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Wide-Angle Digital Breast Tomosynthesis Might Be Used for The Early Detection and Grading of Breast Cancer during Screening Campaigns

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ABSTRACT

Background: Digital breast tomosynthesis (DBT) is a new imaging modality for improving breast cancer detection because it allowed for better detection of abnormalities, especially in females with dense breasts, and the diagnosis of benign lesions, which resulted in fewer recalled cases and negative biopsies, as well as assessing therapeutic efficacy.

Objectives: Evaluation of the diagnostic validity of 3D wide-angle Digital Breast Tomosynthesis (WA-DBT) during screening programs for breast cancer (BC).

Patients and Methods: 449 women with breast lesions who attended the screening campaign were examined by Full-field Digital Mammography (DMG) and WA-DBT using Hologic™ Selenia® Dimensions® 3D Performance System and ultrasound (US) imaging using GE LOGIQ P7® linear probe (7-12 MHz). Then, a surgical biopsy was obtained from women who had lesions of BI-RADS grade 4 or 5 and examined pathologically, the pathological diagnosis was used as the gold standard for comparison of radiological diagnoses.

Results: Pathological diagnosis defined 30 malignant and 9 benign lesions. The performance characteristics of WA-DBT imaging were superior to that of DMG and US and the agreement of diagnoses obtained by WA-DBT and both DMG and US was moderate and substantial with κ coefficient of 0.421 and 0.726, respectively. ROC curve analysis defined WA-DBT as the best diagnostic test with a significantly higher area under the curve (AUC) in relation to the reference AUC as a discriminative diagnostic modality for breast lumps of BI-RADS grade 5 and as the most sensitive modality for differentiation between masses that are probably benign (BI-RADS grade 3) and that suspicious of malignancy (BI-RADS grade 4).

Conclusion: WA-DBT is a valuable radiologic modality for screening women with breast lesions especially those in dense/extremely dense breasts. Also, WA-DBT can precisely identify microcalcifications obscuring very small-to-small breast lesions thus allowing early detection of BC.

Keywords: Breast lump, Screening, Mammography, Tomosynthesis, Ultrasound, Biopsy.

INTRODUCTION

Breast cancer (BC) is the most prevalent cancer among women [(1)]. However, the known risk factors, either reproductive, hormonal, lifestyle, and/or genetic play a role in BC tumorigenesis in about 58% of cases [(2)], and for the remaining cases, the cause is unknown, but microRNAs were found to regulate the expression of key genes in BC tumorigenesis [(1)].

Epidemiological studies indicated a lower mortality rate for women had BC that was diagnosed from mammographic screening than women with symptomatizing BC[(3)]. However, disparities in screening mammography and barriers to access BC screening are most prevalent among low-income women with subsequent significant mortality rates among these populations due to delayed or neglected screening [(4)].

Breast ultrasonography (US) is an alternative to mammography in young asymptomatic individuals and a complimentary examination in screening of women with dense breasts[(5)]. US imaging is preferred over X-ray mammography during needle breast-biopsy taking because of its capability to visualize the biopsy needles without radiation hazards[(6)]. US imaging is the only imaging technique available during breast-conserving surgery [(7)].

Digital breast tomosynthesis (DBT) is an emerging BC screening and diagnostic modality that depends on three-dimensional (3D) breast images to provide detailed assessments of the dense breast tissue [(8)]. DBT was characterized by anisotropic resolution, which resolved intra- and inter-slice quite different from the sharpness of microcalcifications (MCs) in different slices [(9)]. DBT is gradually being implemented in routine clinical breast imaging practice because the technique of image acquisition reduces the confounding effect of overlapping breast tissue, which substantially affects cancer detection [(10)].

This study targets to evaluate the diagnostic validity of 3D wide-angle Digital Breast Tomosynthesis (WA-DBT) during screening programs for breast cancer.

PATIENTS AND METHODS

This was a prospective screening-based comparative study, conducted at the Department of Radiodiagnosis, Interventional Radiology & Medical Imaging, Faculty of Medicine, Menoufia University in conjunction with the General Surgery Department, Benha Faculty of Medicine, and El-Arabi Medical Centers at Menoufia and Qalyubia Provinces.

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Sample Size Calculation:

The number of cases recruited in the current study was determined using OpenEpi software[11] and data reported by **Sung *et al.*** [12] that the recently registered prevalence of cancer breast among screened women complaining of accidentally discovered breast mass is 11.7%; considering the confidence level at 99%, and absolute precision of 5%, an alpha error of 0.05, power of 80% and expected attrition rate of 20%, the minimum sample size was 385. Thus, 449 women were recruited during this mass screening program for cancer breast.

Patients:

During the mass screening program for cancer breast in Menoufia and Qalyubia Governorates, all women complaining of a palpable breast mass or breast-related complaints such as pain, discomfort, or discharge were vulnerable for evaluation and were referred to General Surgery outpatient clinics for evaluation. During the clinical evaluation, the collected data included age, body mass index, age of menarche, fertility status, number of offspring if present, duration of complaints and their progress if any, previous clinical or radiological evaluation and its outcomes.

Exclusion criteria: Lactating and pregnant females, women with endocrinal disturbances, or maintained on hormonal or chemotherapy for any indication, patients with malignancy elsewhere in the body organs, and patients who had systemic diseases affecting the breast.

Inclusion criteria: Women who attended the screening program for cancer breast, who had clinically suspicious breast lesions, and who fulfilled the exclusion criteria were enrolled in the study

Study protocol:

All women who attended the screening campaign and were accepted to undergo the investigation protocol were enrolled in the study. All radiological workup was performed by the author to standardize the human factor, but the author was blinded by the probable clinical diagnosis. Women who had lesions of BI-RADS grade 4 or 5 were referred for biopsy taking and the biopsied tissues were examined by a pathologist who was blinded about the radiologic diagnosis. The results of the radiologic diagnosis were interpreted versus the pathological diagnosis of the obtained biopsy by a statistical analyst who was blinded to the significance of the diagnoses

Methodology:

All patients were examined by Full-field Digital Mammography (DM) and Wide-angle 3D Digital Breast Tomosynthesis (WA-DBT) using Hologic™ Selenia® Dimensions® 3D Performance System, which is an extension of DM that was incorporated onto the DM platform as previously described by **Tirada *et al.*** [13] in literature. US imaging was performed using GE LOGIQ P7® linear probe (7-12 MHz) [Breast preset]. Images that were obtained by DM, US, or DBT were categorized according to the Breast Imaging Reporting and Data System (BI-RADS), with a grading scale from 0 to 6 [14]. Patients with BI-RADS 0-2 and 6 were excluded from the statistical analysis.

Study outcomes

1. The primary outcome is the value of implementing WA-DBT during the mammographic evaluation of BC patients as a screening and diagnostic imaging modality.
2. Verification of DM, WA-DBT, and US as the best predictor for cancer.

Ethical consent:

Approval of the study was obtained from Menoufia University and Benha University Academic and Ethical Committee. Every patient signed informed written consent for the acceptance of participation in the study. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Obtained data were presented as mean, standard deviation, numbers, percentages, median and interquartile range. The Kappa statistics were used to estimate the agreement between the use of WA-DBG and both DMG and US. The strength of the agreement of the kappa coefficients was graded according to the boundaries suggested by **Landis & Koch**[15], poor agreement if the kappa coefficient was <0.2, slight agreement if kappa was in the range of 0.21-0.4, moderate and substantial agreement if kappa was in the range of 0.41-0.6 and 0.61-0.8, respectively and agreement was almost perfect if kappa was >0.81. Performance characteristics of DMG, US, and WA-DBT concerning pathological diagnosis; namely, the sensitivity, specificity, and accuracy rates, and the positive and negative predictive values (PPV & NPV) were calculated. The Receiver Operating Characteristic (ROC) curve was used to determine the predictors of pathological results among imaging modalities as judged by the area under the curve (AUC) and the significance of the AUC was determined in comparison to the AUC for the reference line (AUC=0.5). Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for Windows statistical package. P-value <0.05 was considered statistically significant.

CASE PRESENTATION

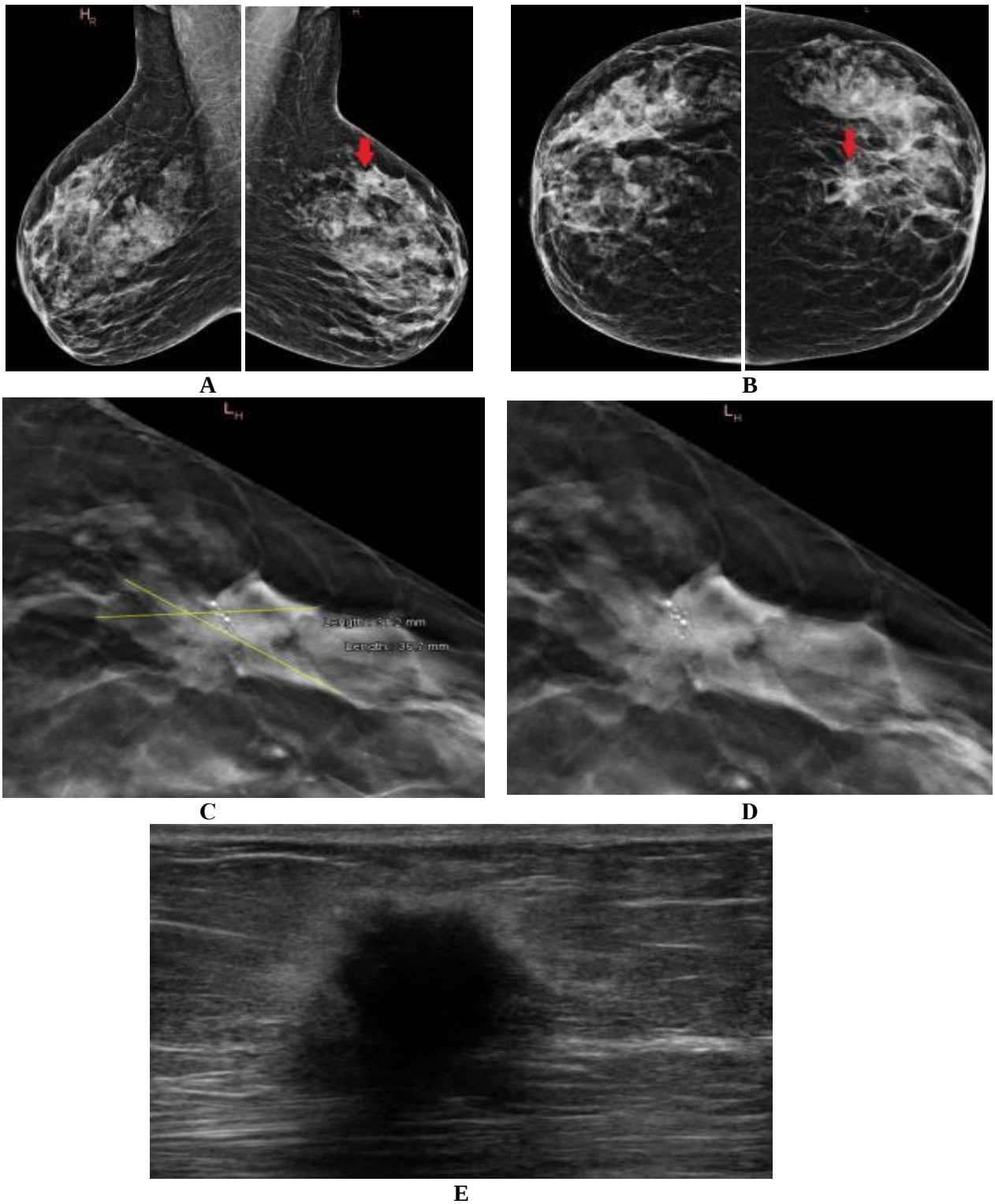
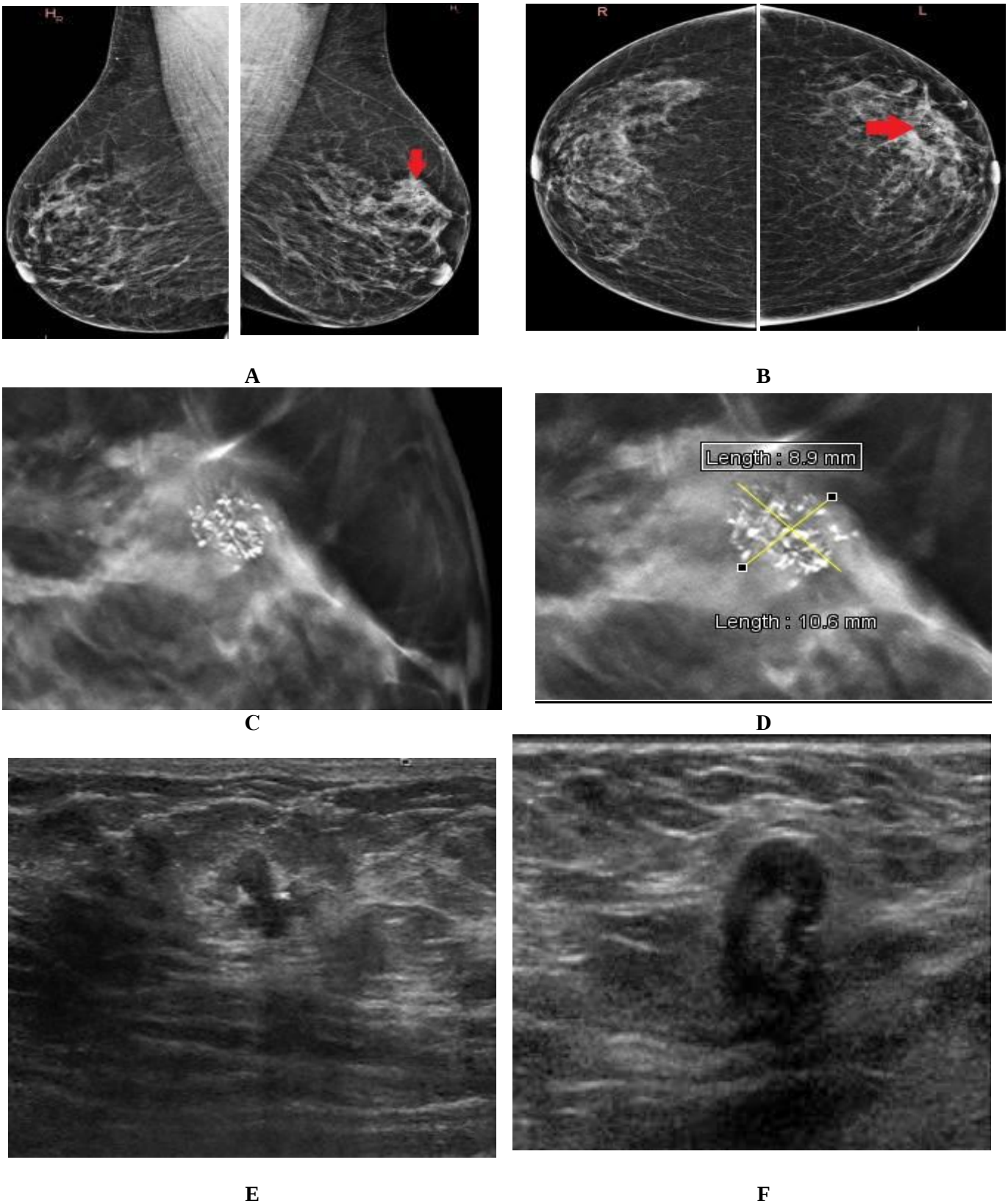


Fig. (1): 60-year-old female patient presented with a left breast lump and was diagnosed clinically as suspicious of being malignant for surgical biopsy taking. **Digital mammography A&B** showed heterogeneously dense breast up to obscuring detection of small lesions **(ACR C),** however, **DM** detected an ill-defined speculated mass of high density, harboring pleomorphic micro-calcifications in the middle third of the upper outer quadrant of the left breast (more appreciated on the CC view), red arrows, and was graded as BI-RADS 4b lesion. **Wide angled digital breast tomosynthesis C& D** provided a more precise assessment of the speculated margins of the lesions and their extension into the surrounding breast tissue [as appreciated in slice no. 35/60], provided an approximate extension of the size of the lesion (~31 x 37 mm) and offered better visualization of the distribution of the overlying micro-calcification. This case was graded as BI-RADS 4c according to **WA-DBT**, using (**2D US**) **E** an ill-defined speculated hypoechoic solid mass lesion was detected at left 12 o'clock with posterior acoustic shadowing, measuring 3 x 2.5 cm, and at depth of 2.8 mm from the skin surface and away from the nipple by more than 5 cm. This lesion was graded as BI-RADS 4c lesion, Histopathological examination of the obtained biopsy assured invasive ductal carcinoma.



A **B**

C **D**

E **F**

Fig. (2): 61-year-old female patient presented with a left breast lump and was diagnosed clinically as suspicious of being malignant for surgical biopsy taking. **Digital mammography A&B** showed scattered fibro-glandular density (ACR B); however, DM detected focal asymmetry (Red arrow) with related parenchymal distortion and overlying grouped, coarse, heterogeneous micro-calcifications in the upper outer quadrant of the left breast and was graded as BI-RADS 4b lesion. **Wide-angle digital breast tomosynthesis C&D** provided a more precise assessment of focal asymmetry and the heterogeneous microcalcifications, [best appreciated on tomosynthesis slice number 25/80], which occupies an area of 9 x 10.6 mm, measured on MLO view (Images 3 & 4). Using, **2D US E&F** altered parenchyma and distortion were detected at 9 mm depth from the skin and 29 mm distance from the nipple with dilated ducts extending to the nipple. 2D US also detected pathological left intra-mammary lymph node measuring 9 mm at 3 o'clock. This lesion was graded as BI-RADS 4c lesion. Histopathological examination of the obtained biopsy assured low-grade invasive ductal carcinoma.

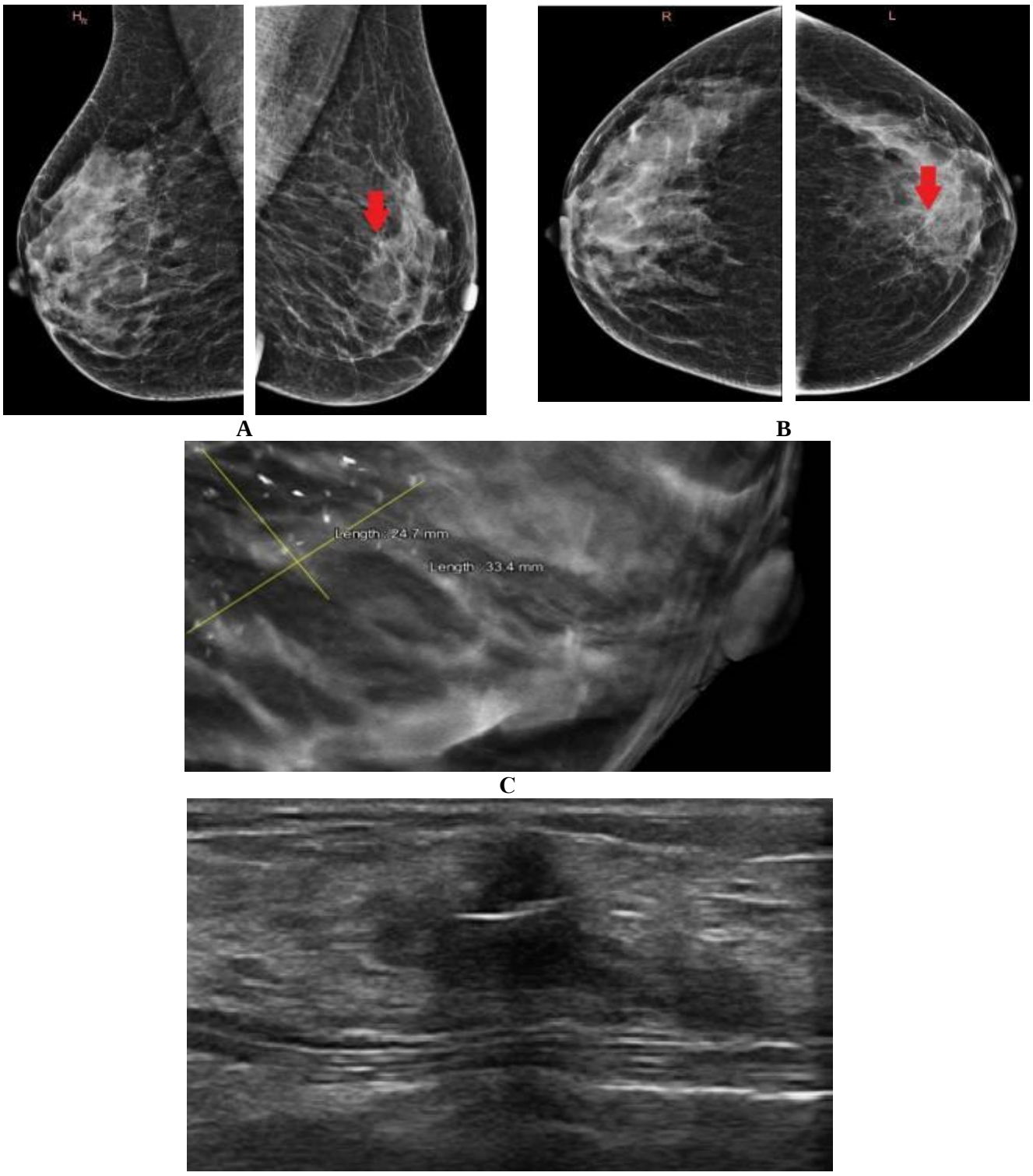


Fig. (3): 43-year-old female patient presented with a small left breast lump and was diagnosed clinically as suspicious of being malignant for surgical biopsy taking. **DM A&B** showed heterogeneously dense breasts up to obscuring detection of small lesions (ACR C), however, DM detected focal asymmetry (Red arrow) with related parenchymal distortion and overlying grouped, fine, subtle micro-calcifications in the middle third of the left breast and was graded as BI-RADS 4a lesion. **WA-DBT C** provided a better assessment of the focal asymmetry and it rendered the subtle microcalcifications, more pronounced, [best appreciated on tomosynthesis slice number 16/52], which occupies an area of 25 x 33 mm, measured on MLO view. This case was graded as BI-RADS 4b according to WA-DBT. **2D US D** showed altered hypoechoic parenchyma and distortion that was seen at 12 o'clock, 7 mm deep to the skin and 37 mm away from the nipple. This lesion was graded as BI-RADS 4b lesion. Histopathological examination of the obtained biopsy assured invasive ductal carcinoma.

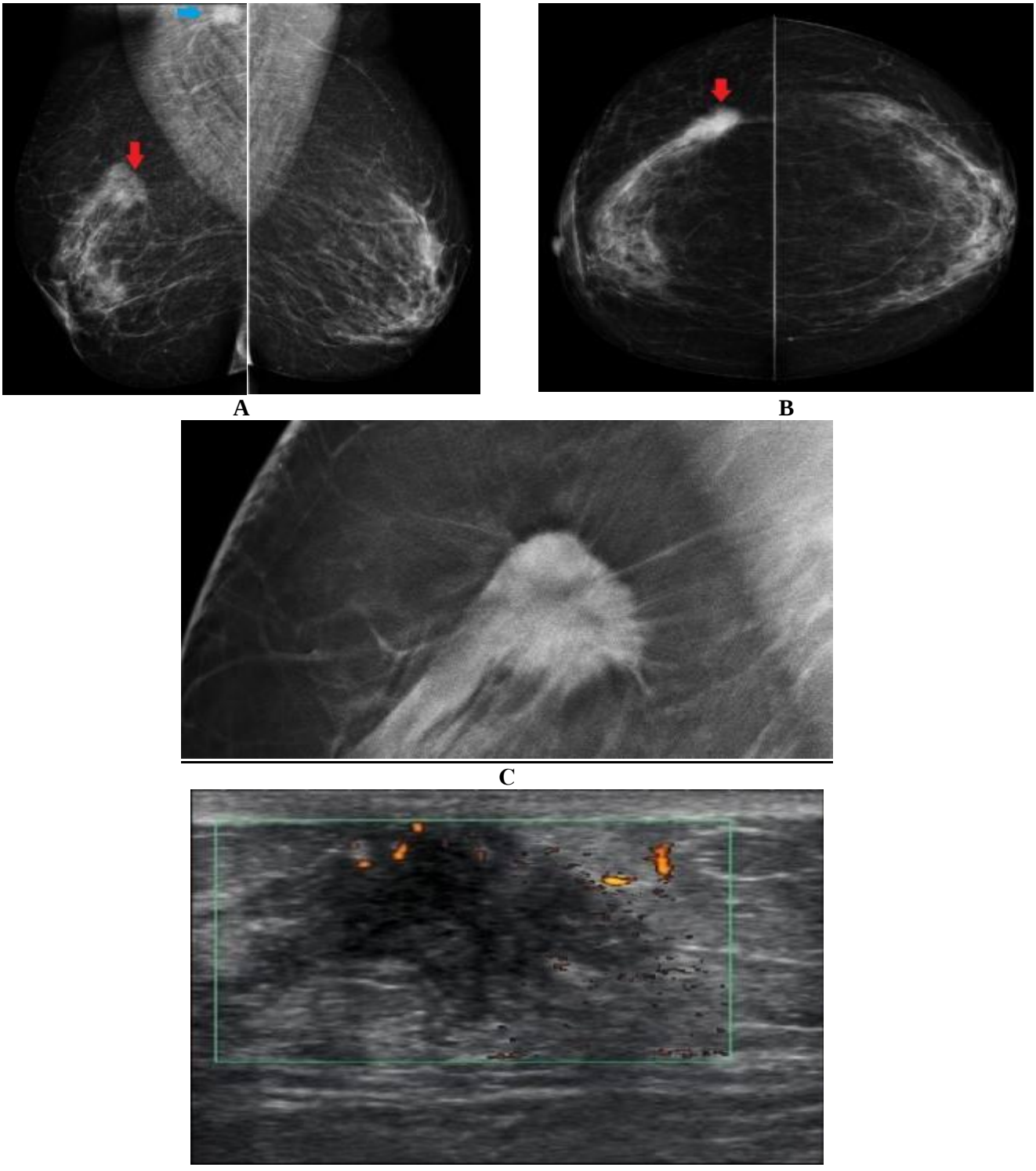


Fig. (4): 50-year-old female patient presented with a right breast lump and was diagnosed clinically as suspicious of being malignant for surgical biopsy taking. **Digital mammography A&B** The breasts show scattered fibro-glandular density (ACR B). However, imaging detected an irregular, speculated mass of high density in the posterior third of the right upper outer quadrant with extension to the overlying skin, causing its retraction (double line) [MLO]. Imaging also detected an enlarged right axillary lymph node with an irregular outline, likely representing extracapsular invasion [MLO], and was graded as BI-RADS 4C lesion. **WA-DBT C** offered a more precise assessment of the fine spicules at the margins of the lesion and its extension into the surrounding breast tissue, reaching the skin with subsequent dimpling and retraction [best appreciated on tomosynthesis slice number 70/171]. Furthermore, tomosynthesis confirmed neither calcifications nor smaller satellite lesions. This case was graded as BI-RADS 5 according to WA-DBT. **2D US D** showed right UOQ 10 o'clock ill-defined large speculated hypoechoic solid mass lesion that measured 6x7 mm with intraductal invasion reaching the nipple. The US also detected enlarged right axillary lymph nodes, which measured about 18 x 27 mm, appeared globular in shape with obliteration of the hilar fat and extra-capsular invasion and low-resistance high vascularity on Doppler interrogation. This lesion was graded as BI-RADS- 5 lesion. Histopathological examination of the obtained biopsy assured invasive lobular carcinoma.

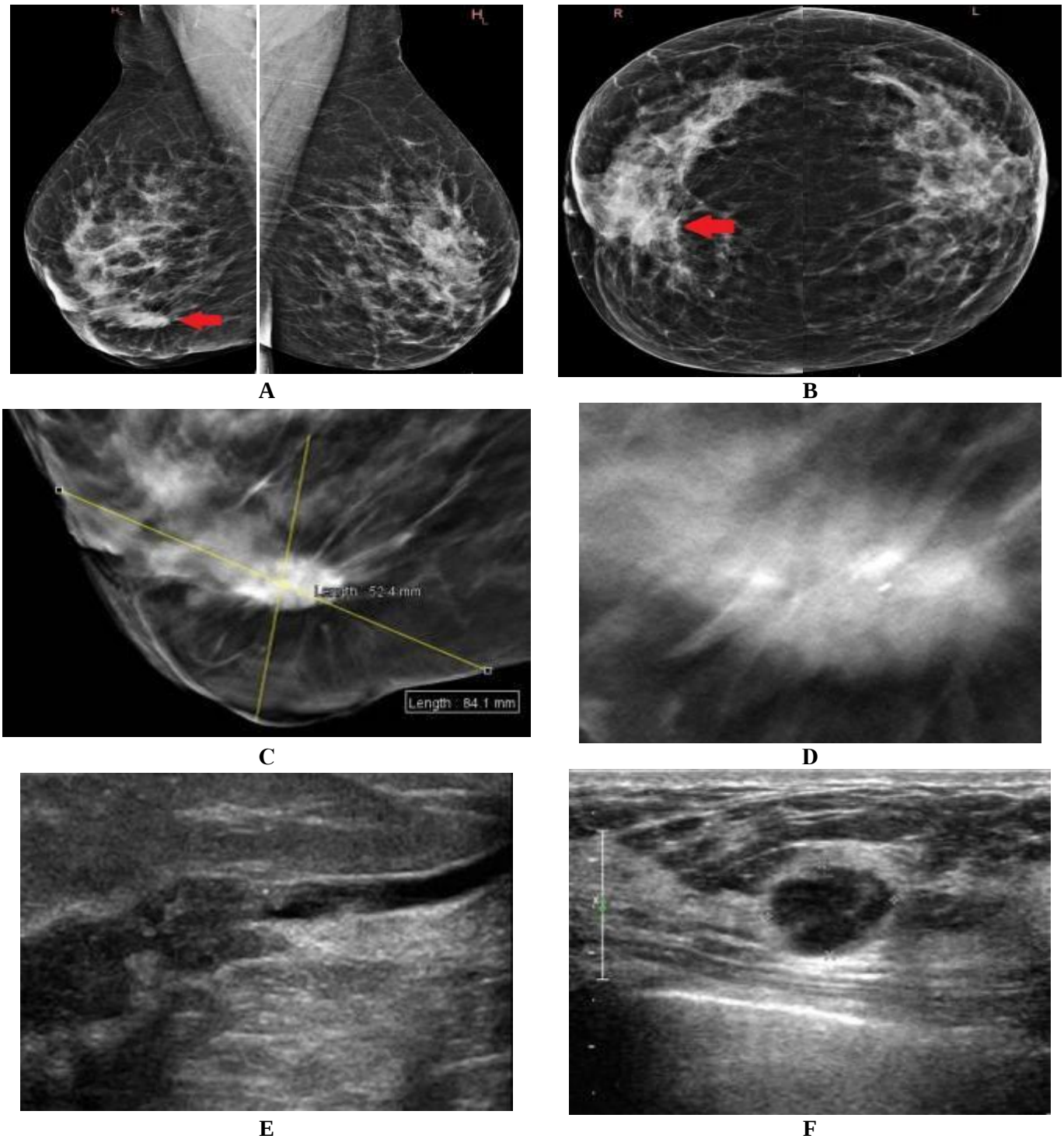


Fig. (5): 68-year-old female patient presented with right breast disfigurement and was diagnosed clinically as highly suspicious of being malignant for surgical biopsy taking. **DM A&B** showed the breasts were heterogeneously dense up to obscuring small lesions (ACR C). imaging of the right breast showed a retro-areolar irregular, partially indistinct mass of high density and harbored pleomorphic micro-calcifications with elongated speculation causing skin & nipple retraction in anterior to middle thirds of the lower inferior quadrant of the right breast and was graded as BI-RADS 4c lesion. **WA-DBT C&D** offered a more precise assessment of the spiculated margins of the lesion & its extension into the surrounding breast tissue, reaching the skin & the nipple, with subsequent dimpling and retraction [best appreciated on tomosynthesis slice number 31/74], occupying an area of 84 x 52 mm, measured on MLO view and was graded as BI-RADS 5 lesion. Furthermore, WA-DBT detected retro-areolar amorphous calcifications occupying an area of about 47 x 26 mm, [best appreciated on tomosynthesis slice number 37/74] and was graded as BI-RADS 4a lesion (Images 3 & 4). **2D US E&F** showed right LOQ 5 O'clock ill-defined speculated hypoechoic solid mass lesion that measured 30 x 20 mm with intraductal extension reaching the nipple occupying an area of 48 x 22 mm and was graded as BI-RADS 5 lesion. The US also detected a Right UOQ 10 o'clock para-areolar small hypoechoic nodule is seen measuring about 5 x 3.2 mm, Histopathological examination of the obtained biopsy assured invasive ductal carcinoma

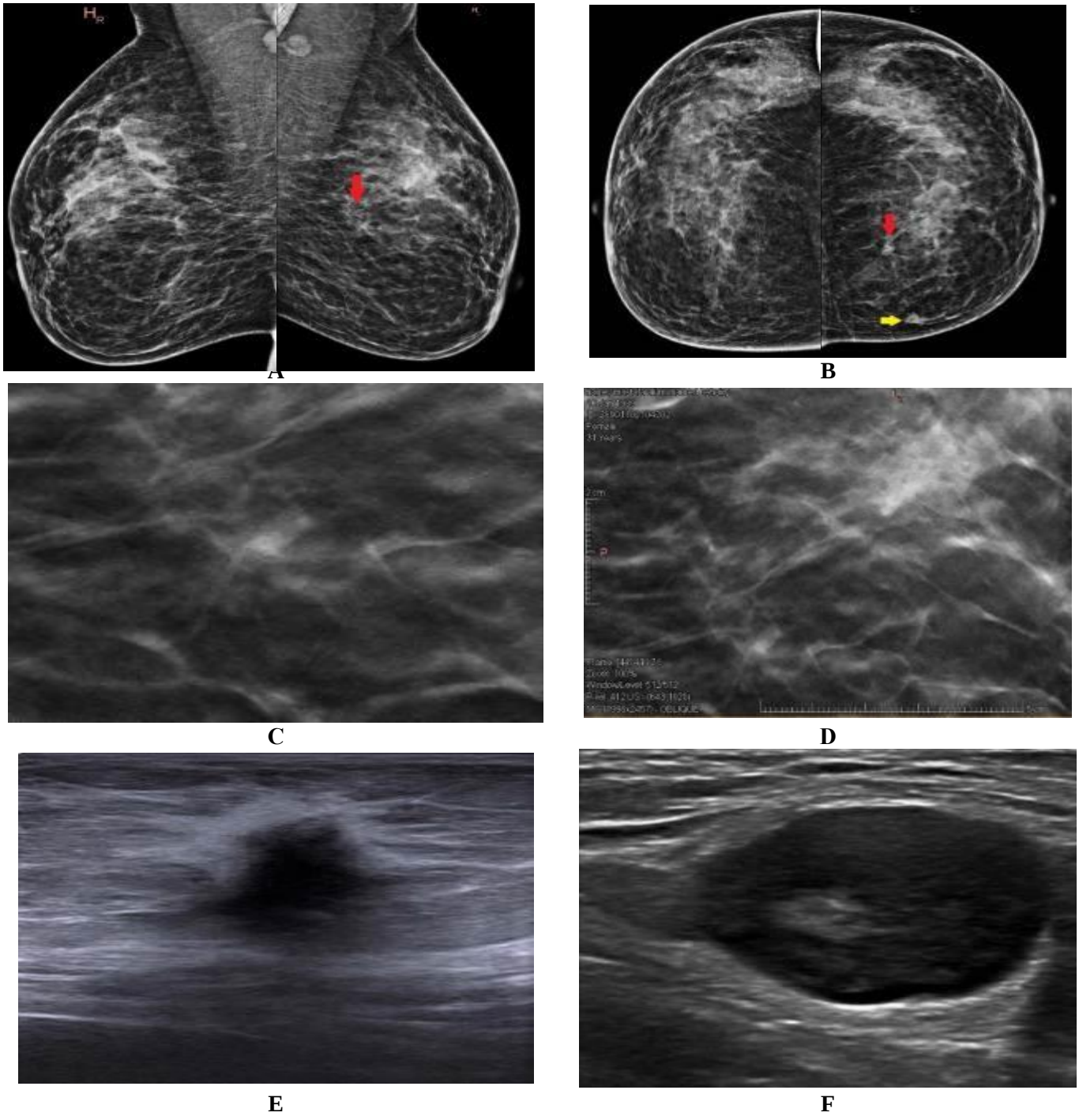


Fig. (6): 32-year-old female patient presented with a left breast lump and was diagnosed clinically as suspicious of being malignant for surgical biopsy taking. **DM A&B** showed that the breasts were heterogeneously dense up to obscuring small lesions (ACR C). Imaging of the left breast showed an irregular small mass with fine speculations in the upper outer quadrant of the left breast. The inner aspect of the left breast as only is appreciated on cc view showed a fat-containing small dense lesion. Moreover, enlarged left axillary lymph nodes with regular outline were detected and the lesion was graded as BI-RADS 4c lesion. **WA-DBT C&D** provided better characterization of the spiculated margins of the lesion and assessment of the more anterior and superior dense area, which was suspected to harbor another spiculated lesion at a distance of 35 mm from the lower one, which suggests the multifocal nature of the lesion [mainly appreciated at slices no. 45/70 & 48/70] that was graded as BI-RADS 4c lesion. **2D US** E& **F** showed left UIQ at 10 o'clock an ill-defined hypoechoic mass lesion with surrounding echogenic halo (Desmoplastic reaction) measuring 17 x 12 mm with 3.4 mm distance to the skin and >5 cm distance from the nipple which confirms the multifocal nature. Another similar yet smaller lesion was detected at left 9 o'clock measuring 10.4 x 12.7 mm. Moreover, a pathologically enlarged left UOQ intramammary lymph node, measuring 12.4 x 5.9 mm with 2 mm cortical thickening. The lesion was graded as a BI-RADS 5 lesion Histopathological examination of the obtained biopsy assured invasive lobular carcinoma.

RESULTS

During the screening campaign, 449 women accepted to join the investigation protocol and underwent clinical examination and 87 women were clinically excluded and 93 women were excluded for not fulfilling the inclusion criteria and 269 women with suspected mass underwent radiologic workup. Radiologic workup defined 228 women were categorized as BI-RADS 0-3 or BI-RADS category 6, while 41 were categorized as BI-RADS 4 and 5. Two patients refused biopsy taking and were excluded from the study, while 39 women underwent biopsy taking **(Fig. 1).** The demographic and clinical data of the enrolled women are shown in **Table 1.**

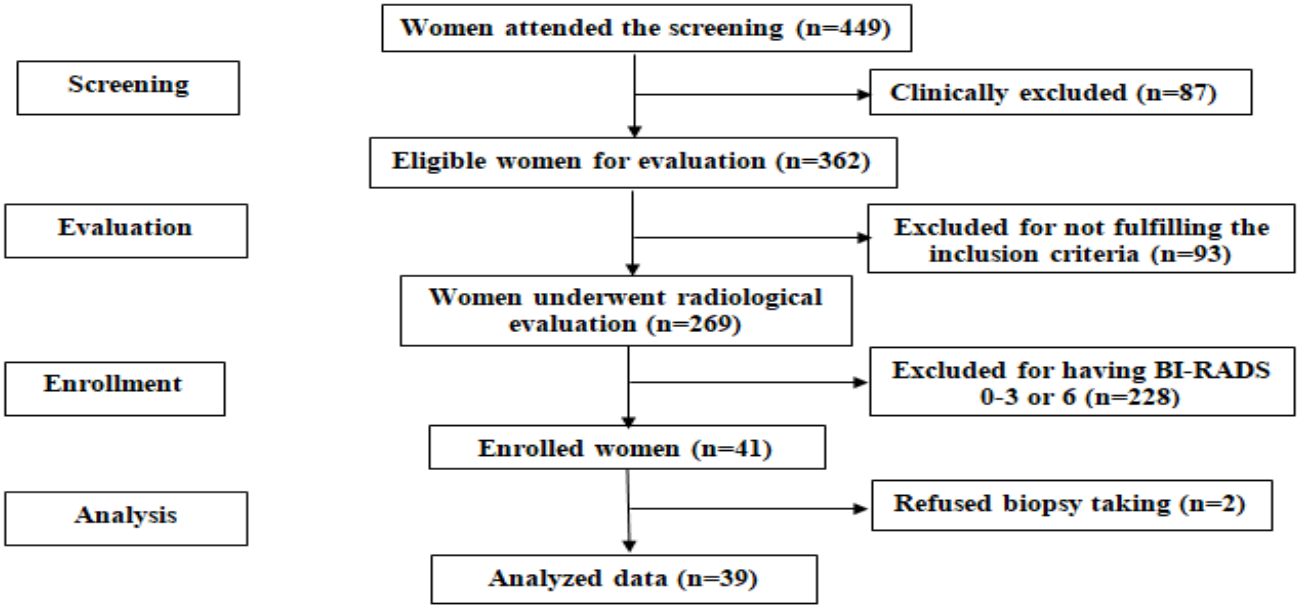


Fig. (7): The study flow chart

Table (1): Demographic and clinical data of enrolled patients

Data		Findings
Age (years)	<40	6 (15.4%)
	40-49	10 (25.6%)
	50-59	15 (38.5%)
	60-69	7 (17.9%)
	≥70	1 (2.6%)
	Mean (±SD)	51.9 (9.9)
Weight (kg)		85.8 (7.1)
Height (cm)		168.8 (2.3)
Body mass index (kg/m^2)	Overweight	17 (43.6%)
	Obese grade I	22 (56.4%)
	Mean (±SD)	30.1 (2.1)
Age of menarche (years)	Mean (±SD)	12.2 (1.2)
Fertility status	Fertile	34 (87.2%)
	Infertile	5 (12.8%)
Number of living offspring	No	5 (12.8%)
	1-2-	7 (17.9%)
	3-4-	22 (56.4%)
	>4	5 (12.8%)
	Median [IQR]*	3 [2-4]
Complaints	Lump	19 (48.7%)
	Pain	8 (20.6%)
	Heaviness	5 (12.8%)
	Bleeding/nipple	7 (17.9%)
Previous Exam	Yes	9 (23.1%)
	No	30 (76.9%)
Previous Radiologic Exam	Yes	7 (17.9%)
	No	32 (82.1%)
Systolic blood pressure (mmHg)	Mean (±SD)	117.4 (3.8)
Diastolic blood pressure (mmHg)	Mean (±SD)	78.9 (4.5)
Random blood glucose (mg/ml)	Mean (±SD)	99.8 (8.3)

Data are presented as numbers, percentages, mean, standard deviation (SD), median, interquartile range (IQR),

Pathological examination of the obtained excisional biopsy detected 30 malignant lesions (76.9%) and 9 benign lesions (23.1%); detailed pathological diagnoses are shown in **Table 2.**

Table (2): Pathological diagnoses of the obtained biopsies

	Pathological diagnosis	**Number (%)**
Benign (n=9; 23.1%)	Intraductal papilloma	3 (7.7%)
	Duct ectasia	2 (5.1%)
	Complex fibroadenomas with evident microcalcifications, which were associated with ductal hyperplasia	2 (5.1%)
	Liponecrosis	1 (2.6%)
	Retention tense cystic lesion	1 (2.6%)
	Total	9 (23.1%)
Malignant (n=30; 76.9%)	Invasive duct carcinoma	12 (30.8%)
	Intraductal carcinoma	4 (10.1%)
	carcinoma-in-situ with neovascularization	2 (5.1%)
	Tubular carcinoma	2 (5.1%)
	Invasive lobular carcinoma	2 (5.1%)
	Micropapillary carcinoma	2 (5.1%)
	Colloid carcinoma	1 (2.6%)
	carcinoma-in-situ with heterogenous calcifications	1 (2.6%)
	Scirrhous carcinoma	1 (2.6%)
	Medullary carcinoma	1 (2.6%)

DMG defined 4 cases as BI-RADS-5 and 35 cases as BI-RADS-4 and US defined 6 cases as BI-RADS-5 and 33 cases as BI-RADS-4, while WA-DBT defined 7 cases as BI-RADS-5 and 32 cases as BI-RADS-4. The agreement between BI-RADS tumor grades as predicted by DBT and DMG was moderate (κ coefficient= 0.421) and between WA-DBT and US was substantial (κ coefficient= 0.726) as shown in **Table 3.**

Table (3): Agreement of BI-RADS tumor grades as predicted by WA-DBT in relation to that predicted by DMG and US

Diagnostic modality		**DMG**				**US**			
	BI-RADS grade	4a	4b	4c	5	4a	4b	4c	5
WA-DBT	4a	8	1	1	0	8	1	1	0
	4b	2	4	3	0	1	8	0	0
	4c	1	6	6	0	1	3	9	0
	5	0	2	1	4	0	0	1	6
	Total	11	13	11	4	10	12	11	6
Kappa coefficient		0.421 (Moderate agreement)				0.726 (Substantial agreement)			

In comparison to the results of histopathological examination of the obtained biopsies, WA-DBT showed the highest performance characteristics as a screening test for the presence and grading of cancer breast among the screened women **(Table 4).**

Table (4): Performance characteristics of DMG, US, DBT in relation to pathological diagnosis of the obtained specimen

	DMG	**US**	**DBT**
Sensitivity (%)	86.7	93.3	96.7
Specificity (%)	77.8	88.9	100.0
PPV (%)	92.9	96.6	100.0
NPV (%)	63.6	80.0	90.0
Accuracy (%)	84.6	92.3	97.4

ROC curve analysis for radiologic modalities as a discriminative diagnostic modality for breast lumps that were highly suggestive of being malignant wherever diagnostic biopsy is very strongly recommended (BI-RADS grade 5) defined imaging

using the WA-DBT as the best diagnostic test with significantly higher AUC in relation to the reference AUC. Despite the significant AUC for US, it was less diagnostic than WA-DBT, while for DM the AUC was non-significant in relation to the reference AUC (Fig. 8). Paired-sample area difference analysis showed a significant difference between AUC for WA-DBT and AUC for DM, while AUC for the US showed a non-significant difference in comparison to AUC for DM and WA-DBT (**Table 5**).

ROC curve analysis defined WA-DBT as the most sensitive modality for differentiation between cases that had a probably benign breast lump (BI-RADS grade 3) and cases having a lump suspicious of malignancy (BI-RADS grade 4) and followed by the US with significant AUC (P=0.012 & 0.026, respectively) in comparison to the reference AUC, while DM was excluded for the non-significant AUC **(Fig. 9).** Despite the non-significant differences between the AUC of the three modalities as a modality for screening the differences were in favor of WA-DBT **(Table 5).**

Table (5): ROC curve analysis for the predictability of radiologic modalities for the pathology of the breast lesion

Identifications of highly suggestive lumps for malignancy									
Analyses	**ROC curve analysis**				**Paired-Sample Area difference under the ROC curves**				
Variables	**AUC**	**SE**	**P**	**95% CI**	**Test pairs**	**AUC difference**	**SE**	**P**	**95% CI**
DM	0.594	0.138	0.508	0.324-864	DM vs. DBT	-0.372	0.411	0.005	0.112-0.633
WA-DBT	0.967	0.040	0.001	0.889-1	DM vs. US	-0.250	0.460	0.072	0.022-0.522
US	0.844	0.090	0.16	0.668-1	DBT vs. US	0.122	0.334	0.100	0.023-0.268
Screening for malignant breast lumps									
Analyses	**ROC curve analysis**				**Paired-Sample Area difference under the ROC curves**				
Variables	**AUC**	**SE**	**P**	**95% CI**	**Test pairs**	**AUC difference**	**SE**	**P**	**95% CI**
DM	0.350	0.138	0.322	0.08-0.62	DM vs. DBT	0.231	0.47	0.174	0.102-0.565
WA-DBT	0.119	0.082	0.012	0-0.279	DM vs. US	0.187	0.47	0.190	0.093-0.468
US	0.163	0.092	0.026	0-0.343	DBT vs. US	-0.044	0.4	0.715	0.278-0.191

AUC: Area under the curve; SE: Standard error; CI: Confidence interval; DM: Digital mammography; WA-DBT: Wide-angle 3D Digital Breast Tomosynthesis; US: Ultrasonography

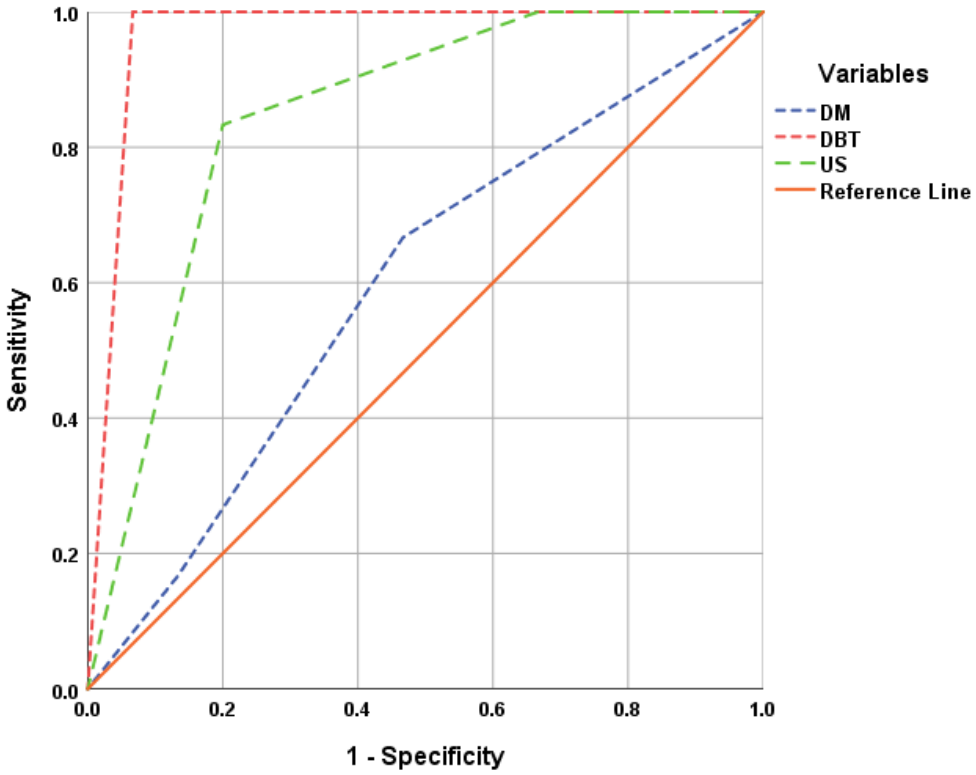


Fig. (8): ROC curve analysis of the diagnostic ability of radiological modalities for lesions of BI-RADS 5

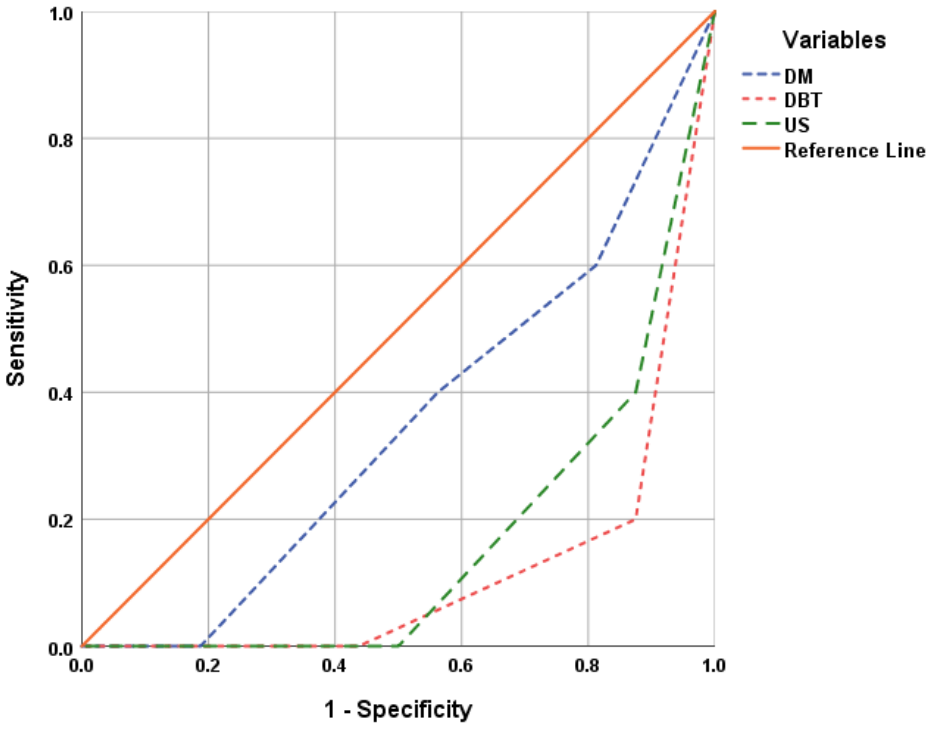


Fig. (9): ROC curve analysis of the discriminative ability of radiological modalities between lesions of BI-RADS 3 and 4

DISCUSSION

The implementation of WA-DBT during the mammographic evaluation of suspicious breast lump improved the diagnostic yield with high-performance characteristics than DMG and US in comparison to the results of pathological examination of the obtained surgical biopsy as a gold standard for comparison. ROC curve analysis assured these findings and defined WA-DBT as the most significant radiologic modality for identification of lumps highly suggestive of malignancy wherever biopsy is highly indicated. On contrary, the sensitivity and PPV, and accuracy of diagnosis depending on the DMG were inferior to that of WA-DBT, and ROC curve analysis excluded it as a diagnostic modality for the probable pathological diagnosis.

These data supported that previously reported by **Ohashi *et al.*** [16] who found the addition of DBT to the conventional DM improved sensitivity and specificity and increased the AUC for the diagnosis of

breast cancer in women with abnormal examination findings or clinical symptoms and concluded that DBT proved effective and should be used to improve the diagnostic performance of breast cancer examinations. Also, **Pattacini *et al.*** [17] in a comparative study found that combined imaging using DBT and DM depicts 90% more cancers in a population previously screened with DM with a greater detection rate for ductal carcinoma in situ, small and medium invasive cancers of <10 mm and 10-19 mm. **Kulkarni *et al.*** [10] concluded that in a diagnostic setting, tomosynthesis allows for improved lesion localization and characterization over conventional imaging, which potentially improves the accuracy and improved workflow efficiency.

The ROC curve analysis defined WA-DBT as the most sensitive modality for differentiation between cases that had a probably benign breast lump (BI-RADS grade 3) and cases having a lump suspicious of malignancy (BI-RADS grade 4), while DMG was excluded for the non-significant AUC. These findings are coincident with the ward of The Verona population-based breast cancer screening program that transitioning to DBT screening may modify the characteristics of screen-detected breast cancer without falsely increasing the proportion of screen-detected ductal carcinoma in situ, and highlight mixed findings on comparative tumor characteristics [18]. Also, **Hofvind *et al.*** [19] found the addition of DBT to DMG screening significantly increased the detection rate of screen-detected cancer, tumors of ≤10 mm, and grade 1 tumors. Thereafter, **Wasan *et al.*** [20] in a comparative study of DBT versus DMG as a screening modality demonstrated 97% accuracy in predicting circumscribed lesions as benign and 94% accuracy when >50% of the margin is sharply defined on DBT.

Ultrasound imaging also did well and was superior to DMG both for screening and diagnosis of the breast lump and can identify the distances of the lesion in relation to the skin surface and areola-nipple complex. This is favorable for cases assigned for areola-nipple complex preserving mastectomy, simple mastectomy, and for preoperative radiotherapy. Despite the lower diagnostic yield of the US in comparison to WA-DBT the difference in AUC was non-significant; thus, allowing relying on the US whenever DBT expertized radiologist is unavailable.

Moreover, both WA-DBT and US imaging of cases had dense breast tissue that obscured detection of small lesions on DM allowing proper evaluation of the breast and accurate prediction of the BI-RADS grade in comparison to the pathological examination of biopsy. These findings go in hand with recent works that evaluated the diagnostic yield of the three modalities solely or in combination with the evaluation of women who had dense breasts and complained of breast lumps, where **Gatta *et al.*** [21] found the evaluation of dense breasts using the US especially the 3D in prone position improved the diagnostic yield of mammography, especially for small and invasive lesions. Also, **Spear and Mendelson** [22] found physician-, technologist-performed handheld US, and automated breast US are appropriate for adjunctive screening of average-risk women with dense breasts. Moreover, **Seitzman *et al.*** [23] found that in about 71% of 2D mammography of an average-risk 50-year-old woman with extremely dense breasts supplemental US improves cancer detection.

Furthermore, **Aragon and Soto-Trujillo** [24] found that re-staging 2DM with 3D tomosynthesis improved cancer detection in extremely dense breasts with a 24/1000 increased prevalence of cancer detection in women with lesions graded BI-RADS 4 and 5 after re-staging and with sensitivity and specificity of 54% and 88% and for suspicious lesions classified BI-RADS 3, 4, or 5 re-staging with 3D tomosynthesis increased the cancer prevalence to 23%, with sensitivity and specificity of 45% and 98%.

Despite the previously documented DMG being the only method to detect breast microcalcifications, its sensitivity varies in dense breasts [6], and the current study detected under-grading of cancers in women who had dense breasts showing microcalcifications on DMG imaging. However, WA-DBT allowed a more precise assessment of these breasts and accurately graded the detected lesions. These findings assured the higher diagnostic value of DBT especially when DMG report is suspicious and assured that previously reported by **Lee *et al.*** [25] who documented that stationary DBT was preferred over mammography for interpreting soft-tissue breast features and providing a more accurate diagnosis and improved microcalcification conspicuity.

CONCLUSION

Implementing DBT with DMG improves its diagnostic and screening ability. DBT is a valuable diagnostic modality for lesions in dense/extremely dense breasts and can precisely identify microcalcifications that may obscure very small-to-small breast lesions thus allowing detection of BC in its early stage and increasing the chance for breast-conserving surgeries. US imaging is a valuable complementary diagnostic modality that helps to determine the topographic location of the lesion in relation to the skin surface and areola-nipple complex.

Limitation: The study is limited to cases highly suspicious of malignancy; however, the diagnostic ability of DBT for breast fibrocystic diseases is also mandatory.

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