

Diagnostic accuracy of contrast enhanced spectral mammography in assessment of indeterminate breast lesions in patients who underwent breast conservation surgery

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ABSTRACT

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Background: Breast cancer stands out as a major health issue globally, being the most common type of cancer diagnosed in women around the world. Its impact in Egypt is particularly pronounced, accounting for a substantial proportion of new cancer cases. Contrast-Enhanced Spectral Mammography (CESM) has emerged as a promising diagnostic tool for breast tumors. By visualizing tumor angiogenesis, CESM offers improved accuracy compared to traditional mammography with or without ultrasound. Its ability to depict tumor neovascularity parallels that of breast magnetic resonance imaging (MRI). This study was done to assess how well CESM can accurately identify the nature of unclear breast lesions in patients who have had breast-conserving surgery (BCS). **Materials and Methods:** We carried out a retrospective study with 30 women who had breast-conserving surgery due to ambiguous breast lesions found by traditional mammography. Their ages varied between 32 and 77, averaging 50.07 years. Each patient received dual-energy contrast-enhanced spectral mammography. The definitive diagnosis was confirmed by examining tissue samples from surgery or biopsy through histopathology. **Results:** Examination of the 30 patients showed that 23 had benign lesions (69.7%) while 10 were malignant (30.3%). The diagnostic performance character of CESM was improved with the use of the malignancy potential score (MPS) in distinguishing between benign and malignant breast lesions. **Conclusion:** The results indicate that CESM serves as an effective supplement to traditional mammography for evaluating unclear breast lesions after breast-conserving surgery. Its enhanced sensitivity and accuracy could lead to better patient management and improved health outcomes.

INTRODUCTION

Breast cancer (BC) remains a major global health concern, representing the second leading cause of cancer-related deaths among women worldwide. In 2022, there were 2.3 million new diagnoses globally, and tragically, an approximate number of 670,000 women died from the disease. Statistics from the American Cancer Society in 2024 estimate approximately 310,720 new cases of invasive breast cancer, 56,500 new cases of ductal carcinoma in situ (DCIS), and around 42,250 deaths due to BC ⁽¹⁾.

Egypt is not exempt from breast cancer's worldwide burden, despite having a lower incidence rate compared to developed nations. However, the mortality rate in Egypt is disproportionately high, resulting in a mortality-to-incidence ratio approximately double that of developed countries. This enormous disparity highlights the critical need for effective early detection measures ⁽²⁾.

Breast cancer mortality rates have demonstrated a consistent descending trend since 1989, resulting in a 42% overall reduction by 2021. This notable

decrease is largely attributed to a combination of factors, including earlier detection through screening initiatives, increased public awareness of the disease, and advancements in therapeutic interventions. It is important to note, however, that the pace of this decline has been changed in recent years ⁽³⁾.

Early diagnosis and appropriate treatment are crucial for improving breast cancer outcomes. Consequently, developing accurate and cost-effective diagnostic tools is imperative to address the diverse needs of women across different populations and socioeconomic backgrounds ⁽⁴⁾.

Digital mammography (DMG) has become a cornerstone of breast cancer screening. However, its effectiveness is limited, especially in females with dense breast tissue. The overlapping densities of breast tissue often obscure underlying malignant masses, leading to increased false-positive (FP) results and decreased sensitivity ⁽⁵⁾.

Breast-conserving surgery (BCS) is typically the first choice for treating early-stage BC. Yet, about 20% of patients end up needing a mastectomy because of conditions like multifocal or multicentric

cancer, widespread DCIS, large tumors, or recurrent cancer ⁽⁶⁾.

Contrast-enhanced spectral mammography (CESM) is a relatively new imaging modality that combines conventional DMG with intravenous contrast administration. By exploiting the principle of tumor angiogenesis, CESM effectively highlights areas of abnormal blood vessel growth within breast tissue. This technique offers superior diagnostic accuracy compared to traditional mammography ⁽⁷⁾.

CESM shares similarities with magnetic resonance imaging (MRI) in terms of contrast enhancement patterns, suggesting comparable diagnostic applications. However, CESM surpasses MRI in several key aspects. It can readily detect microcalcifications and is free from limitations associated with ferromagnetic characteristics and design of the machine. Additionally, CESM is significantly more cost-effective and time-efficient than MRI, with shorter examination times and lower costs for equipment and contrast agents ⁽⁸⁾.

CESM generates low-energy two-dimensional mammographic images, similar to standard digital mammography. However, post-contrast image analysis enables the assessment of tumor neovascularity, a characteristic typically evaluated using magnetic resonance imaging (MRI) ⁽⁹⁾.

Breast conservation therapy (lumpectomy or segmental mastectomy followed by radiation) can result in a variety of breast alterations, including masses, fluid collections, architectural distortion, scarring, swelling (edema), skin thickening, and calcification. These changes can resemble or obscure signs of local breast cancer recurrence. Distinguishing between benign post-treatment alterations and recurrent cancer can be challenging due to overlapping mammographic features ⁽¹⁰⁾.

Following BCS, it's important to differentiate between expected post-treatment changes and potential signs of recurrence. Post-surgical masses and fluid collections typically resolve within a year. Radiation-induced edema generally subsides over time, but increasing edema should raise concern for recurrence. The presence of interspersed radiolucent areas within a poorly defined soft tissue mass often suggests post-surgical scarring, whereas recurrent cancer typically presents as a solid mass without these radiolucencies. Finally, while pleomorphic and granular microcalcifications can be a sign of recurrence, they should be carefully distinguished from benign calcifications associated with scarring ⁽¹⁰⁾.

Indeterminate breast lesions, exhibiting characteristics of both benign and malignant lesions, pose a diagnostic dilemma. In high-risk women, these indeterminate findings warrant aggressive evaluation due to the heightened risk of malignancy ⁽¹⁰⁾.

The study hypothesized that CESM's might enhance breast lesion detection while reducing false

positive and negative results. Thus, the study aimed to evaluate the potential of CESM in improving diagnostic accuracy for postoperative breast cancer surveillance by comparing the findings from CESM with routine full-field digital mammography (FFDM) in patients who underwent breast-conserving surgery (BCS).

MATERIALS AND METHODS

This retrospective study tried to evaluate the role of CESM in assessing indeterminate breast lesions following BCS. The study was conducted at Ain Shams University hospitals and private centers between June 2019 and July 2023. Files of female patients who underwent BCS and presented with indeterminate breast lesions on Sono-mammography were eligible for inclusion without age restrictions. Exclusion criteria included the presence of severe allergy to contrast material or significant renal impairment, defined as a serum creatinine level higher than 1.8 mg/dL or an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m² were excluded from the study.

Ethical approval and patient consent

This study was approved from the ethical committee of Ain Shams University (approval number: FMASU M D 271 / 2019). Before enrollment, written informed consent was obtained from all participants after detailed discussing the purpose for performing the procedure and its duration and potential risks.

Patient data collection

Clinical data, including patient demographics, medical history, and renal function tests (serum creatinine), were recorded for each participant. All patients underwent bilateral digital mammography, CESM, and ultrasound examination. Histopathological findings served as the reference standard for comparison.

Technique

CESM and conventional mammography examinations were conducted using a General Electric Sonograph 2000D full-field digital mammography system with ultrasonographic (US) complimentary imaging. Patients were asked to fast for six hours before the imaging procedure. Before CESM, patients received a 100 mL intravenous injection of a low-osmolar, non-ionic, monomeric iodinated contrast agent (Ultravist 300, manufacturer: Bayer Corporation, Leverkusen, Germany) at a rate of 3 mL/s through a 20-gauge antecubital vein catheter. Due to its superior safety profile, a low-osmolar iodinated contrast agent was preferred for CESM. If venous access was difficult, a 22-gauge catheter was inserted and the injection rate

was adjusted to 2.5 mL/s. Imaging was started 2-8 min after injection to allow the dispersion of the contrast agent within the breast tissue according to the breast density and contrast enhancement. The duration of the imaging procedure was about 10 min.

With the patient was standing, two X-ray images, a low-energy and a high-energy image, were acquired of the same breast location; the low-energy image served as a standard mammogram equivalent, while the high-energy image offered additional details.

Image acquisition and analysis

The low-energy image was digitally subtracted from the high-energy image using the weighted logarithmic technique to enhance the visibility of blood vessels and tumors with a rich blood supply and reduce the appearance of normal breast tissue. Standard images of the examined breast included craniocaudal and mediolateral oblique views. Patients received slightly more radiation than the standard mammogram according to the breast size and composition.

Post-CESM Procedures: Patients were closely monitored during and for at least 30 minutes following the contrast injection, particularly those with no previous exposure to iodinated contrast agents, for any adverse reactions or contrast extravasation. If no side effects of the drug or procedure complications occurred, the intravenous line was removed and patient was discharged. Additionally, breast density was categorized using the American College of Radiology (ACR) classification.

Image Interpretation: Image analysis involved a two-pronged approach: the standard Breast Imaging-Reporting and Data System (BIRADS) scoring system and the specific CESM scoring system. The CESM scoring for high-energy image according to grading of contrast enhancement intensity compared with background enhancement ranged from negative (-1) to intense (2) enhancement. The malignancy potential score (MPS) refers to the sum of the BIRADS and CESM scores and a score <4 indicates a benign lesion, while a score >4 indicates a malignant lesion.

RESULTS

Thirty patients with a history of BCS were included in the study; 27 had ipsilateral (90%) and 3 had bilateral lesions (10%) for a total number of the examined breasts of 33 lesions. Patients' enrolment data are shown in table 1. All patients had surgical excision of the presenting breast mass for histopathological examinations.

Breast US detected 18 solid lesions (54.5%), 5 cystic lesions (15.2%), and two mixed cystic and solid lesions (6.1%), while failed to detect a lesion in 8 cases (24.2%). Regarding lesion' vascularity, US defined 27 non-vascular lesions (81.8%), 4 lesions

(12.1%) showed mild vascularity and two lesions (6.1%) with high vascularity (table 2).

Table 1. Patients' data.

| Data | Findings |
|---------------------------|------------|
| Age (years) | <40 |
| | 4 (13.3%) |
| | 40-49 |
| | 13 (43.4%) |
| | 50-59 |
| Laterality of the lesions | 9 (30%) |
| | ≥60 |
| | 4 (13.3%) |
| | Average |
| | 49.4±9.2 |
| Duration since BCS | Left |
| | 17 (56.7%) |
| | Right |
| | 10 (33.3%) |
| | Bilateral |
| | 3 (10%) |
| | <5 |
| | 14 (46.7%) |
| | 5-9 |
| | 14 (46.7%) |
| | ≥10 |
| | 2 (6.6%) |
| | Average |
| | 4.65±2.8 |

Table 2. US findings.

| Item | Findings | Frequency, n; % |
|---------------------------|-----------------------------|-----------------|
| Type of breast lesion | No lesion | 8 (24.2%) |
| | Cystic lesion | 5 (15.2%) |
| | Solid lesion | 18 (54.5%) |
| | Mixed cystic & Solid lesion | 2 (6.1%) |
| Vascularity of the lesion | Non-vascular | 27 (81.8%) |
| | Mild vascularity | 4 (12.1%) |
| | Vascular | 2 (6.1%) |

Low-energy findings on interpretation of mammographic images were mostly ill-defined lesions in 16 breasts (48.5%) or lesions showing architectural distortions in 9 breasts (27.3%) and defined lesions in 4 breasts (12.1%), while no lesion was detected in the remaining 4 breasts (12.1%). Suspicious calcification was detected in 5 lesions (15.2%) and benign calcification in 6 lesions (18.1%), while no calcification was detected in 22 lesions (66.7%). According to ACR grading for breast density, 17 (51.6%) and 14 breasts (42.4%) were of grades B and C, respectively and one breast (3%) of each of grade A and D. Twenty-four lesions (72.7%) are of BIRADS scoring of <4; 5 (15.2%), 7 (21.2%) and 12 (36.4%) lesions are of BIRADS scores; 1, 2, and 3, respectively. One lesion was scored as both 4 and 4B, two lesions (6.1%) were of score 4A and three lesions (9%) were scored as 4C, and two lesions (6.1%) were of BIRADS score 5 (table 3).

The interpretation of CESM findings defined no enhancement in 20 lesions (60.6%), mild enhancement (30.3%), moderate enhancement in one lesion (3%), and intense enhancement in two lesions (6.1%). According to CESM score, 18 lesions (54.5%) were scored by 0, and 11 lesions (33.3%) were scored by one, while three lesions (9.1%) were scored by 2 and a lesion (3%) by -1.

The calculated MPS defined 19 lesions (67.7%) had a score of <4 which suggests that the lesion is mostly benign, and 14 lesions (42.4%) were scored by ≥4, a score suggesting that the lesion is most probably to be malignant. Considering pathological diagnosis is the gold standard for comparison, it diagnosed 23 lesions (67.7%) as benign lesions, and 10 lesions (33.3%) as malignant ones (table 4, figure 1).

Table 3. Mammographic findings and scorings.

| Low-energy findings | | Calcification | | ACR | | BIRADS Score | |
|--------------------------|------------|---------------|------------|-------|------------|--------------|------------|
| Findings | Frequency | Findings | Frequency | Grade | Frequency | score | Frequency |
| No Lesion | 4 (12.1%) | Absent | 22 (66.7%) | A | 1 (3%) | 1 | 5 (15.2%) |
| Architectural Distortion | 9 (27.3%) | Benign | 6 (18.1%) | B | 17 (51.6%) | 2 | 7 (21.2%) |
| Ill-defined lesion | 16 (48.5%) | Suspicious | 5 (15.2%) | C | 14 (42.4%) | 3 | 12 (36.4%) |
| Defined lesion | 4 (12.1%) | | | D | 1 (2%) | 4 | 1 (3%) |
| | | | | | | 4A | 2 (6.1%) |
| | | | | | | 4B | 1 (3%) |
| | | | | | | 4C | 3 (9%) |
| | | | | | | 5 | 2 (6.1%) |

Table 4. CESM finding and MPS score, and pathological findings.

| Item | | Findings | Frequency, n; % |
|------------------------|----------------|-----------|-----------------|
| CESM | Enhancement | No | 20 (60.6%) |
| | | Mild | 10 (30.3%) |
| | | Moderate | 1 (3%) |
| | | Intense | 2 (6.1%) |
| | Score | -1 | 1 (3%) |
| | | 0 | 18 (54.5%) |
| | | 1 | 11 (33.3%) |
| | | 2 | 3 (9.1%) |
| MPS | Collectively | <4 | 19 (57.6%) |
| | | ≥4 | 14 (42.4%) |
| | Differentially | 1 | 4 (12.1%) |
| | | 2 | 8 (24.2%) |
| | | 3 | 7 (21.2%) |
| | | 4 | 9 (27.3%) |
| | | 5 | 2 (6.1%) |
| | | 6 | 2 (6.1%) |
| | | 7 | 1 (3%) |
| Pathological diagnosis | | Benign | 23 (67.7%) |
| | | Malignant | 10 (33.3%) |

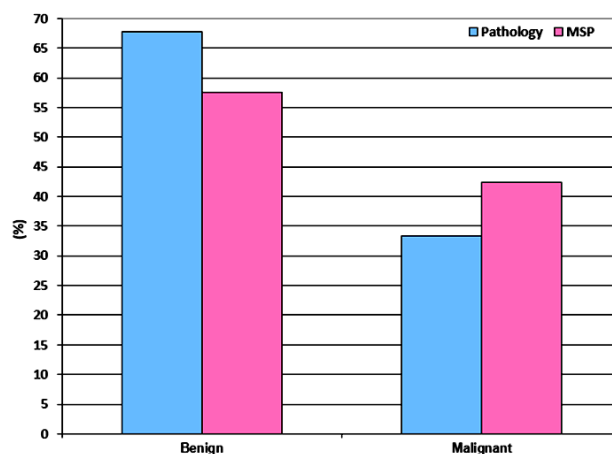


Figure 1. The diagnosis of the studied lesions the MSP.

A comparison of the radiologic findings to the pathological diagnosis, defined high sensitivity and negative predictive values for the MSP score, while the CESM score showed high specificity and positive predictive values. However, the MSP score showed the highest accuracy percentage with the highest 95% confidence interval (table 5).

Table 5. The diagnostic performance values of the radiologic studies.

| Performance | Breast lesion vascularity | CESM score | MSP score |
|-----------------|----------------------------|----------------------------|---------------------------|
| Sensitivity (%) | 30(95% CI: 6.67-65.25) | 57.14(95% CI:28.86-82.34) | 90(95% CI:55.5-99.75) |
| Specificity (%) | 86.96(95% CI: 66.41-97.22) | 89.47(95% CI:66.86-98.7) | 78.26(95% CI: 56.3-92.54) |
| PPV (%) | 50(95% CI: 19.5-80.5) | 80(95% CI:49.98-94.12) | 64.29(95% CI: 44.65-80.1) |
| NPV (%) | 74.07(95% CI: 64.89-81.5) | 73.91(95% CI:60.28-84.1) | 94.74(95% CI: 73.5-99.15) |
| Accuracy (%) | 69.7(95% CI:51.29-84.41) | 75.76(95% CI: 57.74-88.91) | 81.82(95% CI: 64.54-93) |

95% CI: 95% confidence interval.

Cases demonstration

Case 1: A 32-year-old woman with a history of left breast-conserving surgery presented with a growing lump in the surgical bed. Digital mammography demonstrated focal architectural distortion and an ill-defined soft tissue density at the previous cancer site (BI-RADS 4). Contrast-enhanced

spectral mammography (CESM) revealed an intensely heterogeneous enhancing lesion corresponding to the clip marker, with associated regional non-mass enhancement and enlarged axillary lymph nodes. The CESM score was 2, and the malignant potential score (MPS) was 6. Histopathology confirmed recurrent invasive ductal carcinoma (Figure 2). A: Craniocaudal mammogram. B: Craniocaudal CESM. C: Mediolateral oblique mammogram. D: Mediolateral oblique CESM.

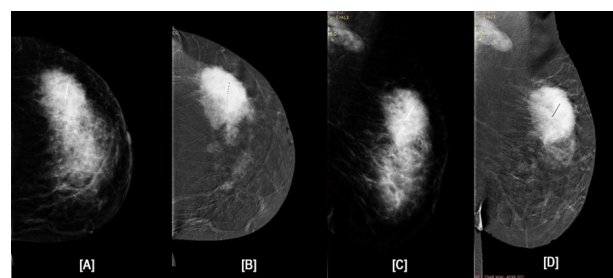


Figure 2. CESM characterization of recurrent invasive ductal carcinoma in a post-lumpectomy patient.

Case 2: a 46-year-old woman with a history of left breast-conserving surgery presented with an enlarging left breast lump. While mammography showed changes consistent with post-surgical effects (diffuse skin thickening and architectural distortion in the upper outer quadrant, BI-RADS 2), CESM revealed a discordant finding: a focal area of faint, heterogeneous non-mass enhancement in the central

lower quadrant. The CESM score was 0, and the malignant potential score (MPS) was 2. Histopathology confirmed mastitis and fat necrosis (Figure 3). A: Craniocaudal mammogram. B: Craniocaudal CESM. C: Mediolateral oblique mammogram. D: Mediolateral oblique CESM.

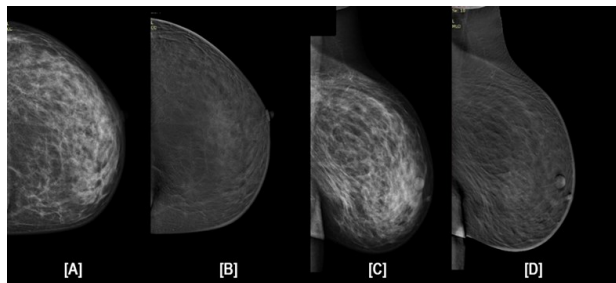


Figure 3. CESM in benign post-lumpectomy changes.

Case 3: A 41-year-old woman with a history of left mastectomy presented with right breast swelling. Mammography showed increased skin thickness, trabeculation, nipple retraction, and a retro-areolar density (BI-RADS 3). CESM demonstrated diffuse enhancement of the thickened skin and breast tissue, predominantly in the retro-areolar region. The CESM score was 2, and the malignant potential score (MPS) was 5. Histopathology confirmed invasive carcinoma with mixed ductal and lobular features (Figure 4). A: Craniocaudal mammogram. B: Craniocaudal CESM. C: Mediolateral oblique mammogram. D: Mediolateral oblique CESM.

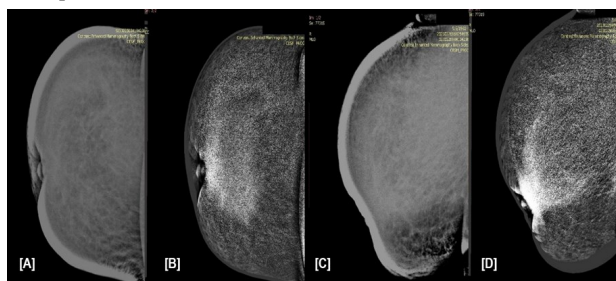


Figure 4. CESM detection of invasive carcinoma in the contralateral breast post-mastectomy.

Case 4: A 41-year-old woman, previously treated for right breast cancer with breast-conserving surgery, presented with diffuse breast edema extending to the contralateral (left) breast. Mammography demonstrated ill-defined lesions and microcalcifications in the left upper outer quadrant, prompting a BI-RADS 4 assessment. Subsequent CESM demonstrated marked contrast uptake consistent with active glandular tissue. The CESM score was 1, and the malignant potential score (MPS) was 5. Histopathology confirmed invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) (Figure 5). A: Craniocaudal mammogram. B: Craniocaudal CESM. C: Mediolateral oblique mammogram. D: Mediolateral oblique CESM.

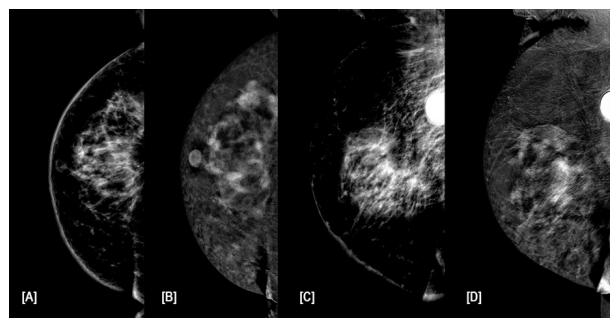


Figure 5. CESM detection of contralateral breast cancer in a patient with post-lumpectomy lymphedema.

DISCUSSION

Histopathological diagnosis of the excised 33 specimens categorized lesions into 23 benign (67.7%) and 10 malignant (33.3%) lesions. Malignant lesions typically exhibited abnormal contrast enhancement within the surgical site, accompanied by irregular shapes, spiculated margins, and heterogeneous enhancement. Benign lesions, conversely, demonstrated no or minimal contrast uptake, with well-defined borders and homogeneous enhancement.

Comparison of CESM and pathology results yielded 8 true positives (24.2%) and 17 true negatives (51.5%). Further the use of the sum of the BI-RADS and the CESM scores to yield the MSP score improved the diagnostic performance of radiologic assessments of breast lesions and raised the frequency of detecting TPs to 9 lesions (27.3%) and TNs to 18 lesions (54.4%). The detected superiority of CESM in characterizing lesion size, extent, and multiplicity compared to conventional mammography (MG) and ultrasound (US).

Numerous earlier studies have demonstrated the superior diagnostic performance of CESM relative to conventional mammography. Diekmann *et al.*⁽¹¹⁾ reported improved sensitivity and specificity when MG was combined with CESM. Dromain *et al.*⁽¹²⁾ found CESM to be effective in identifying tumor angiogenesis with higher sensitivity than MG (93% vs. 78%). Thereafter, Fallenber *et al.*⁽¹⁴⁾ and Kamal *et al.*⁽¹⁰⁾ observed a significantly higher detection rate of malignant breast lesion with CESM than MG, and Helal *et al.*⁽⁵⁾ reported sensitivity and specificity of 91.17% and 75% for CESM in detecting recurrent breast cancer with significantly higher detection rates than MG; 50% and 22%, respectively. Also, while *et al.*⁽¹⁴⁾ found that CESM had a 91.17% sensitivity, a specificity 75.00% and 82.85% accuracy for detection of recurrent breast lesions, and Nada *et al.*⁽³⁾ reported greater diagnostic accuracy following CESM administration than FFDM in postoperative breast cancer patients having architectural distortion with increased breast density.

Recently, Hua *et al.*,⁽¹⁵⁾ who investigated the utility of the BI-RADS in CESM in the differentiation of breast non-mass enhancement (NME) lesions and documented that the applied scoring can significantly improve the diagnostic accuracy compared with BI-RADS (MG) and provided specific advantages for NME with micro-calcifications than BI-RADS (MRI). Also, Sanders *et al.*,⁽¹⁶⁾ found screening examinations for mean glandular dose per breast was higher for CESM than for full-field digital mammography or digital breast tomosynthesis alone. Further, Xu *et al.*,⁽¹⁷⁾ detected high diagnostic value of CESM with kinetic enhancement with 100% sensitivity and NPV for BI-RADS 3-5 papillary breast lesions. Moreover, Long *et al.*,⁽¹⁸⁾ documented that the presence of enhancement and morphology on CESM assessment were identified as independent predictors of malignant calcifications of BI-RADS 4B.

In support of the efficacy of CSEM, Ferrara *et al.*,⁽¹⁹⁾ documented moderate agreement and high reproducibility in breast background parenchymal enhancement assessment between MRI and CESM. Furthermore, multiple recent studies demonstrated the implementation of contrast enhancement in protocols for breast assessments using various diagnostic modalities. Hu *et al.*,⁽²⁰⁾ found that combining contrast-enhanced ultrasonography with CA15-3, HER-2, and sE-cad levels facilitated the differentiation of benign and malignant breast lesions and allowed differentiation between ductal carcinoma in situ and invasive ductal carcinoma, depending on CEUS's ability to show differences in enhancement characteristics and to detect perfusion defects and peripheral high enhancement associated with DCIS⁽²¹⁾.

The generalizability and interpretation of this study's findings should be considered in light of several limitations. The retrospective, single-institution design and physician-directed use of CESM introduce selection bias, likely favoring patients with dense breasts. The absence of a standardized lexicon for interpreting CESM images, unlike that used for DCE-MRI, has led to subjective interpretation and inconsistent management strategies, including variations in subsequent imaging, follow-up, and biopsy. Additionally, the inclusion of early cases may have contributed to a higher recall rate and more likely benign classifications, potentially reflecting a learning curve effect.

CONCLUSION

CESM outperforms conventional mammography, even when combined with the US, in detecting breast cancer, particularly in patients with breast masses after BCS, and has the potential to significantly improve cancer detection rates compared to routine mammography alone.

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Human ethics and consent to participate: Prior to enrollment, written informed consent was obtained from all participants. This study received approval from the ethical committee of Ain Shams University (approval number: FMASU M D 271 / 2019).

Consent for publication: All authors have reviewed the manuscript thoroughly and consent to its publication.

Availability of data and materials:

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

Informed Consent: Informed consent was obtained from all the legally authorized representatives of the participants included in the study.

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Authors' contributions: DAMS led the research idea, study design, and wrote the initial draft. AAB handled data curation, analysis, and manuscript review. NAETC conducted experiments, collected data, and supervised the research. MAMN managed visualization, project administration, and funding acquisition.

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