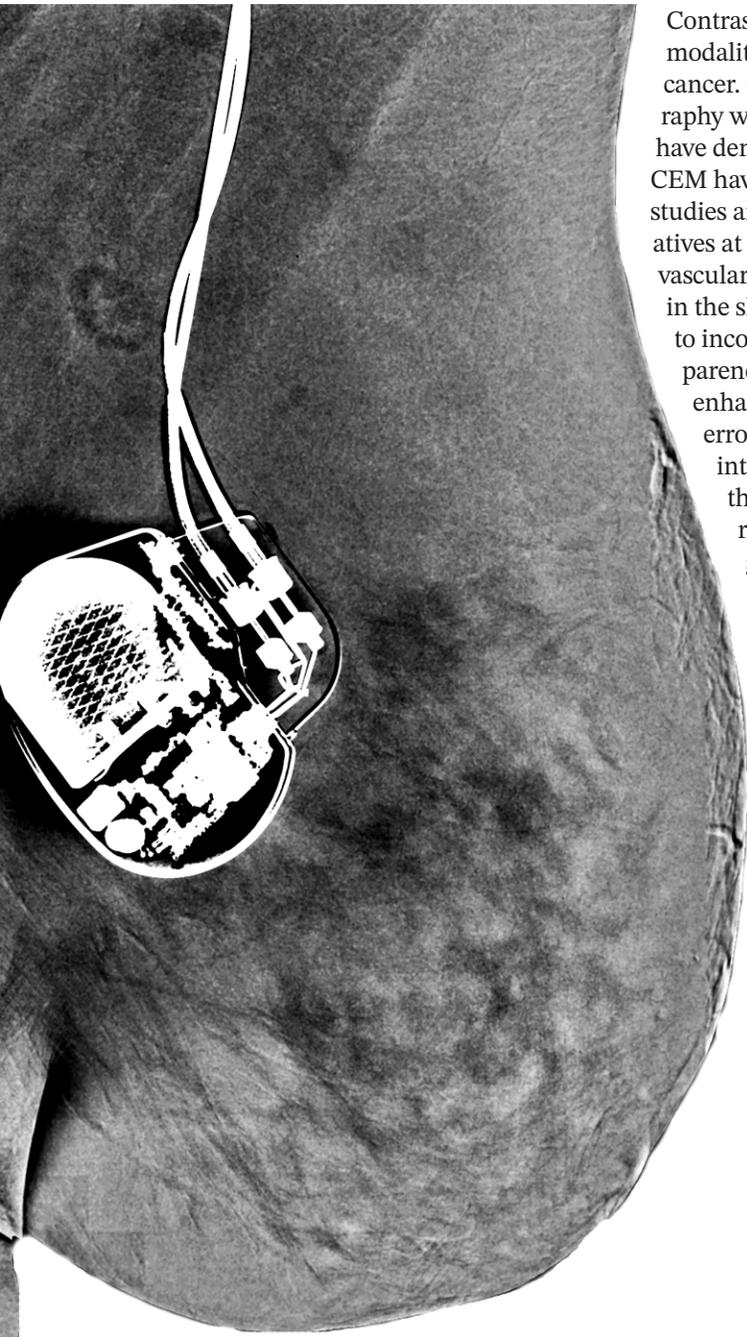# False-Positive and False-Negative Contrast-enhanced Mammograms: Pitfalls and Strategies to Improve Cancer Detection

Molly B. Carnahan, MD • Laura Harper, MD • Parker J. Brown, MD • Asha A. Bhatt, MD • Sarah Eversman, MD
Richard E. Sharpe, Jr, MD, MBA • Bhavika K. Patel, MD

Author affiliations, funding, and conflicts of interest are listed at the end of this article.

Contrast-enhanced mammography (CEM) is a relatively new breast imaging modality that uses intravenous contrast material to increase detection of breast cancer. CEM combines the structural information of conventional mammography with the functional information of tumor neovascularity. Initial studies have demonstrated that CEM and MRI perform with similar accuracies, with CEM having a slightly higher specificity (fewer false positives), although larger studies are needed. There are various reasons for false positives and false negatives at CEM. False positives at CEM can be caused by benign lesions with vascularity, including benign tumors, infection or inflammation, benign lesions in the skin, and imaging artifacts. False negatives at CEM can be attributed to incomplete or inadequate visualization of lesions, marked background parenchymal enhancement (BPE) obscuring cancer, lack of lesion contrast enhancement due to technical issues or less-vascular cancers, artifacts, and errors of lesion perception or characterization. When possible, real-time interpretation of CEM studies is ideal. If additional views are necessary, they may be obtained while contrast material is still in the breast parenchyma. Until recently, a limitation of CEM was the lack of CEM-guided biopsy capability. However, in 2020, the U.S. Food and Drug Administration cleared two devices to support CEM-guided biopsy using a stereotactic biopsy technique. The authors review various causes of false-positive and false-negative contrast-enhanced mammograms and discuss strategies to reduce these diagnostic errors to improve cancer detection while mitigating unnecessary additional imaging and procedures.

©RSNA, 2023 • radiographics.rsna.org

Introduction

Contrast-enhanced mammography (CEM) provides unique advantages in detecting suspicious breast lesions over conventional mammography. Conventional mammography, including digital breast tomosynthesis (DBT), has shown limited sensitivity for cancer detection in women with dense breasts (1). CEM combines the structural information of conventional mammography with the functional information of tumor neovascularity (2). Tumor neovascularity occurs due to vascular permeability in breast tumors, which results in contrast agents extravasating into surrounding tissue, attenuation of x-rays, and highlighting of underlying breast cancers (2,3). The addition of intravenous contrast material allows characterization of tumor vascularity,

TEACHING POINTS

- CEM combines the structural information of conventional mammography with the functional information of tumor neovascularity.

- Inflammation manifests clinically and tends to have nonspecific imaging manifestations, including skin thickening, rim enhancement, or nonmass enhancement (NME). Clinical correlation and immediate clinical care are necessary.

- When possible, real-time interpretation of CEM images is ideal. If additional views are necessary, they may be obtained while contrast material is still in the breast parenchyma.

- Low-grade malignancies may not show enhancement. Therefore, in lesions without CEM enhancement, the decision to pursue core needle biopsy should be based on the most suspicious imaging feature at CEM (LE or recombined images) or US.

- False positives depend on vascularity and can be seen in the setting of enhancing benign lesions, infectious or inflammatory lesions, or contrast material contamination artifact. False negatives can result from inadequate or incomplete inclusion of a lesion, obscuration of a lesion due to BPE, absence of contrast enhancement of a malignancy, or characterization errors.

offering physiologic information in addition to information on mammographic alterations, which leads to increased detection of suspicious breast lesions over that of conventional mammography.

CEM is often compared with contrast-enhanced MRI. CEM and MRI have similar diagnostic accuracies, with CEM having slightly higher specificity (fewer false positives) and MRI having slightly higher sensitivity (4–10). CEM is less costly to perform than MRI and is relatively well tolerated by patients in comparison with MRI (4). Additionally, given the relatively high resolution of x-ray imaging with CEM, suspicious microcalcifications are able to be identified (2). These advantages support the increasing use of CEM.

CEM examinations include acquisition of two images per view of the breast. Low-energy (LE) images are obtained at the same energy spectrum and considered the diagnostic equivalent of standard full-field digital mammography (FFDM); they enable similar performance of microcalcification detection as FFDM, helping with calcification identification (11). High-energy images are nondiagnostic and noninterpretable. Subtracted (or recombined) images provide diagnostic information regarding lesion vascularity.

CEM has been used to evaluate extent of disease in patients with newly diagnosed breast cancer as part of a staging examination and to assess treatment response in patients undergoing neoadjuvant treatment (2). CEM is also being studied in the setting of screening and surveillance; this is especially the case in patients with a history of breast cancer, patients with dense breast tissue, and patients at high risk for developing breast cancer (12–14). Furthermore, lesions that are enhancing at CEM without a mammographic or US correlate can now be biopsied under CEM guidance (see the "Emerging Research" section).

CEM can also be associated with false-positive and false-negative findings, which limits diagnostic accuracy. This article reviews various causes of false positives and false negatives at clinical CEM examinations and provides readers with strategies to improve overall diagnostic accuracy considering these limitations.

Basics of CEM Technique

CEM uses a unique dual-energy method of image acquisition. Approximately 2 minutes after injection of iodinated contrast material, two craniocaudal (CC) images and two mediolateral oblique (MLO) images of each breast are obtained. The first image produced uses a high-energy x-ray beam to achieve maximal attenuation of the contrast agent in the breast (45–49 kVp) (2,15). This is a nondiagnostic image. A second, LE image is obtained simultaneously, which is analogous to an FFDM image (26–30 kVp) (2,15).

After image acquisition, a postprocessed dual-energy subtraction technique is applied to the LE and high-energy images to create a subtracted or recombined diagnostic image, which highlights areas of pooling contrast material while removing nonenhanced fibroglandular tissue (2,15). To minimize motion artifacts, high-energy and LE images are best obtained sequentially for each breast position (2,15).

Standard imaging is relatively quick and is typically completed within 7–10 minutes, but it can often be completed within 4–5 minutes (16). Additional views can be obtained at upward of 10 minutes, with new literature suggesting even later acquisition, if needed (17). Both the LE and recombined images are made available at the time of interpretation and are interpreted in clinical care as a conventional mammographic study (2).

False Positives at CEM

Enhancement depicted at CEM is nonspecific and can correspond to benign morphologic and physiologic enhancement, contributing to false-positive results (9). False-positive results at CEM are due to a variety of factors, including inflammation, benign lesions, and artifacts (Fig 1). False-positive findings can ultimately lead to additional unnecessary imaging or needless biopsy of benign lesions. Recalls and additional evaluation may also cause increased patient anxiety and added medical costs.

When CEM false-positive rates are compared to MRI false-positive rates, CEM rates are reported to be slightly lower at 8%–33% compared with 20%–66% for MRI (9,10), although both studies had small sample sizes (40 and 157 patients, respectively). Furthermore, CEM is reported to have relatively superior specificity (69%–90%) compared with that of MRI (72%–74%) (5,6). From personal clinical experience, we speculate that false positives at CEM may be lower than at MRI because the overall degree of enhancement may not be as avid at CEM, therefore limiting conspicuity of small lesions and foci.

There are benefits of MRI over CEM: for example, delayed imaging with time-intensity curves or T2 characteristics,
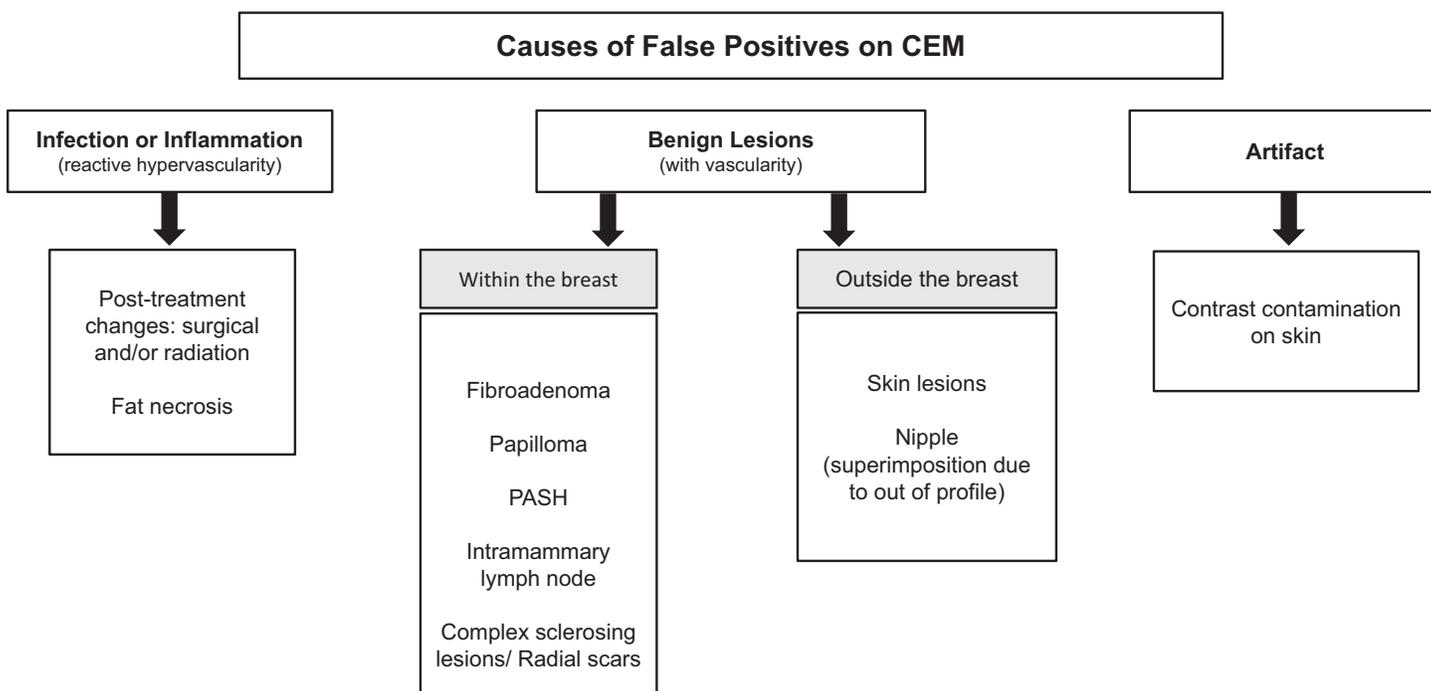
Causes of False Positives on CEM

Infection or Inflammation (reactive hypervascularity)	Benign Lesions (with vascularity)	Artifact

Infection or Inflammation → Post-treatment changes: surgical and/or radiation / Fat necrosis

Benign Lesions

Within the breast:
- Fibroadenoma
- Papilloma
- PASH
- Intramammary lymph node
- Complex sclerosing lesions/ Radial scars

Outside the breast:
- Skin lesions
- Nipple (superimposition due to out of profile)

Artifact → Contrast contamination on skin

Figure 1. Major causes of false positives at CEM under the categories of infection or inflammation, benign lesions within or outside the breast, and artifact. *PASH* = pseudoangiomatous stromal hyperplasia.

which provide the radiologist with additional physiologic or kinetic information regarding lesions in the breast. T2 characteristics and kinetic information are not currently available in standard clinical CEM.

Inflammation (Reactive Hypervascularity)

Inflammation manifests clinically and tends to have nonspecific imaging manifestations, including skin thickening, rim enhancement, or nonmass enhancement (NME). Clinical correlation and immediate clinical care are necessary.

Fat Necrosis.—Fat necrosis is a benign entity that results from ischemia or vascular insult to fat cells within breast tissue (18,19). Blunt trauma to the chest, previous breast surgery or biopsy, and breast irradiation can all lead to development of fat necrosis (18,19). When ischemia or trauma occurs, fat cells hemorrhage and liquefactive necrosis begins, resulting in increased vascularity, allowing fibroblasts, lymphocytes, and histiocytes to infiltrate and wall off the necrotic debris (18). Fibrosis replaces the area of fat necrosis, and this area may eventually be replaced with a scar or persist as fibrous tissue surrounding an oil cyst (18). Fat necrosis may be asymptomatic or manifest as a palpable lump.

Fat necrosis is known to demonstrate a wide variety of imaging features based on the amount of fibrosis within the lesion and may mimic breast cancer (19,20). The presence of a fat-containing circumscribed lesion, rim calcifications, or a fat-fluid level all indicate benign fat necrosis, while a spiculated mass, distortion, or suspicious calcifications may warrant additional imaging and biopsy (21). Owing to the increased vascularity in the pathogenesis of fat necrosis, CEM and MRI may demonstrate variable enhancement patterns in these lesions (20).

At MRI, a lesion likely represents fat necrosis if the signal intensity is similar to that of adjacent fat and it demonstrates no internal enhancement (20). Similarly, at CEM, if there is rim enhancement on the recombined image with internal fat visualized on the LE image, the lesion may be deemed fat necrosis (21). However, if there is any question of enhancement within the lesion or around it or irregular morphology, the lesion should be worked up or biopsied due to the overlapping imaging features of fat necrosis with malignancy (Fig 2) (21).

Posttreatment Changes.—Surgical procedures, including breast conservation surgery and reduction mammoplasty, can result in postinflammatory changes seen at imaging. Tissue and skin manipulation during these procedures can alter the distribution of fibroglandular tissue, resulting in focal asymmetry, architectural distortion, and postoperative inflammatory changes (22).

Additionally, early postoperative inflammatory changes can make images difficult to interpret (Fig S1) and are known to limit sensitivity for detecting residual or new breast cancer with MRI (22,23). Although data are limited, CEM likely has similar limitations as MRI due to the same principle of contrast enhancement. On the basis of prior MRI studies of postlumpectomy patients with positive margins, CEM is not recommended until at least 28 days after surgery to assess for residual disease (24). Radiation treatment as part of breast-conserving therapy can also cause early posttreatment inflammatory changes; therefore, contrast-enhanced imaging is not recommended in the first 9 months after treatment (25). Later changes after radiation therapy seen at contrast-enhanced imaging include asymmetric decreased parenchymal enhancement in the treated breast (26).
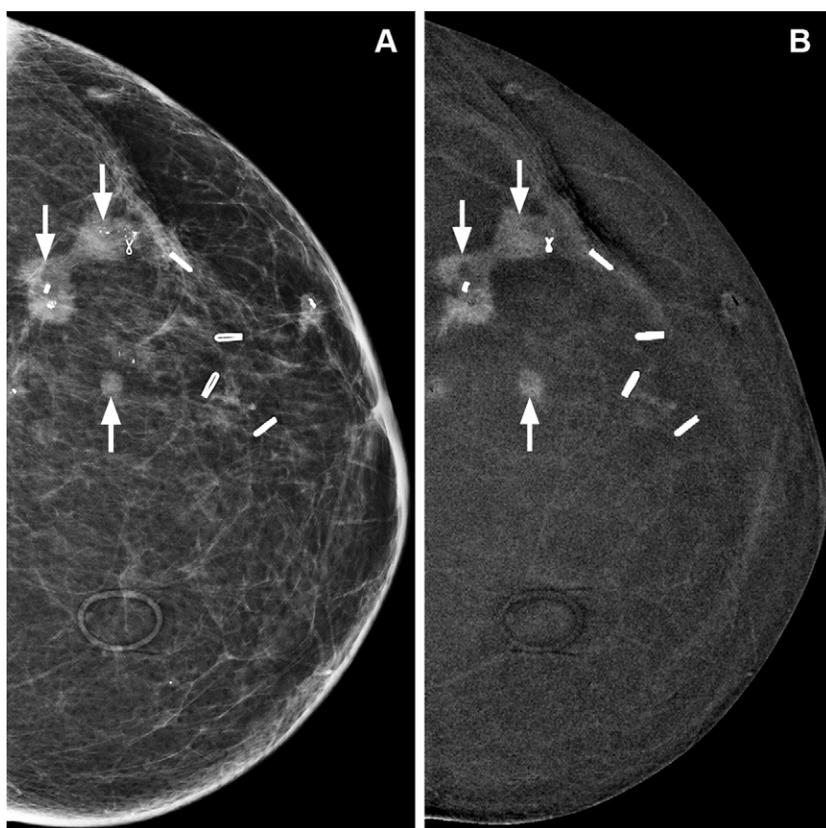
Figure 2.   Fat necrosis in a 70-year-old woman with a history of lumpectomy for left invasive ductal carcinoma (grade 1, estrogen receptor [ER] positive, progesterone receptor [PR] positive, human epidermal growth factor receptor 2 [HER2] negative) 5 years earlier, who presented for annual mammography. **(A)** Left CC LE image shows lumpectomy changes in the outer breast. There are multiple masses (arrows) adjacent to the lumpectomy bed. **(B)** Left CC recombined image shows corresponding enhancement of the masses (arrows), which were known from prior biopsy to represent benign fat necrosis.

As with MRI, thin rim enhancement can be seen around the lumpectomy site or a postoperative fluid collection at CEM, but any irregular or nodular areas of enhancement should be deemed suspicious (27). Rim enhancement on recombined CEM images can be superimposed and mimic nodularity, which is a limitation of CEM compared with multiplanar MRI (Fig 3). In these cases, targeted US or MRI is recommended to better characterize the suspected nodularity.

Idiopathic Granulomatous Mastitis.—Idiopathic granulomatous mastitis (IGM) is an inflammatory condition that consists of noncaseating granulomas in the breast. While the exact cause is uncertain, theorized causes include autoimmune disease, trauma, and lactation (28,29). Cystic neutrophilic granulomatous mastitis (CNGM) is a rare subtype of granulomatous mastitis and is often associated with *Corynebacterium* species (30).

The most common presenting symptom of IGM and CNGM is a tender palpable mass, with less common findings including skin erythema or induration (28,29,31). Axillary lymphadenopathy may be present. This clinical manifestation raises concern for underlying malignancy, prompting diagnostic evaluation (28).

IGM and CNGM demonstrate nonspecific imaging manifestations (28). At mammography, both have been described as a focal asymmetry or irregular mass, and skin thickening may be present (29,31). Owing to their inflammatory cause and mimicking of inflammatory breast cancer, CEM may be performed during the diagnostic evaluation.

CEM findings may also include rim enhancement or NME (Fig 4) (28). Lesions can vary in size, and large lesions may resemble an abscess at CEM. At US, IGM may appear as an irregular hypoechoic mass or masses, with or without posterior acoustic enhancement, and often shows increased vascularity at color Doppler US due to inflammation (29).

IGM or CNGM often requires core needle biopsy for definitive diagnosis. Fine-needle aspiration, although helpful in distinguishing malignant versus nonmalignant lesions, is not an accurate method of securing a diagnosis and is often of low utility (29). IGM has an excellent prognosis when treated with oral steroids or methotrexate with prolactin-lowering medications. If IGM does not respond to these treatments, intralesion steroid injection or surgical excision may be indicated (32). CNGM typically requires prolonged antibiotic therapy (30).

Benign Lesions with Vascularity

Fibroadenoma.—Fibroadenomas are benign solid lesions that consist of proliferative epithelium and stroma of the terminal duct lobular unit. Proliferation of these components is thought to be related to estrogen, as fibroadenomas are most common among younger women (33). The most common presenting symptom of fibroadenoma is a firm painless mass. Although it is more often a solitary lesion, some patients will present with multiple fibroadenomas (33).

At mammography, fibroadenomas are commonly described as round or oval circumscribed masses (33). Fibroadenomas have variable enhancement at CEM but tend to be circumscribed homogeneously enhancing masses (Fig 5) (34,35). Unless the mass is stable at LE imaging, FFDM, or
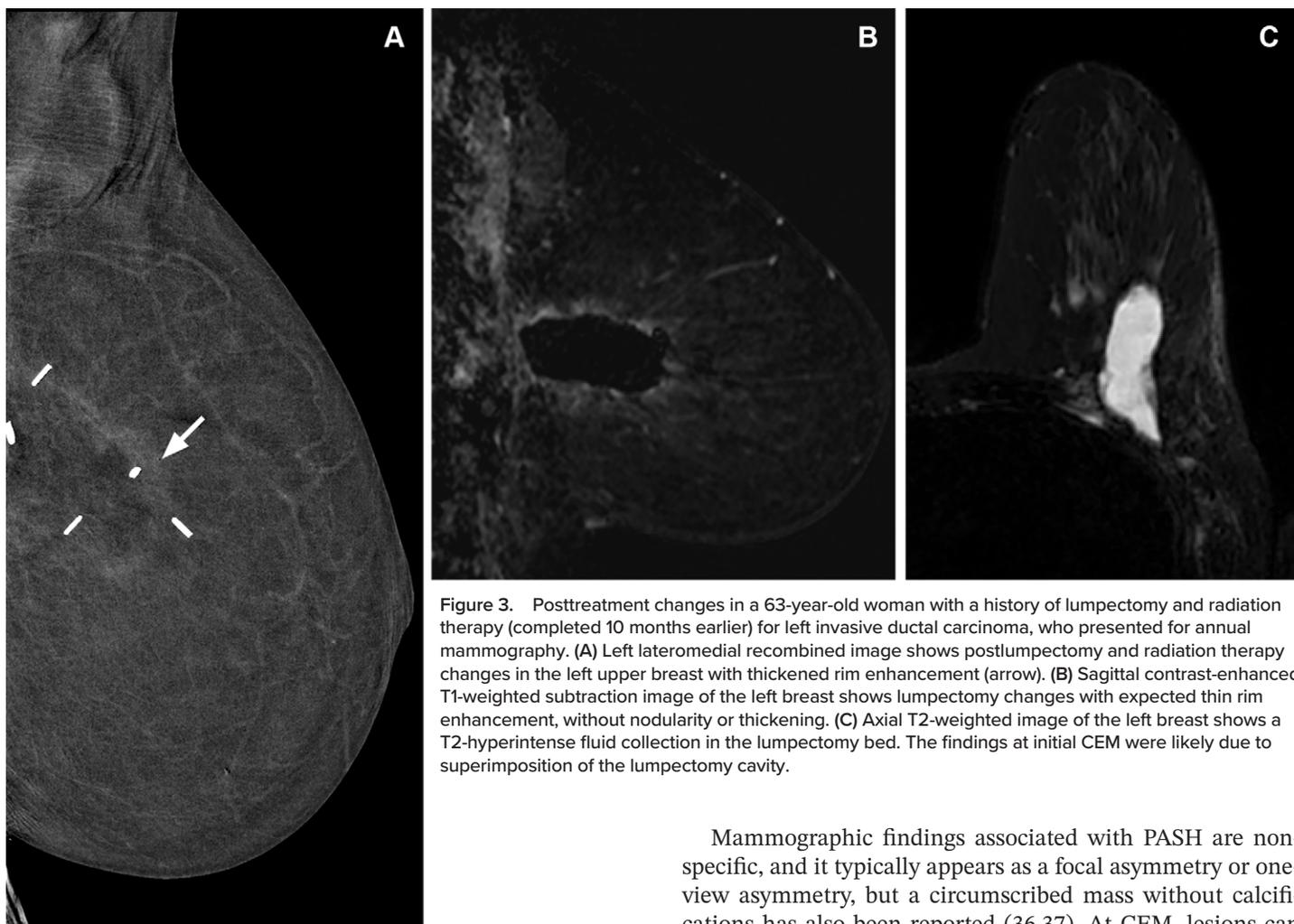
Figure 3. Posttreatment changes in a 63-year-old woman with a history of lumpectomy and radiation therapy (completed 10 months earlier) for left invasive ductal carcinoma, who presented for annual mammography. **(A)** Left lateromedial recombined image shows postlumpectomy and radiation therapy changes in the left upper breast with thickened rim enhancement (arrow). **(B)** Sagittal contrast-enhanced T1-weighted subtraction image of the left breast shows lumpectomy changes with expected thin rim enhancement, without nodularity or thickening. **(C)** Axial T2-weighted image of the left breast shows a T2-hyperintense fluid collection in the lumpectomy bed. The findings at initial CEM were likely due to superimposition of the lumpectomy cavity.

DBT to support a benign cause, as with a majority of enhancing masses, targeted US should be performed. At US, fibroadenomas are typically circumscribed masses and can have internal vascularity (33). Owing to overlapping CEM and US features between fibroadenomas and cancer, these masses often require short-interval imaging follow-up or US-guided biopsy.

If there is no US correlate, but there is an FFDM or DBT correlate, stereotactically guided biopsy can be performed. If there is only a recombined CEM image finding without a US correlate, CEM-guided biopsy is recommended if available. Alternatively, if available, MRI may be warranted for further evaluation. If there is an MRI correlate with classic fibroadenoma features seen at breast MRI (including T2 hyperintensity and nonenhancing internal septa), radiologists may prefer to dismiss the lesion as benign, follow up with short-interval imaging, or still recommend image-guided biopsy if there is a high-risk history or clinical suspicion.

Pseudoangiomatous Stromal Hyperplasia.—Pseudoangiomatous stromal hyperplasia (PASH) is a benign proliferation of breast stroma with a network of slitlike spaces lined with spindle cells resembling vascular channels (36). PASH is a common incidental finding in biopsy specimens and is typically clinically occult but may form a palpable mass (36,37).

Mammographic findings associated with PASH are nonspecific, and it typically appears as a focal asymmetry or one-view asymmetry, but a circumscribed mass without calcifications has also been reported (36,37). At CEM, lesions can demonstrate mass enhancement and NME (Fig 6). The US appearance of PASH is also variable, but it commonly appears as a circumscribed hypoechoic mass (36,37). Given the variable imaging appearances of PASH, core needle biopsy is often required to exclude malignancy.

Papilloma.—Intraductal papillomas are benign proliferations of epithelial and myoepithelial cells with an underlying fibrovascular stalk and protrude into the duct lumen (38). Papillomas can be described as central or peripheral, depending on their anatomic location in the duct.

Most papillomas are clinically occult and are detected at screening mammography. When symptomatic, patients can present with a palpable mass or pathologic nipple discharge (39). Mammographic findings of papillomas include a round or irregular mass with circumscribed or indistinct margins, an associated dilated duct, or microcalcifications (39). Typical US features include duct dilatation with a circumscribed hypoechoic intraductal mass with a vascular stalk (Fig 7) (39). Owing to the central fibrovascular core, papillomas often enhance at CEM and MRI and account for 19% of benign enhancing masses at CEM and 16% at MRI (35,40).

Given that there are no reliable imaging features to predict benign papilloma versus papilloma with atypia or malignancy, core needle biopsy of these lesions is often necessary (41). Papillomas with atypia have a 20%–54% upgrade rate to malignancy
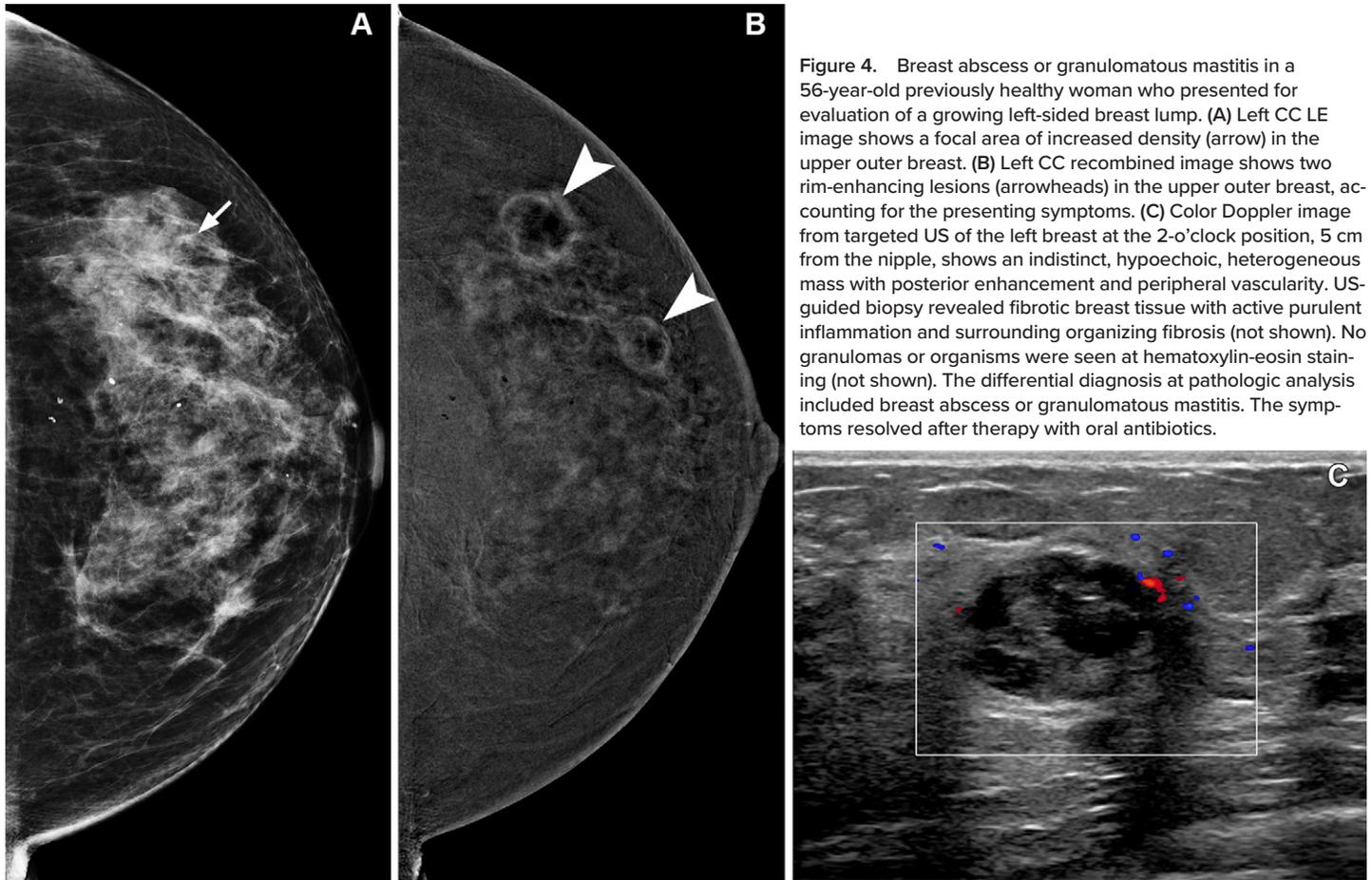
Figure 4. Breast abscess or granulomatous mastitis in a 56-year-old previously healthy woman who presented for evaluation of a growing left-sided breast lump. (A) Left CC LE image shows a focal area of increased density (arrow) in the upper outer breast. (B) Left CC recombined image shows two rim-enhancing lesions (arrowheads) in the upper outer breast, accounting for the presenting symptoms. (C) Color Doppler image from targeted US of the left breast at the 2-o'clock position, 5 cm from the nipple, shows an indistinct, hypoechoic, heterogeneous mass with posterior enhancement and peripheral vascularity. US-guided biopsy revealed fibrotic breast tissue with active purulent inflammation and surrounding organizing fibrosis (not shown). No granulomas or organisms were seen at hematoxylin-eosin staining (not shown). The differential diagnosis at pathologic analysis included breast abscess or granulomatous mastitis. The symptoms resolved after therapy with oral antibiotics.
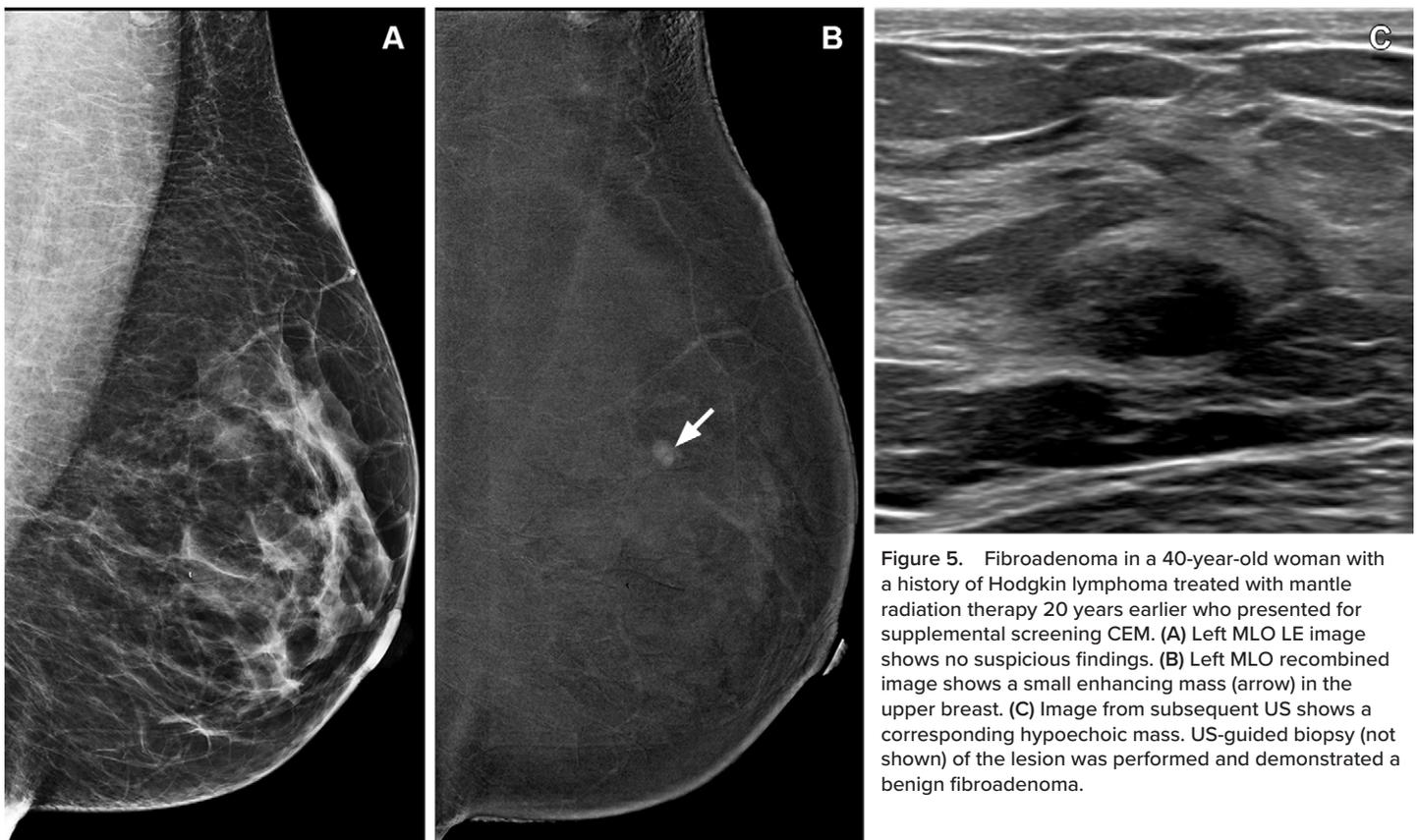
Figure 5. Fibroadenoma in a 40-year-old woman with a history of Hodgkin lymphoma treated with mantle radiation therapy 20 years earlier who presented for supplemental screening CEM. (A) Left MLO LE image shows no suspicious findings. (B) Left MLO recombined image shows a small enhancing mass (arrow) in the upper breast. (C) Image from subsequent US shows a corresponding hypoechoic mass. US-guided biopsy (not shown) of the lesion was performed and demonstrated a benign fibroadenoma.
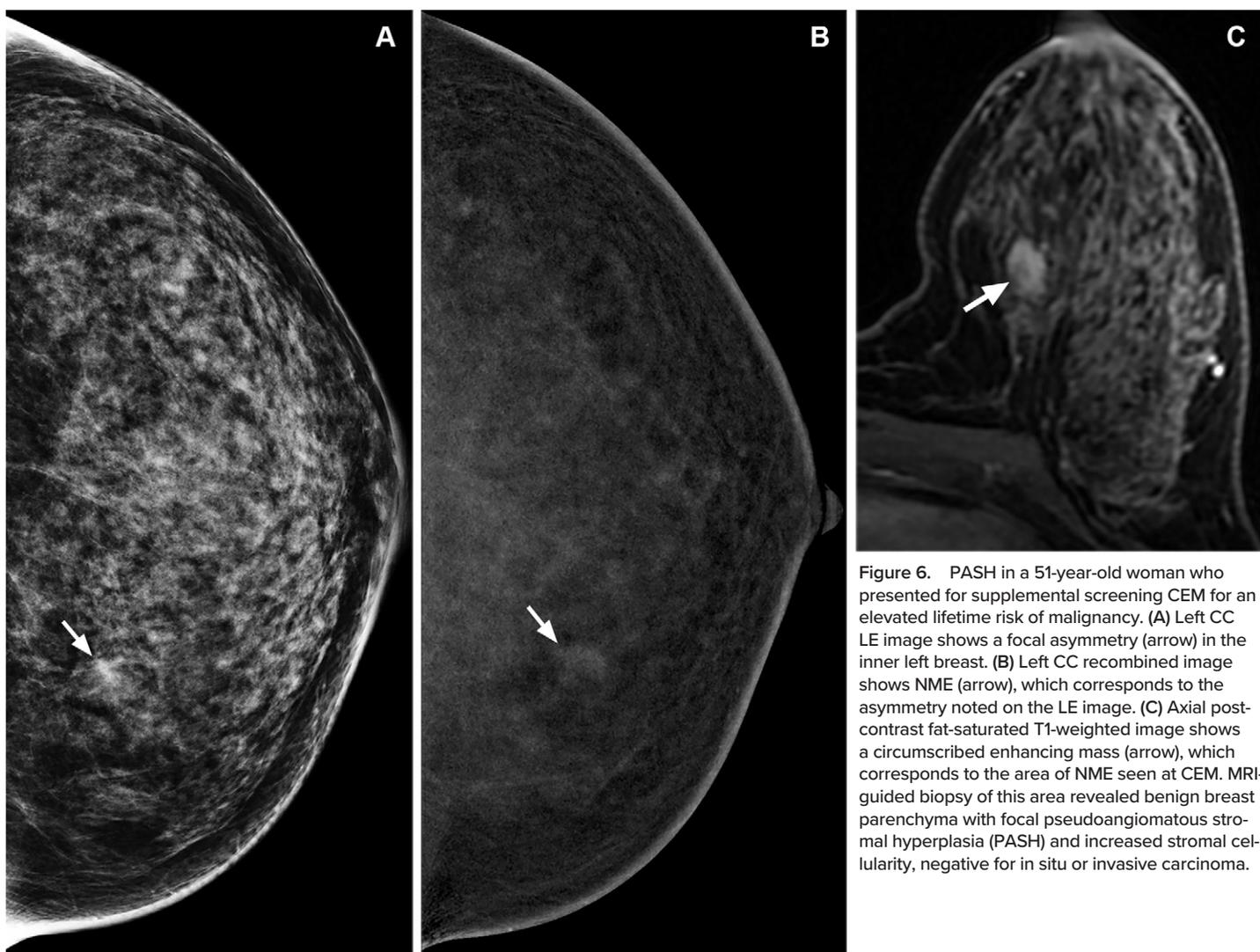
Figure 6. PASH in a 51-year-old woman who presented for supplemental screening CEM for an elevated lifetime risk of malignancy. **(A)** Left CC LE image shows a focal asymmetry (arrow) in the inner left breast. **(B)** Left CC recombined image shows NME (arrow), which corresponds to the asymmetry noted on the LE image. **(C)** Axial postcontrast fat-saturated T1-weighted image shows a circumscribed enhancing mass (arrow), which corresponds to the area of NME seen at CEM. MRI-guided biopsy of this area revealed benign breast parenchyma with focal pseudoangiomatous stromal hyperplasia (PASH) and increased stromal cellularity, negative for in situ or invasive carcinoma.

and should be surgically excised (42,43). Conversely, papillomas without atypia have a low (2.3%) upgrade rate to malignancy, and recent literature suggests selective surgical excision only if patients meet any of five criteria: radiologic-pathologic discordance, symptoms (palpable mass or nipple discharge), patient age 60 years or older, masses 10 mm or larger, or the presence of four or more peripheral papillomas (39). There is no consensus on follow-up recommendations for papillomas without atypia: some reports recommend a return to routine screening, while others recommend short-interval follow-up imaging (44).

Intramammary Lymph Nodes.—Intramammary lymph nodes are an extremely common incidental imaging finding. Normal lymph nodes appear as oval or reniform masses, with a fatty hilum and cortical thickness of 3 mm or less (45). Benign nodes may demonstrate concentric thickening when reacting to a stimulus such as inflammation (45). Abnormal features of intramammary lymph nodes at mammography include large size and associated microcalcifications (45).

Both normal and abnormal intramammary lymph nodes may enhance at CEM (Fig 8). If suspicion remains high, DBT spot compression images and US images should be obtained for better lymph node characterization. US features of abnormal lymph nodes include eccentric cortical thickening and hilar effacement, and it may be difficult to differentiate them from a breast mass with imaging alone (45).

Clinical context is key in evaluation of indeterminate nodes, as many benign conditions may cause intramammary and axillary lymphadenopathy. Examples of benign lymphadenopathy include infection, recent vaccination or surgery, or systemic inflammatory or autoimmune disease (45). US-guided biopsy or short-interval follow-up imaging should be performed for any indeterminate cases. In indeterminate cases where the CEM enhancement has no US correlate, MRI may provide diagnostic confirmation of a benign lymph with characteristic T2 hyperintensity and a fatty hilum on T1-weighted images.

Skin Lesions.—Benign and malignant skin lesions can demonstrate variable enhancement at CEM (46,47). Common examples of focal skin enhancement at CEM include nevus (Fig 9), hemangioma, and sebaceous cyst. Unlike with multiplanar MRI or DBT, it can be difficult to localize skin lesions with CEM alone if no mole markers are present. The most important tips to reduce false positives with skin lesions are to
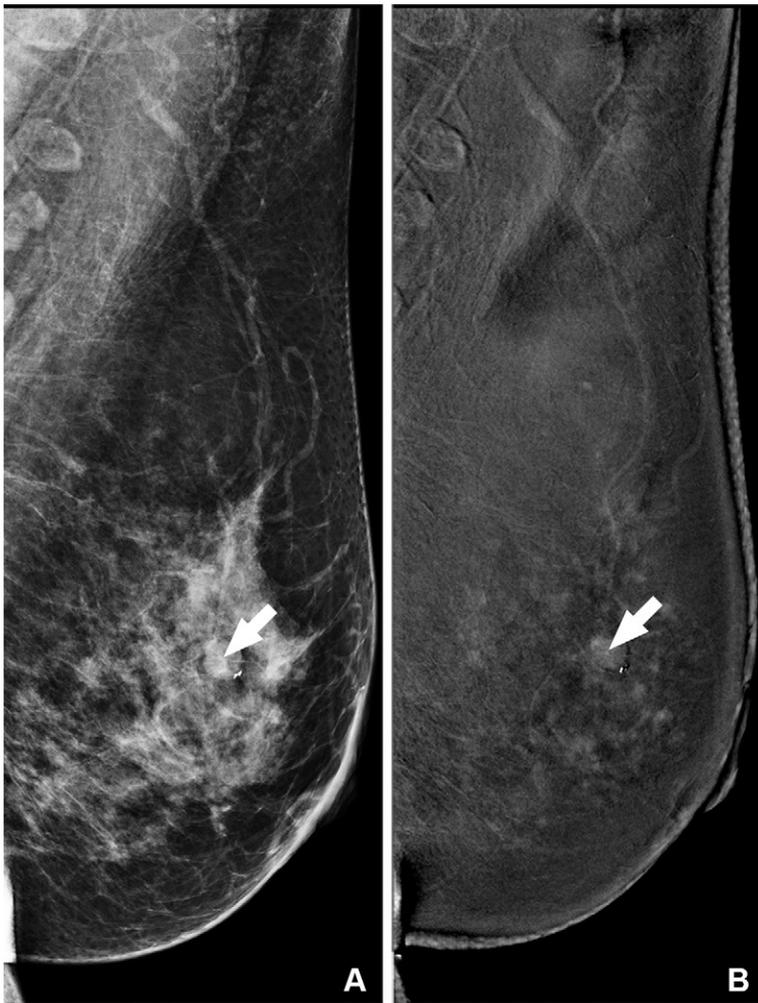
Figure 7.   Papilloma in a 48-year-old woman who presented for short-term follow-up imaging of a biopsy-proven papilloma without atypia in the left breast and CEM performed due to an elevated lifetime risk of malignancy as part of supplemental screening. **(A)** Left MLO LE image shows an oval mass (arrow) in the left upper inner breast, adjacent to a biopsy clip. **(B)** Left MLO recombined image shows homogeneous internal enhancement within the mass (arrow). **(C)** Color Doppler US image shows an oval hypoechoic mass (∗) within a dilated duct (arrowhead) and a vascular stalk (arrow), typical of a papilloma.
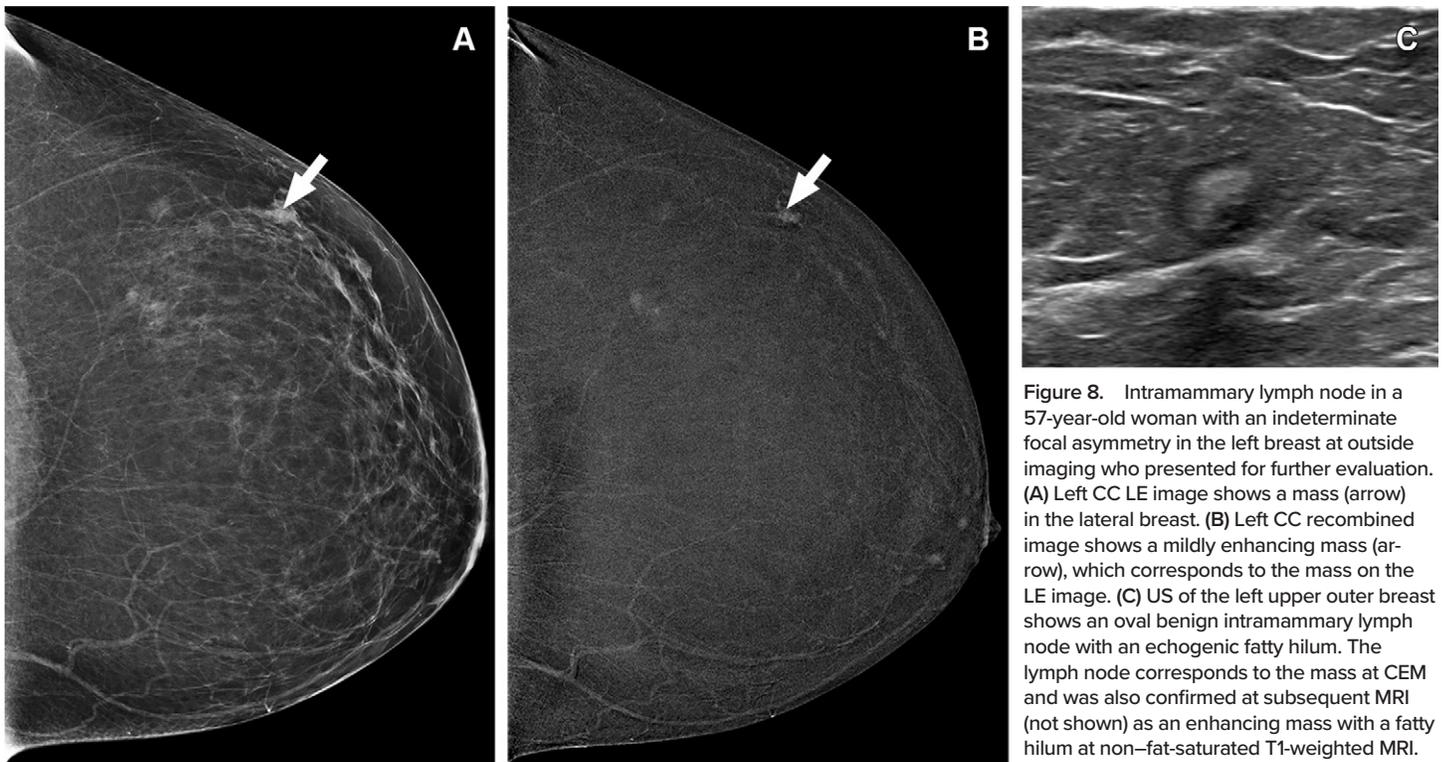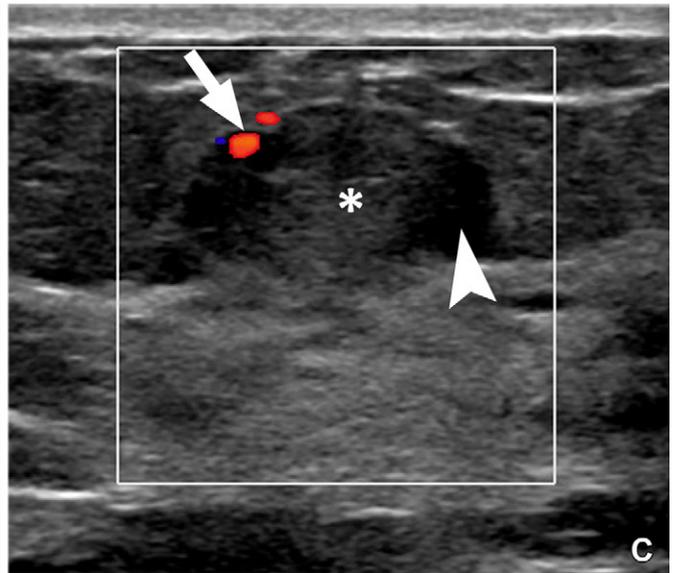

Figure 8.   Intramammary lymph node in a 57-year-old woman with an indeterminate focal asymmetry in the left breast at outside imaging who presented for further evaluation. **(A)** Left CC LE image shows a mass (arrow) in the lateral breast. **(B)** Left CC recombined image shows a mildly enhancing mass (arrow), which corresponds to the mass on the LE image. **(C)** US of the left upper outer breast shows an oval benign intramammary lymph node with an echogenic fatty hilum. The lymph node corresponds to the mass at CEM and was also confirmed at subsequent MRI (not shown) as an enhancing mass with a fatty hilum at non–fat-saturated T1-weighted MRI.
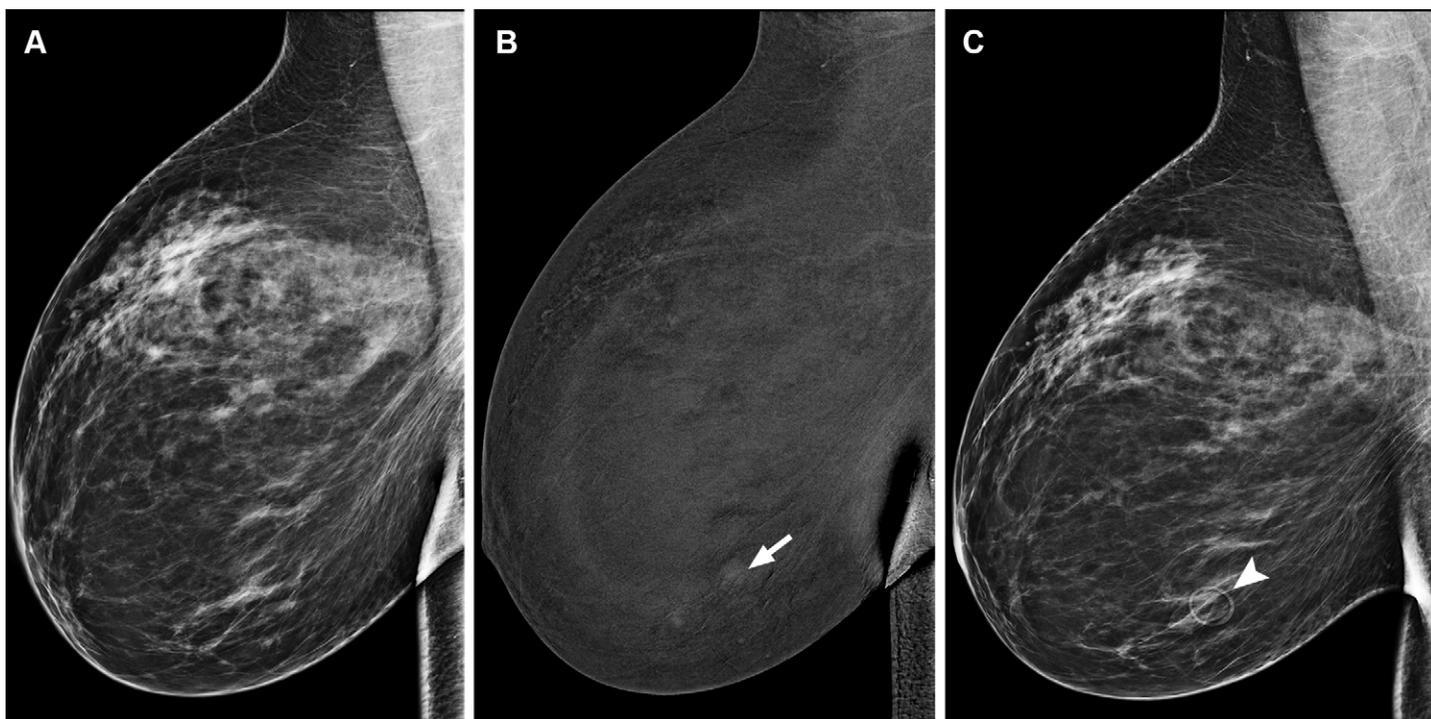
Figure 9. Nevus in a 41-year-old woman who underwent annual CEM for an elevated lifetime risk of malignancy. **(A)** Right MLO LE image is unremarkable. **(B)** Right MLO recombined image shows an enhancing mass (arrow) in the lower inner breast, without a US correlate (not shown). The patient was offered MRI (and possible MRI-guided biopsy) versus CEM-guided biopsy (as part of a clinical trial). The patient chose CEM-guided biopsy. On the day of the biopsy, the enhancement was suspected to be due to a visualized skin lesion. **(C)** Corresponding image from repeat three-dimensional mammography performed after placement of a mole marker (arrowhead) shows that the mole marker corresponds to the area of enhancement seen at prior CEM. The biopsy was canceled.

identify an air-lesion interface on LE images and diligent skin inspection with placement of mole markers before CEM (48).

If CEM enhancement is present and a skin lesion is suspected, direct inspection of the skin and repeat DBT with mole markers should be performed. If there is no skin lesion, targeted US should be performed. If the finding is noted during CEM when contrast material is still present, tangential views can be obtained to localize to skin.

Nipple Enhancement.—Nipple enhancement at CEM is variable but typically symmetric (49). At CEM, benign nipple enhancement when the nipple is out of profile can mimic an enhancing intramammary mass. To minimize this potential false positive, appropriately positioning the patient with the nipple in profile at the time of CEM is important (50).

If nipple enhancement is identified within 10 minutes of contrast material injection, a repeat CEM view with the nipple in profile can be obtained. If there is delayed recognition, a metallic skin BB marker can be placed on the nipple and repeat DBT images can be obtained in the initial position to show overlap of enhancement with the BB (Fig 10). If marking the nipple and repeating the CEM images (LE and recombined), use a mole marker instead of a BB due to metal artifact.

Contrast Material Contamination Artifact
Contrast material spillage onto the patient's skin, the detector, or the paddle from the technologist's hands or from the intravenous line is rare but can mimic NME on recombined images (51). Several imaging features can suggest contrast

material contamination. First, it commonly manifests as NME in only one breast, and when seen in bilateral breasts it can have a mirrored pattern, suggesting contamination on the paddle, the detector, or both (52). Second, the enhancement may have a "dot dash" or speckled appearance on recombined images (Fig 11).

There may or may not be associated LE findings. However, when these are present, there can be linear high attenuation on the LE images in a nearly identical pattern to the "dot dash" NME, due to shine-through artifact (51). Additional findings suggesting that linear high-attenuation apparent calcifications on LE images are contamination artifact includes disappearance of the high attenuation after cleansing the skin or on magnification views. If the finding is still present, it will localize to the skin on DBT or tangential views.

Diligent cleaning of the detector and paddles can prevent contamination-related artifact, and the nurse or technologist administering the contrast material should not assist in patient positioning. Or, if only one technologist is present, then we recommend changing gloves between the injection and patient positioning. If contamination is suspected, cleanse the breast, paddle, and detector before additional imaging.

False Negatives at CEM
False negatives at CEM can result in missed breast cancers and delay necessary treatment. False-negative rates at CEM (4%–9%) and MRI (4%–7%) are reported to be similar (7,8), with the limitation that both studies were small patient cohorts with known breast carcinoma. False negatives at CEM
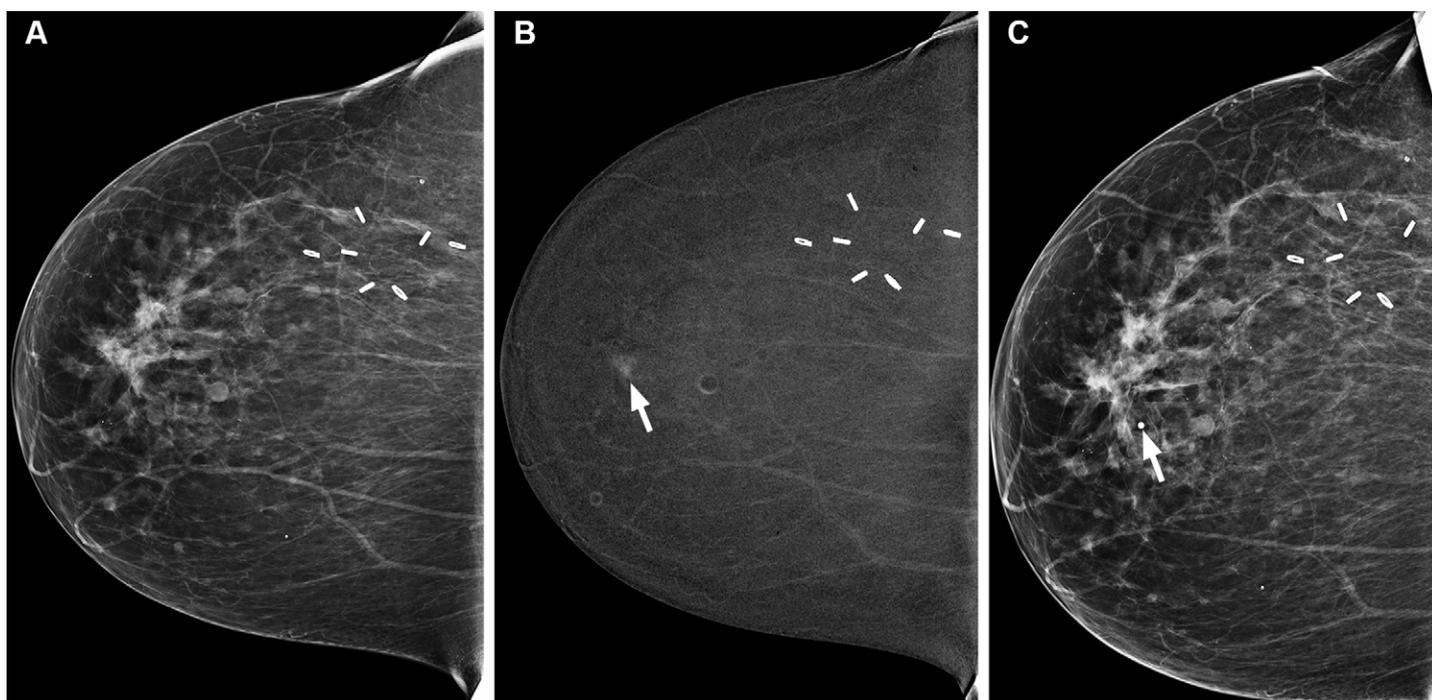
Figure 10. Nipple enhancement in a 63-year-old woman with a history of right malignant lumpectomy who presented for annual mammography, with CEM performed due to an elevated lifetime risk of malignancy and the patient unable to tolerate MRI. **(A)** Right CC LE image shows postlumpectomy changes in the outer breast. **(B)** Right CC recombined image shows NME (arrow) in the lower central breast. It was suspected that this enhancement was the nipple out of profile. A metallic BB marker was placed on the nipple. **(C)** Right CC image from repeat two-dimensional mammography shows that the BB (nipple) overlaps the prior area of NME (arrow), consistent with benign physiologic enhancement of the nipple, which was out of profile on the initial CEM images.
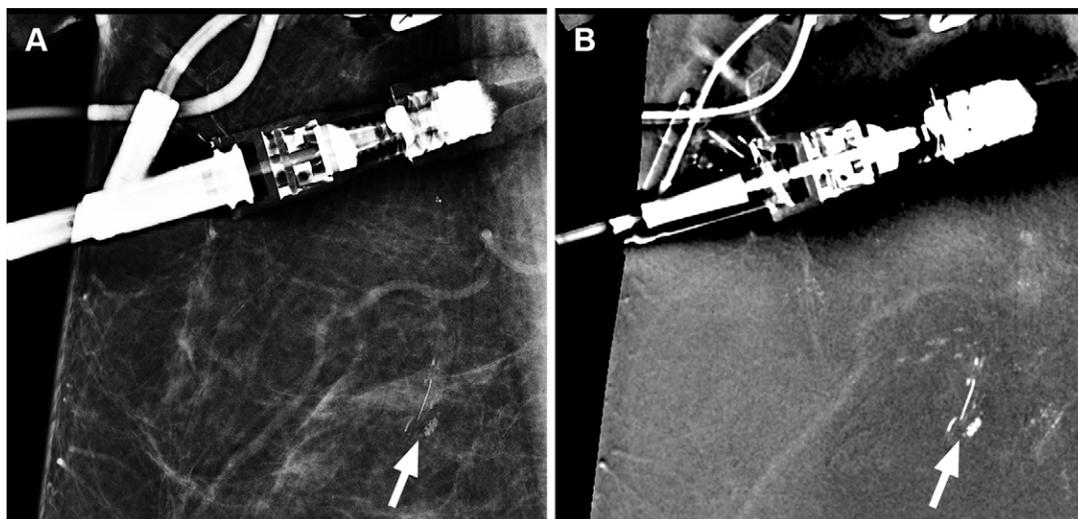
Figure 11. Contrast material contamination artifact in a 71-year-old woman with biopsy-proven left breast cancer who presented for CEM to evaluate response to neoadjuvant chemotherapy. **(A)** Right lateromedial LE image (zoomed in) shows multiple areas of linear high attenuation (arrow) in the upper breast. **(B)** Right lateromedial recombined image (zoomed in) shows linear NME (arrow), which corresponds to the high attenuation on the LE image. There is additional linear NME in a "dot dash" pattern without an LE correlate. The technologist reported that the patient's skin was wet near the port where she was injected, further suggesting skin contamination.

can be due to incomplete or inadequate visualization of a lesion, background parenchymal enhancement (BPE) obscuring lesion enhancement, lack of lesion enhancement, or errors of characterization by the interpreting radiologist (Fig 12).

Incomplete or Inadequate Visualization of a Lesion

Lesion Off the Field of View.—A limited field of view (FOV) is a known limitation of CEM. As with mammography, lesions in the far medial or posterior breast may not be included fully in the FOV (53,54). If the patient is undergoing CEM due to a re-

called finding at screening mammography or as part of staging of a new diagnosis of malignancy and the lesion is in the far medial breast, additional CEM views including the medially exaggerated CC view (XCCM) should be obtained.

For posterior lesions, the technologist should try to obtain as much far posterior tissue as possible and reposition if needed. Additionally, in patients with suspected masses in these areas or suspicion of chest wall involvement, MRI should be performed to evaluate the extent of disease (Fig 13). Additionally, axillary US should be performed if there is suspicion for lymph node involvement, given the limitations of mammography alone.

Causes of False Negatives on CEM

Incomplete or inadequate visualization of lesion	BPE obscuring lesion	Lack of lesion contrast enhancement	Error of characterization

Incomplete or inadequate visualization of lesion:

Lesion off the field of view

Difficult or unable to position due to location of lesion

Lesion obscured due to abutting implant

Lesion obscured by hematoma/seroma

Lack of lesion contrast enhancement:

Lack of IV contrast at time of imaging (i.e. unrecognized contrast extravasation)

Cancers with little or no associated enhancement
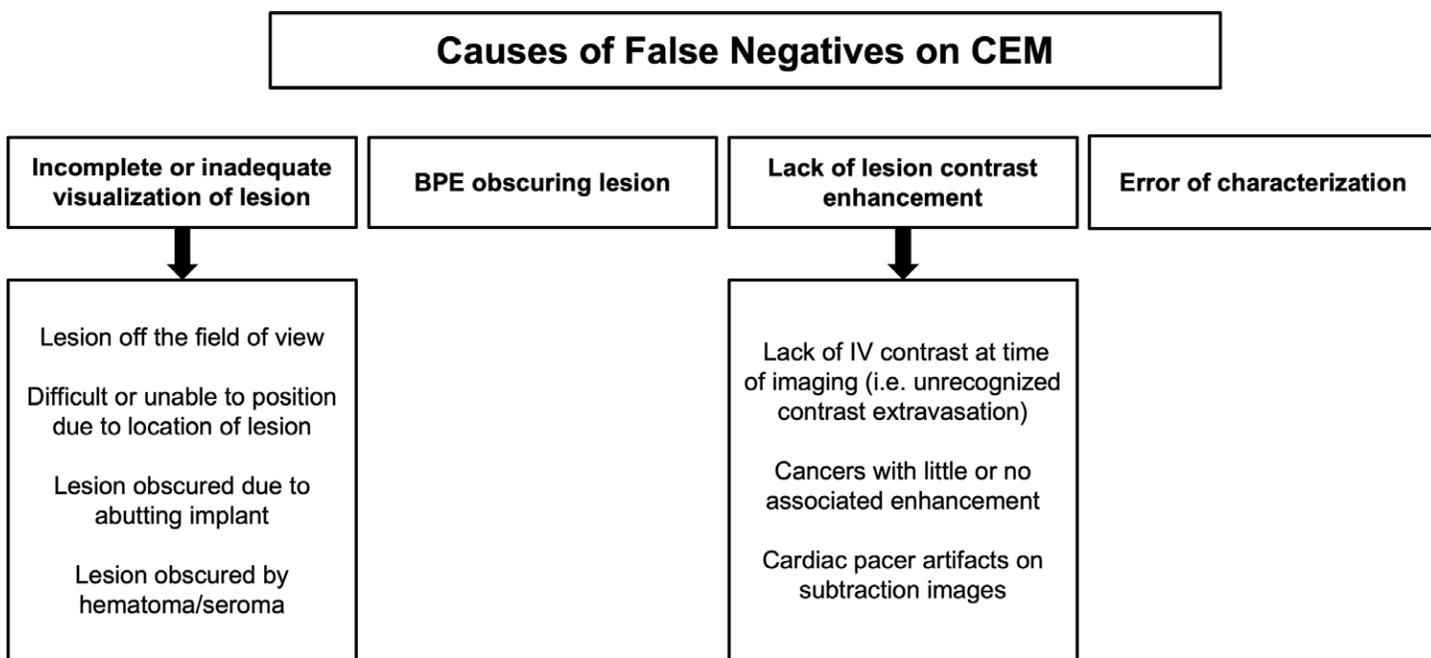
Cardiac pacer artifacts on subtraction images

Figure 12. Major causes of false negatives at CEM under the categories of incomplete or inadequate visualization of a lesion, BPE obscuring a lesion, lack of lesion contrast enhancement, and error of characterization. *IV* = intravenous.

Difficulty in Properly Positioning the Patient or Inability to Do So.—In patients with postoperative changes from prior lumpectomy or breast augmentation, positioning may be difficult and further limit the FOV. CEM images should be evaluated quickly, with prompt repositioning when needed. If unable to reposition appropriately and contrast-enhanced imaging is still desired, MRI should be performed in these patients (Fig 14).

Lesion Abuts Breast Implants.—Although prior studies have found CEM and MRI to be concordant in women with breast augmentation and newly diagnosed breast cancer, there are CEM positioning limitations in these patients, as with mammography (55). When implants are included in the FOV, artifacts on the recombined images have been reported (55). Our standard practice is to perform all CEM studies with implant-displaced views to allow better compression and improved visualization of tissue than with non–implant-displaced views. As noted earlier, in patients with far posterior or medial lesions, MRI is preferred to assess the extent of disease (Fig 15). CEM, like mammography, cannot be used to evaluate implant integrity.

Lesion Obscured by Hematoma or Seroma.—Early postoperative changes and enhancement in the breast can limit evaluation at CEM.

Typically, margins are determined on the pathology specimen and imaging is rarely needed, but occasionally breast imaging is used to determine the extent of residual enhancement in patients with continued positive margins at re-excision or to evaluate when there is concern for missed margins at the time of surgery. As with MRI, false negatives adjacent to postoperative changes can occur at CEM. For example, residual enhancement adjacent to the surgical bed can be falsely attributed to benign postoperative changes (56).

Figure 16 shows the limitations of CEM in the immediate postoperative setting, especially when a large complex hematoma or seroma is present. As noted earlier, contrast-enhanced imaging should be performed no earlier than 28 days after surgery (24). If malignant microcalcifications were present preoperatively, FFDM with magnification views is likely the best diagnostic imaging modality in the early postoperative setting to evaluate the extent of residual disease not removed surgically.

To minimize false negatives at follow-up CEM or MRI in patients with a history of breast cancer, careful correlation with the patient's surgical history should be performed, particularly scrutinizing areas of known positive margins. However, the greater importance of CEM, like MRI, in these patients is to evaluate how far from the lumpectomy site that abnormal enhancement is present to impact the surgical plan.

Marked BPE Obscuring a Lesion
Greater BPE is associated with dense breasts, premenopausal status, and young age (57). The category of BPE is part of the CEM report, like with MRI reporting, and there are varying data regarding if and how BPE affects the accuracy of CEM (58,59). In premenopausal women, early literature suggests that elective CEM should be performed during days 8–14 of the menstrual cycle (60). Physiologic BPE of the breast results in benign breast tissue appearing diffusely bright on recombined images, which may mask underlying suspicious breast lesions (Fig 15).

Lack of Lesion Contrast Enhancement

Lack of Intravenous Contrast Material at the Time of Imaging.—Although rare, lack of contrast enhancement at CEM can be due to contrast material extravasation, peripheral or central vascular occlusion, impaired cardiovascular function,

Figure 13. Invasive ductal carcinoma and invasive lobular carcinoma in a 72-year-old woman with two palpable areas of pain in the left breast, one in the upper outer breast and the other in the lower inner breast. **(A, B)** Left breast CC **(A)** and MLO **(B)** recombined images show architectural distortion (LE finding not shown) with associated NME (arrow) at the lateral area of pain. At the medial area of pain, there is an irregular enhancing mass (arrowhead) extending posteriorly beyond the FOV. US (not shown) of the medial mass showed possible pectoralis invasion, and MRI was recommended. **(C)** Sagittal postcontrast subtraction T1-weighted image shows that the medial mass (arrowhead) invades into the pectoralis muscle. At pathologic analysis, the medial mass was invasive ductal carcinoma (grade 1, ER positive, PR positive, HER2 negative) and the lateral mass was invasive lobular carcinoma (grade 1, ER positive, PR positive, HER2 negative).
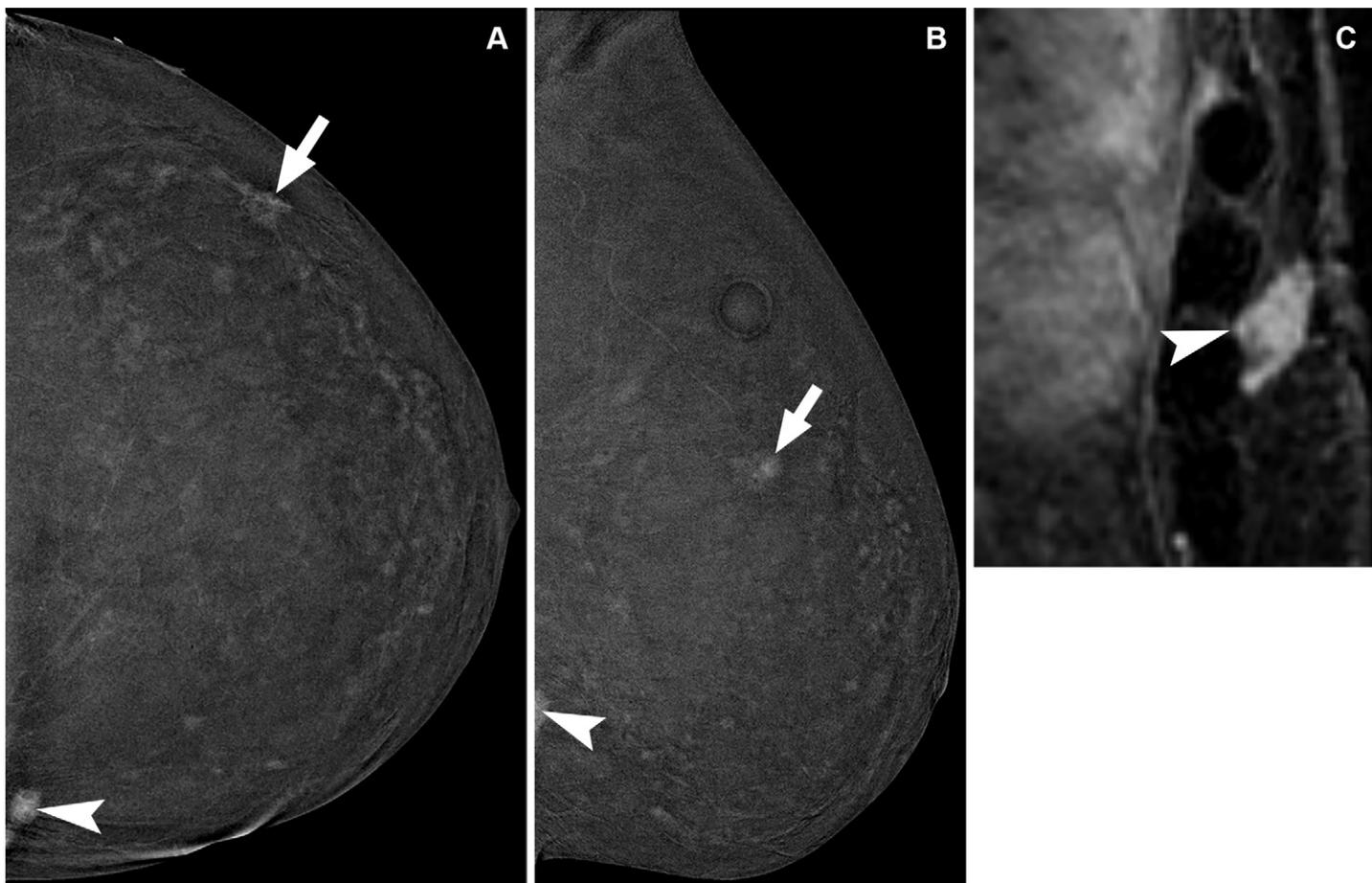

or an inadequate contrast material bolus. If contrast material extravasation was not recognized before imaging, this may result in lack of enhancement on CEM images, which would be a false-negative CEM finding. Unlike with MRI, where the thoracic vasculature can confirm the presence of intravenous contrast material, there is no definitive way to confirm adequate contrast material uptake at CEM. However, contrast material extravasation at CEM is typically noted by the patient or technologist, given the larger contrast material bolus (100 mL).

A patient complication—such as vasovagal response or iodine contrast material allergy—may also be the cause of inadequate contrast material uptake at CEM due to early termination of the contrast material bolus. If any of these complications occur, radiologists should follow their institution's protocols for acute treatment of contrast material extravasation or allergy and timing of repeat CEM if desired.

Cancers with Little or No Associated Enhancement.—A positive CEM finding includes any abnormality on either LE or recombined images. Thus, false negatives can occur at CEM when a cancer has little or no associated enhancement and no LE finding. CEM relies on tumor vascularity, with proliferation of capillaries and new vessel formation after the cancer releases angiogenic factors such as vascular endothelial growth factor (VEGF). However, some subtypes of breast cancer such as invasive lobular carcinoma use non-VEGF growth factors for angiogenesis, and this may explain the difference in enhancement patterns (61,62). Examples of malignant lesions with possible weak or no enhancement include invasive lobular carcinoma and ductal carcinoma in situ (DCIS) (63,64).

In MRI studies, 12.2%–16% of cases of DCIS and 2.6%–3% of invasive carcinomas demonstrated no enhancement (65,66). Although there are few published studies of false negatives at CEM, one study reported that up to 16% of cases of DCIS with associated calcifications lacked enhancement at CEM (Fig 17) (67). Other studies that evaluated calcifications at CEM reported that 96% of calcifications without enhancement represented a false-positive finding, whereas 80% of calcifications with enhancement represented a true-positive cancer (10). However, suspicious calcifications, architectural distortion, or irregular masses with lack of enhancement on LE images must be biopsied regardless of enhancement on CEM images (64).
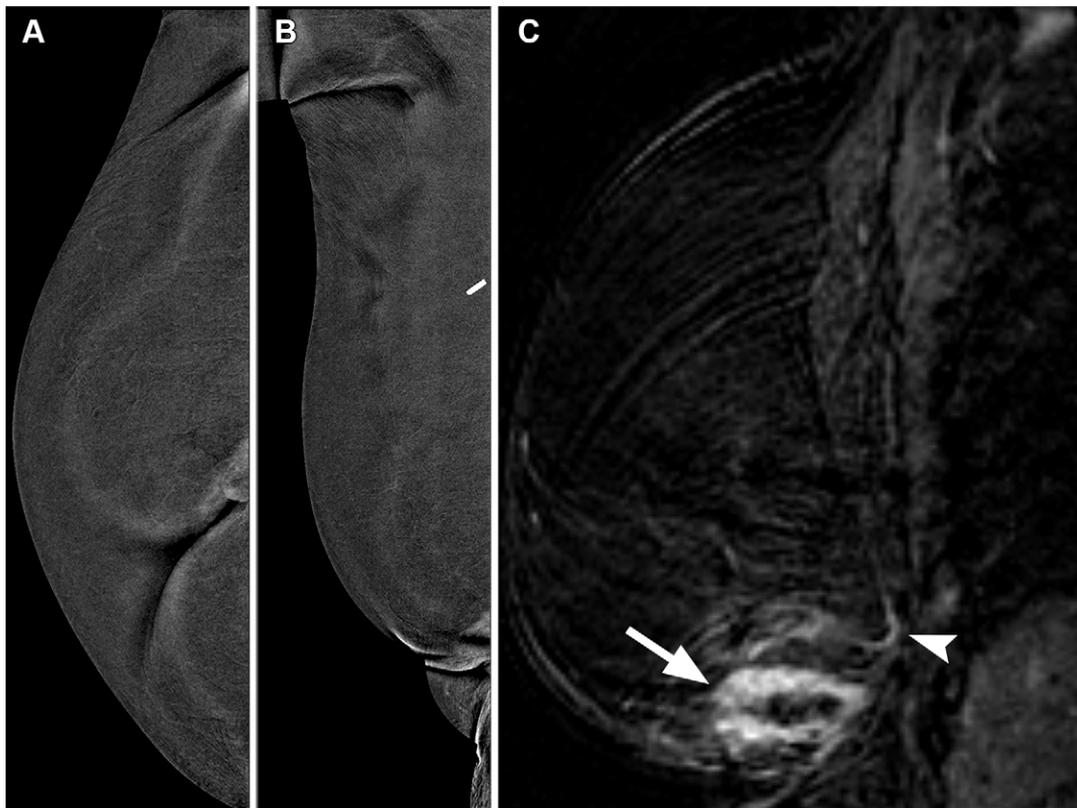
Figure 14. Recurrence in a 78-year-old woman with a history of lumpectomy for invasive adeno-squamous (metaplastic) carcinoma (ER negative, PR negative, HER2 negative) 4 years earlier, with a recent diagnosis of recurrence at skin punch biopsy near the lumpectomy cavity. CEM was performed for preoperative staging. **(A, B)** Right breast CC **(A)** and mediolateral **(B)** recombined images were obtained, but despite multiple attempts at repositioning, it was difficult to include the lumpectomy cavity (site of known recurrence at punch biopsy) within the FOV. US (not shown) was unremarkable. **(C)** Sagittal post-contrast subtraction fat-saturated T1-weighted image shows a rim-enhancing mass (arrow), centered in the lumpectomy cavity, with subtle enhancement extending to the pectoralis muscle (arrowhead). Results of surgical pathologic analysis confirmed recurrence (grade 2, ER negative, PR negative, HER2 negative).
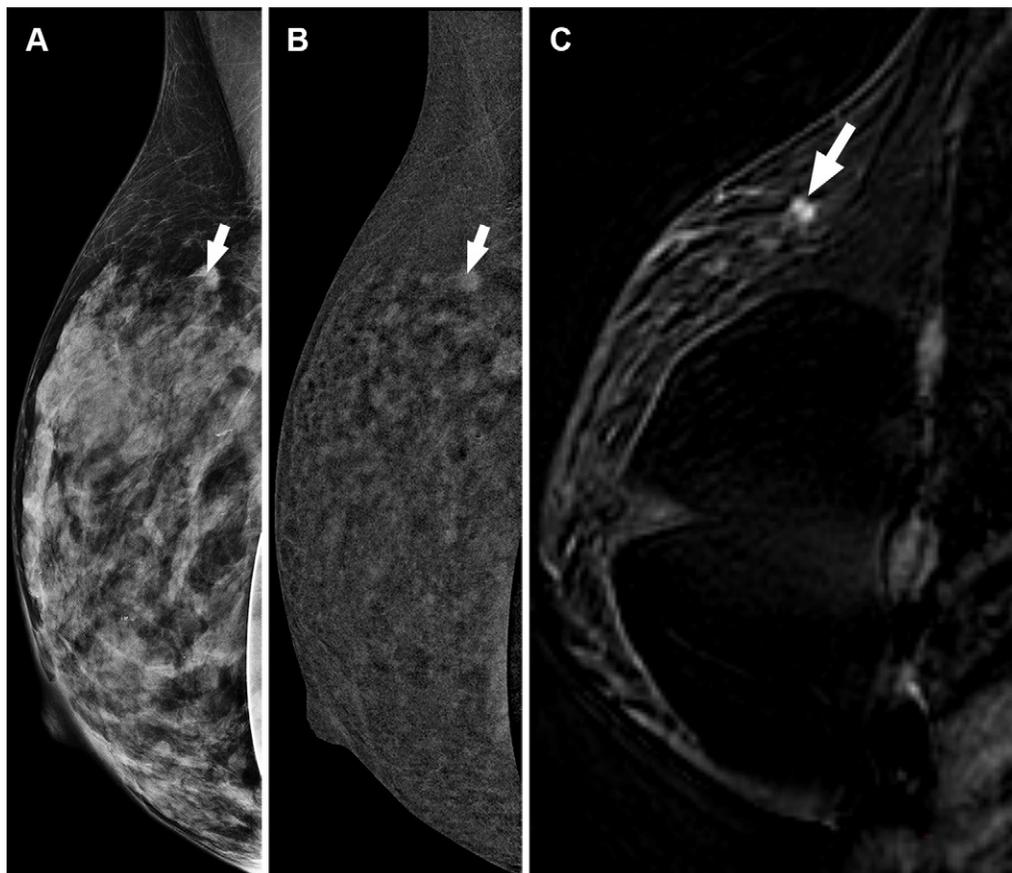
Figure 15. Invasive ductal carcinoma in a 46-year-old woman with bilateral saline implants, who was recalled for an asymmetry in the right upper breast at screening mammography. Owing to her dense breast tissue, CEM was offered to the patient as part of her diagnostic evaluation. **(A, B)** Right breast LE **(A)** and recombined **(B)** images (lateromedial implant-displaced view) show an enhancing mass (arrow) in the upper breast. Despite multiple attempts at repositioning, the mass could be seen only on the lateromedial implant-displaced view. There is moderate BPE. US (not shown) demonstrated an irregular mass at the 1-o'clock position, 12 cm from the nipple, which corresponded to the CEM finding. Incidentally noted at US was a second mass at the 2-o'clock position, 12 cm from the nipple, which did not have a two-dimensional mammographic (LE) or CEM correlate. **(C)** Sagittal postcontrast subtraction T1-weighted image shows an enhancing mass (arrow) in the upper inner posterior breast, which corresponds to the 1-o'clock mass (invasive ductal carcinoma, grade 1, ER positive, PR positive, HER2 negative). There was a second enhancing mass (not shown), which corresponded to the 2-o'clock mass (invasive ductal carcinoma, grade 2, ER positive, PR positive, HER2 negative).
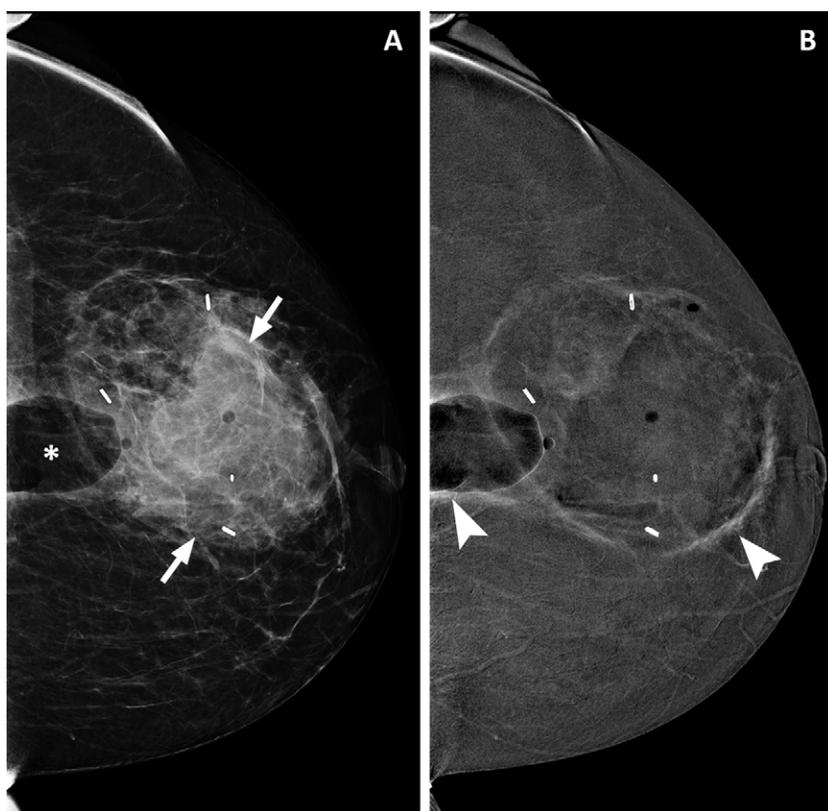
Figure 16. Residual ductal carcinoma in situ (DCIS) in a 63-year-old woman who underwent left lumpectomy for DCIS (grade 3, ER positive, PR positive) but had positive margins at initial lumpectomy pathologic analysis and again along the anterior, lateral, and inferior margins at re-excision. The most recent excision was 4 days before CEM. **(A)** Left breast CC LE image shows postoperative changes, with a large fluid collection (seroma or hematoma) (arrows) in the operative bed and a low-density area (∗) posteriorly, which is likely postoperative air in the lumpectomy cavity. **(B)** Left breast CC recombined image shows predominantly smooth rim enhancement (arrowheads) around both the low-density and higher-density collections. While this may represent benign postprocedure inflammatory changes, the complexity of large collections with overlapping areas of rim enhancement limits evaluation for residual disease. The patient subsequently underwent mastectomy, which demonstrated residual DCIS, with the largest focus along the lateral margin of the prior lumpectomy bed.

Pacemaker with Artifact Obscuring a Lesion.—CEM may be performed in lieu of MRI in patients with incompatible devices such as cardiac pacemakers. However, implantable devices may result in limited visualization of the over- or underlying breast tissue, difficulties with positioning, less compression, and more motion (68). Recombined CEM images can show a dark halo artifact around the high-attenuation pacemaker (52). At our institution, we have also noted a large, square, pixilated appearance throughout all or portions of the breast when the pacemaker is in the FOV, which is thought to be due to the CEM reconstruction algorithm (Fig 18). To reduce these artifacts, the pacemaker should be positioned off the FOV (Fig S2).

Errors of Characterization: Lesions with Seemingly Benign Features at CEM

Errors of characterization are a type of cognitive, or interpretive, error in breast imaging in which a finding was identified but misinterpreted or mischaracterized as benign. False negatives can result when a lesion has a perceived benign shape or morphology (69,70). Although round or oval masses with circumscribed margins are commonly associated with benignity, these features can also be associated with malignancy, especially in patients who are *BRCA* mutation carriers and in triple-negative invasive ductal carcinoma (71). Another example of a false-negative CEM finding includes attributing the perceived enhancement to BPE. To reduce errors of characterization at CEM, a multidimensional approach should be used, including specific training in CEM, self-audits of biopsies and radiologic-pathologic correlation, peer review, and continuing education courses (70).

## Pearls for the Reader

Real-Time Imaging

Artifacts can occur in up to 10% of CEM examinations, either on the LE image alone, on the recombined image alone, or on both the LE and recombined images (72). Most are subtle and rarely cause clinical confusion. However, some artifacts, such as the pacemaker-caused artifact (Fig S2), can result in nondiagnostic recombined CEM images.

Meticulous attention to proper mammographic technique and rapid identification of artifacts are key. When possible, real-time interpretation of CEM images is ideal. If additional views are necessary, they may be obtained while contrast material is still in the breast parenchyma. Ideally, contrast-enhanced images are obtained within 10 minutes after injection; however, newer studies suggest that delayed imaging for up to 1 hour may still result in diagnostic views (17).

CEM BI-RADS Lexicon and Suspicious Features

In 2022, the American College of Radiology released a CEM Breast Imaging Reporting and Data System (BI-RADS) atlas and lexicon to facilitate standardization of CEM interpretation and reporting (34). Per the BI-RADS atlas, CEM findings should be divided into three broad categories, and it should be stated in the report where each finding fits into these categories: LE images only (standard FFDM equivalent), enhancement on recombined images only, or findings seen on LE images with associated enhancement on recombined images (34).

Using these three categories, Amir et al (10) evaluated imaging characteristics of true-positive and false-positive findings
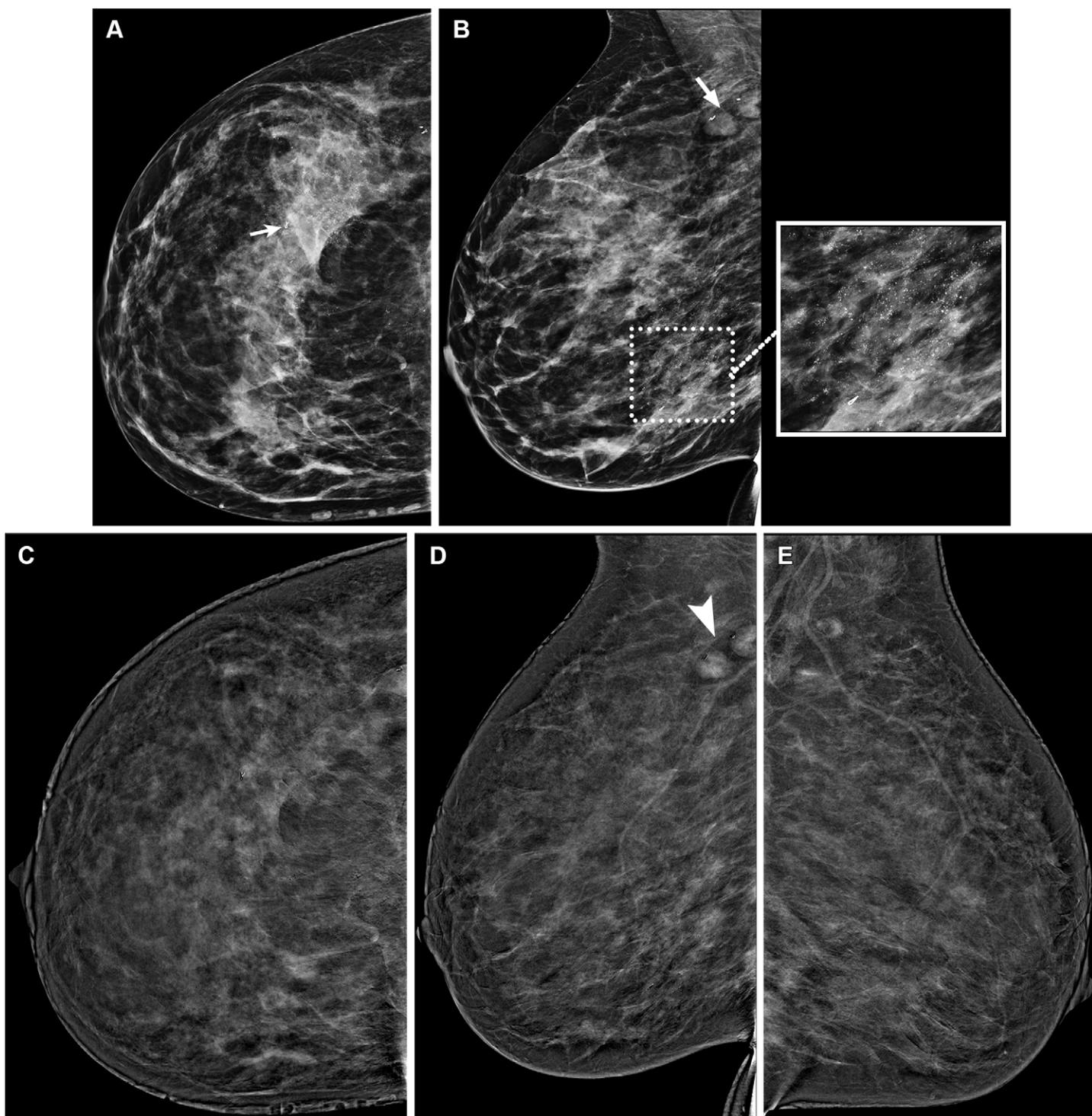
Figure 17.   DCIS and metastatic invasive ductal carcinoma in a 36-year-old pregnant woman with a palpable lump in the right breast. Diagnostic mammography (not shown) showed pleomorphic calcifications in the lower outer breast, which were biopsy-proven DCIS (grade 3, ER positive, PR positive). The palpable abnormality corresponded to enlarged axillary lymph nodes, which were biopsied; pathologic analysis yielded metastatic invasive ductal carcinoma (grade 2, ER positive, PR positive, HER2 negative). CEM was performed for preoperative planning. **(A, B)** Right breast CC **(A)** and MLO **(B)** LE images show extensive pleomorphic calcifications (best seen on the zoomed-in inset in **B**), with a ribbon biopsy clip (arrow in **A**) denoting the site of biopsy-proven DCIS. Multiple enlarged axillary lymph nodes are visualized (arrow in **B**), consistent with biopsy-proven metastatic disease. **(C, D)** Right breast CC **(C)** and mediolateral **(D)** recombined images show moderate BPE and enlarged enhancing axillary lymph nodes (arrowhead in **D**). Otherwise, there is no suspicious enhancement. **(E)** Left MLO recombined image shows moderate BPE but no suspicious enhancement.

at CEM, and their results can help inform radiologists' management of these findings. For example, a true-positive result was less likely when the finding was on only LE images (4%) or on only recombined images (12%), compared with a finding seen on both LE and recombined images (31%). This makes a lesion seen on both LE and recombined images 12.5 times more likely to be a true-positive cancer than a lesion seen on only LE images (10).
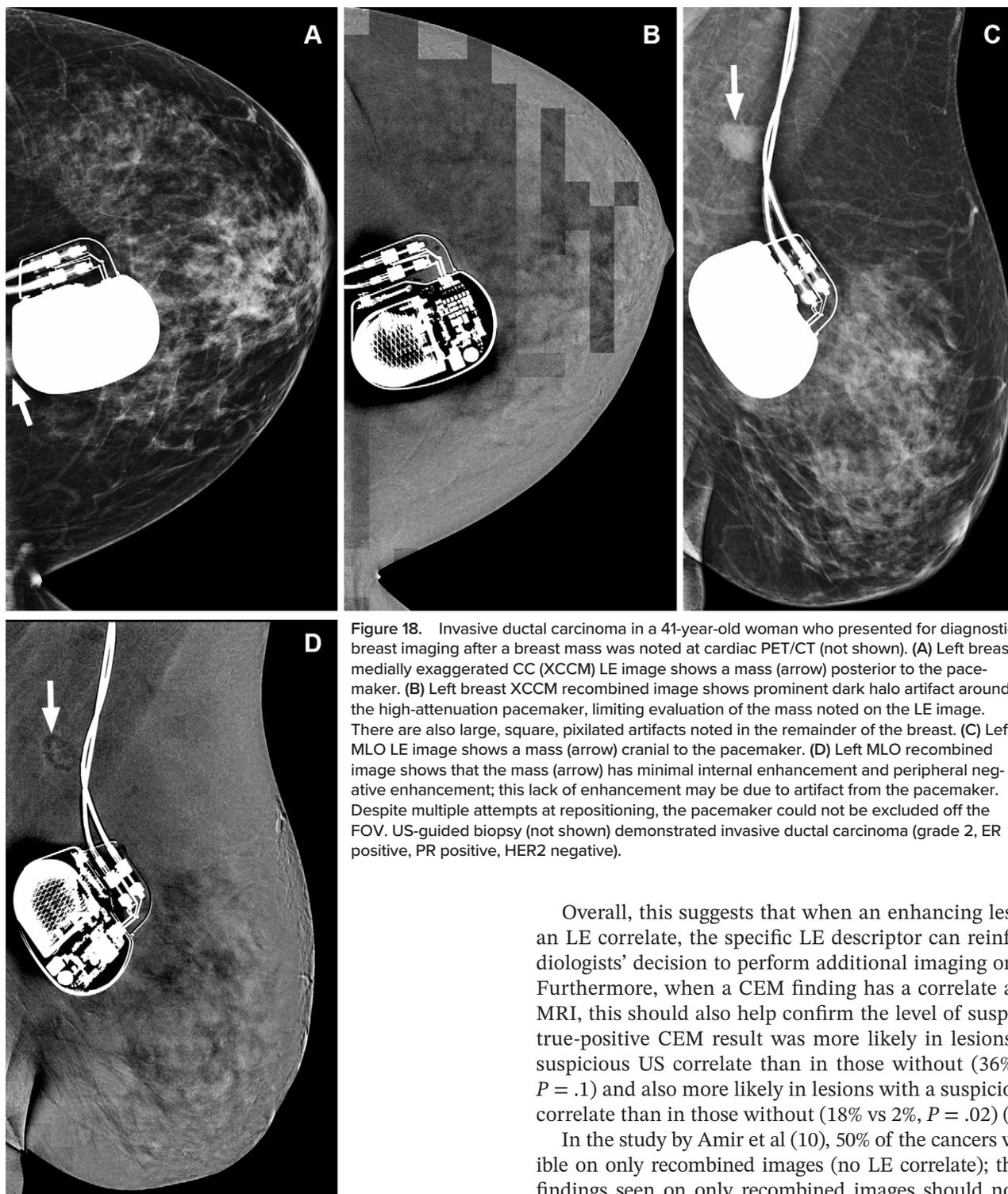
Figure 18. Invasive ductal carcinoma in a 41-year-old woman who presented for diagnostic breast imaging after a breast mass was noted at cardiac PET/CT (not shown). **(A)** Left breast medially exaggerated CC (XCCM) LE image shows a mass (arrow) posterior to the pacemaker. **(B)** Left breast XCCM recombined image shows prominent dark halo artifact around the high-attenuation pacemaker, limiting evaluation of the mass noted on the LE image. There are also large, square, pixilated artifacts noted in the remainder of the breast. **(C)** Left MLO LE image shows a mass (arrow) cranial to the pacemaker. **(D)** Left MLO recombined image shows that the mass (arrow) has minimal internal enhancement and peripheral negative enhancement; this lack of enhancement may be due to artifact from the pacemaker. Despite multiple attempts at repositioning, the pacemaker could not be excluded off the FOV. US-guided biopsy (not shown) demonstrated invasive ductal carcinoma (grade 2, ER positive, PR positive, HER2 negative).

Overall, this suggests that when an enhancing lesion has an LE correlate, the specific LE descriptor can reinforce radiologists' decision to perform additional imaging or biopsy. Furthermore, when a CEM finding has a correlate at US or MRI, this should also help confirm the level of suspicion. A true-positive CEM result was more likely in lesions with a suspicious US correlate than in those without (36% vs 9%, $P = .1$) and also more likely in lesions with a suspicious MRI correlate than in those without (18% vs 2%, $P = .02$) (10).

In the study by Amir et al (10), 50% of the cancers were visible on only recombined images (no LE correlate); therefore, findings seen on only recombined images should not be ignored. In a study on preoperative staging to evaluate for additional sites of disease, the authors reported that an enhancing lesion at CEM was significantly more likely to be malignant than an enhancing lesion at MRI (positive predictive value [PPV] 97% vs 85%, $P < .01$) (7). Together, these data suggest that CEM enhancement is suspicious and should not be dismissed.

The Most Suspicious Finding Trumps Lack of Enhancement

Although enhancement at CEM is suspicious, as noted earlier, sometimes technical factors due to positioning or artifacts

When a lesion was seen on only LE or recombined images, true-positive results were not associated with any specific type of LE (standard mammography) or CEM enhancement descriptors. However, among lesions seen on both LE and recombined images, the type of LE finding was important: calcifications (80%) and asymmetries (46%) were more likely to be a true-positive cancer than a mass (11%) or distortions (0%) (10).

obscure the area of interest on recombined images. Low-grade malignancies may not show enhancement. Therefore, in lesions without CEM enhancement (Fig 17), the decision to pursue core needle biopsy should be based on the most suspicious imaging feature at CEM (LE or recombined images) or US. Remembering that the most suspicious feature should always guide management can help reduce false negatives when interpreting CEM studies.

Emerging Research

Until recently, a limitation of CEM was lack of CEM-guided biopsy capability, especially if MRI or MRI-guided biopsy was not available or the patient could not tolerate MRI. In 2020, the U.S. Food and Drug Administration cleared two devices to support CEM-guided biopsy using stereotactic biopsy (73,74). Figure S3 presents an example of CEM-guided biopsy. Ongoing clinical trials are being conducted, but preliminary results are promising and demonstrate that CEM-guided biopsy is a technically feasible and relatively quick procedure and has high patient satisfaction (98%) (17,75). As future work evolves, CEM and CEM-guided biopsy could provide a cost-effective and relatively fast core needle biopsy mechanism for patients without access to MRI or MRI-guided biopsy.

Conclusion

CEM is a relatively new imaging modality proven to have unique advantages in characterizing and detecting breast lesions. CEM has slightly superior specificity for cancer detection to that of breast MRI and relatively similar sensitivity (4–10). To maximize its efficacy, it is important to understand pathologic conditions and technical considerations that result in false positives and false negatives at CEM.

False positives depend on vascularity and can be seen in the setting of enhancing benign lesions, infectious or inflammatory lesions, or contrast material contamination artifact. False negatives can result from inadequate or incomplete inclusion of a lesion, obscuration of a lesion due to BPE, absence of contrast enhancement of a malignancy, or characterization errors.

Understanding the causes of false positives and false negatives at CEM is not only critical for improving cancer detection and avoiding false-positive imaging workup, follow-up, or biopsy of benign lesions, but awareness can also be used by radiologists and technologists to optimize imaging technique and help overcome pitfalls in practice.

References

1. Comstock CE, Gatsonis C, Newstead GM, et al. Comparison of Abbreviated Breast MRI vs Digital Breast Tomosynthesis for Breast Cancer Detection among Women with Dense Breasts Undergoing Screening. JAMA 2020;323(8):746–756.
2. Jochelson MS, Lobbes MBI. Contrast-enhanced Mammography: State of the Art. Radiology 2021;299(1):36–48.
3. Kuhl C. The current status of breast MR imaging. I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice. Radiology 2007;244(2):356–378.
4. Patel BK, Gray RJ, Pockaj BA. Potential Cost Savings of Contrast-enhanced Digital Mammography. AJR Am J Roentgenol 2017;208(6):W231–W237.
5. Xing D, Lv Y, Sun B, et al. Diagnostic Value of Contrast-enhanced Spectral Mammography in Comparison to Magnetic Resonance Imaging in Breast Lesions. J Comput Assist Tomogr 2019;43(2):245–251.
6. Pötsch N, Vatteroni G, Clauser P, Helbich TH, Baltzer PAT. Contrast-enhanced Mammography versus Contrast-enhanced Breast MRI: a Systematic Review and Meta-analysis. Radiology 2022;305(1):94–103.
7. Jochelson MS, Dershaw DD, Sung JS, et al. Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma. Radiology 2013;266(3):743–751.
8. Sumkin JH, Berg WA, Carter GJ, et al. Diagnostic Performance of MRI, Molecular Breast Imaging, and Contrast-enhanced Mammography in Women with Newly Diagnosed Breast Cancer. Radiology 2019;293(3):531–540.
9. Yüzkan S, Cengiz D, Hekimsoy İ, Sezgin Okçu Ö, Oktay A. Diagnostic Performance of Contrast-enhanced Mammography: Comparison With MRI and Mammography. J Breast Imaging 2021;3(4):448–454.
10. Amir T, Hogan MP, Jacobs S, Sevilimedu V, Sung J, Jochelson MS. Comparison of False-Positive versus True-Positive Findings on Contrast-enhanced Digital Mammography. AJR Am J Roentgenol 2022;218(5):797–808.
11. Francescone MA, Jochelson MS, Dershaw DD, et al. Low energy mammogram obtained in contrast-enhanced digital mammography (CEDM) is comparable to routine full-field digital mammography (FFDM). Eur J Radiol 2014;83(8):1350–1355.
12. Sung JS, Lebron L, Keating D, et al. Performance of Dual-Energy Contrast-enhanced Digital Mammography for Screening Women at Increased Risk of Breast Cancer. Radiology 2019;293(1):81–88.
13. Jochelson MS, Pinker K, Dershaw DD, et al. Comparison of screening CEDM and MRI for women at increased risk for breast cancer: a pilot study. Eur J Radiol 2017;97:37–43.
14. Sorin V, Yagil Y, Yosepovich A, et al. Contrast-enhanced Spectral Mammography in Women with Intermediate Breast Cancer Risk and Dense Breasts. AJR Am J Roentgenol 2018;211(5):W267–W274.
15. Sensakovic WF, Carnahan MB, Czaplicki CD, et al. Contrast-enhanced Mammography: How Does It Work? RadioGraphics 2021;41(3):829–839.
16. Bhimani C, Matta D, Roth RG, et al. Contrast-enhanced Spectral Mammography: Technique, Indications, and Clinical Applications. Acad Radiol 2017;24(1):84–88.
17. Kowalski A, Arefan D, Ganott MA, et al. Contrast-enhanced Mammography-guided Biopsy: Initial Trial and Experience. J Breast Imaging 2023;5(2):148–158.
18. Daly CP, Jaeger B, Sill DS. Variable appearances of fat necrosis on breast MRI. AJR Am J Roentgenol 2008;191(5):1374–1380.
19. Garibotto NL, Chan JKK, Taylor D. Appearance of fat necrosis on contrast-enhanced spectral mammography. BMJ Case Rep 2022;15(3):e246231.
20. Taboada JL, Stephens TW, Krishnamurthy S, Brandt KR, Whitman GJ. The many faces of fat necrosis in the breast. AJR Am J Roentgenol 2009;192(3):815–825.
21. Zamora K, Allen E, Hermecz B. Contrast mammography in clinical practice: current uses and potential diagnostic dilemmas. Clin Imaging 2021;71:126–135.
22. Goudreau SH, Woughter MA, Seiler SJ. Multimodality Review of Imaging Features Following Breast Reduction Surgery. Eur J Breast Health 2021;17(3):206–213.
23. Tang R, Acevedo F, Lanahan C, et al. Incidental breast carcinoma: incidence, management, and outcomes in 4804 bilateral reduction mammoplasties. Breast Cancer Res Treat 2019;177(3):741–748.
24. Frei KA, Kinkel K, Bonel HM, Lu Y, Esserman LJ, Hylton NM. MR imaging of the breast in patients with positive margins after lumpectomy: influence of the time interval between lumpectomy and MR imaging. AJR Am J Roentgenol 2000;175(6):1577–1584.
25. Heywang-Köbrunner SH, Schlegel A, Beck R, et al. Contrast-enhanced MRI of the breast after limited surgery and radiation therapy. J Comput Assist Tomogr 1993;17(6):891–900.
26. Li J, Dershaw DD, Lee CH, Joo S, Morris EA. Breast MRI after conservation therapy: usual findings in routine follow-up examinations. AJR

Am J Roentgenol 2010;195(3):799–807. [Published correction appears in AJR Am J Roentgenol 2010;195(4):1043.]

27. Wang L, Wang D, Fei X, et al. A rim-enhanced mass with central cystic changes on MR imaging: how to distinguish breast cancer from inflammatory breast diseases? PLoS One 2014;9(3):e90355.

28. Fazzio RT, Shah SS, Sandhu NP, Glazebrook KN. Idiopathic granulomatous mastitis: imaging update and review. Insights Imaging 2016;7(4):531–539.

29. Pluguez-Turull CW, Nanyes JE, Quintero CJ, et al. Idiopathic Granulomatous Mastitis: Manifestations at Multimodality Imaging and Pitfalls. RadioGraphics 2018;38(2):330–356.

30. Wu JM, Turashvili G. Cystic neutrophilic granulomatous mastitis: an update. J Clin Pathol 2020;73(8):445–453.

31. Sripathi S, Ayachit A, Bala A, Kadavigere R, Kumar S. Idiopathic granulomatous mastitis: a diagnostic dilemma for the breast radiologist. Insights Imaging 2016;7(4):523–529.

32. Hovanessian Larsen LJ, Peyvandi B, Klipfel N, Grant E, Iyengar G. Granulomatous lobular mastitis: imaging, diagnosis, and treatment. AJR Am J Roentgenol 2009;193(2):574–581.

33. Goel NB, Knight TE, Pandey S, Riddick-Young M, de Paredes ES, Trivedi A. Fibrous lesions of the breast: imaging-pathologic correlation. RadioGraphics 2005;25(6):1547–1559.

34. Lee CH, Sung JS, Lewin JM, Newell MS. ACR BI-RADS Contrast Enhanced Mammography: A Supplement to ACR BI-RADS Mammography 2013 Atlas, Breast Imaging Reporting and Data System. American College of Radiology. https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/BIRADS_CEM_2022.pdf. Published 2022.

35. Houben IPL, Van de Voorde P, Jeukens CRLPN, et al. Contrast-enhanced spectral mammography as work-up tool in patients recalled from breast cancer screening has low risks and might hold clinical benefits. Eur J Radiol 2017;94:31–37.

36. Ferreira M, Albarracin CT, Resetkova E. Pseudoangiomatous stromal hyperplasia tumor: a clinical, radiologic and pathologic study of 26 cases. Mod Pathol 2008;21(2):201–207.

37. Jones KN, Glazebrook KN, Reynolds C. Pseudoangiomatous stromal hyperplasia: imaging findings with pathologic and clinical correlation. AJR Am J Roentgenol 2010;195(4):1036–1042.

38. Zhu Y, Zhang S, Liu P, Lu H, Xu Y, Yang WT. Solitary intraductal papillomas of the breast: MRI features and differentiation from small invasive ductal carcinomas. AJR Am J Roentgenol 2012;199(4):936–942.

39. Lee S-J, Wahab RA, Sobel LD, et al. Analysis of 612 Benign Papillomas Diagnosed at Core Biopsy: Rate of Upgrade to Malignancy, Factors Associated with Upgrade, and a Proposal for Selective Surgical Excision. AJR Am J Roentgenol 2021;217(6):1299–1311.

40. Baltzer PAT, Benndorf M, Dietzel M, Gajda M, Runnebaum IB, Kaiser WA. False-positive findings at contrast-enhanced breast MRI: a BI-RADS descriptor study. AJR Am J Roentgenol 2010;194(6):1658–1663.

41. Okamoto S, Chen S-T, Covelli JD, DeMartini WB, Daniel BL, Ikeda DM. High-risk lesions diagnosed at MRI-guided vacuum-assisted breast biopsy: imaging characteristics, outcome of surgical excision or imaging follow-up. Breast Cancer 2020;27(3):405–414.

42. Corbin H, Bomeisl P, Amin AL, Marshall HN, Gilmore H, Harbhajanka A. Upgrade rates of intraductal papilloma with and without atypia diagnosed on core needle biopsy and clinicopathologic predictors. Hum Pathol 2022;128:90–100.

43. Bernik SF, Troob S, Ying BL, et al. Papillary lesions of the breast diagnosed by core needle biopsy: 71 cases with surgical follow-up. Am J Surg 2009;197(4):473–478.

44. Falomo E, Adejumo C, Carson KA, Harvey S, Mullen L, Myers K. Variability in the Management Recommendations Given for High-Risk Breast Lesions Detected on Image-guided Core Needle Biopsy at U.S. Academic Institutions. Curr Probl Diagn Radiol 2019;48(5):462–466.

45. Bitencourt AG, Ferreira EV, Bastos DC, et al. Intramammary lymph nodes: normal and abnormal multimodality imaging features. Br J Radiol 2019;92(1103):20190517.

46. Giess CS, Raza S, Birdwell RL. Distinguishing breast skin lesions from superficial breast parenchymal lesions: diagnostic criteria, imaging characteristics, and pitfalls. RadioGraphics 2011;31(7):1959–1972.

47. Kalli S, Freer PE, Rafferty EA. Lesions of the skin and superficial tissue at breast MR imaging. RadioGraphics 2010;30(7):1891–1913.

48. Kopans DB. Interpreting the mammogram. In: Kopans DB, ed. Breast Imaging. 3rd ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2007; 365–480.

49. Nicholson BT, Harvey JA, Cohen MA. Nipple-areolar complex: normal anatomy and benign and malignant processes. RadioGraphics 2009;29(2):509–523.

50. Bassett LW, Hirbawi IA, DeBruhl N, Hayes MK. Mammographic positioning: evaluation from the view box. Radiology 1993;188(3):803–806.

51. Gluskin J, Click M, Fleischman R, Dromain C, Morris EA, Jochelson MS. Contamination artifact that mimics in-situ carcinoma on contrast-enhanced digital mammography. Eur J Radiol 2017;95:147–154.

52. Lewis TC, Patel BK, Pizzitola VJ. Navigating contrast-enhanced digital mammography. Appl Radiol 2017;46(3):21–28.

53. Thibault F, Balleyguier C, Tardivon A, Dromain C. Contrast enhanced spectral mammography: better than MRI? Eur J Radiol 2012;81(suppl 1):S162–S164.

54. Ali-Mucheru M, Pockaj B, Patel B, et al. Contrast-enhanced Digital Mammography in the Surgical Management of Breast Cancer. Ann Surg Oncol 2016;23(S5 Suppl 5):649–655.

55. Carnahan MB, Pockaj B, Pizzitola V, et al. Contrast-enhanced Mammography for Newly Diagnosed Breast Cancer in Women with Breast Augmentation: Preliminary Findings. AJR Am J Roentgenol 2021;217(4):855–856.

56. Pages EB, Millet I, Hoa D, Doyon FC, Taourel P. Undiagnosed breast cancer at MR imaging: analysis of causes. Radiology 2012;264(1):40–50.

57. Karimi Z, Phillips J, Slanetz P, et al. Factors Associated with Background Parenchymal Enhancement on Contrast-enhanced Mammography. AJR Am J Roentgenol 2021;216(2):340–348.

58. Kim G, Phillips J, Cole E, et al. Comparison of Contrast-enhanced Mammography with Conventional Digital Mammography in Breast Cancer Screening: a Pilot Study. J Am Coll Radiol 2019;16(10):1456–1463.

59. Youn I, Choi S, Choi YJ, et al. Contrast enhanced digital mammography versus magnetic resonance imaging for accurate measurement of the size of breast cancer. Br J Radiol 2019;92(1098):20180929.

60. Wang S, Sun Y, You C, et al. Association of Clinical Factors and Degree of Early Background Parenchymal Enhancement on Contrast-enhanced Mammography. AJR Am J Roentgenol 2023;221(1):45–55.

61. Kuhl CK, Schild HH. Dynamic image interpretation of MRI of the breast. J Magn Reson Imaging 2000;12(6):965–974.

62. Lee AH, Dublin EA, Bobrow LG, Poulsom R. Invasive lobular and invasive ductal carcinoma of the breast show distinct patterns of vascular endothelial growth factor expression and angiogenesis. J Pathol 1998;185(4):394–401.

63. Shimauchi A, Jansen SA, Abe H, Jaskowiak N, Schmidt RA, Newstead GM. Breast cancers not detected at MRI: review of false-negative lesions. AJR Am J Roentgenol 2010;194(6):1674–1679.

64. van Nijnatten TJ, Jochelson MS, Pinker K, et al. Differences in degree of lesion enhancement on CEM between ILC and IDC. BJR Open 2019;1(1):20180046.

65. Wurdinger S, Kamprath S, Eschrich D, Schneider A, Kaiser WA. False-negative findings of malignant breast lesions on preoperative magnetic resonance mammography. Breast 2001;10(2):131–139.

66. Schnall MD, Blume J, Bluemke DA, et al. Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 2006;238(1):42–53.

67. Cheung YC, Juan YH, Lin YC, et al. Dual-Energy Contrast-enhanced Spectral Mammography: Enhancement Analysis on BI-RADS 4 Non-Mass Microcalcifications in Screened Women. PLoS One 2016;11(9):e0162740.

68. Paap E, Witjes M, van Landsveld-Verhoeven C, Pijnappel RM, Maas AHEM, Broeders MJM. Mammography in females with an implanted medical device: impact on image quality, pain and anxiety. Br J Radiol 2016;89(1066):20160142.

69. Korhonen KE, Zuckerman SP, Weinstein SP, et al. Breast MRI: False-Negative Results and Missed Opportunities. RadioGraphics 2021;41(3):645–664.

70. Lamb LR, Mohallem Fonseca M, Verma R, Seely JM. Missed Breast Cancer: Effects of Subconscious Bias and Lesion Characteristics. RadioGraphics 2020;40(4):941–960.

71. Veltman J, Mann R, Kok T, et al. Breast tumor characteristics of BRCA1 and BRCA2 gene mutation carriers on MRI. Eur Radiol 2008;18(5):931–938.

72. Nori J, Gill MK, Vignoli C, et al. Artefacts in contrast enhanced digital mammography: how can they affect diagnostic image quality and confuse clinical diagnosis? Insights Imaging 2020;11(1):16.

73. Pristina Serena Bright 510(k) premarket notification submission approval letter. U.S. Food and Drug Administration. www.accessdata.fda.gov/cdrh_docs/pdf19/K193334.pdf. Published May 15, 2020. Accessed March 14, 2023.

74. Affirm Contrast Biopsy 510(k) premarket notification submission approval letter. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/cdrh_docs/pdf20/K202294.pdf. Published October 5, 2020. Accessed March 14, 2023.

75. Mousa A, Zuley ML, Sharpe RE, et al. Contrast-enhanced Mammography–guided Biopsy: Multi-Center Clinic Study Results. Presented as a poster at the 108th annual meeting of the Radiological Society of North America, Chicago, Ill, November 27–December 1, 2022.