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RESEARCH

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Postoperative breast cancer surveillance: Can contrast-enhanced spectral mammography solve the diagnostic dilemma?

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Abstract

Background For women worldwide, breast cancer is considered a significant public health concern. The development of enormous changes caused by surgery and irradiation makes diagnosing the postoperative breast a complicated procedure. The current study aimed to detect the additive role of contrast-enhanced spectral mammogram (CESM) to digital mammogram and US in the surveillance of postoperative breast cancer patients.

Methods This research was conducted on 74 female patients with a prior history of surgery for the treatment of previous breast cancer. All patients had undergone sonomammography and CESM. Benign lesions were followed up, while suspicious lesions were biopsied.

Results The current study revealed that CESM can enhance the sensitivity, specificity our overall accuracy of sonomammography in the surveillance of breast cancer patients after surgery.

Conclusion Adding CESM to properly selected patients in the surveillance of breast cancer patients after surgical treatment can enhance the diagnostic performance of conventional imaging modalities.

Keywords Surveillance, Contrast-enhanced mammography, Postoperative

Background

Worldwide, breast cancer affects women's public health significantly. About 29.1% of all deaths linked to cancer are coming from it [1].

In the last 20 years, oncologic and reconstructive breast surgery has markedly progressed. Therefore, radiologic analysis of previously treated breast cancer necessitates knowledge of cutting-edge surgical techniques and related imaging properties, which can assist in avoiding or minimizing false positive imaging findings [2].

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Patients previously treated for breast cancer undergo many changes. Those changes range from scarring, seromas, architectural distortion, and fat necrosis, as well as post-radiation changes that not only change with time but also can mask tumor recurrence [3].

As a result, the enormous variety caused by breast surgery and irradiation, as well as the need for a proper assessment to exclude recurrence; all make diagnosing the postoperative breast a complicated procedure [4].

Following treatment for primary breast cancer, women should get yearly mammography, according to current clinical guidelines. Results can be improved by using additional imaging "along with routine digital mammography," like breast ultrasonography (US), magnetic resonance imaging (MRI), and contrast-enhanced spectral mammography (CESM) [5].

Contrast-enhanced spectral mammography is considered a fast and reproducible method of assessment using breast dosages similar to those used in routine digital mammography. CESM as an additional tool to mammography ± US enhances the diagnostic performance by improving malignant lesion detection in contrast to mammography alone (± US) [6].

In our study, we aimed to detect the role of CESM in addition to digital mammography and the US in the assessment of breast cancer females after surgical interference. The capability of CESM improves lesion detection and reduces false positive and false negative cases, thus improving diagnostic performance in postoperative cancer surveillance.

Methods

Patients

The current study type was a prospective one carried over twenty-four months. Seventy-four breast cancer patients were enrolled in our study who performed previous breast surgery. Every patient was referred from the wards and "Surgical Breast Clinic" to the Women's Imaging Unit in our department.

Seven patients underwent modified radical mastectomy (MRM), while sixty-seven underwent breast conservative surgery (BCS). The age range was from 30 to 80 years (Mean age: 51.9 ± SD). All patients who were involved in our study were primarily examined by sonomammography and then were further evaluated by CESM. Our final diagnosis was reached based on the pathology assessment of fine needle aspiration, core biopsy, excisional biopsy, or surgical biopsy (for lesions designated as BIRADS 4 or 5), while lesions designated BIRADS 2 or 3, close follow-up was recommended after 6 months over a period of 18 months. The ethical committee granted our study approval, and informed written consent was delivered by patients who participated in our work.

Two experienced radiologists with around 10 years of expertise in specialized breast imaging procedures performed mammographic picture interpretation followed by CESM examinations. Inclusion criteria included all patients who were coming for evaluation after surgical treatment of previous breast cancer some of whom were coming for their annual screening, while others were coming with a complaint as pain or lump. Exclusion criteria involved patients who cannot undergo mammography, e.g., pregnancy or conditions where IV contrast is prohibited like renal impairment or a history of previous anaphylactic reaction to contrast media.

Methods

Conventional mammography

Full field digital mammogram (FFDM) was used to provide digital mammography for both breasts in both views "cranio-caudal (CC) and mediolateral oblique" (MLO) views. The machine used was the GE Senograph 2000.

Breast ultrasonography

A linear array transducer with frequency (8–12 MHz). (GE)—Logic 7 machine was used in scanning patients. The patient relaxed her arm and flexed it behind the head during radial scanning of both sides. While the patient was lying in the oblique contralateral position, outer quadrants as well as the axillary tail region were scanned. While in the supine position, medial lesions were examined.

CESM

The antecubital vein of the arm opposite to the affected breast was selected for catheter insertion. A single IV shot of 1.5 mL/body weight of contrast media "non-ionic" was injected "with a rate of 3 mL/s). After passing 2 min from the start of the examination, breast compression was performed in the (MLO) view; a pair of low as well as high-energy images was acquired with twenty seconds delay in between. Thereafter, new compression was done but in the (CC) position. Four minutes right after the start of administration of contrast, another new pair of low- and high-energy exposures were obtained. Finally, proper image modification is used for the generation of two iodine-enhanced images showing contrast uptake data, in MLO as well as in CC views.

Imaging analysis and interpretation

I. *On mammography*, lesions were examined based on their location, size, shape, margin, density, and calcifications. According to the 2013 BIRADS Atlas, we assigned a BIRADS category for each lesion [7].
II. *On ultrasound scanning* of lesions, shape, border, axis, echogenicity, and posterior acoustic criteria were all studied. The condition of the adjacent tissues was also considered. According to the Ultrasound BIRADS Atlas 2013, we allocated a BIRADS category concerning each lesion [7].
III. *In CESM* The size and type of enhancement of the lesions were assessed according to 2022 ACR BIRADS® ATLAS—MAMMOGRAPHY morphology descriptors [8].
IV. *Comparison with histopathological results (for lesions assigned as BIRADS 4 and 5)* FNA or true cut needle biopsy was used to biopsy lesions under

aseptic settings with US guidance (using needles 14–18-gauge), or patients were sent for surgical excision. Finally, histopathological results were collected. When pathology and cytology were not advised (as in lesions classified as BIRADS 2 and 3), follow-up was performed.

V. Statistical analysis

- Data were presented as range, frequencies (number of patients) as well as mean standard deviation (SD).
- The terms sensitivity, specificity, positive predictive value (PPV) as well as negative predictive value (NPV) were all used in our study to demonstrate accuracy.

Results

Seventy-four cases that performed previous breast cancer operations were involved in the current study. All cases performed sonomammography then were further examined by CESM. Out of those 74 patients, 19 patients (25.6%) were symptomatic (presenting with pain or lumps) compared to 55 patients (74.3%) who were asymptomatic at postoperative follow-up. Out of those 74 patients, 74 lesions were obtained.

The 74 lesions were classified by sonomammography into three groups based on the location of the lesions. The first group showed lesions in the operative bed (21/74) representing (28%) (Fig. 1). The second group showed newly discovered ipsilateral breast lesions (42/74) representing (57%) (Fig. 2). The third group showed lesions in the contralateral breast (11/74) representing (15%) (Fig. 3).

Regarding the spectrum of findings detected on sonomammography as shown in Fig. 4, masses were seen in 18 patients, asymmetries were found in 31 patients, suspicious microcalcifications in 9 cases, and postoperative changes were detected in 16 cases (Fig. 5). Lesions were further categorized into two groups based on their final diagnosis, which was determined by pathology results of FNA, biopsies and surgical samples, or consequent follow-up.

The malignant lesions group included 43/74 (58.1%) lesions, while the benign lesions group included 31/74 (41.9%).

Final diagnosis based on sonomammography: In the current study, 46/74 (62.2%) lesions were categorized as benign (BIRADS 2 and 3), and 28/74 (37.8%) lesions were categorized as malignant (BIRADS 4 and 5).

Diagnostic performance of sonomammography in the population studied: Following the correlation of sonomammographic results to the final diagnosis, 19 lesions were considered true positives (TP), 12 lesions were considered false positive (FP), 9 lesions were false negatives (FN), and 12 lesions were true negatives (TN).

Following the prior data, sonomammography showed a sensitivity of 67.86%, a specificity of 73.91%, a positive predictive value (PPV) of 61.29%, a negative predictive value (NPV) of 79.07%, a positive likelihood ratio of 2.60, negative likelihood ratio 0.43 and accuracy of 71.62% (Table 1).

CESM Findings: CESM images were reviewed to detect contrast uptake among the studied population. We found that 38/74 (51.4%) lesions showed contrast uptake, while lesions with no contrast uptake were 36/74 (48.6%).

Enhancing lesions were classified according to ACR BIRADS ATLAS (2022) [8] into enhancing masses 29/38 (76.3%) and non-mass enhancing lesions 9/38 (23.6%), while no enhancing asymmetries were found in our study.

Upon correlation with pathology results, 24/29 (82.7%) masses were malignant compared to 5/29 (17.2%) masses were benign. 8/9 (88.8%) lesions that showed non-mass enhancement (NME) were malignant compared to 1/9 (11.1%) was benign. Our study did not show any case of enhancing asymmetry.

The final diagnosis according to CESM revealed 46/74 (62.2%) lesions were classified as benign (BIRADS 2 and 3) and 28/74 (37.8%) lesions were classified as malignant (BIRADS 4 and 5).

Diagnostic performance of CESM in the population studied relating the CESM results to the final diagnosis results revealed that 25 lesions were categorized as TP, 3 were categorized as FP, 43 were categorized as TN, and 3 were categorized as FN.

Based on the aforementioned data, CESM revealed a sensitivity of 89.29%, a specificity of 93.48%, a PPV of 89.29%, a NPV of 93.48%, a positive likelihood ratio of 13.69, a negative likelihood ratio of 0.11, and finally an accuracy of 91.89%. (Table 1).

Discussion

It is challenging to evaluate the breast following surgery and radiotherapy and rule out recurrence [4].

Breast ultrasound and CESM are examples of surveillance imaging beyond routine digital mammography that may improve results [5].

Additionally, Bozzini A et al. [9] concluded in their study which was performed in the setting of dense breasts that CESM enhances the size assessment of malignant tumors that eventually will guide the selection of the type of surgery suitable for each patient.

The idea of contrast enhancement in CESM depends on the formation of new feeding vessels for tumors. Malignant cells take their nutrition through diffusion.

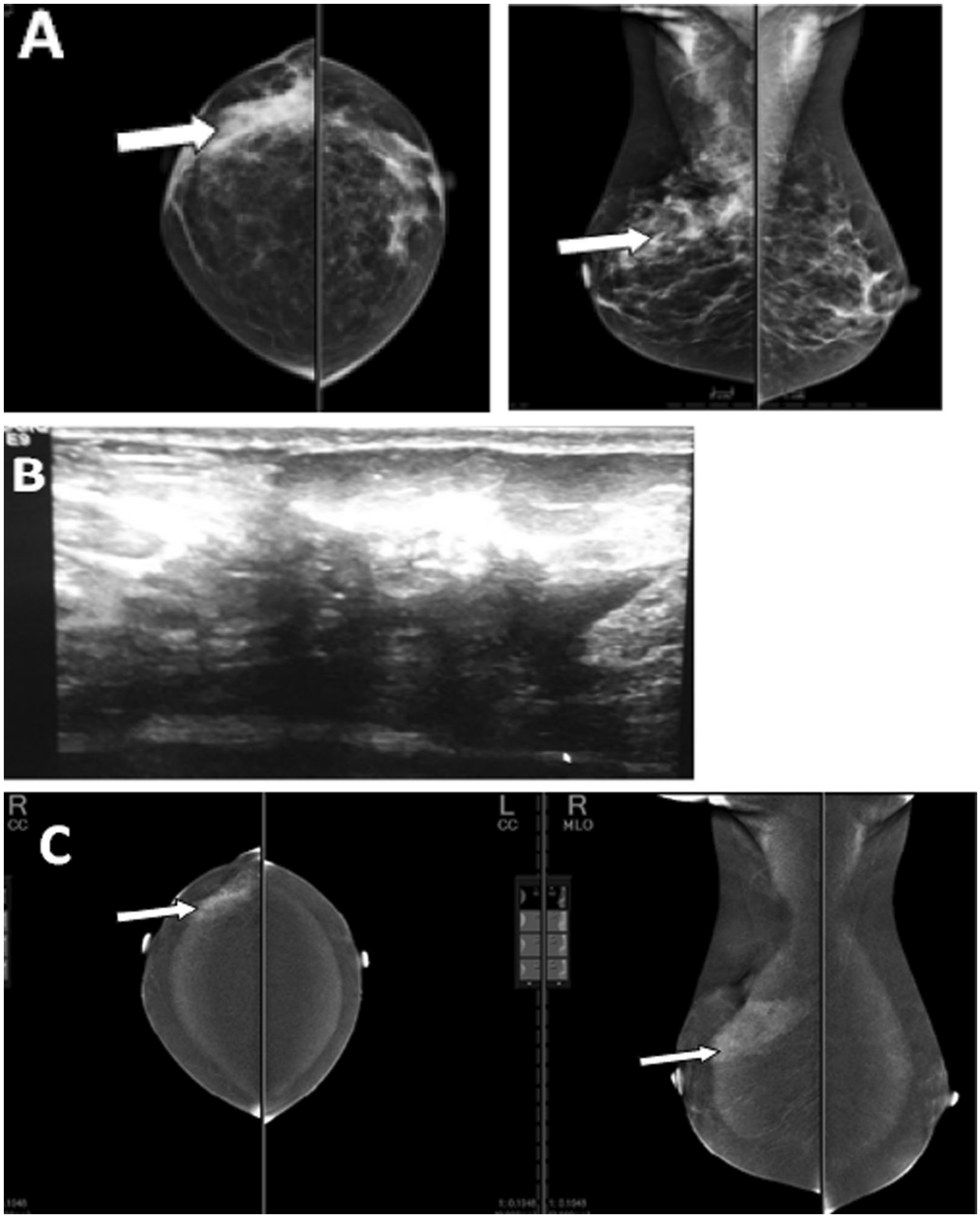

Fig. 1 A 40-year-old asymptomatic patient underwent right CBS for DCIS, presenting for annual follow-up. **A** Mammography (CC and MLO views) revealed: Breast density ACR 'b'. focal asymmetry is seen at right UOQ (white arrow). **B** Complementary ultrasound revealed: Right operative bed changes and scarring that showed no vascularity detected on color Doppler application. **C** Contrast-enhanced spectral mammography revealed: an operative bed segmental area of non-mass enhancement at UOQ of the right breast (white arrow). Final Diagnosis: Pathology: DCIS; operative bed recurrence. Final comment: In this case, sonomammography revealed evidence of extensive operative bed scarring. CESM revealed operative bed recurrence as well as showing the true extent of the lesion

As tumor increases in size, its demands increase releasing vascular growth factors promoting new blood vessel formation in a process called "angiogenesis." As new blood vessels proliferate rapidly, wide gaps between cells occur. Therefore, leaking of intravascular contrast material occurs, which fortunately allows more tumor cell delineation [10, 11].

So the purpose of this work was to detect the additive role of CESM in the surveillance of postoperative breast cancer survivors.

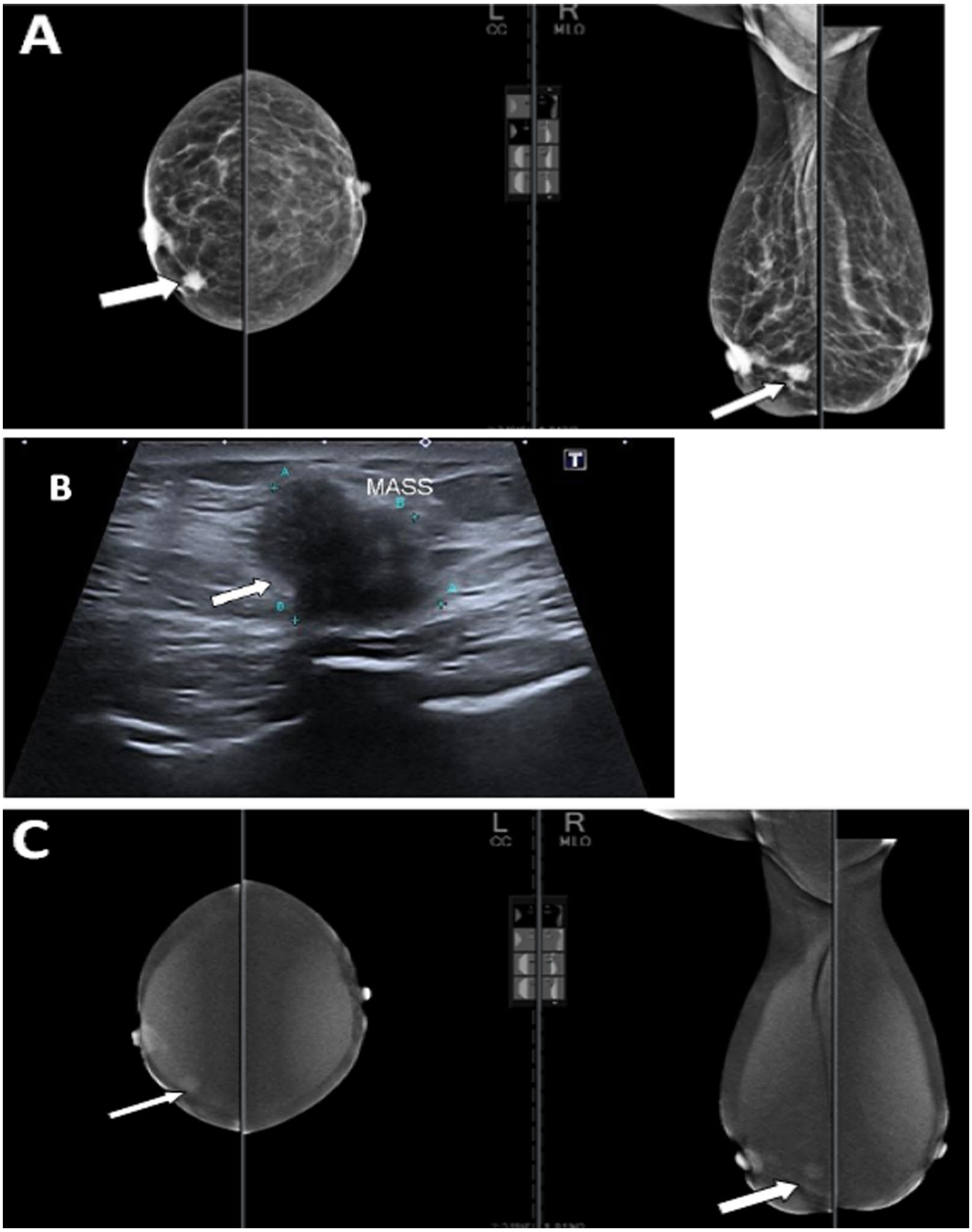

Fig. 2 A 64-year-old female patient underwent right CBS for IDC grade II, presenting with right LIQ palpable lump. **A** Mammography (CC and MLO views) revealed: Breast density ACR 'b'. A hyper-dense lesion in the right LIQ shows irregular borders and multiple speculations showing skin thickening and nipple retraction (white arrow). **B** Complementary ultrasound revealed: an ill-defined antiparallel hypoechoic mass lesion seen in the LIQ of the right breast. **C** Contrast-enhanced spectral mammography revealed: enhancing mass in the right lower inner quadrant with evidence of ductal extension (white arrow). Final Diagnosis: Pathology: IDC. Final comment: In this case, both sonomammography and CESM could detect ipsilateral newly developed malignant-looking lesion with CESM also confirmed intra-ductal extension

Seventy-four patients, who performed breast procedures due to breast cancer, were enrolled in our study population. Seven patients (9.5%) underwent MRM, and 67 patients (90.5%) underwent BCT. After completing a postoperative assessment by MG and ultrasonography, CESM was performed.

Regarding the sonomammographic results, 28/74 (37.8%) lesions were grouped as malignant (BIRADS

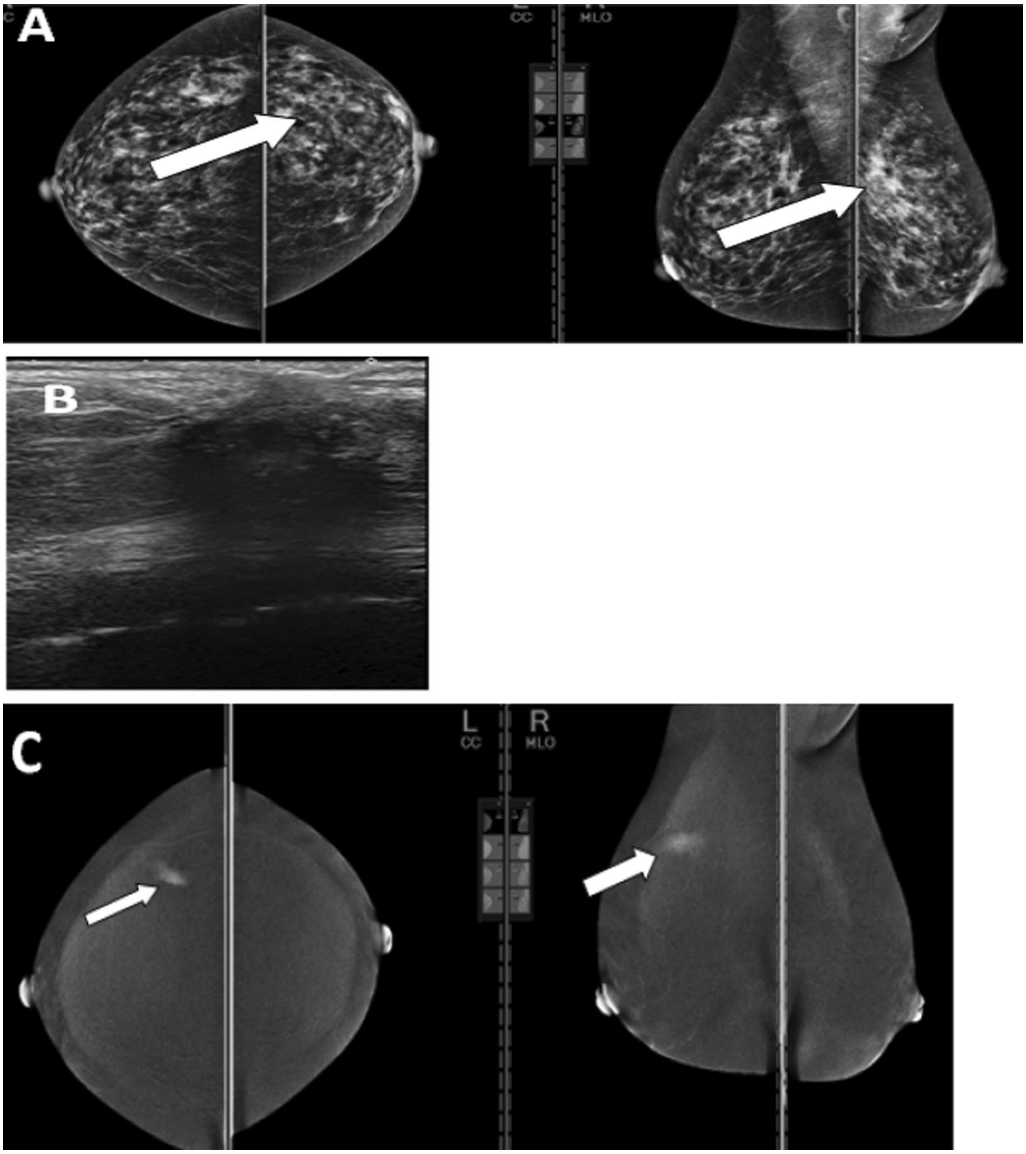

Fig. 3 An 80-year-old asymptomatic female patient underwent left CBS for mucinous carcinoma, presenting for her annual follow-up. **A** Mammography (CC and MLO views) revealed: Breast density ACR 'C' with heterogeneous fibroglandular densities and nodulations. Asymmetry is seen at left UOQ with mild skin thickening (white arrow). **B** Complementary ultrasound revealed: operative bed hypoechoic scarring is seen at left UOQ with no vascularity on color Doppler. **C** Contrast-enhanced spectral mammography revealed: enhancing focus at right UOQ (white arrow), No operative bed-enhancing masses. Final pathology: right breast mucinous carcinoma (contralateral newly developed lesion). Final comment: In this case, sonomammography could not detect the contralateral newly developed lesion, while CESM revealed a contralateral enhancing lesion and excluded operative bed lesions

4 and 5), while 46/74 (62.2%) lesions were grouped as benign (BIRADS 2 and 3).

When the sonomammography results were compared to the final diagnosis, 19 lesions were classified as TP, 12 as FP, 9 as FN, and 12 as TN.

The large prevalence of FP patients in our study was caused by post-treatment edema, parenchymal distortion, and tissue scarring at the site of previous surgical/ radiation procedures. In cases when mammography revealed a false negative result, the tiny denovo lesions that were obscured behind dense breast tissue were unable to be seen or recurrent lesions were masked by the operative bed scaring. This goes in concordance with Nada et al. [3] in their study.

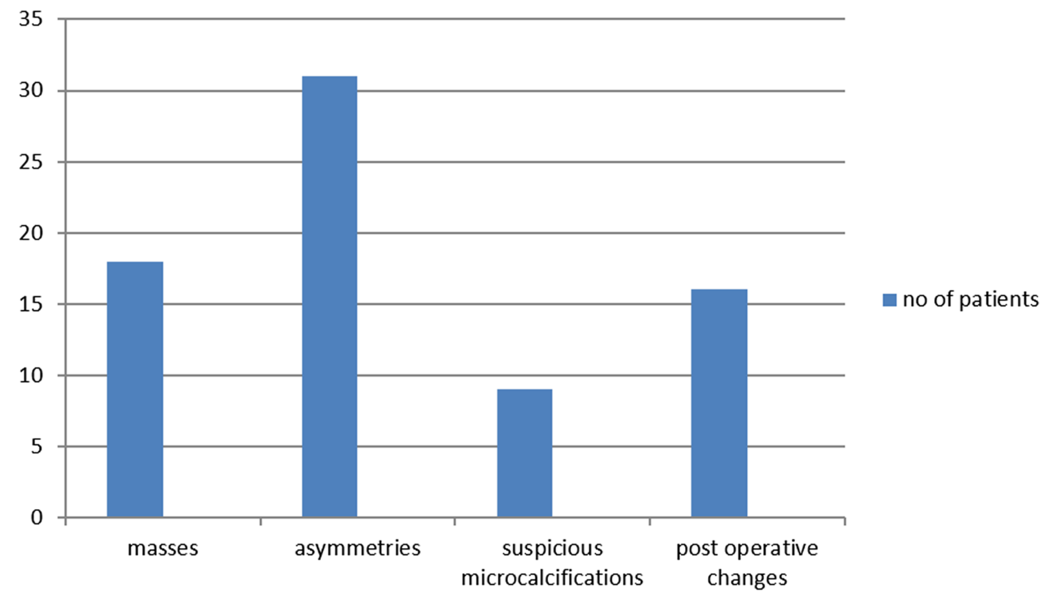

Fig. 4 Represents the spectrum of findings detected on sonomammography

Considering the prior data, sonomammography showed a sensitivity of 67.86%, a specificity of 73.91%, a PPV of 61.29%, a NPV of 79.07%, a positive likelihood ratio representing 2.6, a negative likelihood ratio representing 0.43, and an accuracy of 71.62%.

The current study's low diagnostic indices for mammography results are consistent with those of Yalcinkaya et al. [12]. They came to the conclusion that it is challenging to examine the breast with MG and ultrasonography in patients who performed conservative surgery as well as radiotherapy due to tissue distortion and edematous changes. For those patients, and also for patients with genetic predispositions, contrast-enhanced breast imaging is indicated as the screening method of choice. The rate of false negative mammography diagnoses, which accounts for up to fifteen percent of the population overall, is significantly more prevalent in the aforementioned group.

In the current study, the CESM findings were that 38/74 (51.4%) lesions showed contrast uptake compared to 36/74 (48.6%) of the lesions lacked contrast uptake.

Enhancing lesions were classified according to ACR BIRADS ATLAS (2022) [8] into enhancing masses 29/38 (76.3%) and non-mass enhancing lesions 9/38 (23.6%), while no enhancing asymmetries were found in our study.

CESM characterized that 28/74 (37.8%) of the lesions were assorted as malignant (BIRADS 4 and 5), while 46/74 (62.2%) of the lesions were assorted as benign (BIRADS 1, 2, and 3).

When the CESM results were compared to the final diagnosis, 25 lesions were classified as TP, 3 as FP, 43 as TN, and 3 as FN.

The 3 FN cases were incorrectly diagnosed for the reasons listed below: (a) One patient had an ultrasound diagnosis of axillary carcinoma followed by pathological confirmation; however, CESM missed the axillary lesion since it was outside the film's field of view. (b) Another case was missed by CESM due to the lesion site (mastectomy bed) and (c) the last case was wrongly diagnosed owing to inconspicuous contrast enhancement by the malignant lesions because of the lesion's considerable fibrosis as a post-therapeutic sequelae.

The 3 FP cases were wrongly diagnosed due to the following causes: (a) Two patients showed a small outer portion nodular density in the contralateral breast on CESM but were confirmed by histopathology as being benign adenotic changes (b) The third patient revealed NME at the site of the previous operative procedure and turned out to be inflammatory changes.

Given the earlier data, CESM showed an 89.29% sensitivity, a 93.48% *specificity*, an 89.29% *PPV*, a 93.48% *NPV*, a 13.69 *positive likelihood ratio*, a 0.11 *negative likelihood ratio,* and a 91.89% *accuracy*. Comparing CESM to sonomammography, higher diagnostic indices were seen that were statistically significant with P-value = 0.0082 (< 0.05). This is consistent with Helal et al. [13] study which stated that mammography's performance in the postoperative breast was improved by CESM. It showed

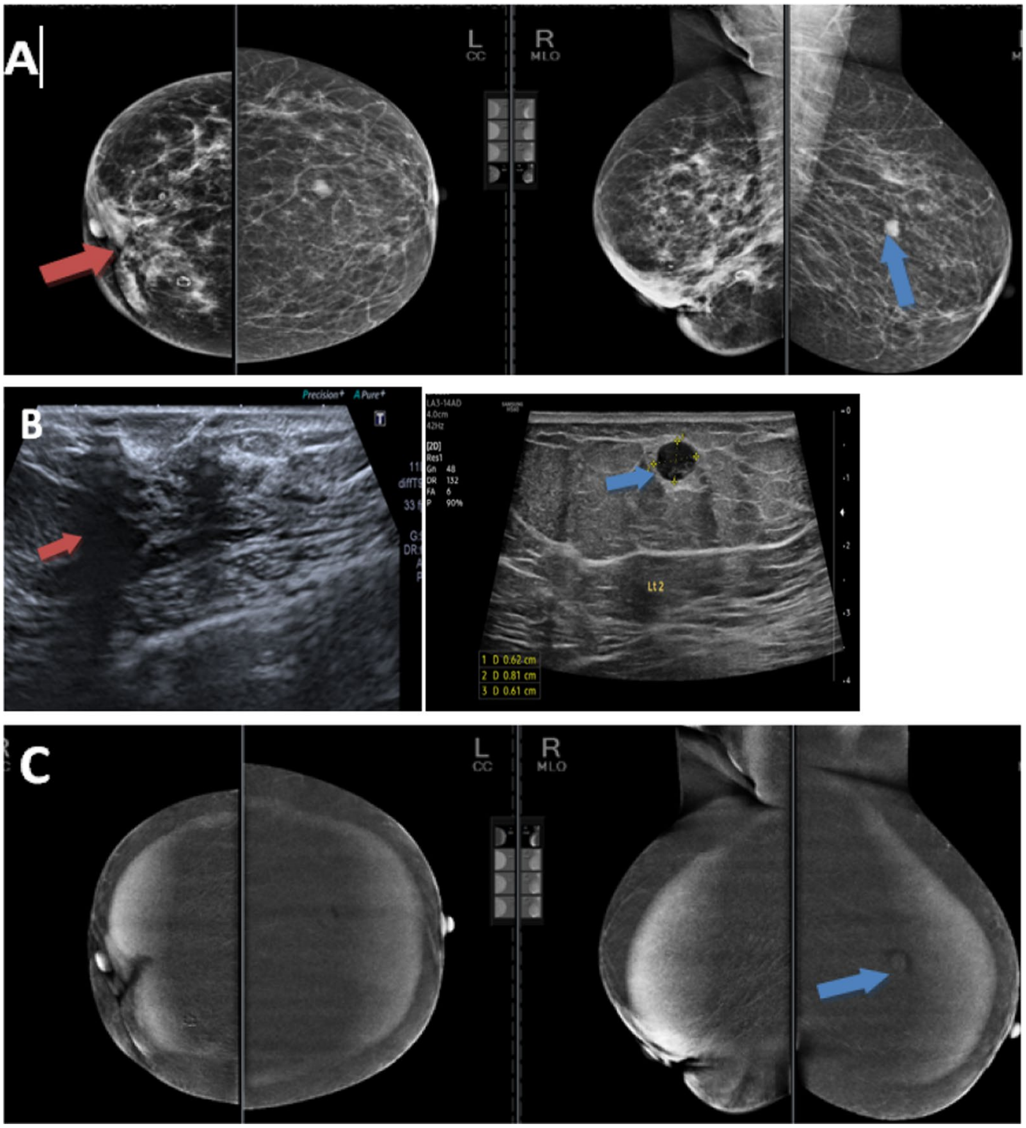

Fig. 5 A 40-year-old asymptomatic female patient underwent right CBS for IDC grade II, presenting for her annual follow-up. **A** Mammography (CC and MLO views) revealed: Breast density ACR 'b'. Asymmetry is seen in the LIO of the right breast (red arrow) with skin thickening and nipple retraction. Multiple right radiolucent lesions with eggshell calcifications; oil cysts. Left UOQ well-defined ovoid-shaped isodense lesion (blue arrow). **B** Complementary ultrasound revealed: hypoechoic extensive operative bed scarring in the LIQ of the right breast (red arrow) and left UOQ well-defined oval-shaped parallel lesion (blue arrow). **C** Contrast-enhanced spectral mammography revealed: No operative bed-enhancing lesions, and left UOQ well-defined enhancing mass (blue arrow). Final Diagnosis: Right breast postoperative changes and Left UOQ fibroadenoma. Final comment: In this case, sonomammography showed suspicious operative bed changes with extensive scarring, while CESM could exclude operative bed lesions

a sensitivity of 91.17%, a specificity of 75%, a PPV of 77.5%, a NPV of 90%, and an accuracy of 82.85%. They concluded that CESM is a reliable technology that could be used to recognize malignancy in the setting of postoperative breast in addition to the standard mammography.

Supporting our study results, Nada et al. [3] also found lower diagnostic performance for mammography performed for postoperative breast cancer patients with increased distortion and breast density. They also reported better diagnostic indices after adding contrast-enhanced study (CESM) to their study group.

Fallenberg et al. [14] proposed that CESM is not inferior to MRI and is superior to digital MG in terms of lesion detection and size assessment. The study they performed has demonstrated that bilateral CESM and MRI are more effective at detecting breast tumors than MG.

Table 1 Diagnostic indices of sonomammography and CESM among the studied population

Statistic	Sonomammography values	CESM values
Sensitivity	67.86%	89.29%
Specificity	73.91%	93.48%
Positive likelihood ratio	2.60	13.69
Negative likelihood ratio	0.43	0.11
Positive predictive value	61.29%	89.29%
Negative predictive value	79.07%	93.48%
Accuracy	71.62%	91.89%

When compared to MG, they discovered that by utilizing CESM, lesion detection increased by 17.5%.

The current study has some limitations; the relatively small sample size included in our work. So we recommend further studies with further increase in the sample size to establish the diagnostic role of CESM, especially in following up with breast cancer survivors coming after treatment.

On the other hand, we must say that CESM has its limitations as in deeply seated lesions or mastectomy bed lesions. Other possible risks are allergic reaction to contrast media as well as risk of local pain or hematoma formation at the site of injection of contrast media.

Conclusions

Mammography (with or without US) become known for being inadequate for accurately assessing some postoperative breast situations. Therefore, additional contrast-enhanced imaging modalities are necessary. Consequently, choosing CESM could be proposed based on sonomammographic or clinical data. Additionally, it needs to be tailored for the operation's type, breast density, and availability of the modality. It also can help in guiding biopsy sites with a performance that is comparable to that of MRI yet more available, less expensive with less examination time.

Abbreviations

ACR	American College of Radiology
BIRADS	Breast imaging and reporting data system
BCS	Breast conservative surgery
CC	Cranio-caudal
CESM	Contrast-enhanced spectral mammography
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
DCIS	Ductal carcinoma in situ
FFDM	Full field digital mammography
FNA	Fine needle aspiration
FN	False negative
FP	False positive
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
MG	Mammogram
MLO	Medio-lateral oblique
MRM	Modified radical mastectomy
NME	Non-mass enhancement
NPV	Negative predictive value
PPV	Positive predictive value
TN	True negative
TP	True positive
US	Ultrasound

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Author contributions
SI had designed this study. NG, RH, YM and MM contributed to the data collection, data analysis and processing. All authors shared together in writing the manuscript. ALL authors read and approved the final manuscript.

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Availability of data and materials
The data supporting the conclusions of this article are available upon reasonable request from the authors.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Research Committee of Faculty of Medicine Cairo University in Egypt. The ethical approval code is D-33-2019. A verbal consent was taken from the legal guardians of all patients accepting to participate in our research work.

Consent for publication
The legal guardians of 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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