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ORIGINAL ARTICLE

The Value of Tomosynthesis in Mammographically Detected Questionable Breast Lesions

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ABSTRACT

Background: Tomosynthesis is a new technique for the evaluation of breast lesions that can overcome the problem of overlapping breast tissue especially in dense breasts. So, it can be used for better evaluation of breast lesions with advantages over digital mammography in accurate detection of margins, precise localization of the lesion, and reduction of false-positive recalls.

Methods: Eighty patients with questionable mammographic breast lesion BIRADS III &IV were encountered in the study and subjected to clinical assessment including full history taking, clinical examination, and imaging assessment by DBT. Both modalities were independently reported as a part of the diagnostic procedure. We determined the BI-RADS category of the lesions in each of the 2 imaging modalities individually according to the BI-RADS lexicon 2013 classification, guided by the results of mammographic findings.

Results: Both modalities were compared regarding detection and diagnosis, each individually assessed, using the Pearson Chi-Square tests. Detection and diagnosis of breast lesions improved when adding 3D tomosynthesis. The sensitivity, specificity, the positive predictive value, the negative predictive value, and accuracy of digital mammography were 62.5%, 59%, 52.1%, 68.8%, and 60.4% compared to those of tomosynthesis which were 90%, 91.1%, 88%, 92.7%, and 91%.

Conclusions: We concluded that Tomosynthesis separates overlapping tissue in the dense breast by the acquisition of multiple images over a limited angular range. Tomosynthesis showed higher sensitivity and specificity and diagnostic accuracy than Mammography as it allowed better detection of breast cancer, characterization of lesions, better margin assessment of masses and decreased false-positive recall rate.

Keywords: Breast; Digital mammography; Digital breast tomosynthesis.

INTRODUCTION

Breast cancer in women is a major public health problem throughout the world. It is the most common cancer among women both in developed and developing countries, accounting for 22.9% of all new female cancers. In Egypt, breast cancer accounts for 37.7% of the total new cancer cases and it is the leading cause of cancer-related mortality accounting for 29.1% of the cancer-related deaths [1].

To reduce the morbidity and mortality associated with breast cancer, early detection becomes a very important job. If the cancers could be diagnosed through regular breast cancer examinations at an earlier stage than it is

currently possible, the survival rate within 5 years would increase to about 95% [2].

Mammography is the basic breast imaging modality for early detection and diagnosis of breast cancer [3].

Full Field Digital Mammography developments have been rapid, enabling high-quality breast images with higher contrast resolution, an improved dynamic range, and rapid processing of data and images when compared with Screen Film Mammography. However, some limitations still persist [4].

One of the genuine limitations of mammography is its use in dense breasts. This remains true even for Digital Mammography, although slightly better than in Screen Film Mammography [5].

Mammography has low sensitivity and specificity in women with radiographically dense breasts due to decrease contrast between a possible tumor and surrounding breast tissue and summation of tissues may obscure lesions [6].

Breast Tomosynthesis is a new tool that can be expected to ameliorate this problem by reducing or eliminating tissue overlap. Breast Tomosynthesis technology is essentially a modification of a Digital Mammography unit to enable the acquisition of a three-dimensional volume of thin section data [7].

An important diagnostic application that may be considered is the role of Tomosynthesis for ruling out suspected abnormalities that are identified during screening [8]. It also allows visualization of cancers not apparent by Mammography [9]. The clearer depiction with Tomosynthesis should allow easier differentiation between benign and malignant lesions [7]**.**

METHODS

A prospective study was performed in the female imaging unit of the National cancer institute (NCI), Cairo University, between April 2018 and November 2018. Written informed consent was obtained from all the participants and the study was approved by the Research and Ethical Committee of the Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The study was conducted on 80 patients whose ages ranged from 35-75 years old presented with palpable breast mass or detected incidentally in the screening program.

Inclusion criteria were female of age group ≥ 30 years old, Mammographic breast lesions of BIRADS III, IV, and dense breast in patients with complaints (BIRADS 0) which needed further assessment.

Exclusion criteria were pregnant females to avoid the hazards of ionizing radiation to the fetus, tender breast which can't tolerate compression for a long time, patients refused examination, or patients whose mammographic BIRADS other than 0, III, and IV.

All cases with suspicious digital mammography lesions underwent 3D tomosynthesis .

Full personal, past, and family history of the patients were taken including age, previous mammograms, prior surgeries, complaints if present, superficial marks (such as prominent moles, scars from an incision), family history of breast cancer, and history of hormonal pills.

The patient was then escorted to the changing room, where she undressed from the waist up and changed into a medical gown with its opening from the front. She was asked to wipe off any deodorants, perfumes, or powders that she may have used that day. And she was taken into the mammography room, where the mammography procedure was explained.

Mammographic examination was performed using a full-field digital mammography machine with 3d digital breast tomosynthesis (Senographe Essential GE healthcare and Hologic Selenia dimension 2D/3D).

Each breast was compressed and positioned carefully. Two standard views craniocaudal and mediolateral oblique were taken and sent to LCD screens for reading and comparing results. No additional views were needed as further processing could be done while viewing the digital images on LCD panels, such as zooming, changing contrast, brightness, and darkness,

inverting the background, and other processing to facilitate lesions detection.

For Digital mammography, the entire procedure including the patients' preparation took about 10 minutes while each exposure took 20 seconds, Tomosynthesis was slower, and each arc projection took about 1 minute.

For 3D Digital Tomosynthesis, two views (MLO and CC) were obtained. Three Dimensional DBT involved the acquisition of twelve to fifteen 2D projection exposures by a digital detector from a mammographic x-ray source that moved over a limited arc angle. The 3D volume of the compressed breast was reconstructed from the 2D projections in the form of a series of images (slices) through the entire breast. Images were assessed on the workstation.

The results of Digital mammography and Tomosynthesis for each patient were compared in terms of detection, visual accuracy, main radiological features, sensitivity, specificity, and BIRADS classification. Breast density was assessed for each patient. Each lesion was evaluated regarding the site and type (mass, focal asymmetry ± calcifications, and size).

Lesions were classified as benign or malignant according to the mammography BI-RADS lexicon morphology descriptors:

Mass lesions: shape, margin, density, and size.

Asymmetry: simple, focal, global, or developing.

Calcifications: morphology and distribution.

Both modalities were independently reported as a part of the diagnostic procedure, we determined the BI-RADS category of the lesions in each of the 2 imaging modalities individually according to the BI-RADS lexicon 2013 classification, guided by the results of mammographic findings**.**

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS software version 25 (IBM, 2017). Data were presented in tables and figures. Continuous data were presented as mean, standard deviation, and range. Qualitative data were presented as frequencies and proportions .Sensitivity, Specificity, Positive predictive value, Negative predicate value, and Accuracy were calculated.

RESULTS

The study included 80 female patients whose ages ranged from 35:75 years old, mean age 46.3 ± 9.4 years as shown in table (1).

Half of the patients in our study had first and second-degree relatives who were positive for breast cancer as 24 had first-degree relatives representing 30% and 16 had second-degree relatives representing 20%. Also, 3 patients with a past history of breast cancer underwent breast-conserving surgery.

Regarding the findings in our study, mass and asymmetry were the most observed findings detected by digital mammography as the following: 40 masses (46.5%), 30 asymmetries (34.9%), 7 architecture distortion (8.1%), 5 clusters of micro-calcification with no underlying mass (5.8%) and 4 dense breasts (BIRADS 0) (4.7%).

While the findings of Tomosynthesis were 76 masses (79.2%), 4 asymmetrical densities,4 architecture distortion (4.2%), 3 Dilated ducts (3.1%), 2 Clusters of micro-calcification with no underlying mass (5.8%), 7 Overlapped glandular tissue (7.3%) as shown in table (2)

On Comparing between mass detection by digital mammography and digital breast tomosynthesis was done, there was a significant difference between DBT and DM in mass detection as 40 cases were true positive, 0 false-positive cases, 14 were true negative and 42 were false negative with a sensitivity of 49%, a specificity of 100%, and an accuracy of 56.3% of DM. While in tomosynthesis, 76 cases were true positive, 0 false-negative cases, 14 were true negative and 6 were false negative with a sensitivity of 92.7%, a specificity of 100%, and an accuracy of 93.7% as shown in table (3), (Fig S6)

In our study, the ACR categories for breast density were 52.5% C category, 33.7% were B category, 8.8 % were D category and 5 % were A category.

The findings by FFDM according to the ACR category were: 4 in ACR A, 29 in ACR B, 46 in ACR C, and 7 in ACR D.

While the findings by DBT according to the ACR category were: 4 in ACR A, 30 in ACR B, 51 in ACR C, and 11 in ACR D. So, 10 lesions were clarified by DBT not seen in DM. These lesions were found in the dense breasts more than non-dense.

The final diagnosis was according to the histopathological analysis of biopsy and surgical samples, fine-needle aspiration cytology, or follow-up. We performed a biopsy on 72 lesions that were discovered in initial tomosynthesis and to 6 lesions after 6 months follow-up. 18 lesions showed no time interval changes on 6 months follow-up and no further management was needed.

The distribution of different pathological entities "benign and malignant lesions" regarding final diagnosis was either by histopathological evaluation or follow-up. The most common benign lesion was fibrocystic changes (41.1%) followed by fibro-adenomas (30.3%) and the most common malignant lesion was invasive duct carcinoma (70%) as shown in table (4).

The comparison between the diagnostic performance of digital mammography and tomosynthesis in all ACR categories was as the following: tomosynthesis detected 96 lesions in which 36 of them were true positive, 5 lesions were false positive, 51 lesions were true negative, and 4 lesions were false negative with a sensitivity of 90%, a specificity of 91.1%, a PPV of 88%, a NPV of 92.7% and accuracy 91%. But Digital Mammography detected 86 lesions with 10 lesions not seen by DM and only clarified by DBT, 25 lesions were true positive, 23 lesions were false positive, 33 lesions were true negative, and 15 lesions were false negative with a sensitivity of 62.5%, a specificity of 59%, a PPV of 52.1%, a NPV of 68.8% and accuracy 60.4% as shown in table (5).

Changes in BIRADS results after using tomosynthesis in findings detected by DM were as the following: 22 were the same BIRADS as DM (25.6%), 30 were upgraded by DBT (34.9%), 34 were downgraded by DBT (39.5%).

Table 1: Demographic data of the study participant (N=80).

Age(years)	Study participant (N=80)
Mean ± SD	46.3 ± 9.4
Median	45.0
Range	35.0 – 75.0

Table 2: Findings detected by both DM and DBT:

Findings	Digital mammography	Tomosynthesis
Mass	40 (46.5%)	76(79.2%)
Asymmetry	30 (34.9%)	4 (4.2%)
Architectural distortion	7 (8.1%)	4 (4.2%)
Clusters of micro-calcifications with no underlying mass	5(5.8%)	2(2.1%)
Dense breast (BIRADS 0)	4 (4.7%)	0 (0.0%)
Dilated ducts	0 (0.0%)	3(3.1%)
Overlapped glandular tissue	0 (0.0%)	7(7.3%)

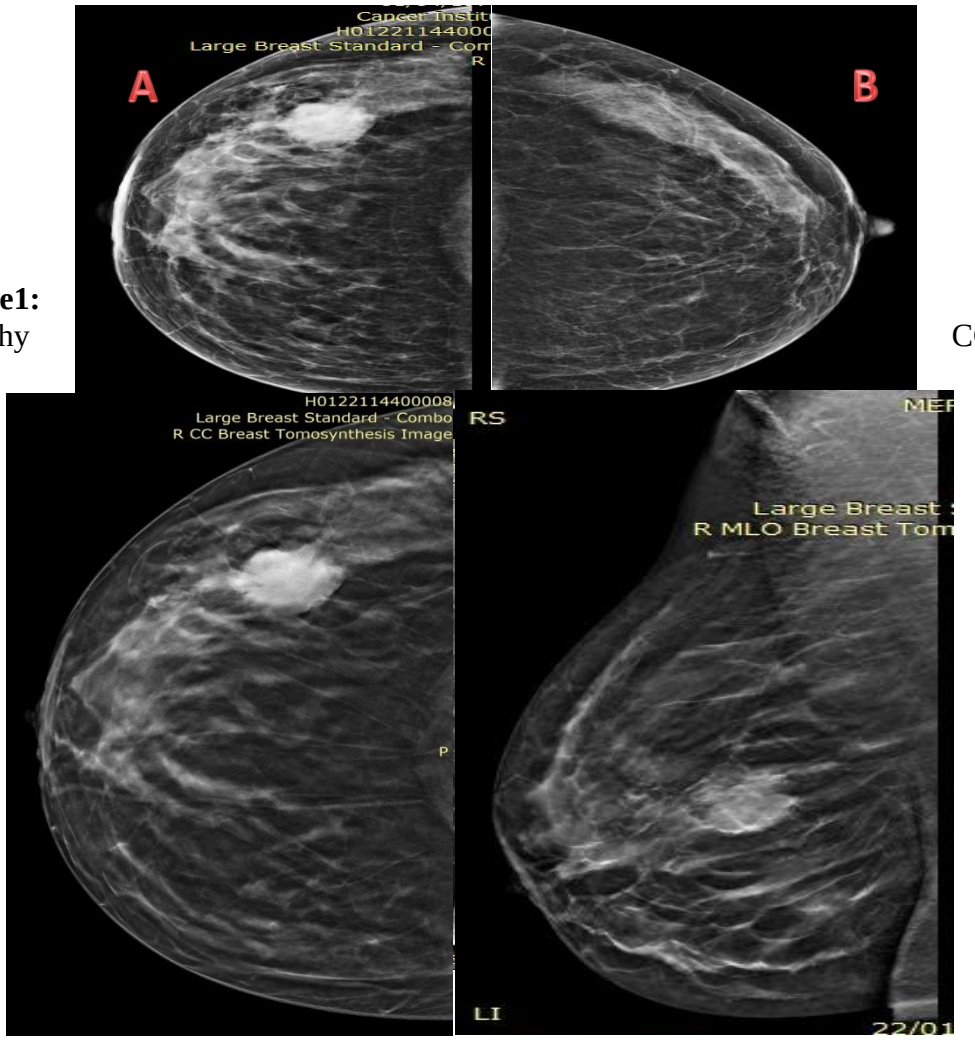
Table 3: Comparison between mass detection by digital mammography and tomosynthesis considering that mass as positive and non-mass as negative.

Mass detection	Digital mammography	Tomosynthesis	X2	P
True positive	40 (41.7%)	76(79.2%)	22.3	<0.001(HS)

False positive	0 (0.0%)	0 (0.0%)	NA	NA
True negative	14 (14.6%)	14 (14.6%)	NA	NA
False negative	42 (43.7%)	6 (6.2%)	27.6	<0.001(HS)
Sensitivity	49%	92.7%	6.5*	<0.001(HS)
Specificity	100%	100%	NA	NA
Accuracy	56.3%	93.7%	5.9*	<0.001(HS)

Table 4: The distribution of different pathological entities "benign and malignant lesions" regarding final diagnosis either by histopathological evaluation or follow-up.

Pathological entities	**N**	**%**
Benign:	56	
Fibrocystic changes.	23	41.1%
Abscess	1	1.8 %
Granulomatous mastitis	2	3.6%
Duct ectasia	2	3.6%
Fibroadenoma	17	30.3%
Benign phyllodes	1	1.8%
Normal	7	12.5%
Postoperative scar	3	5.4%
Malignant:	40	
Invasive ductal carcinoma	28	70%
Invasive lobular carcinoma	7	17.5%
Mucinous carcinoma	2	5%
DCIS	3	7.5%



Case1. Figure1: Digital mammography CC and MLO

Figure2: Tomosynthesis of the right breast CC and MLO views

Case 1: 45-year-old female complaining of a right breast lump.

Digital Mammography revealed:

- ACR B.
- Right breast showed obscured dense lesion in the upper outer quadrant, no spiculated masses, or suspicious micro-calcifications. (BIRADS Iva) (Fig1).
- No enlarged axillary LNs.

Tomosynthesis revealed:

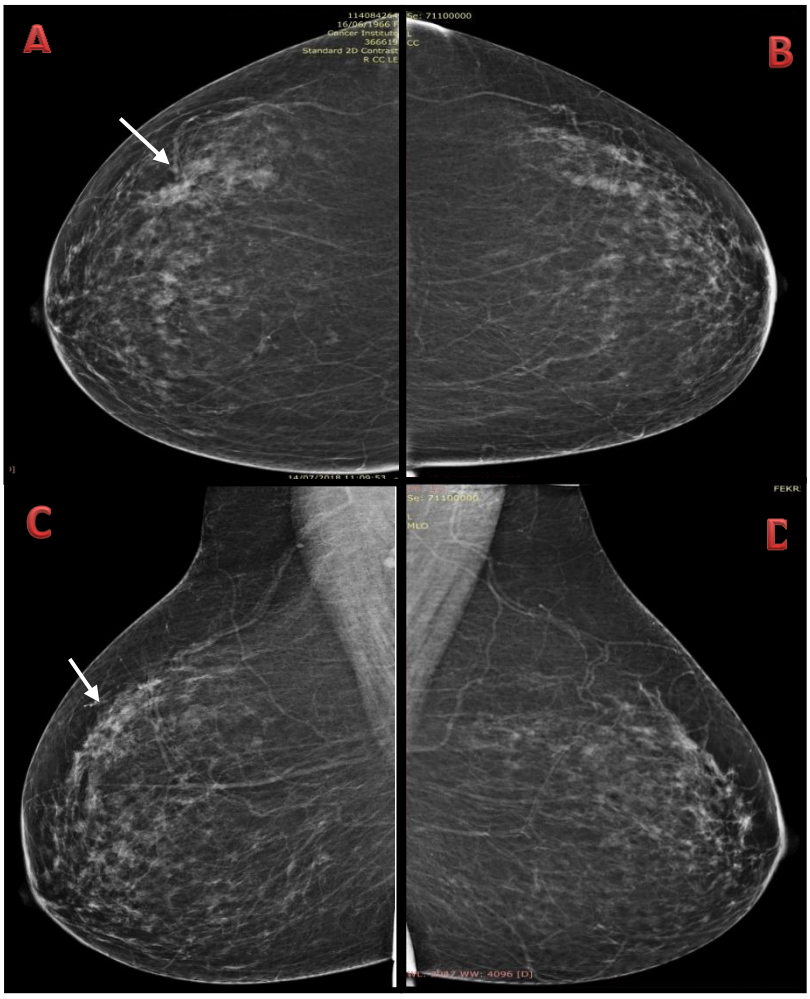
- Right breast showed irregular speculated dense lesion in upper outer quadrant (BIRADS IVc). (Fig2)

Final diagnosis by histopathological evaluation:

- Invasive ductal carcinoma

Conclusion :

- Tomosynthesis better identified the margins of the spiculated lesion at UOQ of the right breast and this changed BIRADS from IVa to IVc. Tomosynthesis upgraded the right breast lesion which proved to be invasive ductal carcinoma.



Case2. Figure3: Digital mammography CC and MLO view

DISCUSSION

In our study, we evaluated the accuracy of DBT in the detection and characterization of mammographically questionable breast lesions BIRADS III and IV, and those with dense breasts (BIRADS 0).

Our study included 80 patients whose ages ranged from 35 - 75 years with a mean of 46.3 ± 9.4 (mean ± SD).

Regarding mammographic findings in our study, we detected 86 lesions classified as 40 (46.5%) lesions presented as mass lesions, 5 (5.8%) presented as micro-calcifications with no underlying mass lesion, 30 (34.9%) presented as asymmetry, 7 (8.1 %) lesions presented as architecture distortion and 4 (4.7%) were dense breast lower sensitivity of mammography.

Regarding Tomosynthesis findings in our study, we detected 96 lesions classified as 76 (79.2%) lesions presented with mass, 2 (2.1%) presented with micro-calcifications with no underlying mass lesion, 4 (4.2%) lesions presented with asymmetry, 4 (4.2%) presented with architecture distortion, 3 (3.1%) lesions presented with dilated ducts and 7 (7.3 %) presented with overlapped glandular tissue. So DBT decreased the recall rate because of the better definition of the lesion.

In our study, DBT detected new 10 lesions not seen in digital mammography, overcame the problem of breast densities in DM, and detected 36 masked masses not seen in DM.

6 masses not seen in DBT were confirmed by pathological confirmation either by stereotactic biopsy, surgical excision, mastectomy, or US-guided biopsy.

In a study done by Poplack et al., they found that digital breast tomosynthesis decreased recalls as it could characterize lesions as benign or malignant. For example, it implied that overlapping tissue had obscured a characteristically benign feature, for example, fat in the intra-mammary lymph node [7].

In our study, the mammography detected 40 (41.7%) masses while Tomosynthesis detected 76 (79.2%) masses. Our results showed a significant difference between tomosynthesis and digital mammography in the detection of masses ($p<0.001$) as the sensitivity of DM for mass detection was 49 % and accuracy 56.3% while in DBT sensitivity for mass detection was 92.7% and accuracy 93.7%.

Waldherr et al. found that in addition to the superior sensitivity of digital breast tomosynthesis, their study revealed a significantly (15–20%) better NPV for digital breast tomosynthesis compared with FFDM (Full Field Digital Mammography) in the detection of masses, resulting from the reduced tissue overlap (especially in small lesions), better delineation of lesion margins, and improved demarcation of radial distortions. NPV is an essential value, especially in a screening situation, where a patient with a negative finding will not be recalled for 1 or even as long as 2 years [10].

Regarding asymmetries, mammography detected 30 (34.9%) asymmetries, 7/30 were confirmed by Tomosynthesis to be only areas of overlapped fibro-glandular tissue while 19/30 proved to have an underlying mass lesion.

In this study, Tomosynthesis overcame the tissue overlap in focal asymmetries and could verify if there was an underlying mass or that was only overlapped fibro-glandular tissue.

Christoph et al. found that Tomosynthesis increased cancer detection by eliminating Digital Mammography interpretive limitations caused by superimposed breast tissue [11].

Skaane, in a study of the added value of Tomosynthesis, suggested that digital breast Tomosynthesis may improve the detection of architectural distortion especially in women with heterogeneously dense breasts. Theoretically, the very thin speculations seen in architectural distortion would be expected to be more easily identified on 1 mm thin slices as compared with a conventional projection mammogram [12].

In our study, we found that tomosynthesis clarified 10 more lesions hardly seen in digital mammography and changed the identified BIRADS category in 64 (74.4%) lesions. It upgraded 30 (34.9%) lesions and downgraded 34 (39.5%) lesions. Tomosynthesis significantly decreased the number of

indeterminate lesions (BIRADS III, Iva) from 84.9% to only 29.2% .

Hakim et al. found that combined FFDM and DBT were perceived to be better than additional mammographic views subjectively compared additional mammographic views for interpretation of known masses, architectural distortions, or asymmetries. In this study, 3D Digital Breast Tomosynthesis showed better lesion BIRADS classification and significantly decreased the number of indeterminate/suspicious lesions, (BIRADS 3 & 4) by either supporting a benign (downgrading) or a malignant (upgrading) diagnosis [13].

Also, in concordant with Raghu et al., who stated that tomosynthesis significantly decreased the number of indeterminate lesions BIRADS III from 33.3% in DM to only 16.4% by DBT with P <0.0001. But on contrary to them who reported no change in BIRADS category (4 and 5) after addition tomosynthesis [14].

Mansour et al. stated that three-dimensional tomosynthesis images significantly decreased the number of indeterminate/suspicious lesions, (BIRADS 3 & 4) by either supporting a benign (downgrading) or a malignant (upgrading) diagnosis [15].

Upon correlating with the final diagnosis by histopathological analysis, there were 56 (58.3%) benign lesions and 40 (41.7%) malignant lesions. Within the 56 benign lesions, 41.1% of them were fibrocystic changes, 1.8 % was breast abscess, 3.6 % were diagnosed as granulomatous mastitis, 3.6 % were duct ectasia, 30.3% were fibroadenoma, 1.8% were benign phyllodes, 12.5% were diagnosed as normal and 5.2% were postoperative scarring.

Close to Mariscotti et al., who reported 89 benign lesions, 25/89 (28.1%) of lesions were fibroadenomas and 21/89 (23.5%) were fibrocystic changes [16].

Also close to Asbeutah et al., who stated that the most common benign lesions were fibroadenoma and fibrocystic changes [17] .

Because a large fraction of biopsies was performed for benign entities and the ability to assess lesion margins when using DBT was frequently exquisite, it is possible that DBT may be helpful in reducing the number of benign lesions that undergo biopsy [7]. In our study, malignant lesions were (41.7%) of the total cases, 70 % of them were invasive ductal carcinoma, 17.5% were invasive lobular carcinoma, 5% mucinous carcinoma and 7.5% were DCIS and the most common malignant tumor was invasive ductal carcinoma (70%).

Similar to Ali et al., who stated that out of the total 145 breast lesions, 67 were cancers, of which 34 (50.8%) were invasive ductal cancers. [18].

Also similar to Förnvik et al., who stated that the most common malignant tumor was invasive ductal carcinoma 43/73 (59%). [19]

Also similar to Asbeutah et al., who reported that the most common malignant tumor was invasive ductal carcinoma 29/34 (85.3%). [17].

Mammography BIRADS category was given for each lesion according to the BIRADS mammography morphology descriptors; 48 (50%) lesions were considered benign or no detected abnormality (BIRADS 0 and 3) while, 48 (50%) lesions were considered malignant (BIRAD 4)

After revising the pathology results and follow up 25 (26%) lesions were true positives, 23 (24%) lesions were false positives, 15 (15.6%) lesions were false negatives, and 33 (34.4%) lesions were true negatives.

In this study, the false positive results were due to over-lapping of fibro-glandular tissue, increased breast density, or obscured margins of a benign lesion. So, mammography had a sensitivity for detection of malignant lesions of 62.5% a specificity of 59%, a positive predictive value of 52.1%, a negative predictive value of 68.8%, and diagnostic accuracy of 60.4%.

Mansour et al. performed a prospective analysis of mammography findings in 166 mammograms. The calculated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were, 60%, 20.7%, 62%, 20%, and 48% respectively [15].

Waldherr et al., in a study comparing the role of Mammography and Tomosynthesis in the

diagnostic workup, showed that Digital mammography showed a sensitivity of 70.5%, a specificity of 80.8%, a PPV of 86.1%, and a NPV of 61.8% [10].

Tamaki et al. performed a retrospective analysis of mammography findings in 1267 Japanese women. The calculated sensitivity, specificity, and positive predictive values were 92.8, 31.4, and 63.1%, respectively [20].

Elizalde et al. performed a retrospective study to assess the addition of DBT or US after digital mammography to know which one was the best combination. The calculated sensitivity and specificity of DM alone were 69.05% and 88.2 % respectively and the sensitivity of DM after the addition of tomosynthesis increased from 69.05% by DM alone to 86.9 by the combination of both modalities. But, contrary to this study which stated that the specificity decreased after the addition of DBT from 88.2% to 83.5%, as BIRADS 3 lesions were considered as positive, and this was a possible explanation for the lower specificity of additional DBT in this study [21].

Lei et al. conducted a meta-analysis study that compared the diagnostic performance of DM with Tomo, showing that the sensitivity and specificity of DM were 89.0 % and 72 % respectively. They calculated the sensitivity and specificity of Tomo as 90.0% and 79.0%, respectively [22].

A BIRADS category was given to lesions identified on 3D Digital Tomosynthesis according to the Mammography BIRADS Lexicon and accordingly, 55(57.3 %) lesions were considered benign (BIRADS 1, 2, and 3) while 41(42.7%) lesions were considered malignant (BIRADS 4).

After revising the pathology results, 36 (37.5%) lesions were true positives, 5 (5.2%) lesions were false positives, 4 (4.2 %) lesions were false negatives, and 51 (53.1%) lesions were true negatives.

The false positive results were less (5 instead of 23 cases) when compared to digital mammography. Tomosynthesis overcame the tissue overlap in focal asymmetries and was able to verify if there is an underlying mass and if it was single or multiple masses with better characterization of margins or whether it is only overlapping fibro-glandular tissue. The false positive results were due to dense breasts or irregular margins of the lesions .

The false positive result was due to two cases of granulomatous mastitis and three cases of postoperative scar. While the false negative result was due to two cases of mucinous carcinoma, diffuse subtle infiltration in two cases with diffuses edema.

Tomosynthesis had a sensitivity of 90%, a specificity of 91.1%, a positive predictive value of 88 %, a negative predictive value of 92.7%, and an accuracy of 91%.

Waldherr et al., in a study comparing the role of Mammography and Tomosynthesis in the diagnostic workup, showed that Digital Breast Tomosynthesis had a sensitivity of 84%, a specificity of 83.9%, a positive predictive value of 89.4%, and a negative predictive value of 76.5% [10].

Mansour et al., in a prospective study of 166 indeterminate mammograms comparing Mammography to Tomosynthesis in the evaluation of breast lesions, showed that Digital Breast Tomosynthesis had a sensitivity of 94.5%, a specificity of 74%, a positive predictive value of 92%, and a negative predictive value of 80% and an accuracy of 89.7% [15].

Lei et al., reported in their comparative large study, that Tomo has a higher sensitivity and specificity in breast diagnosis than DM. They calculated sensitivity and specificity of Tomo as 90.0% and 79.0%, and for DM they were 89.0% and 72.0%, respectively [22].

CONCLUSIONS

In our study, we concluded that Tomosynthesis separated overlapping tissue in the dense breast by the acquisition of multiple images over a limited angular range. Tomosynthesis showed higher sensitivity and specificity and diagnostic accuracy than Mammography as it allowed better detection of breast cancer, characterization of lesions, better margin assessment of masses, and decreased false positive recall rate. Also, Superior

resolution has paved the way for making an accurate diagnosis.

Conflict of Interest: The authors report no conflicts of interest.

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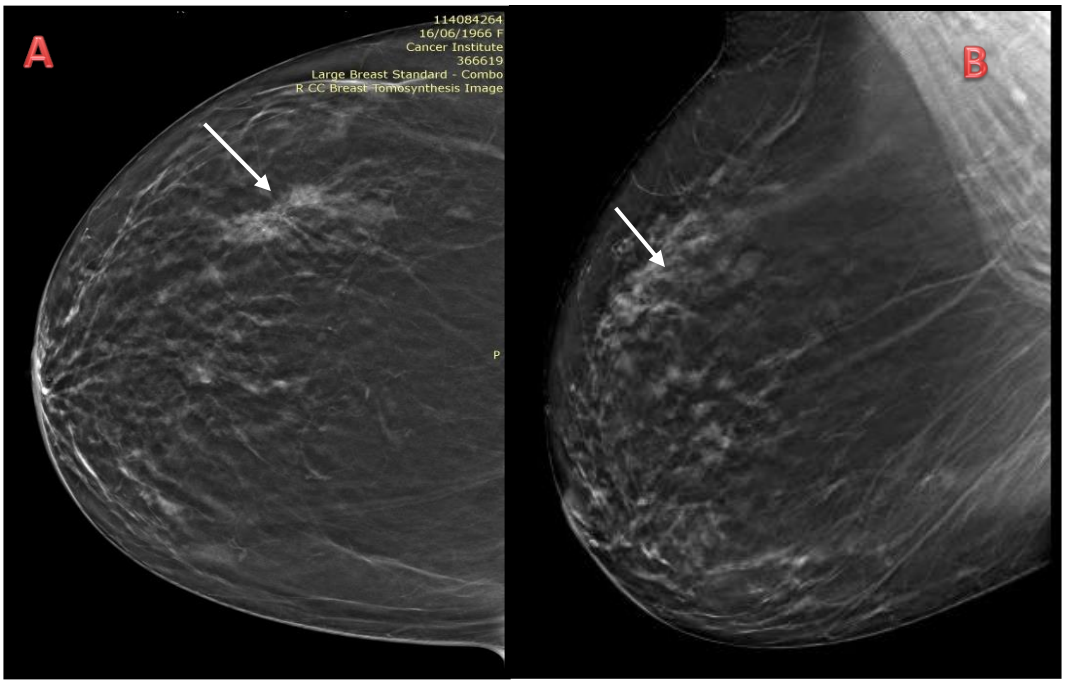


Case2. Figure S1: Tomosynthesis CC and MLO of right breast

Case 2: 52-year-old female coming for screening mammography.

Digital Mammography revealed:

- ACR A.
- Right UOQ area of architecture distortion (BIRADS IVa).
- No spiculated masses or suspicious micro-calcifications.
- No enlarged axillary lymph nodes (Fig.3).

3D Tomosynthesis revealed:

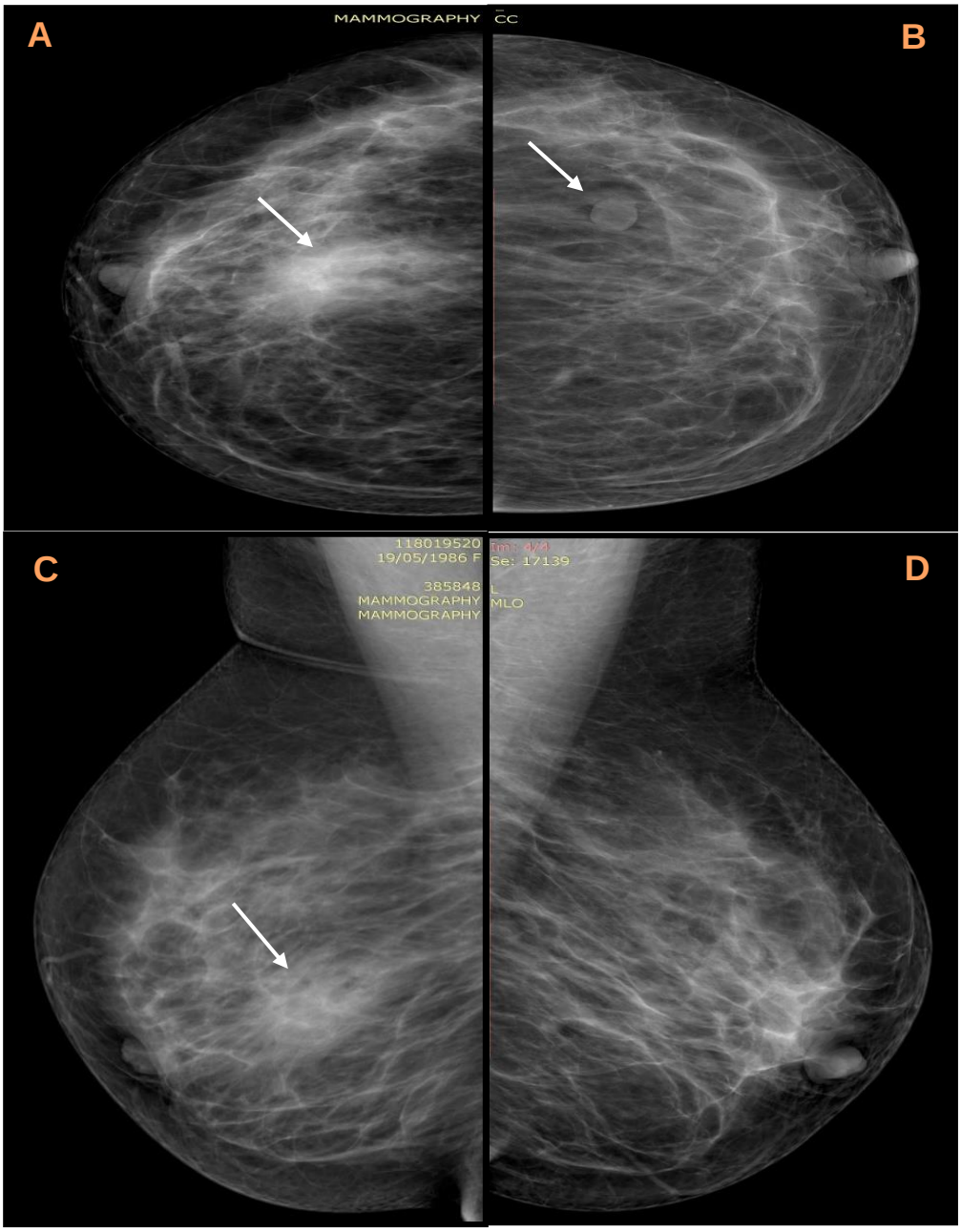
- Right breast showed UOQ ill-defined dense mass with irregular outline and spiculated margins measures about 32x24mm, no suspicious micro-calcifications (BIRADS IVc) (Fig. S1).

Final diagnosis by histopathology:

- Invasive ductal carcinoma.

Conclusion:

- 3D Digital Tomosynthesis upgraded right breast lesion from IVa to IVc which proved to be invasive ductal carcinoma.



Case3. Figure S2: Digital mammography CC and MLO views

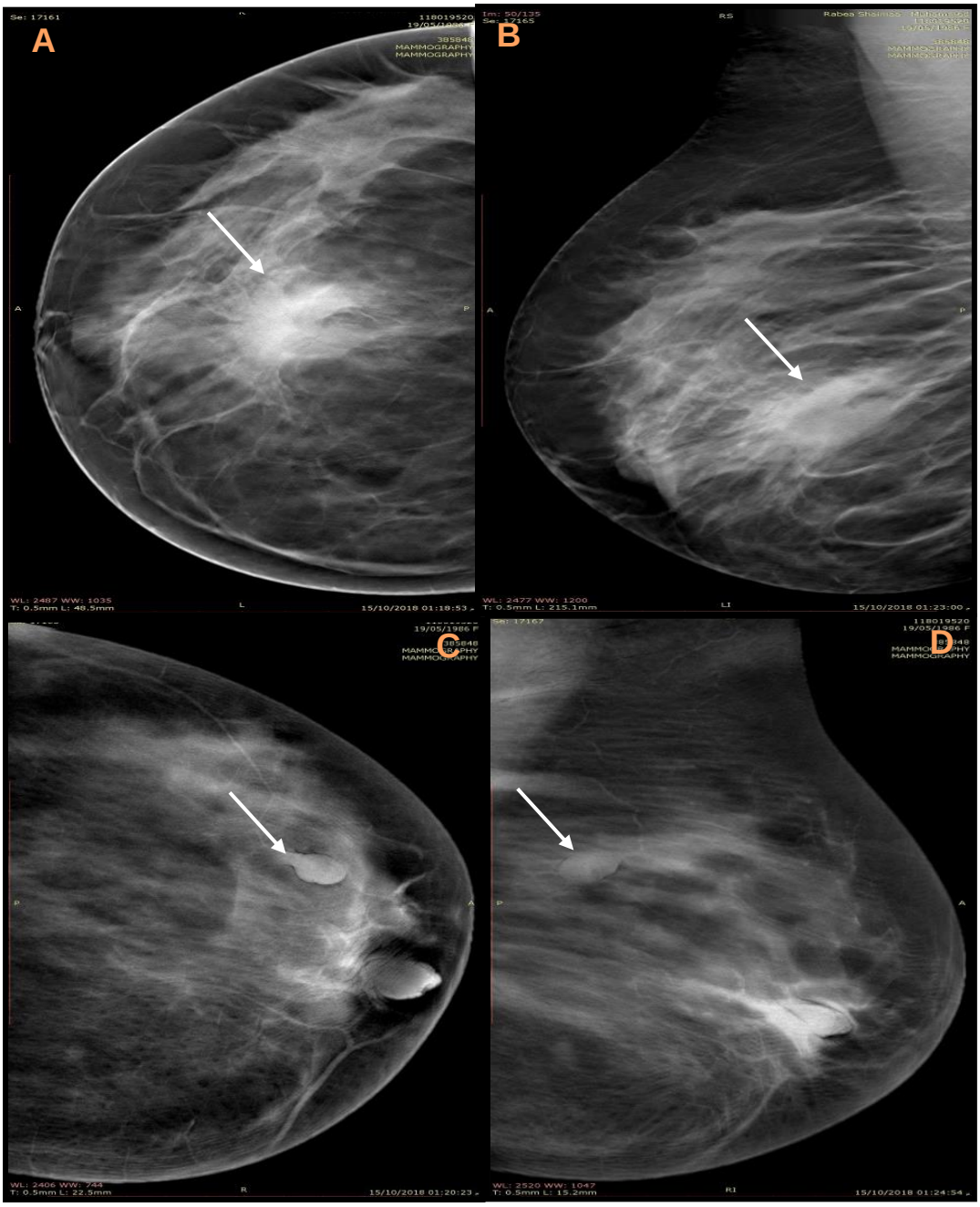


Figure S3: Tomosynthesis CC and MLO views

Case 3: 36-year-old female complaining from right nipple retraction.

Digital Mammography revealed:

- ACR B: Scattered fibro-glandular parenchyma.
- Right nipple retraction with central retro-areolar asymmetrical density (BIRADS IVa).
- Left well defined medium density lesion in UOQ seen in CC view and obscured in MLO due to summation of glandular tissue measuring about 11x12.5 mm. (BIRADS III). (Fig. S2)

3D Tomosynthesis revealed:

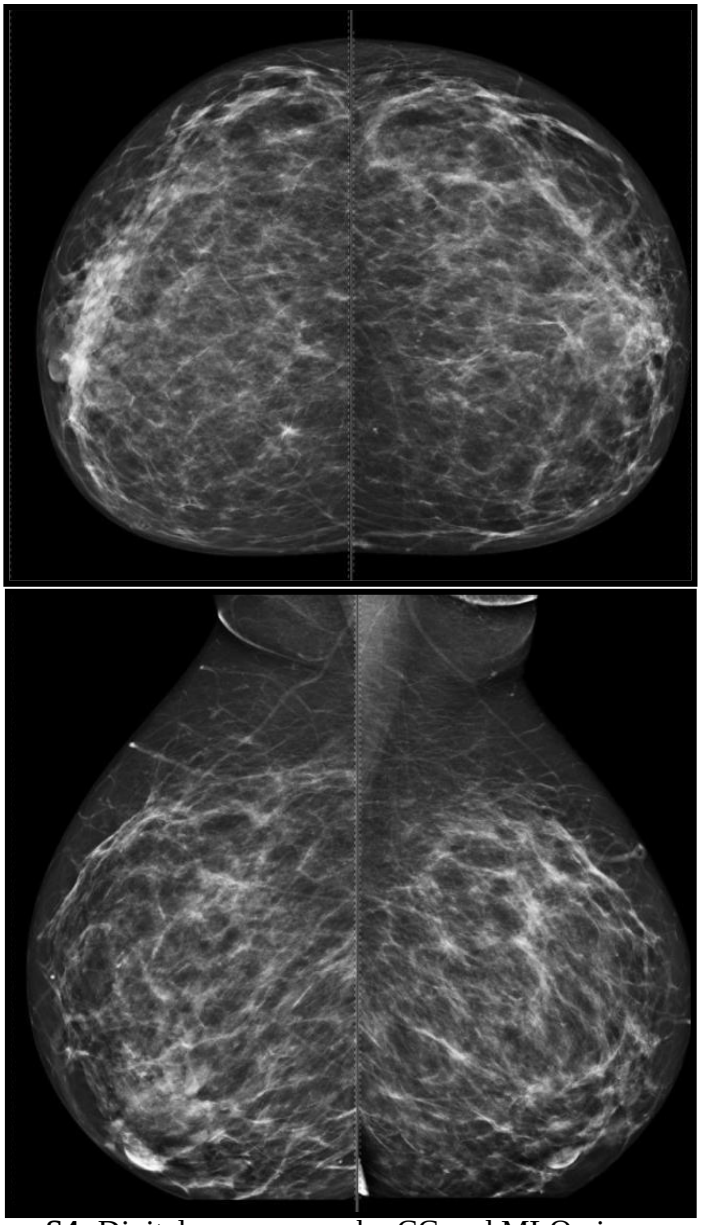
- Right central retro-areolar dense mass with irregular outline and spiculated margins associated with retracted nipple measuring about 35x21mm (BIRADS IVc) and left UOQ well defined medium dense lesion with a better definition of margins in both CC and MLO views measured about 13x11mm. (BIRADS III). (Fig. S3)

Final diagnosis by histopathology:

- Right invasive lobular carcinoma and left fibroadenoma.

Conclusion:

- Tomosynthesis upgraded right breast lesions from III to IVc with better delineation of its margins which proved to be invasive lobular carcinoma. However, tomosynthesis had the same BIRADS of the left breast lesion as DM with better characterization for its margins which proved to be a fibroadenoma.



Case4. Figure S4: Digital mammography CC and MLO views

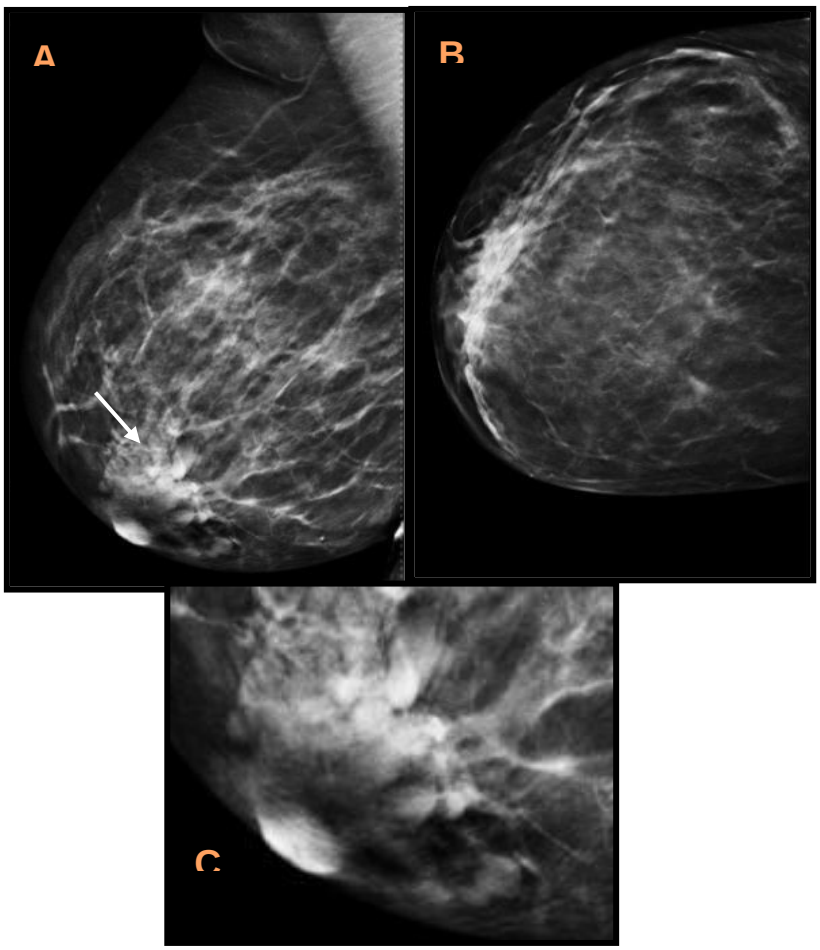


Figure S5

Fig S5: Tomosynthesis of the right breast

Case 4:
Clinical Background: 69-year-old female was coming for screening mammography.
Mammography revealed:

- ACR B scattered fibro glandular parenchyma.
- Right retro-areola area of focal asymmetry (BIRADS III).
- No spiculated masses or suspicious micro-calcifications.

3D Tomosynthesis revealed:

- On 3D Digital Breast Tomosynthesis, the focal asymmetry proved to be right retro-areolar dilated ducts (BIRADS II).

Final diagnosis:

- Duct ectasia.

Conclusion:

- The Tomosynthesis detected the masked duct ectasia by the overlapped glandular tissues in Mammography and downgraded the BIRADS classification from III to II confirming the benignity of the lesion and giving a definite diagnosis which saved more investigations and recall.

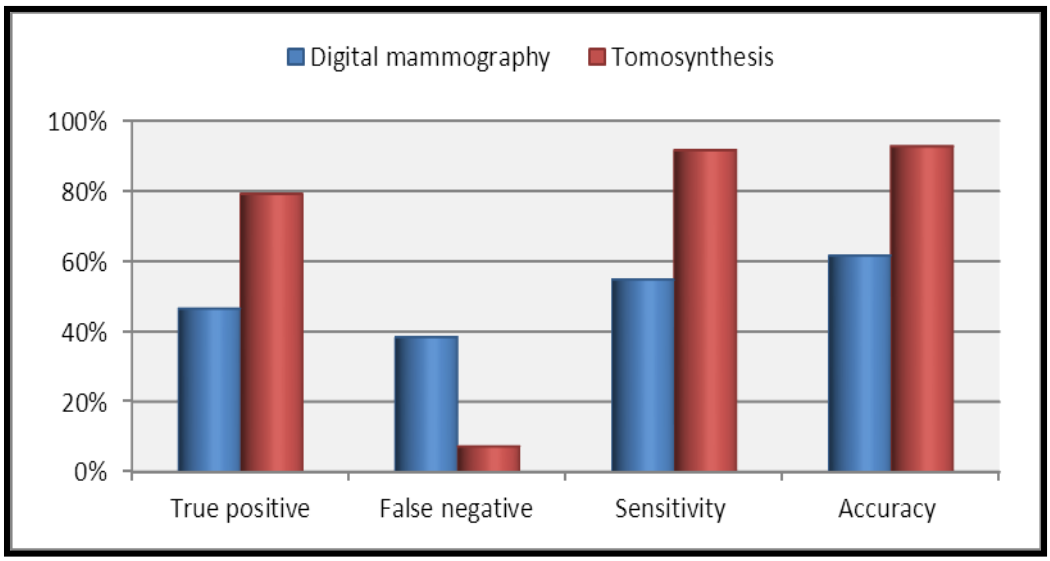


Figure S6: Comparison between mass detection by digital mammography and tomosynthesis

Table S1: Comparison between the diagnostic performance of digital mammography and tomosynthesis in all ACR categories:

Final diagnosis	Digital mammography	Tomosynthesis	X^2	P
True positive	25 (26%)	36 (37.5%)	2.9	0.08
False positive	23 (24%)	5 (5.2%)	Fisher	<0.001(HS)
True negative	33 (34.4%)	51 (53.1%)	7.6	0.005(S)
False negative	15 (15.6%)	4 (4.2%)	Fisher	0.01(S)
Sensitivity	62.5%	90%	4.5*	<0.001(HS)
Specificity	59.0%	91.1%	5.1*	<0.001(HS)
PPV	52.1%	88%	5.4*	<0.001(HS)
NPV	68.8%	92.7%	4.1*	<0.001(HS)
Accuracy	60.4%	91%	4.9*	<0.001(HS)