Contrast-enhanced spectral mammography: successful initial clinical institute experience

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Abstract

Background: Contrast-enhanced spectral mammography (CESM) is a relatively newly developed advanced application with modification of digital mammography by the use of a contrast agent, but still has little known efficacy among Egyptian patients. Our aim in this study is to share our initial experience in evaluating symptomatic patients with different ACR breast parenchyma especially in dense breast parenchyma as it is always challenging in diagnosis.

Results: CESM in this study gave a sensitivity of 92% and specificity of 85% in characterization of benign and malignant lesions. For postoperative cases, sensitivity was 85% and specificity was 60%. For chemotherapy cases, sensitivity was 85% and specificity was 76%. Contrast uptake was noted in 68% of masses. Cavitary benign lesions were noted in 22.1% of cases. Multifocal and multicentric carcinomas were detected in 39.7% of pathologically proved malignant masses. Statistical analysis revealed sensitivity, specificity, and accuracy of 82.9%, 76.5%, and 81.0% for conventional mammograms as compared to 92.7%, 82.4%, and 89.7% for CESM respectively.

Conclusion: CESM is a promising technique that can enhance the specificity of conventional mammograms. It is an easy, simple, and rapid contrast-based procedure, especially for characterization of lesions in dense breast parenchyma. It performs proper diagnosis for high-risk patients and follow-up response to different lines of management.

Keywords: Dense breast, Breast cancer, Contrast-enhanced spectral mammography (CESM)

Background

Full-field digital mammography (FFDM) is a rapid procedure with high-quality images and higher contrast resolution with improved dynamic range, and rapid processing of data and images as compared to screen-film mammography [1, 2]. Its diagnostic accuracy has been shown to be at least equivalent to film-screen mammography [1, 3]. However, some limitations still exist, mainly in dense breast tissue, fibrocystic disease, and during follow-up after breast-conserving/adjuvant therapy. A new procedure has been developed using contrast media for the detection of angiogenesis by tracing contrast agent uptake and washout in suspicious lesions. Contrast-enhanced spectral mammography (CESM) is one of them [4, 5]. CESM provides data about the degree of vascularization of the lesion in addition to morphological information. According to recent studies, CESM is considered superior

to conventional mammography in breast cancer detection with less false negatives especially in dense breasts [6]. A clinical study by Dromain et al. [7] showed that digital mammography plus CESM had higher sensitivity in the detection of suspicious lesions in dense breasts.

Contrast-enhanced breast MRI is currently considered the most sensitive imaging technique for the detection of breast carcinoma and hence, has many indications in diagnosis, treatment and follow-up of breast cancer cases [8]. However, MRI has limited specificity, widely available, expensive, and not suitable for claustrophobic patients.

In August 2017, our Pristina Senograhe FFDM and tomosynthesis machine was installed in the outpatient clinic in our institutional hospitals.

In April 2018, we started using CESM.

From August 2018 to date, we did 123 cases with over 80 cases of biopsy-proven malignancy. In most of the

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cases, US-guided biopsy was taken on the same day and place where the study took place.

The aim of this work was to share our experience during the first year of using the CESM technique and discuss and illustrate its potential clinical applications.

Methods

The machine was first installed in August 2017 at our breast radiology outpatient clinic, which serves about 1000 patients per year, with mostly diagnostic imaging services. The machine installed was a GE Senographe Pristina mammography system, the first to be installed in Egypt and the whole of Africa. Our practice during the first year of the use of dual-energy contrast-enhanced spectral mammography spanning from April 2018 to March 2019 was assessed.

Patients

This study was approved by the local institutional review board. Objectives and methodology were clearly explained to the patients, written informed consent was provided to all participating patients.

Our challenge, like most practices, is providing value-based care. We began using CESM in April 2018. Since then, we have used CESM in a variety of clinical applications that would have been evaluated with MRI. From April 2018 to March 2019, we enrolled 123 patients aged 27–72 years (mean 44.95 years).

The study population included women referred from the clinic for screening and diagnostic mammogram; examinations were performed for staging of proven breast cancer in 23 patients (18.7%), clarify the nature of indeterminate lesions in 63 patients (55.7%) that included evaluation of focal asymmetry in 24 patients (19.5%), parenchymal distortion in 13 patients (10.6%), and mass in dense breasts in 9 patients (7.3%), and 17 patients (13.8%) had a suspicious lesion on mammography with no ultrasound correlate. The examination was also done for postoperative follow-up in 12 patients (9.8%). Patients were sent from the oncology department for follow-up of neoadjuvant chemotherapy (NAC) and 25 (20.3%) patients were included in our study.

Patients underwent diagnostic conventional mammograms, ultrasound, and then followed by CESM. A detailed history of the patient with a review of her previous studies is done. A review of the serum creatinine as well as the history of allergy or previous reaction is noted.

Exclusion criteria included pregnancy, breast implants, renal insufficiency, and history of allergic reaction to iodinated contrast agents.

Digital mammography

All patients performed digital mammography (including craniocaudal (CC) and mediolateral oblique (MLO) views) and were evaluated retrospectively to CESM interpretation.

Contrast-enhanced digital mammography examination

The procedure was done in two steps: contrast administration and imaging. A catheter was placed into the antecubital vein of the contralateral arm to the affected breast. A dose of 300 mg I/ml of non-ionic iodinated contrast agent, iopromide (Ultravist), was administrated. It was delivered intravenously as a single shot to the patient at a dose of 1.5-mmol/Kg body weight. CESM imaging proceeds at 2 min after the initiation of the contrast agent administration, the "normal" breast was compressed first in a CC and MLO views and a dual-energy of low- and high-energy images was acquired. The procedure was followed by CC and MLO views for the concerned breast to increase the likelihood of contrast uptake. After the CESM examination, patients were observed for 30 min for the possibility of any allergic reaction to iodinated contrast agents. The first low-energy (26–30 kVp) image is a standard 2D mammogram and the second high energy (45–49 kVp) image is a high-kV mammogram. Then, the two images are combined to enhance areas of contrast uptake. The total duration of the examination was 7 min.

Senographe Pristina is FDA-approved mammography and delivers CESM at the same low dose as 2D FFDM.

Image analysis

Two experienced, independent radiologists with 10 years' interpretation experience in breast imaging have evaluated all lesions. Digital mammography images were evaluated using BI-RADS (ACR) lexicon assessment.

The radiologists reviewed the processed images in the workstation. A dual-energy CESM examination provides two images of each view, one at low energy which is similar to conventional mammography with a high contrast-to-noise ratio of micro calcifications and the other one acquired at high energy giving a high contrast-to-noise ratio of iodine. Analysis of low-energy images was completed regarding the following: breast density, location, and type of each finding (asymmetry, mass, density, calcification, asymmetry, architectural distortions, intramammary lymph nodes, and scars) according to the 2013 BI-RADS (ACR) lexicon [9].

After that, the subtracted images are reviewed using the reading criteria based on lesion morphology description as well as the degree of contrast enhancement intensity in comparison to background enhancement. Lesions on CESM were described using the same MRI description according to the 2013 MRI BI-RADS lexicon as there is no CESM specific lexicon [10]. The degree of background parenchymal enhancement was reported, and lesions were classified into non-enhancing, mild, moderate, and

markedly enhanced. Non-enhancing and mildly enhancing lesions usually reflect benign morphology and subjected to follow-up. Moderately and markedly enhancing lesions showing malignant morphology and were subjected to immediate core biopsy.

Patients with suspicious findings underwent ultrasound-guided or stereotactic-guided core biopsy. US-guided biopsy was obtained on the same day and place where the study took place. Written patient consent was obtained for all biopsy procedures.

Cystic lesions were subjected to ultrasound-guided fine-needle aspiration and cytological assessment.

Histopathological results were collected from surgery for patients who were under follow-up of neoadjuvant chemotherapy and also for patients who underwent examination for the staging of proven breast cancer.

Patients without suspicious findings were subjected to follow-up every 6 months to assure the absence of cancer.

Statistical analysis

MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium) and XLSTAT version 2014.5.03 (Addinsoft, NY, USA) systems were used for data analysis.

The histopathological results (or follow-up) were the gold standard tests.

The following diagnostic indices were calculated: specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios, as well as correct classification and misclassification rates.

Inter-method agreement for binary outcomes was examined by calculation of Cohen's kappa (κ), Scott's bias-adjusted kappa (BAK, π), and Bennett's prevalence-adjusted bias-adjusted kappa (PABAK). Agreement for ordinal variables was examined using the weighted kappa coefficient. A *p*-value less than 0.05 was considered statistically significant.

Results

We retrospectively analyzed CESM of 123 patients with 133 lesions (3 multifocal and 7 multicentric IDC). We considered the histopathological results of the surgical piece as the gold standard for the 49 malignant lesions obtained from the patients who underwent surgery. True cut biopsy was done for 56 cases and was correlated with the histopathological results as a gold standard. Cytology results of 5 benign cystic lesions was employed as the gold standard. Follow-up was performed on the remaining 13 benign lesions every 6 months. According to histopathology and outcome of follow-up, 86 patients proved to have malignant pathology and 37 had benign pathology.

Breast parenchymal density was evaluated on the low energy mammographic images: 49/123 (39.8%) cases were classified as ACR "a" or "b" and 74/123 (60.1%) were classified as ACR "c" or "d."

Further assessment was performed for staging of proved malignancy in 18.7% of cases *(n = 23)* and to clarify the nature of indeterminate lesions including suspicious postoperative cases in another 61.7% *(n = 76).* Follow-up cases post neoadjuvant chemotherapy were 20.3% *(n = 25).*

Benign lesions (in order of frequency) included: 8 fibroadenomas (10.6 %) (Fig. 1); 5 benign postsurgical changes (13.5%); 5 cysts (13.5%); 4 cases granulomatous mastitis (10.8%); 3 sclerosing adenosis (8.1%); 3 fibrocystic lesions (8.1%); 3 fat necrosis (8.1%); 3 atypical ductal hyperplasia (8.1%); 2 intramammary lymph nodes (5.4%); 2 papilloma (5.4%); 1 hamartoma (2.7%); and 1 lipoma (2.7%).

Malignant lesions included: 25 invasive ductal carcinoma (33.25%); 13 invasive lobular carcinoma (15.1%) (Fig. 2); 11 cases with ductal carcinoma in situ (DCIS) (12.7%); 11 IDC with in situ component (12.7%); and 2 cases of mucinous carcinoma (2.3%). 25 cases were NAC under follow-up (33.25%) and 4 cases of recurrent IDC were diagnosed among cases under postoperative follow-up, 2 cases were false positive cases of sclerosing adenosis.

Statistical methods

Data were analyzed using MedCalc© version 18.2.1 (MedCalc© Software bvba, Ostend, Belgium) and XLSTAT© version 2014.5.03 (Addinsoft©, NY, USA).

Categorical data were presented as number and percentage and inter-group differences were compared using the Pearson chi-squared test (for nominal data) or the chi-squared test for trend (for ordinal data).

The diagnostic value of radiological tools for discrimination between malignant and benign lesions was examined versus the result of histopathology (or follow-up) as the gold standard test. The following diagnostic indices were calculated: sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and correct classification and misclassification rates.

Inter-method agreement for binary outcomes was examined by calculation of Cohen's kappa (κ), Scott's bias-adjusted kappa (BAK, π), and Bennett's prevalence-adjusted bias-adjusted kappa (PABAK). Agreement for ordinal variables was examined using the weighted kappa coefficient. The agreement coefficients are interpreted as follows in Table 1.

Variable parameters of whole study population characteristics are included in Table 2.

The radiological characteristics of benign and malignant lesions are assessed and included in Table 3.

Sonomammography in our study showed sensitivity of 93% and 67% specificity as in Table 4.
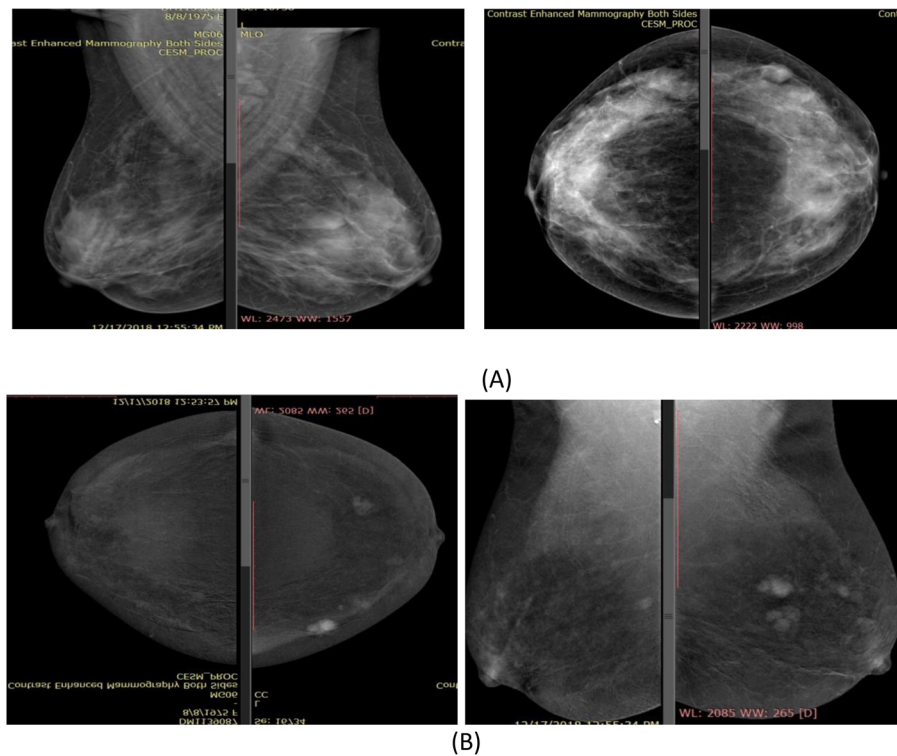
Fig. 1 44-year-old female with left palpable mass. **A** CC and MLO low-energy CESM images showed heterogenously dense breasts with asymmetric density seen at lateral left breast. **B** CC and MLO recombined images showed multiple bilateral enhancing lesions that were revealed to be fibrosclerotic tissue core with focal fibroadenomatous hyperplasia

Sonomammography showed 98% sensitivity and 71% specificity in ACR A/B breast parenchymal density as shown in Table 5.

Sonomammography assessed lesions in ACR grade C/D and showed 92% sensitivity and 72%specificity as shown in Table 6.

CESM gave 100% sensitivity of diagnostic accuracy and 89% specificity as in Table 7.

CESM showed 100 sensitivity and 92% specificity when tested in patients with ACR A/B as shown in Table 8.

CESM showed 100% sensitivity and 91% specificity when tested in patients with ACR grade C/D as in Table 9.

CESM in staging of proved malignancy

An 18.7% of the cases included in our study (n = 23) were pathologically proven to be malignant (BI-RADS 6) and were referred for staging. The accuracy of sonomammography and CESM regarding lesions multiplicity was calculated (Table 1, Fig. 3) The gold standard reference for malignant lesions multiplicity was the histopathological analysis of the surgical specimen.

CESM showed high sensitivity as regards the identification of multiplicity reaching up to 99.7% (with little limitation due to breast density) but with specificity of 97.3% as some benign lesions could display a significant
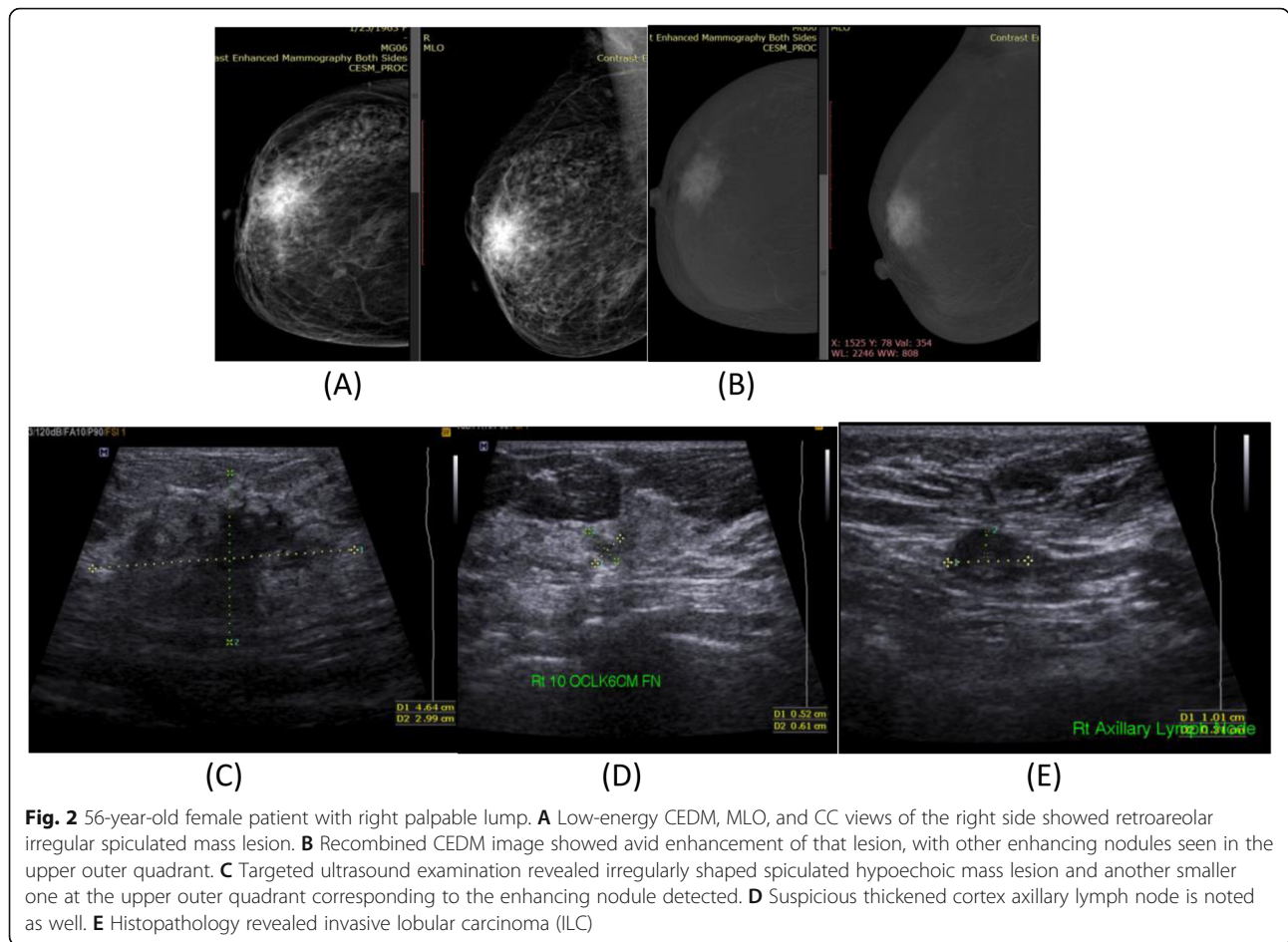
enhancement such as in inflammatory lesions, some benign tumors like fibroadenoma and, intra ductal papillomas. CESM showed a good positive predictive value of 96.4% and negative predictive value of 98% (Table 10, 11, 12, 13, 14, 15, 16, 17 and 18).

CESM for evaluation of indeterminate lesions

CESM findings of 76 suspicious or indeterminate findings in 123 patients done at our "Radiology outpatient breast clinic" were retrospectively analyzed. 17 patients had suspicious lesions on mammography with no correlated ultrasound findings, 9 patients had lesions in dense breast, 13 patients with parenchymal distortion, 24 patients had focal asymmetry, and 12 patients were subjected to postoperative follow-up.

According to histopathology results and outcomes of follow-up studies, 31/76 (41.3%) patients turned out to be benign or probably benign lesions (**BI-RADS 2 and 3**), while 45/76 (59.2%) patients proved to be malignant lesions (**BI-RADS 4 and 5**).

Asymmetries were then classified into single view (6%), focal (82%), global (4%), and developing (8%). The presence of global, focal, or developing asymmetry are strongly correlated with an underlying malignant pathology (p-value 0.001) (Table 2). Associated mammography findings

Fig. 2 56-year-old female patient with right palpable lump. **A** Low-energy CEDM, MLO, and CC views of the right side showed retroareolar irregular spiculated mass lesion. **B** Recombined CEDM image showed avid enhancement of that lesion, with other enhancing nodules seen in the upper outer quadrant. **C** Targeted ultrasound examination revealed irregularly shaped spiculated hypoechoic mass lesion and another smaller one at the upper outer quadrant corresponding to the enhancing nodule detected. **D** Suspicious thickened cortex axillary lymph node is noted as well. **E** Histopathology revealed invasive lobular carcinoma (ILC)

(e.g., skin thickening, edema, calcification, and parenchymal distortion) were seen in 56 cases (78%) cases. On evaluating the low-energy mammographic images, a considerable number of false negative (36%) and false positive (48%) and false negative (36%) asymmetries were encountered.

CESM in following up cases under neoadjuvant chemotherapy

As regards patients with locally advanced breast cancer under neoadjuvant chemotherapy for follow-up (n = 25)

Table 1 Agreement for ordinal variables was examined using the weighted kappa coefficient. The agreement coefficients are interpreted as follows

Coefficient of agreement	Strength of agreement
0.0–0.20	Slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–1.0	Nearly perfect agreement

p-values < 0.05 were considered statistically significant

(20.3%), initial bilateral mammography and complementary US were done (or reviewed if available) in order to determine the tumor location and its baseline size. Insertion of pre-therapy clips was done to localize the tumor for further follow-up and assessment of therapy response (Fig. 4).

Interpretation was done using response evaluation criteria in solid tumors (RECIST) guidelines for evaluation of target lesions [11]: that was agreed upon with the oncology department during our weekly meeting.

Complete response (CR): complete resolution of all main lesions with reduction of the short axis of pathological lymph nodes to < 10 mm.

Partial response (PR): at least 30% reduction in the diameters of the main lesion.

Progressive disease (PD): At least 20% increase in the diameters of main lesions when compared to the smallest sum diameters. De novo lesions are also considered progression.

Stable disease (SD): the lesion remains stable in diameter as compared to the smallest sum diameters of the original lesion.

The patterns of contrast enhancement of the residual tumors had various patterns and were interpreted as

Table 2 Characteristics of the whole study population

Variable		N	%
Age category	≤ 40 years	44	35.8%
	> 40 years	79	64.2%
ACR grade	Grade A	4	3.3%
	Grade B	45	36.6%
	Grade C	68	55.3%
	Grade D	6	4.9%
Number of lesions by SMG	Nil	6	4.9%
	Single lesion	96	78.0%
	2 lesions	12	9.8%
	3 lesions	5	4.1%
	4 lesions	4	3.3%
BIRADS class by SMG	BIRADS1	7	5.7%
	BIRADS 2	0	0.0%
	BIRADS 3	23	18.7%
	BIRADS 4	40	32.5%
	BIRADS 5	4	3.3%
	BIRADS 6	49	39.8%
Indication for CESM	Follow-up of neo-adjuvant chemotherapy	25	20.3%
	Mass in dense breast	8	6.5%
	Staging of breast cancer	23	18.7%
	Suspicious lesion on mammography with no US correlate	17	13.8%
	Focal asymmetry	24	19.5%
	Postoperative follow-up	12	9.8%
	Parenchymal distortion	13	10.6%
	Suspicious palpable lesion	1	0.8%
Number of lesions by CESM	Nil	22	17.9%
	Single lesion	61	49.6%
	2 lesions	12	9.8%
	3 lesions	22	17.9%
	4 lesions	5	4.1%
	5 lesions	1	0.8%
Grade of enhancement	No enhancement	24	19.5%
	Minimal	12	9.8%
	Mild	11	8.9%
	Moderate	14	11.4%
	Marked	62	50.4%
BIRADS class by CESM	BIRADS 2	29	23.6%
	BIRADS 3	2	1.6%
	BIRADS 4	37	30.1%
	BIRADS 5	8	6.5%
	BIRADS 6	47	38.2%

Table 2 Characteristics of the whole study population *(Continued)*

Variable		N	%
Pathological type and course	Adenosis	3	2.4%
	Atypical ductal hyperplasia	3	2.4%
	Benign postoperative changes	5	4.1%
	Complete response	8	6.5%
	Cyst	4	3.3%
	DCIS	11	8.9%
	Fat necrosis	3	2.4%
	Fibroadenoma	5	4.1%
	Fibrocystic changes	3	2.4%
	Granulomatous mastitis	4	3.3%
	Hamartoma	1	0.8%
	IDC	18	14.6%
	IDC within in-situ component	11	8.9%
	ILC	13	10.6%
	IMLN	2	1.6%
	Infected cyst	1	0.8%
	Lipoma	1	0.8%
	Minimal residual disease	5	4.1%
	Mucinous carcinoma	2	1.6%
	Papilloma	2	1.6%
	Partial response	2	1.6%
	Recurrent IDC	4	3.3%
	Stationary disease	12	9.8%
Reference index	Follow-up	13	10.6%
	Needle aspiration	5	4.1%
	Tru-Cut biopsy	55	44.7%
	Surgical biopsy	49	39.8%
	Stereotactic biopsy	1	0.8%
Final diagnosis	Benign	37	30.1%
	Malignant	86	69.9%

Data are number (*N*) and percentage (%)

follows: No contrast uptake indicates complete therapeutic response (CR); intense contrast enhancement denotes chemo-resistance: stable disease (SD) or progressive disease (PD); faint uptake and homogenous background uptake indicate minimal residual disease and considered partial response (PR).

Histopathological diagnosis is used as the gold standard.

We had only two cases (about 2.5% of cases) showing partial response with intense CESM enhancement. Complete pathological response was achieved in 37% of cases (30 patients). CESM showed complete response in 29 out of 30 cases by showing no enhancement pattern.

Table 3 Radiological characteristics of benign or malignant lesions

Variable		Final diagnosis				χ^2(df,1)	*p*-value
		Benign (*n* = 37)		Malignant (*n* = 86)			
		n	%	*n*	%		
Number of lesions by SMG	Nil	6	16.2%	0	0.0%	14.506	< 0.001*
	Single lesion	31	83.8%	65	75.6%		
	2 lesions	0	0.0%	12	14.0%		
	3 lesions	0	0.0%	5	5.8%		
	4 lesions	0	0.0%	4	4.7%		
BIRADS class by SMG	**BIRADS 1**	4	10.8%	3	3.5%	31.321	< 0.001*
	BIRADS 2	0	0.0%	0	0.0%		
	BIRADS 3	15	40.5%	8	9.3%		
	BIRADS 4	16	43.2%	24	27.9%		
	BIRADS 5	1	2.7%	3	3.5%		
	BIRADS 6	1	2.7%	48	55.8%		
Number of enhanced lesions by CESM	Nil	14	37.8%	8	9.3%	22.991	< 0.001*
	Single lesion	22	59.5%	39	45.3%		
	2 lesions	0	0.0%	12	14.0%		
	3 lesions	1	2.7%	21	24.4%		
	4 lesions	0	0.0%	5	5.8%		
	5 lesions	0	0.0%	1	1.2%		
Grade of enhancement	No enhancement	16	43.2%	8	9.3%	25.294	< 0.001*
	Minimal	0	0.0%	12	14.0%		
	Mild	10	27.0%	1	1.2%		
	Moderate	8	21.6%	6	7.0%		
	Marked	3	8.1%	59	68.6%		
BIRADS class by CESM	BIRADS 1	0	0.0%	0	0.0%	71.990	< 0.001*
	BIRADS 2	28	75.7%	1	1.2%		
	BIRADS 3	1	2.7%	1	1.2%		
	BIRADS 4	7	18.9%	30	34.9%		
	BIRADS 5	0	0.0%	8	9.3%		
	BIRADS 6	1	2.7%	46	53.5%		
BIRADS class by SMG	Probably benign (**BIRADS 1–3**)	19	51.4%	11	12.8%	20.859	< 0.001§
	Probably malignant **BIRADS 4–6**	18	48.6%	75	87.2%		
BIRADS class by CESM	Probably benign (**BIRADS 1–3**)	29	78.4%	2	2.3%	79.375	< 0.001§
	Probably malignant **BIRADS 4–6**	8	21.6%	84	97.7%		
Marked enhancement	No to moderate enhancement	34	91.9%	27	31.4%	37.874	< 0.001§
	Marked enhancement	3	8.1%	59	68.6%		

Data are number (n) and percentage (%). χ^2, chi-squared statistic; df,1
*Pearson chi-squared test. §Chi-squared test for trend

One case showed contrast enhancement, yet had complete response evident by pathology (false positive). The specificity of CESM in our study for prediction of complete response is 68.6% and the negative predictive value is 100% with a 96% CI = 40.2–100.00%.

Minimal residual disease represented 16% of the tumor responses and in 4 out of 5Bcases and was presented by faint enhancement pattern that was concordant to pathological response and one case showed marked tumor size reduction with faint homogenous background enhancement on CESM that also was concordant with the pathological response.

Forty-eight percent (12 cases) represented chemo-resistant tumors in the final pathologic tumor response of locally advanced breast cancer, three cases showed

Table 4 Diagnostic accuracy of sonomammography tested in the whole study cohort versus the result of biopsy or follow-up as the gold standard for lesion classification

Lesion classification by SMG	Final diagnosis		Total
	Malignant	*Benign*	
*Probably malignant (**BI-RADS 4–6**)*	75	18	93
*Probably benign (**BI-RADS 1–3**)*	11	19	30
Total	86	37	123
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	76%	69%	84%
Misclassification	24%	16%	31%
Sensitivity	87%	78%	93%
Specificity	51%	36%	67%
False positive rate	49%	33%	64%
False negative rate	13%	6%	20%
Prevalence	70%	62%	78%
Positive predictive value (PPV)	81%	73%	89%
Negative predictive value (NPV)	63%	46%	81%
Positive likelihood ratio (LR+)	1.79	1.27	2.52
Negative likelihood ratio (LR−)	0.25	0.13	0.47
Relative risk	2.20	1.38	3.51
Odds ratio	7.20	2.96	17.50

Data in cross-tables are counts

Table 5 Diagnostic accuracy of SMG in tested patients with ACR grade A/B versus the result of biopsy or follow-up as the gold standard for lesion classification

Lesion classification by SMG	Final diagnosis		Total
	Malignant	*Benign*	
Probably malignant (BIRADS 4–6)	33	7	40
Probably benign (BIRADS 1–3)	3	6	9
Total	36	13	49
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	80%	68%	91%
Misclassification	20%	9%	32%
Sensitivity	92%	77%	98%
Specificity	46%	23%	71%
False positive rate	54%	30%	78%
False negative rate	8%	0%	17%
Prevalence	73%	61%	86%
Positive predictive value (PPV)	83%	71%	94%
Negative predictive value (NPV)	67%	36%	97%
Positive likelihood ratio (LR+)	1.70	1.02	2.84
Negative likelihood ratio (LR−)	0.18	0.05	0.62
Relative risk	2.48	1.06	5.76
Odds ratio	9.43	2.06	43.18

Data in cross-tables are counts

Table 6 Diagnostic accuracy of SMG in tested patients with ACR grade C/D versus the result of biopsy or follow-up as the gold standard for lesion classification

Lesion classification by SMG	Final diagnosis		
	Malignant	**Benign**	**Total**
*Probably malignant (**BIRADS 4–6**)*	42	11	53
*Probably benign (**BIRADS 1–3**)*	8	13	21
Total	50	24	74
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	74%	64%	84%
Misclassification	26%	16%	36%
Sensitivity	84%	71%	92%
Specificity	54%	35%	72%
False positive rate	46%	27%	64%
False negative rate	16%	6%	26%
Prevalence	68%	57%	78%
Positive predictive value (PPV)	79%	68%	90%
Negative predictive value (NPV)	62%	41%	83%
Positive likelihood ratio (LR+)	1.83	1.17	2.88
Negative likelihood ratio (LR−)	0.30	0.14	0.62
Relative risk	2.08	1.21	3.57
Odds ratio	6.20	2.11	18.22

Data in cross-tables are counts

Table 7 Diagnostic accuracy of CESM in the whole study cohort versus the result of biopsy or follow-up as the gold standard for lesion classification

Lesion classification by SMG	Final diagnosis		
	Malignant	**Benign**	**Total**
*Probably malignant (BIRADS **4–6**)*	84	8	92
*Probably benign (BIRADS **1–3**)*	2	29	31
Total	86	37	123
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	92%	87%	97%
Misclassification	8%	3%	13%
Sensitivity	98%	91%	100%
Specificity	78%	62%	89%
False positive rate	22%	9%	34%
False negative rate	2%	0%	5%
Prevalence	70%	62%	78%
Positive predictive value (PPV)	91%	86%	97%
Negative predictive value (NPV)	94%	85%	100%
Positive likelihood ratio (LR+)	4.52	2.44	8.35
Negative likelihood ratio (LR−)	0.03	0.01	0.12
Relative risk	14.15	4.30	46.57
Odds ratio	152.25	34.97	662.91

Data in cross-tables are counts

intense enhancement which corresponded to poor therapy or chemo-resistance in final pathology (true positive), and seven cases showed faint enhancement (false negative) resulting in 31.8% sensitivity for detection of chemo-resistant tumors post NAC.

The sensitivity, specificity, NPV, and PPV of CESM for prediction of various tumor responses to therapy are 41%, 93%, 61.8%, and 82% respectively.

The calculated sensitivity of mammography with US was 82.9%, specificity was 76.5%, and the total accuracy was 8 1.0%. The PPV and NPV were 89.5% and 65.0% respectively.

The calculated sensitivity of CESM was 92.7%, specificity was 82.4%, and the total accuracy was 89.7%. The PPV and NPV were 92.7% and 82.4% respectively.

The gold standard references in our study were the histopathology results and follow-up of the patients during the adjuvant therapy.

Discussion

Contrast-enhanced spectral mammography is an advanced technique of digital mammography done with intravenous injection of an iodinated contrast agent. Dual-energy subtraction imaging exploits the energy dependence of X-ray attenuation through different breast compositions. Post-contrast dual low- and high-energy images are obtained and then the two images are combined and subtracted in order to highlight areas of contrast enhancement. This novel breast imaging technique can be easily implemented clinically using the current digital mammography system with minor modification as well as usage of commercially available iodinated contrast agents.

CESM has been shown to improve the probability of malignancy and BI-RADS assessment in comparison to the conventional mammography alone. The potential clinical applications are localization of disease extent of mammographically equivocal lesions, proper depiction of occult lesions on standard mammography, especially in dense breast, and chemotherapy response monitoring.

CESM implementation is easily accessible in the mammography suite. No specific further training is needed for the radiographers for patient positioning nor for image acquisition, as they are similar to the well-known conventional mammography. CESM examination is well accepted by patients in case of needful complete assessment in contrast to MRI that seems to be unacceptable to some patients. CESM can be performed immediately following mammography, in the same mammography suite with no need for a new appointment and time waste. Moreover, it provides faster imaging when compared to MRI.

Suspicious contrast uptake detected on subtracted CESM images can be easily analyzed retrospectively in correlation to conventional mammograms. The "subtracted" CESM images can be interpreted very easily and rapidly by radiologists and understood by oncologists and surgeons.

The main disadvantage of CESM is the need for intravenous administration of an iodinated contrast agent. CESM is therefore contra-indicated in patients with renal impairment or known allergy or limitations to iodinated contrast agents.

Another disadvantage of CESM as compared with MRI is that CESM is radiation-dependant technique. However, a controlled dose is delivered to the patient, which is approximately equivalent to two conventional mammography examination.

As in all mammography reports, certain essential points should be included in the report for a CESM, including the indication for the examination, comparison if available, findings, ACR BI-RADS lexicon evaluation, and management recommendations. Unique to CESM as compared to conventional mammography reports, background enhancement and lesion contrast enhancement characteristics should be included in the report [12].

Various technical and clinical experience has been acquired with promising results have been published during the last few years regarding CESM.

The temporal subtraction procedure was first acquired with an approach similar to that of breast MRI (Jong et al. [13]; Dromain et al. [14];).

These initial studies, with a limited patient sample, showed that CESM was able to depict tumor angiogenesis in breast cancer.

Jong et al. (2003) examined 22 women with 12 benign and 10 malignant lesions with temporal CESM. Enhancement was noted in 89% of the invasive cancers. Two false negatives were observed, one case was corresponding to ductal carcinoma in situ and the other one was invasive ductal carcinoma. Among the 12 patients with a benign breast lesion, initially considered worrisome at conventional mammography or US, 5 had nodular enhancement corresponding to 3 fibroadenomas and 2 cases of fibrocystic change with focal intraductal hyperplasia; 7 had no significant enhancement.

Another study was performed by Dromain et al. [14] in which CESM examinations were performed in 20 patients with 22 malignant tumors. The sensitivity of CESM in breast carcinoma detection was 80%. There was a concordance between the histopathology size and the size of enhanced lesion measured on CESM subtracted images. As in the study by Jong et al., most of the cancers showed progressive enhancement without a washout pattern. A poor correlation between the intratumor mean vascular density evaluated on CD34-immunostained histological sections and quantitative characteristics of enhancement kinetics curves was observed, probably due to

Table 8 Diagnostic accuracy of CESM tested in patients with ACR grade A/B versus the result of biopsy or follow-up as the gold standard for lesion classification
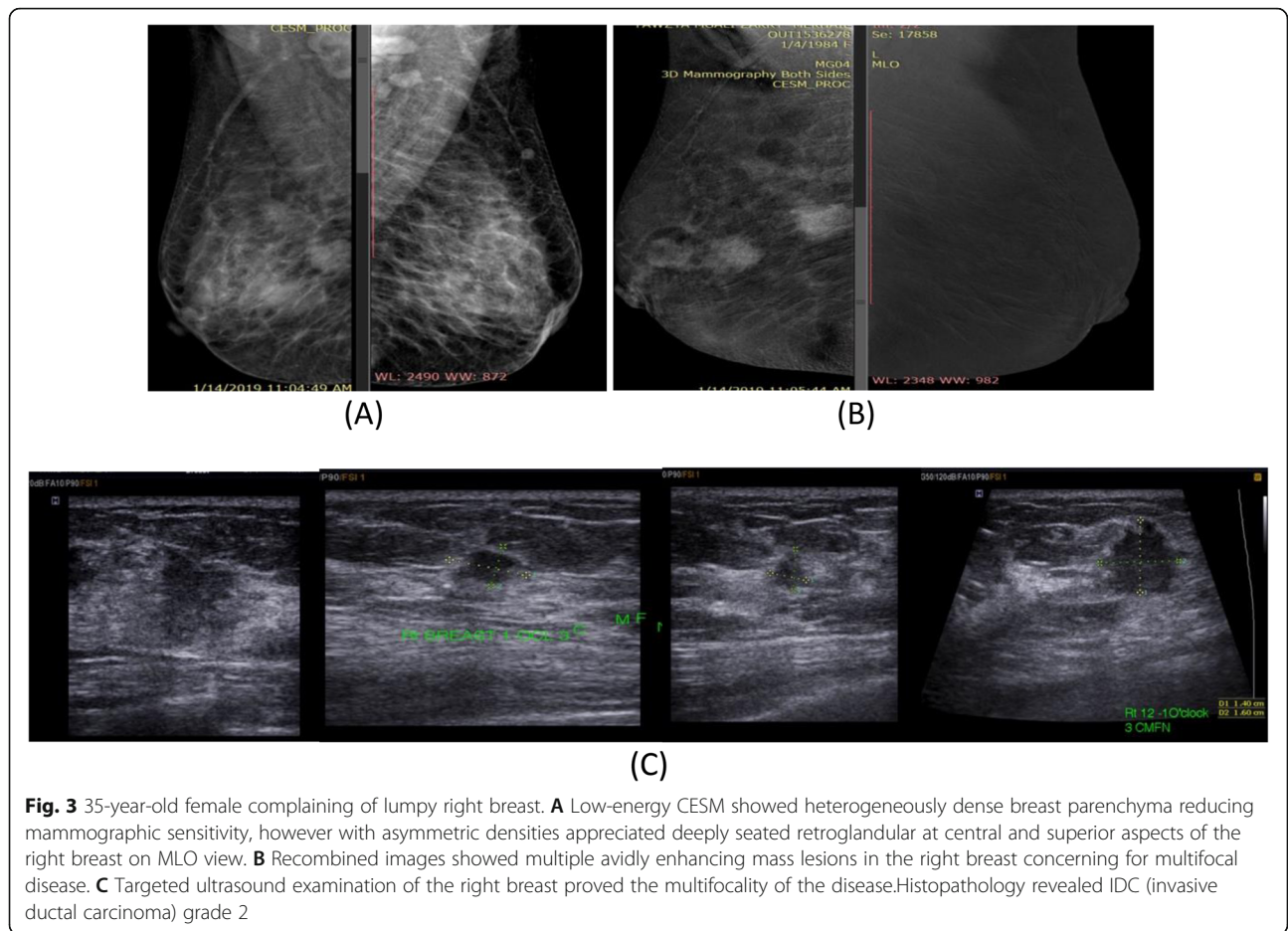
Lesion classification by SMG	Final diagnosis		
	Malignant	*Benign*	**Total**
Probably malignant (BIRADS 4–6)	35	3	38
Probably benign (BIRADS 1–3)	1	10	11
Total	36	13	49
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	92%	84%	100%
Misclassification	8%	0%	16%
Sensitivity	97%	84%	100%
Specificity	77%	49%	92%
False positive rate	23%	3%	43%
False negative rate	3%	0%	8%
Prevalence	73%	61%	86%
Positive predictive value (PPV)	92%	84%	100%
Negative predictive value (NPV)	91%	74%	100%
Positive likelihood ratio (LR+)	4.21	1.56	11.38
Negative likelihood ratio (LR−)	0.04	0.01	0.26
Relative risk	10.13	2.27	45.19
Odds ratio	116.67	15.28	890.87

Data in cross-tables are counts

Table 9 Diagnostic accuracy of CESM tested in patients with ACR grade C/D versus the result of biopsy or follow-up as the gold standard for lesion classification

Lesion classification by SMG	Final diagnosis		
	Malignant	*Benign*	**Total**
Probably malignant (BIRADS 4–6)	49	5	54
Probably benign (BIRADS 1–3)	1	19	20
Total	50	24	74
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	92%	86%	98%
Misclassification	8%	2%	14%
Sensitivity	98%	88%	100%
Specificity	79%	59%	91%
False positive rate	21%	6%	36%
False negative rate	2%	0%	6%
Prevalence	68%	57%	78%
Positive predictive value (PPV)	91%	83%	98%
Negative predictive value (NPV)	95%	85%	100%
Positive likelihood ratio (LR+)	4.70	2.15	10.27
Negative likelihood ratio (LR−)	0.03	0.00	0.18
Relative risk	18.15	3.88	84.90
Odds ratio	186.20	28.42	1220.14

Data in cross-tables are counts

Fig. 3 35-year-old female complaining of lumpy right breast. **A** Low-energy CESM showed heterogeneously dense breast parenchyma reducing mammographic sensitivity, however with asymmetric densities appreciated deeply seated retroglandular at central and superior aspects of the right breast on MLO view. **B** Recombined images showed multiple avidly enhancing mass lesions in the right breast concerning for multifocal disease. **C** Targeted ultrasound examination of the right breast proved the multifocality of the disease. Histopathology revealed IDC (invasive ductal carcinoma) grade 2

Table 10 Agreement between SMG and CESM as regards the BIRADS classification in the whole study population

BIRADS by CESM	BIRADS by SMG						Total
	BIRADS I	BIRADS II	BIRADS III	BIRADS IV	BIRADS V	BIRADS VI	
BIRADS 1	0	0	0	0	0	0	0 (0.0%)
BIRADS 2	3	0	8	17	1	0	29 (23.6%)
BIRADS 3	0	0	1	0	0	1	2 (1.6%)
BIRADS 4	3	0	14	19	0	1	37 (30.1%)
BIRADS 5	0	0	0	4	3	1	8 (6.5%)
BIRADS 6	1	0	0	0	0	46	47 (38.2%)
Total	7 (5.7%)	0 (0.0%)	23 (18.7%)	40 (32.5%)	4 (3.3%)	49 (39.8%)	123
Inter-method agreement							
Weighted kappa	0.58[a]						
Standard error	0.04						
95% CI	0.49 to 0.67						

Data in cross-tables are counts
[a]Moderate agreement

Table 11 Agreement between SMG and CESM as regards the BIRADS classification in patients with ACR grade A/B

BIRADS by CESM	BIRADS by SMG						Total
	BIRADS I	BIRADS II	BIRADS III	BIRADS IV	BIRADS V	BIRADS VI	
BIRADS 1	0	0	0	0	0	0	0 (0.0%)
BIRADS 2	0	0	3	7	1	0	11 (22.4%)
BIRADS 3	0	0	0	0	0	0	0 (0.0%)
BIRADS 4	1	0	4	6	0	0	11 (22.4%)
BIRADS 5	0	0	0	0	1	0	1 (2.0%)
BIRADS 6	1	0	0	0	0	25	26 (53.1%)
Total	2 (4.1%)	0 (0.0%)	7 (14.3%)	13 (26.5%)	2 (4.1%)	25 (51.0%)	49
Inter-method agreement							
Weighted kappa	0.59[a]						
Standard error	0.07						
95% CI	0.45 to 0.73						

Data in cross-tables are counts
[a]Moderate agreement

difficulty in performing a quantitative assessment on projection images acquired from breasts under compression.

Indeed, CESM images are projections of the entire breast and enhancement depends on the tumor size. Moreover, enhancement is not exclusively due to the number of vessels but is also most likely related to some other functional parameters such as vessel permeability, especially when using a contrast agent capable of migration to the extracellular fluid space.

In our study, the sensitivity of CESM for the detection of breast carcinoma was 92.7%. There was an excellent concordance between the histopathology size and the size of the enhancement. Most of the cancers showed progressive enhancement without washout.

A multicentric retrospective study was performed by Diekmann et al. [15] aimed at comparing the diagnostic accuracy of CESM with the diagnostic accuracy of mammography alone was performed.

Data were collected at four centers in Europe and North America in 75 women with 85 lesions (17 benign and 68 malignant).

The average sensitivity and specificity across the readers for the probability of cancer increased with mammography plus CESM from 0.81 to 0.86 and 0.62 to 0.66, respectively. The area under the ROC curve for

Table 12 Agreement between SMG and CESM as regards the BIRADS classification in patients with ACR grade C/D

CESM_BIRADS	SMG_BIRADS						
	BIRADS I	BIRADS II	BIRADS III	BIRADS IV	BIRADS V	BIRADS VI	
BIRADS 1	0	0	0	0	0	0	0 (0.0%)
BIRADS 2	3	0	5	10	0	0	18 (24.3%)
BIRADS 3	0	0	1	0	0	1	2 (2.7%)
BIRADS 4	2	0	10	13	0	1	26 (35.1%)
BIRADS 5	0	0	0	4	2	1	7 (9.5%)
BIRADS 6	0	0	0	0	0	21	21 (28.4%)
Total	5 (6.8%)	0 (0.0%)	16 (21.6%)	27 (36.5%)	2 (2.7%)	24 (32.4%)	74
Inter-method agreement							
Weighted kappa	0.55[a]						
Standard error	0.06						
95% CI	0.44 to 0.67						

Data in cross-tables are counts
[a]Moderate agreement

Table 13 Agreement between SMG and CESM regarding lesion classification as probably malignant or probably benign in the whole study population

CESM	SMG		Total
	Probably benign (BIRADS I–III)	*Probably malignant (BIRADS IV–VI)*	
Probably benign (BIRADS 1–3)	12	19	31
Probably malignant (BIRADS 4–6)	18	74	92
Total	30	93	123
Agreement statistics			
Cohen's kappa (κ)			0.19[a]
Scott's bias-adjusted kappa (BAK, π)			0.19[a]
Bennet's prevalence- and bias-adjusted kappa (PABAK)			0.40[b]

Data in cross-tables are counts
[a]Slight agreement
[b]Fair agreement

mammography + CESM using the probability of cancer scale, was higher than the area under the ROC curve mammography alone for all readers.

The study by Lewin et al. [16] is the only published preliminary clinical experience using the dual-energy technique. They studied 26 women with 13 invasive carcinomas. Eight (85%) of the invasive carcinoma displayed intense enhancement, 3 showed moderate enhancement, and 1 showed mild enhancement. 5 among those lesions were not detected on conventional mammograms.

Dromain et al., in 2008, have evaluated the dual-energy CESM technique in 120 patients referred for screening mammograms recall with indeterminate mammographic findings.

In our study, we have evaluated 123 patients, For each CESM examination, a pair of low- and high-energy images was acquired using a modified full-field digital mammography system (Senographe DS GE healthcare) with an MLO view at 2 min and a CC view at 4 min after injection of 1.5 mL/kg of an iodinated contrast agent. Compared to mammography alone, CESM yielded

significantly higher sensitivity (93% vs. 78%) and a negative predictive value (87% vs.67%) and had a clearly greater area under the ROC curve. When we compared CESM with the standard examinations (mammography + US), sensitivity was less evident but still exists; however, dual energy had a significant higher specificity than mammography plus US.

CESM is of interest also in the diagnostic setting. It cannot replace mammography but can be helpful in selected cases where clinical and conventional mammography evaluation are still non-conclusive.

In our study, it was of added value in questionable cases with dense breast parenchyma (ACR-C, ACR-D). It was also valuable in the detection of multicentricity and multifocality of breast cancer.

CESM has the potential to increase the cancer detection rate and to improve patient selection for biopsy to avoid unnecessary biopsies.

Basically, the potential indications are closely similar to those of breast MRI. The potential indications for CESM include the evaluation of newly diagnosed breast

Table 14 Agreement between SMG and CESM regarding lesion classification as probably malignant or probably benign in patients with ACR A/B

CESM	SMG		Total
	Probably benign (BIRADS I–III)	*Probably malignant (BIRADS IV–VI)*	
Probably benign (BIRADS 1–3)	3	8	11
Probably malignant (BIRADS 4–6)	6	32	38
Total	9	40	49
Agreement statistics			
Cohen's kappa (κ)			0.12[a]
Scott's bias-adjusted kappa (BAK, π)			0.12[a]
Bennet's prevalence- and bias-adjusted kappa (PABAK)			0.43[b]

Data in cross-tables are counts
[a]Slight agreement
[b]Moderate agreement

Table 15 Agreement between SMG and CESM regarding lesion classification as probably malignant or probably benign in patients with ACR C/D

CESM	SMG		Total
	Probably benign (BIRADS 1–3)	*Probably malignant (BIRADS 4–6)*	
Probably benign (BIRADS 1–3)	9	11	20
Probably malignant (BIRADS 4–6)	12	42	54
Total	21	53	74
Agreement statistics			
Cohen's kappa (κ)			0.22[a]
Scott's bias-adjusted kappa (BAK, π)			0.22[a]
Bennet's prevalence- and bias-adjusted kappa (PABAK)			0.38[a]

Data in cross-tables are counts
[a]Fair agreement

cancer, to assess the extent of disease and to evaluate possible contralateral disease, multicentricity, and multifocality, and evaluation of residual disease after a lumpectomy with positive margins, follow-up after chemotherapy, or neoadjuvant therapy to assess for various tumor responses.

Few indications for breast MRI appear superior to CESM: screening of high-risk women (BRCA1/2) due to their sensitivity to radiation exposure, the assessment of response to neoadjuvant chemotherapy as several follow-up imaging examinations are usually needed and will best be performed using a non-radiating imaging method, superior in assessment of axillary lymph nodes and skin assessment.

Our CESM machine is considered among Food and Drug Administration-approved machines.

Interpretation pitfalls and limitations

It is essential for CESM readers to avoid the pitfall of false negative lesions that have morphologically suspicious findings on low-energy images with no significant enhancement on recombined images. The reader must give adequate consideration to the suspicious morphologic

Table 16 Diagnostic accuracy of marked enhancement on CESM in the whole study cohort

| Lesion classification by SMG	Final diagnosis		
	Malignant	*Benign*	Total
Marked enhancement	59	3	62
No to moderate enhancement	27	34	61
Total	86	37	123
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	76%	68%	83%
Misclassification	24%	17%	32%
Sensitivity	69%	58%	77%
Specificity	92%	78%	98%
False positive rate	8%	0%	16%
False negative rate	31%	22%	41%
Prevalence	70%	62%	78%
Positive predictive value (PPV)	95%	90%	100%
Negative predictive value (NPV)	56%	43%	68%
Positive likelihood ratio (LR+)	8.46	2.83	25.27
Negative likelihood ratio (LR−)	0.34	0.25	0.47
Relative risk	2.15	1.62	2.85
Odds ratio	24.77	7.54	81.31

Data in cross-tables are counts

Table 17 Diagnostic accuracy of marked enhancement on CESM in patients with ACR grade A/B

Lesion classification by SMG	Final diagnosis		
	Malignant	*Benign*	Total
Marked enhancement	21	1	22
No to moderate enhancement	15	12	27
Total	36	13	49
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	67%	54%	80%
Misclassification	33%	20%	46%
Sensitivity	58%	42%	73%
Specificity	92%	64%	100%
False positive rate	8%	0%	20%
False negative rate	42%	26%	57%
Prevalence	73%	61%	86%
Positive predictive value (PPV)	95%	87%	100%
Negative predictive value (NPV)	44%	26%	63%
Positive likelihood ratio (LR+)	7.58	1.13	50.86
Negative likelihood ratio (LR−)	0.45	0.30	0.69
Relative risk	1.72	1.22	2.42
Odds ratio	16.80	2.74	103.19

Data in cross-tables are counts

Table 18 Diagnostic accuracy of marked enhancement on CESM in patients with ACR grade C/D

Lesion classification by SMG	Final diagnosis		
	Malignant	*Benign*	Total
Marked enhancement	38	2	40
No to moderate enhancement	12	22	34
Total	50	24	74
Statistic	Value	Lower bound (95%)	Upper bound (95%)
Correct classification	81%	72%	90%
Misclassification	19%	10%	28%
Sensitivity	76%	62%	86%
Specificity	92%	73%	99%
False positive rate	8%	0%	19%
False negative rate	24%	13%	35%
Prevalence	68%	57%	78%
Positive predictive value (PPV)	95%	88%	100%
Negative predictive value (NPV)	65%	49%	81%
Positive likelihood ratio (LR+)	9.12	2.40	34.69
Negative likelihood ratio (LR−)	0.26	0.16	0.44
Relative risk	2.69	1.72	4.21
Odds ratio	34.83	8.14	149.11

Data in cross-tables are counts
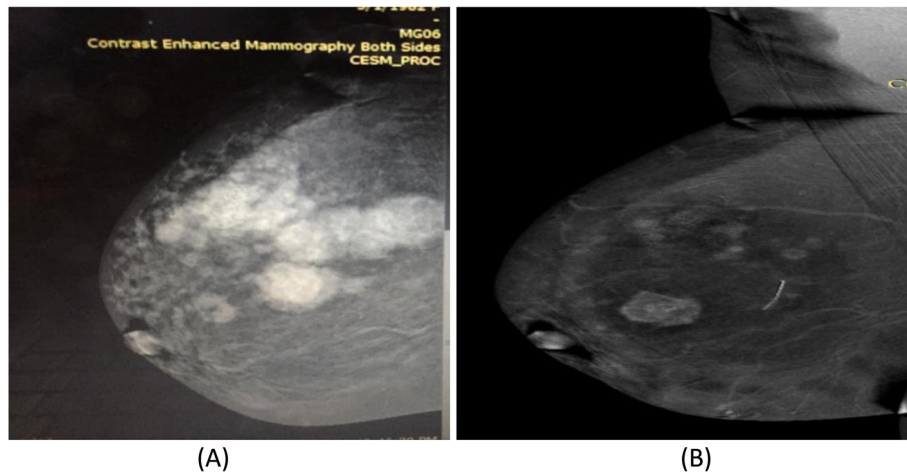
Fig. 4 37-year-old, pathologically proven multicentric disease: IDC. **A** MLO recombined image prior to NAC revealed locally advanced disease with extensive mass and non-mass enhancement occupying most of the superior and central right breast. **B** Post 6 cycles of NAC showing marked disease regression and partial response

findings on the low-energy images when ultimately determining the appropriate BI-RADS category [12].

Our study has some limitations and pitfalls

Few benign-looking lesions like fibroadenoma were considered false positive results as they displayed contrast enhancement. A study by Badr et al. [17] showed enhancement in 33% of 27 benign lesions. Jochelson et al. [18] observed 2 false positive findings in 52 cases. Lobbes et al. [19] detected 5 false positive findings in a study including 113 women recalled from screening, most of them. Most of these false positive lesions are caused by fibroadenomas

Faint ring enhancement occurred with one lesion is mucinous carcinoma, and considered a false negative result.

Athough two experienced radiologists evaluated the digital mammography and CESM findings, intraobserver and interobserver variability were not evaluated.

Conclusion

CESM is a potential promising technique in the evaluation of patients with mammographically inconclusive findings especially those with mammographically dense breasts.

CESM is feasible and has an important role in proper characterization of breast lesions especially in dense breast parenchyma. CESM showed higher sensitivity and specificity compared to digital mammography with ultrasound.

CESM is cosidered a cost-effective, good, alternative to dynamic contrast-enhanced MRI (DCE-MRI) for the staging of newly diagnosed breast cancer.

Availability of data and materials

The data used and analyzed during this study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The protocol was reviewed and approved by the local ethical committee of "Research Ethics Committee at the Faculty of Medicine, Ain Shams University." It stated that no formal ethics approval was required in a retrospective study, and so, no reference number was given by the IRB.

Consent for publication

Although this research is based on a retrospective study, written consent for publication was obtained for these cases.

Competing interests

No financial or non-financial competing interest.

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