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# Adding the merits of contrast to the ease of mammography; can we highlight what's behind breast asymmetries?

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## Abstract

**Background:** Breast symmetry is one of the major things that radiologists assess when looking at mammograms and is one of the most challenging mammographic findings to evaluate. Contrast-enhanced spectral mammography (CESM) is an emerging mammography technique that has shown comparable sensitivity and specificity to MRI. The purpose of this study is to assess the value of CESM in characterization of breast asymmetries (BAs) and if it should be incorporated in its diagnostic work-up.

**Results:** Three hundred sixty-five patients with mean age of 47 years were included in the study. CESM was performed aiming for characterization of 380 *suspicious* or *indeterminate* breast asymmetries. Assessment of subtracted high-energy images (HEI) markedly improves the overall accuracy reaching 88.4%. Further improvement of the overall accuracy was achieved on combined assessment of the low-energy images (LEI), subtracted high-energy images (HEI), and ultrasound reaching 91.3%.

**Conclusion:** CESM is considered as a valuable complementary imaging tool considering the evaluation of breast asymmetries and should be incorporated in its diagnostic work-up in cases not resolved on an initial combined mammography and targeted ultrasound study especially in the presence of a heterogeneous dense breast parenchyma. Yet, this may be hindered in the presence of inflammatory signs because of the overlapping imaging criteria.

**Keywords:** Contrast-enhanced spectral mammogram, Breast asymmetry

## Background

Breast symmetry is one of the major things that radiologists assess when looking at mammograms, and it has been renowned for improved ease and accuracy of mammography interpretation. Radiologists usually perceive both breasts as symmetric in size and distribution of fibroglandular tissue [1, 2]. Breast asymmetries (BAs) can be quite normal and are often secondary to variations in normal breast tissue. Nevertheless, in some cases, they may indicate an underlying serious pathology [1, 3].

Breast asymmetries are one of the most challenging mammographic findings to evaluate, and they often

entail further assessment with additional mammography views and a targeted ultrasound study [4–6]. Ultrasound can provide useful information when a correlate is found, but the situation becomes complicated when no correlate is identified and an underlying malignancy could not be dismissed. Further imaging such as dynamic contrast-enhanced MRI might be requested, and sometimes, a short-term follow-up protocol may be adopted in less suspicious asymmetries [7–9].

Contrast-enhanced spectral mammography (CESM) is an emerging mammography technique that has shown comparable sensitivity and specificity to MRI, yet potentially, it is easier, faster, and more cost-effective [10]. The purpose of this study is to assess the impact of incorporating CESM in the characterization and diagnostic work-up of BAs.

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## Methods

The study is a prospective analytical study which included 365 females with 380 BAs. The study was approved by the ethical committee of a multidisciplinary “Breast Cancer Hospital,” and an informed written consent was taken from all subjects.

## Subjects

The subjects in this study were females with indeterminate and suspicious BAs that were not completely resolved with mammography and ultrasound. The commonest complaint for younger age group was mastalgia followed by breast lump, while in older age group, it was mostly following screening mammogram. Mammograms performed were both diagnostic and screening exams. CESM was requested aiming both for asymmetry characterization and for identifying the extent of underlying lesions.

## Technique of CESM

A single shot of 1.5 mL/kg of non-ionic iodinated contrast agent was injected. Compression was then applied starting by the contralateral side of concern to increase the likelihood of contrast uptake by the breast of concern. A pair of low (26–30 kVp) and high (45–49 kVp) energy exposures during each mammographic position was taken. A weighted subtraction was performed automatically generating an image with enhanced conspicuity of contrast agent uptake.

## Image evaluation

Distinct analysis of the low- and the high-energy images was accomplished by independent double reading by 2 different breast imaging radiologists with at least 10 years' experience in mammography and 5 and 7 years' experience in contrast mammography. Readers were blinded to each other's analysis and to ultrasound results. In case of disagreement between the two radiologists, the mammograms were re-evaluated in consultation and agreement was achieved. Findings were then correlated with histopathology results of core and operative specimens and/or follow-up outcomes for at least 18 months to ascertain a benign diagnosis.

The *low-energy mammography images (LEMI)* were evaluated in accordance to the 2013 mammography BI-RADS lexicon [5], the breast density was recorded, the type of asymmetry was specified (single view, global, focal, or developing), and the associated features were reported (microcalcifications, skin thickening, associated parenchymal distortion, and axillary lymph node status).

The *contrast images* were evaluated in accordance to the 2013 MRI BI-RADS lexicon as there is no CESM-specified lexicon [11]. The degree of background parenchymal enhancement (BPE) was recorded, and lesions

were classified into non-enhancing and enhancing (focus, mass, and non-mass). Breast asymmetries with underlying non-enhancing lesions and enhancing lesions showing benign morphology descriptors were classified as *benign* and were subjected to a short-term follow-up study for at least 18 months. Lesions that showed an increase in size or conspicuity on follow-up studies were biopsied. Asymmetries with underlying enhancing lesions showing malignant morphology descriptors were subjected to immediate core biopsy.

## Statistical analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using frequency (count) and relative frequency (percentage) for categorical data. Standard accuracy measures including positive and negative likelihood ratios and overall accuracy were calculated for the different diagnostic tests. The degree of uncertainty of the accuracy measures was described by calculating the 95% confidence interval (CI). For comparing categorical data, chi-square ( $\chi^2$ ) test was performed. *p* value less than 0.05 was considered significant.

## Results

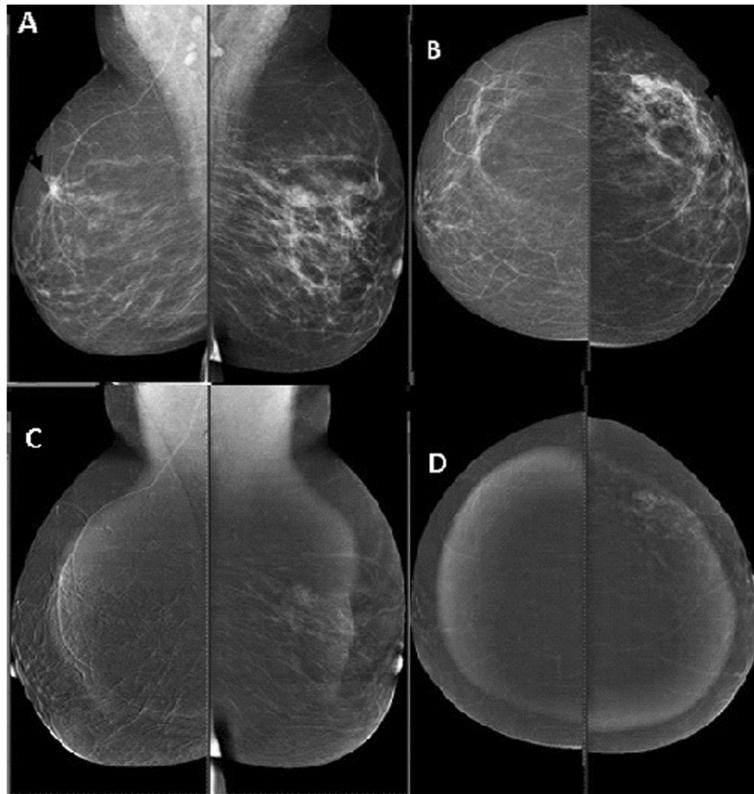
We prospectively analyzed the CESM findings of 380 *suspicious* or *indeterminate* BAs in 365 patients who attended a “Multidisciplinary Breast Cancer Hospital.” Fifteen patients had multiple lesions: 5 patients presented 2 asymmetries in the same breast and 10 patients presented bilateral asymmetries (Fig. 1). Their ages ranged from 29 to 69 years (mean age 47 years).

According to *histopathology results* and outcomes of *follow-up* studies, 35/380 (9.2%) asymmetries were overlapping tissues, 88/380 (23.2%) were benign lesions, and 257/380 (67.6%) were malignant lesions. Biopsy was performed for 286 asymmetries: instantly in 269 cases and postponed to the follow-up study in 17 cases that showed an increase in lesion size and/or conspicuity (Table 1).

The breast density was assessed on the LEMI: 100/365 (27.4%) cases were classified as ACR “a” or “b” and 265/365 (72.6%) were classified as ACR “c” or “d.”

Asymmetries were then classified into single view (20/380, 5.3%), global (128/380, 33.7%), focal (228/380, 60%), and developing (4/380, 1%). The presence of a global, focal, or developing asymmetry strongly correlated with an underlying malignant pathology (*p* value 0.001; Table 2). Associated mammography findings (edema, skin thickening, parenchymal distortion, and calcifications) were seen in 106/365 (29%) cases.

On evaluating the LEMI, a considerable number of false-negative (44/380, 11.6%) and false-positive (66/380, 17.4%) asymmetries were encountered. The commonest



**Fig. 1** Right breast focal asymmetry (straight arrow) (a). Left breast global asymmetry (curved arrow) (b). The right breast asymmetry was an adenotic nodule and did not show contrast uptake (c) while the left breast asymmetry was an invasive lobular carcinoma and showed heterogeneous non-mass contrast uptake (d)

**Table 1** Classification of the 380 breast asymmetries according to histopathology results and outcome of follow-up studies

Pathology	Number	Percentage
Normal overlapping parenchyma	35	9.2
Benign pathology	88	22.4
- Fibroadenoma	21	23.9
- Inflammatory lesion	24	27.2
- Fibroadenosis	16	18.2
- Fibrocystic changes	14	15.9
- Benign precancerous	5	5.7
- Operative bed	8	9.1
Malignant pathology	257*	68.4*
- DCIS	16	6.3
- IDC	202	78.6
- ILC	25	9.7
- Others	14	5.4

\*Underlying malignant lesions are significantly higher than normal and benign lesions ( $p < 0.001$ )

cause for the false-negative asymmetries is the heterogeneous dense breast parenchyma (27/44, 61.4%). The commonest causes of false-positive asymmetries are the heterogeneous dense breast (23/66, 34.8%) and the inflammatory breast lesions (21/66, 31.8%) (Table 3). The LEMI showed a positive and negative likelihood ratio of 1.54 (95% CI 1.30–1.84) and 0.37 (95% CI 0.27–0.51), respectively, and an overall accuracy of 71% (95% CI 66.2–75.5) (Table 4).

On performing a targeted ultrasound examination, *no ultrasound correlate* was seen in 90/380 (23.7%) asymmetries, an *indeterminate ultrasound correlate* was identified in 61/380 (16%) asymmetries, and a *probably malignant ultrasound correlate* was identified in 229/380 (60.3%) (Figs. 2 and 3). The heterogeneous dense parenchyma and inflammatory breast lesions still constitute

**Table 2** Correlation between the type of asymmetry and its characterization

	Simple		Global		Focal		Developing	
Normal	7	35%	5	3.9%	23	10.0%	0	–
Benign	4	20%	26	20.3%	58	25.4%	0	–
Malignant	9	45%	97	75.8%	147	64.6%	4	100%
Total	20	100%	128	100%	228	100%	4	100%

**Table 3** Comparison between the number and frequency of the false-positive and false-negative lesions using the different imaging modalities

	Mammography	Sonomammogram	CESM	Combined
False-negative lesions	44 lesions	28 lesions	14 lesions	3 lesions
• Heterogeneous dense parenchyma	27/44, 61.4%	20/28, 71.5%	–	–
• Single view asymmetries	8/44, 18.2%	1/28, 3.6%	–	–
• Operative bed recurrence	4/44, 9.1%	2/28, 7.1%	–	–
• Non-calcified DCIS	3/44, 6.8%	3/28, 10.7%	–	–
• Bilateral asymmetries	2/44, 4.5%	2/28, 7.1%	–	–
• Non-enhancing malignant lesions	–	–	9/14, 64.3%	2/3, 66.6%
• Faintly enhancing lesions	–	–	5/14, 35.7%	1/3, 33.4%
False-positive lesions	66 lesions	46 lesions	30 lesions	30 lesions
• Heterogeneous dense breast	23/66, 34.8%	15/46, 32.6%	–	–
• Inflammatory lesions	21/66, 31.8%	15/46, 32.6%	17/30, 56.7%	17/30, 56.7%
• Benign masses	11/66, 16.7%	5/46, 10.9%	–	–
• Benign precancerous lesions	4/66, 6.1%	4/46, 8.7%	3/30, 10.0%	3/30, 10.0%
• Asymmetric breasts	4/66, 6.1%	4/46, 8.7%	–	–
• Operative bed scarring	3/66, 4.5%	3/46, 6.5%	–	–
• Benign enhancing lesions	–	–	10/30, 33.3%	10/30, 33.3%

the majority of cases. After adding the targeted ultrasound evaluation, the number of false-negative and false-positive cases was reduced to become 28/380 (7.8%) and 46/380 (12%), respectively. Combining the results of targeted ultrasound and LEMI showed a positive and negative likelihood ratio of 2.38 (95% CI 1.89–3.01) and 0.17 (95% CI 0.12–0.25), respectively, and an overall accuracy of 80.53% (95% CI 67.18–84.3).

The first step in evaluating the contrast images was to assess the correlation between the breast density and the background parenchymal enhancement (BPE). A very weak positive correlation coefficient was calculated between the breast density and the intensity of the BPE ( $R$  0.3704,  $p$  value 0.00001) as 300/365 (82.2%) cases showed minimal and mild BPE in comparison to only 65/365 (17.8%) cases that showed moderate and severe BPE.

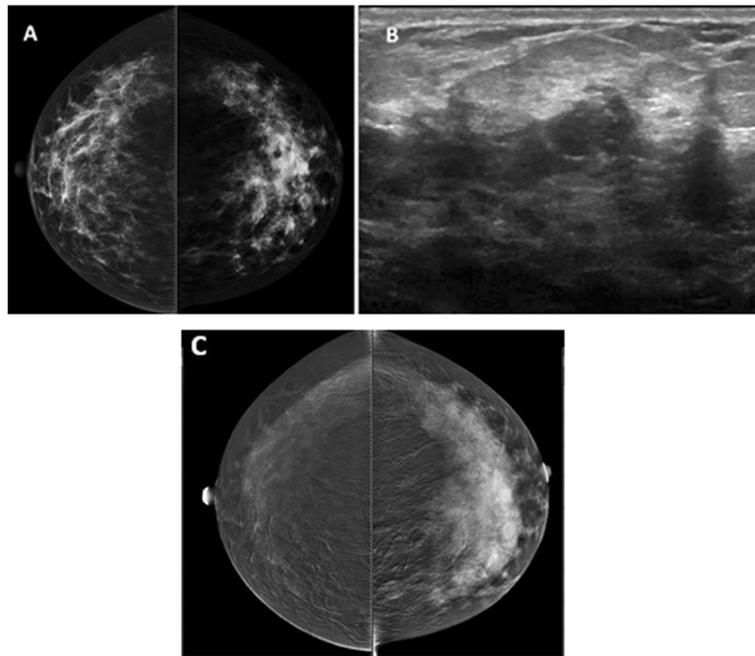
Contrast enhancement was identified in 293/380 asymmetries. The presence of enhancing lesions underlying asymmetries was significantly higher in malignant than in benign lesions ( $p$  value 0.05).

After evaluating the contrast images, the number of false-negative and false-positive cases was further reduced to become 14/380 (3.7%) and 30/380 (7.9%), respectively. Non-enhancing malignant tumors (9/14, 64.3%) constituted the majority of false-negative results, and the inflammatory breast lesions (17/30, 56.7%) and enhancing benign lesions (10/30, 33.3%) constituted the majority of false-positive cases. The calculated positive and negative likelihood ratio of the contrast images was 3.88 (95% CI 2.84–5.30) and 0.07 (95% CI 0.04–0.12), respectively, and an overall accuracy was 88.4% (95% CI 84.7–91.4) (Table 4).

The actual extension of malignant asymmetries for staging and pre-operative planning was also evaluated on the contrast images (Fig. 4). Additional lesions within the same breast were encountered in 5/257 malignant asymmetries, and in the contra lateral breast in 10/257 malignant asymmetries. A wider extension was also identified on the contrast images in 42/257 asymmetries (Figs. 3 and 4).

**Table 4** The positive predictive value, negative predictive value, and overall accuracy of different imaging modalities in assessment of breast asymmetries

	Positive predictive value	Negative predictive value	Overall accuracy (%)
Mammography	1.54	0.37	71
Sonomammography	2.38	0.17	80.53
CESM	3.88	0.07	88.4
Combined	4.05	0.02	91.32



**Fig. 2** Global asymmetry of the left breast (a). Ultrasound showed subtle diffusely altered parenchyma (indeterminate ultrasound correlate) (b). CESM showed diffuse heterogeneous malignant non-mass enhancement (c). Biopsy revealed invasive lobular carcinoma

Combining the assessment of the contrast images and complementary ultrasound reduced the false-negative lesions (3/380, 0.78%) and had no effect on the false-positive lesions (30/380, 7.9%) that were mainly attributed to the inflammatory breast lesions (17 cases) (Fig. 5). The calculated positive and negative likelihood ratio of the combined assessment was 4.05 (95% CI 2.97–5.53) and 0.02 (95% CI 0.00–0.05), respectively, and an overall accuracy was 91.32% (95% CI 88.02–93.95).

## Discussion

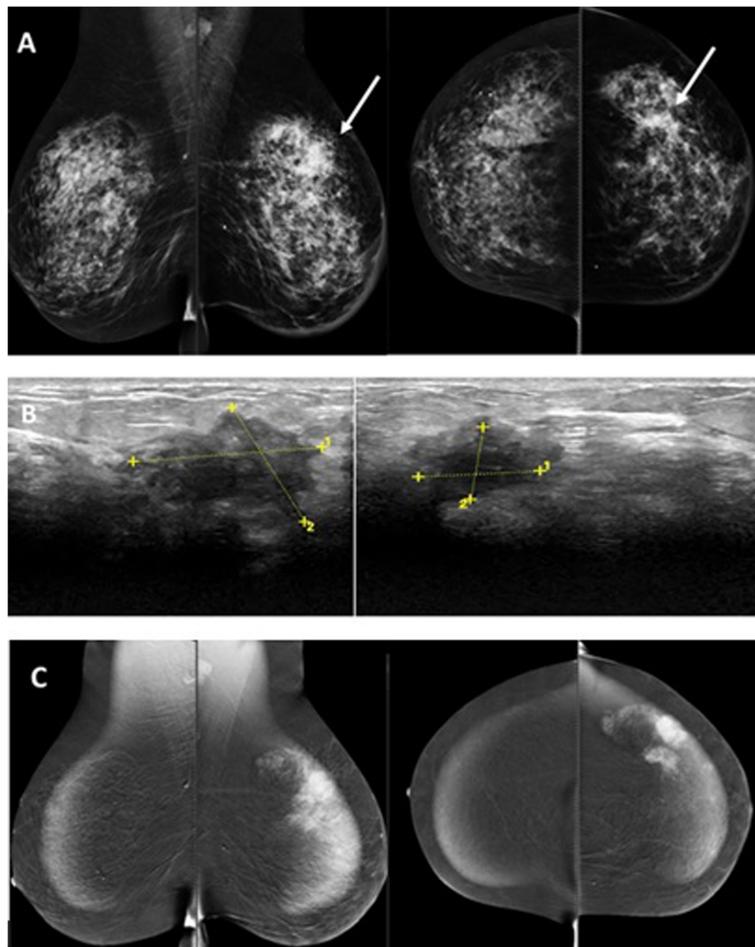
The diagnostic work-up of BAs poses a diagnostic challenge. When asymmetries appear on mammograms, they usually entail further assessment by supplementary imaging tools including extra mammography views, breast ultrasound, and sometimes even MRI [3].

The advanced mammography techniques have offered less expensive and less time-consuming alternatives to MRI. One of these techniques is the CESM which has comparable sensitivity and specificity to MRI. CESM combines the *ease* and the ability of digital mammography to characterize microcalcifications together with the *merits* of contrast injection and high sensitivity of MRI [12]. Previous studies have proved that CESM is superior to mammography in the identification of multiplicity, extent, and size of malignant lesions especially in the dense breast parenchyma [10, 13–15].

In the current study, we aimed to assess the impact of incorporating CESM in the characterization and diagnostic work-up of BAs in 365 females with 380 indeterminate and suspicious asymmetries, with and without an ultrasound correlate. This explains the significantly higher number ( $p$  0.001) of malignant lesions (257/ 380, 68.4%) than what was reported in previous studies [16–18].

The authors started the analysis of the LEMI by reporting the breast density with high-density breasts constituted the majority (72.6%) of the cases. The low-energy mammography images showed a positive and negative likelihood ratio of 1.54 and 0.37, respectively, and an overall accuracy of 71%. The poor results were mainly attributed to the predominant heterogeneous dense breast parenchyma among the study population which resulted in both over- and underestimation of the nature of BAs. The associated diffuse edema pattern that accompanied inflammatory breast lesions also increased the number of misinterpreted lesions resulting in 21/66 false-positive cases (31.8%).

The role of incorporating ultrasound in the evaluation of breast asymmetries is not clearly defined in literature. Targeted ultrasound examination is usually performed to clarify the benign or malignant lesions underlying breast asymmetries. The presence of an underlying ultrasound correlate increases the level of suspicion for malignancy. However, in a study performed by Leung and Sickles [19], they affirmed that the lack of a ultrasound



**Fig. 3** Focal asymmetry associated with diffuse skin thickening (arrow) in a heterogeneous dense parenchyma seen in CC and MLO views (a). An evident underlying malignant ultrasound correlate was seen (b). CESM was performed to identify the actual extent of the malignant lesion (c). Wider tumor extension was identified on the contrast images. Biopsy revealed IDC2

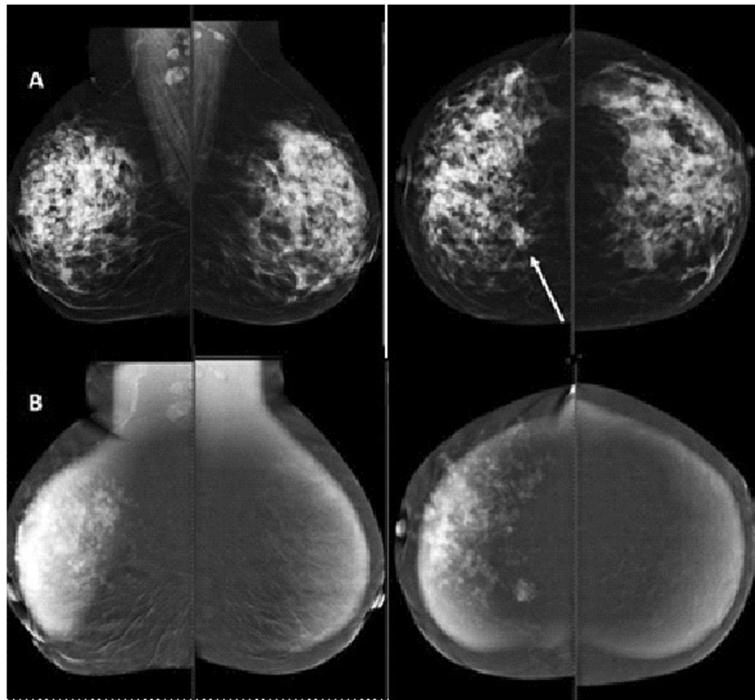
(US) correlate which was reported in 5/21 malignant lesions in their study should not exclude biopsy or further imaging.

In the current study, the authors reported no ultrasound correlate in 90/380 (23.7%) BAs, an indeterminate ultrasound correlate in 61/380 (16%) BAs, and a malignant correlate in 229/380 (60.3%) BAs. Adding ultrasound improved the overall accuracy of assessment to become 80.5% with the heterogeneous dense parenchyma and inflammatory breast lesions still contributing to a considerable number of FP and FN results.

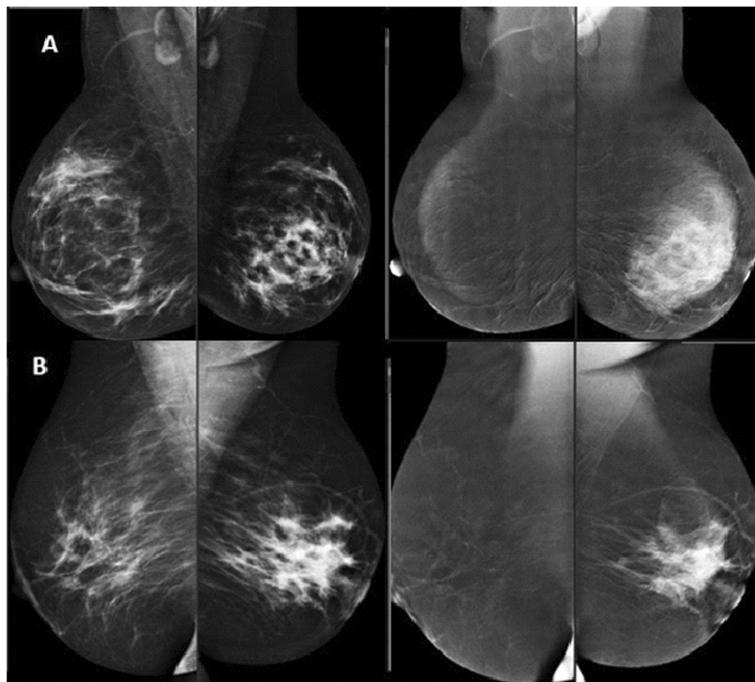
Lee and coauthors [10, 12, 13] found that MRI was a convenient modality for mammographic findings that were not adequately localized with mammography and US [20]. Areas showing enhancement may also guide for further biopsy intervention. CESM is an easier and cheaper alternative to mammography with comparable reported sensitivity and specificity.

In accordance to the study performed by Kamal and colleagues, the current study confirmed that non-enhancement strongly correlated with a benign pathology ( $p$  value 0.05) [21]. Another advantage of the contrast images over the mammography images is that the heterogeneous dense parenchyma did not correlate with a corresponding degree of BPE ( $R$  0.37,  $p$  value 0.00001). Similar correlation was reported in several studies addressing parenchymal enhancement on MRI [22–24]. The absence of parenchymal enhancement on the contrast images resulted in a significant drop in the FP and FN results with an overall accuracy reaching 88.5%. The calculated positive and negative likelihood ratio of the contrast images was 3.88 and 0.07, respectively.

The subtracted breast parenchyma allowed for better lesion extension and multiplicity identification. A wider extension was identified in 42 asymmetries, and additional lesions were identified in another 12 asymmetries;



**Fig. 4** Deeply seated lobular carcinoma presenting as a single view asymmetry (arrow) on the low-energy images in a heterogeneous dense breast parenchyma (a). A much wider tumor extension was identified on the contrast images (b). Patient management changed from conservative surgery to modified radical mastectomy



**Fig. 5** Two different false-positive inflammatory lesions on both the low- and subtracted high-energy images. Biopsy revealed granulomatous mastitis (a) and periductal mastitis (b)

this had a major influence on the accuracy of patient management.

Combining the sonomammography and contrast images had an impact on reducing the false-negative results, but no similar impact was perceived on the false-positive results. This was mainly attributed to the intense enhancement that accompanied inflammatory breast lesions in a pattern that mimicked malignant lesions. The overall accuracy of the combined assessment reached 91.8%.

## Conclusion

Combining the *ease* of doing a mammogram and the *merits* of contrast, CESM should be considered in the diagnostic work-up of breast asymmetries not resolved on an initial combined mammography and targeted ultrasound study especially in the presence of a heterogeneous dense breast parenchyma. CESM helps in asymmetry characterization and can help in identifying the actual size, multiplicity, and extension of malignant lesions. However, the accuracy of CESM becomes questionable in the presence of inflammatory breast lesions due to the overlap of enhancement patterns between inflammatory and malignant lesions.

## Abbreviations

BA: Breast asymmetries; BPE: Background parenchymal enhancement; CESM: Contrast-enhanced spectral mammogram; HEMI: High-energy mammography images; LEMI: Low-energy mammography images; US: ultrasound

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## Authors' contributions

RK wrote the manuscript. AM collected the patient data and is responsible for the correspondence to journal. SF contributed to the image processing and collection of patient images. EK participated in the design of the study and performed the statistical analysis. AR conceived of the study, participated in its design and coordination, and helped to draft the manuscript. AH was responsible for the revision of the draft from clinical point of view. MH contributed to the surgical data collection and statistical analysis. All authors have read and approved the manuscript.

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## Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The study was approved by the ethical committee of a multidisciplinary "Breast Cancer Hospital," and informed written consent was taken from all subjects.

## Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study.

## Competing interests

The authors declare that they have no competing interests.

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