

Contrast Enhanced Mammography Implementation Guide

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SECTION I: Introduction

Purpose. Contrast Enhanced Mammography (CEM) is a powerful tool combining functional information (derived from iodinated contrast administration) with structural imaging (derived from anatomic 2D mammographic views), previously only available from breast magnetic resonance imaging (MRI). CEM has higher specificity, but lower sensitivity, than bMRI¹ and is a more cost-effective alternative to MRI². This manual will provide an in-depth guide for CEM implementation into clinical practice.

Technical aspects of CEM image acquisition.^{3,4}

CEM utilizes a dual-energy technique predicated on the attenuation differences of breast tissue and iodinated contrast. A standard CEM acquisition requires two exposures per view: one at high-energy and the other at low energy.

The high-energy exposure utilizes a copper filter and is performed above the k-edge of iodine (33.2 keV). High energy x-ray photons are preferentially absorbed at the locations of increased iodine accumulation, relative to the absorption in these same locations with lower energy photons, whereas absorption in regions of normal breast tissue do not exhibit this large absorption change as a function of x-ray energy. The high-energy image is not interpretable but is used in the calculation of the iodine map.

The low-energy image is produced in the low-energy x-ray spectrum (28-32 kVp) and uses standard mammographic filters. The image produced is comparable to full-field digital mammography (FFDM) and may be utilized for morphologic characterization of lesions.

The recombined, or "subtracted", image is created by post-processing subtraction of the low-energy image from the high-energy image. The recombined image appears as a subtracted image highlighting iodine accumulation while eliminating the surrounding breast

tissue. Iodine accumulation is based upon principles of angiogenesis, similar to contrast enhancement in MRI. Following the CEM examination, only the low energy images and the recombined images are available for interpretation on PACS.

Literature review. Mammography is the only imaging modality known to reduce mortality from breast cancer.²⁶ The ability to detect a breast cancer at a smaller size, typically before palpation, is associated with reduced mortality.²⁵

The sensitivity of mammography for detecting a breast malignancy is reduced in women with dense breast tissue, reportedly 40-70%.⁵ This decreases even further in those women with dense breast tissue and an inherited genetic predisposition/elevated lifetime risk for breast cancer. The masking effect of FFDM is partially overcome with digital breast tomosynthesis (DBT) by obtaining multiple low dose images at various angles, producing a semi-three dimensional image set. DBT has repeatedly shown to improve cancer detection rate (CDR) and positive predictive value (PPV) while lowering the false positive rate.⁶ However, the utility of DBT is constrained by a fundamental need for an attenuation difference between the malignant lesion and the surrounding normal glandular breast tissue. DBT has shown a modest performance improvement in women with dense breast tissue, yielding an additional 1.4 cancers per 1000 women screened and no statistically significant difference in CDR with the addition of DBT in women with extremely dense tissue.⁷

CEM improves upon FFDM and DBT by adding functional information to established anatomic imaging. CEM demonstrates improved performance compared to FFDM in the diagnostic setting: sensitivity 100% vs 96%, specificity 97.7% vs 42.0%, PPV 76.2% vs 39.7%.⁸ In addition, CEM shows similar sensitivity compared to breast MRI (96% vs 96%).⁹ In a multi-reader study

comparing CEM with breast MRI in women with known malignancy, 93-98% of known malignancies are seen at CEM compared to 89-93% at breast MRI.¹⁰ When CEM is utilized to assess extent of malignancy, there is no statistically significant difference between extent of disease on CEM compared with breast MRI when assessed at final pathology.

The use of CEM compared to breast MRI for neoadjuvant chemotherapy (NAC) response demonstrates that CEM outperformed MRI in sensitivity (100% vs 87%) and specificity (84% vs 60%).¹¹

Women at elevated risk for breast cancer may additionally benefit from CEM. Not all women at elevated risk for breast cancer undergoes breast MRI, which may be secondary to inability to have a breast MRI for physical limitations (body habitus, anxiety), implanted devices, or financial burden. Hobbs et al demonstrated an increased overall patient preference of CEM compared to MRI citing a reduction in imaging time, anxiety, and noise.¹² In a study of evaluating CEM compared to breast MRI in 307 elevated risk patients for lesion detection, specificity and PPV are similar. Sensitivity is statistically higher in MRI secondary to a small number (n=3) of malignancies identified.¹³ Furthermore, CEM outperforms the sensitivity of FFDM (87.5% vs 50%).¹⁴ References cited use equipment from various manufacturers.

SECTION II: Clinical Utilization

Paradigmatically, CEM may be utilized in preprocedural or postprocedural diagnostic settings, and many other diagnostic indications.^{7,28,29,30} The CEM examination is pragmatic, efficient, and expeditiously interpreted in each setting, leading to high patient satisfaction, and often truncating the final time to diagnostic resolution in those patients recently diagnosed with breast neoplasm.

Preprocedural setting. CEM has been utilized for Diagnostic BI-RADS 4c/BI-RADS 5 lesions in which there is a high propensity of diagnosis of breast neoplasm, to present the breast surgeon with full breast staging prior to cancer consultation.

Postprocedural setting. CEM is most utilized for preoperative disease extent evaluation in patients recently diagnosed with breast neoplasm, most commonly lobular origin neoplasm, diagnosis of breast neoplasm in the setting of heterogeneously dense or extremely dense breasts, unexpected histopathology upon breast biopsy (i.e., spindle cell neoplasm). CEM is used for post neoadjuvant follow-up, oftentimes in conjunction with targeted breast ultrasound and diagnosis of breast cancer metastases to the axilla without known breast primary location. CEM is also utilized

for persisting clinical symptomatology with negative initial diagnostic breast imaging examination, such as persisting palpable abnormality, bloody nipple discharge, and unexplained unilateral breast dermal changes.

SECTION III: Implementation

Equipment requirements. The addition of CEM requires I-View® software, a hardware upgrade (addition of a Copper filter) to the 3Dimensions™ system and a power injector for contrast injection.¹⁵ Given resource constraints for many breast centers, the multifunctionality of Hologic Selenia® Dimensions® systems in screening mammography, upright stereotactic guided core biopsy (both 2D and 3D™), CEM, image-guided localization and diagnostic mammography is particularly useful.

A power injector is the recommended method for CEM, allowing for a consistent, desired rate of 3 mL/second and the post injection saline bolus.¹⁶

A crash cart or a contrast reaction kit should be easily assessable by staff in the breast center. Patients are monitored in the department for contrast reaction for 15 minutes following the CEM examination.

Point of care methodology such as i-STAT (Abbott, NJ) allows for expeditious assessment of creatinine levels. To minimize the risk of contrast induced nephropathy (CIN), the ACR recommends serum creatinine level when patients meet one or more of the following factors: >60 years of age, a history of renal disease (dialysis, kidney transplantation, single kidney, renal cancer, renal surgery), hypertension (HTN) requiring treatment, diabetes mellitus (DM), or use of Metformin.

Staffing requirements. Preprocedural IV line should be placed according to your institution's protocol; this may include placement by mammography technologists, breast center nurses/ navigators or other radiology departmental technologists/nurses. Both nurses and technologists may perform pre-CEM contrast screening as well as postprocedural patient education. During the CEM exam, a radiologist or other licensed physician must be physically present in the facility to evaluate and treat any contrast associated reaction, as well as interpret this diagnostic examination.¹⁷

Radiologist requirements. The time needed for radiologists to feel confident reading CEM is relatively short.¹⁸ CEM images are more efficiently and expeditiously interpreted than breast MR images, with a total mean interpretation time of 1-2 minutes.² Serious contrast reactions necessitating physician involvement, as described below, are rare.

The references related to CEM used in this document are a helpful collection of information new users will find

beneficial as they implement CEM into their practices.

Clinical workflow. Separate areas designated for both IV insertion prior to the exam and for patient monitoring after the examination assist with efficiency of utilization of the 3Dimensions system.

Education. Regarding initiating and expanding the CEM service line, referring provider education can be reliably performed through breast cancer multidisciplinary tumor board, grand rounds presentations, through the medical staff office, and via patient-specific direct communications to ordering providers. To maintain referring provider confidence in this modality, oftentimes the CEM reader pool is initially restricted to minimize downstream MR imaging following the CEM examination.

Initial in-service for mammography technologists and breast center staff is critical for smooth clinical workflow.

Gaining experience. Even though reading CEM can be “easily learned”, it is helpful to gain experience with cases where you have some comparison to imaging findings on conventional stereotactic imaging and/or MRI. This can include patients with abnormal MRI, patients with imaging findings requiring biopsy or symptomatic patients like those with palpable findings. Spot compression images may be performed as part of the CEM encounter.

Contrast. The rate of severe contrast reactions is rare (0.04%)¹⁵, with rare incidence of mortality reported at 0-10/1 million.^{19,20,21} In general, protocols regarding administration of IV contrast for CEM parallel institutional protocols for computed tomography. Mild reactions may receive premedication per institutional protocols. Severe contrast reactions are a contraindication to the CEM examination. It is recommended to have the ACR contrast reaction card in the mammography room for quick reference should a contrast reaction occur.

Pre-imaging screening. When scheduling, staff should ask questions related to a history of allergies to contrast media, review of medications (specifically Metformin or HTN treatment), history of DM and HTN, and known renal disease.

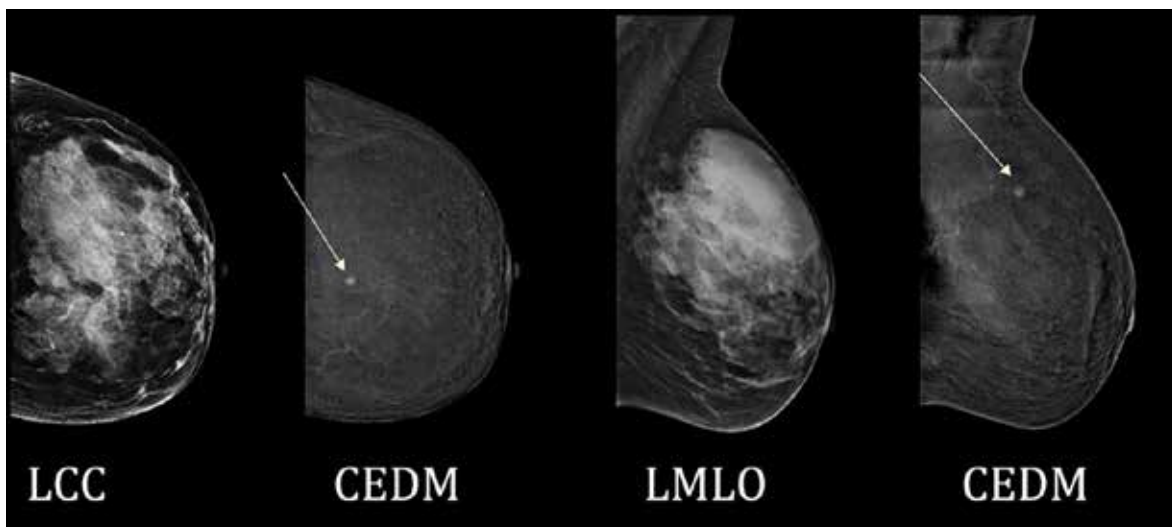
Contraindications to intravenous contrast include a GFR of less than 30 mL/minute per 1.73 m² and a known moderate to severe allergy to iodinated contrast. The ACR Manual on Contrast media is a good reference guide.

The literature²² demonstrates that CEM dose is approximately 1.5x that of FFDM, and DBT is approximately 1.2x that of FFDM. In a recent Hologic software release, the CEM radiation dose is now lower at 1.25x of FFDM (Hologic MAN-06383-002).

Coordinating the CEM exam with the patient’s menstrual luteal phase, to minimize background parenchymal enhancement, may be considered although is not necessary, particularly for preoperative disease extent evaluation in recently diagnosed breast neoplasm.¹⁷

Imaging workflow. Diagnostic radiologists review all images and clinical information to protocol the examination before patient arrives. Antecubital venous access using a ≥ 20 -g needle is preferred.¹⁵ Care should be taken to place the IV into the arm contralateral to a prior axillary dissection. The patient should be informed about any side effects related to contrast injections such as a diffuse sensation of warmth, flushing, a metallic taste in mouth, and even urinary incontinence. Also, the patient can be educated about injection site issues including pain and swelling.

Imaging protocol. Contrast is typically administered to an upright, seated patient with a power injector. A multitude of iodinated contrast agents may be utilized. For CEM, it is helpful to parallel institutional CT iodinated



contrast protocols. Follow the product labeling for dose recommendations.

Imaging should include the standard four views with imaging of both breasts. Spot compression and additional full views such as XCCL and ML can also be performed. Imaging should be started approximately two minutes after completion of the contrast injection and ideally completed within a 6 minute window to minimize contrast washout, although imaging may be undertaken up to 20 minutes post contrast injection.²³ However, in those lesions with exceptionally low mitotic index, delayed images out to 20 minutes have occasionally been obtained.

Many institutions acquire images in the following sequence, affected breast MLO – unaffected breast MLO – affected breast CC – unaffected breast CC.¹⁶ In order to finish imaging within the ideal window, it is helpful for an institution to have a reproducible protocol.

For diagnostic CEM studies the radiologists may choose to be present in the imaging suite, especially in the initial stages of the CEM program. This can allow for real-time review of images and decision making regarding the need for additional views.

Post imaging. The injection site should be checked for any signs of contrast extravasation. Extravasation occurs from 0.1% to 1.2% in studies of patients having CT exams with power injectors.¹⁹ Signs of extravasation include patient complaints of swelling or tightness,

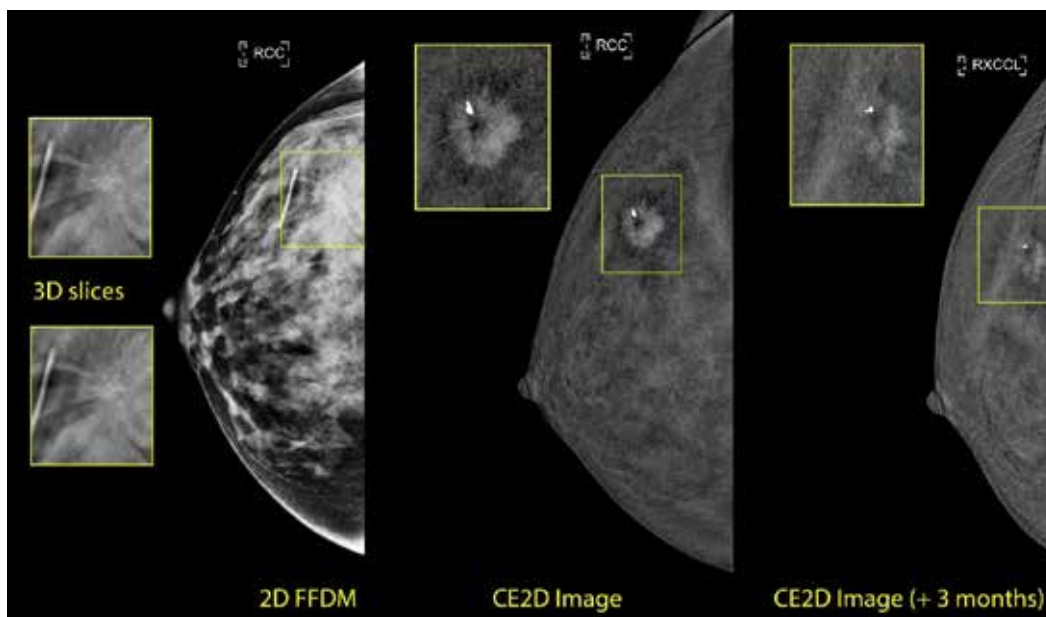
stinging or burning pain at the site of extravasation, or no discomfort at all.²⁴ On physical examination, the extravasation site may be edematous, erythematous, and tender, although the vast majority recover without long

term complications.²⁴ Patients who have had prior axillary dissection are at increased risk for extravasation in the affected extremity; therefore, contralateral extremity is typically utilized for the examination.

Mild immediate contrast reactions typically do not require medical treatment, although nursing should monitor vitals and the physician should be notified. The ability to check vital signs is important in a breast center that offers CEM. Any patient with a mild allergic-like reaction should be observed for a minimum of 30 minutes to ensure clinical stability or recovery. Treatment with an antihistamine may be instituted for mild symptomatic allergic-like urticarial reactions, but often is not necessary.²⁰ Please refer to the ACR manual on contrast reaction for more information regarding managing contrast reactions.

SECTION IV: Reporting and Image Interpretation

CEM reporting and image interpretation parallels breast MRI reporting and image interpretation. Firstly, degree of background parenchymal enhancement is specified, as normal breast tissue can also enhance at CEM. This enhancement of breast tissue is described as background parenchymal enhancement (BPE). Normal background parenchymal enhancement is classified as minimal (<25% of glandular tissue demonstrating enhancement), mild (25%–50% enhancement), moderate (50%–75% enhancement), or marked (>75% enhancement). Degree of symmetry of BPE is also reported, as to whether BPE is symmetric or asymmetric. Standard BI-RADS nomenclature is followed. The technique section is inclusive of contrast dose and



presence or absence of periprocedural complications. The report is often linked with any other diagnostic examinations performed during the CEM encounter, such as targeted breast ultrasound, to issue one comprehensive BI-RADS designation.

Notably, it is important to render image interpretation of both the morphologic 2D and/or 3D™ images. Occasionally a patient with multifocal intraductal neoplasm has satellite regions of subtle microcalcifications discerned predominantly on morphologic imaging, which may not exhibit significant enhancement on recombined images and yet, may require further action in the pretreatment setting. Image interpretation and subsequent recommendations arising from the CEM encounter, as in other breast imaging modalities, is primarily governed by the most suspicious imaging feature, whether that is discerned from morphologic imaging (2D/3D™) or the targeted ultrasound arising from the CEM encounter. Commonly, benign lesions such as fibroadenoma may exhibit brisk enhancement which parallels that of a malignant lesion. Lesions on CEM are characterized as solitary (unifocal) or multifocal, the degree of enhancement is characterized as non-mass enhancement (linear vs clumped, regional vs segmental) vs mass, and any concerning features in the axilla are described. In newly characterized neoplasms, comments may additionally be made regarding status of the nipple in the affected breast (ie. nipple inversion), degree (if any) of dermal thickening, parenchymal edema versus post biopsy hematoma about biopsied neoplasm, and distance from neoplasm to nipple anteriorly and chest wall posteriorly.

SECTION V: Billing and Coding

CEM is uniformly billed as a Diagnostic Breast Imaging Contrast Examination with added charge for intravenous contrast. Adjunct targeted ultrasound or adjunct downstream ultrasound-guided or stereotactic-guided biopsy with or without contrast arising from CEM examination is billed separately. All these examinations are discussed with the patient as per your typical practice for diagnostic breast imaging.

SECTION VI: FAQs

What were the barriers to implementation of Contrast Enhanced Mammography (CEM) in your practice?

The barriers to implementation of CEM at the authors' institutions are extrinsic to image quality and clinical workflow and primarily revolve around preprocedural operational measures such as IV placement, standardizing response to contrast reactions given presence in freestanding outpatient imaging center, and familiarizing mammography technologists with power injector for administration of intravenous contrast.

What happens if the lesion of interest does not enhance?

If a lesion has a low mitotic index, represents intraductal neoplasm, or exhibits mucinous or papillary features, a delayed image in one view (MLO view, for example) may be necessitated at 4, 8 or even 12 minutes to optimize lesion conspicuity. In the authors' institutional experience, delayed images of up to 20 minutes may be undertaken following contrast injection.

What is the frequency of contrast reactions following CEM?

In the authors' institutional experience of over 500 cases, there have been no severe contrast reactions following CEM examination. If patients historically demonstrated mild reaction to intravenous contrast administration, premedication protocol is administered (which parallels institutional premedication protocol for Computed Tomography (CT)). Patients should be forewarned prior to the examination that along with intravenous contrast examination, there is often a feeling of generalized full-body warmth/flushing and that they may have the sensation to urinate. No significant side effects have been observed because of intravenous contrast administration.

Who places the IV for the CEM examination?

Who places the IV can depend upon whether the CEM examination is performed in the outpatient or inpatient setting, as well as the institutional protocol. For example, an outpatient facility procedure may allow the IV to be placed by the breast center nurse navigators, breast center nurses, or mammography technologists. At some institutions, diagnostic imaging inclusive of MRI and CT is additionally performed in the breast center building and, as such, the IV is placed by the CT technologists. In the inpatient setting, Interventional Radiology nurses and CT/MR technologists may provide a useful adjunct to placing the IV to optimize the examination.

How often is MRI performed for problem solving following CEM examination? MRI is not utilized for problem solving following CEM examination at the authors' institution. If there are additional foci of enhancement within the ipsilateral affected breast or contralateral unaffected breast on CEM, a targeted ultrasound is performed to discern these lesions. An ultrasound slot and biopsy slot are held for all CEM patients. If the enhancing lesion(s) of interest are not discerned upon targeted breast ultrasound, upright 3D™-directed biopsy is performed based upon landmarks for the CEM-detected lesions of concern. Contrast enhanced biopsies are also an option.

How is a meaningful referral base for CEM built? CEM may be initially presented in breast oncologic multidisciplinary tumor board; when a CEM is performed which subsequently alters surgical management or in which impactful new data is discerned from the CEM examination, these cases are presented in tumor board. In this manner, a virtuous feedback loop can be built with all CEM ordering providers across disciplines inclusive of medical oncology and breast surgery. Additionally, these cases can be presented in Grand Rounds to the primary care specialties of internal medicine, obstetrics and gynecology, and family medicine.

Has CEM negatively impacted diagnostic MRI volumes at your institution? No. In the authors' experiences, CEM has heightened awareness of the importance of preoperative disease extent evaluation in newly diagnosed neoplasms, particularly in those patients with heterogeneously dense/extremely dense breasts or in those with unexpected pathologic findings. As such, many newly diagnosed neoplasms are counseled by breast surgery regarding the importance of preoperative disease extent evaluation and given the option of pretreatment breast MRI vs CEM. Many of those patients were subsequently elected for CEM. The volume of breast MRI has remained stable to slightly increased in the authors' institutions.

What is the imaging protocol for CEM? There are many ways to perform the imaging sequence for CEM. At the authors' institutions, following a delay of two minutes after contrast injection for intraductal neoplasms, four minutes following contrast injection for lobular neoplasms, and 2-minute contrast delay for all other indications, the affected MLO performed first, followed by MLO view of unaffected breast, affected CC, followed by unaffected CC view. Finally, in those CEM cases performed for preoperative disease extent evaluation in newly diagnosed neoplasms, an axillary spot view is performed of the affected axilla for enhanced axillary visualization.

At the authors' institutions, we have nearly 100% utilization of DBT for screening and diagnostic purposes. By the time of the CEM encounter, many patients have already had two separate DBT encounters. Therefore, the CEM is performed as a 2D examination coupled with the subtracted sequences.

Power injector for CEM? A power injector will significantly help to improve workflow. If you are interested in a power injector, please contact manufacturers of CT injectors. Guerbet, Sinomdt, and MEDRAD are examples of power injector manufacturers. It is the sole responsibility of the medical professional to determine which technique or protocol is appropriate. It is advised to parallel institutional guidelines for contrast. The websites below are for your reference.

- <https://www.radiologysolutions.bayer.com/products/injection-systems/medrad-stellant-flex-ct>
- <https://www.guerbet.com/products-solutions/>
- <https://sinomdt-global.com/product/contrast-media-injector/>

Do radiologists monitor CEM examinations? All these examinations are performed as diagnostic mammographic examinations and, as such, are only performed with a radiologist on-site for supervision and intervention. Please follow the laws, rules and regulations applicable to your facility. For the first 50 examinations, a diagnostic breast imaging radiologist should be monitoring these examinations in the actual imaging suite to monitor for contrast extravasation, monitor efficiency of protocol, and monitor the actual images and the imaging protocol. Once the clinical protocol had been optimized, in-suite monitoring was no longer necessary. All patients are counseled following CEM examination by the diagnostic radiologist, paralleling the diagnostic breast imaging workflow.

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