Contrast-enhanced Mammography: State of the Art

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Contrast-enhanced mammography (CEM) has emerged as a viable alternative to contrast-enhanced breast MRI, and it may increase access to vascular imaging while reducing examination cost. Intravenous iodinated contrast materials are used in CEM to enhance the visualization of tumor neovascularity. After injection, imaging is performed with dual-energy digital mammography, which helps provide a low-energy image and a recombined or iodine image that depict enhancing lesions in the breast. CEM has been demonstrated to help improve accuracy compared with digital mammography and US in women with abnormal screening mammographic findings or symptoms of breast cancer. It has also been demonstrated to approach the accuracy of breast MRI in preoperative staging of patients with breast cancer and in monitoring response after neoadjuvant chemotherapy. There are early encouraging results from trials evaluating CEM in the screening of women who are at an increased risk of breast cancer. Although CEM is a promising tool, it slightly increases radiation dose and carries a small risk of adverse reactions to contrast materials. This review details the CEM technique, diagnostic and screening uses, and future applications, including artificial intelligence and radiomics.

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Contrast-enhanced mammography (CEM) is an emerging technique that uses iodinated contrast materials for the visualization of breast neovascularity in a fashion similar to MRI (1). Vessels formed through the process of angiogenesis often leak the contrast material (2), and contrast diffuses within tumor tissue, resulting in an iodine-enhanced image. This allows a malignant tumor to be seen despite overlying dense breast tissue. Other names for CEM include contrast-enhanced spectral mammography, contrast-enhanced digital mammography, and contrast-enhanced dual-energy mammography.

Full-field digital mammography (FFDM) and digital breast tomosynthesis (DBT) rely on anatomic changes in the breast caused by breast cancer. Currently, they are pivotal in breast cancer screening and in assessment of symptomatic patients, although they have limited accuracy in women with dense breasts (1,2). For example, one study (3) reported that mammography sensitivity is 87.0% in women with entirely fatty breasts, but it decreases to 62.9% in women with extremely dense breasts (with specificity decreasing from 96.9% to 89.1%). A more recent study (4) using digital mammography also demonstrated a reduction of sensitivity with increasing breast density. Sensitivity was 79.9% overall, 100% for fatty breasts, 83.9% for breasts with scattered fibroglandular tissue, 72.9% for heterogeneously dense breasts, and 50% for extremely dense breasts. Although other studies (5) have demonstrated US to be superior to DBT as a supplemental examination, Kim et al (6) reported that DBT is comparable to US as an adjunct to FFDM for helping detect breast cancer, except in women with extremely dense breasts. Meanwhile, although supplemental imaging with MRI can be used to better evaluate women with dense breasts and those at an intermediate risk of breast cancer, CEM is less expensive and may be accessible to larger numbers of women.

In CEM, a dual-energy mammogram is acquired approximately 2 minutes after the intravenous injection of iodinated contrast material. The radiologist is provided with two images per breast and per view—one like a regular mammogram and the other highlighting areas of contrast uptake. CEM has the advantage of demonstrating both anatomic changes and local changes in breast perfusion, presumably caused by tumor angiogenesis. In a study involving 89 women with dense breasts and 100 lesions (7), CEM in addition to mammography improved sensitivity from 71.5% to 92.7% and specificity from 51.8% to 67.9%. Another study (8) reported that 13 of 14 cancers (93%) detected at CEM that were not seen at FFDM were seen in women with dense breasts.

The purpose of this review is to discuss the CEM technique, its use in diagnostic and screening settings, and its potential for future applications, including early data on artificial intelligence and radiomics. Where CEM is compared with mammography, the review compares CEM with two-dimensional mammography and does not consider tomosynthesis unless otherwise specified.

Imaging Protocol and Acquisition

CEM is currently available in four commercial systems offered by three vendors, as follows: *(a)* contrast-enhanced spectral mammography (GE Healthcare), *(b)* contrast-enhanced two-dimensional imaging (Hologic), and *(c)* Titanium CEM, or TiCEM (Siemens Healthineers). Table 1 outlines current systems that are commercially available.

Abbreviations

CEM = contrast-enhanced mammography, DBT = digital breast tomography, DCIS = ductal carcinoma in situ, FFDM = full-field digital mammography, LE = low energy, NAC = neoadjuvant chemotherapy

Summary

Contrast-enhanced mammography is an emerging breast imaging modality that helps improve diagnostic accuracy when routine breast imaging produces inconclusive findings and that may serve as an alternative to breast MRI.

Essentials

- Contrast-enhanced mammography (CEM) is helpful in resolving equivocal findings detected at conventional breast imaging examinations.
- CEM can be used for the preoperative staging of breast cancer to evaluate the extent of disease.
- Screening CEM could be performed as an alternative to breast MRI in women who are at an increased risk of developing breast cancer.
- CEM can accurately monitor response to neoadjuvant chemotherapy in patients with breast cancer.
- Areas of active investigation of CEM developments include CEM-guided biopsy systems and artificial intelligence applications.

Although no studies have been published that document optimal imaging parameters for CEM (including contrast material concentration, dose, flow rate, and time interval between administration and image acquisition), generally accepted guidelines exist. A low-osmolarity iodine-based contrast material is intravenously injected before image acquisition. The intravenous line is placed by either a nurse or a technologist, depending on the institution. The iodine concentration of the contrast material can vary from 300 mg/mL to 370 mg/mL. A total volume of 1.5 mL/kg of body weight (with a maximum of 150 mL) is administered, preferably using an injector (injection rate, 2–3 mL/sec), followed by a saline flush.

Image acquisition begins 2–2.5 minutes after contrast material injection. Standard craniocaudal and mediolateral oblique views of each breast are acquired (Fig 1). As contrast material may remain present in tissue for up to 10 minutes, there is often enough time for additional views (eg, rolled or compression views) if needed. Although some radiologists may prefer to image the symptomatic breast first, there is currently no scientific evidence to support this approach. It is our expert opinion and experience that image acquisition is best performed in the identical order that routine mammography is performed. To prevent contrast material splatter or contamination on the detector or breast, technologists should wear gloves and then remove them between contrast material administration and patient positioning. Alternatively, one technologist could administer the contrast material, while the other positions the patient.

During CEM, low-energy (LE) and high-energy images are obtained in quick succession while the breast remains compressed. The x-ray spectrum of the LE exposure is that of FFDM using a tube voltage of 25–34 kV. Molybdenum, rhodium, or tungsten are typically used as anode material, whereas molybdenum, rhodium, or silver are typically used as filter material.

Considering these settings, the LE image may replace the FFDM image with a similar performance (9,10). The high-energy image is obtained by using a higher tube voltage of 45–49 kV, and it uses similar anode materials with titanium or copper as filter material. The high-energy image is not suitable for diagnostic purposes but is used in postprocessing to generate the recombined or iodine image that shows areas of contrast enhancement. The total breast compression time of a single exposure depends on breast composition and thickness, and the time may vary from 2 seconds to 20 seconds (Table 1) (11).

When the energy of a photon is high enough to match the energy needed to eject an electron of iodine's innermost K shell (during the high-energy exposure), the x-ray photon absorption probability rises by a factor of five, subsequently decreasing again with increasing photon energy. This is called the k-edge of iodine (33.2 keV). By acquiring the high energy above the level of this k-edge and by using this image for postprocessing of the recombined image, areas of iodine enhancement can be identified while unenhanced background tissue is eliminated (12). In clinical practice, the radiologist reads the LE and recombined (or iodine-enhanced) images. It should be stressed that the results of CEM examination are provided in a single report that includes the results of the LE images (using the Breast Imaging Reporting and Data System mammography lexicon) and the iodine-enhanced images (using part of the Breast Imaging Reporting and Data System MRI lexicon) (13). Kinetic curves are not used with CEM because there is only a single time point for each image, whereas other enhancement characteristics are specific to CEM. The American College of Radiology Breast Imaging Reporting and Data System group is in the process of developing a specific lexicon for CEM.

Evaluation of Abnormalities Found at Screening Mammography

One of the earlier studied uses of CEM and still one of its most common indications is the assessment of abnormalities detected at screening mammography (Fig 2). Four initial studies (14–17) including 649 women (Table 2) demonstrated that the sensitivity of CEM ranged from 93% to 100% and specificity ranged from 63% to 88%. Three of these studies compared CEM with FFDM and showed significant improvement in specificity and sensitivity with CEM compared with FFDM, with increases in the ranges of 5%–46% and 3%–15%, respectively (14,15,17). One study (16) did not directly compare CEM to FFDM but used CEM as an adjunct to FFDM and US in postscreening evaluation; CEM sensitivity and specificity were 94% and 77%, respectively. Additionally, the study by Lalji et al (17) found that diagnostic performance was similar among radiologists with and without experience reading images from CEM, which suggests that the learning curve for CEM is not very steep, particularly for radiologists already experienced in reading images from FFDM and breast MRI examinations.

Several issues should be considered when using CEM to evaluate equivocal mammographic findings. First, benign lesions can show enhancement (Fig 3); the most commonly observed benign enhancing lesions in one study (18) were fibroadenomas,

Table 1: Overview of Machine Characteristics of CEM Units Worldwide

Machine Characteristic	GE Healthcare Senographe Essential and Senobright	GE Healthcare Pristina and Senobright HD	Hologic Selenia Dimensions and 3Dimensions I-View	Siemens Healthineers Mammomat Revelation Titanium CEM
Low-energy imaging				
Anode and filter material	Mo and Mo; Mo and Rh; Rh and Rh	Mo and Mo; Rh and Ag	W and Rh; W and Ag	W and Rh
Filter thickness (mm)	Mo, 0.03; Rh, 0.025	Mo, 0.03; Ag, 0.03	0.050	0.050
Tube voltage range (kV)	26–31	26–34	25–33	28–34
High-energy imaging				
Anode and filter material	Mo and AI plus Cu; Rh and AI plus Cu	Mo and Cu; Rh and Cu	W and Cu	W and Ti
Filter thickness (mm)	AI, 0.3; Cu, 0.3	0.25	0.3	1.0
Tube voltage range (kV)	45–49	49	45–49	49
Complete examination				
Mean glandular dose (mGy)	1.6–2.8	0.7–2.3	3.0	Not published
Total acquisition time (sec)	3–8	2–5	<2	15–22

Note.—Adapted, with permission, from reference 12. Ag = silver, Al = aluminum, Cu = copper, Mo = molybdenum, Rh = rhodium, Ti = titanium, W = tungsten.
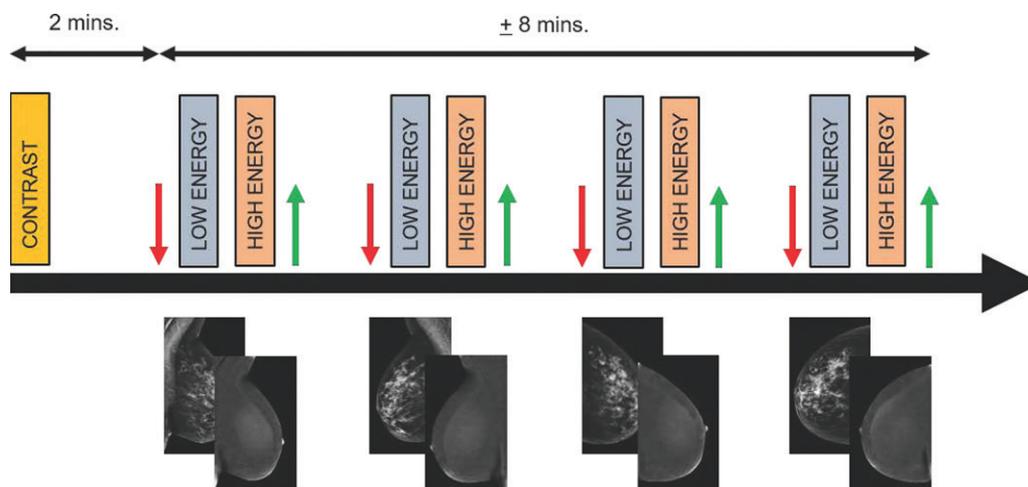
Figure 1: Diagram of imaging protocol for contrast-enhanced mammography. Two minutes before image acquisition, iodine-based contrast material is injected. Next, at minimum, both breasts are imaged in craniocaudal and mediolateral oblique views. In each step, compression is applied (red arrow), followed by rapid acquisition of low- and high-energy images. These images are processed to generate low-energy and recombined images. After each exposure, compression is released (green arrow). Images are considered to be of diagnostic value if they are acquired within 10 minutes after contrast material administration. mins. = minutes.

papillomas, and hyperplasia. Second, cysts have a classic appearance at CEM. On LE images, cysts are commonly observed as well-defined round or oval masses, but the assessment of margins may be partly obscured by fibroglandular tissue. On recombined images, cysts show no enhancement except for a thin enhancing rim. As in breast MRI, an inflamed cyst may have a thicker enhancing wall (Fig 4).

With respect to the assessment of suspicious microcalcifications, CEM might be beneficial. In one study (19), the enhancement of calcifications suggested underlying breast cancer or ductal carcinoma in situ (DCIS) (sensitivity and specificity of CEM were 88.9% and 86.6%, respectively). However, in another study with a comparable population (20), differences in diagnostic performance between CEM and conventional mammography were negligible (sensitivity of 93.8% and specificity of 36.6% for CEM vs sensitivity of 90.8% and specificity of 39.1% for conventional mammography). Hence, it was concluded that there was no clear benefit in using CEM to evaluate suspicious breast calcifications. Therefore, as with MRI, suspicious calcifications at mammography should be biopsied whether or not they show enhancement on CEM images.

Despite the success of CEM for the evaluation of abnormalities found at screening, most studies cited within this section are retrospective and considered only scenarios with a high prevalence of breast cancer. Prospective randomized clinical trials are underway to compare the work-up of women recalled with either conventional imaging or CEM (21).
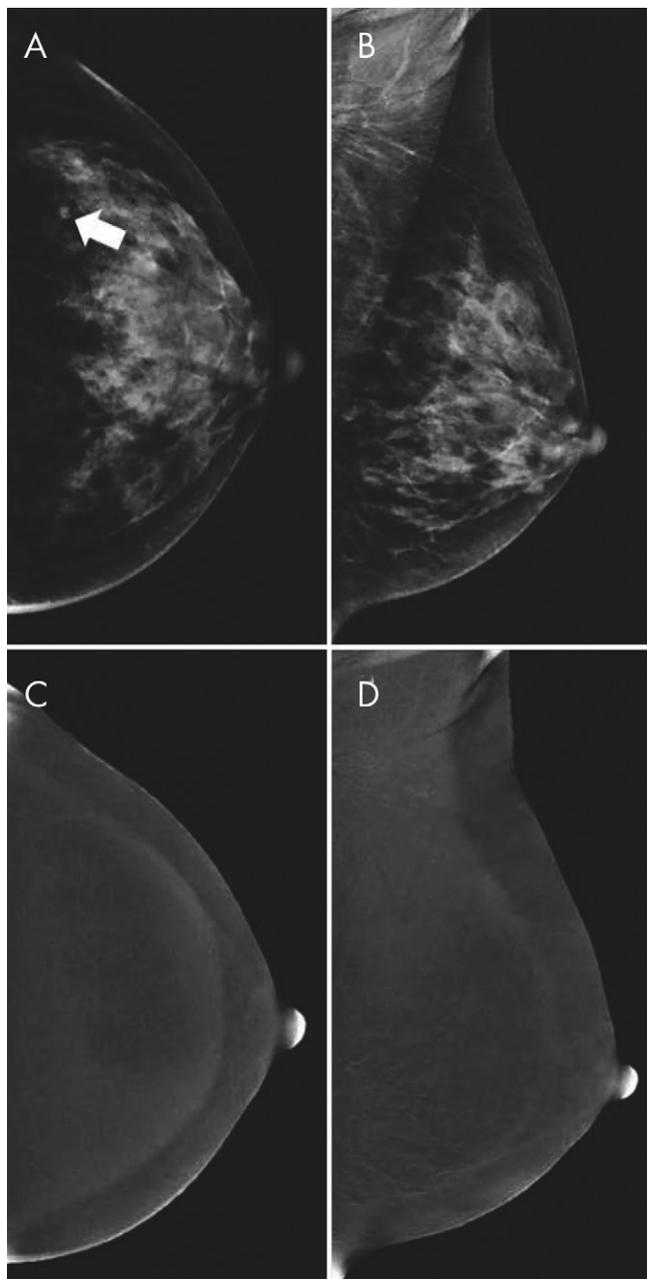
Figure 2: *A, B,* Contrast-enhanced mammographic (CEM) images in 52-year-old woman recalled from screening for new ill-defined mass (arrow in *A*) visible on, *A,* low-energy craniocaudal view but not visible on, *B,* low-energy mediolateral oblique view. *C, D,* Subsequent evaluation of recombined CEM images revealed no suspicious enhancement. Targeted US showed no lesions, but because of small lesion size, patient was categorized as having Breast Imaging Reporting and Data System category 3 lesion (follow-up after 6 months showed no breast cancer). Two subsequent rounds of screening (up to 4 years after primary evaluation) revealed no breast cancer.

Evaluation of Symptomatic Patients

One of the most common symptoms among women presenting for breast imaging is a palpable mass. In a multireader study involving 100 women with palpable abnormalities (22), 73% of whom had a malignancy, CEM outperformed mammography in sensitivity (95% vs 84%; $P < .025$) and specificity (81% vs 63; $P < .025$). However, when CEM was compared with US in 115 symptomatic women, 89% of whom had palpable masses, there

were no significant differences in performance between the two modalities (23). A third study (24) demonstrated the superior sensitivity of CEM compared with LE images. To our knowledge, no studies are dedicated to CEM in women experiencing other symptoms.

Preoperative Assessment of Extent of Local Disease Using CCEM

Another setting in which CEM was first studied was for the preoperative staging of women with newly diagnosed breast cancer. This imaging indication for breast MRI has been used worldwide for many years, albeit with some controversy because of its high cost, limited availability, and false-positive findings that can lead to additional biopsies, patient anxiety, and in some cases, mastectomy. CEM can be an alternative to MRI, although CEM does not enable evaluation of the axilla or other local nodal groups. As CEM contains information of both an FFDM examination (in the LE image) and a vascular image in a single appointment, those women who undergo CEM as part of their initial diagnostic work-up and are subsequently diagnosed with breast cancer will have already had preoperative (in-breast) staging.

To ensure a reliable staging test, it is important to accurately assess the size and extent of the index tumor. A few studies (25–27) have shown that tumor sizes measured with CEM ranged from 0.03 mm to 5 mm of the actual tumor size measured at the time of surgery. Although one study (8) showed that CEM was most highly correlated with surgical specimens (Pearson correlation coefficients were 0.73 for CEM, 0.65 for MRI, and 0.6 for LE images), another study (28) showed better accuracy with MRI than with LE or CEM for size at microscopy (Pearson correlation coefficients were 0.84 for MRI, 0.44 for LE, and 0.77 for CEM, with $P < .001$ for all). Once the initial size of the index tumor is assessed, CEM can be used to accurately determine if the disease is unifocal, multifocal, multicentric, or bilateral (Fig 5). These determinations may lead to valuable improvements in treatment.

As to the value of CEM in assessing disease extent of the index tumor, the first study to evaluate this (25) demonstrated that CEM was significantly better than FFDM in depicting the index tumor and was equal in sensitivity to MRI. In the ipsilateral breast, MRI depicted more additional sites of cancer than did CEM (22 sites with MRI vs 14 sites with CEM). In the contralateral breast, a single cancer was missed with both CEM and MRI (Paget disease). The additional sensitivity of MRI was at the expense of a much higher false-positive rate compared with CEM (13 false-positive findings with MRI vs two false-positive findings with CEM). Additional findings appropriately altered treatment in 11 patients who underwent MRI compared with eight patients who underwent CEM. A later study in 80 women (8) demonstrated equal sensitivity of CEM and MRI for both the index tumor and additional lesions. A third study comparing the diagnostic performance of CEM and MRI in 84 women with newly diagnosed invasive breast cancer and DCIS (29) found no significant difference in sensitivity to detect index cancers or additional lesions in either the ipsilateral or contralateral breasts, with similar changes in surgical management.

Table 2: Overview of Studies Assessing CEM Alone Compared to FFDM

Author	Year	Study Design	Population Size	Cancer Prevention (%)	Sensitivity (%)	Specificity (%)	Difference in Sensitivity (%)*	Difference in Specificity (%)*	*P* Value for Sensitivity	*P* Value for Specificity
Dromain et al (14)	2011	Prospective	142	56.3	93	63	15	5	<.001	.63
Lobbes et al (15)	2014	Retrospective	113	28.3	100	87.7	3.1	45.7	<.0001	<.0001
Tardivel et al (16)	2016	Retrospective	195	73.9	94	77	NA	NA	N/A	N/A
Lalji et al (17)	2016	Retrospective	199	29.6	96.9	69.7	3.9	33.8	.0002	<.00001

Note.—CEM = contrast-enhanced mammography, FFDM = full-field digital mammography, N/A = not applicable.

* Increase when compared to FFDM.

In a study evaluating change in surgical management based on CEM findings (30), CEM depicted 98% of index lesions among 128 women with breast cancer, missing one finding of Paget disease and a parasternal lesion not included in the field of view. Twelve percent of patients required additional biopsies based on CEM findings, 67% of which were cancers. CEM changed surgical management in 20% of patients, leading to mastectomy in 4%.

Altogether, studies of CEM in preoperative staging show that CEM can be a viable alternative to MRI, with accurate assessment of index tumor size, similar or possibly slightly inferior detection of additional sites of disease, and superior positive predictive value for detected additional lesions.

CEM in Monitoring Response to Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NAC) is increasingly used before definitive breast cancer surgery to improve the likelihood of candidacy for breast conservation or to improve cosmetic outcomes in women with locally advanced tumors. The use of chemotherapy to treat the intact tumor is informed by the effectiveness of the drug combination for a specific breast cancer. Accurate delineation of disease extent is critical in planning breast conservation in the neoadjuvant setting. Multiple studies (31,32) have demonstrated the superiority of MRI to physical examination, mammography, and US in evaluating response to NAC. Early data suggest that the same may be true of CEM (Fig 6).

In the first study to compare the ability of CEM and MRI to assess response to NAC(33), 54 women prospectively underwent both imaging examinations before and after completion of NAC. The examinations were read independently, and readers were blinded to the results of the other examination. Forty-six women (85%) completed the study. CEM was superior to MRI in the prediction of pathologic complete response (the Lin coefficient was 0.81 for CEM vs 0.59 for MRI). The extent of residual disease was slightly underestimated with both imaging examinations, with CEM estimating more accurately than MRI (mean underestimation, 4.1 mm with CEM vs 7.5 mm with breast MRI). In another prospective study involving 21 women, CEM was also shown to be valuable in the prediction of tumor

response after neoadjuvant chemotherapy (34), with a negative predictive value of 80.0% and a positive predictive value of 62.5%.

A third study (35), which was retrospective, compared the results of CEM and MRI in 65 patients who underwent NAC, using surgical pathologic findings as the reference standard. Both modalities indicated equivalence to the histopathologic results within 1 cm. Sensitivity, specificity, positive predictive value, and negative predictive value in predicting complete response were also equivalent. In comparison, a prospective study comparing the results of CEM to MRI among 33 women undergoing NAC (36) found that performance metrics varied between MRI and CEM for sensitivity (92% vs 76%), specificity (75% vs 87.5%), positive predictive value (92% vs 95%), and negative predictive value (75% vs 86.4%), and the mean differences in residual tumor size assessment using CEM or MRI (compared with histopathologic results) were 0.8 cm and 1.8 cm, respectively.

It is important to clarify the definition of pathologic complete response when evaluating the results of neoadjuvant imaging trials. Although the presence or absence of residual DCIS must be accurately defined for surgical purposes, the absence of residual invasive cancer is defined as a pathologic complete response in some studies (ie, residual DCIS is allowable). In other studies, complete absence of any residual tumor (both in situ and invasive) is required to be considered a pathologic complete response. Only the study by Barra et al (36) defined pathologic complete response as the absence of any invasive residual breast cancer regardless of the presence of DCIS.

Thus far, early data regarding the use of CEM to assess response to NAC are promising. Although the number of patients studied after receiving NAC is small, the results appear consistent. Additionally, the LE image replaces and obviates the need for an additional FFDM examination so that the patient needs only one appointment after therapy.

CEM as a Screening Tool

Contrast-enhanced breast MRI is recommended for women at high risk of developing breast cancer (ie, >20% lifetime risk of developing breast cancer); it is the most sensitive breast cancer screening tool, reported to have sensitivity of up to 97% (37,38), largely because of its ability to help detect neovascular-
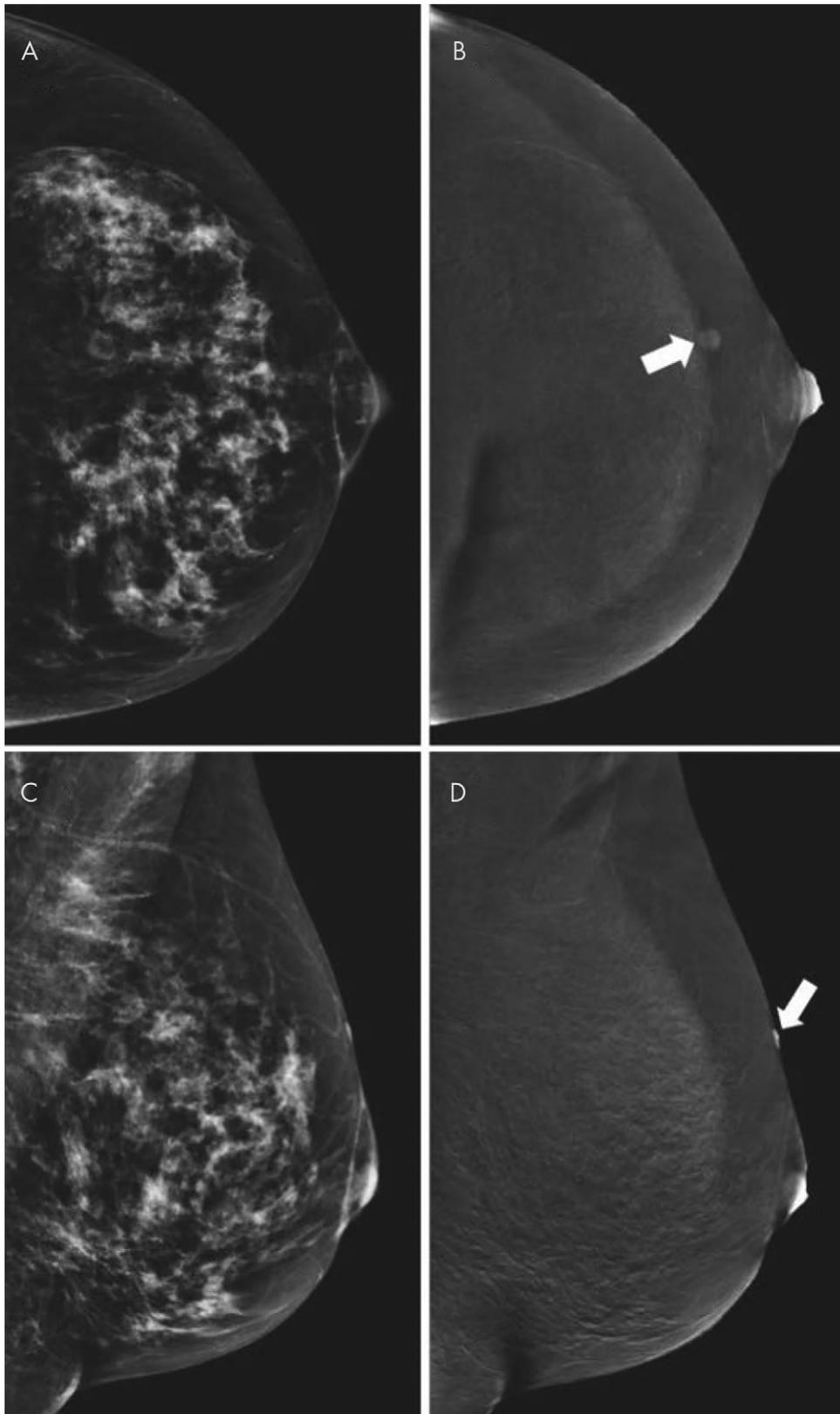
Figure 3: Contrast-enhanced mammographic images of enhancing benign lesion in 50-year-old woman. *A,* Low-energy craniocaudal image. *B,* Contrast-enhanced recombined craniocaudal image. *C,* Low-energy mediolateral oblique image. *D,* Contrast-enhanced recombined mediolateral oblique image. Contrast-enhanced craniocaudal view of left breast demonstrates a small, well-defined enhancing mass (arrow in *B*). Mediolateral oblique view of same breast demonstrates that lesion is located on skin (arrow in *D*). Visual inspection revealed skin hemangioma.
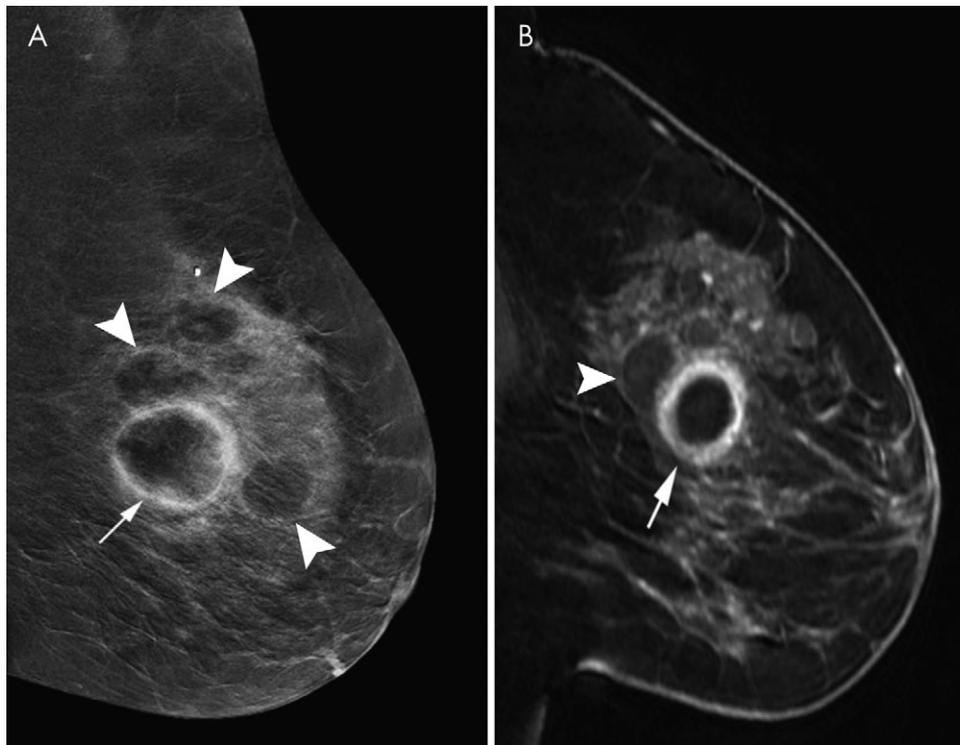
Figure 4: Images in 44-year-old woman presenting with palpable abnormality in left breast illustrate that cysts have different appearance at contrast-enhanced mammography (CEM) and contrast-enhanced breast MRI. *A,* Recombined CEM image of left breast in mediolateral oblique view. *B,* Corresponding contrast-enhanced fat-suppressed T1-weighted breast MRI scan reconstructed in sagittal view. On both images, simple cysts (arrowheads) can be identified as well-defined masses showing no or negative enhancement. Inflamed cysts (arrow) may show thickened and often slightly irregular wall, which enhances after contrast material administration.

ity. However, in addition to women at high risk of developing breast cancer, many women at intermediate risk (15%–20% lifetime risk) and many with dense breasts may also benefit from supplemental screening. This includes women with a family history of breast cancer, women with certain high-risk lesions, as well as 3.8 million survivors of breast cancer and 25 million women with dense breasts in the United States alone (39). Currently, it is difficult to accommodate such a large number of patients requiring MRI or even abbreviated breast MRI. As extensive data demonstrate that CEM may help improve sensitivity and specificity when compared with digital mammography alone or to mammography plus US, particularly in patients with dense breasts (6,7,16,19,25,27,36), CEM may provide additional vascular imaging capacity to better screen patients at intermediate risk of breast cancer and patients with dense breasts.

The first prospective study comparing CEM to MRI (using the LE image as a substitute for the FFDM image) (40) involved 307 women at increased risk of breast cancer who had undergone yearly screening with MRI and mammography. No cancers were detected on the LE image. MRI and CEM depicted the same two invasive lobular cancers. A third patient with a focus of enhancement at MRI that was occult at CEM demonstrated atypical ductal hyperplasia at biopsy 1 year later (the patient delayed follow-up examination), and the lesion was upgraded to DCIS at surgery. There were no symptomatic interval cancers, but two screening-detected cancers were detected at MRI at 1-year

follow-up. Specificity of CEM was equivalent to that of MRI in this study. Although the specificity of CEM was expected to be better than that of MRI according to previous data, it is possible that it was lower in this study as all CEM examinations were prevalence studies (as opposed to MRI, where multiple previous examinations were available for comparison), leading to a higher false-positive rate and therefore lower specificity.

Three other studies have addressed the potential of CEM to be used in screening in different ways. One retrospective study (41) compared CEM to US in a cohort of 953 patients, 725 (76%) of whom were asymptomatic screening patients, to determine the value of US after CEM. Because CEM outperformed US in sensitivity (97% vs 92%) and specificity (40% vs 8%), the investigators concluded that the use of US was questionable in the setting of a negative CEM finding, as it could lead to unnecessary biopsies. Another retrospective study (24) compared CEM and US to screening mammography in 611 women with dense breasts at an increased risk of breast cancer. CEM outperformed mammography in sensitivity (90.5% vs 52.4%; P = .0008) but had reduced specificity (76.1% vs 90.5%; P = .001). This study also showed the potential disadvantage of screening US in women undergoing CEM, as 74 lesions were detected at US that did not enhance, leading to additional biopsies with no added cancers. Last, a retrospective study comparing 904 baseline screening CEM examinations with conventional mammography (77% of participants had dense breasts, and more than 90% had other risk factors) (42) showed that CEM depicted 15
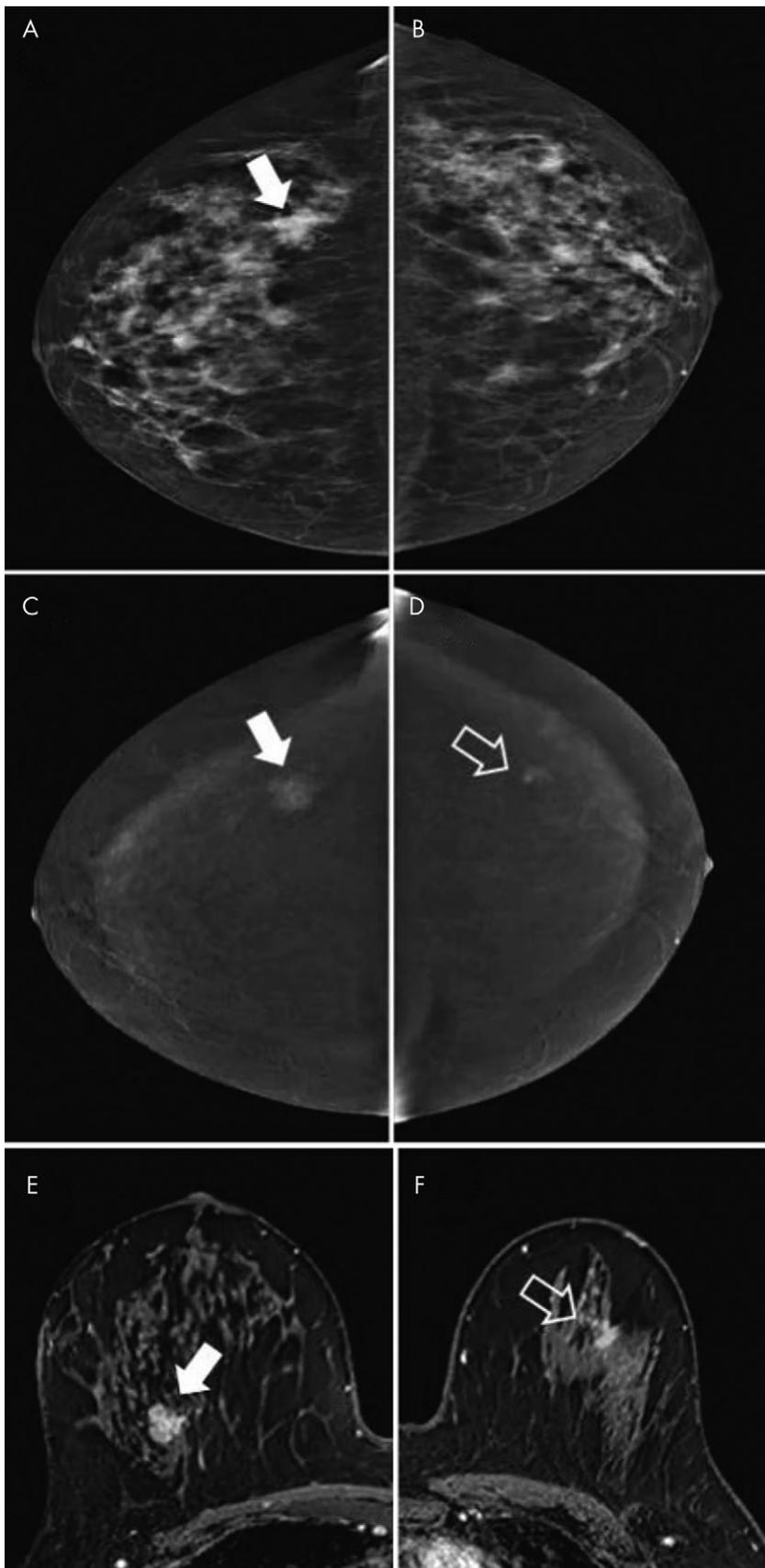
Figure 5: Images obtained for disease extent assessment in 64-year-old woman recalled from screening for irregular mass in right breast. *A,* Low-energy image of right breast (craniocaudal view) shows irregular mass (arrow). *B,* No lesion is seen on low-energy image in contralateral breast. *C,* Image from contrast-enhanced mammography (CEM) (right craniocaudal view) shows enhancement of mass (arrow). *D,* CEM image shows contralateral irregular enhancing mass (arrow), which was not visible on low-energy image. *E, F,* Contrast-enhanced MRI scans of, *E,* right breast and, *F,* left breast show both lesions (arrow). Lesions were diagnosed as invasive breast cancer of no special type (estrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor type 2 negative).

cancers in 14 patients, corresponding to a cancer detection rate of 15.5 per 1000 examinations, similar to that reported for MRI. Six of the 16 cancers (38%) were detected on contrast-enhanced images alone.

CEM may be a viable tool for imaging women at an increased risk of breast cancer, and it is important to determine if specific subgroups of women may benefit from CEM. The number of patients in the current literature is too small for adequate subgroup analysis, but researchers have used early data to begin to define those populations. A recent study among 132 women with a history of lobular neoplasia (43) demonstrated the value of CEM in detecting six cancers (sensitivity, 100%; specificity, 88%; negative predictive value, 100%; and accuracy, 88%).

Thus, preliminary data on the use of CEM in the screening setting are promising. Results suggest that CEM is more sensitive than FFDM alone, more sensitive than FFDM plus US, and more specific than FFDM plus US (24,41,42). The sensitivity of CEM approaches that of breast MRI, and CEM is likely more specific (44). Currently, the total number of patients studied thus far is small. Prospective multicenter trials that compare cancer detection rates and other metrics of CEM with those of standard screening studies, such as FFDM or DBT, with screening US or breast MRI (complete or abbreviated) are needed. The forthcoming American College of Radiology Contrast-enhanced Mammography Imaging Screening Trial will determine if CEM can help improve breast cancer detection compared with that of DBT plus screening US in patients with dense breasts and with an average to intermediate risk of breast cancer. Secondary end points will compare the tumor biologic characteristics of invasive cancers and DCIS detected at CEM and DBT plus screening US. The study is intended to have 2500 enrolled patients who will undergo two rounds of screening and 1-year follow-up.

In addition to favorable performance metrics, CEM is well tolerated by patients. When 49 women were interviewed regarding their preference of CEM compared with MRI, the women indicated that they preferred CEM because it was faster, more comfortable, and less noisy ($P < .001$) (45). In a different prospective screening trial (46), 79% of women preferred CEM to MRI if the examinations had equal sensitivity. Therefore, CEM can be considered a good alternative for women who are unable or unwilling to undergo MRI.

Limitations of CEM

The most substantial limitation of CEM is the possibility of contrast material reactions, which can range from mild to fatal hypersensitivity reactions. In a systematic review of 84 articles involving 14,012 patients, Zanardo et al (47) reported that the pooled reaction rate in 17 of 84 of the studies was 0.82% (of 30 reactions, 26 were mild, three were moderate, and one was a severe nonfatal reaction). Nevertheless, patients should always be screened for contrast material allergy history, and patients with such a history, even if mild, should be considered for MRI rather than CEM.

Contrast material–induced renal insufficiency is extremely rare. Older patients or those with potential renal insufficiency

are screened in advance, and anyone with abnormal renal function does not receive iodinated contrast material.

CEM requires an increased radiation dose varying from 20% to 80% depending on system settings, breast thickness, and type of mammographic device (48,49). This includes using the LE images as the routine mammogram (9,10,50). Although minimizing radiation exposure is important, the radiation dose of CEM is less than that of FFDM plus DBT, falls within the Mammography Quality Standards Act guidelines, and does not result in an important increase of lifetime attributable risk factors (37). Some breast lesions cannot be visualized because of their position within the breast. Lesions close to the chest wall or in the medial part of the breast may be overlooked (17), and breast MRI should be considered if lesions are suspected in these locations.

Artifacts observed at FFDM, such as hair or antiperspirant, may also be seen on CEM images (51). Additionally, some breast lesions cannot be visualized because of their position within the breast. Lesions close to the chest wall or in the medial part of the breast may be overlooked (17), and supplemental breast MRI should be considered if lesions are suspected in these locations. Artifacts specific to CEM, such as those caused by contrast material contamination, are seen on the recombined image (52,53). A summary of the appearance, cause, and solutions to frequently observed artifacts is presented in Table 3. Most artifacts occur in older CEM systems, and image quality has improved in newer systems.

Although the negative predictive value of CEM varies from 94% to 100% (15,24), some breast cancer phenotypes (eg, mucinous carcinoma or invasive lobular carcinoma) may show weak or even no enhancement at CEM and may also be overlooked with breast MRI (17,54). As these studies demonstrate, lack of enhancement may be a false-negative finding, but faintly enhancing lesions may be malignant and should be followed up. Noncalcified DCIS is known to be missed at mammography. If there is also no enhancement, then this could be another potential false-negative lesion.

Finally, it should be emphasized that scientific evidence on the use of CEM is largely based on single-center studies with relatively small study cohorts. The results of these studies should be interpreted with this limitation in mind. It also confirms the need for larger, multicenter prospective trials using CEM to further confirm its potential as a breast imaging tool.

The Future of CEM

CEM is becoming more commonly used, with an increasing number of units installed, examinations performed, and studies published (47). Continuous developments in this field are to be expected.

Since the advent of CEM, DBT has been increasingly used for routine mammography, particularly in the United States, where it may eventually replace two-dimensional mammography to some extent. Data evaluating contrast-enhanced DBT are limited. Although there has not yet been a direct comparison of CEM to DBT in the screening setting, vascular imaging has been compared with nonvascular imaging in 185 patients with Breast Imaging Reporting
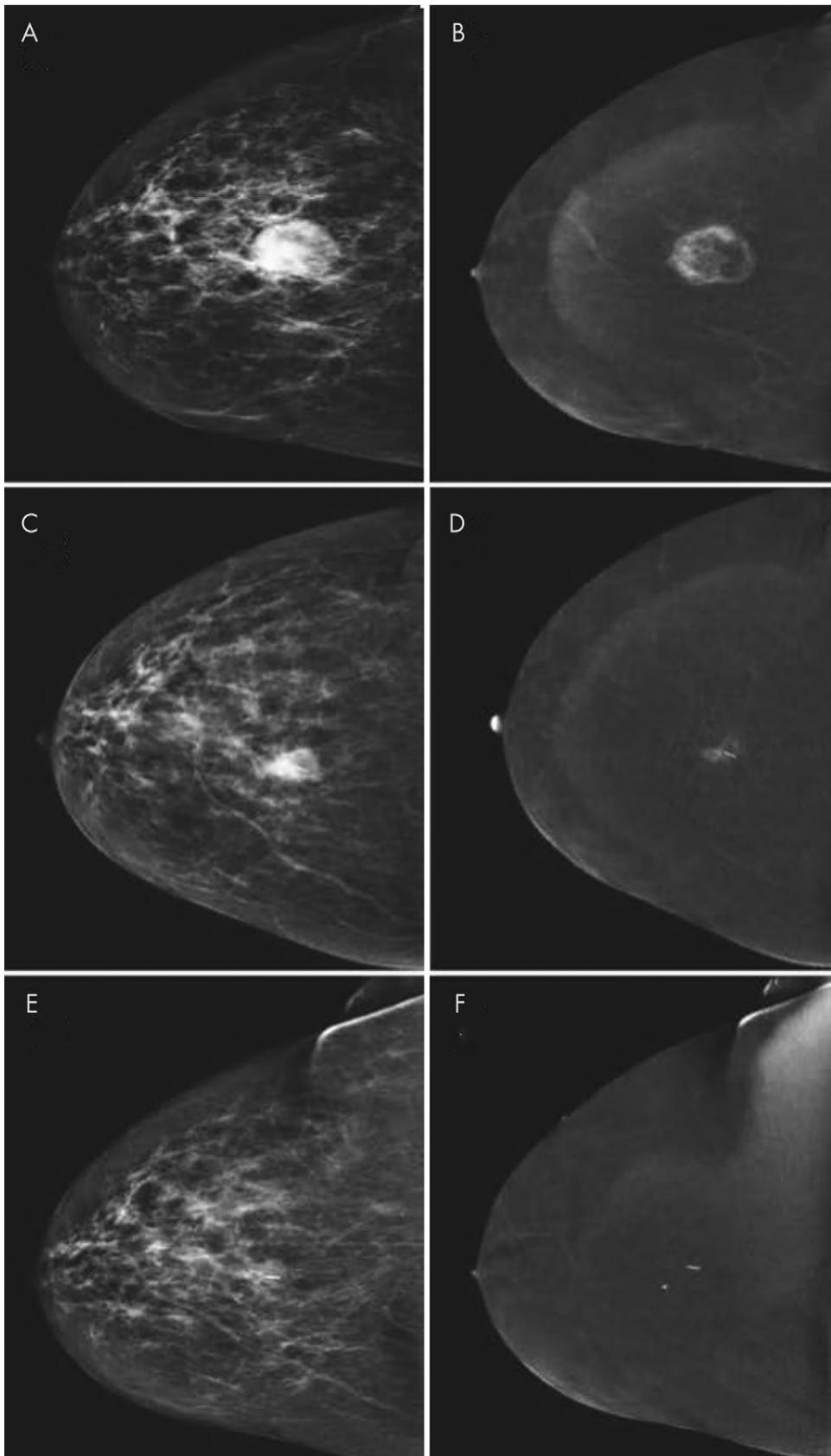
Figure 6: Images of response monitoring using contrast-enhanced mammography in a 54-year-old woman diagnosed with 3.0-cm invasive breast cancer of no special type (grade 3, estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor type 2 positive). *A*, Low-energy image in craniocaudal view shows cancer. *B*, Recombined image shows peripheral enhancement, which is suggestive of central necrosis. The patient underwent neoadjuvant systemic therapy. *C*, Low-energy, and, *D*, recombined craniocaudal views obtained during treatment show decrease in index tumor size *(C)* with decrease in enhancement *(D)*. *E*, Low-energy and, *F*, recombined images obtained after completion of therapy. There was no residual mass on low-energy image. Resolution of enhancement on recombined image was consistent with complete radiologic response. Surgical specimen showed pathologic complete response without any residual ductal carcinoma in situ.

Table 3: Overview of CEM-specific Artifacts

Artifact Type	Appearance	Cause	Solution
Air trapping	Prominent black lines appearing in skin folds	Air trapped in skin folds	Re-acquire image(s), while considering proper mammographic positioning.
Axillary line	Well-defined line(s) extending across axilla	High sensitivity of high-energy images to lag. Line corresponds to collimator positioning in previously acquired collimated images	Recalibrate system.
Breast implants and cardiac devices	Prominent black or white areas surrounding implant or device	CEM protocol is not optimized to distinguish between materials other than breast tissue (fat or fibroglandular tissue). Distinction between more materials would require third acquisition with another x-ray spectrum, thus causing more noise in recombined images	Consider breast MRI in women with implants. Remove breast jewelry if possible. Cardiac devices are not a contraindication for CEM, but locally, recombined images can be distorted.
Breast in breast and rim	Peripheral band of decreased gray value, mimicking double-breast contour	Different patterns of scatter radiation in LE and high-energy images, while the reconstruction algorithm presumes these are identical. Antiscatter grids in older-generation systems were not designed with CEM in mind, causing this artifact	Less pronounced or absent in newer-generation CEM units
Contrast material splatter	Mimicking microcalcifications on LE images, but unlike calcifications, they appear white on recombined images and are often visible in all images with same appearance	Contrast material contamination on breast or detector because of contamination on technician's hands or patient's breast while procedure is performed	Technician injecting contrast material should not be same as technician positioning patient. Wear gloves and remove them during positioning. When noticed, clean breast and detector before next acquisition.
Ghosting	Latent image from previous exposure can be detected superimposed on newly acquired image	High sensitivity of high-energy images to lag	Recalibrate system
Ripple motion	Fine black and white lines arranged in a ripple-like and wavy fashion layered on breast in recombined image	Motion of patient between acquisition of LE and high-energy images, causing slight mismatch in recombined image	Proper patient instruction and coaching. Consider breath holding during image acquisition.
Skin line enhancement	Segmental area of skin showing pronounced whitening on recombined images without any underlying skin thickening visible on LE images	Image filtration applied to recombined image to equalize breast thickness	Less pronounced or absent in newer-generation CEM units

Note.—CEM = contrast-enhanced mammography, LE = low energy.

and Data System category 4 or 5 lesions (55). Not surprisingly, MRI, CEM, and contrast-enhanced tomosynthesis were more sensitive than unenhanced DBT. In another study (56), contrast-enhanced DBT in 21 patients enabled improved lesion margin assessment compared with CEM, without reduced contrast enhancement of the lesions. Clearly, contrast-enhanced DBT is a promising area for future research.

Although most lesions detected at CEM have a correlate on the LE images or at US scans, some enhancing lesions may be observed without a mammographic or sonographic correlate for image-guided biopsy. Currently, MRI is performed to enable an image-guided biopsy, and some institutions might even consider CT-guided biopsies. The U.S. Food and Drug Administration has approved a CEM biopsy device developed by GE Healthcare (57). Once it becomes more available, this will obviate the need for MRI-guided biopsies.

In line with current developments in artificial intelligence and radiomics in breast imaging research, investigators have begun to evaluate artificial intelligence with CEM. By using machine learning algorithms based on morphologic and textural features of 50 breast lesions derived from both LE and recombined images, Patel et al (58) correctly classified 45 of 50 breast lesions (90% accuracy). By applying radiomics to CEM images, Marino et al (59) were able to distinguish between invasive and noninvasive breast cancers, hormone receptor–positive and hormone receptor–negative cancers, human epidermal growth factor receptor 2–positive and/or hormone receptor–negative and human epidermal growth factor receptor 2–negative and/or hormone receptor–positive breast cancers, triple-negative and triple-positive breast cancers, and triple-negative and hormone receptor–positive breast cancers, with accuracies from 78.4% to 100%. These preliminary results establish the promise of these techniques in CEM.

Conclusion

Contrast-enhanced mammography (CEM) was commercially introduced in 2011 and is an emerging breast imaging tool. CEM unit installations, examinations, and scientific publications have all increased. CEM is easy to perform in everyday clinical practice and is useful in indications including abnormal screenings, symptomatic patients, preoperative staging of breast cancer, evaluation of response to neoadjuvant chemotherapy, screening women with dense breasts, and screening women at an increased risk of developing breast cancer. As CEM vendors increase and expected improvements in the technique evolve, the use of CEM will further expand, especially where breast MRI availability is limited.

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