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Equivocal and Suspicious Breast Lesions: Can Contrast Enhanced Spectral Mammography Alter their BIRADS Categorization?

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Abstract

Background: Contrast Enhanced Spectral Mammography (CESM) is an advanced technique to detect the tumor neoangiogenesis by using the dual energy technique with acquisition of a pair of low and high-energy images only after contrast medium injection. The potential clinical applications are the clarification of mammographically equivocal lesions, the detection of occult lesions on standard mammography, particularly in dense breast, the determination of the extent of disease, the assessment of recurrent disease and the monitoring of the response to chemotherapy.

Aim of Study: To assess the potential of Contrast Enhanced Spectral Mammography (CESM) to upstage/downdstage the BIRADS category of equivocal and suspicious breast lesions.

Patients and Methods: Thirty female patients with 44 equivocal and suspicious breast lesions, were enrolled in the study, age ranged from 20 to 76 years. All patients underwent conventional mammography and ultrasound then CESM.

Results: Mammography + Ultrasound categorized 40/44 lesions (90.9%) lesions to be malignant (BIRADS 4,5) and 4/44 lesions (9.1%) to be benign (BIRADS 1,3). CESM categorized 35/44 lesions (79.5%) to be malignant (BIRADS 4,5) and 9/44 lesions (20.5%) to be benign (BIRADS1,3). Disagreement about BIRADS category was observed in 25% of the examined lesions including upgraded and downgraded lesions in 11.36% and 13.6% respectively. 100% of up/down graded lesions also proved CESM to be correct in reference to the final diagnosis.

Conclusion: CESM has better diagnostic performance than mammography plus Ultrasound and provides a valuable tool to accurately evaluate equivocal and suspicious breast lesions.

Key Words: *Contrast Enhanced Spectral Mammography (CESM) – Suspicious breast lesions.*

Introduction

CONTRAST Enhanced Digital Mammography (CEDM) is an advanced technique to detect the tumor neoangiogenesis by using two techniques either the temporal subtraction technique with acquisition of high-energy images before and after contrast medium injection or the dual energy technique with acquisition of a pair of low and high-energy images only after contrast medium injection. The temporal subtraction technique is beneficial in analyzing the kinetic curve of enhancement of breast lesions, in a way similar to breast MRI. Although the dual energy technique lacks information about the kinetics of tumor enhancement, it allows the acquisition of multiple views of the same breast and bilateral examination, being less sensitive to patient motion than temporal CEDM **[1]**.

Initial clinical experience has shown the ability of CEDM to map the distribution of neovasculature induced by cancer using mammography. Moreover, previous studies have shown a superiority of Mx (mammography) + CEDM, either for the assessment of the probability of malignancy or for BI-RADS assessment comparing to Mx alone. The potential clinical applications are the clarification of mammographically equivocal lesions, the detection of occult lesions on standard mammography, particularly in dense breast, the determination of the extent of disease, the assessment of recurrent disease and the monitoring of the response to chemotherapy **[2]**.

Retrospective reading studies comparing CESM (contrast-enhanced spectral mammography) with standard two-dimensional (2D) mammography have shown a significant improvement in the sensitivity and specificity of CESM for detecting breast carcinomas. The improvement in sensitivity is due to the ability of CESM to identify tumors that would ordinarily be masked by the denser breast parenchyma on a conventional mammogram **[3]**.

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Lobbes et al., demonstrated accurate sizing of the index tumor with CESM, reporting strong correlations between tumour size measurement on CESM, MRI, and histopathological size as determined by surgical resection. The average difference between the tumour size as determined by CESM and histopathology was 0.03mm: MRI tended to slightly overestimate tumour size with a mean difference of 2.12mm [4].

Local staging of breast cancer not only depends on the identification of multifocal, multicentric, or contralateral disease, but also requires reliable tumour sizing to aid surgical planning. MRI is more accurate than conventional mammography and ultrasound for sizing primary breast cancer, but still not perfect with over and underestimation of tumour size reported [3].

In their pilot study, Jochelson et al., found out that both CEDM and MRI detected additional cancers not seen on conventional mammography, primarily invasive cancers and concluded that CEDM could be valuable as a supplemental imaging exam for women at increased risk for breast cancer who do not meet the criteria for MRI or for who have limited access to MRI [5].

In a study by Elsaied et al., of 21 women undergoing neoadjuvant chemotherapy, CESM had 100% sensitivity in detecting a complete pathological response, but a lower specificity at 67%, with six false negatives [6].

The pitfalls and limitations of Contrast-Enhanced Digital Mammography (CEDM), based on clinical experience and the current literature, include: Radiation exposure, contrast-related factors (possibility of allergic reactions, absolute or relative contraindications in the case of underlying medical illness, fasting required), false negatives, false positives, background parenchymal enhancement [7].

Patients and Methods

In the university hospital of Ain Shams, Demerdash breast imaging outpatient clinic, between April 2018 and January 2019, thirty female patients with forty-four breast lesions were enrolled in this study. It is a prospective observational study, approved by our institutional ethics committee. The patients' age ranges from 20-76 years old. They were all referred from the breast surgery clinic to the Demerdash breast imaging outpatient clinic for conventional digital mammography (GE Senographe pristina machine) and high resolution superficial ultrasound (standard examination on a GE Logic P9 machine using a superficial matrix linear 12-15 frequency probe).

Inclusion criteria:

BIRADS 3 lesions particularly in patients >3 years old or with positive family history, BIRADS 4 lesions, and BIRADS 5 lesions with the need to exclude multifocality or multicentricity.

Our exclusion criteria were renal impairment (serum creatinine >2mg/dl) and allergy to contrast medium.

All patients were subjected to clinical examination and conventional imaging (conventional mammography and ultrasound). The procedure, possible associated risks and complications were verbally explained to all the included patients. In addition, a written informed consent was obtained from each patient before the examination.

Contrast enhanced mammography studies were performed using Senographe Pristina, GE healthcare contrast enhanced mammography device. A single shot of 1.5ml/kg body weight, iodinated non-ionic contrast agent (ultravist 300), was administered using manual intravenous injection. Maximum allowed dosage was 100mL.

Two minutes after the initiation of contrast agent administration; a pair of LE (low energy) and HE (high energy) exposures were performed, the breast of concern was compressed in a CC position then the other breast. Then view of breast of concern in MLO position and last view of other breast in MLO position, in order to generate two subtracted images with contrast agent uptake information (one in the MLO and one in the CC view). The mean examination duration was approximately 10min (ranging from 6 to 12min).

Imaging analysis and interpretation:

As regards mammography and ultrasonography examination, the lesions were evaluated according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon designed by the American College of Radiology (ACR), site of the lesions, type (mass, architectural distortion, focal asymmetry), margin, definition and ± calcifications, then each lesion was assigned a BIRADS category accordingly.

In post contrast mammography examination, CESM MLO and CC views were assessed for the presence or absence of enhancement that was described as follows:

1- *Mass enhancement:* Indicating a mass lesion measuring 5mm or larger in its greatest dimension, seen in both mammography views. The following parameters were evaluated in enhancing mass lesions:

Shape: Oval, rounded or irregular.

Margins: Circumscribed (smooth or well defined), or ill-circumscribed including irregular/irregular and speculated margins.

Pattern of enhancement: Homogenous, heterogeneous or ring pattern.

Degree of enhancement: Mild, moderate or intense.

2- *Non mass enhancement:* Denoting an area of contrast enhancement with no actual space-occupying lesion. NME was described according to:

Distribution: Focal, linear, segmental or regional.

Pattern of enhancement: Homogenous or heterogeneous.

Intensity of enhancement: Mild, moderate or intense.

3- Non enhancing lesion.

Each lesion was assigned a BIRADS category according to its enhancement criteria and morphology descriptors, based on the (BI-RADS) lexicon designed by the American College of Radiology (ACR) for breast MR imaging.

Final diagnosis of malignant lesions was made according to the histopathological assessment of the lesion, obtained by core biopsy, surgical excision or radical surgery. Benign lesions were diagnosed by histopathology as well, however three patients refused undergoing core biopsy and therefore we relied on resolution/stability of the lesion on follow-up after ≥6 months to rule out underlying malignancy.

Results

Mammography and ultrasound examination of the 44 breast lesions included in this study revealed 4/44 (9.1%) benign lesions (i.e. BI-RADS 1 or 3) and 40/44 (90.9%) malignant lesions (i.e. BIRADS 4,5) (Table 1). Correlation with the final diagnoses revealed that 3/4 (75%) lesions were truly benign, while 1/4 (25%) lesion turned out to be histopathologically malignant. 22/40 (55%) were truly malignant, and 18/40 lesions (45%) were said to be malignant by FFDM + US (full-field digital mammography) but proved to be benign by histopathology.

Table (1): Demonstrating the results by FFDM + US in comparison to the final diagnoses.

FFDM + US	Final diagnosis		Total
	B	M	
1, 2, 3:			
Count	3	1	4
%	14.3%	4.3%	9.1%
4, 5:			
Count	18	22	40
%	85.7%	95.7%	90.9%
Total:			
Count	21	23	44
%	100.0%	100.0%	100.0%

Based on these findings, FFDM + US had a sensitivity of 95.7%, a specificity of 14.3%, a positive predictive value of 55% (PPV), a negative predictive value of 75% (NPV) and efficacy 56.8%.

Contrast Enhanced Spectral Mammography (CESM) was then performed to evaluated these 44 breast lesions. 9/44 (20.5%) lesions were categorized by CESM as benign lesions (i.e. BI-RADS 1 or 3) and 35/44 (79.5%) were categorized as malignant lesions (BIRADS 4,5). Correlation with the final diagnoses (Table 2) revealed that all 9 lesions were truly benign and 23/35 (65.7%) were truly malignant, while 12/35 (34.3%) turned out to be benign.

Table (2): Demonstrating the results of CESM in comparison to the final diagnoses.

CESM	Final diagnosis		Total
	B	M	
1, 2, 3:			
Count	9	0	9
%	42.9%	0.0%	20.5%
4, 5:			
Count	12	23	35
%	57.1%	100.0%	79.5%
Total:			
Count	21	23	44
%	100.0%	100.0%	100.0%

p-value <0.001.

Therefore, in our study CESM had a sensitivity of 100%, a specificity of 42.9%, a Positive Predictive Value of 65.7% (PPV), a Negative Predictive Value of 100% (NPV) and efficacy 72.7%.

7 lesions out of the total 44 lesions demonstrated contradiction between the conventional imaging (FFDM + US) and CESM regarding the benign/malignant nature of lesions and therefore essentially their BIRADS category. These lesions were up-

graded/downgraded after performing CESM as follows:

6/7 lesions were said to be malignant by FFDM + US but were said to be free of malignancy by CESM; where 5 lesions were categorized as BIRADS 4 and 1 was categorized as BIRADS 5 by FFDM + US, but all 6/7 lesions revealed no corresponding enhancement (i.e. BIRADS 1) and were diagnosed as benign or normal tissue by histopathology.

1/7 lesions was considered probably benign (BIRADS 3) by FFDM + US but probably malignant (BIRADS 4) by CESM, and turned out to be invasive ductal carcinoma by post-operative histopathological assessment.

4 out of 44 lesions showed different BIRADS categorization by conventional imaging and CESM, however both modalities still agreed about their nature; 3/4 were probably malignant by FFDM + US (BIRADS 4) and typically malignant by CESM (BIRADS 5), all three proved to be malignant by histopatholology Fig. (1).

1/4 lesion was not detected by FFDM + US (BIRADS 1) and was seen as a small oval shaped ring enhancing lesion for follow-up (BIRADS 3), which resolved on follow-up CESM after 6 months.

In other words, 11/44 lesions demonstrated disagreement between the conventional imaging and CESM, about either BIRADS categorization only or both BIRADS category and histopathological nature of the lesion (7/44 and 4/44 respectively) as emphasized above.

The remaining 33/44 lesions, represented agreement between FFDM + US and CESM about BIRADS categorization and essentially the nature of lesions; 15/44 lesions were considered BIRADS 5 by both FFDM + US and CESM and turned out to be malignant on histopathology.

2/44 lesions were considered BIRADS 3 lesions by both FFDM + US and CESM and both proved to be benign lesions Fig. (2).

On the other hand, 15/44 lesions were categorized as BIRADS 4 by both CESM and FFDM + US; 4 lesions only out of 15 turned out to be malignant on histopathological assessment, while 11 leisons were diagnosed as benign lesions.

The remaining 1/44 lesion was assigned BIRADS 5 category by both FFDM + US and CESM and proved to be benign by histopathological assessment.

Among the 30 patients enrolled in our study, 6 cases had multifocal/multicentric disease; 3/6 (50%) were detected by FFDM, 5/6 (83.3%) were detected by US, while 6/6 (100%) were detected by CESM.

According to the above mentioned results, when comparing diagnostic indices for CESM and FFDM + US (Table 3), CESM showed higher sensitivity than FFDM + US (100% and 95.7% respectively) for the detection of breast cancer with specificity of 42.9% and 14.3% in favor of CESM. The PPV and the NPV for CESM was 65.7% and 100% respectively compared to FFDM + US which was 55% and 95.7% respectively. CESM achieved efficacy of 72.7% in comparison to FFDM + US: 56.8%. Besides, Area Under the Curve (AUC) demonstrated that the diagnostic performance of the CESM was higher than FFDM + US in our study (AUC: FFDM + US=0.870 and CESM= 0.946).

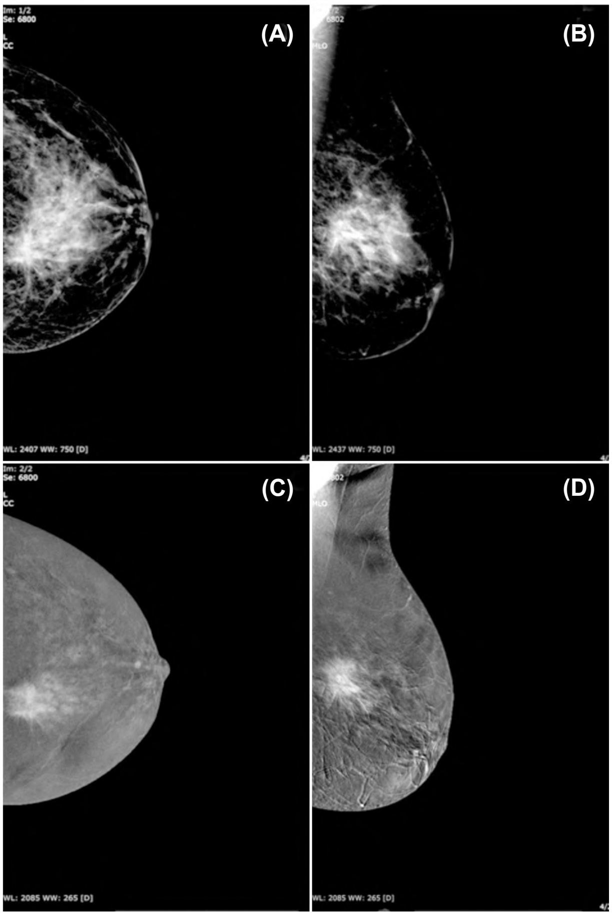

Fig. (1): 68 year old patient complaining of left breast lump, Mammography images (A, B) Craniocaudal CC and mediolateral oblique MLO): Revealed a suspicious left breast architectural distortion, (C, D) Recombined images RI, CC and MLO, after contrast administration a suspicious breast mass was revealed with irregular shape, spiculated margins with moderate heterogenous contrast enhancement and multiple satellite foci around, histopathological assessment revealed invasive ductal carcinoma GII.

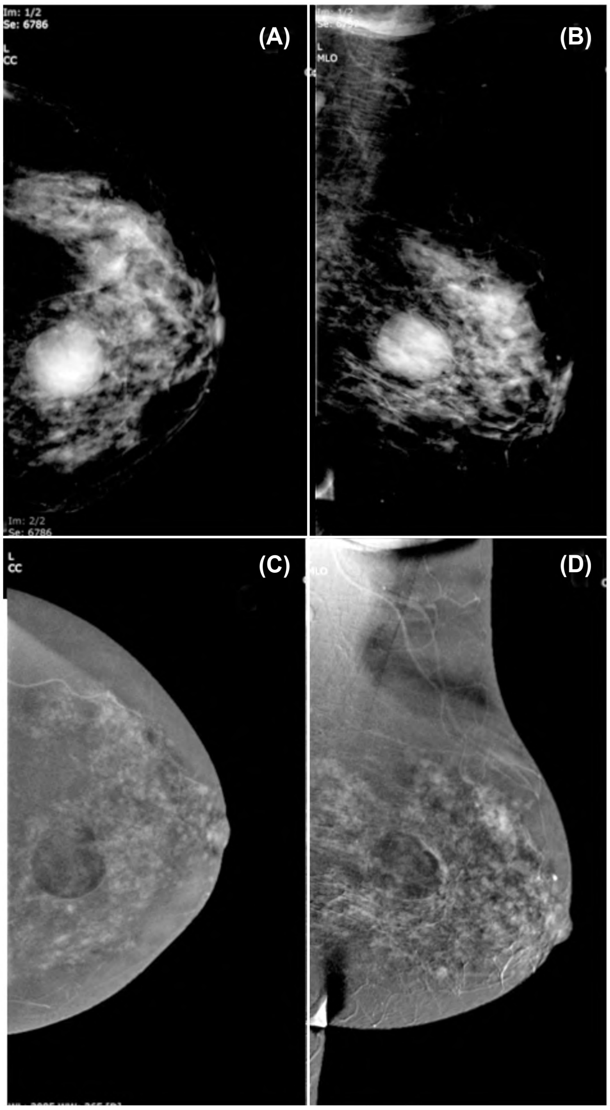

Fig. (2): 51 year old patient presented with left breast lump, (A, B) Craniocaudal CC and mediolateral oblique MLO Mammography images showed an oval shaped radio-opaque mass with well circumscribed margins, (B, C) after IV contrast administration, the recombined images RI (CC and MLO) the lesion showed peripheral thin, regular, faint ring enhancement suggestive of benign lesion by CESM criteria. FNAC revealed pus cells i.e. complicated cyst.

Table (3): Demonstrating the diagnostic performance of both CESM and FFDM + US.

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Efficacy (%)
CESM	100	42.9	100	65.7	72.7
FFDM + US	95.7	14.3	95.7	55	56.8

Discussion

CESM has been widely researched over the last few years. Initial studies done by Dromain et al., concluded that the adjunctive use of temporal CESM improved the sensitivity and specificity of detection and characterization of breast masses than conventional mammography alone [2].

Dual-energy CESM provides the functional information, besides the advantage of bilateral breast exams with potentially only one contrast agent injection. It is a fast imaging technique that provides a direct correlation with conventional mammograms [6].

In the meta-analysis by Tagliafico et al., 2016, the estimated sensitivity from 8 eligible studies (all were published in 2013-2105) was: 98% (95% CI: 0.96-1.00). Specificity was estimated from 6 studies reporting raw data: 58% (95% CI: 0.38-0.77), concluding that CESM has a high sensitivity but very low specificity [10].

These results correlated with our study; CESM achieved sensitivity 100%, specificity 42.9%, NPV 100% and PPV 65.7%. Our results were also comparable to Helal et al., in their study in 2017 which included 30 female patients with 35 breast lesions, they reported that the sensitivity of dual energy CESM 95.2% and NPV 90%, which proved to be higher than those of FFDM and US [9].

Saraya et al., 2017 also stated that the sensitivity and NPV of CESM were 93.75% and 95.4% respectively, significantly higher than FFDM, in agreement with our results [1]. However both studies reported specificity and PPV considerably higher than those in our study (sp.: 91.3% and PPV: 88.2% by Saraya et al. 2017-sp.: 64.3% and PPV: 80% by Kamal et al., in 2017).

Moustafa et al., in their study in 2018, concerned with detection of multiplicity of lesions in dense breasts, reported that 100% of multifocal/multicentric disease were detected by CESM in comparison to 81.8% by sonomammography [8]. This was also observed by Helal et al., in 2017, where 100% of multifocal/multicenteric disease cases were diagnosed by CESM, 6/7 (85.7%) by US and 2/7 (28.6%) by FFDM [9].

CESM proved to be reliable in detection of multifocal/multicenteric disease in our study as well; all cases were detected by CESM 6/6 (100%), 5/6 (83.3%) by US and 3/6 (50%) by FFDM.

In the study by Saraya et al., in 2017, they included 34 female patients with 39 BIRADS 3 and 4 breast lesions. These patients were subjected to FFDM and CESM examinations, comparing BIRADS categorization by both modalities in reference to histopathological diagnosis. They observed disagreement between FFDM and CESM about 35.89% of the lesions, where 23.07% of the lesions' BIRADS scores were upgraded and 12.8% down graded. In reference to histopathological diagnoses, CESM BIRADS categorization was more accurate in 100% of up/down graded lesions [1] . These results were comparable to our results. Although our study was concerned with comparing FFDM + US and CESM BIRADS categorization, 100% of up/down graded lesions also proved CESM to be correct in reference to the final diagnosis. With 25% disagreement including upstaged and down staged lesions in 11.36% and 13.6% respectively.

Conclusion:

CESM has better diagnostic performance than mammography plus Ultrasound and provides a valuable tool to accurately evaluate equivocal and suspicious breast lesions.

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آفات الثدى الملتبسة والمريبة:
هل يمكن أن يغير تصوير الثدى بالأشعة الطيفية بالصبغة
من تصنيف ال (BIRADS) قاموس تقارير تصوير الثدى ونظام البيانات؟

الهدف من البحث هو تقييم إمكانات فحص الماموجرام بالصبغة فى تغيير الدرجة الموكلة لآفات الثدى المريبة والملتبسة لدرجة أعلى أو أقل بعد إستخدام الآشعة بالصبغة.

أدرج فى الدراسة ثلاثين سيدة (٤٤ آفة ملتبسة ومريبة) تتراوح أعمارهم من ال ٢٠ ال ٧٦ عاماً كل السيدات خضعن لفحص الموجات الصوتية والماموجرام التقليدى ثم آشعة الماموجرام بالصبغة.

فحص الموجات الصوتية والماموجرام التقليدى صنف ٤٠/٤٤ آفة (٩٠.٩٪) كمريبة و٤/٤٤ أى (٩.١٪) كحميدة. آشعة الماموجرام بالصبغة صنفت ٣٥/٤٤ آفة (٧٩.٥٪) كخبيثة و٩/٤٤ آفة (٢٠.٥٪) كحميدة. إذاً عدم التطابق بين النتائج لوحظ فى ٢٥٪ من الحالات سواءاً بالزيادة أو النقصان فى التصنيف، ١١.٣٦٪ و٦، ١٣٪ على التوالى. ١٠٠٪ من التصنيف الذى أدرجته آشعة الماموجرام بالصبغة أثبتت صحتها فى التشخيص النهائى.

آشعة الماموجرام بالصبغة لديها أداء تشخيصى أفضل من تصوير الماموجرام التقليدى للثدى بالإضافة إلى الموجات فوق الصوتية ويوفر أداة قيمة لتقييم آفات الثدى الملتبسة والمريبة بدقة.