Contrast Enhanced Digital Mammography

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Introduction

Screening mammography has been shown to reduce breast cancer mortality in randomized clinical trials. It has been an effective screening test for the past 4 decades due to its short exam time, patient convenience and low cost. The sensitivity of mammography for the detection of cancer in screening populations ranges from approximately 60% to more than 90% depending on breast density, meaning that in the densest breasts, 4 of 10 cancers will not be detected by screening mammography prior to their becoming palpable (1). It is well accepted that supplemental imaging can be of value to improve early cancer detection particularly in women at increased risk for cancer as well as those with dense breasts. Improved detection is seen with tomosynthesis, which can detect an additional 1.5-2.0 cancers/1000 women (2), and ultrasound, which detects an additional 3.1-4.0 cancers/ 1000 women (3).

Contrast-enhanced breast MRI, on the other hand, has a much higher sensitivity, approaching 100% (4), and has been demonstrated to detect approximately 15 additional cancers per 1000 screened women at elevated-risk who have both normal mammograms and screening ultrasound examinations (5). The high sensitivity of MRI is primarily due to its ability to use contrast to detect neovascularity associated with cancer, at times before a discrete mass can be seen. Non-contrast breast MRI has very low cancer detection capability. In 2007 the American Cancer Society guidelines recommended that yearly contrast-enhanced breast MRI be offered, in addition to mammography, for women at greater than 20% lifetime risk for developing breast cancer (6). MRI is costly, however, and availability for the large numbers of women at intermediate (15-20%) risk and women with dense breasts is limited.

With the adoption of digital mammography as a replacement for film mammography, work began in the early 2000's to develop a technique that would allow digital mammography to be used with contrast enhancement to depict cancers that would otherwise be occult on standard unenhanced mammography. Those efforts resulted in the development and clinical testing of contrast-enhanced digital mammography (CEM) using the dual energy subtraction technique (7). Today CEDM is available commercially for clinical use. It is estimated that over 200,000 CEDM examinations have been performed to date in both research and clinical settings.

Performance of the examination

To perform a CEDM examination, an IV is placed in the forearm or antecubital vein and a low osmolar iodinated contrast agent is administered at approximately 3ml/s using a power injector. Contrast agents with iodine concentration between 300 mg/ml and 370 mg/ml are typically used. The volume of contrast is similar to that used for a CT scan, approximately 1.5 ml/kg body weight, typically around 90-150 ml. After a delay of at least 90 seconds from the end of the injection, the patient is positioned for 2 standard mammography views (craniocaudal and mediolateral oblique) of each breast. Rather than a

standard single energy mammogram, however, the CEM device acquires dual-energy image pairs in each projection.   Since there is less than 1 second between the low-energy and high energy images, the imaging time is the same as that needed for a standard mammogram. Additional projections may be obtained since optimally enhanced images can typically be obtained up to 7-10 minutes following injection (8).

Following image acquisition, contrast-enhanced subtraction images are produced using a weighted logarithmic subtraction of the low energy image from the high energy image. Because the difference in iodine absorption between the images is larger than the difference in tissue absorption, this dual energy subtraction technique has the effect of increasing the visibility of the iodine while almost completely eliminating the visibility of background tissue. The resulting images are sent to a review workstation or PACS for interpretation by the radiologist.   The low energy images, which are identical to standard unenhanced mammograms (9, 10), are also used in the interpretation. Figure 1 shows an example of a typical CEDM study. Since there is typically only a single time point for each image, no kinetic information is available.

The risks of CEDM include the risks of contrast administration including allergic reactions and renal function abnormalities. Just as with CT, patients should be screened for allergy history and possible renal function abnormalities. Allergic or physiologic reaction are reported to occur in less than 1% of patients when using low osmolar contrast agents although this increases in patients with prior reactions(11,12). Severe acute reactions occur in 4/10,000 (0.04%) of patients (13). It is also therefore incumbent that breast imaging radiologists be familiar with the treatment of contrast reactions.

Literature Review

So far, most of the published data on the performance of CEDM stem from use in the diagnostic setting, i.e., patients with abnormal screening mammograms and/or symptoms. As would be predicted, multiple studies have shown that CEDM is more sensitive for the detection of cancer than standard unenhanced mammography (14, 15). These studies also showed CEDM to be more accurate, as measured by the area under the receiver operating characteristic (ROC) curve.   In women with dense breasts, Cheung et al demonstrated that CEDM is superior to mammography in both sensitivity with improvement from 71.5% to 92.7% and specificity from 51.8% to 67.9%(16).

More interesting is the comparison of CEDM to contrast-enhanced breast MRI.   A European study of 80 subjects with newly diagnosed breast cancer showed equivalence in detection of the index cancer between CEDM and MRI, with the trend favoring CEDM (80/80 for CEDM vs 78/80 for MRI) (17). A similarly designed study at Memorial Sloan Kettering with 52 subjects also showed equal sensitivity between CEDM and MRI (50/52 for each) (6). MRI found more additional malignant foci (22/25 vs 14/25) but at the cost of more false positives (13 vs 2) (6). Of interest, just as with MRI, the sensitivity of contrast enhancement on CEDM for detection of cancers manifesting as microcalcifications is more limited than for those evident as masses (18). For this reason, suspicious microcalcifications seen on the low energy images should be biopsied even if they do not show surrounding enhancement. A study from

Hobbes et al (19) has demonstrated that patients prefer CEDM to MRI since patients are averse to the noise and claustrophobia associated with breast MRI.

A two-site Taiwan – U.S. study of a mixture of malignant and benign lesions used receiver operating curve (ROC) analysis to compare CEDM, MRI and *contrast-enhanced tomosynthesis*, an experimental technique in which dual energy tomosynthesis is performed following a contrast injection. The study found no difference among the three techniques in accuracy by area under the ROC curve (20). The study also included two non-contrast enhanced techniques, mammography and digital breast tomosynthesis. As expected from earlier results, the two contrast-enhanced techniques performed significantly better than the non-contrast enhanced techniques. The addition of contrast-enhanced tomosynthesis to CEDM did not result in improved accuracy.

Proposed uses for CEDM

With the promising data in the diagnostic setting, a frequent use of CEDM is to further evaluate either clinical or imaging abnormalities from abnormal screening exams. This has the additional advantage of doubling as a preoperative extent-of-disease exam in those patients who are diagnosed with cancer. Due to its superior specificity in this setting, CEDM has the potential to reduce unnecessary biopsy of benign low suspicion (BI-RADS 4a) masses. Ongoing studies are investigating its use for this purpose. CEDM can be used in situations where contrast-enhanced breast MRI would be employed, including staging of a newly diagnosed cancer and problem solving where conventional imaging, i.e. mammography (or tomosynthesis) and ultrasound, fail to resolve an ambiguous finding on screening mammography. CEDM is also under investigation as a means of monitoring response to neoadjuvant chemotherapy; preliminary results are promising [Lotti, V. Presented at RSNA 2016, Abstract SSJ01-06]. CEDM may be useful for screening women at high risk of developing breast cancer; high-risk screening research studies are currently in progress.

A major barrier to widespread use of CEDM at this time is the inability to perform CEDM-guided biopsy although there is a prototype in development. Lesions detected on CEDM that can be seen on low energy images may undergo stereotactic biopsy. If there is a mass that can be seen on ultrasound, ultrasound guidance can be used. Otherwise, an MRI may be required; as the lesions are usually apparent on MRI so that MR-guided biopsy may be performed.

Lexicon

Work is under way to develop a standardized lexicon for CEDM for incorporation into the American College of Radiology Breast Imaging and Reporting Data System (BI-RADS[TM]). Under consideration is a scoring system that will include a combination of the BI-RADS assessment of the low energy mammogram with an adaptation of the feature descriptors from the MRI BI-RADS lexicon without kinetics.

Summary

Based on its ability to image neovascularity in a fashion similar to MRI, CEDM is a promising technique for depicting cancers that are not visible on standard unenhanced mammography. It is approved for clinical use and is performed on commercial systems. Results of clinical studies show it to be significantly more sensitive and specific than mammography alone and to have sensitivity and specificity comparable to contrast-enhanced breast MRI. Current and proposed uses include additional evaluation of symptomatic patients or patients with abnormal screening examinations, assessing local extent of newly diagnosed breast cancers, problem solving, monitoring of neoadjuvant chemotherapy and high-risk screening.

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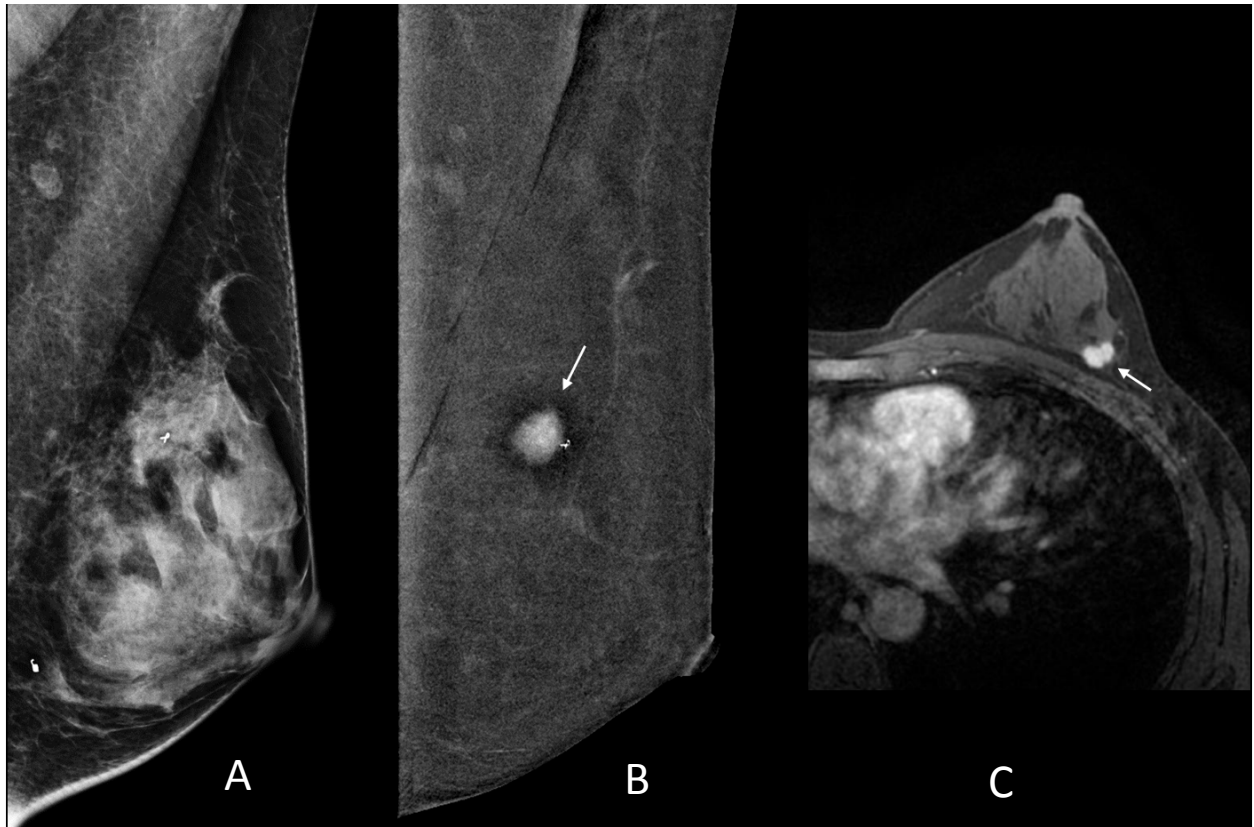
Figure 1. Contrast-enhanced digital mammography study of a 54-year-old female with a previously biopsied grade 2 invasive ductal carcinoma of the left breast. A. Low- energy MLO mammogram (equivalent to a standard unenhanced mammogram) shows the metallic marker at the cancer site, but the cancer is obscured by heterogeneously dense parenchyma. B. Corresponding dual-energy subtraction image clearly depicts the cancer (arrow) as an intensely enhancing irregular mass. Note that the background non-enhancing fibroglandular tissue is subtracted out. C. Image from a contrast-enhanced MRI performed the following day shows the lesion as an enhancing irregular mass (arrow). Note the similarity of the appearance on the CEDM and MRI studies.
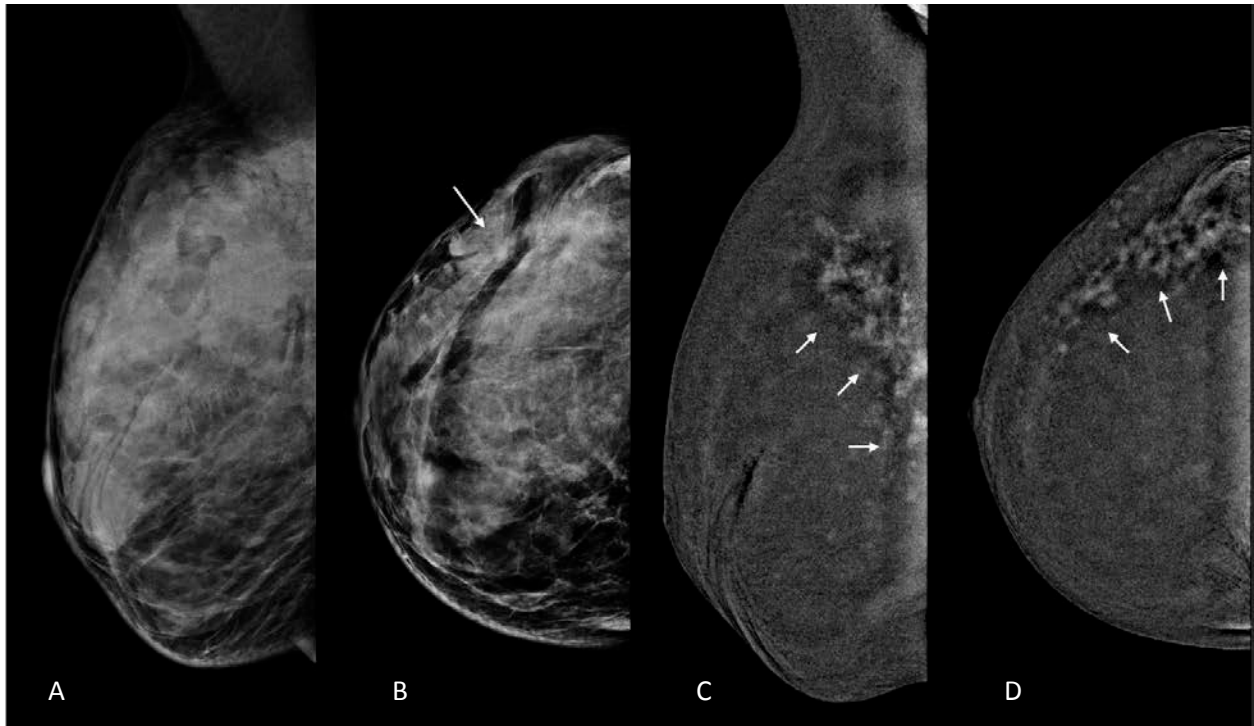
Figure 2. 48-year-old woman with screening detected invasive lobular carcinoma. Standard MLO and CC mammograms (A,B) show extremely dense parenchyma with subtle distortion on the CC view (long arrow). MLO and CC CEDM subtracted images (C,D) show the cancer as segmental nonmass clumped enhancement (short arrows).
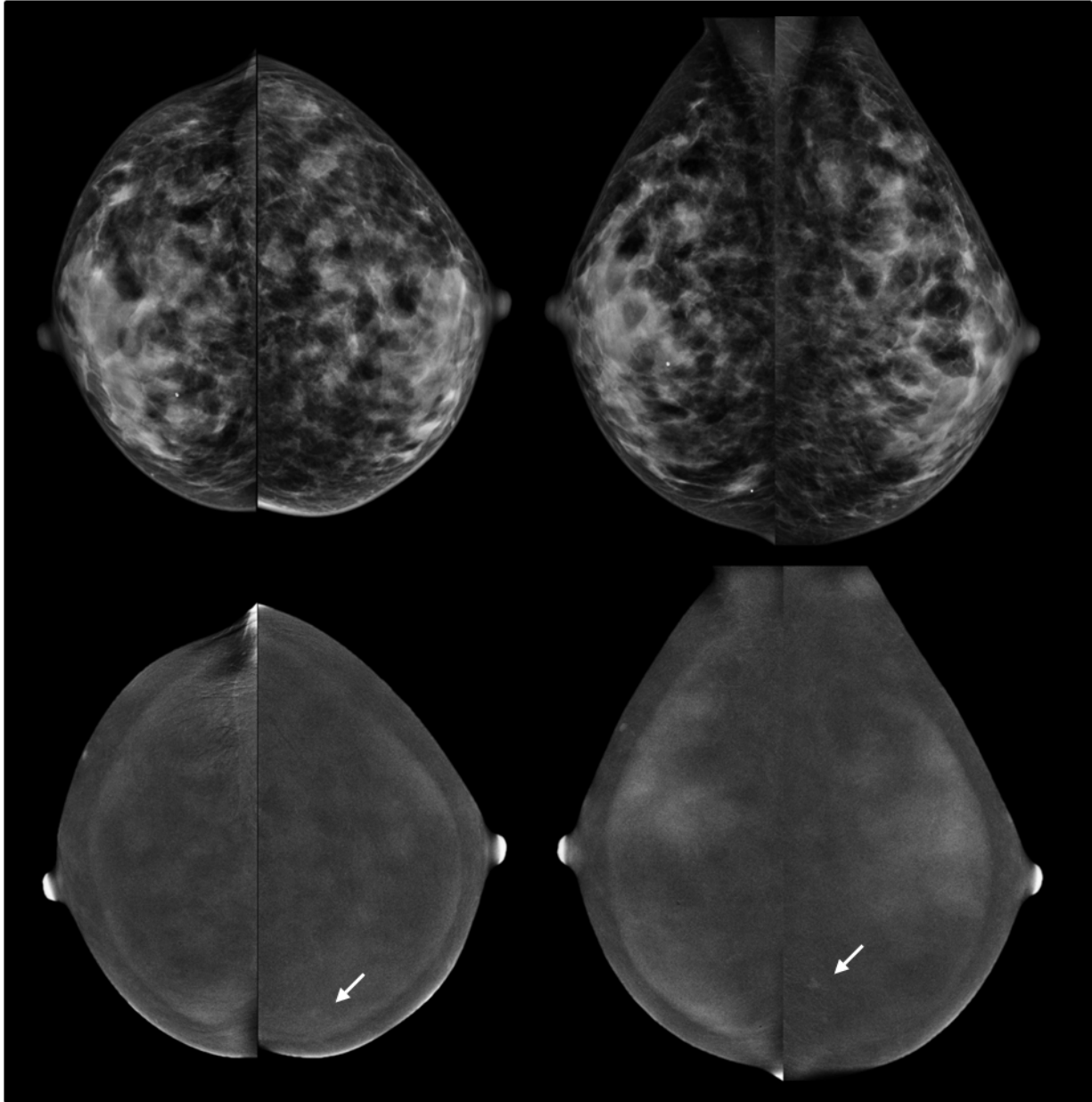
Figure 3. 56-year-old woman with heterogeneously dense breasts on standard mammography (upper images) and moderate risk of breast cancer. Screening CEDM (lower images) shows focal enhancement in the left breast at 8 o'clock (arrow). The finding was identified on ultrasound, and US-guided biopsy showed invasive ductal carcinoma. Note the background parenchymal enhancement, analogous to that seen in contrast-enhanced MRI. *Images courtesy of Jennifer Harvey, MD.*
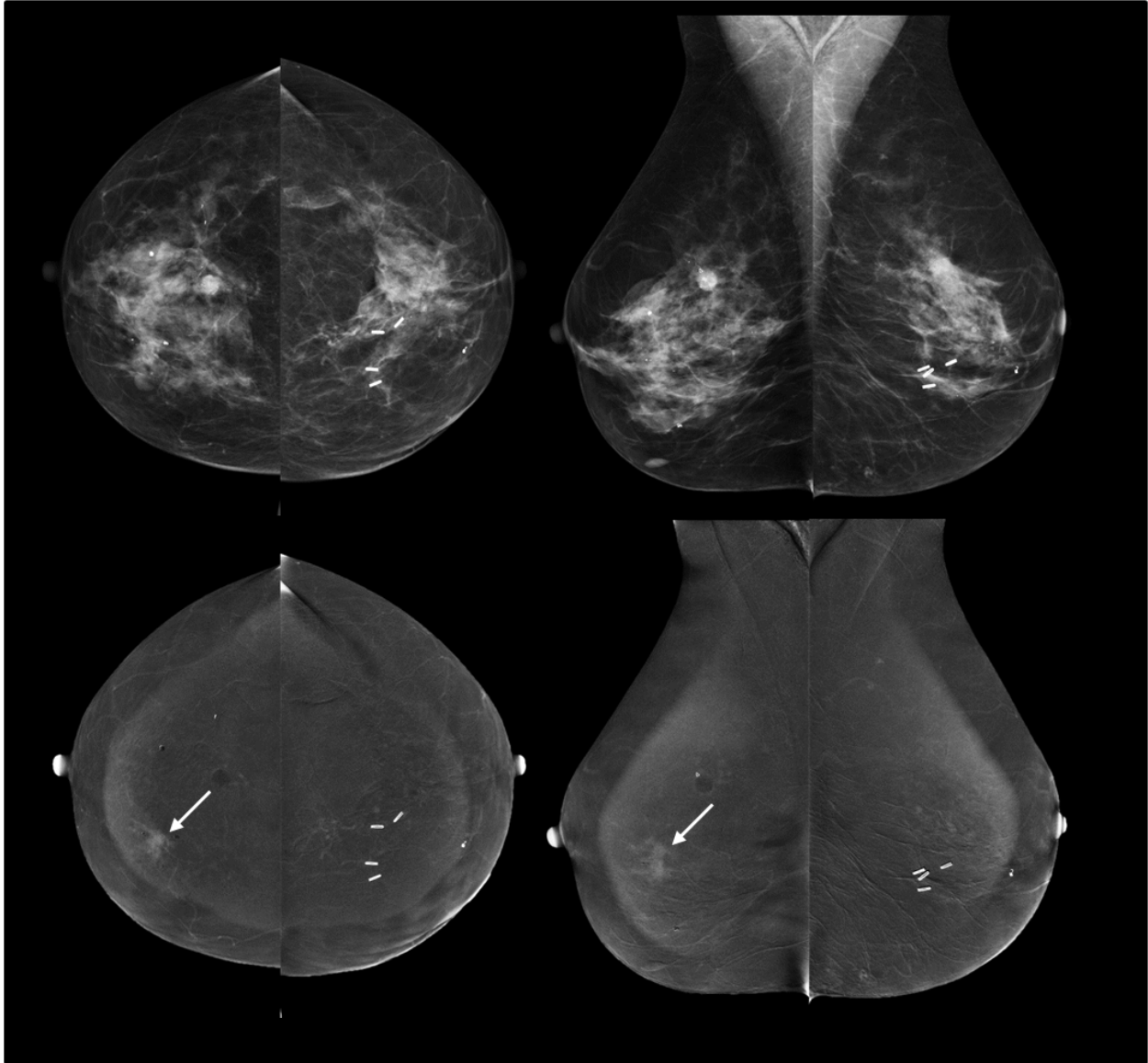
Figure 4. High-risk screening CEDM. 57-year-old woman with high lifetime risk of breast cancer due to family history. Standard digital mammograms (upper images) show heterogeneously dense parenchyma, benign-appearing round mass upper right breast and surgical clips left breast. Patient chose to undergo CEDM (lower images) instead of MRI due to high out-of-pocket costs with MRI. Non-mass enhancement is seen in the right breast at 4 o'clock (arrows). Biopsy of an US correlate showing fibrocystic changes was considered discordant. Excisional biopsy showed high grade DCIS. *Images courtesy of Jennifer Harvey, MD.*