



Clinically Indeterminate Breast Lesions with Normal Imaging: A Retrospective Study in a Symptomatic Breast Care Unit

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Abstract

Background: Triple assessment of breast pathologies is a very important pathway to detect breast cancers earlier.

Objectives: To ascertain the necessity of clinical-guided core biopsy (CGCB) or fine-needle aspiration cytology (FNAC) for investigating clinically indeterminate breast lesions with no significant imaging findings.

Patients and Methods: Retrospective analysis of 72 patients who had clinical core biopsy or fine-needle cytology was carried out to investigate clinically indeterminate breast lesions with normal imaging during the period from September 2017 to September 2019.

Results: Out of 72 patients, 61 clinically indeterminate breast lesions (P3) were investigated and showed that 39 lesions (63.9%) were graded as B1, 17 lesions (27.8%) were graded as B2, two lesions (3.2%) were graded as B3 showing atypia, no lesions were graded as B4, two lesions (3.2%) were graded as B5 (one [1.6%] was found to be invasive lobular carcinoma [ILC] and the other one [1.6%] was found to be metastatic colorectal cancer to the breast), while one lesion investigated by FNAC was graded as C2 (1.6%).

Conclusion: CGCB or FNAC is still necessary and vital for investigating clinically indeterminate breast lesions with normal imaging.

Keywords: Indeterminate Breast Lesions, Ultrasound Scan, Mammogram, Core Biopsy, Fine-Needle Aspiration Cytology

1. Background

Breast cancer is one of the top causes of cancer related mortalities among females. It was responsible for 2.1 million new cases and 626,679 cancer related deaths that were reported worldwide in 2018. Fair access to clinical and radiological assessment is crucial to early detection of breast cancer (1).

Although some guidelines and task forces have discarded clinical breast examination (CBE) (2), there is no doubt that CBE performed by appropriately trained breast physicians plays an important role in detecting breast cancer (3). Triple assessment ([CBE], imaging, and histopathological assessment) of breast pathologies is a very important method to detect breast cancer earlier.

The vast majority of palpable lumps are benign, but one cannot give %100 reassurance in terms of excluding malignant masses (4). Roughly, one-third of breast biopsies come back with diagnosis of breast cancer (5). This retrospective study aimed to ascertain the necessity of clinical-guided core biopsy (CGCB) or fine needle aspira-

tion cytology (FNAC) for investigating clinically indeterminate breast lesions that have no significant imaging findings.

2. Objectives

The objective was to ascertain the necessity of clinical-guided core biopsy or fine-needle aspiration cytology for investigating clinically indeterminate breast lesions with no significant imaging findings.

3. Patients and Methods

We conducted a retrospective observational analysis of our current practice of 72 patients (who had undergone clinical core biopsy or FNAC) to investigate clinically palpable breast lesions that had normal imaging during the period from September 2017 to September 2019.

Based on our inclusion and exclusion criteria, we excluded 16 patients who were clinically graded as P4/P5, so the final number of patients included was 56 patients.

Clinical and radiological assessment pathway for breast care unit patients is demonstrated in [Figure 1](#). Radiological examinations were carried out by four dedicated breast radiologists who are board certified from the United Kingdom (UK) (the first radiologist with more than 30 years of experience, the second and third with more than 15 years of experience, and the fourth, with two years of experience).

Ultrasound scans were carried out with the patient in the supine position, using two GE Logiq E9 stand alone machines, with transverse probes (ML6-15 MHz transducer) and elastography, color and power Doppler options.

Mammographic examinations were carried out in the standing position using GE Senographe Essential™ digital mammography, and average breast thickness (60 mm, mAs 86.4, Kv 31, filter Rh [Radium], Target Rh).

Clinical core biopsies were performed by dedicated UK board certified breast surgeons, breast physicians and breast care nurses using 14 G Achieve™ core biopsy needle fully cocked technique.

Data was collected from the hospital clinic biopsy register, info-flex (Electronic patient records), and imaging and histopathology reports.

Clinical breast examination (CBE) and mammographic and ultrasound grading used for reporting was based on the UK 5-point breast imaging and reporting data system (UK BI-RADS) (R1: normal, R 2: benign 3: indeterminate /probably benign, R4: suspicious of malignancy and R5:highly suspicious of malignancy), which matched the 5-point clinical P grading system (U1, normal; U2, benign; U3, indeterminate/probably benign; U4, suspicious of malignancy; and U5, highly suspicious of malignancy), which matched the 5-point clinical P grading system ([Table 1](#)) ([6](#), [7](#)).

None of the 56 patients had post biopsy complications and all underwent written informed consent prior to the biopsy procedures.

4. Results

The total number of patients was 56 patients, the median age and mean age (standard deviation [SD]) were 46 years, and 48.3 years (14.8), respectively. Ten patients (17.8%) were younger than 40 years, while 46 patients (82.1%) were older than 40 years.

Fifty-five patients (98.2%) were female and only one patient (1.7%) was male.

The total number of examined breast lesions was 61 lesions, 27 patients (48.2%) had lesions on the right side, and 24 (42.8%) had left-sided lesions, while five (8.9%) had bilateral breast lesions.

Clinical assessment of index breast lesions was graded using P grading. All 61 included lesions were graded as P3.

Imaging modalities in the one-stop clinic included breast ultrasound as well as mammographic assessment, ultrasound scan was graded as U1 in 47 lesions (77%), U2 in 13 lesions (21.3%), and none were graded as U3, U4, and U5. One lesion (1.6%) did not have an ultrasound scan, as there was no suspicious lesion seen on mammogram.

Mammograms were not carried out for 20 patients (one male patient (1.7%), 10 patients (17.8%) younger than 40 years, and nine patients (16%) who had recent mammograms), 32 lesions (52.4%) were graded as R1 and nine lesions (14.7%) were graded as R2, none were graded as R3, R4, or R5.

Histological assessment of clinical core biopsy revealed that 39 lesions (63.9%) were graded as B1, of which 17 were predominantly adipose tissue, and 22 were fibroglandular breast tissue.

Seventeen lesions (27.8%) were graded as B2, of which 10 were fibrous breast tissue, two fibrocystic disease, two chronic inflammation, one fat necrosis, one columnar cell change, and one pseudoangiomatous stromal hyperplasia (PASH).

Two lesions (3.2%) were graded as B3, one was atypical intraductal epithelial.

proliferation (AIDEP), and the other was flat epithelial atypia.

Two lesions (3.2%) were graded as B5 (one [1.6%] was found to be invasive lobular carcinoma [ILC], and the other one [1.6%] was found to be metastatic colorectal cancer to the breast). One lesion (1.6%) was investigated by FNAC; cytology was graded as C2 showing adipocytes in keeping with a lipoma ([Figure 2](#)).

5. Discussion

Breast cancer is the most common cancer in the UK, accounting for 15% of all newly diagnosed cancer cases per year. Fifty-five thousand women are diagnosed with breast cancer in the UK every year, (150 diagnosed every day).

The incidence of breast cancer is estimated to rise by 2% in the UK between 2014 and 2035. It may well reach to 210 cases per 100,000 females by 2035 ([8](#)). While a palpable breast lump is the most common presenting symptom

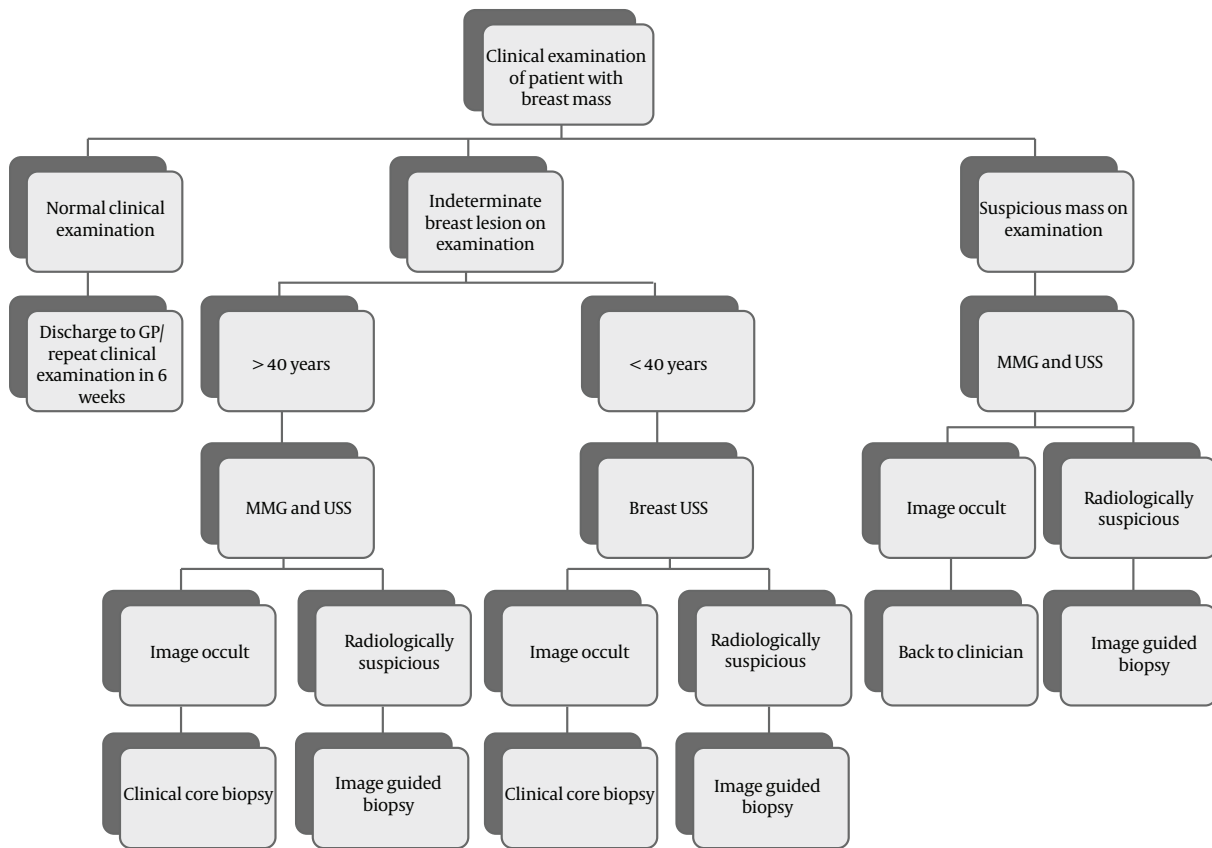


Figure 1. Patient management flow chart. USS, ultrasound scan ; MMG, mammography; GP, general physician.

Table 1. UK 5-Point Breast Clinical Examination and Imaging Classification

Clinical	Ultrasound scan	Mammogram	MRI	Histopathology	Cytology
Px: Previous biopsy					
P1: Normal	U1: normal	R1: normal	MRI 1: normal	B1: normal	C1: normal
P2: Benign	U2: benign	R2: benign	MRI2: benign	B2: benign	C2: benign
P3: Indeterminate	U3: indeterminate	R3: indeterminate	MRI3: indeterminate	B3: indeterminate	C3: indeterminate
P4: Suspicious	U4: suspicious	R4: suspicious	MRI4: suspicious	B4: suspicious	C4: suspicious
P5: Highly suspicious	U5: malignant	R5: malignant	MRI5: malignant	B5a: non invasive cancer	C5: malignant
				B5b: invasive cancer	

Abbreviation: MRI, magnetic resonance imaging.

^aSource: (6, 7).

of breast cancer, as reported by Mutar et al. (9) representing 71.3%, breast pain represents 18.9% of presenting symptoms.

Clinical breast examination usually precedes imaging for patients presenting to the breast clinic. Mutar et al.

(9) and Koo et al. (10) found that patients usually demand breast examination if they experience a persistent lump other than other kinds of breast complaints.

Clinical breast examination is a simple non-invasive and cheap way to detect breast cancers, but adjunct imag-

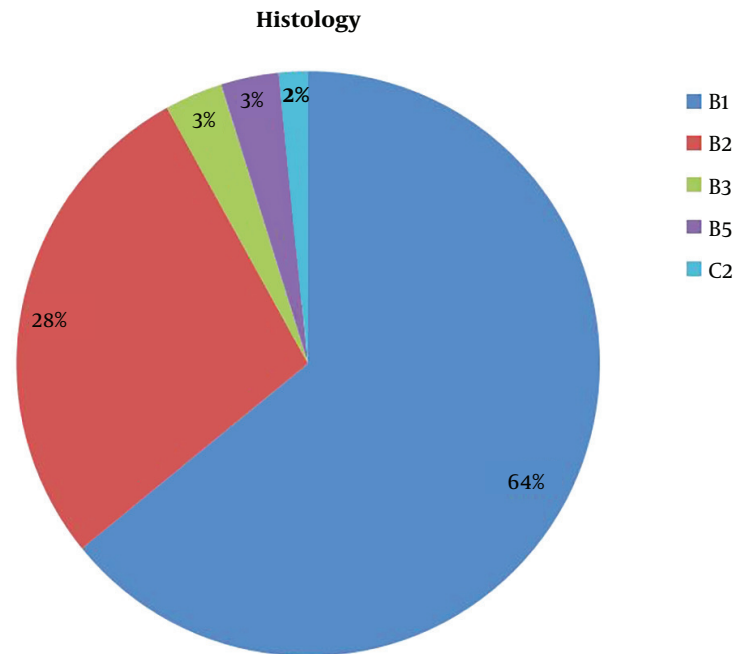


Figure 2. Histopathological distribution of indeterminate breast lesions

ing should be added to increase the final accuracy.

60% - 80% of breast biopsies usually show benign findings (11-13). Breast ultrasound and mammography could increase breast cancer detection rate by 4.2 cancers per 1000 screened women compared to women who undergo screening mammography alone (14).

Benson et al. reported the sensitivity of breast ultrasound as 89% (15). Houssami et al. (16) reported that the overall sensitivity of mammography and ultrasound is 96%.

The perception of a subtle mass or cluster of microcalcifications can be picked up by mammograms in case the image contrast is adjusted. Pisano et al. (17) and Yunus et al. (18) reported about 25% - 43% of non-palpable cancers can be detected on mammography in the presence of microcalcification.

In addition, Pisano et al. (19) found that the sensitivity and specificity of digital mammography in pre- or perimenopausal women less than 50 years with non-dense breasts is 85% and 90%, respectively.

According to a study conducted by Dennis et al. (20), they followed up 540 breast lumps without ultrasound findings for at least 2 years, and they found that none of the lumps turned to be breast cancer or any other form of malignancy. This interesting result represents a negative

predictive value of ultrasound is reaching 100%. Therefore, they advised ignoring clinical breast biopsy when imaging is negative (20).

According to Kaiser et al. (21), who conducted a prospective study with a patient cohort of 103, they followed up palpable breast thickening patients and reached a 100% negative predictive value of ultrasound imaging. Houssami et al. (22) reported that clinically guided biopsy (CGB) could have a high false negative rate compared to image-guided core or FNA sampling. Ward et al. (23) found that the diagnostic accuracy increases in case of image guided sampling.

Larger patient cohort studies have already demonstrated that core biopsy sampling approach has a better diagnostic outcome to FNAB in terms of sensitivity, specificity and correct histological grading (24-26).

Gumus et al. (27) advised that breast ultrasound scan should be performed for clinically palpable, mammographically occult breast lesions followed by clinically or ultrasound guided core biopsy.

The vast majority of our patients had a normal or benign findings on mammogram and ultrasound scans (Figures 3 and 4), yet clinicians opted to do a clinically guided needle biopsy to ascertain the final diagnosis.

In our patient cohort, we picked up two malignancies

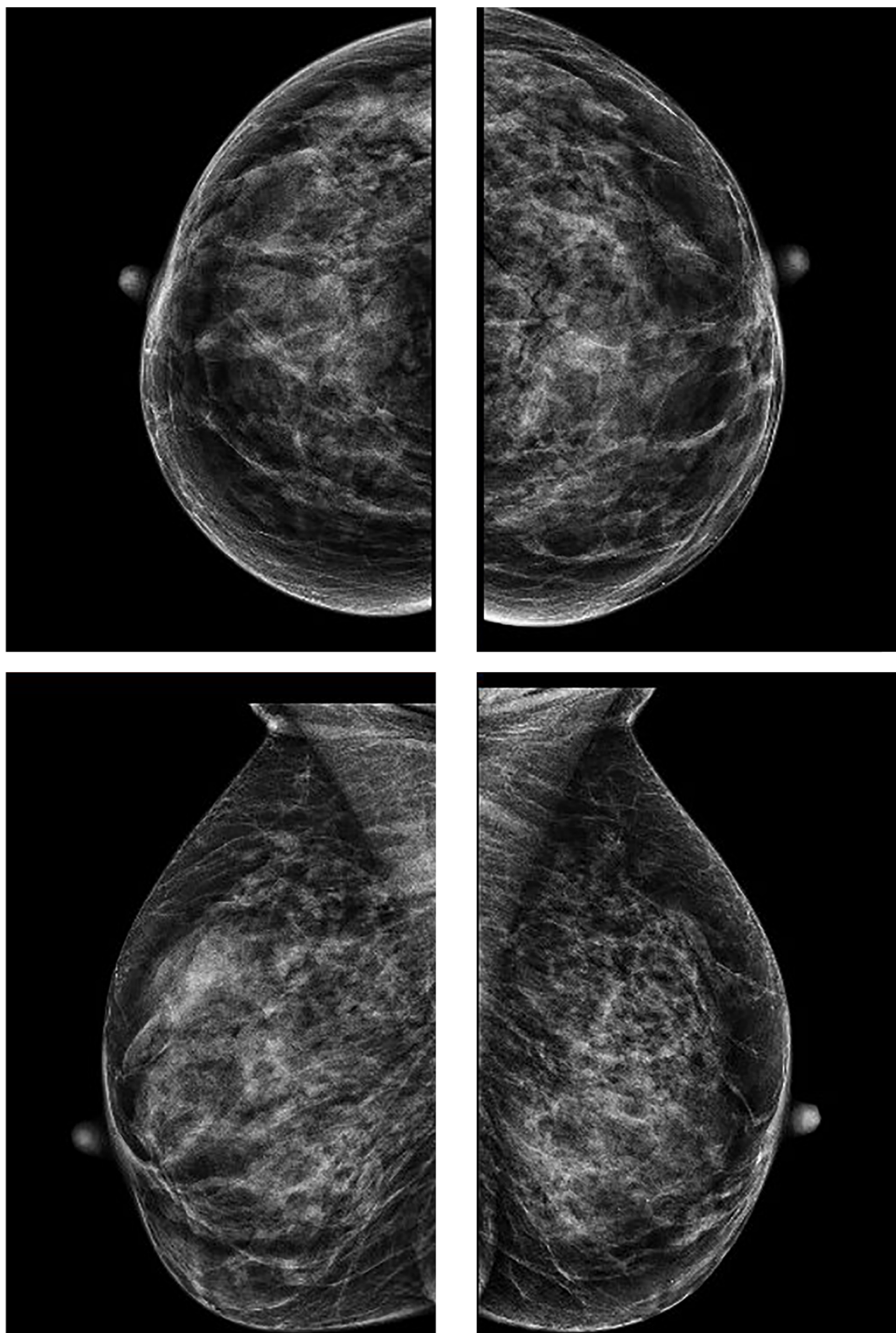


Figure 3. Bilateral mammogram of a 93-year-old patient presenting with palpable clinically indeterminate breast lump showing no suspicious findings

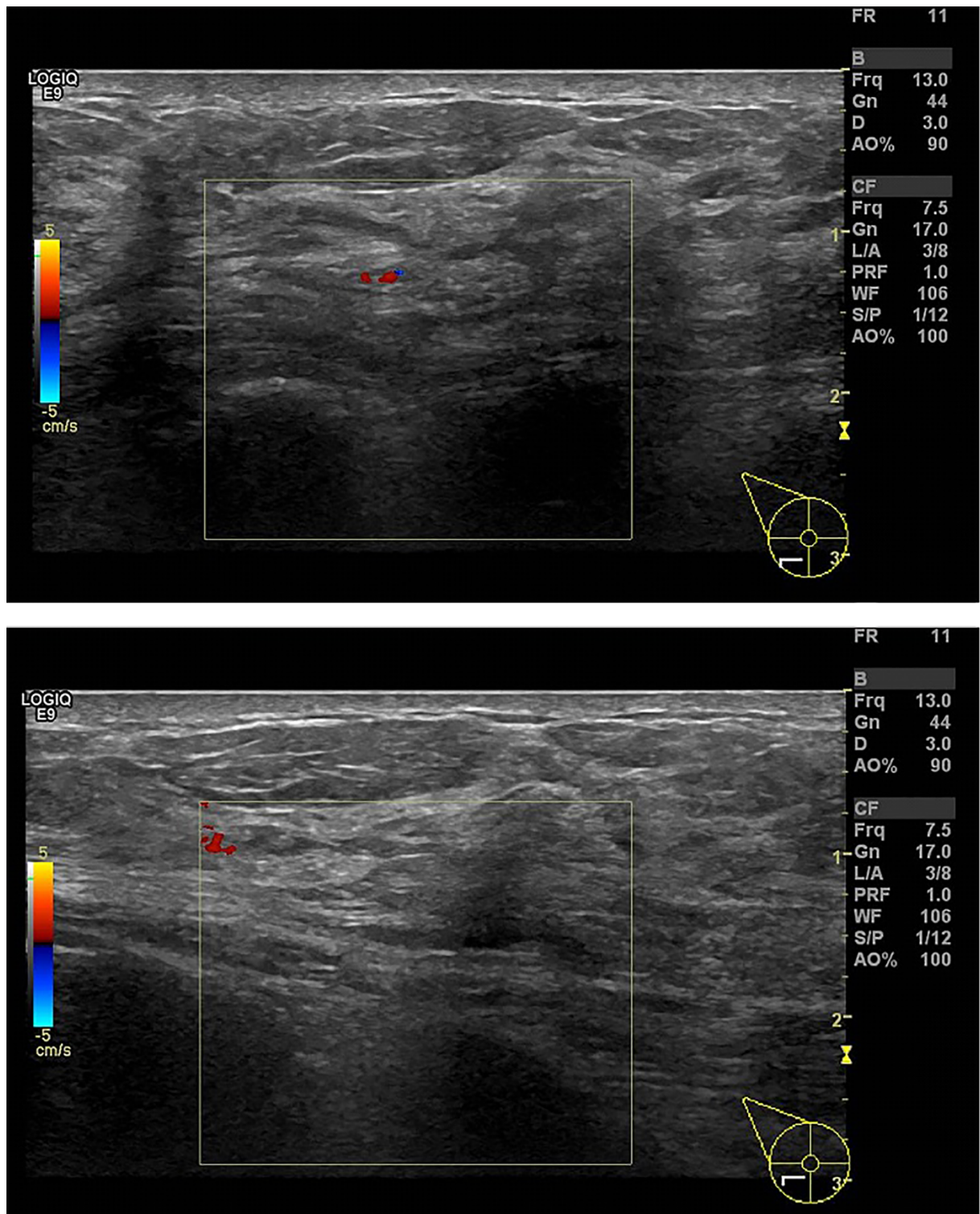


Figure 4. Two-breast B-mode ultrasound scan pictures with Doppler facility of the same patient showing non-specific shadowing in the palpable area with non-significant Doppler signals

while Dennis et al. (20) and Kaiser et al. (21) reported none. One case was found to be ILC which is well known to be a hideous malignancy and can disguise itself even on MRI, while the second case was metastatic colorectal cancer to the breast. Therefore, any indeterminate breast lesions with negative imaging should be biopsied clinically, preferably with a core biopsy. The value of breast MRI scan can be arguable, it could be very valuable for most breast cancers, but hideous ILC or even invasive ductal carcinoma (IDC) can still be MRI negative (28).

Clinical assessment of palpable breast masses with normal imaging is challenging and harbour potential breast cancer misses. A no biopsy approach policy would result in potential delay in diagnosis. Ignoring the normal imaging findings and doing relentless CGB for all breast patients may result in too many unnecessary procedures.

Salzman et al. (29) introduced an algorithm/pathway for the management of patients presenting with breast lumps advising when to proceed with clinical guided biopsy and when to refer for imaging. In our breast unit, we have been using a similar algorithm with differences to meet our imaging guidelines (Figure 1).

Limitations of our study included, a small sample size, symptomatic patient cohort without screening patients, and clinicians' and radiologists wide range of experience.

In conclusion, CGCB or FNAC are still valid approaches for investigating clinically indeterminate breast lesions with normal imaging. Multi-centric studies including a larger cohort of patients are still needed to come up with more robust results to deliver better patient care.

Footnotes

Authors' Contributions: EP developed the original idea and the protocol, abstracted and analyzed data, wrote the manuscript, and was a guarantor. ME and SM contributed to the development of the protocol, abstracted data, and prepared the manuscript.

Conflict of Interests: The authors declare that there are no conflicts of interest.

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