

Contrast-Enhanced Digital Mammography

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KEYWORDS

• Digital mammography • Contrast • Neovascularity • MR imaging

KEY POINTS

- Contrast-enhanced mammography can improve the sensitivity of digital mammography.
- Contrast-enhanced mammography is less sensitive but more specific than breast MR imaging.
- Contrast mammography is significantly less expensive than MR imaging and could potentially be used for screening patients who are unable to undergo breast MR imaging.

CONTRAST-ENHANCED MAMMOGRAPHY

Mammography remains the only breast screening examination proved to reduce breast cancer mortality in the general screening population. Multiple randomized studies have demonstrated a 30% to 40% reduction in mortality for women actually screened.^{1–3} Mammography is inexpensive and widely available, but its sensitivity is limited: 70% to 85% overall but dropping to 30% to 50% in high-risk women with dense breast tissue.^{4–6}

Certain breast cancers are more likely to be associated with false-negative mammograms. Among them are lobular carcinomas, which grow in a linear pattern and, therefore, may not form a discrete mass, and noncalcified ductal carcinoma in situ. Small nonspiculated masses are common sources of false-negative mammograms. Oval-shaped circumscribed masses may be misinterpreted as benign.

Once a cancer is diagnosed, mammography may underestimate the size and/or extent of a primary tumor. As a result, re-excision is necessary in approximately 30% of patients^{7,8} undergoing breast conservation. Also, mammography may not identify additional foci of malignancy in other quadrants of the breast.

There is continuing improvement in mammography, most recently due to the conversion from analog to digital mammography. Although digital mammography does not improve the overall sensitivity of mammography, it has been shown to improve sensitivity in women with dense breast tissue.⁹ More importantly, digital mammography has provided a template on which to develop more-advanced breast imaging technology. Tomosynthesis was developed as a method to image the breast by removing overlying layers of breast tissue so that lesion characteristics and margins are better seen. This topic has been discussed in an article elsewhere in this issue. As stated by Johns and Yaffe,¹⁰ however, removal of overlying structures may not be sufficient to guarantee lesion detection because the difference in attenuation coefficients between fibroglandular and cancerous tissue ranges from only 4% at 15 keV to 1% at 25 keV.

Contrast-enhanced mammography is the second type of advanced technology stemming from the digital platform. The theory behind contrast mammography is based on the success of breast MR imaging, which is currently the most sensitive of all breast imaging techniques, with sensitivities reported up to 98%.^{11,12} MR imaging detects

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occult breast cancers in approximately 4/100 to 5/100 high-risk women. It also detects occult multifocal or multicentric cancers in approximately 16% of all patients with known breast cancer.¹³ The exquisite sensitivity of MR imaging is the result of a combination of anatomic and physiologic imaging. The physiologic component of MR imaging is primarily its ability to detect enhancing tumor vascularity after contrast administration. Tumor vascularity may be detected before a discrete mass is present. As a result, MR imaging has been shown to demonstrate cancers at an earlier stage in high-risk women who are screened yearly with MR imaging compared with those screened with mammography alone.¹⁴ In this population, MR imaging has also been shown to improve overall survival (93% vs 74.5% in historical cohorts).^{15,16}

MR imaging is expensive and time consuming, however, and cannot be performed on all patients. Additionally, good-quality MR imaging is not universally available. Women who are claustrophobic and women with pacemakers or other implanted metallic materials cannot undergo breast MR imaging. Therefore, there is a need for an alternate method to use both contrast enhancement and anatomy for detection of breast cancer. The performance of mammography using contrast material to diagnose breast cancer has been studied for several decades.

DIGITAL SUBTRACTION ANGIOGRAPHY

In 1985, Ackerman and colleagues¹⁷ reported their experience using digital subtraction angiography (DSA) of the breast in 22 patients in an attempt to differentiate benign from malignant disease without performing a surgical biopsy. They injected 30 mL of contrast at 25 mL/s into the right atrium; 32 to 40 images were obtained. In this initial group there were 7 true positive results, 11 true negative results, 2 false-positive results, 1 false-negative result, and 1 equivocal case. These results must be interpreted, however, with caution. One of the malignant lesions was considered a true negative because the mammogram was negative. Additionally, lesions less than 2 cm were not well seen. This somewhat invasive procedure, therefore, did not perform well enough to continue with its use.

It was observed that the degree of tumor angiogenesis correlates with tumor growth and metastatic potential.¹⁸ Haga and colleagues¹⁹ investigated whether tumor enhancement on DSA correlated with disease-free survival. They performed DSA in 103 women and found all tumors enhanced. They compared maximum densities of enhancement and demonstrated that

higher densities of enhancement were associated with decreased disease-free survival.

TEMPORAL TECHNIQUE

More recently, contrast-enhanced mammography has been performed using a temporal technique. A baseline image is obtained in a single view performed just above the K-edge of iodine (33 KeV) with the breast mildly compressed. The same iodinated contrast used for CT scans is injected intravenously after which multiple images of the breast are obtained over a period of 5 to 7 minutes. The noncontrast image is subtracted from the contrast images. This technique is successful in detecting cancers. Jong and colleagues²⁰ studied 22 women who were to undergo breast biopsies for suspected breast cancers. They demonstrated enhancement in 8/10 (80%) of the cancers in their study. Seven of 12 benign lesions did not enhance, but there were 5/22 (23%) false-positive examinations. These included 3 fibroadenomas and 2 patients with fibrocystic changes.

Diekmann and colleagues²¹ performed a multi-reader study involving 70 patients with 80 lesions and demonstrated that the addition of contrast to digital mammography improved sensitivity from 43% to 62%. Not surprisingly, improvement in sensitivity was more likely to occur in women with dense breasts than women with fatty breasts. Dromain studied 20 women with suspicious mammographic findings. There was enhancement in 16/20 (80%) cancers. The size of 97% of the tumors correlated well with size at histology. In her study, the enhancement curves in the cancers differed from those seen with MR imaging. With contrast-enhanced mammography, most cancers demonstrated gradually increasing enhancement as opposed to the rapid enhancement with washout pattern classically seen with cancers on MR imaging. Rapid enhancement with wash out was only seen in 4 of the patients having contrast mammography. It is uncertain as to whether this difference in enhancement pattern is related to the breast compression performed with the temporal technique or is a characteristic of the difference between gadolinium and the iodinated contrast used for contrast mammography. Additionally, the enhancement patterns in Dromain and colleagues²² series did not correlate with the microvessel counts demonstrated on pathology.

Although the technique of temporal contrast-enhanced mammography is able to demonstrate cancers with good sensitivity, there are several disadvantages associated with this technique.

Despite breast compression, patient motion caused artifacts; it is difficult for patients to remain still for 7 minutes. Additionally only 1 view of one breast can be obtained per injection, making it difficult to localize abnormalities. Moreover, the contralateral breast is not imaged at all.

CONTRAST-ENHANCED DUAL-ENERGY DIGITAL MAMMOGRAPHY

Contrast-enhanced dual-energy digital mammography (CEDM) is an alternate attempt at combining contrast enhancement with digital mammography. This technique uses nonionic iodinated contrast at 1.5 mL/kg. Each exposure provides a low-energy image below the K-edge of iodine (33 KeV) and a high-energy image above the K-edge of iodine. The tube voltage used is based on breast thickness and glandularity and ranges from 26 to 30 kV (peak) for low-energy images to between 45 and 49 kV (peak) (Fig. 1) for the high-energy images. The 2 images are recombined, the background breast parenchyma is eliminated, and an image with any iodine-enhanced lesions is produced.

Lewin and colleagues²³ first performed mammography with dual-energy technique using a mammography unit that was not designed for use with contrast. Nevertheless, they successfully injected contrast followed by the performance of the low- and high-energy images while the breast was compressed. Subtraction of the 2 images yielded an iodine image; 26 patients with mammographic or clinical findings were imaged. There were 13 invasive cancers; 11 of them enhanced strongly and 2 enhanced weakly, confirming the ability of contrast-enhanced mammography using

dual-energy technique to demonstrate breast cancer.²³

As a result of this promising study, a dedicated unit was developed to perform CEDM. It basically adapted a digital mammography unit (Senographe DS, GE Healthcare, Buc, France) for this purpose. The standard digital mammography unit was modified to allow the use of a specialized filter, which could shape the x-ray spectrum specifically to perform CEDM. The prototype unit used manual technique for breast thickness and density. Newer units allow for automated or manual technique. Iodinated contrast is administered using a power injector with a high flow rate. Patients are seated during intravenous injection of the contrast material. When injection is complete, they begin what for them seems routine mammography. With the new dual-energy units, compression time is no greater than 15 seconds per view and the entire study can be performed within 5 minutes.

The earliest clinical trials were performed imaging 2 views of a single breast. Dromain and colleagues²⁴ studied 120 women with either abnormalities detected on screening or with clinical problems not resolved by routine mammography or ultrasound. They reported that 74/80 (92%) of cancers enhanced and 13/50 (26%) of benign lesions enhanced. The addition of contrast-enhanced mammography to mammography had significantly better results than mammography alone. Contrast-enhanced mammography plus mammography trended toward improvement over mammography and ultrasound²⁴ but this did not reach statistical significance.

With positive results of CEDM in a single breast, the next step was to attempt bilateral

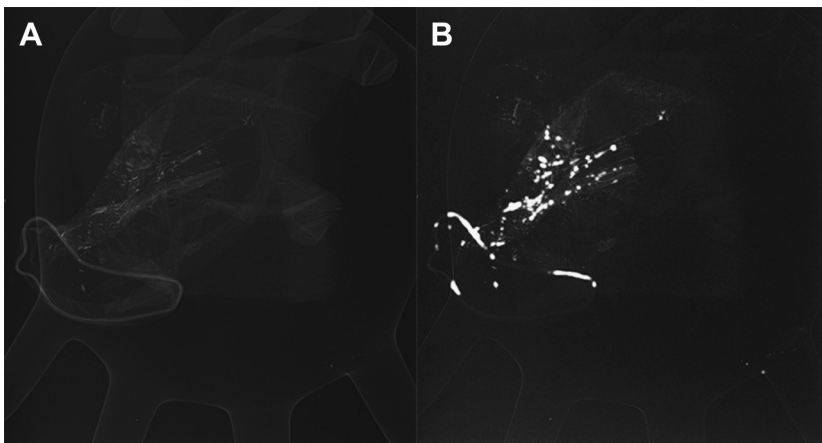


Fig. 1. (A) Glove lined with iodinated contrast filmed with keV under 33 shows contrast as water density. (B) Same glove with recombination of low-energy and high-energy images demonstrates the iodine. (Courtesy of D. David Dershaw, MD, New York, NY.)

contrast-enhanced digital mammography. Jochelson and colleagues²⁵ performed a 2-phase study. The purpose of the initial phase was to determine the feasibility and if need be optimize the technique of performing bilateral CEDM. The second part of the study was to evaluate the ability of CEDM to detect a known cancer within the breast and compare its sensitivity with digital mammography and breast MR imaging. The ability to detect multifocal/centric disease was also evaluated and compared with mammography and MR imaging for both sensitivity and specificity; 82 patients were enrolled.

The first portion of the trial included 10 patients and demonstrated that bilateral CEDM was feasible and easy to accomplish. The optimal time to begin imaging after contrast enhancement was determined to be approximately 3 minutes. The order in which the images were obtained was varied to determine if it mattered if the side containing the cancer was imaged early or late or whether the *craniocaudal* (CC) or mediolateral oblique (MLO) images needed to be performed in a certain order. The study demonstrated that the order did not matter. Tumor enhancement was seen for up to 10 minutes after injection. All patients tolerated the procedure well with no adverse effects.

Fifty-two patients were available for data analysis to determine the accuracy of CEDM compared with digital mammography and MR imaging. CEDM and MR imaging each detected 50/52 (96%) of the index lesions (Fig. 2), which was significantly better than mammography, which detected 42/52 (81%). All but 2 of the lesions detected by CEDM were within 5 mm of the actual size of the tumor at pathology. Both invasive and intraductal cancers were detected.

Two additional malignant lesions were present in the ipsilateral breast in this group of patients. CEDM detected 14/25 (56%) whereas MR imaging detected 22/25 (88%) (Fig. 3). CEDM demonstrated 2 false-positive lesions and MR imaging found 8 in the ipsilateral breast. In the contralateral breast there was a single cancer, Paget disease, which was not demonstrated by either CEDM or MR imaging. There were 5 false-positive results on MR imaging and none on CEDM in the contralateral breast. The overall lesion detection rate was 64/77 (83%) for CEDM and 72/77 (94%) for MR imaging. Although CEDM was less sensitive, the true positive rate was significantly higher than MR imaging: 64/66 (97%) for CEDM versus 72/85 (85%) for MR imaging.²⁵

Entities other than cancer enhance. Just as with MR imaging, the walls of cysts and seroma

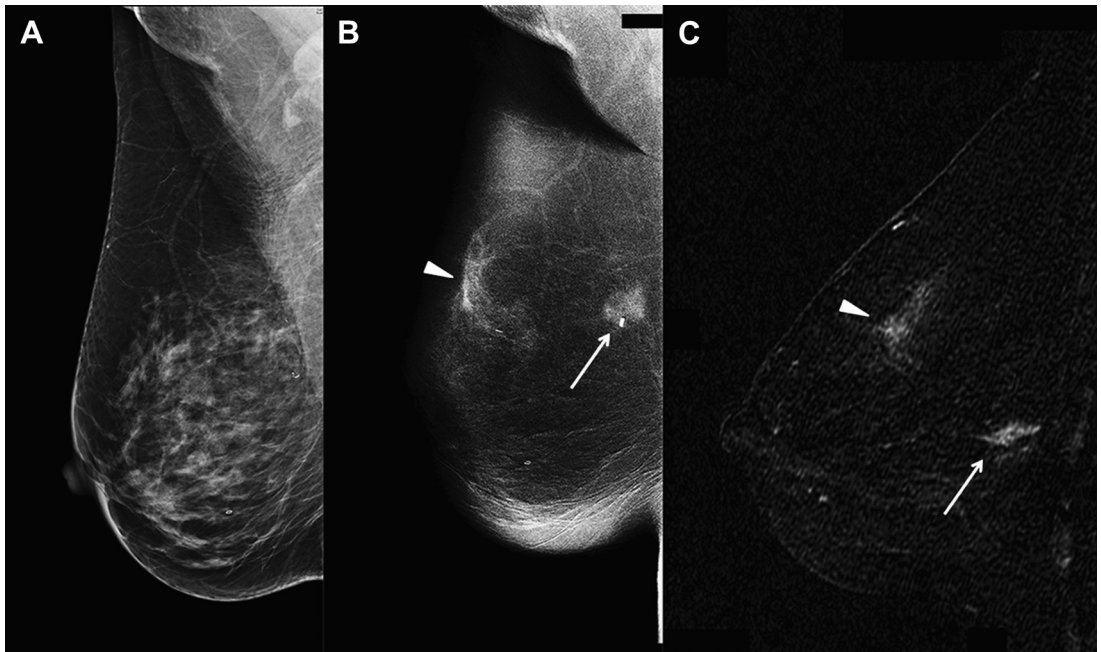


Fig. 2. A 58-year-old woman with mammographically occult invasive ductal carcinoma of the right breast. (A) Right MLO mammogram shows no abnormality. (B) CEDM demonstrates rounded area of enhancement surrounding a biopsy clip (arrow) consistent with known cancer. More anterior area of enhancement due to uptake in seroma after benign biopsy (arrowhead). (C) Sagittal subtraction image from MR imaging demonstrates the cancer posteriorly (arrow) and seroma anteriorly (arrowhead).

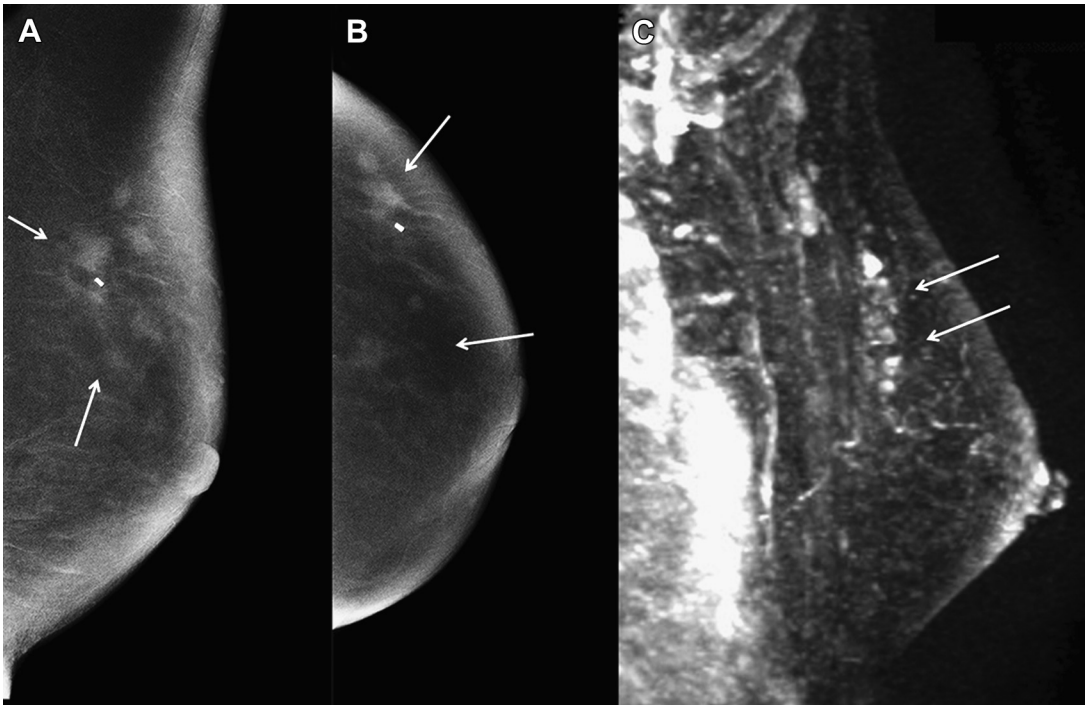


Fig. 3. A 49-year-old woman with a palpable mass left upper outer quadrant biopsy proved to be invasive lobular carcinoma. (A) CEDM MLO and (B) CEDM CC views show multiple enhancing lesions consistent with multicentric cancer (arrows). (C) MR imaging, maximum intensity projection image, of the left breast demonstrating multiples lesions (arrows).

cavities may enhance (Fig. 4). These findings are easy to recognize and do not warrant histologic confirmation. False-positive findings may be seen, however, in benign lesions, such as fibroadenomas, pseudoangiomatous stromal hyperplasia (PASH) (Fig. 5), and radial scars that have enhanced on contrast mammography, requiring histologic confirmation. Additionally, just as with MR imaging, there may be background parenchymal enhancement (BPE). At this time, it is uncertain as to whether it is related to timing in regard to menstrual cycle as it is on MR imaging. It is also uncertain as to whether it is a sign of increased cancer risk as has been suggested with BPE on MR imaging.²⁶

At this time a method to perform biopsies using CEDM is not available. Abnormalities detected by CEDM are often also seen on MR imaging so that MR imaging-guided core biopsy may be performed. Alternatively, targeted ultrasound may also identify some of these lesions. As with all new modalities, however, a method for performing biopsies is necessary. Work is under way to accomplish this.

Another contrast-enhanced breast imaging technology to consider is contrast-enhanced digital breast tomosynthesis (CE-DBT). Chen and

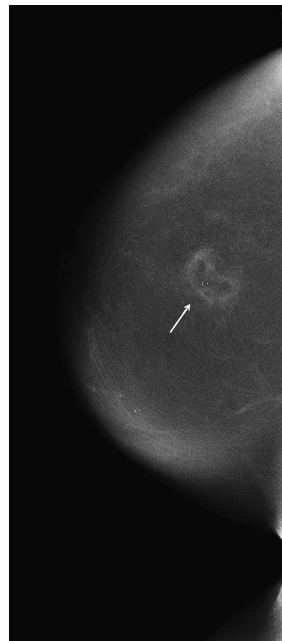


Fig. 4. A 58-year-old woman status post-benign core biopsy right breast with a peripherally enhancing seroma (arrow).

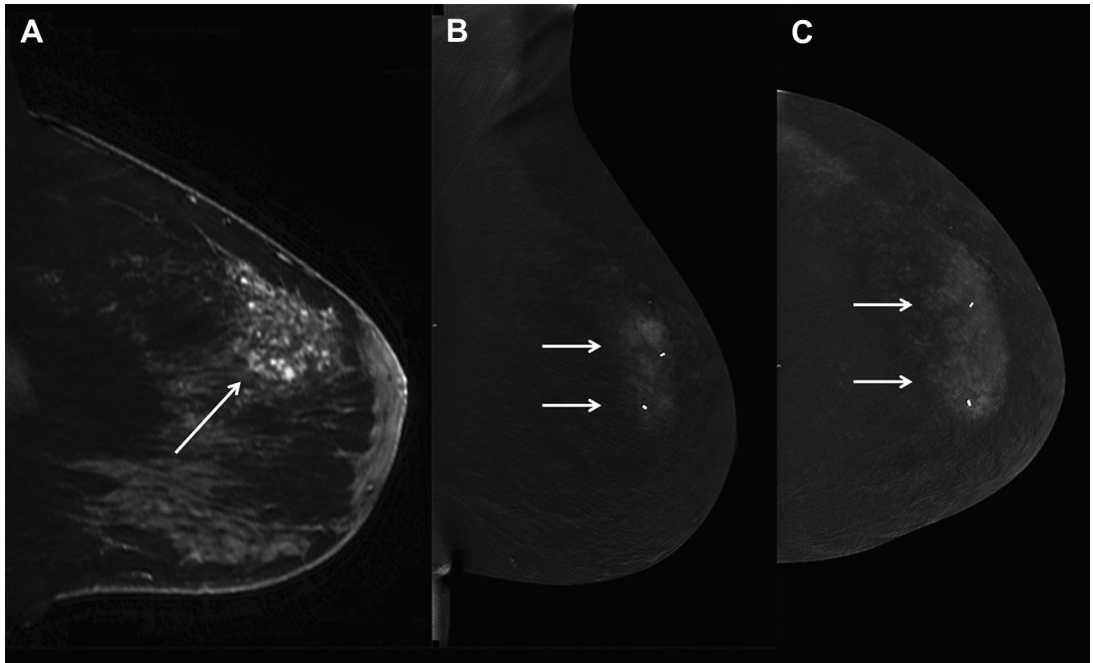


Fig. 5. PASH. (A) A 47-year-old high-risk woman who had focal non-mass enhancement (*arrow*) during screening MR imaging. Biopsy showed PASH. (B) CEDM MLO and (C) CEDM CC views also demonstrate a focal area of enhancement corresponding to the MR imaging finding (*arrows*).

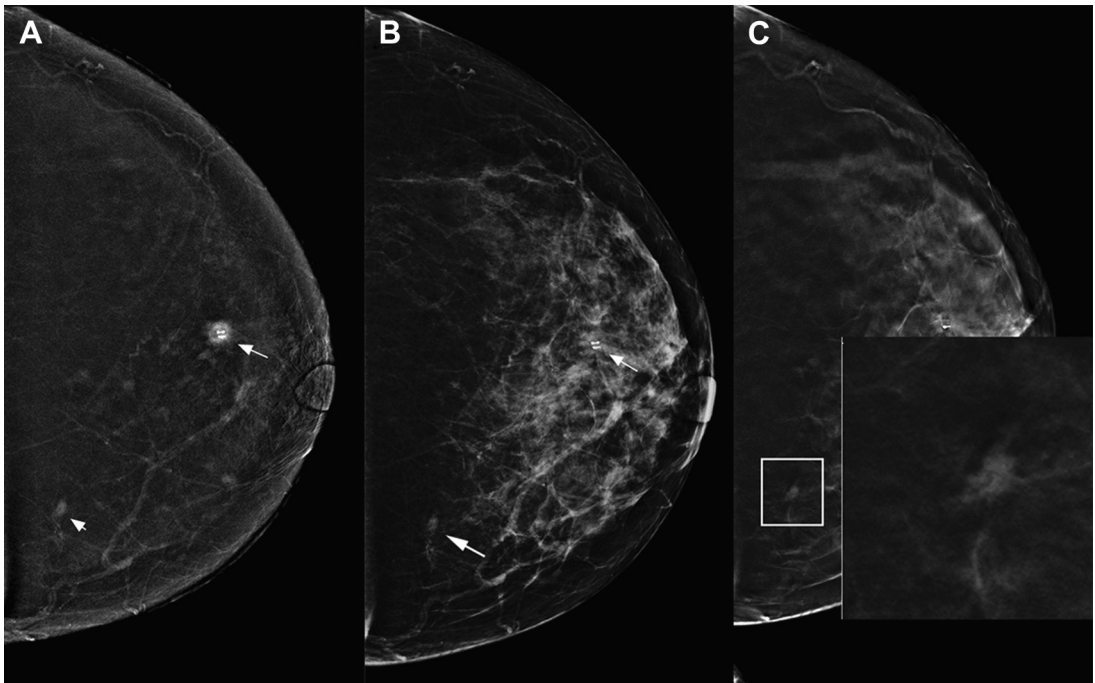


Fig. 6. A 45-year-old woman with biopsy-proved invasive ductal carcinoma. (A) Standard mammogram shows biopsy markers (*long arrow*) at the site of the biopsy-proved cancer. The lesion is not visible; a 5-mm lesion is identified in the medial breast (*short arrow*). (B) Dual-energy CEDM image shows the known cancer (*long arrow*). A 5-mm enhancing focus in the medial breast (*short arrow*) cannot be characterized. (C) Low-energy tomosynthesis image acquired as part of the CEDM study shows the enhancing lesion (*box*) irregularly shaped (*inset*), greatly raising the likelihood of malignancy. The lesion was later proved a second invasive ductal carcinoma. (Courtesy of John Lewin, MD, Denver, CO.)

colleagues²⁷ performed a pilot study in 13 patients with Breast Imaging Reporting and Data System 4 or 5 lesions on mammography and ultrasound. There were 11 cancers of which 10 enhanced. They concluded that CE-DBT could be used as an adjunct to digital mammography for breast lesion characterization. Carton and colleagues²⁸ performed CE-DBT on a single patient with known breast cancer and compared it with MR imaging. They used both temporal and dual-energy techniques. As in prior studies, there was less motion artifact with dual energy compared with temporal imaging. They were able to demonstrate that the CE-DBT examination compared favorably with MR imaging.²⁸ Tomosynthesis used after CEDM enables improved lesion and margin analysis so may add to the specificity of CEDM (Fig. 6).

At the time this article is being written, CEDM has been studied only in patients with known cancers or in patients with clinical and/or imaging abnormalities so that the results of the data until now cannot be applied to screening. To my knowledge, no prospective trial to evaluate the accuracy of CEDM in the screening setting has been published, although such trials are under way.

SUMMARY

CEDM is a promising new technology that combines anatomic evaluation of the breast with the physiologic characteristic of contrast enhancement of the neovascularity associated with malignant tumors. Early experience suggests that CEDM is more sensitive than digital mammography and more specific than MR imaging. Potential uses may include staging of known breast cancers, additional evaluation of mammographic or clinical abnormalities, evaluation of the post-lumpectomy breast for recurrent tumor, and screening for cancer. It may be an alternative to screening MR imaging and even potentially screening ultrasound. A great deal more prospective research is required to better assess its ability to screen.

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