



Contrast-enhanced mammography in breast cancer screening

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ABSTRACT

Contrast-enhanced mammography (CEM) is a promising vascular-based breast imaging technique with high diagnostic performance in detecting breast cancer. Dual-energy acquisition using low and high energy x-ray spectra following intravenous iodinated contrast injection provides both anatomic and functional information in the same examination. The low-energy images are equivalent to standard digital mammography and the post-processed recombined images depict enhancement analogous to contrast-enhanced breast magnetic resonance imaging (MRI). Thus, CEM has the potential to detect abnormal morphologic features as well as neovascularity associated with breast cancer. Since its emergence in 2011, CEM has consistently demonstrated superior performance compared with standard mammography and mammography plus ultrasound, particularly in women with dense breasts, with high sensitivity approaching that of MRI, supporting its use as a cost-effective diagnostic and screening tool. CEM has been primarily used in the diagnostic setting to evaluate patients with screening abnormalities or with symptomatic breasts, to perform preoperative staging of newly diagnosed breast cancer, and to evaluate response to neoadjuvant chemotherapy. More recently, CEM has been performed to screen women who have an intermediate to high lifetime risk of developing breast cancer. In addition to its high diagnostic performance, CEM is less expensive and more accessible than MRI and potentially better tolerated by patients. Minor drawbacks to CEM include a slightly increased radiation dose compared with standard mammography and a low risk for contrast allergy reaction. The aim of this study is to review the background, current literature, and future applications of CEM in breast cancer screening.

1. Introduction

Contrast-enhanced mammography (CEM) is a novel vascular-based breast imaging technique which, like breast magnetic resonance imaging (MRI), utilizes contrast media to depict neovascularity. Angiogenesis, which drives breast cancer, recruits blood vessels that are more permeable to contrast, resulting in enhancement on imaging, sometimes before a discrete mass can be detected. A CEM study uses iodinated contrast media and is comprised of paired enhanced and unenhanced images for each of the four standard mammographic views and depicts both anatomic and functional changes in the breast.

Mammography is a morphology-based modality limited by the masking effect of dense tissue, which can obscure an underlying cancer. Early studies in film screen mammography show that its sensitivity decreases as breast density increases, to as low as 62.9% in women with extremely dense breasts [1,2]. In comparison, MRI is the most sensitive

modality for detecting breast cancer, with a sensitivity of 100% when screening women at average and high risk for breast cancer [3,4]. Due to its high cost and limited availability, however, MRI is reserved for screening women at a greater than 20% lifetime risk for developing breast cancer.

Since its emergence a decade ago, CEM has consistently demonstrated superior performance to standard mammography, with a high sensitivity approaching that of MRI [5–8]. Potential advantages of CEM over MRI include lower costs, increased availability, and faster acquisition. In a 2017 study analyzing the potential cost savings of CEM, the cost of screening MRI in the United States was estimated to be four times that of CEM based on Medicare rates (\$775 for MRI vs \$196 for CEM) [9]. CEM can be a one-stop shop exam since both the anatomic and physiologic exams can be performed in a single appointment. Furthermore, CEM can be performed in patients who have contraindications to MRI. Thus, CEM may be a safe and affordable vascular-based alternative

Abbreviations: CEM, contrast-enhanced mammography; MRI, magnetic resonance imaging; US, ultrasound; BIRADS, Breast Imaging Reporting Data System; BPE, background parenchymal enhancement; CT, computed tomography; DBT, digital breast tomosynthesis; CET, contrast-enhanced tomosynthesis; AI, artificial intelligence.

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Table 1
CEM System Characteristics.

Vendor	Anode/Filter		Filter thickness (mm)		Tube voltage range (kV)	
	LE	HE	LE	HE	LE	HE
GE Healthcare Senographe Essential and Senobright	Mo/ Mo; Mo/Rh; Rh/Rh	Mo/AI plus Cu; Rh/AI plus Cu	0.03; 0.25	0.3; 0.3	26–31	45–49
GE Healthcare Pristina and Senobright HD	Mo/ Mo; Rh/Ag	Mo/ Cu; Rh/Cu	0.25 0.03; Ag	26–34	49	
Hologic Selenia Dimensions and 3Dimensions I-View	W/Rh; W/Ag	W/Cu	0.05	0.3	25–33	45–49
Siemens Healthineers Mammomat Revelation Titatitanium CEM	W/Rh	W/Ti	0.05	1.0	28–34	49

Ag = silver; Al = aluminum; Cu = copper; LE = low energy imaging; HE = high energy imaging; Mo = molybdenum; Rh = rhodium; Ti = titanium; W = tungsten.

to MRI.

This review will encompass the fundamentals of CEM technique, interpretation, and clinical performance in breast cancer screening.

2. Imaging technique

CEM employs a dual energy technique that capitalizes on the difference in X-ray attenuation between breast tissue and iodine when low and high energy spectra are used. CEM examinations are comprised of paired low-energy and high-energy images obtained from utilizing X-ray energies below and above iodine's k-edge (33 keV), respectively. From these paired exposures acquired in the same compression, a recombined image is generated using a post-processing algorithm that isolates the

iodine concentration only.

Commercially available CEM systems are currently offered by four vendors (Table 1). Existing mammography units may be upgraded with CEM systems at a lower cost [9].

Before imaging, an intravenous line is placed by either a nurse or technologist. A non-ionic low-osmolar iodinated contrast agent is then injected with the breast out of compression to facilitate greatest blood flow. Iodine concentration varies from 300 mg/mL to 370 mg/mL. Although standardized imaging parameters for CEM have not yet been published, it is generally accepted to administer a volume of 1.5 mL/kg body weight (maximum of 150 mL) at a rate of 2–3 mL/sec preferably using a power injector. Fig. 1 illustrates a CEM imaging acquisition sequence. Around 2–3 min after contrast is injected, paired low-energy and high-energy images are acquired with the breast in compression for the four standard craniocaudal and mediolateral oblique views. Additional views may be performed if they can be obtained within 10 min of injection. Recombined images for each acquired view are generated using post-processing.

CEM does not provide dynamic contrast enhancement kinetics. However, a few recent studies that included a delayed acquisition obtained around 6–8 min after contrast injection demonstrated an improvement in CEM specificity from 83% to 89% among women undergoing CEM to assess response to neoadjuvant chemotherapy [10] and from 80% to 92% among women with dense breasts and suspicious mass lesions [11].

3. Interpretation

Since a CEM examination includes low-energy and recombined images, a finding may be seen on the low-energy images only, on the recombined images only, or on both. The low-energy images are analogous to a standard digital mammogram and interpreted in an identical fashion using the mammogram lexicon outlined in the 2013 American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) atlas [12]. The recombined images are interpreted to identify any abnormal enhancement that may or may not have a correlate on the low-energy images. A recently published supplement to the 2013 ACR BI-

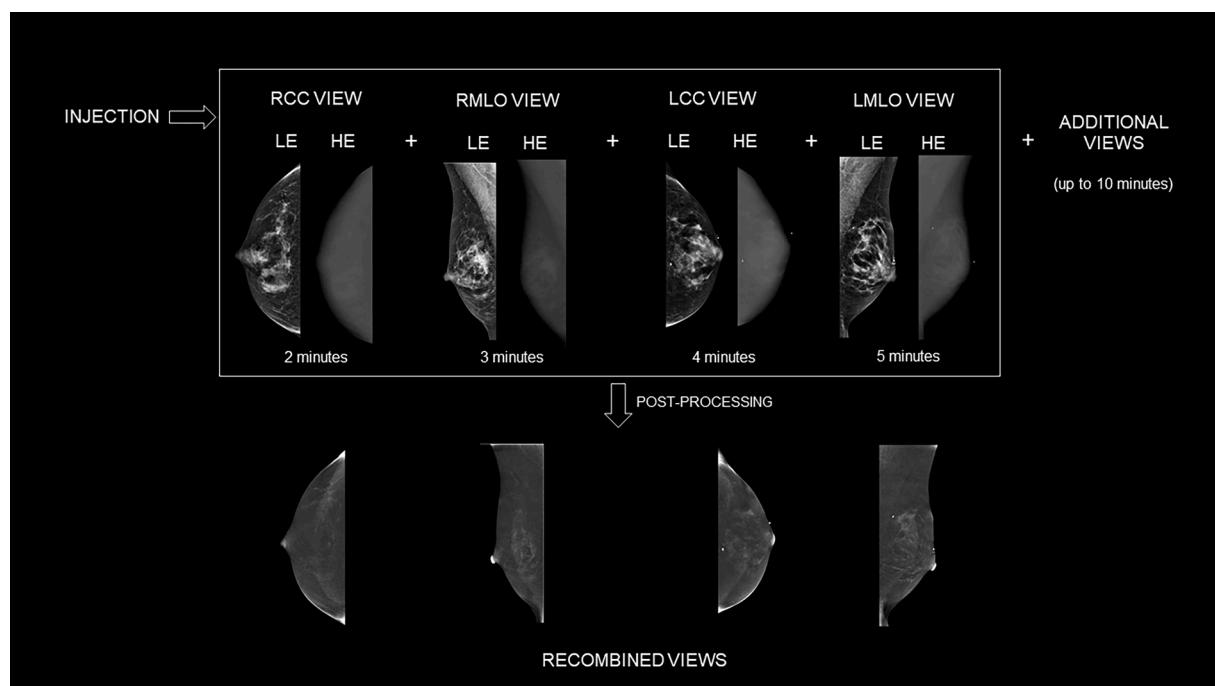


Fig. 1. Example of a CEM imaging acquisition. Paired low-energy (LE) and high-energy (HE) exposures are sequentially obtained for each of the four standard mammographic views after contrast injection. Post-processing generates the recombined views.

Table 2

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon for contrast-enhanced mammography.

Findings on Recombined Images Only		
Mass	Shape	Oval Round Irregular
Non-mass Enhancement	Margins	Circumscribed Not circumscribed Irregular Spiculated
		Homogeneous Heterogeneous Rim Enhancement
	Distribution	Diffuse Multiple regions Regional Focal Linear Segmental
		Homogeneous Heterogeneous
		Homogeneous Heterogeneous Clumped
Enhancing Asymmetry	Internal Enhancement	Homogeneous Heterogeneous Clumped
		Homogeneous Heterogeneous Clumped
		Homogeneous Heterogeneous Clumped
Lesion Conspicuity	Low Moderate High	Homogeneous Heterogeneous Clumped
		Homogeneous Heterogeneous Clumped
		Homogeneous Heterogeneous Clumped
Findings on Both Low Energy and Recombined Images		
Lesion conspicuity	Morphology*	Homogeneous
	Internal Enhancement	Heterogeneous
	Extent of Enhancement	Rim Enhancement
		Mammographic lesion partially enhances
		Mammography lesion completely enhances
		Enhancement extends beyond mammographic lesion
		No enhancement of the mammographic lesion but enhancement in the adjacent tissue
		No enhancement of the mammographic lesion but enhancement in the adjacent tissue
Lesion conspicuity	Low Moderate High	No enhancement of the mammographic lesion but enhancement in the adjacent tissue
		No enhancement of the mammographic lesion but enhancement in the adjacent tissue
		No enhancement of the mammographic lesion but enhancement in the adjacent tissue

*Refer to BI-RADS mammography lexicon.

RADS atlas specific for CEM findings is summarized in Table 2 [13]. Two new BI-RADS terms introduced in the CEM lexicon include *enhancing asymmetry* and *lesion conspicuity*. An enhancing asymmetry is a one-view finding seen either on the recombined images only or on both the recombined and low-energy images. Lesion conspicuity refers to the degree of lesion enhancement relative to background parenchymal enhancement (BPE). This CEM BI-RADS lexicon will ensure reporting standardization and consistency that is essential for the implementation of CEM as a screening tool on a larger scale.

As with MRI, categories for both breast density and BPE should also be reported when interpreting a CEM study. BPE describes the physiologic enhancement of normal breast tissue after intravenous contrast administration. Sogani et al demonstrated a substantial intra-reader agreement for BPE assessment on CEM and MRI [14]. Of note, BPE has been shown to significantly increase with higher breast density and younger patient age, although no association has been shown between BPE and the last menstrual period in pre-menopausal women, suggesting that CEM need not be timed with the menstrual cycle [15-17]. In another study, Sorin et al found that BPE on CEM was significantly predictive of breast cancer (odds ratio (OR) of 2.24), particularly in the screening population (OR of 6.27).

Since CEM provides anatomic and vascular information in the same examination, the final assessment should be based on the interpretation

of both low-energy and recombined images. A recent meta-analysis inclusive of 60 studies found that the pooled sensitivity and specificity of CEM was significantly improved when interpreting both low-energy and recombined images compared with recombined images alone [18]. Any suspicious finding seen only on the low-energy and/or recombined images warrants further evaluation with imaging or biopsy. Like MRI, malignant calcifications may not enhance, and therefore the lack of enhancement should not preclude biopsy of suspicious appearing calcifications on the low-energy images. In two retrospective studies, a total of 146 women recalled from screening for calcifications underwent CEM prior to biopsy. Five (9.8%) of 51 cancers detected in both studies did not enhance (2/22 and 3/27), all of which were ductal carcinoma in situ [19,20]. A later retrospective study of 147 women with screen-detected calcifications found that 11/65 cancers (17%) demonstrated no enhancement on the recombined images, with no difference between invasive and *in situ* disease [21]. Compared with the low-energy images only, the addition of the recombined views did not significantly alter surgical management for the 65 patients who had cancer.

Conversely, any abnormal enhancement on the recombined images without a low-energy correlate may be further evaluated with ultrasound (US) and possibly MRI for additional characterization and identification of a biopsy target. In a retrospective study of 153 enhancing lesions on CEM, the likelihood of malignancy was greater among those with a correlate on US, which occurred in 47/153 (31%) enhancing lesions [22]. A more recent study similarly found that a CEM lesion was 4.87 times and 10.5 times more likely to be malignant if a correlate was identified on US and MRI, respectively [23]. If a biopsy is performed using US or MRI guidance, it is imperative to confirm the biopsy marker correlates with the location of the original enhancement on the post-procedure mammogram (Fig. 2).

Until recently, there was not a mechanism for biopsy using CEM guidance. Thus, MRI has been performed to further evaluate enhancing CEM lesions not identified on the low-energy images or on US (Fig. 3). If the MRI shows no suspicious finding, a short-term follow-up CEM may not be necessary given the high negative predictive value of MRI. In a recent meta-analysis of 7 studies, MRI demonstrated a higher maximum pretest probability for ruling out cancer compared with CEM (33% vs 14%) [24]. Additionally, preliminary data from our institution found that of 81 CEM lesions that had a subsequent negative MRI, only one (1.2%) cancer was detected at the 6-month interval, suggesting that a 1-year follow-up CEM may be sufficient [25].

CEM-guided biopsy capability recently became commercially available and has the potential to streamline the workflow by obviating the need to perform MRI when the low-energy images and US are negative. In 2020, the United States Food and Drug Administration (FDA) approved a GE Healthcare biopsy system (Pristina Serena Bright) which enables standard upright stereotactic and tomosynthesis-guided biopsies as well as CEM-guided biopsies. Technical success has already been reported with a total biopsy time under 10 min [26]. Alternatively, biopsy may also be accomplished using Hologic's latest software (I-View) to localize an enhancing target within a combined 2D CEM and tomosynthesis acquisition and to perform a tomosynthesis-guided biopsy.

4. Performance in screening

Women who are at increased risk for developing breast cancer benefit from supplemental screening with either US or MRI. MRI is the most sensitive screening tool but is currently only recommended for women who have a high (greater than 20%) lifetime risk of developing breast cancer due to its high cost and limited availability. Women who have an intermediate (15–20%) lifetime risk include those with a family history of breast cancer, personal history of breast cancer, prior biopsy-proven high-risk lesion, and dense breasts. These women have the option to undergo supplemental screening with US that may detect additional mammographically occult cancers. Increasing data suggest that screening CEM in women with elevated breast cancer risk further

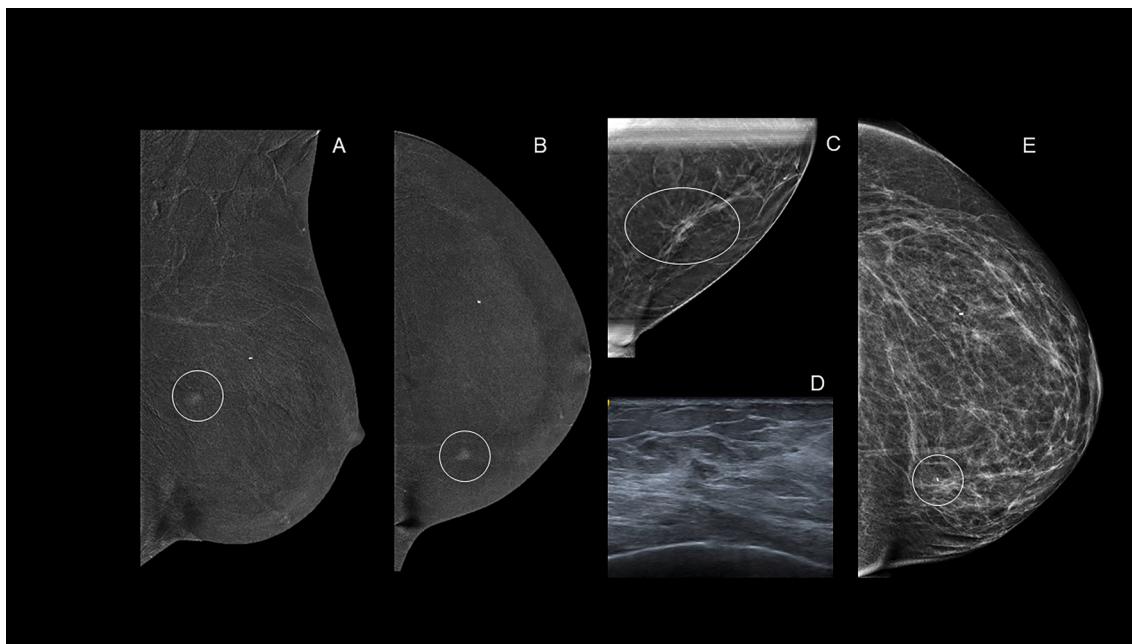


Fig. 2. 62-year-old with history of right breast cancer and recent bilateral breast reduction surgery. Recombined left mediolateral oblique (A) and craniocaudal (B) views show an enhancing focal asymmetry at the 9:00 axis in the region of the reduction scar on spot compression tomosynthesis (C). Targeted ultrasound (D) shows a corresponding 0.6 cm irregular mass in the 9:00 axis. Ultrasound-guided biopsy yielded benign fat necrosis and foreign body giant cell reaction consistent with prior procedure. Biopsy marker corresponds to site of enhancement on the post-biopsy mammogram (E).

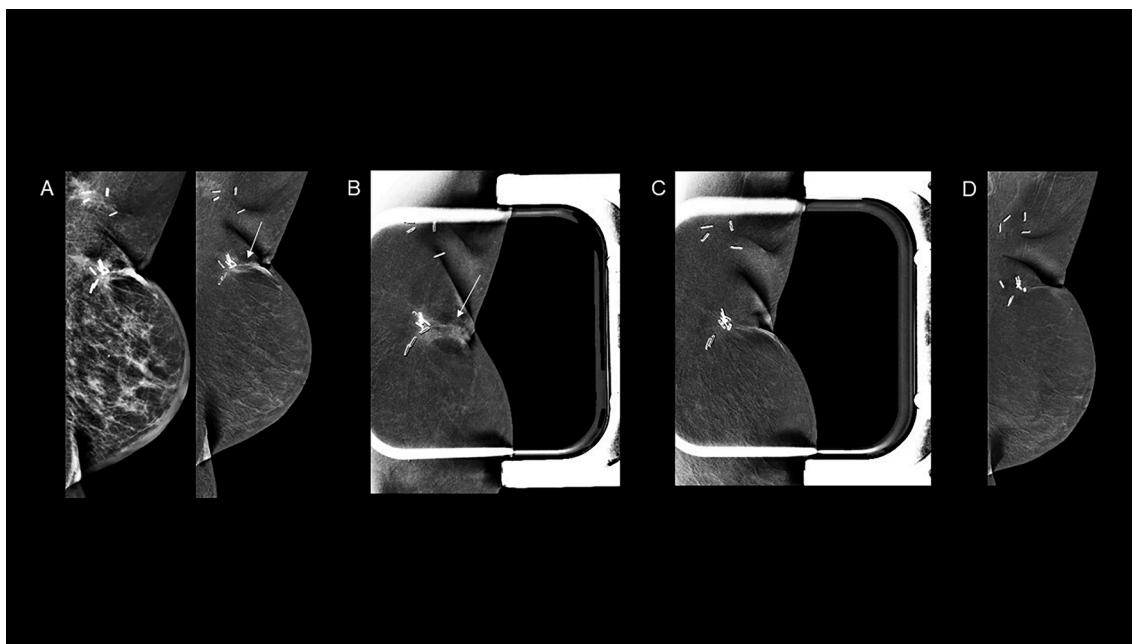


Fig. 3. 64-year-old with history of recent left lumpectomy and radiation for breast cancer. The first post-treatment contrast-enhanced mammography shows an enhancing asymmetry at the lumpectomy site extending to the skin on low-energy and recombined mediolateral oblique views (A), including spot compression recombined view (B). As no corresponding abnormality was identified on targeted ultrasound, enhancement was probably benign post-treatment change. Enhancement resolved on follow-up contrast-enhanced mammography performed at six months (C) and at one year (D), confirming the benign etiology.

improves the sensitivity and specificity of detecting breast cancer compared to digital mammography alone and to mammography plus US, with a diagnostic performance approaching that of MRI (Table 3, Figs. 4–6) [23,27–31].

The first prospective pilot study comparing CEM to MRI as a screening tool included 307 women with intermediate and high lifetime risk [31]. All patients underwent CEM and MRI and were followed for 2 years. Three cancers were detected during the first round of screening, of

which two invasive cancers were seen on both CEM and MRI, one ductal carcinoma in situ was seen on MRI only, and none were seen on low-energy mammogram. Specificity was comparable between CEM and MRI (94.7% and 94.1%, respectively) and no palpable interval cancers were detected.

In a retrospective study of 953 women who underwent CEM and concurrent screening US, CEM had a higher sensitivity and specificity of 97.3% and 40.0% respectively, compared to a sensitivity of 91.9% and

Table 3

Overview of Screening CEM Studies.

Author	Jochelson et al	Klang et al	Sorin et al	Sung et al	Hogan et al	Amir et al
Year	2013	2018	2018	2019	2021	2021
Country	US	Israel	Israel	US	US	US
Study design	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
No. of patients	307	953	611	858	132	157
No. of exams	307	953	611	858	306	157
Imaging	LE and Recombined	LE and Recombined	LE and Recombined	LE and Recombined	LE and Recombined	LE and Recombined
Contrast concentration and dose	Omnipaque 350; 1.5 ml/kg	Iopamiro 370; 1.5 ml/kg	Iopamiro 370; 1.5 ml/kg	Omnipaque 350; 1.5 ml/kg	Omnipaque 350; 1.5 ml/kg	Omnipaque 350; 1.5 ml/kg
Vendor unit(s)	GE Healthcare SenoBright	GE Healthcare Senographe Essential	GE Healthcare Senographe Essential	GE Healthcare Senographe Essential	GE Healthcare Senographe Essential	GE Healthcare Senographe Essential, Hologic 3Dimensions
Reference standard	Pathology and follow-up	Pathology and follow-up	Pathology and follow-up	Pathology and follow-up	Pathology and follow-up	Pathology and follow-up
True positive	2	36	19	14	6	24
True negative	287	20	449	789	264	1503
False positive	17	30	141	53	36	133
False negative	1	1	2	2	0	5

LE = low energy.

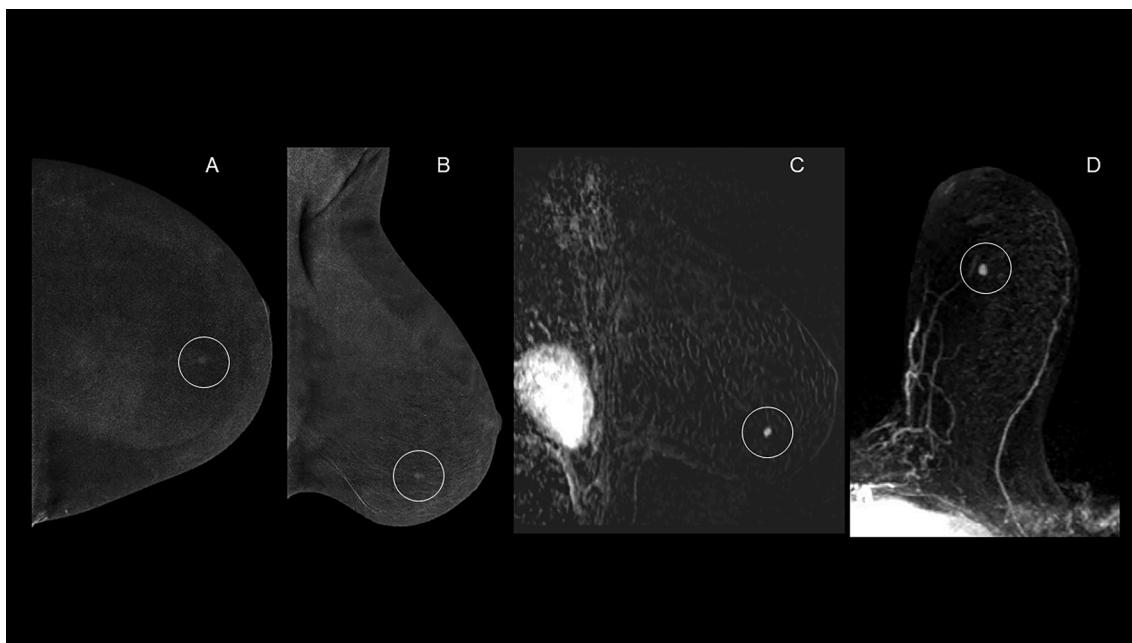


Fig. 4. 64-year-old with family history of breast cancer. Recombined left craniocaudal (A) and mediolateral oblique (B) views show a 0.5 cm enhancing mass in the lower inner quadrant. No corresponding abnormality was identified on low-energy images or targeted ultrasound. Magnetic resonance imaging sagittal (C) and maximum intensity projection (D) image show a corresponding 0.5 cm enhancing mass in the 7:00 axis. Magnetic resonance imaging-guided biopsy yielded invasive ductal carcinoma.

specificity of 8.0% with US [27]. None of the 37 cancers detected were benign-appearing on CEM whereas 3 cancers were benign-appearing on US. The authors concluded that routine screening US following a normal CEM study may only result in unnecessary biopsies.

When used as a screening tool among intermediate-risk women with dense breasts, CEM was significantly more sensitive than standard digital mammography in a retrospective study of 611 women (90.5% vs 52.4%, $p = 0.0008$). However, CEM was less specific (76.1% vs 90.5%, $p = 0.001$) [28]. The incremental cancer detection rate for CEM was 13.1 per 1000 women. Adjunct US further reduced specificity by detecting 73 false positives and no additional cancer, again suggesting that US may not be necessary after a negative CEM examination. Similar results were reported in a subsequent larger retrospective study that included 904 women with higher-than-average risk for breast cancer, 78% of whom had dense breasts, who underwent a baseline screening

CEM examination [29]. CEM improved the sensitivity of standard 2D mammography (87.5% vs 50.0%, $p = 0.03$) with an incremental cancer detection rate of 6.6 per 1000 women. The overall cancer detection rate was 15.5 per 1000 women, which is similar to MRI. Follow-up data for these patients are currently pending.

Among a small cohort of 132 women who had elevated risk due to a personal history of lobular neoplasia, screening CEM demonstrated a sensitivity of 100% in detecting 6 cancers that were all occult on standard digital mammography [30]. Specificity was 88%.

A recent retrospective study of 157 patients with intermediate or high breast cancer risk who underwent baseline screening CEM found 26 cancers, of which 12 (46%) were evident on both the low-energy and recombined images, 13 (50%) were contrast-only findings, and one (4%) was evident on the low-energy images only [23]. Lesions seen on both low-energy and recombined images were significantly more likely to be

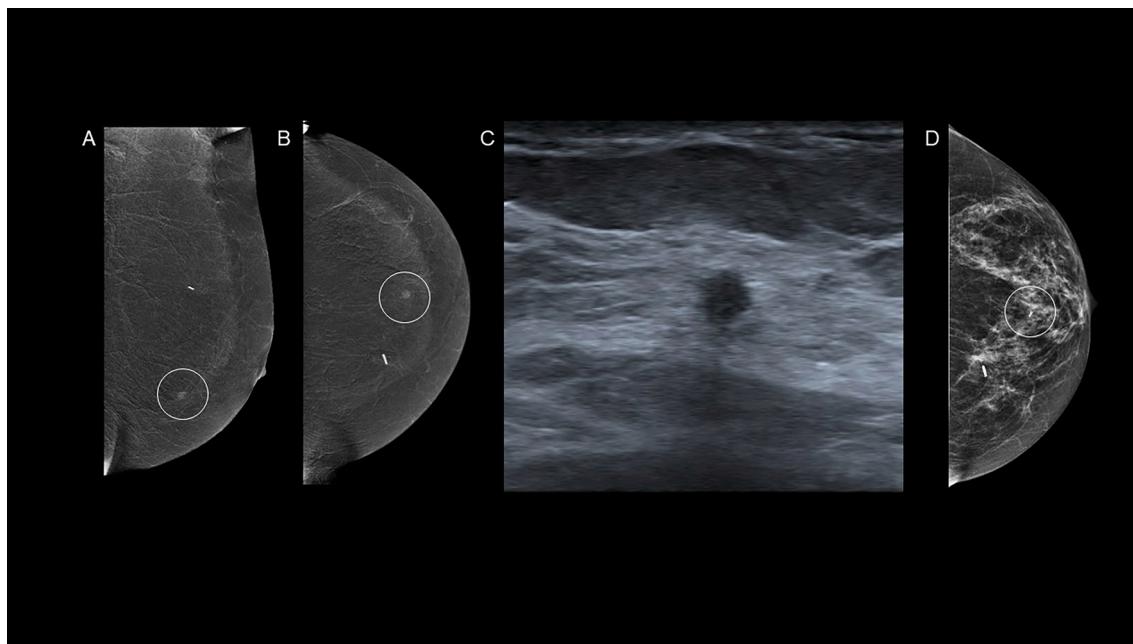


Fig. 5. 57-year-old with history of left breast lobular carcinoma in situ. Recombined left mediolateral oblique (A) and craniocaudal (B) views show a 0.4 cm enhancing mass in the lower central breast. Targeted ultrasound (C) shows a corresponding 0.4 cm irregular mass in the 6:00 axis. Ultrasound-guided biopsy yielded invasive lobular carcinoma. Biopsy marker corresponds to site of enhancement on the post-biopsy mammogram (D).

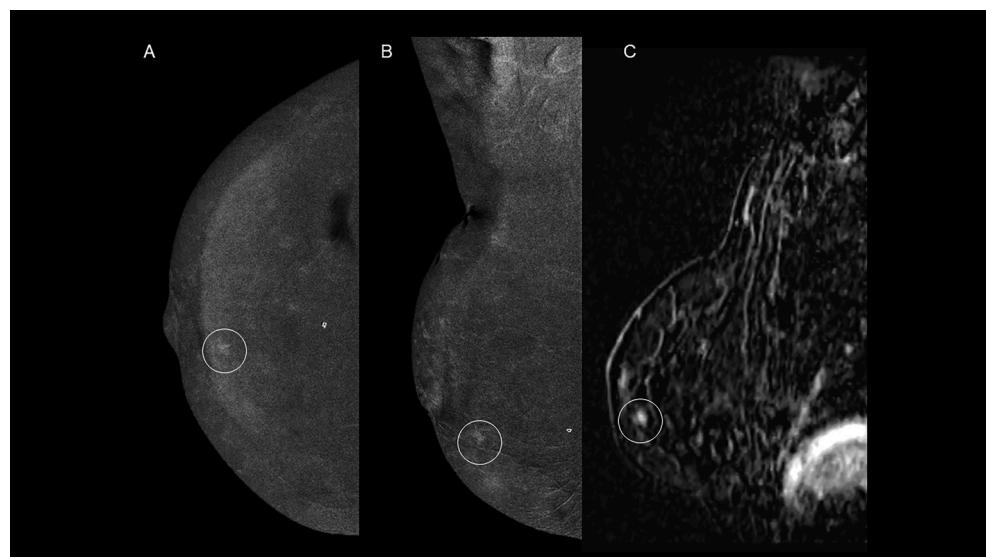


Fig. 6. 63-year-old with history of left breast cancer. Recombined right craniocaudal (A) and right mediolateral oblique (B) views show a 0.5 cm enhancing mass lower central breast. No corresponding abnormality was identified on low-energy images or targeted ultrasound. Magnetic resonance imaging sagittal image (C) shows a corresponding 0.5 cm enhancing mass in right 6:00 axis. Magnetic resonance imaging-guided biopsy yielded invasive mammary carcinoma.

malignant if the finding was an asymmetry or calcifications ($p < 0.001$). Four of 5 (80%) malignant calcifications had corresponding enhancement while 24/25 (96%) benign calcifications had no enhancement.

In addition to being potentially more cost-effective and accessible than MRI, CEM has other benefits in the screening setting. Women with elevated risk for breast cancer who cannot undergo MRI due to claustrophobia, metallic implants, or gadolinium-based contrast allergies can safely undergo CEM. If given the choice, most patients prefer having CEM examination instead of MRI [32,33]. In a study of 49 patients who underwent both CEM and MRI, Hobbs et al. found that patients significantly preferred the overall experience of CEM ($p < 0.001$) due to faster acquisition, less noise, and greater comfort, and reported significantly

lower rates of anxiety ($p = 0.009$) [33].

5. Limitations

The main drawbacks of CEM compared to standard mammography are workflow issues and the potential for contrast reactions. Since contrast is being administered, patients require intravenous placement prior to the CEM examination, which may lead to prolonged appointment times. A physician must also be on site to evaluate and treat any potential adverse contrast reaction. Allergic reactions to low-osmolar iodinated contrast are infrequent, with rates from 0.2 to 0.7% reported in contrast-enhanced computed tomography (CT) studies [34].

Severe allergic reactions are rare, occurring in 0.04% of CT studies. In a meta-analysis of CEM studies, the pooled reaction rate was similar at 0.8% [35]. Preliminary data at our institution found that of 2419 patients who underwent CEM from 2014 to 2021, 23 patients (0.95%) had a documented reaction (0.48% of 5235 examinations), of which none were severe and most were mild [36]. Although a recent meta-analysis showed that higher iodine concentration significantly increased sensitivity of CEM ($P = 0.04$), specificity was reduced ($P < 0.001$), and would likely lead to more adverse effects [24]. Renal insufficiency is relatively uncommon in the healthy population but must be considered in patients who may be at increased risk.

Since at least eight exposures are acquired for a four-view exam, CEM has a slightly increased radiation dose compared with standard digital mammography, although the dose remains below the regulatory dose limit according to the Mammography Quality Standards Act guidelines. The estimated dose increase varies between 20% and 80%, as it depends on breast thickness, breast density, and vendor [37]. This slightly increased radiation dose may be clinically significant among young high-risk patients such as BRCA1 gene mutation carriers in whom studies have shown enhanced chromosomal radiosensitivity and higher breast cancer risk from radiation exposure [38–40].

Compared with MRI, CEM has a more limited field of view of the posterior breast, chest wall, and axilla. Furthermore, CEM lacks three-dimensional and kinetic information provided by dynamic contrast-enhanced MRI.

6. Future directions

While data are promising for screening CEM, most studies to date have been retrospective, single-institution investigations with a small number of patients. Further prospective and multicenter trials are needed to compare the performance of screening CEM with conventional imaging on a larger scale. The American College of Radiology Contrast-Enhanced Mammographic Screening Trial (CMIST) is a prospective multisite study that will compare screening outcomes between digital breast tomosynthesis (DBT) and CEM in intermediate risk women with dense breasts. All patients will undergo two screening rounds with DBT and CEM with 1 year follow-up. Approximately 2023 participants are anticipated, and enrollment is expected to begin at the end of 2022.

Contrast-enhanced tomosynthesis (CET) is another emerging technique that has shown promising results in feasibility studies utilizing temporal subtraction, dual energy, and photon-counting techniques [41–43]. In 2015, a reader study performed of 185 patients with BI-RADS 4 and 5 lesions concluded that CEM and CET were comparable to MRI, and all contrast studies (CEM, CET, MRI) were superior to non-contrast studies (standard mammography, DBT) without showing a significant advantage of CET over CEM [44].

Artificial intelligence (AI) applied to CEM has led to the development of computer-aided detection systems designed to characterize breast masses as benign or malignant using machine learning algorithms and radiomic analysis of morphology and textural features [45,46]. These AI models have also showed promise in determining histoprogностic factors of cancers from CEM, such as invasive disease, hormone receptor status, and tumor grade [47,48].

7. Conclusion

Growing literature supports the use of CEM as a screening tool that is more sensitive than standard digital mammography in detecting breast cancer due to its depiction of both anatomic and vascular tumoral changes. CEM is a safe procedure with a low frequency of reported allergic reactions which are predominantly mild in severity. Although more data are needed to compare the diagnostic performance of CEM to MRI in the screening setting, CEM is a promising technique that may be an affordable alternative to MRI where MRI is not readily available. Larger prospective multisite clinical trials are ongoing to confirm the

future role of CEM in breast cancer screening.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] P.A. Carney, D.L. Miglioretti, B.C. Yankaskas, K. Kerlikowske, R. Rosenberg, C. M. Rutter, B.M. Geller, L.A. Abraham, S.H. Taplin, M. Dignan, G. Cutter, R. Ballard-Barbash, Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography, *Ann. Intern. Med.* 138 (3) (2003) 168–175.
- [2] E.D. Pisano, C. Gatsonis, E. Hendrick, M. Yaffe, J.K. Baum, S. Acharyya, E.F. Conant, L.L. Fajardo, L. Bassett, C. D'Orsi, R. Jong, M. Rebner, G. Digital Mammographic Imaging Screening Trial Investigators, Diagnostic performance of digital versus film mammography for breast-cancer screening, *N Engl. J. Med.* 353 (17) (2005) 1773–1783.
- [3] E. Warner, H. Messersmith, P. Causier, A. Eisen, R. Shumak, D. Plewes, Systematic review: using magnetic resonance imaging to screen women at high risk for breast cancer, *Ann. Intern. Med.* 148 (9) (2008) 671–679.
- [4] C.K. Kuhl, K. Strobel, H. Bieling, C. Leutner, H.H. Schild, S. Schrading, Supplemental Breast MR Imaging Screening of Women with Average Risk of Breast Cancer, *Radiology* 283 (2) (2017) 361–370.
- [5] Q. Wang, K. Li, L. Wang, J. Zhang, Z. Zhou, Y. Feng, Preclinical study of diagnostic performances of contrast-enhanced spectral mammography versus MRI for breast diseases in China, *Springerplus* 5 (1) (2016) 763.
- [6] E.M. Fallenberg, F.F. Schmitzberger, H. Amer, B. Ingold-Heppner, C. Balleyguier, F. Diekmann, F. Engelken, R.M. Mann, D.M. Renz, U. Bick, B. Hamm, C. Dromain, Contrast-enhanced spectral mammography vs. mammography and MRI - clinical performance in a multi-reader evaluation, *Eur. Radiol.* 27 (7) (2017) 2752–2764.
- [7] E. Luczynska, S. Heinze-Paluchowska, E. Hendrick, S. Dyczek, J. Rys, K. Herman, P. Blecharz, J. Jakubowicz, Comparison between breast MRI and contrast-enhanced spectral mammography, *Med. Sci. Monit.* 21 (2015) 1358–1367.
- [8] W. Xiang, H. Rao, L. Zhou, A meta-analysis of contrast-enhanced spectral mammography versus MRI in the diagnosis of breast cancer, *Thorac. Cancer* 11 (6) (2020) 1423–1432.
- [9] B.K. Patel, R.J. Gray, B.A. Pockaj, Potential Cost Savings of Contrast-Enhanced Digital Mammography, *AJR. Am. J. Roentgenol.* 208 (6) (2017) W231–W237.
- [10] D. Bernardi, G. Vatteroni, A. Acquaviva, M. Valentini, V. Sabatino, I. Bolengo, M. Pellegrini, C. Fanto, R.M. Trimboi, Contrast-enhanced mammography versus MRI in the evaluation of neoadjuvant therapy response in patients with breast cancer: a prospective study, *AJR. Am. J. Roentgenol.* (2022).
- [11] A. Serikova Ainakulova, Z. Zholdybay Zholdybay, D. Radikovna Kaidarovna, N. Igorevna Inozemtseva, M. Orazaykyzy Gabdullina, Z. Kabdualevna Zhakenova, A. Sergeevna Panina, D. Kairatovich Toleshbayev, J. Mukhtarovich Amankulov, Contrast-enhanced spectral mammography without and with a delayed image for diagnosing malignancy among mass lesions in dense breast, *Contemp. Oncol. (Pozn.)* 25 (1) (2021) 17–22.
- [12] E.A. Sickles, C.J. D'Orsi, L.W. Bassett, et al., ACR BI-RADS Mammography. ACR BI-RADS Atlas: Breast Imaging Reporting and Data System, American College of Radiology, Reston, VA, 2013.
- [13] C. Lee, J. Phillips, J. Sung, et al., ACR BI-RADS CEM Supplement, American College of Radiology, Reston, VA, 2022.
- [14] J. Sogani, E.A. Morris, J.B. Kaplan, D. D'Alessio, D. Goldman, C.S. Moskowitz, M. S. Jochelson, Comparison of Background Parenchymal Enhancement at Contrast-enhanced Spectral Mammography and Breast MR Imaging, *Radiology* 282 (1) (2017) 63–73.
- [15] V. Sorin, Y. Yagil, A. Salmon, M. Gotlieb, R. Faermann, O. Halshtok-Neiman, M. Sklair-Levy, Background Parenchymal Enhancement at Contrast-Enhanced Spectral Mammography (CESM) as a Breast Cancer Risk Factor, *Academic. Radiol.* 27 (9) (2020) 1234–1240.
- [16] Z. Karimi, J. Phillips, P. Slanetz, P. Lotfi, V. Dialani, J. Karimova, T. Mehta, Factors Associated With Background Parenchymal Enhancement on Contrast-Enhanced Mammography, *AJR. Am. J. Roentgenol.* 216 (2) (2021) 340–348.
- [17] S.L. Savaridas, D.B. Taylor, D. Gunawardana, M. Phillips, Could parenchymal enhancement on contrast-enhanced spectral mammography (CESM) represent a new breast cancer risk factor? Correlation with known radiology risk factors, *Clin. Radiol.* 72(12) (2017) 1085 e1–1085 e9.
- [18] A. Cozzi, V. Magni, M. Zanardo, S. Schiaffino, F. Sardanelli, Contrast-enhanced mammography: a systematic review and meta-analysis of diagnostic performance, *Radiology* 302 (3) (2022) 568–581.
- [19] Y.C. Cheung, H.P. Tsai, Y.F. Lo, S.H. Ueng, P.C. Huang, S.C. Chen, Clinical utility of dual-energy contrast-enhanced spectral mammography for breast microcalcifications without associated mass: a preliminary analysis, *Eur. Radiol.* 26 (4) (2016) 1082–1089.
- [20] Y.-C. Cheung, Y.-H. Juan, Y.-C. Lin, Y.-F. Lo, H.-P. Tsai, S.-H. Ueng, S.-C. Chen, P.-Y. Chu, Dual-energy contrast-enhanced spectral mammography: enhancement analysis on BI-RADS 4 non-mass microcalcifications in screened women, *PLoS. One* 11 (9) (2016) e0162740.

- [21] I.P. Houben, S. Vanwetswinkel, V. Kalia, T. Thywissen, P.J. Nelemans, E.M. Heuts, M.L. Smidt, A. Meyer-Baese, J.E. Wildberger, M. Lobbes, Contrast-enhanced spectral mammography in the evaluation of breast suspicious calcifications: diagnostic accuracy and impact on surgical management, *Acta radiologica* (Stockholm, Sweden: 1987) 60 (9) (2019) 1110–1117.
- [22] K. Coffey, J. Sung, C. Comstock, G. Askin, M.S. Jochelson, E.A. Morris, D. D'Alessio, Utility of targeted ultrasound to predict malignancy among lesions detected on contrast-enhanced digital mammography, *AJR Am. J. Roentgenol.* 217 (3) (2021) 595–604.
- [23] T. Amir, M.P. Hogan, S. Jacobs, V. Seviliemedu, J. Sung, M.S. Jochelson, Comparison of false-positive versus true-positive findings on contrast-enhanced digital mammography, *AJR. American. journal. of. roentgenology* 218 (5) (2022) 797–808.
- [24] N. Pötsch, G. Vatteroni, P. Clauer, T.H. Helbich, P.A.T. Baltzer, Contrast-enhanced Mammography versus Contrast-enhanced Breast MRI: A Systematic Review and Meta-Analysis, *Radiology* 0(0) 212530.
- [25] K. Coffey, L. Dixon, M. Jochelson, J. Sung, Short Interval Follow-up of Contrast Enhanced Mammography Lesions after Negative Breast MRI, Society of Breast Imaging Annual Meeting, Savannah, GA, 2022.
- [26] J. James, Contrast-enhanced spectral mammography (CESM)-guided breast biopsy as an alternative to MRI-guided biopsy, *Br. J. Radiol* 95 (1132) (2022) 20211287.
- [27] E. Klang, A. Krosser, M.M. Amitai, V. Sorin, O. Halshtok Neiman, A. Shalmon, M. Gotlieb, M. Sklair-Levy, Utility of routine use of breast ultrasound following contrast-enhanced spectral mammography, *Clinical. Radiology* 73 (10) (2018) 908.e11–908.e16.
- [28] V. Sorin, Y. Yagil, A. Yosepovich, A. Shalmon, M. Gotlieb, O.H. Neiman, M. Sklair-Levy, Contrast-Enhanced Spectral Mammography in Women With Intermediate Breast Cancer Risk and Dense Breasts, *AJR. Am. J. Roentgenol.* 211 (5) (2018) W267–W274.
- [29] J.S. Sung, L. Lebron, D. Keating, D. D'Alessio, C.E. Comstock, C.H. Lee, M.C. Pike, M. Ayhan, C.S. Moskowitz, E.A. Morris, M.S. Jochelson, Performance of dual-energy contrast-enhanced digital mammography for screening women at increased risk of breast cancer, *Radiology* 293 (1) (2019) 81–88.
- [30] M.P. Hogan, T. Amir, V. Seviliemedu, J. Sung, E.A. Morris, M.S. Jochelson, Contrast-enhanced digital mammography screening for intermediate-risk women with a history of Lobular Neoplasia, *AJR Am. J. roentgenol.* 216 (6) (2021) 1486–1491.
- [31] M.S. Jochelson, K. Pinker, D.D. Dershaw, M. Hughes, G.F. Gibbons, K. Rahbar, M. E. Robson, D.A. Mangino, D. Goldman, C.S. Moskowitz, E.A. Morris, J.S. Sung, Comparison of screening CEDM and MRI for women at increased risk for breast cancer: A pilot study, *Eur. J. Radiol.* 97 (2017) 37–43.
- [32] J. Phillips, M.M. Miller, T.S. Mehta, V. Fein-Zachary, A. Nathanson, W. Hori, R. Monahan-Earley, P.J. Slanetz, Contrast-enhanced spectral mammography (CESM) versus MRI in the high-risk screening setting: patient preferences and attitudes, *Clinical. imaging* 42 (2017) 193–197.
- [33] M.M. Hobbs, D.B. Taylor, S. Buzynski, R.E. Peake, Contrast-enhanced spectral mammography (CESM) and contrast enhanced MRI (CEMRI): Patient preferences and tolerance, *J. Med. Imaging. Radiat. Oncol.* 59 (3) (2015) 300–305.
- [34] R. Kodzwa, ACR Manual on Contrast Media: 2018 Updates, *Radiol. Technol.* 91 (1) (2019) 97–100.
- [35] M. Zanardo, A. Cozzi, R.M. Trimboli, O. Labaj, C.B. Monti, S. Schiaffino, L. A. Carbonaro, F. Sardanelli, Technique, protocols and adverse reactions for contrast-enhanced spectral mammography (CESM): a systematic review, *Insights. into. imaging* 10 (1) (2019) 76.
- [36] K. Coffey, L. Dixon, T. Amir, J. Sung, M. Jochelson, Retrospective Analysis of Adverse Reactions to Contrast Enhanced Mammography, Society of Breast Imaging Annual Meeting, Savannah, GA, 2022.
- [37] J.R. James, W. Pavlicek, J.A. Hanson, T.F. Boltz, B.K. Patel, Breast radiation dose with CESM compared with 2D FFDM and 3D tomosynthesis mammography, *Am. J. Roentgenol.* 208 (2) (2017) 362–372.
- [38] M.C. Jansen-van der Weide, M.J. Greuter, L. Jansen, J.C. Oosterwijk, R. M. Pijnappel, G.H. de Bock, Exposure to low-dose radiation and the risk of breast cancer among women with a familial or genetic predisposition: a meta-analysis, *Eur. Radiol.* 20 (11) (2010) 2547–2556.
- [39] A. Berrington de Gonzalez, C.D. Berg, K. Visvanathan, M. Robson, Estimated risk of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers, *J. Natl. Cancer. Inst.* 101 (3) (2009) 205–209.
- [40] B. Ernestos, P. Nikolaos, G. Koulis, R. Eleni, B. Konstantinos, G. Alexandra, K. Michael, Increased chromosomal radiosensitivity in women carrying BRCA1/BRCA2 mutations assessed with the G2 assay, *Int. J. Radiat. Oncol. Biol. Phys.* 76 (4) (2010) 1199–1205.
- [41] S.C. Chen, A.K. Carton, M. Albert, E.F. Conant, M.D. Schnall, A.D. Maidment, Initial clinical experience with contrast-enhanced digital breast tomosynthesis, *Acad. Radiol.* 14 (2) (2007) 229–238.
- [42] A.K. Carton, S.C. Gavenonis, J.A. Curryan, E.F. Conant, M.D. Schnall, A. D. Maidment, Dual-energy contrast-enhanced digital breast tomosynthesis—a feasibility study, *Br. J. Radiol.* 83 (988) (2010) 344–350.
- [43] F.F. Schmitzberger, E.M. Fallenberg, R. Lawaczeck, M. Hemmendorff, E. Moa, M. Danielsson, U. Bick, S. Diekmann, A. Pollinger, F.J. Engelken, F. Diekmann, Development of low-dose photon-counting contrast-enhanced tomosynthesis with spectral imaging, *Radiology* 259 (2) (2011) 558–564.
- [44] C.P. Chou, J.M. Lewin, C.L. Chiang, B.H. Hung, T.L. Yang, J.S. Huang, J.B. Liao, H. B. Pan, Clinical evaluation of contrast-enhanced digital mammography and contrast enhanced tomosynthesis—Comparison to contrast-enhanced breast MRI, *Eur. J. Radiol.* 84 (12) (2015) 2501–2508.
- [45] B.K. Patel, S. Ranjbar, T. Wu, B.A. Pockaj, J. Li, N. Zhang, M. Lobbes, B. Zhang, J. R. Mitchell, Computer-aided diagnosis of contrast-enhanced spectral mammography: A feasibility study, *Eur. J. Radiol.* 98 (2018) 207–213.
- [46] R. Massafra, S. Bove, V. Lorusso, A. Biafora, M.C. Comes, V. Didonna, S. Diotaiautti, A. Fanizzi, A. Nardone, A. Nolasco, C.M. Ressa, P. Tamborra, A. Terenzio, D. La Forgia, Radiomic Feature Reduction Approach to Predict Breast Cancer by Contrast-Enhanced Spectral Mammography Images, *Diagnostics* (Basel, Switzerland) 11(4) (2021).
- [47] M.A. Marino, K. Pinker, D. Leithner, J. Sung, D. Avendano, E.A. Morris, M. Jochelson, Contrast-Enhanced Mammography and Radiomics Analysis for Noninvasive Breast Cancer Characterization: Initial Results, *Mol. Imaging Biol.* 22 (3) (2020) 780–787.
- [48] C. Dominique, F. Callonnec, A. Berghian, D. Defta, P. Vera, R. Modzelewski, P. Decazes, Deep learning analysis of contrast-enhanced spectral mammography to determine histoprognostic factors of malignant breast tumours, *Eur. Radiol.* (2022).