Contrast-Enhanced Digital Mammography Versus Digital Mammography in The Discrimination between Benign and Malignant Breast Lesions

Omar M Mahmoud[1*], Roaa M A Shehata[1], Mostafa A M El-Sharkawy[2], Hosam M Kamel[1]
Radiology Department, South Egypt Cancer Institute[1], Radiology Department,
Faculty of Medicine[2], Assiut University, Assiut, Egypt
Corresponding author: Omar M Mahmoud, e-mail: omr.mohamed@aun.edu.eg. Mobile phone: 01005781938,
ORCID:0000-0002-9663-1733

ABSTRACT
Background: The diagnosis of breast cancer is based on a clinical examination, sono-mammography, and magnetic resonance imaging. Mammography is considered a key tool in the diagnosis and early identification of breast cancer. However, a quarter of malignant cases are missed by using mammographic screening alone. Contrast-enhanced digital mammography (CEDM) has increased the opportunity for early detection and better Breast Imaging-Reporting and Data System (BI-RADS). assessment of breast cancer patients. **Results:** This prospective study included 115 patients, 75% were malignant and 25% were benign. Full-field digital mammography (FFDM) and CEDM were performed using the FUJIFILM Innovality mammography machine unit. The receiver operating characteristic (ROC) curve and Youden index analysis showed increased overall diagnostic performance of CEDM over FFDM alone, with the area under the curve (AUC) of 0.900 versus 0.755 (P = 0.0020). CEDM showed increased specificity 80% versus 65%, sensitivity 94.7% versus 86%, and accuracy 88.3% versus 80.5% (P <0.001) compared to FFDM alone. The calculated accuracy of CEDM in the detection of the multiplicity of malignant lesions was increased by 44.4% versus 27% compared to FFDM alone. CEDM improved the BI-RADS categorization of breast lesions and increased the accuracy in the detection of bilateral malignant breast lesions by 8.3% versus 5.5% compared to FFDM.
Conclusion: CEDM is a more potent imaging modality than FFDM alone in the discrimination between benign and malignant breast lesions, it improves the accuracy of BI-RADS categorization of breast lesions and is better in the evaluation of the multiplicity of breast cancer.
Keywords: Benign, Breast, Contrast-enhanced digital mammography, Malignant.

INTRODUCTION

The most frequent cancer in women that can lead to death is breast cancer. It is the most prevalent cancer in women in both industrialized and developing nations, accounting for 22.9% of all new cases of female cancer [1]. Breast cancer diagnosis relies heavily on mammography [2]. Mammographic screening for early diagnosis of breast cancer especially in clinically occult diseases decreases breast cancer-related mortality [3]. But the dense breast and surgically modified breast restrict the diagnostic accuracy of mammography as the lesions are obscured by surrounding fibroglandular tissues [4]. Contrast-enhanced digital mammography (CEDM) is an emerging imaging modality that is based on the utilization of IV contrast material for the detection of breast neovascularity in a way similar to breast MRI. In breast cancer patients, the vessels formed through the angiogenesis process leak the contrast material, and the contrast spreads through the tumor tissue, leading to an enhanced image. This makes the malignant tumor be visualized through the dense breast tissue [5-9].

CEDM can be beneficial in the classification of breast lesions. It can also detect the extent of the disease more properly. Moreover, it can be helpful for biopsy or excision guidance. Once it is available, it will be comparatively less cost-effective than the MRI method [10].

This research aims to compare the sensitivity, specificity, and accuracy of CEDM and FFDM in the evaluation of breast lesions.

PATIENTS AND METHODS

In this prospective study 115 female patients aged 25-75 years, "mean age 49.9", with clinically or radiologically detected breast lesions were diagnosed pathologically either by tru-cut needle biopsy (TCNB) (98 patients) or excisional biopsy (17 patients) after they were examined by FFDM and CEDM. This study was performed between August 2020 and February 2022.

Ethical approval:
Approval of this study was decided by the Ethics Committee of South Egypt Cancer Institute and the researchers took informed written consent from each patient. This research is in the agreement with Declaration of Helsinki, the ethical code of the World Medical Association for research including human experiments.

Exclusion criteria:
We excluded patients with any contraindications to X-ray exposure, patients who had hypersensitivity to intravenous contrast material injection, or those with high renal function tests or who had bad general conditions.

Mammography examination:
Our examination protocol started with:
- Place an intravenous line in the arm or forearm vein opposite the side of the breast lesion of concern.
- FFDM examination for the breasts using (FUJIFILM Innovality mammography machine unit, *JAPAN)* with craniocaudal (CC), and mediolateral oblique (MLO) views.
- Dual-energy CEDM acquisitions set time about 4-7 minutes (min) maximally with applying good

compression of the breast after contrast injection to minimize the motion artifact.

o Each mammographic exposure yields two sets of images: a low-energy (26-31 Kvp), high energy (45-94 Kvp), and a recombined subtracted image.

o The initial exposure began two minutes after the manual injection of a single dose of 1.5 mL/Kg body weight of a non-ionic iodinated contrast medium in the CC position for the normal breast, then CC and MLO positions for the breast of concern, and finally MLO position of the normal breast.

Analysis of images:

Two radiologists with 22 and 12 years of experience in breast imaging concurrently examined the images.

FFDM: The images were examined for the existence of lesions and their characterization was done concerning type (foci, mass, architectural distortion, focal asymmetry, or global asymmetry), density (hypo-dense, iso-dense, or hyper-dense), margins (regular circumscribed, lobulated, obscured, indistinct margins, or speculated margins), presence of calcification (micro-calcifications, macro-calcifications, or did not have calcifications), BI-RADS score, the multiplicity of lesions (single, multifocal, multicentric or bilateral) and ACR density (A, B, C, or D) of the examined breasts.

After **CEDM**, the subtracted images were analyzed for the presence or absence of contrast enhancement. If enhancement was detected we classified it into a mass or non-mass enhancement.

As regards the mass enhancement, they were assessed:

- Enhancement pattern (homogenous, heterogeneous, or marginal rim post-contrast enhancement).
- Enhancement intensity (faint, mild, moderate, and intense enhancement).

Table 1: Patient demographic data (N-115)

- Multiplicity of the lesions (single, multifocal, or multicentric).
- Bilaterally of the masses.

As regards non-mass enhancement, they were evaluated concerning:

- Distribution of enhancement (linear ductal, segmental, regional, or diffuse).
- Enhancement pattern (homogenous, heterogeneous, or peripheral ring enhancement).
- Enhancement intensity (faint, mild, moderate, or intense enhancement).

As there isn't a standardized BI-RADS Lexicon to CEDM, each breast lesion was evaluated using the BI-RADS category according to the MRI American College of Radiology Breast-Imaging Reporting and Data System (BI-RADS) 2013 [11].

Statistical analysis

By using IBM SPSS version 20, statistical analysis was done and we assessed the efficacies of the significant parameters by using Fisher's Exact test. We compared the specificity, sensitivity, negative predictive value (NPV), positive predictive value (PPV), and the accuracy of FFDM and CEDM using a ROC curve and Youden index. P value <0.05 was considered significant.

RESULTS

Among the 115 female patients, 86 were malignant (74.8 %) and 29 were benign (25.2%). The pathological diagnosis was done either by surgical excision (17 cases) or TCNB (98 cases) of the lesion. 3 cases (2.6%) had a previous history of breast cancer. One case (0.9%) had a history of ovarian cancer, one case (0.9%) had a history of epithelioid sarcoma of the hand, and 2 cases (1.7%) had a history of fibroadenoma excision. 5 cases (4.3%) had received previous chemotherapy and radiotherapy. Table 1 lists the demographic information and clinical presentation of the patients.

Demographic data		No.	Percent
Menopausal state	premenopausal	50	43.5%
	postmenopausal	65	56.5%
Marital state	Married	103	89.6%
	Unmarried	12	10.4%
Parity state	Nulliparous	16	13.9%
	Multiparous	99	86.1%
Symptoms	Breast mass	46	40%
	Bleeding per nipple	2	1.7%
	Breast pain	2	1.7%
	Incidentally discovered	1	0.9%
Family history of breast cancer	Yes	11	9.6%
	No	104	90.4%

Surgical and histopathological findings

This study included 115 patients. 86 patients had malignant lesions while 29 patients had benign lesions. The number of breast lesions in each pathological type is shown in table 2.

Table 2: Histopathological types of 115 breast lesions

Pathological type of the lesion	Number of cases	Percent
Invasive ductal carcinoma	73	63.5%
Ductal carcinoma in situ	5	4.3%
Lobular carcinoma	3	2.6%
Undifferentiated carcinoma	3	2.6%
Lymphoma	2	1.7%
Fibroadenoma	15	13.0%
Focal adenosis	3	2.6%
Intraductal papilloma	3	2.6%
Phyllodes tumor	2	1.7%
Granulomatous mastitis	2	1.7%
Foreign body granuloma	1	0.9%
Fibrocystic disease	3	2.6%
Total	115	100%

- 29 cases were found to have multiple malignant breast lesions,
  - 19 of them were diagnosed pathologically as multifocal.
  - 10 of them were diagnosed pathologically as multicentric.
- 42 of the cases had a single malignant breast lesion for each case.
- 6 cases had bilateral malignant lesions.
- 6 cases were found to have multiple benign breast lesions.
- 5 cases had bilateral benign lesions.
- 9 patients had both benign and malignant lesions.
- 9 cases had a single benign breast lesion.

Image analysis:
1-Full field digital mammography images analysis
Type of lesions: 91 lesions were described as a mass, 2 lesions were described as architectural distortion, 11 lesions were described as focal asymmetry, 9 lesions were described as global asymmetry, and 2 lesions weren't detected by digital mammography.

Density: 3 masses were hypo-dense, 49 masses were iso-dense, and 39 masses were hyper-dense.

Margins: Regular margins were present in 6 masses, lobulated margins in 10, obscured margins in 8, indistinct margins in 49, and speculated margins in 18 masses.

Presence of calcifications: 31 lesions showed micro-calcifications, 9 lesions showed macro-calcifications, and 75 did not have calcifications.

According to the FFDM BI-RADS scoring system of the breast, the lesions were as follows:
- 2 lesions were BI-RAD 0.
- 2 lesions were BI-RAD 1.
- 2 lesions were BI-RADS 2.
- 24 lesions were BI-RADS 3.
- 69 lesions were BI-RADS 4 (4a: 29, 4b: 6, 4c: 34 lesions).
- 16 lesions were BI-RADS 5.

The ACR density of the examined breasts was as follows:
- 6 breast densities were ACR A.
- 68 breast densities were ACR B.
- 35 breast densities were ACR C.
- 6 breast densities were ACR D.

The multiplicity of the lesions:
- 20 cases (17.4%) were found to have multiple malignant breast lesions,
  - 13 (11.3%) of them were diagnosed as multifocal.
  - 7 (6.1%) of them were diagnosed as multicentric.
- 3 cases (2.6%) had bilateral malignant lesions.
- 5 cases (4.3%) were found to have multiple benign breast lesions.
- 3 cases (2.6%) had bilateral benign lesions.

By FFDM when considering BI-RADS 4 and 5 as malignant, efficacies of the significant parameters at (P <0.001) were summarized in table 3.

2-Contrast enhanced digital mammography (CEDM) image analysis:
Presence of post-contrast enhancement:
- 98 lesions showed post-contrast enhancement.
- 17 did not show post-contrast enhancement.

Type of enhancement:
- 91 were described as a mass enhancement.
- 10 were described as a non-mass enhancement.
- 14 were described as non-enhancing mass.

As regards the mass enhancement, they were evaluated as follows:
The pattern of enhancement:
- 13 masses displayed homogenous post-contrast enhancement,
- 74 masses displayed heterogeneous post-contrast enhancement.
- 4 mass displayed marginal rim post-contrast enhancement.

The intensity of enhancement:
- 7 lesions displayed faint enhancement.
- 22 lesions displayed mild enhancement.
- 46 lesions displayed moderate enhancement.
- 16 lesions displayed intense enhancement.

As regards non-mass enhancement, they were evaluated as follows:
Distribution of enhancement:
- 3 lesions showed regional distribution.
- 1 lesion showed ductal distribution.
- 3 lesions showed segmental distribution.
- 3 lesions showed diffuse distribution.

The pattern of enhancement:
- 1 lesion showed homogenous enhancement.
- 8 lesions showed heterogeneous enhancement.
- 1 lesion showed peripheral ring enhancement.

The intensity of enhancement:
- 1 lesion displayed mild enhancement.
- 8 lesions displayed moderate enhancement.
- 1 lesion displayed intense enhancement.

According to the BI-RADS scoring system of the breast, the lesions after CEDM were as follows:
- 15 lesions (13%) were BI-RADS 2.
- 9 lesions (7.8%) were BI-RADS 3.
- 37 lesions (32.2%) were BI-RADS 4 (4a: 9, 4b: 1, 4c: 15 lesions).
- 54 lesions (47%) were BI-RADS 5.

The multiplicity of the lesions:
- 29 cases (25.2%) had multiple malignant breast masses.
  - 19 (16.5%) of them were diagnosed pathologically as multifocal.
  - 10 (8.7%) of them were diagnosed pathologically as multicentric.
- 5 cases (4.3%) had bilateral malignant masses.
- 6 cases (5.2%) were found to have multiple benign breast lesions,
- 1 case (0.9%) had bilateral multiple benign lesions.

By CEDM, none or faint contrast uptake was considered benign and mild, moderate and intense contrast was considered malignant, and regarding the enhancement pattern, homogenous enhancement was considered benign, while heterogeneous, and marginal rim enhancement was considered malignant, and BI-RADS 4 and 5 were considered malignant lesions. Table 3 provides a summary of the efficacy of the significant parameters at (P <0.001) using Fisher's Exact test. Comparing the specificity and sensitivity between CEDM and FFDM using a ROC curve and Youden index, we found a significant difference in diagnostic performance between them (P = 0.002) with AUC for CEDM being 0.900 and for FFDM being 0.755.

Table 3: CEDM efficacy parameters at (P <0.001)

Efficacy parameter	FFDM	CEDM
Specificity	65%	80%
Sensitivity	86%	94.7%
PPV	87.5%	93.1%
NPV	61.9%	84.2%
Accuracy	80.5%	88.3%

FFDM=Full field digital mammography. CEDM=Contrast-enhanced digital mammography. PPV=Positive predictive value. NPV=Negative predictive value.

We found that the accuracy of CEDM in the detection of the multiplicity of malignant lesions was increased by 25.2% versus17.4% compared to FFDM, after the exclusion of benign patients (29 patients). CEDM accuracy was increased in the detection of bilateral malignant breast lesions by 4.3% versus 2.6% compared to FFDM.
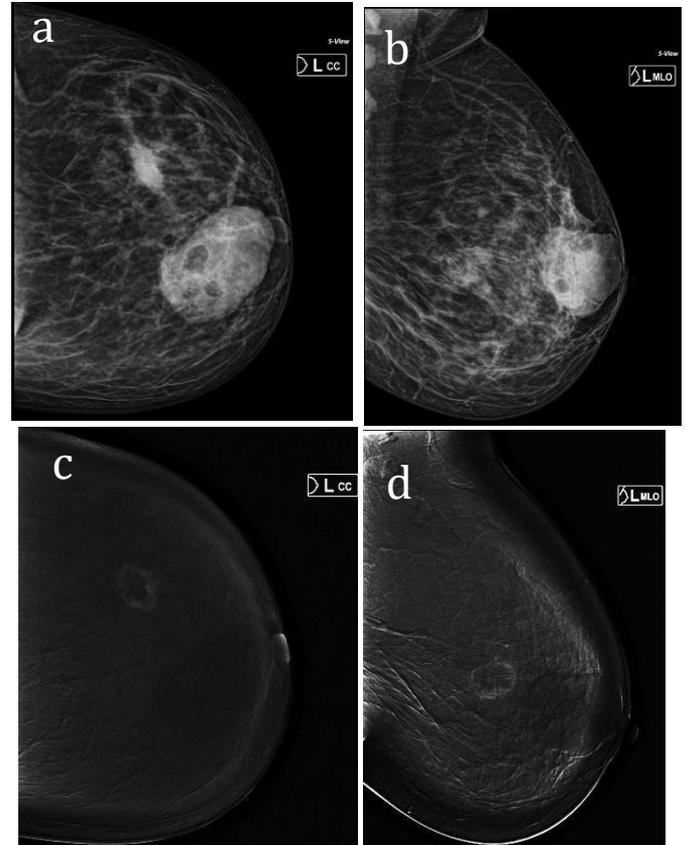

Figure 1: A 40-year-old lady, presented with a left breast mass and breast pain, she had a history of recurrent epithelioid carcinoma of the right hand. Digital mammographic CC (a) and MLO (b) views demonstrate two breast masses; one of them is a well-defined oval-shaped radio-opaque left retro-areolar lesion with lucent areas within, no detected micro or macro calcifications, intact overlying skin. The other lesion is an ill-defined hyper-dense lesion in the upper outer quadrant with an irregular outline, no detected calcifications inside, and intact overlying skin. BI-RADS 4b.

CEDM CC (c) and MLO (d) views demonstrate the first described lesion doesn't show post-contrast enhancement, and the second one show thick wall irregular peripheral rim heterogeneous moderate enhancement. BI-RADS 5. Pathologic findings of the first lesion revealed fibroadenoma and the second lesion revealed invasive duct carcinoma, NST, grade II.
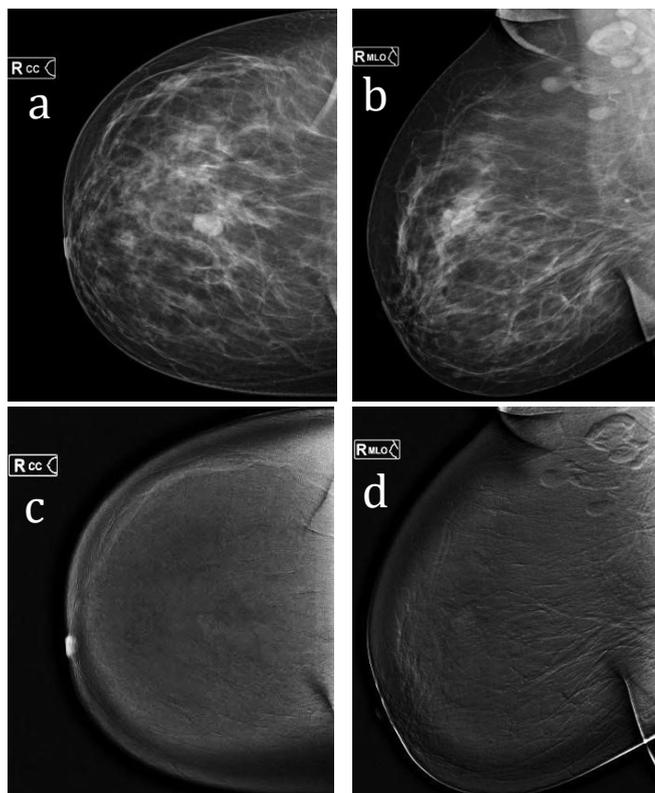
Figure 2: A 40-year-old lady, presented with a right breast mass. Digital mammographic CC (a) and MLO (b) views demonstrate a well-defined lobulated right upper outer quadrant iso-dense breast mass, no detected calcifications inside, and intact overlying skin. BI-RADS 4a. CEDM CC (c) and MLO (d) views show no post-contrast enhancement. Pathologic findings revealed benign proliferative breast disease mostly fibroadenoma.
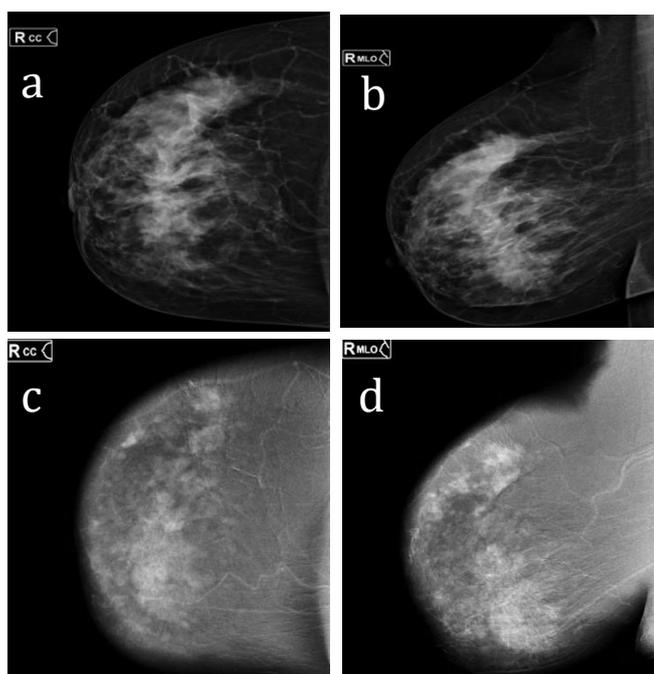

Figure 3: A 45-year-old patient, presented with a right breast mass. Digital mammographic CC (a) and MLO (b) views of the right breast demonstrate an area of distorted architecture with focal asymmetry at the lower inner quadrant of the right breast, no detected

calcifications inside, and normal skin thickness. CEDM CC (c) and MLO (d) views demonstrate this lesion shows moderate heterogeneous enhancement with multiple stellate nodules at the upper outer quadrant denoting multicentric malignant breast mass. Pathologic findings revealed invasive micropapillary carcinoma.

DISCUSSION

Dual-energy CEDM is a novel breast imaging modality that can be utilized alongside mammography for breast cancer detection [8]. CEDM works with a similar mechanism to DCE-MRI in detecting tumor angiogenesis for early breast cancer diagnosis with the more convenient and relatively less costly mammography [12].

In this study, the AUC of 0.900 for CEDM versus 0.755 for FFDM (P = 0.002) demonstrated that CEDM had superior diagnostic performance than FFDM alone in the discriminating of benign and malignant breast lesions, as determined by Fisher's Exact test, ROC curve, and Youden index analysis. When compared to FFDM alone, CEDM had a higher specificity of 80 % versus 65 %, a higher sensitivity of 94.7 % versus 86 %, and a higher accuracy of 88.3 % versus 80.5 % (P < 0.001).

CEDM exhibited a statistically significant difference and was a more effective imaging modality in the discrimination and characterization of breast lesions than FFDM alone, improved BI-RADS categorization of breast lesions, and it was superior in the diagnosis of multifocality, multicentricity, and bilaterality of breast cancer.

Our results were comparable to CEDM sensitivity and specificity in the detection and discrimination of breast lesions as reported by other studies such as **Mori et al.** [9], **Tennant et al.** [13], and **Jochelson et al.** [14].

In a study of 142 breast lesions, **Tennant et al.** [13] found that CEDM had a higher sensitivity (93%) than conventional mammography alone (78%) (P < .001), but the specificity remained equal. They concluded that CEDM improved breast cancer detection and staging and could be used as the primary mammographic investigative method.

According to **Jochelson et al.** [14], CEDM showed a sensitivity of 96% and PPV 97% (P =0.01), which was greater than conventional digital mammography and equivalent to MRI. **Mori et al.** [9] study reported that CEDM is superior to conventional mammography (MG) for breast cancer diagnosis with a sensitivity of 86.2%, and specificity of 94.1%.

Because of the large number of cases studied by **Lalji et al.** [2], **Lobbes et al.** [8], and **Łuczyńska et al.** [15], our study results regarding CEDM sensitivity and specificity in discrimination of breast lesions were lower than them. However, our study results concluded that differences between conventional mammography

and CEDM were statistically significantly similar to their results.

In a study by **Łuczyńska** *et al.* [15] on 225 breast lesions identified by CEDM and MG, they found that CEDM's sensitivity was higher than MG's (100 % vs. 90%, respectively, p=0.010), and in a study by **Lalji** *et al.* [2] on 199 patients, CEDM had a specificity of 70% and a sensitivity of 97% in comparison to conventional mammography. In contrast to mammography, **Lobbes** *et al.* [8] reported that CEDM had a sensitivity of 100 % and a specificity of 87.7% in a sample of 113 patients. They found that there is a statistically significant difference between conventional mammography and CEDM (p<0.0001) [6].

Our study results regarding the superiority of CEDM over FFDM in the diagnosis of multifocality, multicentricity, and bilaterality of breast cancer matches those reported by **Moustafa** *et al.* [16] who concluded that CEDM had an offered value in the preoperative assessment of breast masses by enhancing the accuracy of lesions identification and multiplicity and **Hashem** *et al.* [17] reported that CEDM enhances the BI-RADS evaluation of malignant cases and it is also useful in the detection of multifocal and multicentric lesions.

LIMITATIONS
- The limitation of this work is that it was conducted on Fujifilm Innovality machine and its specific software, which allows for subjective and qualitative assessment, and doesn't allow for quantitative assessment of lesions enhancement.
- Another limitation is a relatively small number of studied patients.

CONCLUSION

CEDM is a more potent and powerful imaging modality than FFDM alone in the characterization of benign and malignant breast lesions, it improves the accuracy of BI-RADS categorization of the breast lesions and it is better in the diagnosis of the multifocality, multicentricity, and bilaterality of breast cancer.

REFERENCES
1. **Helal M, Samra M, Ibraheem M** *et al.* **(2017):** Accuracy of CESM versus conventional mammography and ultrasound in the evaluation of BI-RADS 3 and 4 breast lesions with pathological correlation. *The Egyptian Journal of Radiology and Nuclear Medicine*, 48(3): 741-750.
2. **Lalji U, Houben I, Prevos R** *et al.* **(2016):** Contrast-enhanced spectral mammography in recalls from the Dutch breast cancer screening program: validation of results in a large multireader, multicase study. *European radiology*, 26(12): 4371-4379.
3. **Lee C, Dershaw D, Kopans D** *et al.* **(2010):** Breast cancer screening with imaging: recommendations from the Society of Breast Imaging and the ACR on the use of mammography, breast MRI, breast ultrasound, and other technologies for the detection of clinically occult breast cancer. *Journal of the American college of radiology*, 7(1): 18-27.
4. **Weidner N, Semple J, Welch W** *et al.* **(1991):** Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma. *New England Journal of Medicine*, 324(1): 1-8.
5. **Sung J, Lebron L, Keating D** *et al.* **(2019):** Performance of dual-energy contrast-enhanced digital mammography for screening women at increased risk of breast cancer. *Radiology*, 293(1): 81.
6. **Jochelson M and Lobbes M (2021):** Contrast-enhanced mammography: State of the art. *Radiology*, 299(1): 36-48.
7. **Ghaderi K, Phillips J, Perry H** *et al.* **(2019):** Contrast-enhanced mammography: current applications and future directions. *Radiographics*, 39(7): 1907-1920.
8. **Lobbes M, Lalji U, Houwers J** *et al.* **(2014):** Contrast-enhanced spectral mammography in patients referred from the breast cancer screening programme. *European radiology*, 24(7): 1668-1676.
9. **Mori M, Akashi-Tanaka S, Suzuki S** *et al.* **(2017):** Diagnostic accuracy of contrast-enhanced spectral mammography in comparison to conventional full-field digital mammography in a population of women with dense breasts. *Breast Cancer*, 24(1): 104-110.
10. **Cheung Y, Lin Y, Wan Y** *et al.* **(2014):** Diagnostic performance of dual-energy contrast-enhanced subtracted mammography in dense breasts compared to mammography alone: interobserver blind-reading analysis. *European radiology*, 24(10): 2394-2403.
11. **Edwards S, Lipson J, Ikeda D** *et al.* **(2013):** Updates and revisions to the BI-RADS magnetic resonance imaging lexicon. Magnetic Resonance Imaging Clinics, 21(3): 483-93.
12. **Polat D, Evans W and Dogan B (2020):** Contrast-enhanced digital mammography: technique, clinical applications, and pitfalls. *American Journal of Roentgenology*, 215(5): 1267-1278.
13. **Tennant S, James J, Cornford E** *et al.* **(2016):** Contrast-enhanced spectral mammography improves diagnostic accuracy in the symptomatic setting. *Clinical radiology*, 71(11): 1148-1155.
14. **Jochelson M, Dershaw D, Sung J** *et al.* **(2013):** Bilateral contrast-enhanced dual-energy digital mammography: feasibility and comparison with conventional digital mammography and MR imaging in women with known breast carcinoma. *Radiology*, 266(3): 743.
15. **Łuczyńska E, Niemiec J, Hendrick E** *et al.* *(2016):* Degree of enhancement on contrast enhanced spectral mammography (CESM) and lesion type on mammography (MG): comparison based on histological results. *Medical science monitor: International medical journal of experimental and clinical research*, 22: 3886.
16. **Moustafa A, Kamal E, Hassan M** *et al.* **(2018):** The added value of contrast-enhanced spectral mammography in the identification of multiplicity of suspicious lesions in dense breast. *The Egyptian Journal of Radiology and Nuclear Medicine*, 49(1): 259-264.
17. **Hashem L, Abd El Hamid N, Kamal R** *et al.* **(2021):** Does contrast-enhanced mammography have an impact on the detection of cancer in patients with risk of developing breast cancer? *Egyptian Journal of Radiology and Nuclear Medicine*, 52(1): 1-10.