

Comparison of Diagnostic Accuracy of Digital Mammography, Digital Breast Tomosynthesis and Contrast Enhanced Mammography in the Preoperative Assessment of BI-RADS III and above Lesions in Dense Breasts: A Cross-sectional Study

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ABSTRACT

Introduction: Women belonging to breast density category C and D have high mammographic density and are at an increased risk for developing breast cancer. Although mammogram is the gold standard technique for the detection and diagnosis of breast cancer, extremely dense breasts due to reduced contrast between tumours and surrounding tissue pose significant limitations in the identification and diagnosis. This limitation has been overcome by introduction of 3D Digital Breast Tomosynthesis (3D DBT) and other newer imaging modalities like Contrast-Enhanced Mammography (CEM), breast ultrasound and Magnetic Resonance Imaging (MRI).

Aim: To compare the diagnostic accuracy of CEM, Digital Mammography (DM), and DBT in assessing cancer detection rate in dense breasts.

Materials and Methods: A cross-sectional study was conducted with a sample size of 53 patients in the Department of Radiodiagnosis at Malabar Institute of Medical Sciences (MIMS) Calicut, Kerala, India, from October 2022 to September 2023. DM, DBT, and CEM images were taken for each patient and were visually assessed to identify primary and satellite lesions, measure the size of the index lesions and classify them according to Breast Imaging Reporting and Data System (BI-

RADS) American College of Radiology (ACR) lexicon category. Results were then compared to histopathology. Categorical variables were summarised in terms of frequency with % and tested using Chi-square test. Continuous variables were summarised as mean \pm standard deviation or median with interquartile range.

Results: A total of 53 subjects were included in the final analysis, with an average age of 51.7 ± 11.5 years. Among three modalities, CEM proved best for maximum Cancer Detection Rate (CDR), accounting for 100% sensitivity, an 81% Positive Predictive Value (PPV), and 81% diagnostic accuracy for detecting malignancy. Whereas DBT had 79% diagnostic accuracy and DM had 73.5% diagnostic accuracy for detecting malignancy. Mean volume of the lesions evaluated by histopathology was 5.6, while those measured by DM, DBT, and CEM were 7.8, 6.4, and 6.2. All three modalities overestimated lesion sizes compared to histopathology, with CEM showing a smaller difference. In case of additional lesion evaluation, CEM detected 16 more cases that were undetected on DM and 12 more cases that were undetected on DBT.

Conclusion: CEM is superior diagnostic modality in evaluation of cancer detection in dense breasts and can be a suitable alternative for DM and DBT in dense breasts with certain limitations.

Keywords: Breast cancer, Breast imaging reporting and data system, Cancer detection rate, Satellite lesions

INTRODUCTION

Breast cancer has now become the most commonly diagnosed cancer worldwide, replacing lung cancer, with over 2.3 million new cases and an estimated 685,000 deaths in 2020 [1]. Mammography remains the single breast imaging examination proven to reduce breast cancer mortality, with a sensitivity rate of 75 to 80% [2]. There are certain guidelines for imaging patients according to patient's age, with mammography being the primary modality for evaluating those more than 40 years of age and ultrasonography for those younger than 30 years of age [3]. Since the performance of mammography is dependent on breast density, not all women benefit equally from mammography alone. Breast density is analysed either visually or quantitatively by assessing relative proportion of fibroglandular tissue to the fat [4]. The ACR BI-RADS Lexicon 5th edition breast density categories are: a) entirely fatty; b) predominantly fatty with scattered fibroglandular tissue; c) heterogeneously dense; and d) extremely dense breast parenchyma. Women belonging to category

C and D are considered to have high mammographic density, and the 2 major problems: an increased risk of developing breast cancer and decreased sensitivity and specificity of mammography in dense breasts [5]. Women with extremely dense breasts have a four- to five fold greater risk of breast cancer compared to women with less density breasts [4].

Although mammogram is the gold standard technique in the detection and diagnosis of breast cancer, extremely dense breasts due to reduced contrast between tumours and surrounding superimposed tissue cause significant limitation in identification of diagnosis. This has resulted in an increased rate of False-Negative (FN) mammograms and False-Positive (FP) mammograms, causing unnecessary increase in the recall rates [5]. The sensitivity range of mammography accounts for 81 to 93% for category A breasts, 84 to 90% for category B breasts, 69 to 81% for category C breasts, and 57 to 71% for category D breasts [6]. Women more than 40 year-old with heterogeneously dense breasts accounts for nearly

36%, while those with extremely dense breasts accounts for approximately 7% [7].

Mammographic sensitivity decreases with the increase of parenchymal density due to a superimposition of dense breast tissue on a two-dimensional (2D) mammographic projection. This limitation has been overcome by introduction of 3D DBT (3D DBT) and other newer imaging modalities, like CEM, breast ultrasound, and MRI [8]. 3D DBT permits visualisation of individual planes of the breast while reducing the impact of overlapping tissue. DBT, when performed alone or in combination with Digital Mammography (DM), DM have the diagnostic capabilities of capturing mass-like lesions, asymmetries, architectural distortions, as well as to assess microcalcifications and lesion's conspicuity [9]. CEM is a promising diagnostic technique that utilises iodinated contrast material for visualisation of breast lesions with neovascularity. Since there is angiogenesis in breast cancer tissue, the vessels that formed through the process leaks the contrast material, and contrast diffuses within tumour tissue, resulting in iodine-enhanced tissue. This allows for superior demonstration of the tumour over dense breast parenchyma [10]. The combination of DBT and contrast-enhanced dual-energy DM has superior diagnostic accuracy compared to DBT alone in identifying and classifying breast lesions and detecting multifocal and bilateral cancers, if present [11].

Many previous studies have evaluated the diagnostic accuracy of CEM, DBT and DM in preoperative assessment of BI-RADS IV lesions and above in both dense [12,13] and non dense breasts [11,14]. A few other studies have included all BI-RADS lesions in dense breasts [5,15,16]; however, this is the first study in Southern India comparing the results of DM, DBT and CEM in dense breasts for preoperative assessment of BI-RADS III and above lesions. No studies have been done in Southern India comparing the lesion size estimation with histopathology and additional lesion evaluation using three modalities. With this background, this study was conducted to compare the diagnostic accuracy of DM, DBT and CEM as tools to detect BI-RADS III and above lesions in dense breasts.

MATERIALS AND METHODS

A hospital-based cross-sectional observational study was conducted in the Department of Radiodiagnosis at Malabar Institute of Medical Sciences (MIMS) in Calicut, Kerala, India, from October 2022 to September 2023. Approval from the Scientific Research Committee (SRC) and Institutional Ethical Committee (IEC) was obtained before the study began, and the participants' informed consent was waived. The certificate number (IEC number) is IEC Reg. No: EC/NEW/INST/2022/KL/0056 & ECR/301/Inst/KL/2013/RR-19.

Inclusion criteria:

1. Symptomatic patients with mammographically dense breasts classified as C or D according to ACR BI-RADS lexicon breast density classification.
2. Patients with mammographically dense breasts who had inconclusive findings on screening ultrasound (USG).

Exclusion criteria:

1. Unavailability of surgical and postsurgical data.
2. Neoadjuvant treatment before surgery.
3. Incomplete breast imaging (including bilateral DM, DBT and CEM).
4. Pregnant women.
5. Women with previous allergic reactions to contrast agents.
6. Patients with compromised kidney or bladder functions, tested with abnormal serum creatinine levels (>2.0 mg/dL).
7. Patients with breast density classified as ACR A or B.

Sample size estimation: Based on the previous literature (Girometti R et al.,) [15], the sample size was calculated considering the sensitivity of CEM as (97%). Using this

$$n = \frac{(1.96)^2 * S_n(1-S_n)}{L^2p}$$

Where, S_n is the anticipated sensitivity, L is the allowable error and P is expected positive proportion:

$$n = \frac{(1.96)^2 * 0.97(1-0.97)}{(0.08)^2(0.33)} = 53$$

The required minimum sample was 53.

Study Procedure

DM, 3D Tomosynthesis and CEM were performed using a Selenia mammography system (Hologic). Mammography included Craniocaudal (CC) and Mediolateral Oblique (MLO) views, as well as other projections (such as lateral or spot views) when indicated by the standard of care. For the 3D DBT, 15 low-dose 2D projection exposures were taken, and 3D volume of the compressed breast was reconstructed from the 2D projections in the form of a series of images throughout the entire breast.

CEM examinations consisted of a current Full-Field Digital Mammography (FFDM) system using a flat panel detector with a cesium iodide absorber, field size 24 × 31 cm, a 2394 × 3062 image matrix with a pixel pitch of 100 µm, and specific software and hardware for rapid acquisition and processing of dual-energy images. A one-shot intravenous (i.v.) injection of 1.5 mL/kg of non ionic contrast agent (Iopromide, Ultravist 370) was then performed using a power injector (Optistar™) at a rate of 3 mL/s, with a bolus chase of 30 mL saline. After a countdown of two minutes, the breast with a suspected lesion was imaged first, followed by the breast without a suspected lesion using a pair of low- and high-energy exposures.

Compression time for each view was a maximum of 15 seconds. The total duration of the examination was typically 10 minutes. Processed images were transferred directly to the workstation for review by the radiologist.

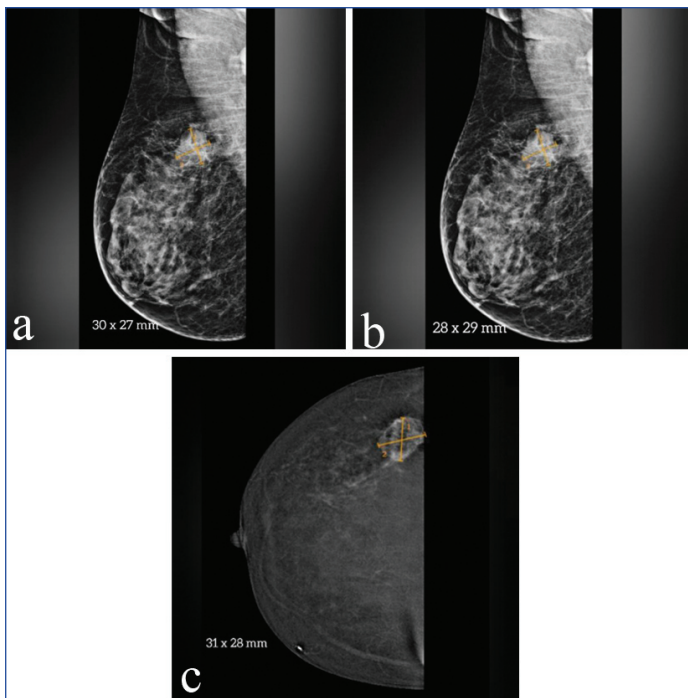
A single radiologist visually assessed images in multiple sittings to classify them according to BI-RADS ACR lexicon category 1-5 after analysing margins, internal characteristics, and enhancement pattern [17]. The evaluation forms for DM, DBT and CEM included the following data for each enhancing lesion found by the reader to be appropriate:

- Localisation (quadrant)
- Size of the lesion
- Degree of enhancement in the suspicious breast (none, slightly, medium, rapid)
- Enhancement pattern

BI-RADS classification from combined DM, DBT and CEM modalities was compared to histopathology and divided into four groups: BI-RADS ≥4 and proven cancer on histopathology were classified as True Positives (TP), while BI-RADS ≤ 3 and benign lesion on histopathology as True Negatives (TN). The sizes of the lesions on DM, DBT and CEM were measured and compared to the histopathological results [Table/Fig-1a-c].

STATISTICAL ANALYSIS

Data were analysed using SPSS version 21.0. Categorical variables were summarised in terms of frequency with % and tested using Chi-square or Fisher's exact test. Continuous variables were summarised as mean±standard deviation or median with interquartile range. The ability of DM, DBT and CEM diagnosing breast cancer and additional lesions were assessed by calculating sensitivity, specificity, FP rate,



[Table/Fig-1]: Representative images showing size measurement of the lesion in DM, DBT and Contrast mammography. (a) DM in MLO view of right breast in homogeneously dense breast parenchyma (ACR D) showing size measurement (30 x 27 mm) of the lesion in upper outer quadrant. (b) DBT in MLO view of right breast in homogeneously dense breast parenchyma (ACR D) showing size measurement of the lesion (28 x 29 mm) in upper outer quadrant. (c) CEM CC view showing size measurement of the lesion (31 x 28 mm) in outer quadrant.

patients were graded as BI-RADS 3, 11 (20.8%) were graded as BI-RADS 4a, 1 (1.9%) was graded as BI-RADS 4b, 3 (5.7%) were graded as BI-RADS 4c, and 35 (66%) were graded as BI-RADS 5.

Histopathological evaluation showed that among the 53 study participants, 43 (81.1%) as TPs and remaining 10 (18.9%) were True Negatives. Among 53 study population, DM detected 37 lesions, while 16 cases were undetected. Among 37 lesions, 33 cases were TPs and four were False Positives (FPs). Among 16 undetected cases, 10 were False Negatives (FNs) and six were TNs. For Digital Breast Tomosynthesis (DBT), 46 cases were detected, consisting of 39 TP and seven were FP. Among 7 DBT undetected cases four were FN and three cases were TN. Contrast-Enhanced Mammography (CEM) detected all 53 cases, with 43 being TP and 10 were FP. No TNs or FNs were there as CEM detected all 53 cases [Table/Fig-2,3].

Lesion size was evaluated by taking the volumes of each lesions detected by each modality and comparing them with the volume of postoperative histopathology size. So, evaluation of size of lesions from CEM modality was found to be more accurate than those from DM and DBT. All three modalities overestimated lesion sizes compared to histopathology, with a statistically significant difference (p -value <0.05). However, the difference was smaller for CEM [Table/Fig-4].

Additional lesion detection rate of DM, DBT, and CEM: Out of 53 study population, only 24 cases (45.3%) had additional lesions as proven by histopathology. DM detected eight additional lesions, while 16 cases went undetected. DBT detected 12 cases, whereas

	Gold standard		Sensitivity	Specificity	PPV	NPV	Accuracy
	Positive	Negative					
DM							
Positive	33	4	76.7%	60.0%	89.2%	37.5%	73.5% 95%CI (64.8-82.2%)
Negative	10	6					
DBT							
Positive	39	7	90.7%	30.0%	84.8%	42.9%	79.2% 95% CI (71.2-87.2%)
Negative	4	3					
CEM							
Positive	43	10	100.0%	-	81.1%	-	81.1% 95% CI (73.4-88.8%)
Negative	0	0					

[Table/Fig-2]: Malignancy detection rate of DM, DBT and CEM.

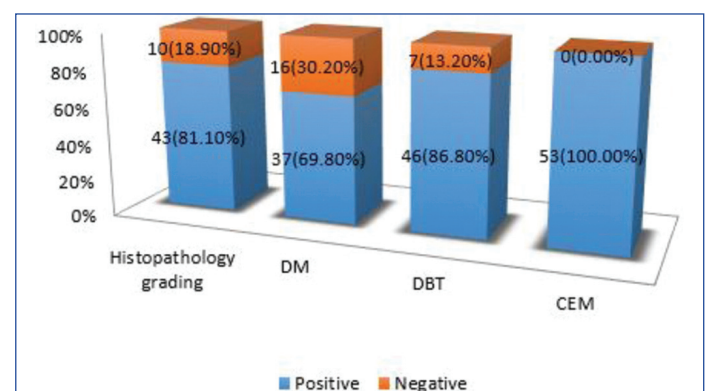
False Negative (FN) rate, PPV, Negative Predictive Value (NPV), and diagnostic accuracy, along with their 95% Confidence Intervals (CIs). To compare the preoperative lesion size assessment using DM, DBT and CEM with estimated pathological size Mann-Whitney U test was used. A p -value <0.05 was considered statistically significant.

RESULTS

Age distribution: A total of 53 subjects were included in the final analysis. Nine (17%) patients were aged between 30-40 years, 17 (32.1%) participants were aged between 41-50 years, 16 (30.2%) patients were aged between 51-60 years, 8 (15.1%) patients were aged between 61-70 years, and 3 (5.7%) patients were aged between 71-80 years. Average age of the study sample was 51.7 ± 11.5 years.

Among the study population, 31 (58.5%) patients belonged to the C category (Heterogeneously dense breast parenchyma), and 22 (41.5%) patients belongs to the D category (Extremely dense breast parenchyma).

Lesion classification according to BI-RADS grading by combined three modalities: Among the study population, 3 (5.7%)



[Table/Fig-3]: Bar diagram depicting Outcomes of DM, DBT and CEM in assessing lesion detection.

CEM detected all 24 additional lesions proven by histopathology [Table/Fig-5].

Receiver Operating Characteristic (ROC) curves based on combined BI-RADS assessment by three modalities showed very good tests for detecting malignancy. Area under the curve was 0.88 (95% CI: 0.75-1.00). The cut-off combined BI-RADS value for predicting

Size evaluation	Size (in Volume)	p-value
DM	7.8 (3.9-18.4)	0.002
Histopathology	5.6 (2.2-22.5)	
Size evaluation	Size (in Volume)	p-value
DBT	6.4 (2.7-13.8)	0.005
Histopathology	5.6 (2.2-22.5)	
Size evaluation	Size (in Volume)	p-value
CEM	6.2 (2.6-17.8)	0.034
Histopathology	5.6 (2.2-22.5)	

[Table/Fig-4]: Comparison of lesion size in DM, DBT and CEM with histopathology size.
Mann Whitney U test was used

The drawbacks of DM in detection of lesions in dense breast with increase in FP and FN values and decreased sensitivity, led to the development of DBT and contrast mammography [5]. According to Chiu SYH et al., sensitivity of mammography in dense breast was 62.8% compared to 82% in fatty breasts; likewise, there was a reduction in specificity as reported by 89.6% in dense breasts compared to 96.5% in fatty breast [19]. Present study, had a sensitivity of 76.7% sensitivity and 60% specificity by DM. Von Euler-Chelpin M et al., reported that the sensitivity of mammography in fatty breast parenchyma was 80%, which markedly reduced to 41% in dense breasts [20]. Present study found that the diagnostic performance of CEM in cancer detection was higher compared to both DBT and DM. In line with demonstrated increase in sensitivity,

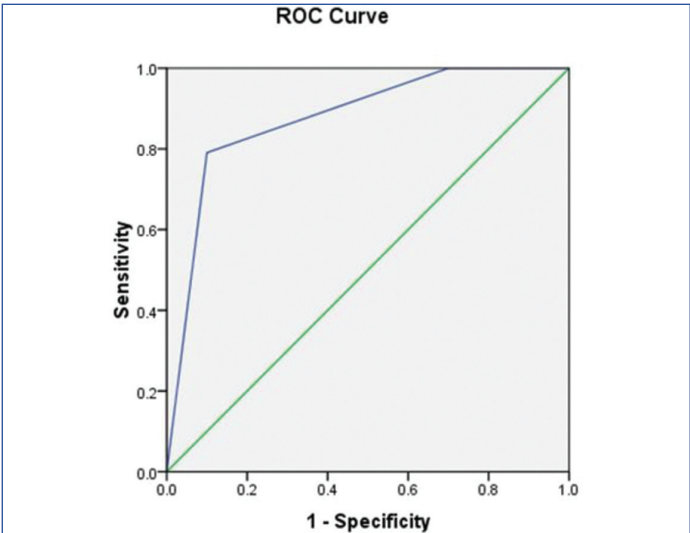
DM	Gold standard		Sensitivity	Specificity	PPV	NPV	Accuracy
	Present	Not present					
Detected	8	0	33.3%	100.0%	100.0%	64.4%	69.8% 95% CI (60.8-78.8%)
Not detected	16	29					
DBT	Gold standard		Sensitivity	Specificity	PPV	NPV	Accuracy
	Present	Not present					
Detected	12	0	50.0%	100.0%	100.0%	70.7%	77.4% 95% CI (69.2-85.6%)
Not detected	12	29					
CEM	Gold standard		Sensitivity	Specificity	PPV	NPV	Accuracy
	Present	Not present					
Detected	24	0	100.0%	100.0%	100.0%	100.0%	100.0% 95% CI (100-100%)
Not detected	0	29					

[Table/Fig-5]: Diagnostic indices for detecting additional lesions by DM, DBT and CEM.

malignancy was found to be four, with a sensitivity of 79.1% and specificity of 90.0% [Table/Fig-6,7]. A few representative images are shown in [Table/Fig-8,9].

AUC	95% CI	p-value	Cut-off	Sensitivity	Specificity
0.88	0.75-1.00	0.001	4	79.1%	90.0%

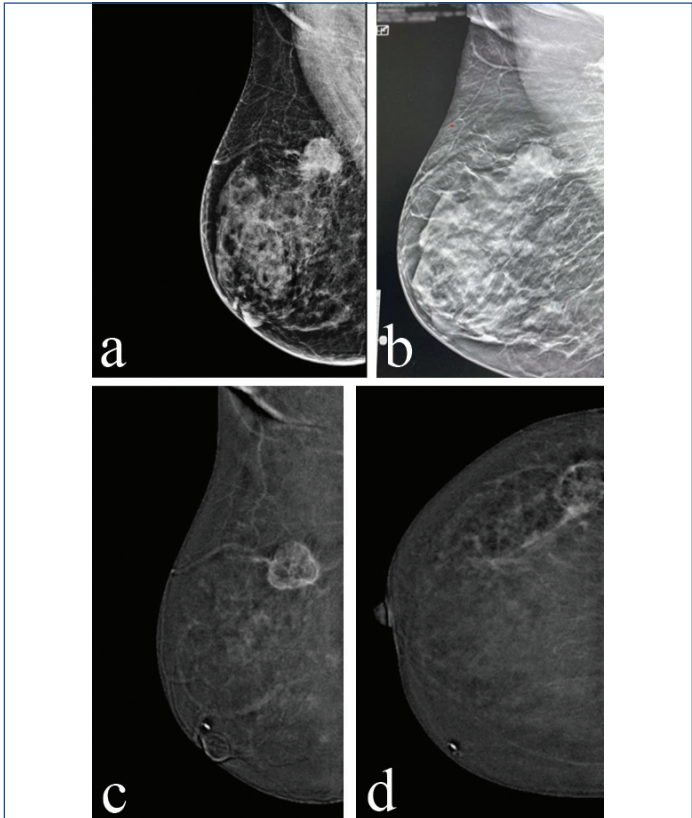
[Table/Fig-6]: Prediction of malignancy using combined BIRADS grading by three modalities.
Chi-square test was used



[Table/Fig-7]: ROC curve based on combined BIRADS assessment by three modalities

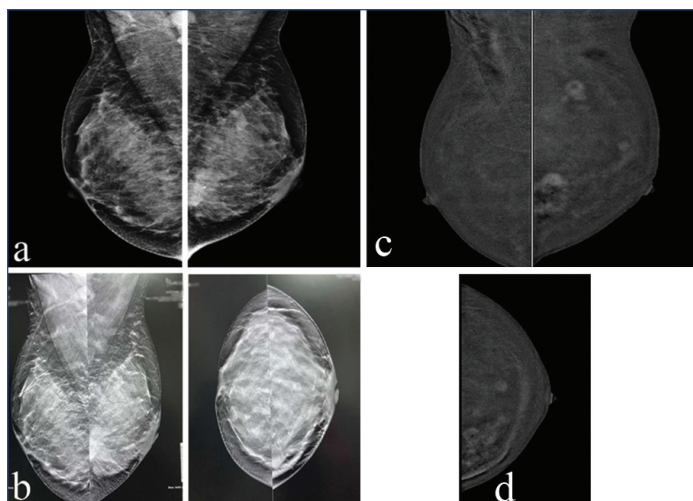
DISCUSSION

Mammographically dense breast tissues have a higher composition of stroma, higher relative gland counts and a lower proportion of fat than low mammographic density counterparts, thus increasing the risk of developing breast cancer. Fat appears dark on mammogram, whereas breast epithelium and stroma appears light which is referred to as mammographic density [18].



[Table/Fig-8]: 45 year old patient presented with right breast lump (a) DM in MLO view of right breast shows heterogeneously dense breast parenchyma (ACR C). Upper outer quadrant shows a relatively well defined high density lesion without any calcifications within. (b) DBT MLO view of right breast shows right upper outer quadrant mass with well defined borders. (c) CEM MLO view shows moderate heterogenous enhancement of the lesion in right upper outer quadrant with few peripheral enhancing spiculations. (d) Delayed CEM CC view of right breast shows non peripheral heterogenous wash out. Trucut biopsy revealed High grade Invasive ductal carcinoma.

PPV, and diagnostic accuracy in the studies of Girometti R et al., showed that CESM improves detection of index lesions significantly



[Table/Fig-9]: 30 year old patient presented with left breast lump (a) DM MLO views of right and left breast showing extremely dense breast parenchyma. DM MLO view of left breast showed irregular spiculated heterogeneously high density lesion in lower inner quadrant with multiple punctate microcalcifications within. Retroareolar dermal thickening with nipple retraction of left breast noted; (b) DBT MLO views of right and left breast showed irregular spiculated high density lesion in lower inner quadrant approx. 3.3x1.7 cm with multiple punctate microcalcifications; (c) CEM MLO views of both breasts showed heterogenous predominantly peripheral enhancement of the lesion. Additionally multiple enhancing lesions are noted in upper outer and retroareolar regions measuring 13x10 mm and 8.4x6 mm - possibly satellite lesions; (d) Delayed CEM CC view of left breast shows mild heterogenous wash out of the lesions. Trucut biopsy revealed Invasive ductal carcinoma with high grade ductal carcinoma in situ in solid and comedo pattern in satellite lesions.

[15]. CEM achieved higher CDR than DM+DBT for additional lesions, most of which were ≤ 1.0 cm in size, and mainly in the setting of dense breasts [15] which may influence surgical planning for BC. However, there was no added value in the subset of non dense breasts, suggesting that in large-volume centers, adding preoperative CEM might be indicated in the case of dense breasts.

According to Azzam H et al., adding contrast to the mammography improved diagnostic indices, with a sensitivity of 89%, specificity of 89%, PPV of 91%, NPV of 86%, and a diagnostic accuracy of 89% for CESM [5]. In current study, CESM detected 53 lesions, which included 3 cases categorised as BI-RADS 3, 11 (BI-RADS 4a), 1 (BI-RADS 4b), 3 (BI-RADS 4c), and 35 (BI-RADS 5). Out of which 43 cases were proven malignant and 10 were proven benign by histopathology. Thereby CEM had a sensitivity of 100%, PPV of 81%, and a diagnostic accuracy of 81%.

Sung JS et al., showed 87.5% sensitivity and a specificity of 93.7% for Contrast-Enhanced Digital Mammography (CEDM), compared to a sensitivity in DM while screening women at increased risk for breast cancer. Thus suggests that CEDM has the potential to be an alternative screening technique to 2D full-field DM in women at increased risk of breast cancer [21].

According to Sorin V et al., Contrast-Enhanced Spectral Mammography (CESM) increased CDR beyond that of mammography, with an incremental cancer detection rate of 13.1 per 1,000 screens, which was higher than what was reported for supplemental whole-breast US, thereby concluding the potential of CESM as a supplemental screening imaging modality for women at intermediate breast cancer risk and women with dense breasts [12].

Mori M et al., performed studies comparing the diagnostic accuracy of contrast-enhanced spectral mammography to conventional full-field DM in a population of women with dense breasts. They proved CESM is superior to conventional mammography alone for detecting breast cancer, with a higher accuracy of 90.9% [16].

In a study conducted by Takahashi TA et al., it was found that DBT increases CDR and reduces recall rates by masking the tissue overlap and noises which were the main drawbacks encountered in DM [22].

A study by Azzam H et al., showed 86% sensitivity of 86%, specificity, 86% PPV, 81 % NPV and a diagnostic accuracy of 84% [5]. Phi XA

et al., showed that DBT increased the CDR in both screening and diagnosis; however, it did not showed significance in specificity in diagnosis, like present study [23]. The results of present study were matching with Bian T et al., and Asbeutah AM et al., results in which they found that DBT showed increased sensitivity and specificity compared to mammography in dense breasts [13,24].

All these three modalities, including CEM, DM and DBT, overestimated cancer size preoperatively when compared to histopathological size. However, near-accurate values were obtained by CEM. Girometti R et al., used multireader comparison study for evaluation of lesion and they obtained comparable results from CEM and the combination of DM and DBT in cancer size assessment, according to Bland-Altman analysis [15]. No overestimation of lesion size was obtained by Girometti R study as contrary to Sumkin JH et al., who found an overestimation of lesion size by MRI, Molecular Breast Imaging (MBI), and CEM [25]. The frequency of overestimation was less by CEM (11%) compared to 15% by MBI and 24% by MRI.

But Helal MH et al.'s study were slightly different. They found DBT as better modality for predicting cancer size [26]. According to Helal MH et al., who compared CEM to DM and DBT in 98 women with dense breasts, the CDR of additional lesions were 0.92 by CEM, 0.53 by DM, and 0.77 by DBT. Present study results were also comparable to the results of Helal MH et al., [26].

CEM can be a suitable alternative for DM and DBT in the detection of lesions and size assessments in dense breasts. But, the majority of index lesions were picked up even by DBT. Only advantage of CEM is the evaluation of additional lesions in dense breasts. Ductal distribution of calcifications which is a marker of carcinoma, cannot be detected by CEM alone. This limitation that should be accounted before implementing CEM as the alternative. Other disadvantages were high cost and invasive nature of the procedure due to the use of contrast agents.

Limitation(s)

First, the study population was very small, possibly due to the minority of dense breasts; therefore, further studies with more sample size, including more trial centres, are required for complete validation of the results. Secondly, this study had a limitation of detection of calcifications by the modalities, so need for more studies that comparing the diagnostic performance of each modalities in terms of the morphological shape and pattern of calcifications. Third, there was a difference in preoperative lesion size by three modalities from histopathological size. This discrepancy might be partially due to discrepancy in measurement methods in imaging and histopathology.

CONCLUSION(S)

Among the three modalities, CEM had superior diagnostic accuracy in detecting malignancy and has better diagnostic performance in evaluating preoperative lesion sizes than DM and DBT). Finally, CEM achieved a higher additional lesion detection rate than both DM and DBT.

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