyperplasia or lobular hyperplasia.[7] Although this type of error may bring about an unnecessary investigation, the incidence rate is quite low.

On the other hand, 12 patients with false-negative lesions were found and should be of concern because these could result in missed or delayed diagnosis and treatment. On this detail, there were 4 cases of scant cell cytology, 3 cases suggestive of intraductal papilloma/papillary neoplasm, 1 case of sclerosing lesion, 1 case of benign lesion, such as fibroadenoma, and 3 cases of benign breast lesions.

False negatives of the scant cell cases were probably caused by (1) poor sampling technique especially in a very small lesion, or (2) tumor with minimal atypia component, which was known to be the limitation of the FNA study.

With regard to the cases of intraductal papillary lesions, since there is an overlap of imaging patterns between benign intraductal papilloma and other potential papillary cancers, including intraductal papilloma with ADH, papillary ductal carcinoma in situ and invasive papillary carcinoma, the cases with radiographic features demonstrate suspicion for papillary lesions and should be examined by core needle

Table 5. Discordant lesions of patients between FNA cytology and surgical pathology.

No	Type	BI-RADS	Radiographic findings	FNAC findings	Gold Standard findings
1	C	4C	A 1.6 x 1.4-cm ill-defined hypodense nodule at inner mid part of right breast (taller than wide, posterior acoustic shadow, indistinct margin)	No malignancy	IDC grade I/II, presence of cribiform DCIS
2	C	4C	A 0.8 x 1.0-cm ill-defined hypodense nodule with angulate margin in left upper mid part of left breast	Benign; Fibroadenoma	IDC of NOS grade II
3	B	4A	Slightly increased size of a 1.1 x 0.9 x 0.9-cm lobulated hypoechoic mass in RUIQ	Suggestive of ADH, DCIS or papillary neoplasm	Fibroadenomatous hyperplasia and adenosis
4	C	4B	A small stellate lesion at RUOQ, ultrasound showing focal shadowing area in RUOQ. Please consider wired localized wide excision even if FNA is negative	Sclerosing lesion	IDC grade I and cribiform DCIS focus
5	C	4B	Increased size of a 0.5 x 1.3-cm well-defined lobulated hypoechoic nodule in LUOQ with new 0.8 x 0.6-cm ill-defined hypoechoic lesion with focal shadow at left central area	Benign proliferative breast disease or papillary neoplasm	Multifocal IDC grade II with LVI
6	C	4B	A 0.6 x 0.5-cm ill-defined hypoechoic lesion at RUOQ	Probably benign	Intermediate grade DCIS with comedonecrosis
7	C	4A	Increased size of a 1.2 x 0.8-cm lobulated hypoechoic lesion at right subareolar area with internal vascularity	Benign breast nodule	IDC grade II with fibroadenomatous change
8	C	4A	A 0.6 x 0.9-cm partially defined hypoechoic nodule with echogenic rim at right outer mid part	Scant cell	Early fibrocystic change with ADH
9	C	4A	A 0.4-cm ill-defined hypoechoic nodule at LUIQ	Scant cell	ADH
10	C	4C	A 0.6 x 0.8-cm ill-defined irregular hypoechoic nodule with echogenic rim at LUIQ	Suggestive of intraductal papilloma	Papillary lesion with area of invasive tumor
11	C	4A	A 0.7 x 1.2-cm well-defined lobulated hypoechoic mass at RUOQ	Scant cell	IDC grade II
12	C	4B	A well-defined lobulated cystic mass with internal solid component and increased vascularity at RUOQ, possible papilloma or papillary CA	Suggestive of intraductal papilloma	Encapsulated papillary carcinoma with IDC component
13	C	4C	A 0.6 x 0.7-cm ill-defined irregular hypoechoic lesion with taller than wide at RUOQ	Scant cell	Invasive mammary carcinoma
14	B	4A	A 0.5 x 0.2-cm irregular ill-defined hypoechoic nodule at RUIQ	Suggestive of low-grade ductal cancer	Fibroadenoma
15	B	4A	A 0.7 x 0.6 x 0.6-cm ill-defined hypoechoic nodule in RUIQ, adjacent to the surgical scar (Sclerosing fibroadenoma)	Suspicious malignant cell	Foreign body granuloma (suture)
16	B	4A	A 0.4 x 0.3-cm partially ill-defined hypoechoic nodule with posterior shadow at RLOQ	Presence of atypical ductal cell	Fibrocystic change

B - False positive lesion, C = False negative lesion, ADH = Atypical ductal hyperplasia, IDC = Invasive ductal carcinoma, DCIS = Ductal carcinoma in situ, LVI = Lymphovascular invasion, RUOQ = Right Upper Outer Quadrant, LUIQ = Left Upper Outer Quadrant, CA = Cancer

biopsy (CNB) instead of FNA because CNB can provide a larger specimen and reduce the rate of inadequate or suspicious results[8] (Figure 2). Likewise, the complex sclerosing lesion (CLS) or radial scar (RS), and benign radiological and histological entities are recommended to be examined by an excision due to the difficulty in differentiating them from carcinoma[9] (Figure 3).

Regarding 4 cases of benign breast cytology, their radiographs were retrospectively reviewed and malignant features were found in most of them, such as irregular/angular margin, taller than wide appearance, or posterior shadowing, which was discordant with the benign cytological results. Therefore, further tissue diagnosis was required (Figure 4).

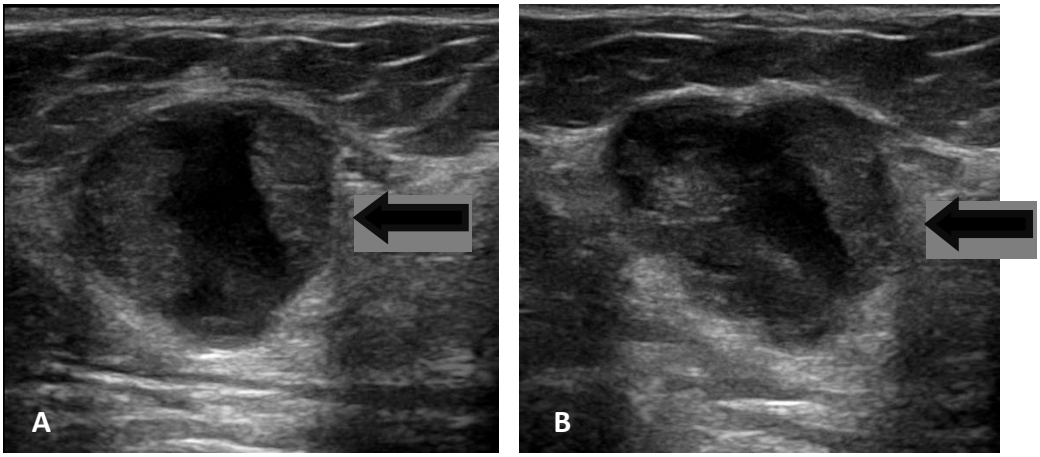

Figure 2. Discordant lesion-Intraductal papillary lesion: (A) and (B) An ultrasound of the right breast in two perpendicular views: A 4.2 × 3.9-cm well-defined lobulated cystic mass with internal solid component (arrows) and increased vascularity (not shown) at RUOQ (BI-RADS 4b), possible papilloma or papillary cancer. The surgical pathology revealed papillary carcinoma with IDC component.

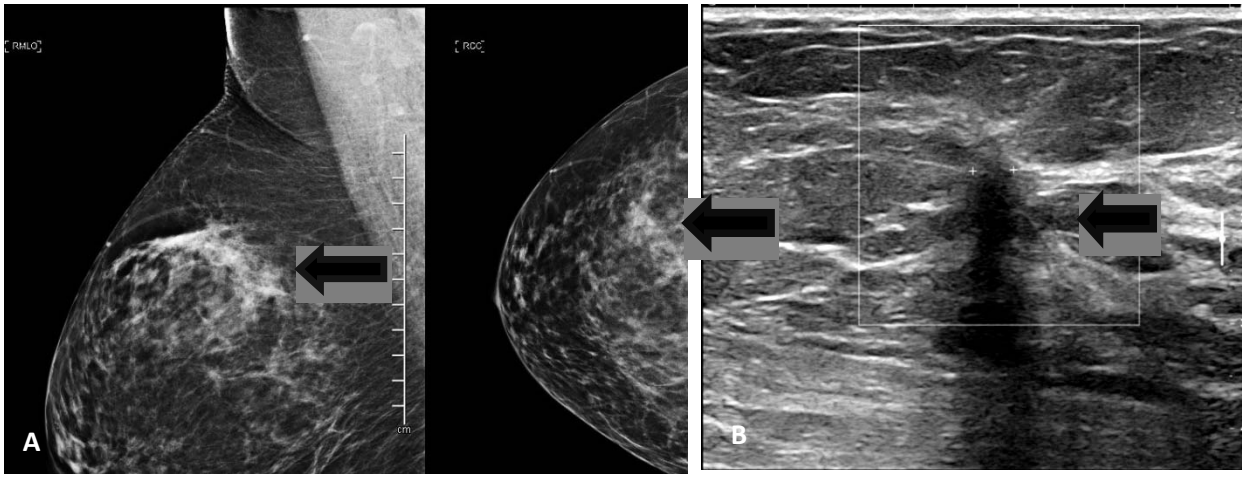

Figure 3. Discordant lesion - Sclerosing lesion/Radial scar: (A) A mammogram in MLO and CC views; and (B) an ultrasound of the right breast: A 1.8 × 0.6-cm spiculate mass at RUOQ and the additional ultrasound was seen as an ill-defined mass with posterior shadow (arrows). The surgical pathology revealed IDC grade I and cribiform DCIS focus.

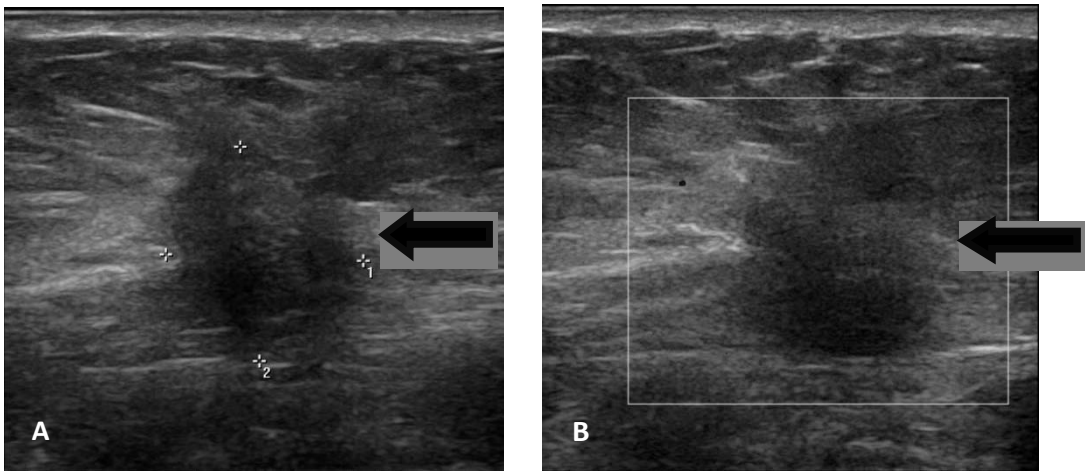

Figure 4. Discordant lesion - Malignant features: (A) An ultrasound of the right breast (B) with color doppler: A 1.6 × 1.4-cm ill-defined hypoechoic nodule at inner mid part of right breast with angular margin and taller than wide, no demonstrable internal vascularity (arrows). The FNA cytology was negative and the surgical pathology revealed IDC with cribiform DCIS, accounting for 10% of total tumor volume.

With respect to the 71 patients who had inadequate cytological results (C1), most of them (94.4%) turned out to be benign from either surgical pathology or follow-up imaging for at least 2 years. However, 5.6% of this group showed a malignant result which was to be concerned. As a consequence, triple assessment, including clinical breast examination, radiographic findings, and pathological assessment, should be individually re-evaluated in the suspicious cases to avoid missed or delayed treatment.

Conclusion

Current evidence from this study has proved that ultrasound-guided vacuum-assisted FNA is a reliable diagnostic tool for BI-RADS 4 lesions. With its high sensitivity and specificity, most benign and malignant breast lesions can be accurately diagnosed. Still, there are some limitations of the FNA study which may cause false negatives, especially in the case of a very small lesion, an inexperienced performer, or other uncontrollable factors, e.g., heterogeneity or type of the tumor. Thus, patient should be properly selected to prevent an error. The cases where radiographic features show suspicion for papillary lesions or they can be initially considered as intraductal papillary lesions by FNA, should undergo CNB since it can provide a larger specimen and can reduce the rate of inadequate or suspicious results. On the subject of complex sclerosing lesion, it should be examined by wide excision, although the CNB result was negative, to exclude a sampling error or an inadequate sampling.

Inadequate samples (C1) are more likely to be benign (94.4%) than malignant (5.6%). Nevertheless, triple assessment should be individually re-evaluated in a suspicious case to prevent missed or delayed treatment.

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