

Technique and clinical applications of dual-energy contrast-enhanced digital mammography (CEDM) in breast cancer evaluation: a pictorial essay

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ABSTRACT

This pictorial essay illustrates an overview of the basic technique used in acquiring dual-energy contrast-enhanced digital mammography (CEDM) images and its potential clinical applications in regular practice. CEDM may be used as a low-cost alternative to magnetic resonance imaging (MRI), as a problem-solving tool in clinical practice and for therapeutic planning of breast cancer, which may include high-risk screening, dense breast evaluation, mammographically equivocal lesions, local staging, treatment response evaluation, and post treatment follow-up. We share our experience of CEDM at a tertiary care cancer hospital.

Contrast-enhanced digital mammography (CEDM) is a new technique in which full-field digital mammography (FFDM) is supplemented with the use of intravenous iodinated contrast administration. In this technique, contrast-enhanced digitally subtracted images are used to assess the tumor neo-angiogenesis, in a similar manner as in contrast-enhanced magnetic resonance imaging (MRI), with near complete subtraction of background parenchyma (1–3). Tumor neo-angiogenesis occurs due to increased formation of small random blood vessels within the mass, which are more permeable to contrast media resulting in tumor enhancement after administration of iodinated contrast media compared with the surrounding normal breast tissue (3, 4). Contrast enhancement can be seen in both benign and malignant tumors; however, it tends to be more frequent and intense in malignant tumors compared with benign ones (5, 6). Currently, MRI is considered the most sensitive imaging modality for breast cancer detection and is used as a problem-solving tool in dense breast and equivocal cases. Contrast-enhanced mammography technique received FDA approval in 2011 and has been used as a problem-solving tool in clinical practice, such as evaluation of dense breast, screening of high-risk patients as an alternative to MRI, evaluation of breast lesions with equivocal findings on mammogram, local staging of breast cancer, assessment of patients with metastasis elsewhere with occult breast primary, post chemotherapy response evaluation, therapeutic planning, and detection of residual or recurrent breast cancer after breast conserving surgery or excisional biopsy (7, 8).

We have used this technology in more than 500 patients since its implementation at our center, a tertiary care cancer hospital, as a problem-solving tool with histopathologic correlation and the results are very promising. In this pictorial essay, we illustrate the technique of acquiring CEDM images and potential clinical applications in routine practice.

CEDM technique

Dual-energy contrast-enhanced mammography is an x-ray based technique in which a pair of high and low energy images are acquired after intravenous administration of iodinated contrast.

Contraindications to CEDM

CEDM should be avoided in pregnant women, those with history of allergy to iodinated contrast media, and those with renal insufficiency.

Contrast administration

A trained technologist obtains the peripheral intravenous access preferably using a 18-gauge needle. A dose of 1.5 mL/kg bodyweight of iodinated contrast media (Omnipaque

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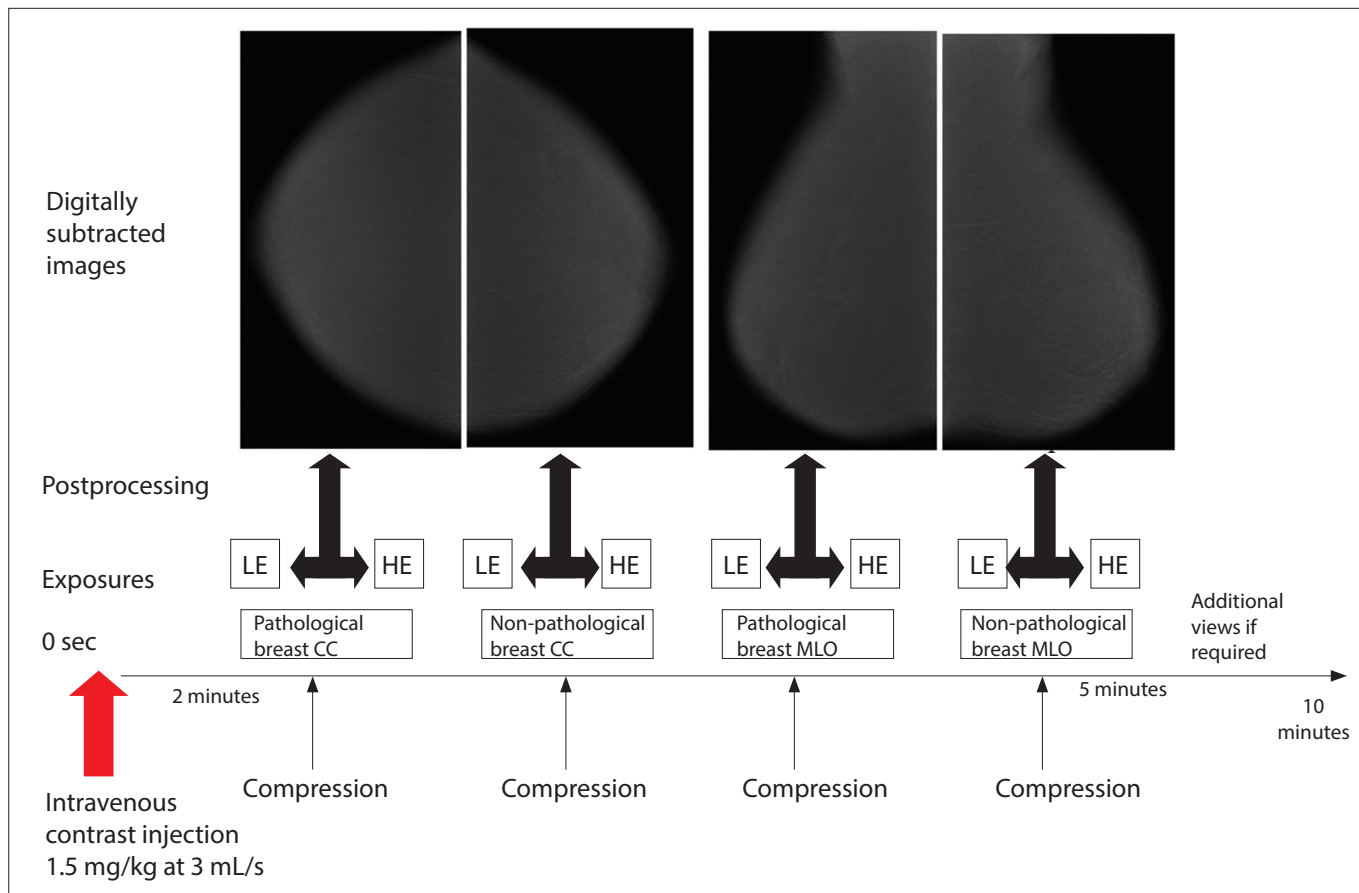


Figure 1. Schematic diagram of contrast-enhanced digital mammography (CEDM) image acquisition according to time line. CC, craniocaudal; MLO, mediolateral oblique; LE, low-energy exposure; HE, high-energy exposure.

Main points

- CEDM is an emerging technique in which digital mammography is supplemented with the use of intravenous iodinated contrast administration.
- Recombined images are used to assess the tumor angiogenesis in which the normal background parenchyma is subtracted and regions with contrast enhancement are highlighted.
- All non-enhancing lesions are considered benign except in the rare situation where enhancing malignant lesion is obscured by the background parenchymal enhancement.
- Enhancing lesions with suspicious morphology on conventional imaging are considered malignant; however, many of the benign pathologies including fibroadenosis, fibroadenoma, infection/inflammation, papilloma, pseudoangiomatous stromal hyperplasia, and radial scar may show false positive enhancement due to hypervascularity.
- CEDM may be used as a problem-solving tool in the evaluation of dense breast, equivocal lesions, local staging, differentiation of aggressive and non-aggressive microcalcifications, post neoadjuvant chemotherapy response evaluation, and differentiation of scar from residual tumor or tumor recurrence.

350; GE Healthcare) is administered using power injector at the rate of 3 mL/s without compression of the breast. Initiation of contrast administration is taken as 0 s.

Image acquisition

After 2 minutes of contrast injection, patient is positioned under mammography for CEDM image acquisition in craniocaudal (CC) and mediolateral oblique (MLO) projections of each breast. In patients with suspicious lesion or in those already diagnosed with breast cancer, CC or MLO projection of pathologic breast is taken first followed by the same view of non-pathologic breast, and the other view of the pathologic and non-pathologic breast. Each projection is exposed to a pair of low (26–32 kVp) and high (45–49 kVp) energy exposures and all images are obtained within 5–7 minutes of contrast injection. Additional diagnostic imaging, if required, should be performed within 10 minutes after the contrast material administration (Fig. 1). Subtracted or recombined images are produced by post-processing in which background parenchyma or noise is subtracted from high-energy

images and only contrast enhancing lesions are displayed. The low-energy images are equivalent to the 2D-FFDM which is used to assess the morphology, and subtracted images are used to assess the contrast enhancement. The radiation exposure dose can change depending on the size and density of the breast. According to studies reported earlier, the mean glandular dose of CEDM is 20%–80% higher than that of conventional mammography (9, 10). However, the mean glandular dose still remains well within the international dose limits for mammography.

Clinical applications

1. As a supplementary or replacement tool to mammography in the evaluation of dense breast or high-risk screening

Women with dense breasts or higher than average lifetime risk of breast cancer may benefit from CEDM in place of mammography or as a supplementary screening tool to mammography. According to the current ACR guidelines, supplemental annual MRI screening is indicated for high-risk

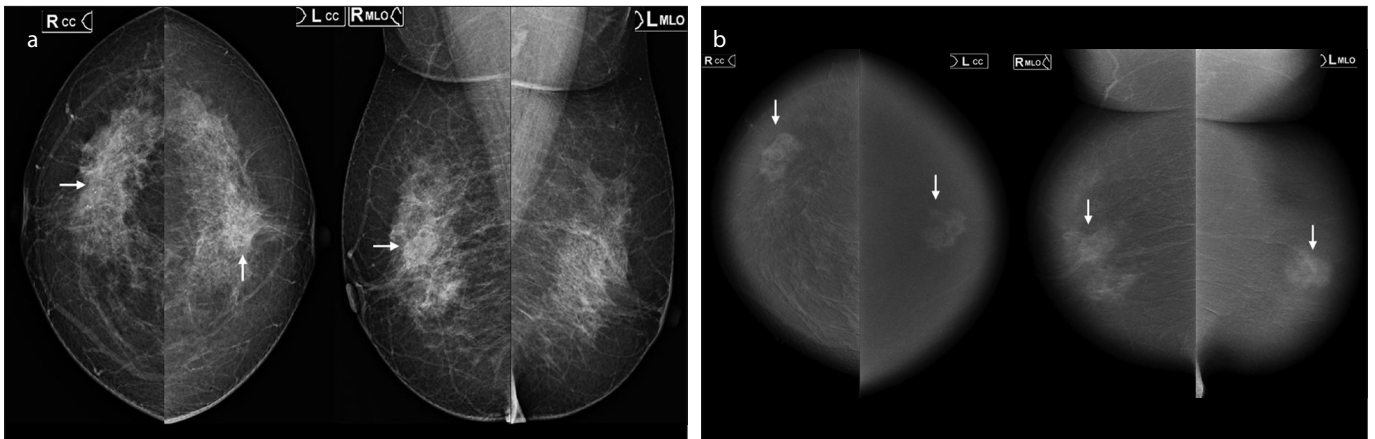


Figure 2. a, b. CEDM images in a 45-year-old woman with bilateral invasive cancer hidden within dense breasts. Low-energy image (a) with craniocaudal (CC) and mediolateral oblique (MLO) views of both breasts show asymmetric density with subtle architectural distortion and microcalcification in upper outer and central right breast (arrows in right CC and MLO views), and subtle asymmetric density in retroareolar left breast (arrow in left CC view). Contrast image (b) of both breasts show heterogeneously enhancing non-circumscribed mass with irregular margins in right breast (arrow) in the corresponding region of abnormalities depicted in (a), with another circumscribed enhancing mass with irregular margins in retroareolar left breast (arrow in left CC and MLO views). Subsequent biopsies from both breasts diagnosed invasive ductal carcinomas, grade 2 in right breast, and grade 1 in left breast.

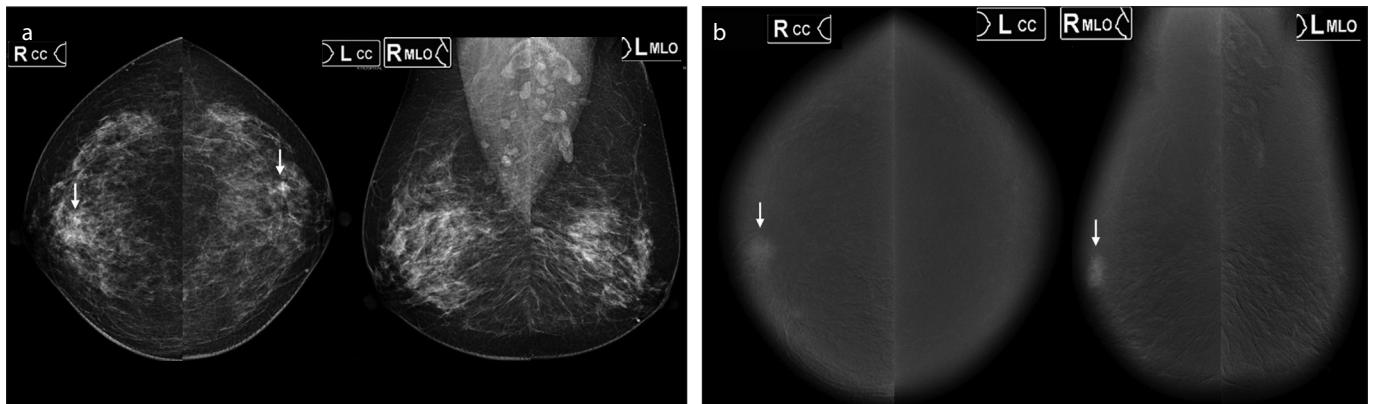


Figure 3. a, b. CEDM images in a 42-year-old, high-risk woman (BRCA2 positive) with invasive ductal carcinoma. In image (a), CC and MLO views show heterogeneously dense breast tissue with subtle focal asymmetric densities in bilateral breast seen only in CC views (arrows). Contrast image (b) shows an enhancing mass with irregular margins in retroareolar right breast (arrow), corresponding to the region of abnormality noted in (a); however, there is no enhancing focus/mass in left breast, suggesting that left breast focal asymmetric density noted in (a) is not due to neoplastic etiology. Subsequent biopsy from right breast mass yielded invasive ductal carcinoma, grade 2.

women of any breast density, and annual surveillance breast MRI for women with dense breast with personal history of breast cancer, or those women who are diagnosed before the age of 50. However, MRI is cost effective as a supplemental screening tool only for women with a >20% life-time risk of getting breast cancer, such as women with BRCA1 or BRCA2 mutations (11, 12). Initial investigations done by other authors have shown that CEDM has significantly higher sensitivity and negative predictive value than 2D mammography and comparable to MRI (8, 13, 14). Hence, CEDM may be a suitable low-cost alternative in women with dense breasts or among those having higher than average life-time risk of breast cancer especially when MRI is not available or it cannot be performed (Figs. 2, 3).

2. As a problem-solving tool to mammographically equivocal lesions

Occasionally at the completion of mammography work up, it may be difficult to determine whether the potential lesion (asymmetric densities, distortion or mass) is real and clinically significant or not. Studies have reported CEDM as a problem-solving tool in equivocal cases by providing additional information of contrast enhancement and changed the diagnosis and treatment strategies in a significant number of patients (15). On CEDM, all non-enhancing lesions in the breast are considered benign except in the rare situation where enhancing lesion is obscured by the background parenchymal enhancement (Fig. 4). Enhancing lesions are con-

sidered malignant; however, similar to MRI, many of the benign conditions such as myxomatous fibroadenoma, benign phyllodes, infective or inflammatory mastitis, papilloma, pseudoangiomatous stromal hyperplasia and radial scar may show false positive enhancement due to vascularization. Hence, enhancement features should be correlated with morphological features to avoid misdiagnosis. Fibroadenomas might display homogeneous enhancement with characteristic non-enhancing thin internal septations on CEDM, but this is not a rule (Fig. 5).

3. Local staging of the tumor

Accurate determination of the size, extent of the breast cancer and detection of

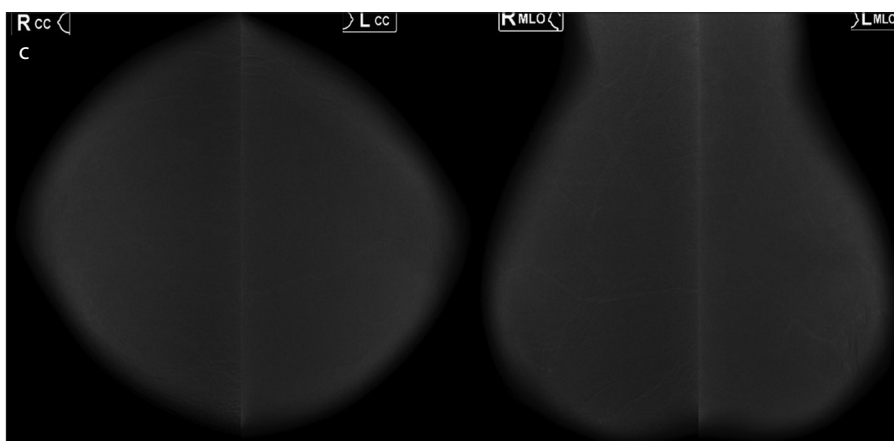
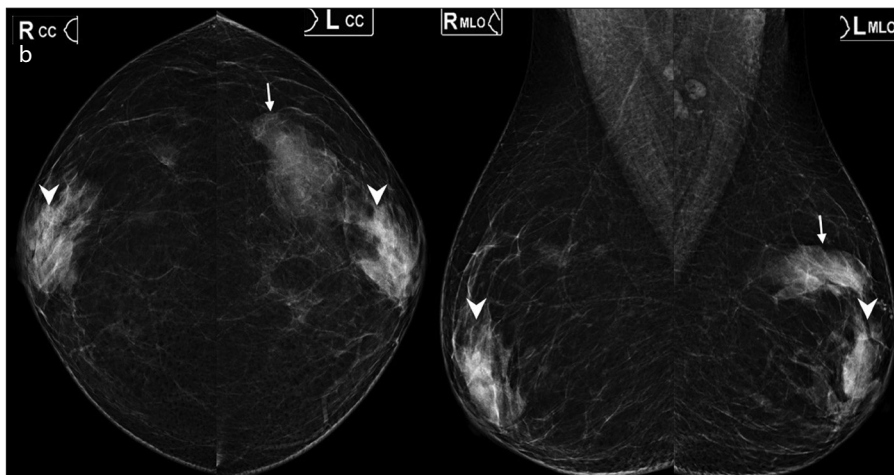
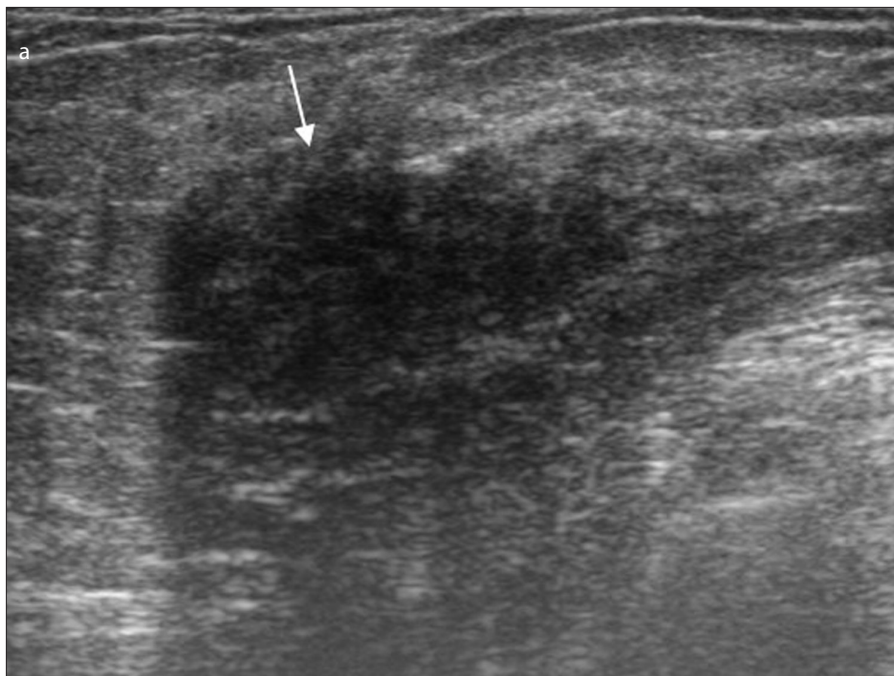


Figure 4. a–c. High-resolution ultrasound (HRUS) and CEDM images in a 44-year-old woman with equivocal left breast lump. HRUS image (a) shows non-circumscribed heterogeneous hypoechoic area (2.8×1.6 cm) in left upper outer quadrant. Low-energy CC and MLO views of both breasts in panel (b) show bilateral symmetrical retroareolar dense breast (arrowhead) and focal asymmetric density in left upper outer quadrant (arrow) corresponding to the US findings. Contrast image (c) shows no enhancement of the asymmetric density noted in (a). Subsequently, ultrasound-guided biopsy of the left breast lump yielded fibroadenosis.

additional malignant lesions in the same breast or contralateral breast are crucial for staging and therapeutic planning. Initial studies suggest that delineation of the tumor border and size as measured on CEDM are more accurately correlated with the pathological size than the tumor size on digital mammography and ultrasound (16). A study comparing CEDM and MRI for local staging of breast cancer found both to have similar sensitivity (94% for CEDM vs. 99% for MRI) with much lower false positive rates for CEDM (5% vs. 45%) (17). CEDM is cost effective, has much shorter examination time and is well tolerated by patients. Hence, it can be used as a low-cost alternative to MRI to assess the extent of breast cancer (Fig. 6).

4. Evaluation of microcalcification

Microcalcifications are the earliest and may be the only sign of non-palpable breast cancer, which can be detected on screening mammography and they are usually diagnosed to have ductal carcinoma in situ (DCIS). Microcalcifications can also be seen in invasive cancers (18). Low-grade DCIS may be overdiagnosed as they do not have any impact on survival; however, most often, it is not possible to differentiate low-grade from high-grade DCIS on the basis of morphologic features of microcalcifications. CEDM helps in distinction of low-grade and aggressive microcalcifications by demonstrating enhancement around the calcification due to neo-angiogenesis. In our experience of 95 patients who were evaluated with CEDM and subsequently underwent vacuum-assisted breast biopsy or excision biopsy, all patients with suspicious microcalcifications and enhancement around microcalcifications on CEDM (54 of 95 patients) were diagnosed to have intermediate or high-grade DCIS with or without invasive component on histopathology (Fig. 7). Microcalcifications without enhancement (41 of 95) on CEDM were either low-grade DCIS (6 of 41) or benign breast tissue (35 of 41) (Fig. 8). Initial investigations done by other authors found that CEDM has very high sensitivity (88.89%), specificity (86.56%), negative predictive value (95.08%) and accuracy (87.24%) for detecting breast cancer in patients with microcalcifications (19). Hence, morphological criteria as well as the contrast enhancement are important for evaluation of malignancy potential in microcalcifications.

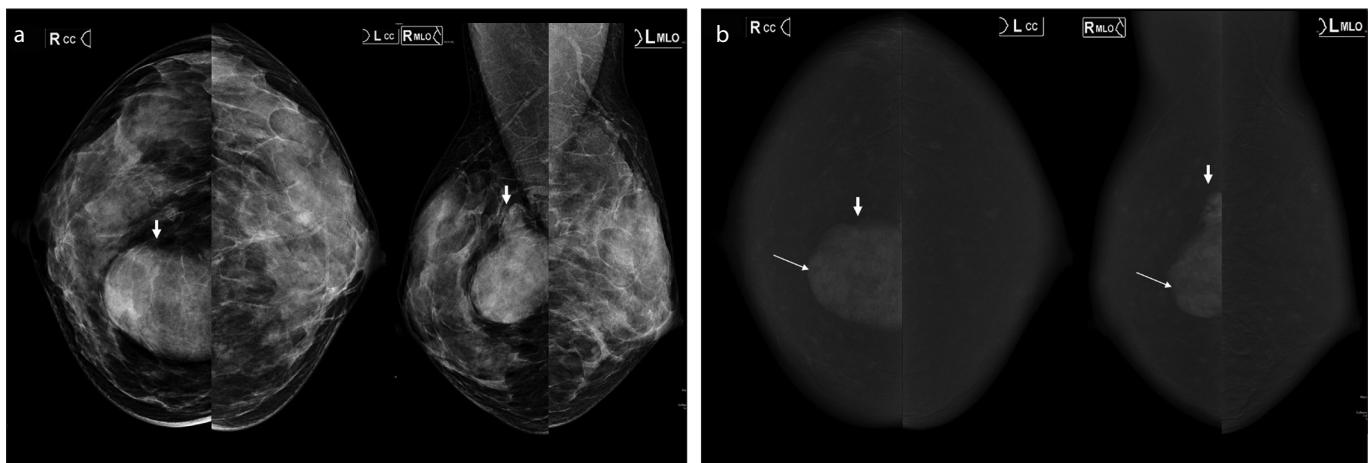


Figure 5. a, b. CEDM images of a 42-year-old woman with large solid mass in right breast. Low-energy CC and MLO views in panel (a) show bilateral dense breast with a large iso- to hyperdense mass with smooth lobulated margins in inner central quadrant of the right breast (arrow). Contrast image (b) shows enhancement of the mass with non-enhancing thin linear hypodense areas (arrows) which could represent fibrous septations in fibroadenoma. Subsequent histopathologic examination yielded proven myxomatous fibroadenoma.

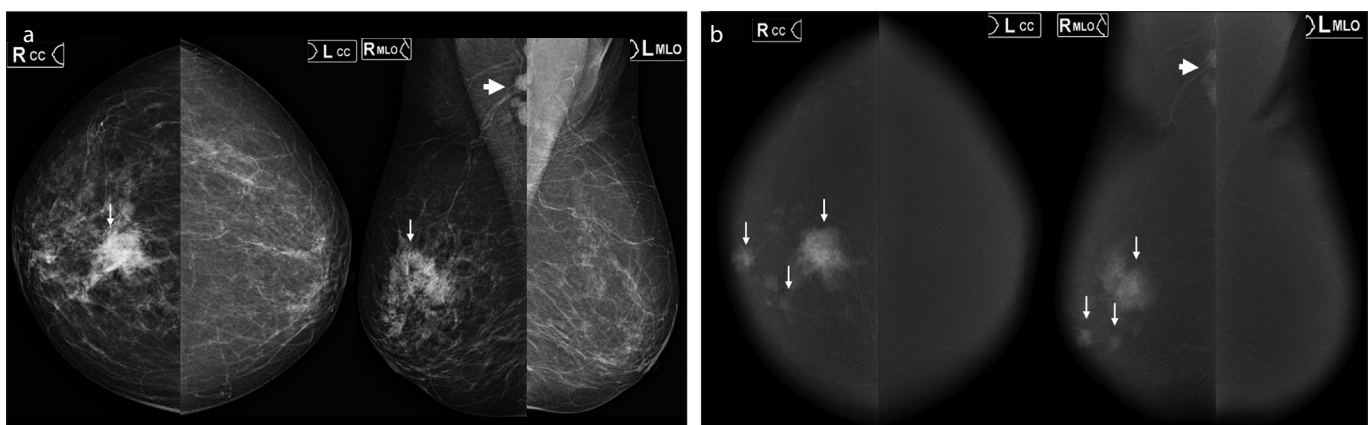


Figure 6. a, b. CEDM images in a 70-year-old woman with multifocal invasive breast cancer and ipsilateral axillary node metastasis. Low-energy CC and MLO views in panel (a) show a non-circumscribed hyperdense irregular mass with architectural distortion in central and upper inner quadrant of right breast (arrow) and enlarged right axillary nodes. Contrast image (b) shows intense heterogeneous enhancement of the mass identified in (a) with multiple additional small enhancing irregular nodules in ductal distribution in retroareolar and lower inner quadrant with enhancing right axillary lymph nodes (arrowhead). Subsequent histopathology yielded infiltrating ductal carcinoma with ductal carcinoma in situ (DCIS), intermediate nuclear grade, and cytology of the right axillary node showed metastasis from carcinoma breast.

5. Metastatic axillary node with occult primary breast cancer

Management of isolated axillary node metastasis with suspected primary cancer in the breast without clinical or radiological evidence of primary mass is very challenging and it is not uncommon to find this type of presentation in clinical practice. Currently, MRI is indicated to detect the occult primary breast cancer (20). We have used CEDM to identify and localize the primary occult lesion in the breast, and the results have been very promising so far (Fig. 9).

6. Evaluation of breast with multiple lesions

Among patients with multiple breast masses with varying imaging morphol-

ogies, identification of most suspicious mass is important to avoid multiple unnecessary or repeated biopsies. CEDM is more specific than mammography and aids in selecting the most appropriate site for biopsy by demonstrating tumor morphology as well as the enhancement (Fig. 10). It also helps in identification of multifocal or multicentric or bilateral breast cancers, which were either obscured in dense breast or equivocal on mammography (Fig. 11).

7. Post neoadjuvant chemotherapy response evaluation

Neoadjuvant chemotherapy has become the standard of care for the treatment of locally advanced breast cancer

prior to surgery to increase the chances of breast conservative surgery in place of radical mastectomy. Currently, MRI is considered the gold standard for response evaluation; however, it may not be possible to do MRI in all patients due to certain limitations and contraindications. Similar to a study reported by El Said et al. (21) we also found CEDM to have high accuracy (comparable to MRI) in predicting the pathological complete response and residual tumor size (Figs.12, 13).

8. Tumor recurrence versus postoperative scar after breast conservative surgery and radiotherapy

Detection of recurrence at the prior lumpectomy site is challenging for radiol-

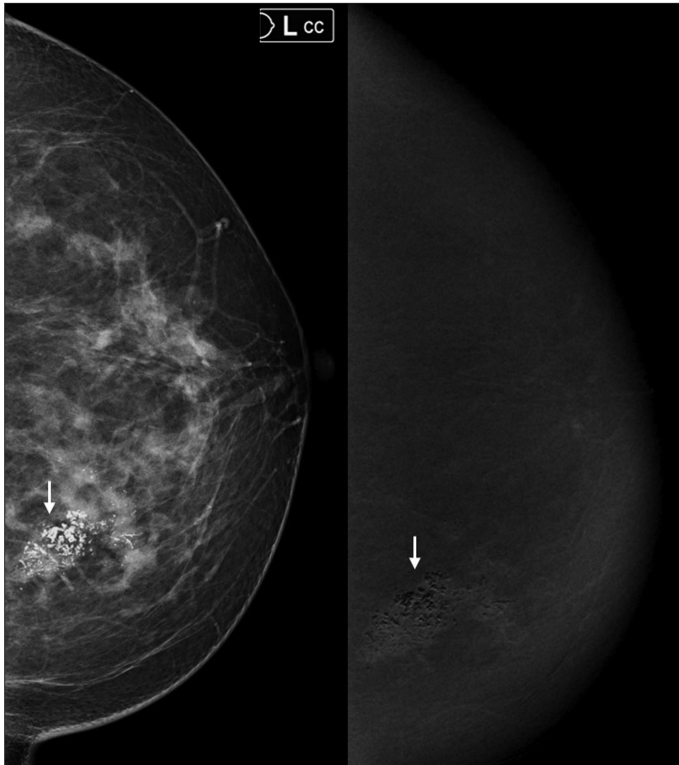


Figure 7. Left breast CC low energy and contrast images in a 53-year-old woman show a group of coarse heterogeneous calcifications with non-mass enhancement around the calcifications in segmental distribution (*arrow*). Subsequent stereotactic and excision biopsy diagnosed DCIS, intermediate nuclear grade without invasive cancer.

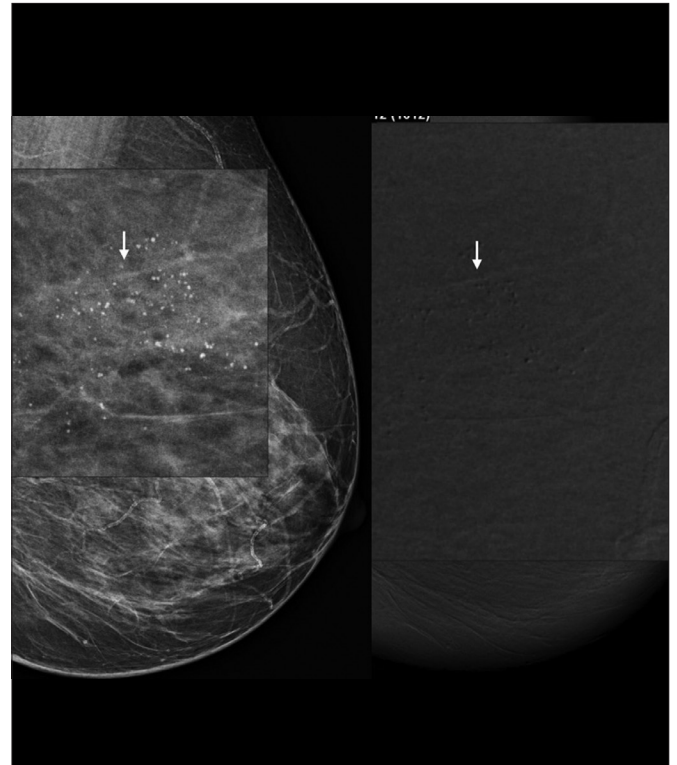


Figure 8. Left breast MLO magnified view in a 51-year-old woman shows a group of microcalcifications. Contrast image shows no enhancement (*arrow*). Subsequent vacuum-assisted breast biopsy proved benign breast tissue.

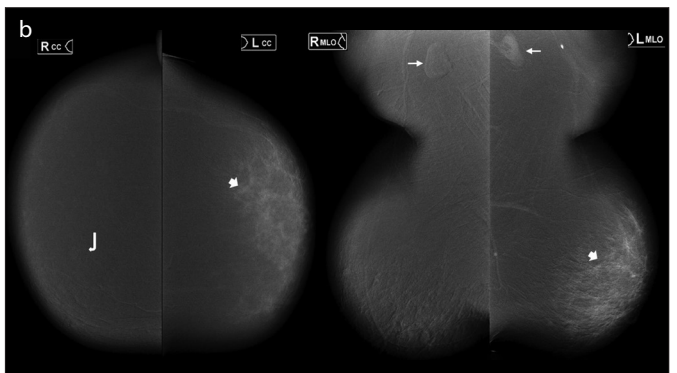


Figure 9. a, b. CEDM images in a 48-year-old woman with axillary node metastasis with unknown primary. Low-energy CC and MLO views in panel (a) show bilateral axillary nodes (*arrows*) with a small circumscribed nodule in lower inner quadrant (*curved arrow*). Contrast image (b) shows diffuse non-mass enhancing lesion in left breast, predominantly in upper outer quadrant (*thick arrows*) with enhancing bilateral axillary nodes (*thin arrows*) and a non-enhancing small fibroadenoma in right breast (*curved arrow*). Subsequent biopsy from left breast yielded infiltrating carcinoma with lobular features.

ogists because of post-treatment changes in the breast tissue. Clinical examination, mammography and ultrasound findings of breast may raise suspicion of recurrence requiring biopsy or surgery. On CEDM, recurrent lesion shows enhancement due to neo-angiogenesis and surgical scar does not show enhancement because of hypovascular fibrotic tissue (Figs. 14, 15).

Conclusion

Although mammography and ultrasound remain the primary diagnostic imaging modalities for the breast evaluation worldwide, several studies and our initial experience also confirmed CEDM to have higher diagnostic accuracy than mammography alone or with ultrasound. CEDM can be used as a low-cost

alternative to MRI as a problem-solving tool in regular clinical practice and therapeutic planning of breast cancer, which may include high-risk screening, dense breast evaluation, equivocal cases, microcalcifications, local staging, treatment response evaluation and post-treatment follow-up. However, CEDM has a few limitations such as administration of iodinated contrast media with low risk of

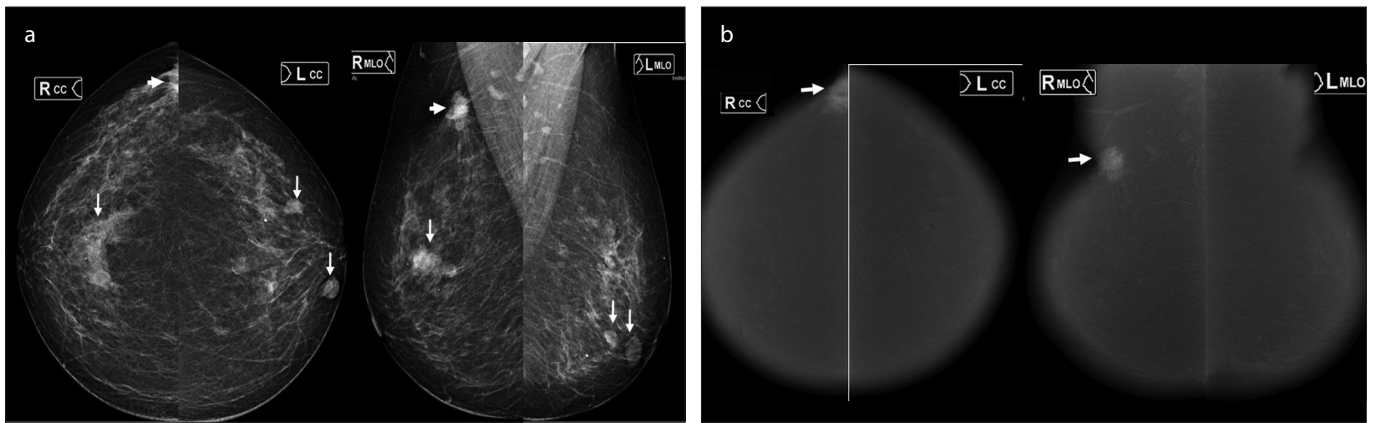


Figure 10. a, b. CEDM images in a 54-year-old woman who presented with right breast lump. Low-energy CC and MLO views in panel (a) show multiple masses of varying morphologies in both breasts (*arrows*). Contrast image (b) shows only one enhancing mass in right axillary tail region with spiculated margins (*arrow*) and rest of the lesions depicted in (a) are non-enhancing consistent with benign pathology. Subsequent core biopsy from the enhancing mass yielded infiltrating ductal carcinoma, grade 2 and non-enhancing right breast mass depicted in mammogram yielded fibroadenosis.

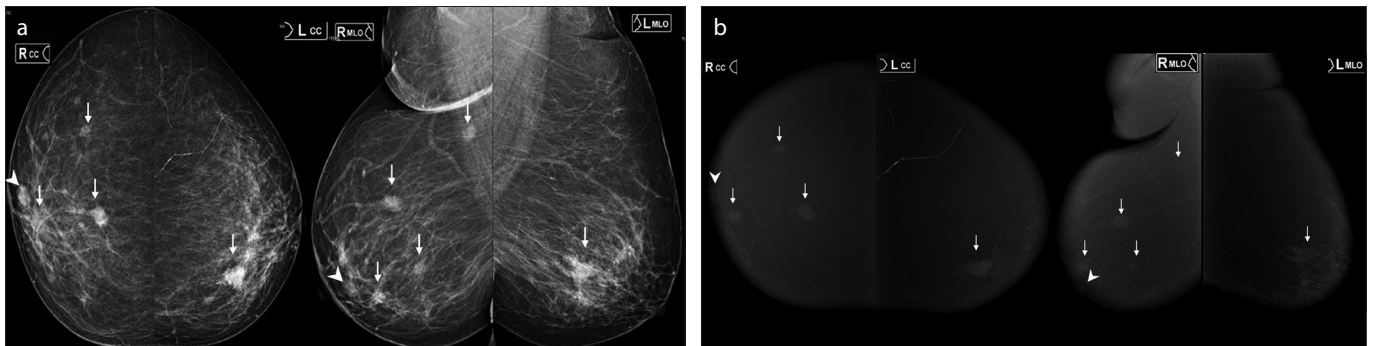


Figure 11. a, b. CEDM images in a 58-year-old woman with multicentric and bilateral breast cancer. Low-energy CC and MLO views in panel (a) show multiple small lesions of varying morphologies in both breasts (*arrows* and *arrowhead*). Contrast image (b) demonstrates heterogeneous enhancement of all the lesions noted in both breasts except the one indicated with *arrowhead* in (a). Subsequent core biopsy from each enhancing mass from both breasts yielded infiltrating ductal carcinoma and the non-enhancing mass proved to be a fibroadenoma .

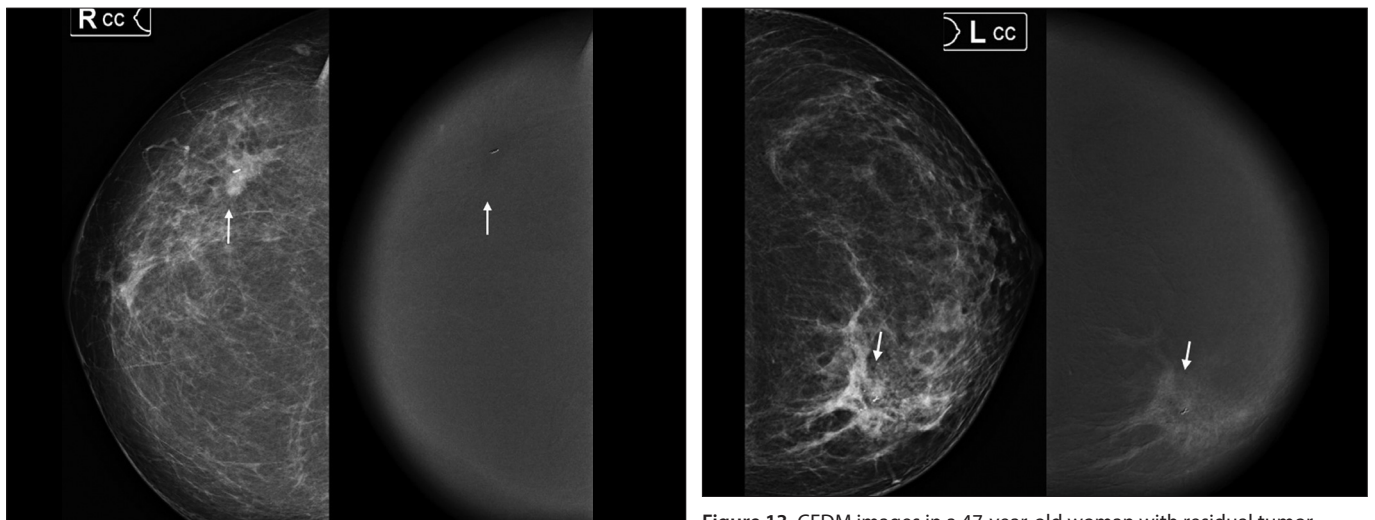


Figure 12. CEDM images in a 55-year-old woman with pathological complete response after neoadjuvant chemotherapy. Low-energy right CC image shows a focal asymmetric density with architectural distortion around the clip in outer quadrant (*arrow*). Contrast image shows no enhancement (*arrow*), concordant with the subsequently proven histopathological diagnosis.

Figure 13. CEDM images in a 47-year-old woman with residual tumor after 4 cycles of chemotherapy. Low-energy CC image shows asymmetric density around the clip with architectural distortion in inner quadrant (*arrow*). Contrast image shows non-mass heterogeneous enhancement with better delineation of tumor borders and extent (*arrow*). Subsequently, patient underwent breast conservative surgery and histopathology yielded infiltrating carcinoma with DCIS.

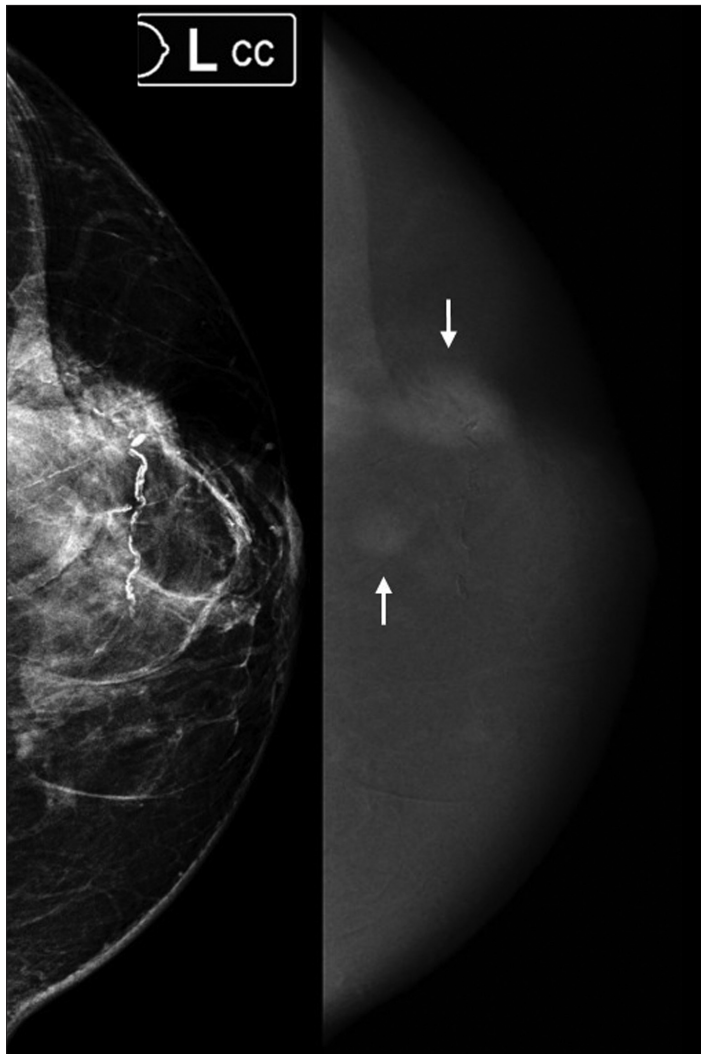


Figure 14. CEDM images in a 57-year-old woman with recurrence at the post-operative site. Left CC view shows focal distortion with skin retraction in outer quadrant (*arrow*). Contrast image shows multiple enhancing nodules at the corresponding site (*arrows*). Subsequent histopathology diagnosed invasive ductal carcinoma.

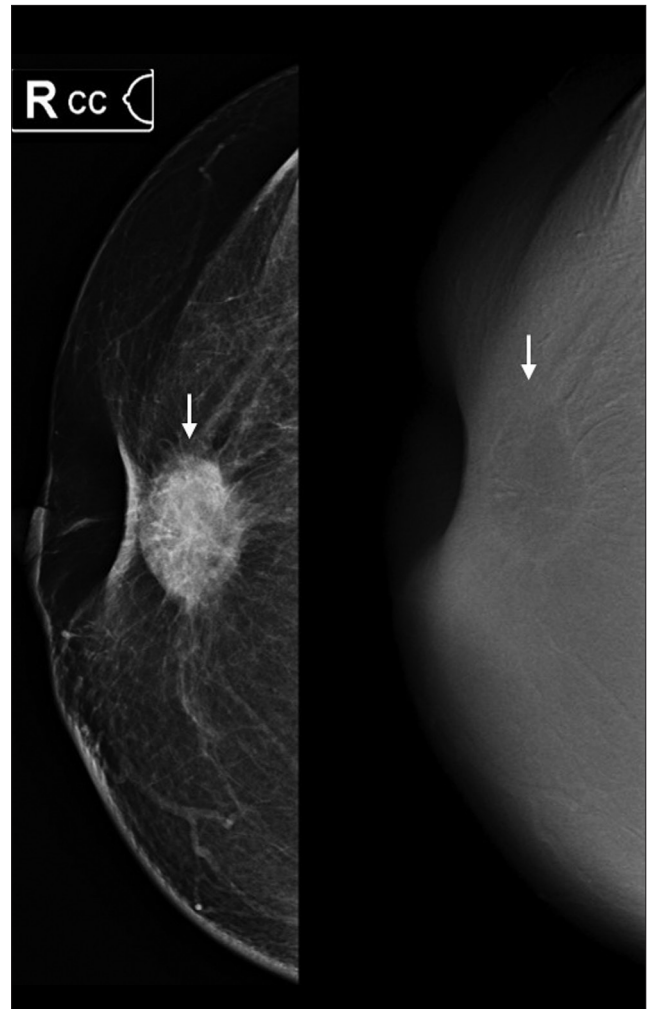


Figure 15. CEDM images in a 54-year-old woman with post-operative organized collection 2 years after the breast conservative surgery. CC view of right breast shows rounded dense mass with spiculated margins in retroareolar breast with skin retraction (*arrow*) suggests strong suspicion of recurrence at the post-operative site. Contrast image shows thin rim enhancement, consistent with loculated collection (*arrow*) and rules out tumor recurrence.

contrast reactions, theoretical risk from radiation exposure and low rates of false positive and false negative results.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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