

Contrast Enhanced Digital Mammography

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Summary

This white paper will delineate the benefits of Contrast Enhanced Digital Mammography (CEDM) in comparison with Breast MRI in achieving final diagnostic resolution for multiple clinical indications. Specifically, this paper will describe our clinical experience with the Hologic I-View™ iodine-imaging software for the 3Dimensions® Mammography System. This paper describes clinical indications of CEDM, imaging protocol and implementation of CEDM, relative value-add to breast imaging workup in comparison with breast MRI, and will include example cases of CEDM. The primary benefits of CEDM are listed in Table 1.

Clinical Benefits of CEDM (Table 1)

Ease of scheduling - No preauthorization insurance process required for CEDM	CEDM fraction of cost (billed as diagnostic mammogram) of Breast MRI
Real-time results shared with patients in CEDM workflow as compared to breast MRI. Same day workup of additional lesions detected on CEDM	Higher patient satisfaction secondary to reduced scan time with CEDM (8-15 minutes) vs MRI (45-60 minutes)
Reported higher specificity of CEDM as compared to breast MRI, with comparable sensitivity	Ease of performing in patients with contraindications, relative or otherwise, to MRI
Higher patient satisfaction secondary to upright/seated positioning instead of prone positioning	Ease of utilization in claustrophobic patients. No premedication required for CEDM

Background

There are greater than 3.5 million breast cancer survivors in the United States, with an estimated 271,270 new invasive breast cancer cases in women in the US in 2019 and 42,260 breast cancer deaths¹. Breast cancer represents the 2nd most common cancer diagnosis in women. To date, screening mammography is the only breast imaging modality demonstrated to reduce mortality secondary to breast cancer in randomized, controlled clinical trials. The sensitivity of screening mammography ranges from 75-85%, often decreasing to 30-50% in patients with dense breasts or patients with BRCA genetic mutation^{28,5,9}. With dense breast inform legislation on both the state and federal level, there is progressive need for personalized, supplemental screening tests based on lifetime risk and breast density. Digital Breast Tomosynthesis, although routinely conferring increased invasive cancer detection rates and decreased recall

rates, exhibits relatively constrained supplemental cancer detection rate of 1.3/1000 in patients with dense breasts^{6,26}. Contrast Enhanced Digital Mammography (CEDM), although a relatively newer imaging modality, has demonstrated utility along the imaging spectrum from screening to diagnosis and will be discussed herein.

Contrast Enhanced Digital Mammography: Background

Contrast Enhanced Digital Mammography (CEDM) couples anatomic 3D or 2D Full Field Digital Mammographic (FFDM) imaging with functional imaging derived from contrast enhancement within lesions that either demonstrate neovascularity from tumoral angiogenesis and/or leakage of contrast media into interstitial tissue as a result of immature tumoral vessels. On conventional mammography, lesions of concern may be obscured secondary to overlapping fibroglandular tissue. This effect is exacerbated in patients with dense breasts. In CEDM, both low energy conventional 2D or 3D FFDM “low energy” images are obtained (below the K-edge of iodine of 33 KeV) and “high energy” images are obtained (above the K-edge of iodine). The images are subtracted from one another to provide subtracted post-contrast images, in which regions of concern are subsequently enhanced as parenchymal tissue is subtracted from the image. For interpretive purposes, the software provides the radiologist with the low energy FFDM images and subtracted post-contrast images. The morphology and enhancement of lesions are then described as foci, NME (nonmass enhancement) or masses similar to breast MRI descriptors, with final designation assigned Breast Imaging Reporting and Data System category 1 through 5.

CEDM simply requires a software upgrade, insertion of copper filter which can be retrofit to existing Dimensions systems, and a power injector to administer intravenous contrast. In this regard, CEDM involves minimal upfront capital expenditure to operationalize. As CEDM may be performed on the same unit utilized for screening FFDM (2D and 3D) and upright stereotactic guided core biopsy (both 2D and 3D), it is practical in regards to real estate constraints of continually expanding breast imaging centers.

Patient related costs of CEDM are limited to the cost of a diagnostic mammogram and the contrast utilized for the examination, oftentimes 20-25% the total cost of a breast MR and approximately 9% more than the standard diagnostic mammogram charge^{3,5}. Institutional burden related to CEDM is also reduced given that no insurance preauthorization is required, exam time significantly truncated as compared to breast MRI and initial hardware and software expenditures for CEDM a fraction of those for MR.

CEDM: Screening of Patients

There are multiple institutional processes followed prior to scheduling patients for CEDM. If patients are deemed “high-risk” (age >60, prior renal disease necessitating renal transplant, solitary kidney, renal tumor, active gout, autoimmune disease, collagen vascular diseases such as lupus, scleroderma, rheumatoid arthritis, hypertension, diabetes, multiple myeloma), laboratory value for calculated creatinine clearance is obtained within 4 weeks of the examination. Breast centers in outpatient settings may utilize single-use iSTAT cartridges, resulting the creatinine in less than 90 seconds. Paralleling institutional CT guidelines, patients do not receive contrast if creatinine is greater than 1.6 mg/dL.

Allergies, including contrast allergies, are reviewed prior to examination. Mild contrast allergies (mild hives, sneezing) may be premedicated utilizing standard institutional protocol of PO methylprednisolone 32 mg both 12 hours and 2 hours prior to examination. If the patient is diabetic, they are instructed to stop certain medications for 48 hours post IV contrast administration (ie. Metformin, Glucophage, Carbophage, Riomet, Fortamet, Gluzmeta, Obiment, Gluformin, Diaben, Diabex, Diaformin, Siofor, Metagamma). Patients who are pregnant or breastfeeding, those with prior history of anaphylaxis/ anaphylactoid reactions to iodinated contrast, patients with chronic renal disease or GFR<30 are excluded from CEDM examination. The risk of severe contrast reactions can be inferred from CT contrast reactions at 0.2 -0.4% as compared to the rate of adverse gadolinium reactions for breast MR at 0.001-0.01%⁵. However, recent studies have demonstrated neuronal deposition of gadolinium despite normal renal function; as utilization of MRI has increased more than twentyfold over the years with screening MRI assuming an increased role, neuronal deposition and gadolinium reactions assume increased importance⁵.

Figure 1a

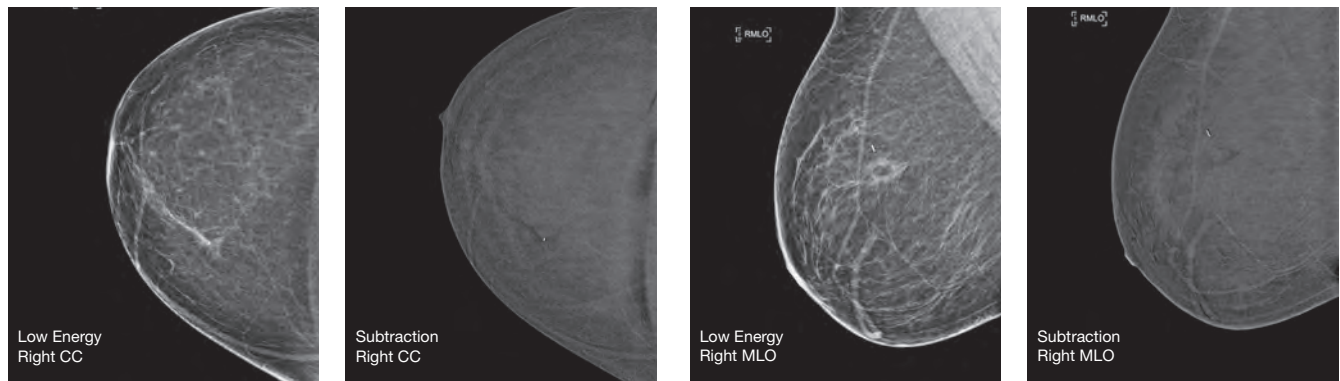


Figure 1a. Right breast images from patient presenting for annual asymptomatic high-risk surveillance status post right breast excisional biopsy for ADH. No pathologic findings are identified on 2D FFDM images. No suspicious enhancement is identified on post-contrast subtracted sequences.

Figure 1b

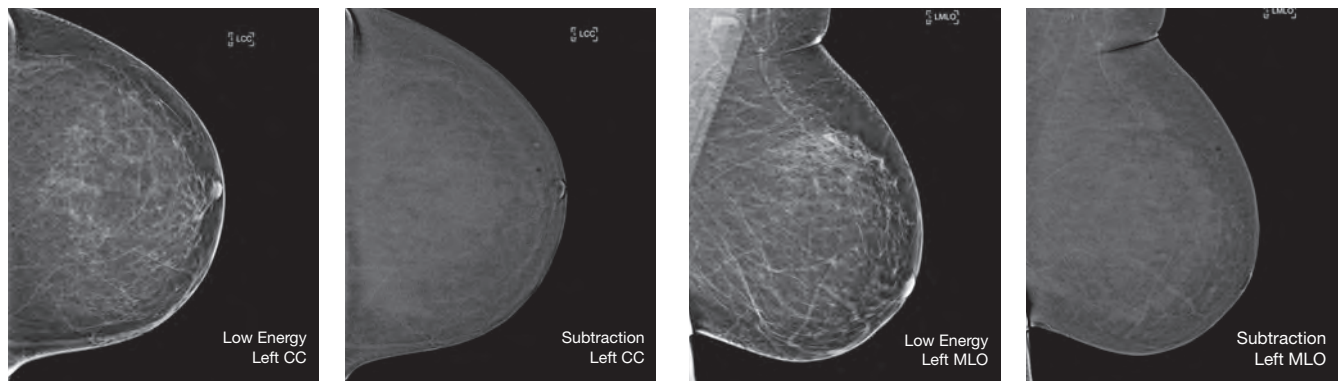


Figure 1b. Left breast images from patient presenting for annual asymptomatic high-risk surveillance status post right breast excisional biopsy for ADH. No pathologic findings are identified on 2D FFDM images. No suspicious enhancement is identified on post-contrast subtracted sequences.

CEDM: Clinical Indications

CEDM is commonly utilized for multiple imaging indications along the spectrum from screening to final diagnosis, including asymptomatic high-risk surveillance in those with genetic predisposition to breast cancer (ie. BRCA 1 or BRCA2) or prior high-risk benign biopsy (Figure 1 a/b), preoperative disease extent evaluation in those recently diagnosed with breast cancer for assessment of multifocality and multicentricity in the affected breast and preoperative assessment of the contralateral unaffected breast (Figures 2a-2d, Figures 3-5), response to neoadjuvant chemotherapy (Figures 6a-6d), assessment of indeterminate mammographic or sonographic abnormalities, and assessment of persisting clinical symptoms with negative initial imaging evaluation^{5,7}.

Literature unequivocally supports the superiority of CEDM in comparison to conventional mammography^{4,11,14,28}. Jochelson *et al.* reported index cancer detection of 96% for both CEDM and MR in their cohort, as compared to 81% index cancer detection for conventional

mammography, as well as superior specificity of CEDM as compared to MRI²⁸. Dromain *et al* reported CEDM sensitivity of 93% versus 78% for conventional mammography¹⁴. Another study demonstrated index cancer detection of 83% for conventional mammography, 100% for CEDM and 97% for breast MRI, with no significant difference identified between lesion size measurement on breast MRI and CEDM as compared to final histopathology¹¹. Cheung *et al* reported that utilization of CEDM as compared to conventional mammography increased sensitivity by 21.2% (71.5% to 92.7%), increased specificity by 16.1% (51.8% to 67.9%), and increased accuracy by 19.8% (65.9% to 85.8%)¹². Unquestionably, CEDM exceeds that of conventional mammography in sensitivity of cancer detection.

Data also supports non inferiority of CEDM as compared to breast MRI for index cancer detection, with reports of improved specificity as compared to breast MRI and improved negative predictive value^{2,3,28}. Breast MRI exhibits less than optimal specificity, with specificity inferior to that even of conventional mammography in

Figure 2a

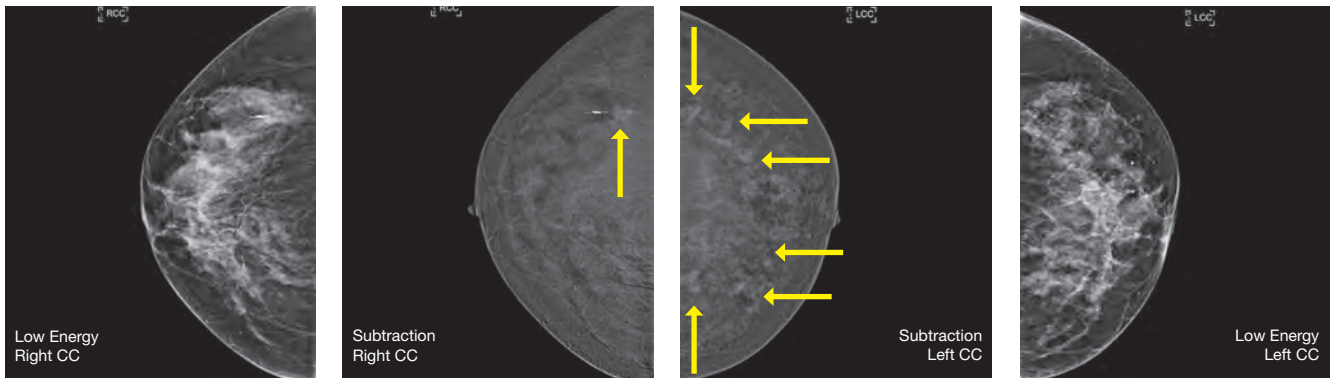


Figure 2a. Images from postmenopausal patient initially diagnosed with malignant concordant RIGHT Breast Invasive Lobular Carcinoma Grade 1 (as denoted by microclip). Aggressively enhancing subcentimeter mass is identified on post-contrast right breast subtracted views (right breast, yellow arrow). However, extensive, clumped, aggressive appearing non-mass enhancement is seen in the entire contra-lateral LEFT breast on post-contrast subtracted images (Left breast, multiple yellow arrows).

Figure 2b

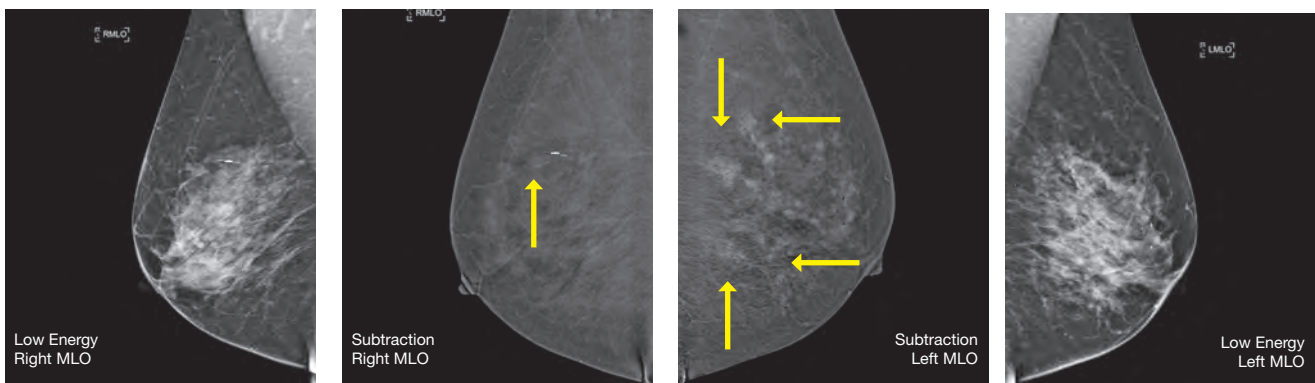


Figure 2b. Images from postmenopausal patient initially diagnosed with malignant concordant RIGHT Breast Invasive Lobular Carcinoma Grade 1 (as denoted by microclip). Aggressively enhancing subcentimeter mass is identified on post-contrast right breast subtracted views (right breast, yellow arrow). However, extensive, clumped, aggressive appearing non-mass enhancement is seen in the entire contra-lateral LEFT breast on post-contrast subtracted images (Left breast, multiple yellow arrows).

Figure 2c

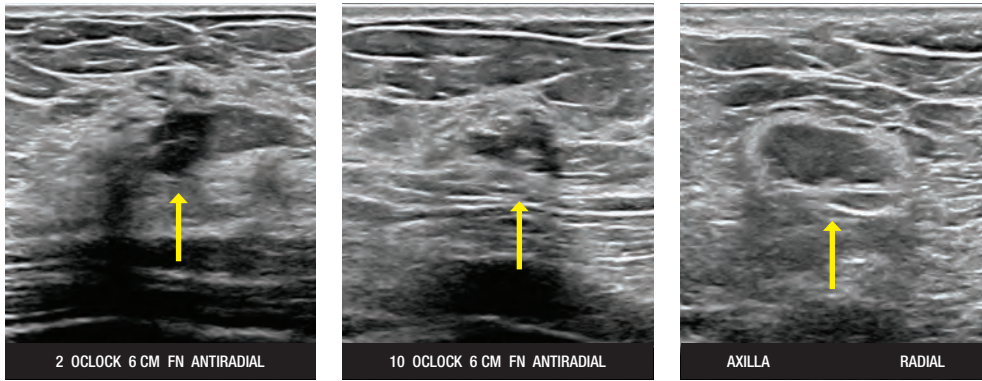


Figure 2c. Based on the extensive pathologic clumped non-mass enhancement within the contra-lateral LEFT breast on CEDM, left whole breast ultrasound and left axillary ultrasound was undertaken. At least four suspicious obscured, hypoechoic, solid breast masses were identified as well as concerning left axillary lymphadenopathy (all denoted by yellow arrows).

Figure 2d

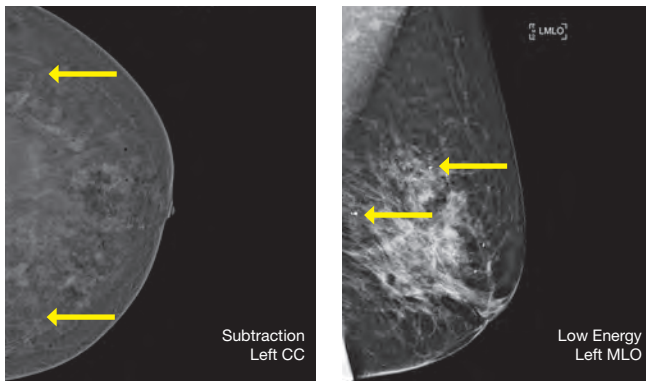


Figure 2d. Final pathology on LEFT breast biopsied breast lesions revealed malignant concordant Ductal Carcinoma In Situ, Grade 2, with benign concordant left axillary lymph node. Given post-procedure disease extent of 10.8 cm on Left CC view (yellow arrows), left breast mastectomy was performed. Review of final pathologic specimen reveals that the entire interrogated left breast was infiltrated by DCIS2, despite having had mammographically stable left breast mammogram for four years.

On the original affected Right side for malignant concordant ILC1, patient received lumpectomy with negative margins.

Figure 3

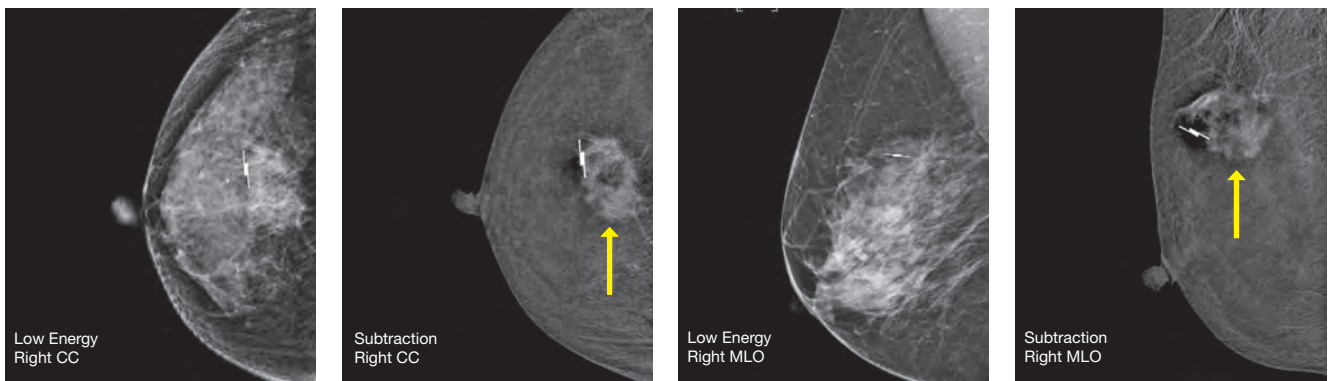


Figure 3. Images of postmenopausal patient diagnosed with malignant concordant Invasive Lobular Carcinoma Grade 2 Right breast, 12:00 axis, posterior depth. This lesion was difficult to discern on standard 2D images in this dense breast. Given histopathology of Invasive Lobular Carcinoma, 4 minute post-contrast delay is utilized. Post-contrast images demonstrate aggressively enhancing 2.8 cm mass corresponding to malignancy (as denoted by microclip alongst anterior margin).

Figure 4

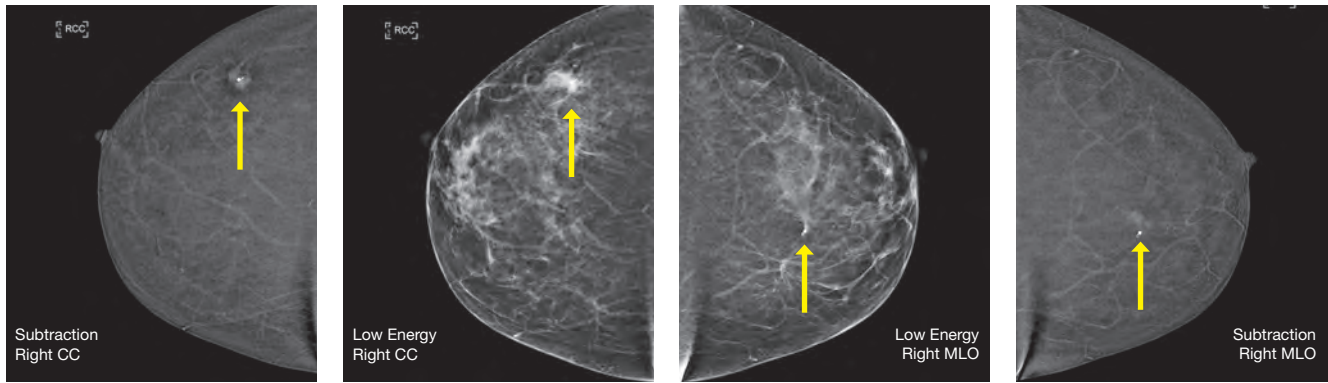


Figure 4. Images of postmenopausal patient diagnosed with synchronous bilateral Invasive Ductal Carcinoma Grade 1 (microclip, yellow arrows on all images). The bilateral neoplasms are difficult to discern on standard 2D images and demonstrate aggressive, focal enhancement on CEDM images. The bilateral masses were originally discerned on Digital Breast Tomosynthesis (DBT) images.

Figure 5

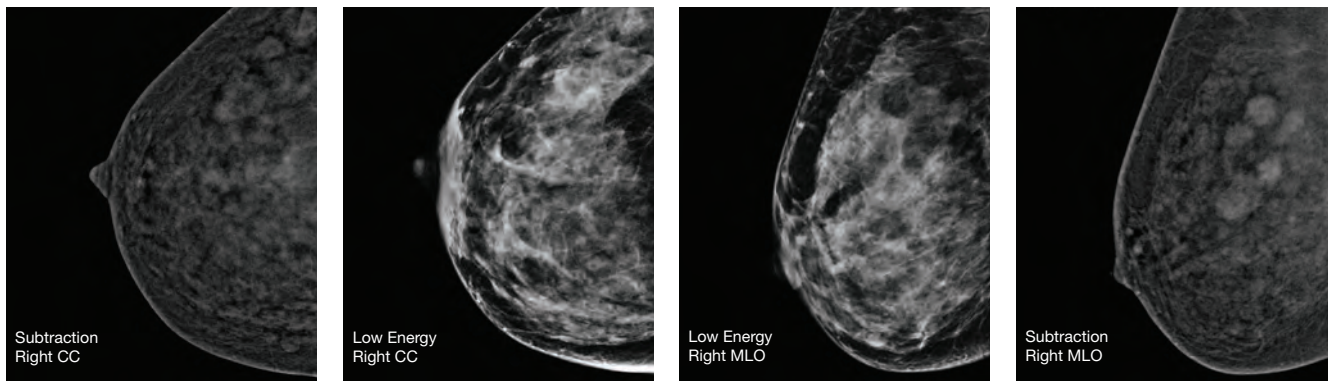


Figure 5. Patient presented with biopsy proven right axillary nodal metastases, IDC3, malignant, unknown primary right breast. CEDM was performed to identify the primary lesions. Four enhancing macro-lobulated lesions were identified. Biopsy undertaken of three of these for extent. All malignant concordant IDC3. Patient underwent mastectomy/nodal dissection.

multiple reports. A recent study of 52 women with 120 breast lesions demonstrated that CEDM had similar sensitivity to MRI (94 vs 99%), a significantly higher PPV than Breast MR Imaging (93% vs 60%), fewer false positives than MR imaging (5 vs 45 lesions) with high sensitivity for secondary cancer detection as compared to MRI (100% vs 91%, $P < 0.001$ for all results)². Another recent study reports index cancer detection rate of 98% in CEDM, with prospective change in surgical plan arising from CEDM as 20%, confirmed to be histopathologically appropriate upon final pathologic interrogation³. Fallenberg *et al.* reports mean index cancer sensitivities of 81% for conventional mammography, 95% for MRI, 94% for CEDM and 94% for CEDM coupled with conventional mammography, with sensitivities for all lesions (index and secondary) identified to be superior in MRI vs CEDM (76% vs 72%)⁴. However, it is important to note in this study that the specificity of CEDM exceeded that of MRI (94% versus 88%). Less than optimal breast MR specificity often leads to unnecessary downstream utilization of 2nd look ultrasound and image guided biopsy, often prolonging the time from index imaging encounter to final diagnostic resolution in patients.

Given the superiority of CEDM to conventional mammography, there are early reports of CEDM utilization for surveillance in those patients of intermediate risk (10-20%, dense breast tissue) and high-risk (lifetime risk greater than 20%), particularly given that the CEDM may be coupled to both 2D or 3D FFDM imaging during the contrast imaging encounter. Fallenberg *et al* demonstrates that CEDM alone and MRI exhibit the biggest benefit for dense breasts, with significant variance in ROC AUCs as compared to conventional mammography (AUC dense: 0.84, MRI 0.86, MG: 0.73; non-dense CEDM AUC: 0.85, MRI:0.84, MG: 0.79)⁴. CEDM will increasingly be utilized for dense breast screening and asymptomatic high-risk surveillance given increased adoption of dense breast inform legislation nationwide.

Limitations of CEDM include increased radiation exposure and limited anatomic visualization in specific cases (anatomically far posterior lesions, characterization of chest wall invasion, characterization of axillary, subpectoral and internal mammary chain lymphadenopathy). Radiation dose for CEDM is estimated at 1.25x the dose for conventional digital mammography,

Figure 6a

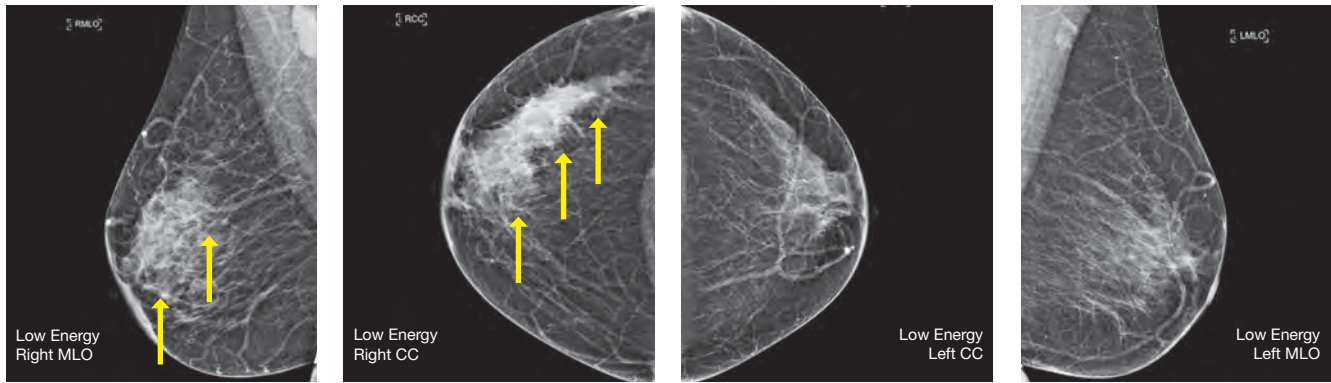


Figure 6a. Diagnostic images of patient with 10 cm palpable spiculated, high density mass upper outer quadrant right breast (denoted by yellow arrows). No mammographic evidence malignancy contralateral unaffected left breast.

Figure 6b

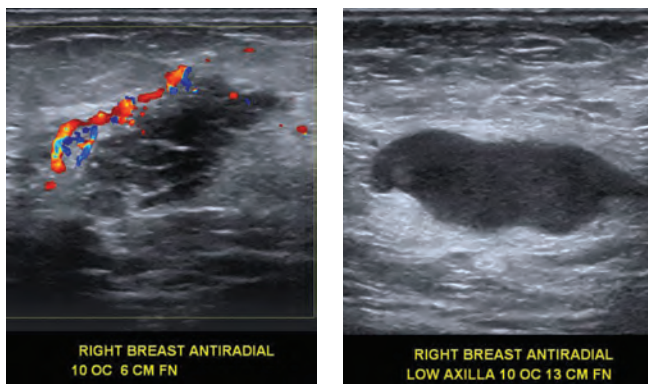


Figure 6b. Diagnostic ultrasound images demonstrated longitudinally extensive 10 cm hypoechoic breast mass at the 10:00 axis, 6 cm FN and a pathologic right axillary lymph node within low right axilla, 10:00 axis, 13 cm FN. The right breast lesion was biopsied and returned malignant concordant Invasive Ductal Carcinoma and the lymph node returned as positive for metastatic disease.

with the high energy projections assuming 20% of the dose of conventional mammography¹⁴. However, CEDM is a high quality alternative to those patients with contraindications or relative contraindications to breast MR imaging, including pacemakers, contraindicated metallic implantables and claustrophobia, with the ability to avoid premedication with sedatives in patients otherwise requiring these measures to tolerate breast MRI.

CEDM: Methods/Workflow

There are reports that state that CEDM may be performed irrespective of menstrual cycle timing in premenopausal patients and other reports that CEDM is optimally performed in the luteal phase of the menstrual cycle. At our institution, CEDM is not timed to the menstrual cycle. Once the patient is cleared to proceed with CEDM, a 22-gauge antecubital IV is placed. In a seated position, the patient receives weight based (1.5 mL/kg) iodinated contrast agent (Omnipaque™ 350) via power injector at a rate of 3 mL/sec followed by a 10-mL bolus of saline.

Following the administration of intravenous contrast, there are varying delays to the initiation of imaging based upon

the clinical indication. Contrast washout from suspicious lesions on CEDM does not parallel breast MRI, likely secondary to differences between iodinated contrast and gadolinium. Breast neoplasms tend to enhance gradually on CEDM, unlike rapid enhancement with washout kinetics as typically discerned on breast MRI¹¹. Therefore, contrast imaging may be undertaken at up to 10-12 minutes following contrast injection without degradation of image quality or contrast enhancement. For patients receiving preoperative disease extent evaluation for recently diagnosed neoplasm, delay to initiation of imaging is based upon histopathology of index neoplasm. For patients with lobular neoplasms, there is a four-minute delay following contrast injection until the first image is acquired. For patients with intraductal neoplasms and ductal morphology invasive neoplasms, a standard 2-minute delay is performed. Patients with other indications including asymptomatic high-risk surveillance, persistent clinical abnormality with negative initial imaging workup, indeterminate mammographic findings receive standard 2-minute delay to imaging following contrast administration.

The peripheral intravenous line is disconnected from the injector prior to initiation of imaging. Standard mammographic projections are acquired in the upright position at 90 second intervals in the following order: upright MLO (affected breast), contralateral MLO (unaffected breast), upright CC (affected breast), contralateral CC (unaffected breast), spot compression affected axilla for nodal evaluation. For each projection, low and high energy images are obtained automatically in rapid sequence, and subtraction images are generated. On the CEDM encounter date, there is the option to perform multiple variations of the examination: 2D low energy exposure and subtracted post-contrast images, 3D low energy exposure and subtracted post-contrast images, or “3-in-1” 2D, 3D and subtracted post-contrast exposures which facilitate ease of biopsy given morphologic detail of lesions conferred by combination of 2D and 3D examinations. At those sites with

Figure 6c

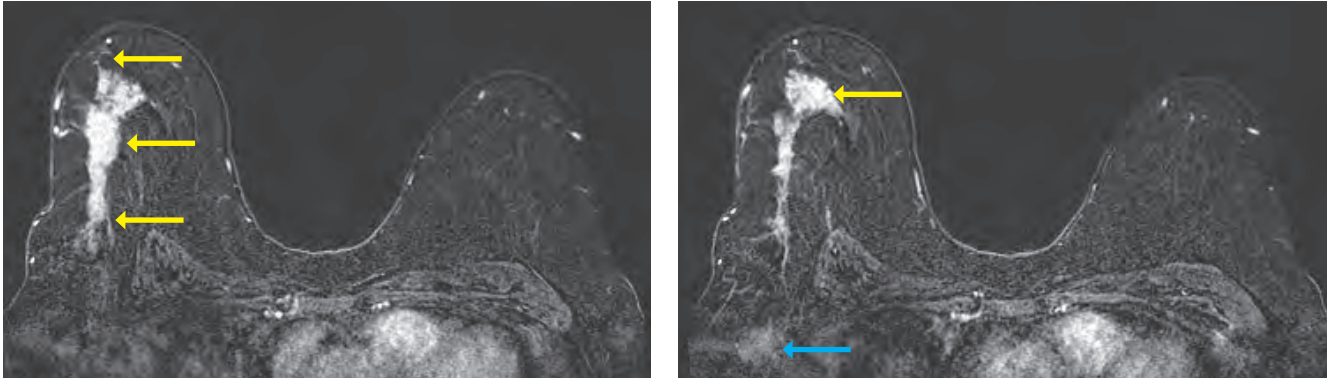


Figure 6c. Post-contrast axial T1 breast MRI images demonstrate longitudinally extensive Invasive Ductal Carcinoma 11 cm upper outer right breast extending to the nipple areolar complex (yellow arrows) with associated nodal metastatic disease (blue arrow).

Figure 6d

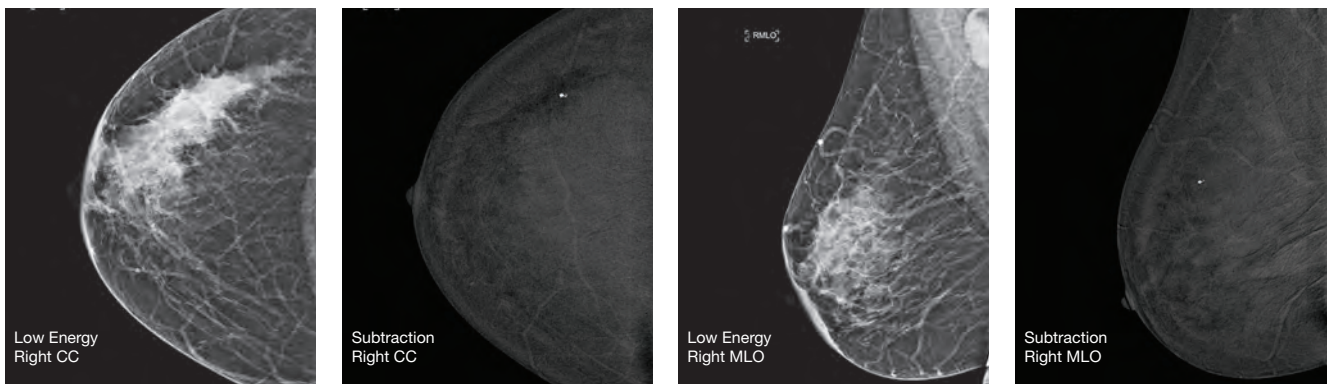


Figure 6d. Post-contrast CEDM images following neoadjuvant therapy in this patient demonstrates complete radiographic post-neoadjuvant treatment response. No residual pathologic enhancement within the upper outer quadrant is identified. There is interval resolution dermal thickening of the right breast.

predominant 3D screen utilization, CEDM consists mostly of low energy 2D exposures coupled to subtracted post-contrast images.

As per the diagnostic paradigm, images are interpreted in real time by the radiologist with additional regions of CEDM concern evaluated with immediate 2nd look ultrasound. Any additional regions of concern are biopsied during the same encounter. If the CEDM is undertaken for preoperative disease extent evaluation, the lesion is identified to be solitary on contrast imaging, and the patient elects for breast conservation, the patient then undergoes immediate localization in the department with a wireless localization device. In this manner, CEDM routinely and meaningfully truncates the time from index imaging encounter to final diagnostic resolution, leading to higher patient and referring provider satisfaction and lower patient/institutional costs.

Summary

Contrast Enhanced Digital Mammography represents a practical, highly sensitive, breast imaging modality coupling morphologic lesion depiction (especially inclusive of microcalcifications) with functional imaging

at a fraction of the cost of breast MRI. Although at this time there is no direct methodology to proceed directly from CEDM to biopsy, the majority of enhancing lesions are found during 2nd look ultrasound. In our practice, those lesions that are not discerned upon 2nd look ultrasound may often be triangulated for biopsy utilizing upright stereotactic biopsy incorporating mammographic landmarks discerned from index DBT screening or diagnostic encounter. CEDM is expeditiously interpreted by radiologists, with substantial inter-reader agreement independent of radiology reader experience level⁴ and ease of interpretation additionally by breast surgical colleagues. CEDM offers more efficient image acquisition and higher specificity than breast MRI imaging, which can routinely shorten time to final diagnostic resolution and often results in improved patient satisfaction with decreased unnecessary downstream resource utilization. Although current fee-for-service payment models favor breast MR utilization given higher reimbursement, it is believed CEDM utilization would conversely be favored in a value-based model.

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