

Uses of Contrast-Enhanced Mammography in a Regional Clinical Institute: A Pictorial Essay

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INTRODUCTION

Contrast-enhanced mammography (CEM) is a modality used as an adjunct to non-contrast mammographic imaging for multiple clinical indications, including evaluation of indeterminate abnormalities on mammography, workup of symptomatic patients, staging of breast cancer, and monitoring response to neoadjuvant chemotherapy.

Our centre provides diagnostic imaging for patients with breast symptoms through combined full-field digital mammography with tomosynthesis and ultrasound. We introduced CEM in 2019. This pictorial essay highlights the uses of CEM in daily clinical practice through selected cases.

IMAGING PROTOCOL

We use a Selenia Dimensions 3D Digital Mammography system (Hologic, Glasgow [DE], US) to acquire CEM images. Two minutes prior to image acquisition, iohexol (Omnipaque 300; GE Healthcare, Milwaukee [WI], US) is administered intravenously at 1.5 mL/kg and a rate of 3 mL/s, followed by a saline flush. The breasts are not

compressed during injection to facilitate blood flow.

A pair of images (one low-energy image and one high-energy image) is acquired in the standard craniocaudal and mediolateral oblique views for each breast. Additional views, including magnification or spot compression, can be acquired if needed using conventional mammographic technique. The ideal imaging window is within 10 minutes after contrast administration before contrast washout commences.^{1,2}

The low-energy images used in subtraction have been shown to have equivalent diagnostic value compared to full-field digital mammography, as their K-edge is lower than that of iodine, eliminating the need for an additional set of conventional images.³ These images are reported using the latest BI-RADS (Breast Imaging Reporting and Data System) mammography lexicon.⁴ The high-energy images are used to subtract the low-energy images, emphasising the areas of iodine uptake. The subtracted images are interpreted using the BI-RADS 2022 CEM lexicon.⁵

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There is currently no universal consensus on the imaging sequence.¹ Our centre prefers to start with the symptomatic breast as it presumably has the highest concentration of contrast agent and, therefore, better lesion conspicuity at the beginning of image acquisition.² No consensus has been reached regarding the optimal timing of CEM within the menstrual cycle.^{6,7}

DIAGNOSTIC PERFORMANCE OF CONTRAST-ENHANCED MAMMOGRAPHY

Full-field digital mammography and/or tomosynthesis and ultrasound remain the mainstays of breast assessment. However, the sensitivity of mammography decreases in dense breast parenchyma. Magnetic resonance imaging (MRI) is an advanced imaging modality known for its high sensitivity and negative predictive value (NPV), though its use is compromised by high cost and limited availability.

CEM, a relatively recent and more affordable adjunct for assessing both lesion morphology and vascularity, has gained popularity. Various studies have evaluated its diagnostic performance. CEM has been shown to have superior clinical performance compared to full-field digital mammography and/or ultrasound.⁸⁻¹⁰ Cheung et al⁸ showed that CEM increased sensitivity from 71.5% to 92.7% and specificity from 51.8% to 67.9% in dense breasts, compared to mammography alone. In a meta-analysis by Cozzi et al,¹¹ CEM had a pooled sensitivity of 95% and specificity of 81% in breast cancer detection. CEM shares MRI's sensitivity for diagnosing breast cancer.^{12,13} It may be a reliable alternative when MRI is contraindicated or not tolerated, or when simultaneous assessment of suspicious calcifications and contrast enhancement is needed. However, lesion location may affect the feasibility of CEM as an alternative. Lesions in obscured areas on conventional mammography and nodal status are not well assessed by CEM since they share same field of view and might be overlooked.¹⁴

EVALUATION OF ARCHITECTURAL DISTORTION

The BI-RADS lexicon defines architectural distortion (AD) as "a distortion of breast tissue with no definite visible mass but with spiculations that radiate from a point with focal retraction or distortion at the edge of the parenchyma".⁴ Differential diagnoses include both malignant and benign entities, such as radial scars,

complex sclerosing lesions, and postoperative changes. Image-guided biopsy or surgical excision is typically recommended for suspicious AD.

With the increasing use of digital breast tomosynthesis, the detection rate of AD has risen.¹⁵ One study reported that nearly 60% of AD foci are benign.¹⁶ Identifying features that support or discourage biopsy may be helpful. Contrast-enhanced modalities such as MRI enable further evaluation of AD, especially if the finding is equivocal, by assessing areas of contrast enhancement, presumably related to angiogenesis and vascular leakage in malignancies.¹⁷ MRI has shown a high NPV (98%) when there is no enhancement in AD,¹⁸ but it is not easily accessible due to high costs and long queuing times in a busy clinical institute setting.

CEM is a promising alternative for AD assessment, with lower cost and shorter acquisition time. Patel et al¹⁹ reported a high NPV (92%) for malignancy when primary AD showed no enhancement on CEM. While this supports using CEM as an additional tool for assessing tomosynthesis-detected AD, our centre still recommends image-guided biopsy as the likelihood of malignancy remains in BI-RADS category 4A lesions, and some low-grade malignant lesions may not enhance.

Conversely, the high NPV in non-enhancing primary AD could be applied in cases where a histological diagnosis had already been obtained to help confirm imaging-histopathologic concordance in cases with benign biopsy results.²⁰ The increasing number of AD biopsies yielding non-malignant pathology, due to the better detection rate of AD on digital breast tomosynthesis, adds complexity. The absence of contrast enhancement on CEM can help confirm concordance in these cases (Figure 1).

ASSESSMENT OF CALCIFICATIONS

The approach to calcifications varies with the degree of malignancy risk based on BI-RADS descriptors.⁴ Biopsy is offered for suspicious cases, while short-interval follow-up imaging is recommended for those deemed probably benign.

Sometimes suspicious calcifications can be challenging to manage, especially when unaccompanied by soft-tissue abnormalities and with no corresponding sonographic lesion to allow further actions such as localisation or biopsy in a readily feasible way. As CEM

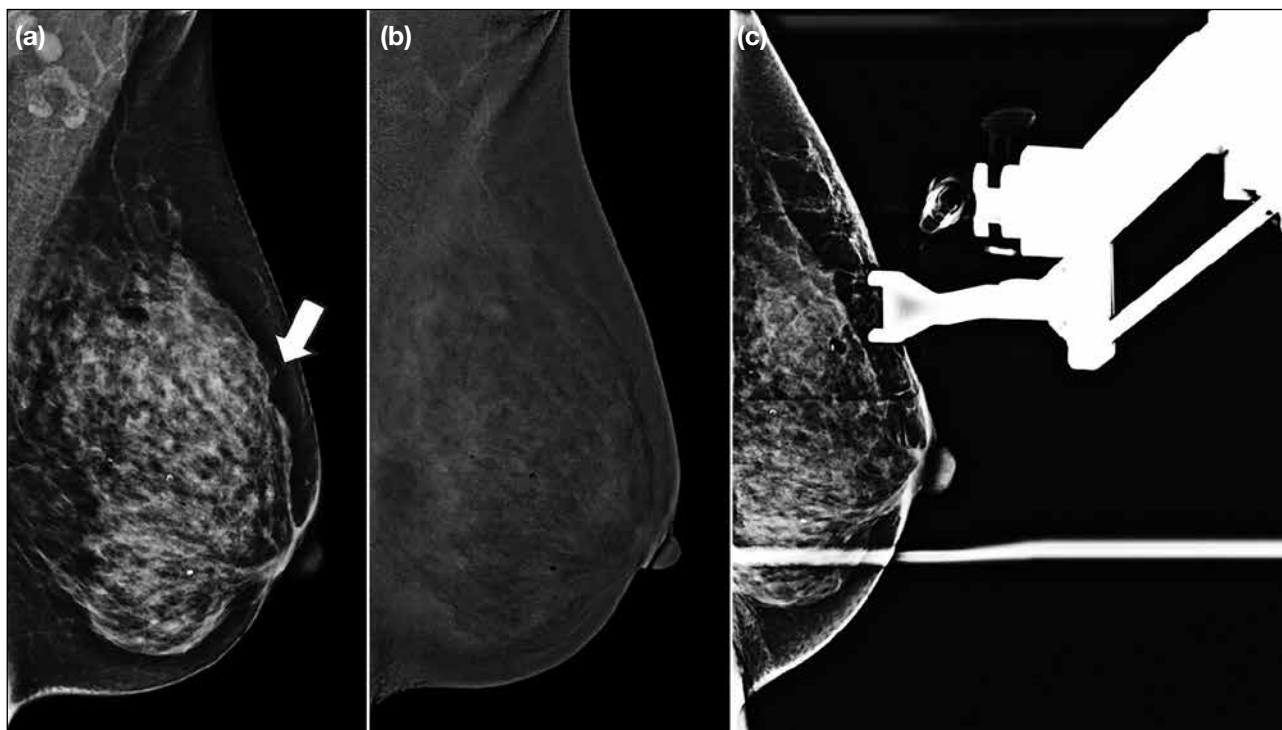


Figure 1. Case of a 53-year-old woman. (a) Low-energy mediolateral oblique view showing architectural distortion (arrow) in the upper left breast. (b) Corresponding recombined images showing no associated enhancement or focal mass. (c) Stereotactic-guided vacuum-assisted biopsy was performed and the postprocedural image demonstrates a marker within the region of the biopsied architectural distortion. Histopathological analysis revealed proliferative fibrocystic changes and a possible sclerosing lesion.

consists of both low-energy and subtracted images, this allows for the simultaneous delineation of calcifications and associated contrast enhancement. The presence of associated contrast enhancement correlates well with the likelihood of malignancy.^{21,22} Therefore, it may be useful for selecting lesions for CEM-guided localisation, particularly in cases of nonpalpable lesions that are invisible on sonography (Figure 2). Again, however, the absence of contrast enhancement does not exclude malignancy.^{21,22} The morphology and distribution of calcifications remain the key determinants. Further exploration of this application is warranted.

PREOPERATIVE STAGING OF BREAST CANCER

It is often difficult to determine the optimal surgical approach, namely, breast-conserving treatment or mastectomy, in patients with suspected additional tumour foci in the ipsilateral or contralateral breast. In addition, the Asian population often has dense breast tissue,²³ which lowers the sensitivity of mammography and complicates the surgical decision making.

The application of CEM in assessing tumour extent has been compared to conventional mammography, ultrasound, and MRI. Both CEM and MRI have higher sensitivity for cancer detection compared to conventional mammography and ultrasound alone (Figures 3 to 6).^{24,25} Compared to MRI, CEM exhibits similar sensitivity in detecting the index cancer and secondary cancer.^{25,26} Preliminary results from the studies²⁴⁻²⁶ demonstrate that CEM may be a feasible and cost-effective modality for preoperative staging.

MONITORING RESPONSE TO NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy (NAC) has been an important strategy for patients with locally advanced breast cancer. NAC helps improve surgical and cosmetic outcomes by shrinking tumour size, downgrading the nodal status, and increasing the likelihood of successful breast conservation.

Accurate imaging assessment of treatment response is therefore essential, and MRI is a reliable tool, superior

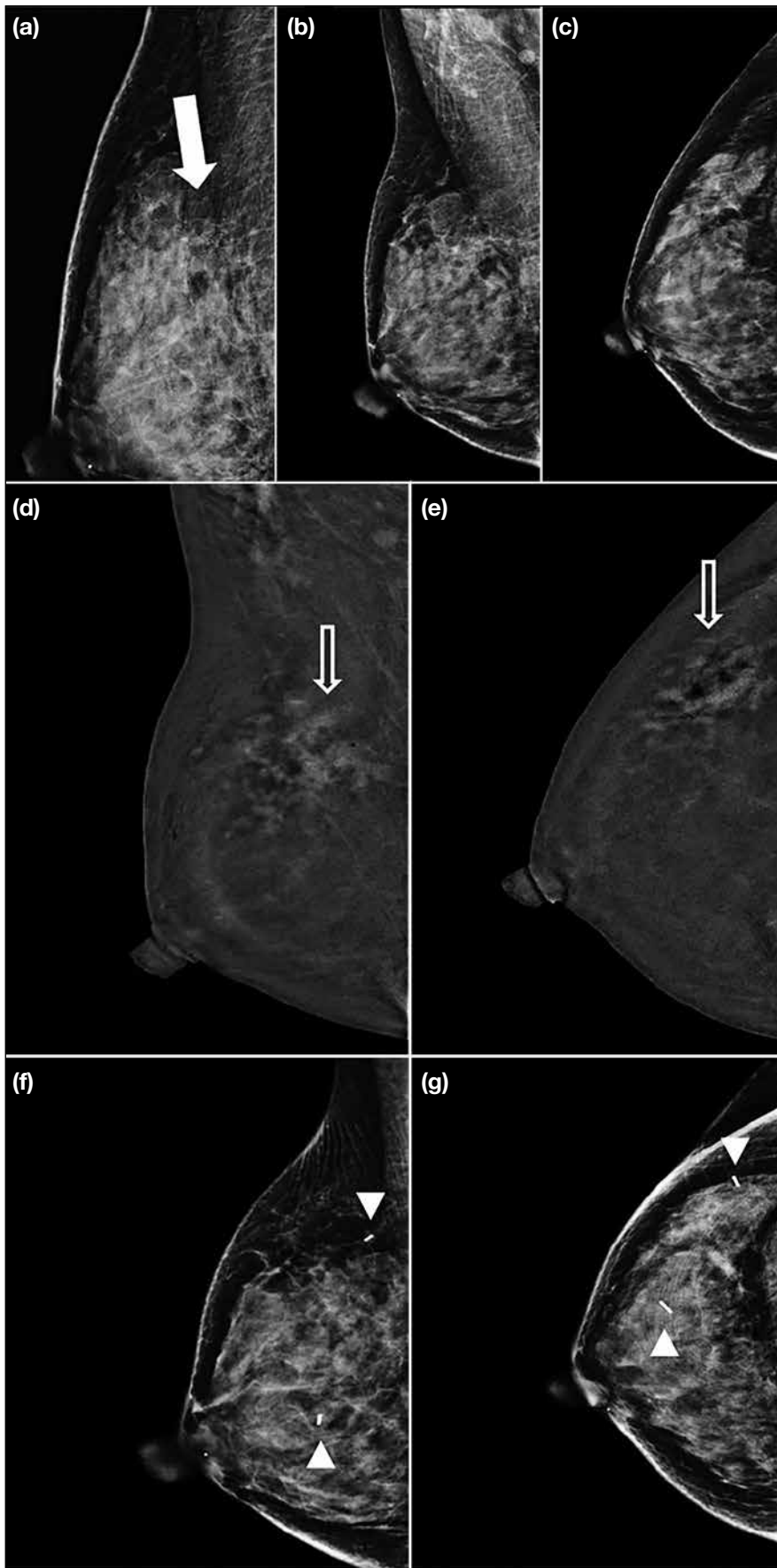


Figure 2. A 48-year-old woman recalled from screening for suspicious calcifications; clinically, no palpable lesion was noted. (a) Magnification view of low-energy image of right breast upper portion. (b-e) Low-energy and subtracted contrast-enhanced mammography (CEM) images of the right breast in craniocaudal (CC) and mediolateral oblique (MLO) views. CEM images demonstrated segmental fine pleomorphic and coarse heterogeneous calcifications (arrow), with associated clumped non-mass enhancement (open arrows) in the upper outer quadrant of the right breast. These findings were highly suspicious for malignancy and biopsy-confirmed ductal carcinoma in situ. (f, g) Mammography of the right breast in CC and MLO views. Breast-conserving treatment was planned. Stereotactic-guided marker placement (arrowheads) was performed for lesion bracketing.

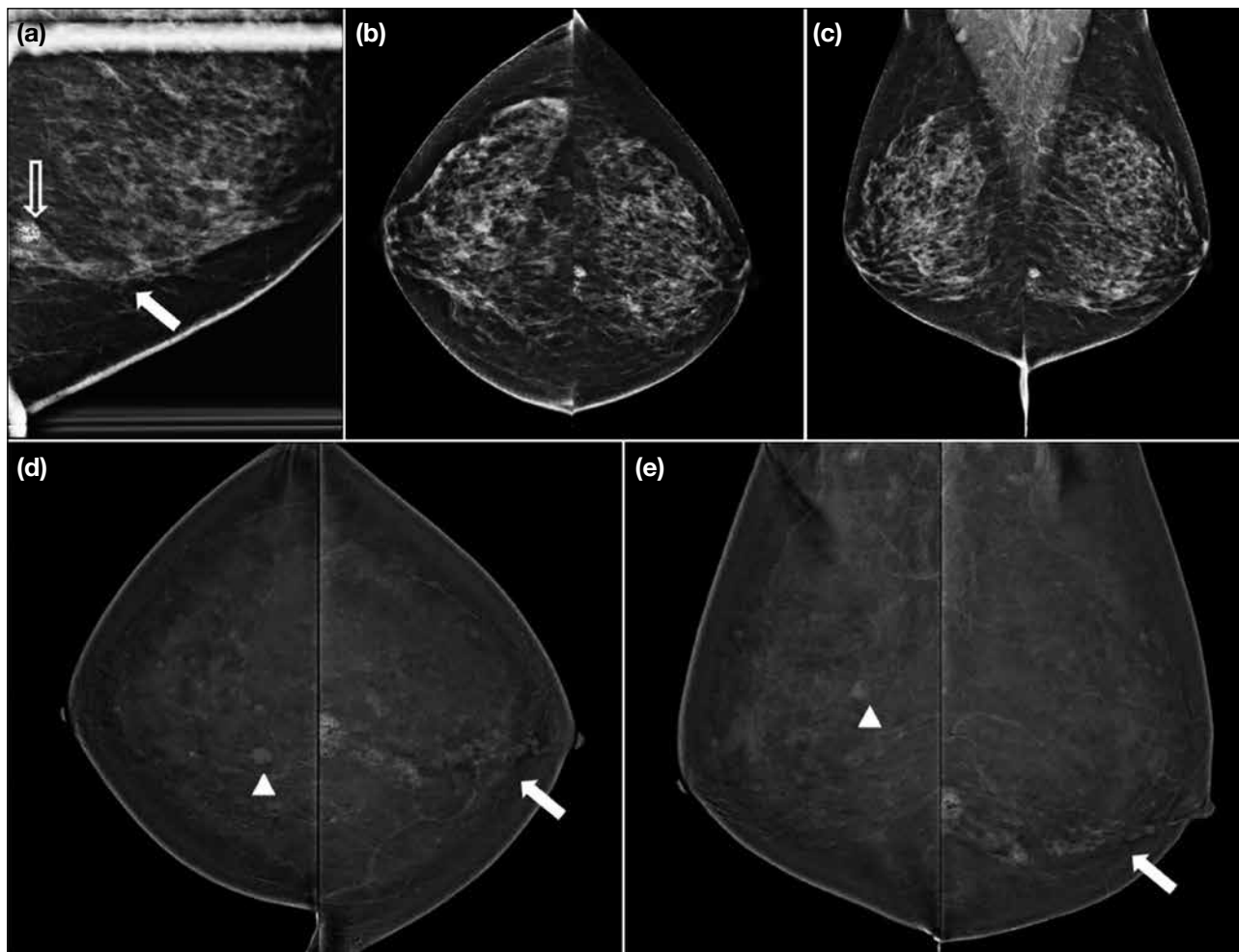


Figure 3. A 53-year-old woman with preoperative staging for newly diagnosed left breast malignancy. (a) Contrast-enhanced mammography (CEM) magnification view of low-energy image of the left breast inner portion shows an oval circumscribed lesion with internal calcification (open arrow) and heterogeneous enhancement (arrow) at the lower outer quadrant, which was subsequently biopsied and confirmed as malignant. (b-e) CEM low-energy and recombined images of bilateral breasts in craniocaudal and mediolateral oblique views demonstrate coarse heterogeneous and fine pleomorphic calcifications in segmental distribution at the lower central portion of the left breast, with associated clumped non-mass enhancement extending towards the left nipple (arrows), suggestive of malignancy. An irregular lesion with homogeneous enhancement is noted in the upper inner quadrant in the right breast (arrowheads), with low suspicion for malignancy; this lesion was not seen on prior breast imaging.

to the combination of clinical examination, conventional mammography, and ultrasound.²⁷ Nonetheless, MRI is not always readily available due to limited access and patient-related factors such as long wait times, allergy to contrast agents, kidney problems, claustrophobia, or the presence of metallic devices (Figures 7 and 8). CEM has a lower cost in terms of examination time and resources; it has been an increasingly popular tool to assess treatment response. The results are promising, showing comparable performance between MRI and CEM in evaluating the pathological response of breast cancer to NAC (Figures 9 and 10).²⁸

OTHER CONSIDERATIONS: BREAST CANCER SCREENING

MRI is recommended as a supplemental screening tool in breast cancer screening for high-risk populations, defined as women with a lifetime risk of more than 20% according to the American Cancer Society and the American College of Radiology.²⁹ For women at intermediate risk, defined as those with a lifetime risk between 15% and 20%, breast MRI is suggested for those with dense breasts and a history of breast cancer diagnosed before the age of 50 years, according to the American College of Radiology.²⁹ The introduction of

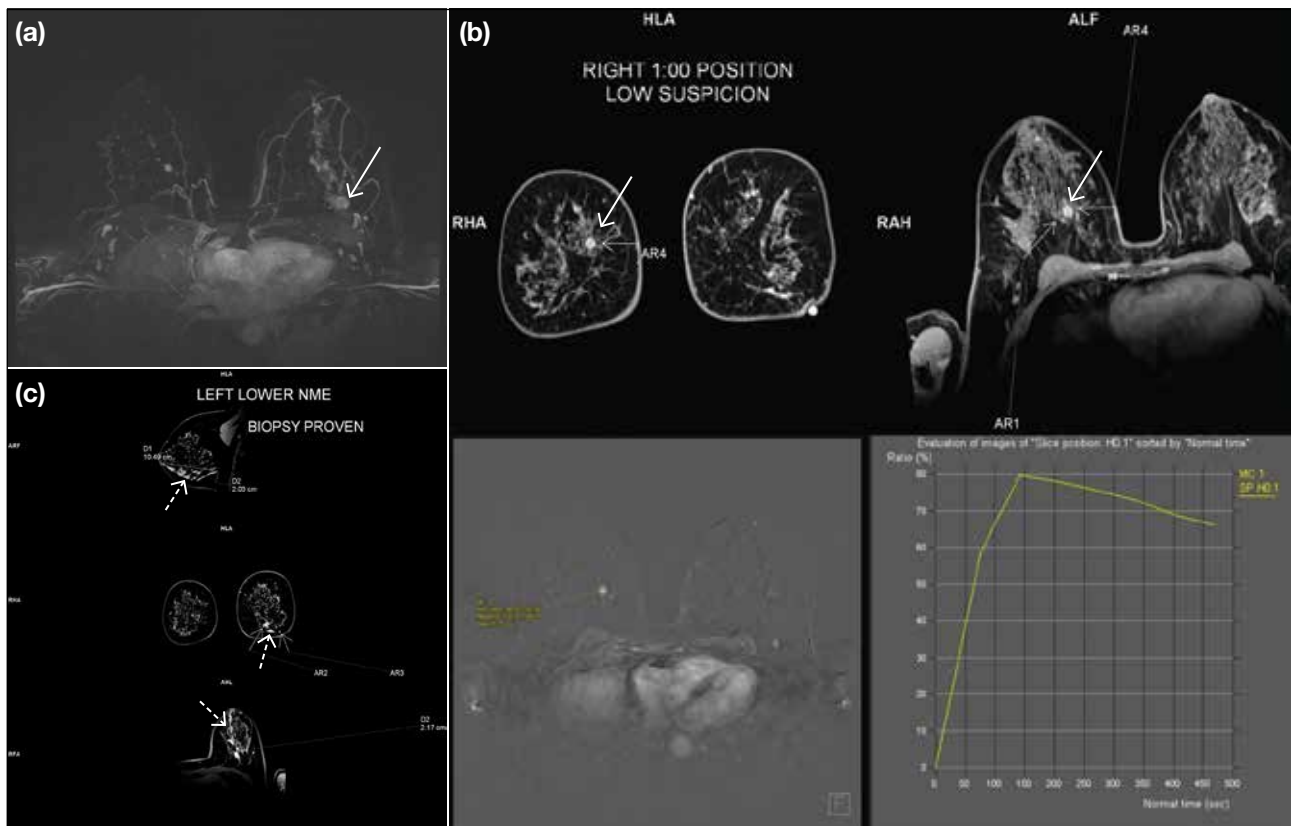


Figure 4. Same patient as Figure 3. (a) Magnetic resonance images showing similar findings to those on contrast-enhanced mammography. (b) Enhancing lesion in the upper inner quadrant of the right breast (arrows) with restricted diffusion and a type III curve, suspicious for malignancy. (c) Lower central enhancing lesion in the left breast corresponding to the biopsy-proven malignancy (not shown in [c], arrow in [a]), associated with segmental clumped non-mass enhancement (dashed arrows).

CEM has aroused radiologists' interest in its role in screening and surveillance, particularly given the large number of intermediate-risk women who could benefit. In a pilot study by Jochelson et al,³⁰ 307 patients at increased risk for breast cancer underwent both screening CEM and MRI. Both modalities detected additional invasive cancers that were occult on conventional mammography, with comparable specificity and positive predictive value.³⁰ Two other studies showed that CEM outperformed two-dimensional full-field digital mammography when screening women with higher-than-average risk for breast cancer, with greater sensitivity (e.g., 87.5% vs. 50%,³¹ 90.5% vs. 52.4%³²). Preliminary study results are encouraging but the role of CEM warrants further research.

LIMITATIONS AND PITFALLS OF CONTRAST-ENHANCED MAMMOGRAPHY

Adverse reaction to iodinated contrast agent is a concern,

including the risks of extravasation, allergy, and contrast-induced acute kidney injury. Volume expansion by 0.9% normal saline prior to the contrast administration is a feasible preventive measure for those at risk.³³ The image quality of CEM can be degraded by patient motion. CEM is more prone to motion artifacts (Figure 11) due to its longer exposure and compression time, resulting in blurred images. There are many technical artifacts that are specific to CEM. For instance, the use of an undersized compression paddle may cause horizontal lines across the axilla (Figure 12). Suboptimal breast compression may lead to air trapping within skin folds or scars, resulting in poor contact between the skin and the detector or compression paddle (Figure 13). Macrocalcifications, cysts or, post-biopsy haematomas may not enhance and appear as low-density areas compared to background enhancement on subtracted images, which is known as negative contrast enhancement^{14,34} (Figure 11).

Subtracted CEM allows delineation of contrast

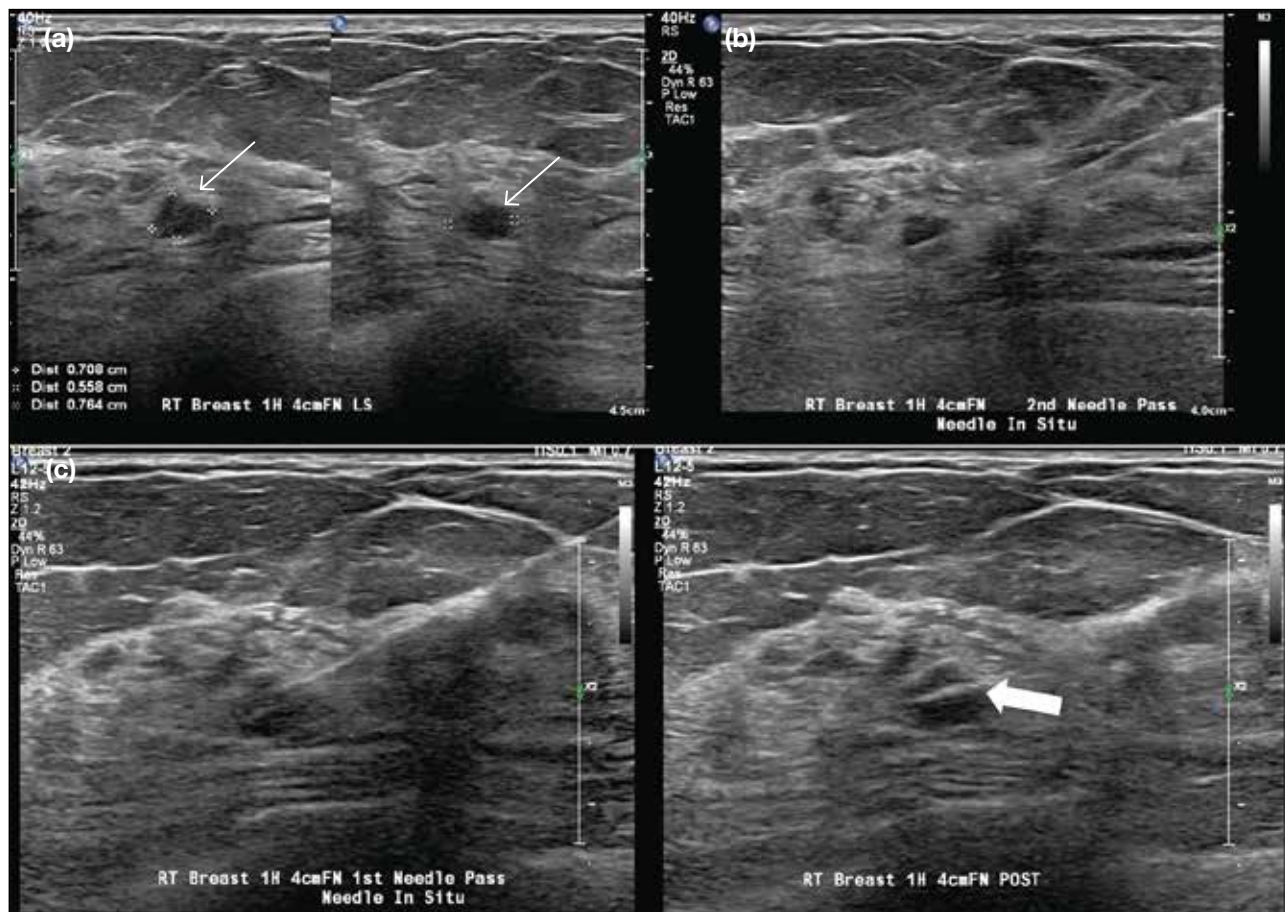


Figure 5. Second-look sonographic images of the right breast in the same patient as Figure 3. (a) An irregular hypoechoic lesion with angulated margin is seen at 1 o'clock position of the right breast, 4 cm from the nipple. This lesion was previously identified on contrast-enhanced mammography and magnetic resonance imaging, with low suspicion for malignancy. (b) Ultrasound-guided biopsy was performed, and histopathology showed invasive carcinoma. (c) Insertion of the deployment needle preloaded with Magseed into the targeted right breast lesion (left). Postprocedural image indicating successful marking of the targeted right breast lesion with Magseed, indicated by the arrow (right).

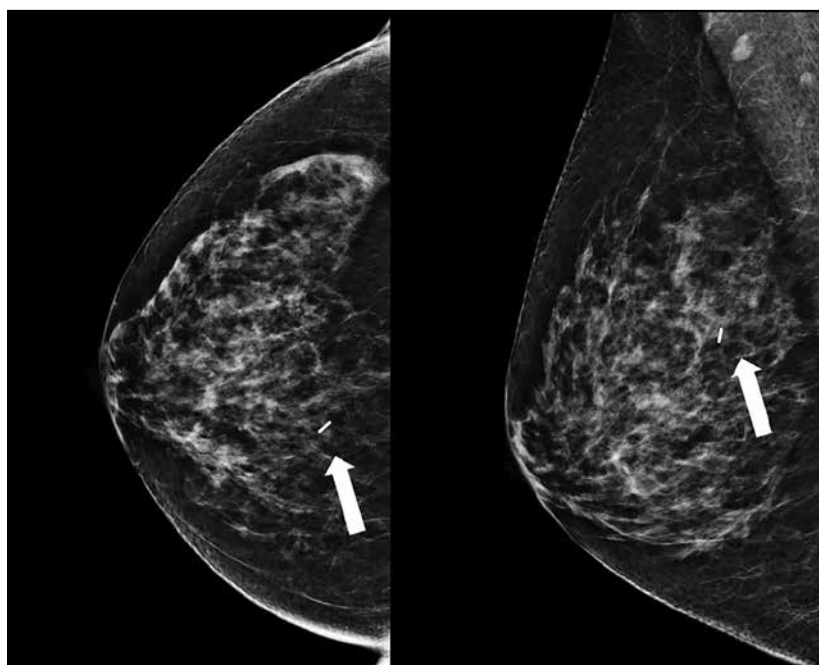


Figure 6. In same patient as Figure 3, a subsequent mammogram was performed to confirm the Magseed marker (arrows) located deep in the upper inner quadrant of the right breast, corresponding to the site of the previously noted irregular enhancing lesion seen in Figure 3.

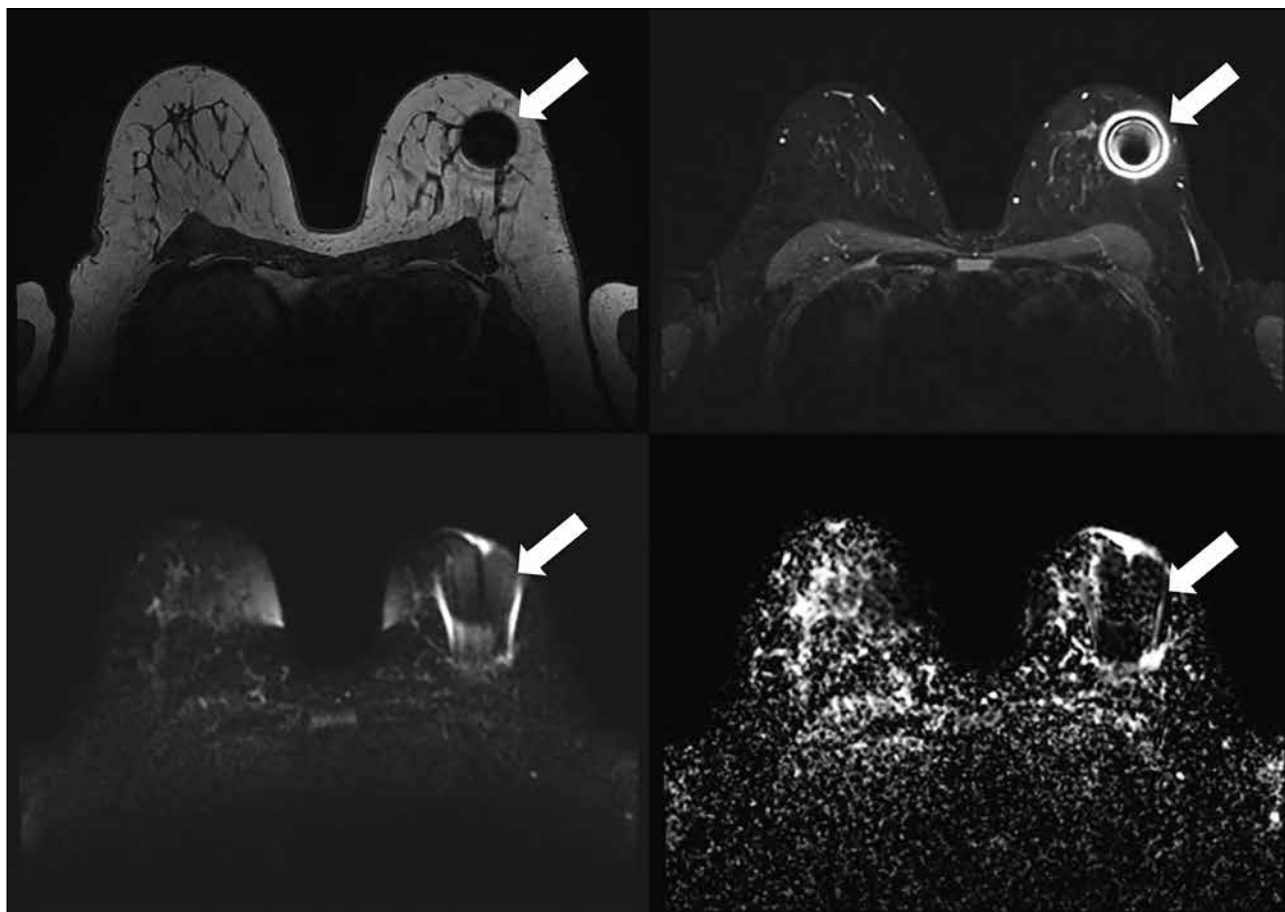


Figure 7. Magnetic resonance images of a 40-year-old woman with biopsy-proven left breast malignancy and prior Magseed insertion, for treatment response after neoadjuvant chemotherapy. Most of the left breast was obscured due to significant metallic artifact (arrows) produced by the Magseed.

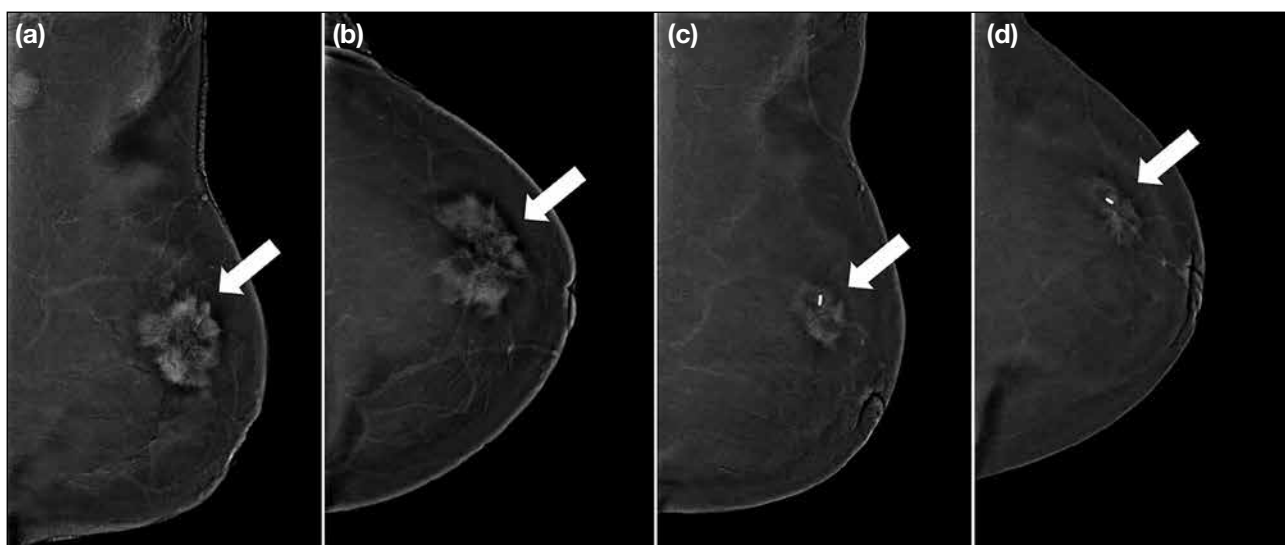


Figure 8. Contrast-enhanced mammographic images of the same patient as Figure 7. (a, b) Pretreatment recombined images of the left breast showed a spiculated enhancing mass (arrows) in the upper outer quadrant, corresponding to the biopsy-proven malignancy. (c, d) Post-treatment recombined images of the left breast revealed interval reduction in the size of the index cancer (arrows).

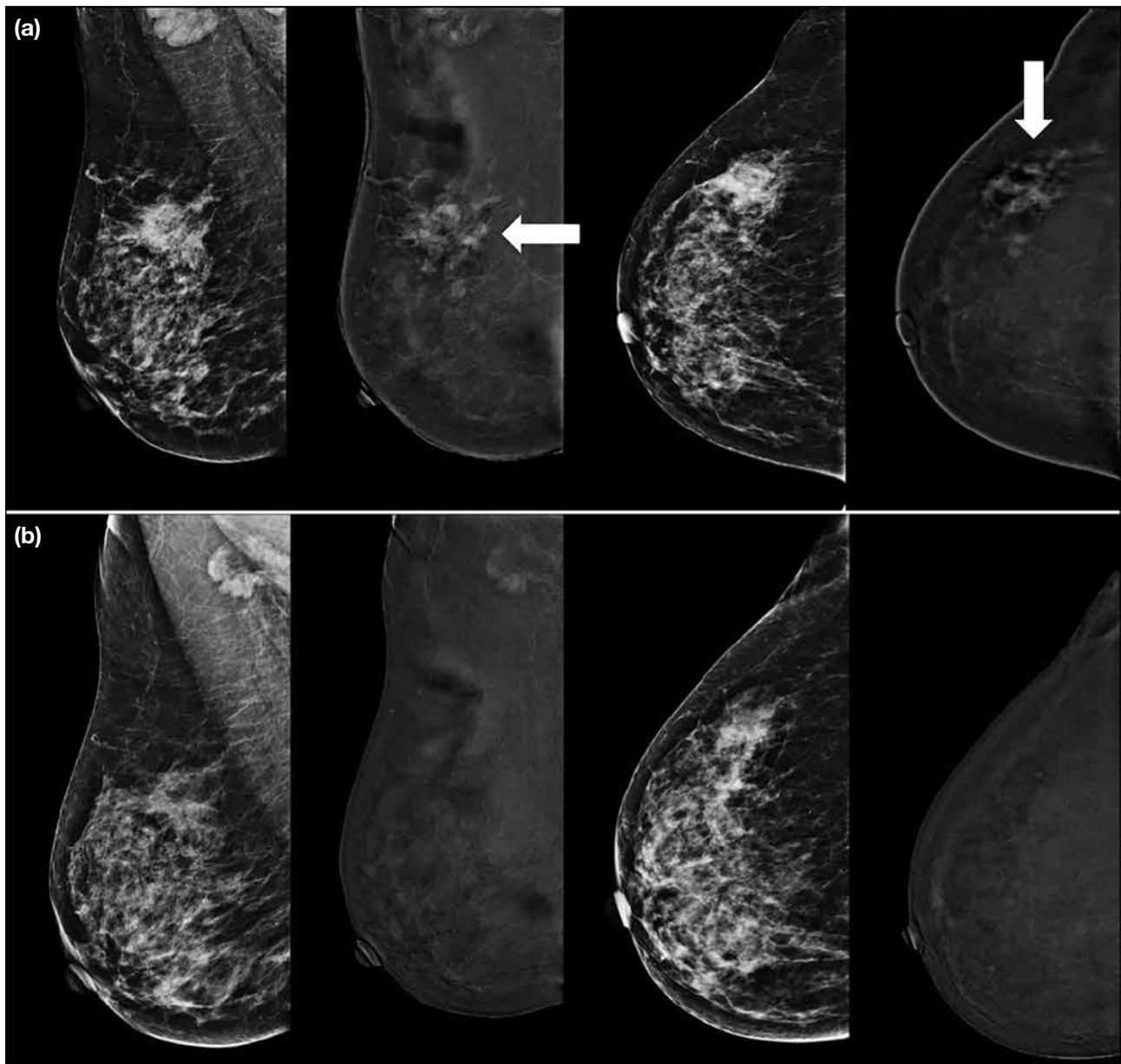


Figure 9. Contrast-enhanced mammographic images of the right breast in a 57-year-old woman with biopsy-proven malignancy in the upper outer quadrant for neoadjuvant chemotherapy. (a) Baseline images. (b) Post-treatment images. Serial images showing interval reduction in the size of the index cancer. Associated non-mass enhancement beyond the confines of index cancer had largely resolved (arrows in [a]).

enhancement based on the degree of angiogenesis in the lesions. However, contrast enhancement may also be seen in benign lesions such as fibroadenomas, intraductal papillomas, and fat necrosis,¹⁴ making it difficult to determine the nature of the lesion and potentially resulting in false-positive findings. Varying degrees of angiogenesis and contrast enhancement are also seen among different subtypes of malignancy. Lesions with

less pronounced enhancement, such as ductal carcinoma in situ or lobular carcinoma, may be overlooked,¹⁴ leading to false-negative findings.

Additionally, the intensity of background parenchymal enhancement can affect interpretation, as it may obscure underlying lesions¹⁴ (Figure 14). Since the field of view in CEM is identical to that of conventional mammography,

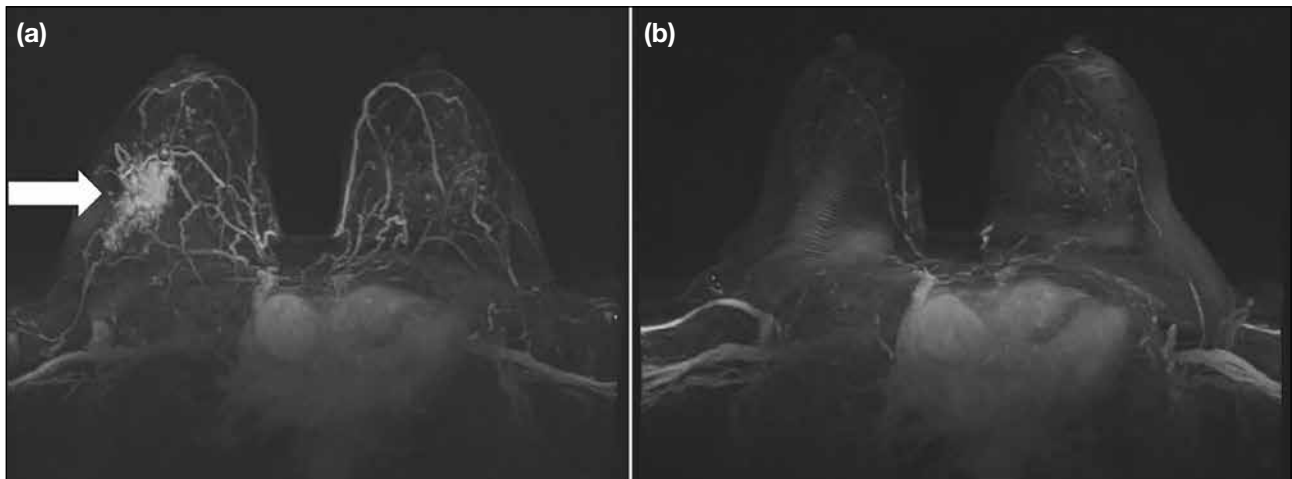


Figure 10. Magnetic resonance images of the same patient as Figure 9 at baseline (a) and post-treatment (b). Interval resolution of right breast index cancer and associated non-mass enhancement (arrow in [a]) was noted.

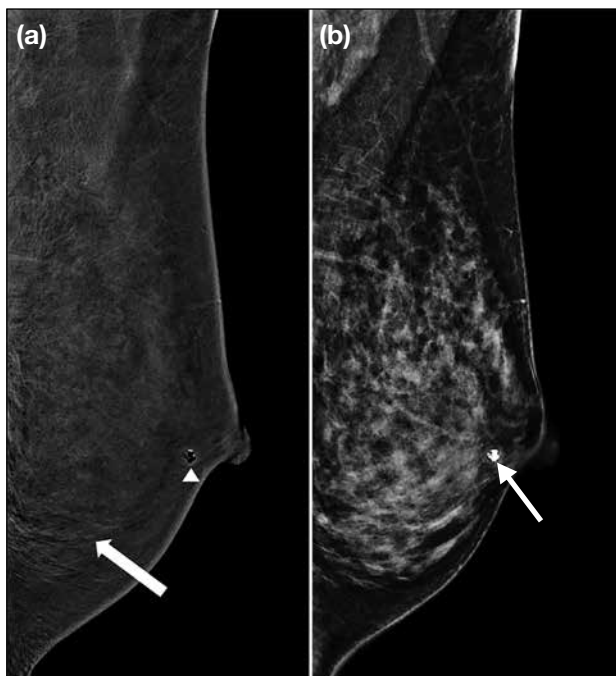


Figure 11. Contrast-enhanced mammographic images of the left breast in a middle-aged woman. (a) Recombined image of mediolateral oblique view showing ripple artifact with alternating black and white lines in the lower portion (arrow), attributed to patient motion during low- and high-energy image acquisition. (b) Low-energy image showing coarse calcification in the retro-areolar region (arrow) with corresponding negative contrast enhancement in the recombined image (arrowhead in [a]).



Figure 12. Contrast-enhanced mammographic image of the right breast in mediolateral oblique view showing axillary line artifact (arrow).

lesions located in blind spots, such as those near the chest wall, might not be visualised¹⁴ and should be further evaluated with MRI.

Currently, there are not good biopsy tools that work directly with CEM. Lesions identified on CEM should be correlated with other imaging modalities (e.g., standard

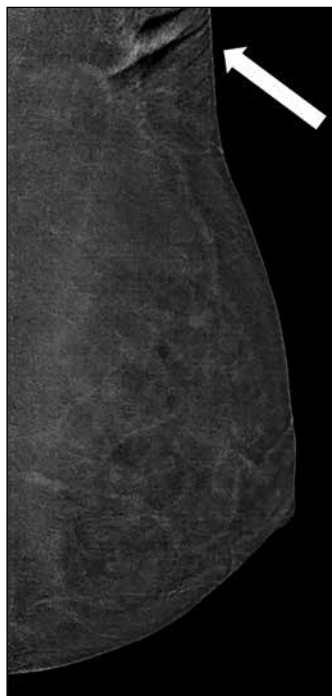


Figure 13. Contrast-enhanced mammographic image of the left breast in mediolateral oblique view showing air trapping in the axilla (arrow), which appears as black lines on the recombined image.

digital mammography, ultrasound, or breast MRI) if biopsy is planned. Ultrasound is often preferred due to its accessibility, lower cost, and suitability for ultrasound-guided biopsy.

CONCLUSION

Combined full-field digital mammography with tomosynthesis and ultrasound remains the mainstay of breast assessment in our centre. Incorporation of CEM into daily clinical practice provides further additional information in certain circumstances and is commonly used for evaluating disease extent and monitoring treatment response. CEM is increasingly regarded as a more affordable and accessible modality in settings with limited resources, or as an alternative when MRI is contraindicated or not tolerated. Further exploration of its role in breast imaging is anticipated.

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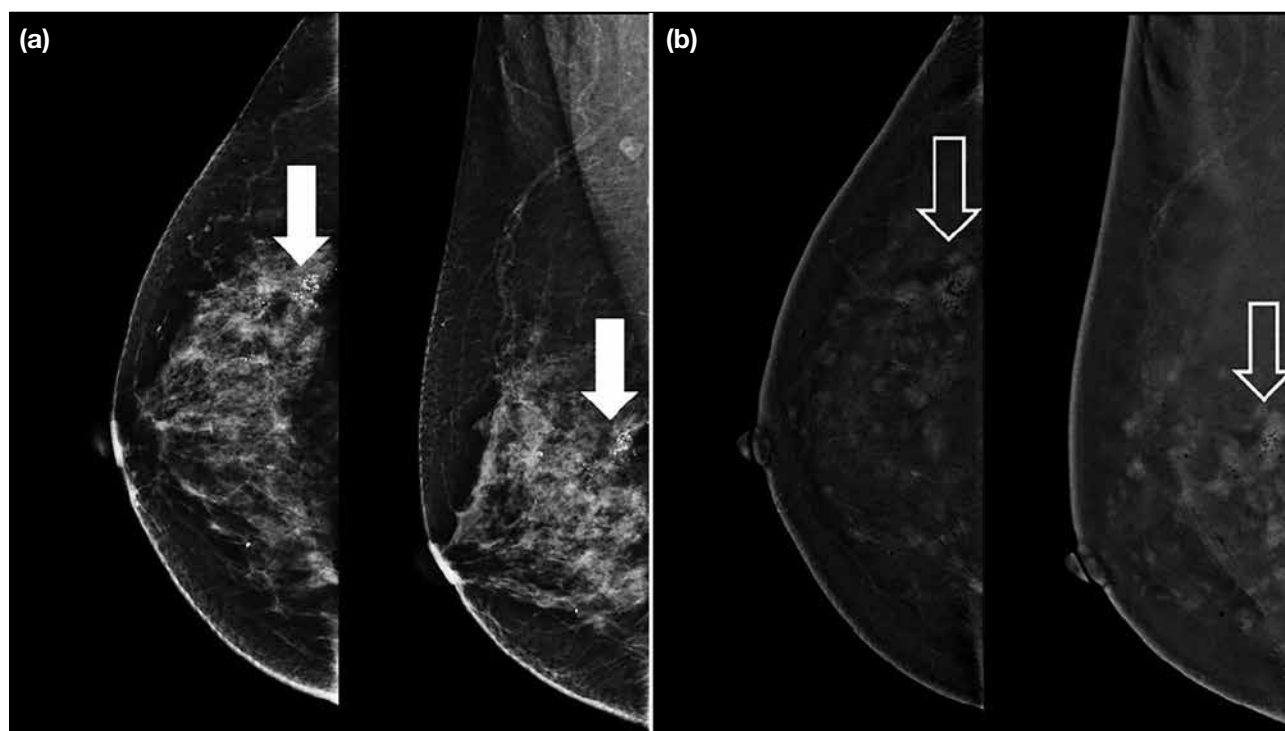


Figure 14. Contrast-enhanced mammographic images of the right breast in a 65-year-old woman with newly diagnosed right breast malignancy. (a) Low-energy images showing fine pleomorphic, coarse heterogeneous, and amorphous calcifications in segmental distribution in the upper outer quadrant of the right breast (arrows). (b) Subtracted contrast-enhanced images revealed clumped segmental non-mass enhancement and irregular enhancing mass of high conspicuity (open arrows), extending beyond the span of calcifications, in the setting of marked background parenchymal enhancement. Determining exact extent of non-mass enhancement is limited by marked background parenchymal enhancement, rendering precise bracketing localisation difficult. If breast conservation therapy was elected, there would be an increased risk of incomplete excision. Eventually, the surgical team planned for mastectomy.

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