Role of Contrast Enhanced Mammography in Assessment of Focal Breast Asymmetry

Ghada S. Eliwa[a] , Hesham E. Elshaikh[b] , Gamal E. Elhabbaa[c], Lamia A. Salah Eldin [b]

[a] Department of radiology, Mshtoul hospital ,Mashtoul, Sharkia, Egypt. [b] Department of radiology, Benha faculty of medicine, Banha University, Egypt. [c] Department of surgery, Benha faculty of medicine, Banha University, Egypt.

Correspondence to: Ghada S. Eliwa, Department of radiology, Mshtoul hospital ,Mashtoul, Sharkia, Egypt

Email:

ghada.salah.elsisi@gmail.com

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Abstract

Background: Contrast enhanced mammography (CESM) is one of the relatively novel imaging modalities. Many studies have suggested that CESM is superior to mammography in the identification of multiplicity, extent and size of malignant lesions especially in the dense breast parenchyma **Aim:** Characterization of focal breast asymmetry by using intravenous contrast material with full-field digital mammography. **Methods:** This study included 60 female patients who presented for screening and diagnostic mammogram at mammography unit in Egyptian National Cancer Institute. All enrolled cases had focal breast asymmetries detected on mammogram. Ultrasound examination and CESM using dual-energy acquisitions were performed for all included patients. Histopathology after ultrasound guided true cut biopsy was the standard reference for detecting lesions **Results:** Regarding overall validity of CESM, it was found that CESM had sensitivity 92.85%, specificity 88.9%. PVP and PVN were 95.1% and 84.42% respectively with accuracy 91.66%. CESM sensitivity increased to 93.9% in detection of mass enhanced lesions with accuracy 92.5%. In non-mass enhanced CESM sensitivity decreased to 88.9% with accuracy 90% while its specificity was 90.9%. In mass enhanced lesions shape of the mass had the highest sensitivity 90.0% and specificity 85.7% with accuracy 90.0%. In non-mass lesions pattern of enhancement had the highest sensitivity 88.9%. **Conclusion:** CESM is valid and reliable tool in assessment of focal asymmetries. Enhancement and morphology characteristics are valuable in differentiation of benign and malignant breast lesions.

Key words: Contrast Enhanced Mammography, focal asymmetry, validity

List of Abbreviations:

(CC) Craniocaudal

(MLO) mediolateral oblique

(CAD) computer-aided detection

(DBT) digital breast tomosynthesis

(DCIS) ductal carcinoma in situ

(BI-RADS) Breast Imaging Reporting and Data System

(FDA) Food and Drug Administration

(MD) Mammographic density

(IMLN) Intramammary lymph nodes

(US). Ultrasonography

(CEM) Contrast enhanced mammography

(SE) single-energy

(DE) dual-energy

(MRI) magnetic resonance imaging

(CESM) contrast-enhanced spectral mammography

(IDC) invasive ductal carcinoma

(BPE) Background parenchymal enhancement

(NME) non-mass enhancement

Introduction

Breast cancer is a major health problem and a leading cause of death among women in Egypt. Early detection of breast cancer aims to reduce morbidity and mortality rates. Mammography has been established as the imaging modality for screening and early detection of breast cancer; however, it is accused of having low sensitivity and specificity in women with dense breasts**.** [(1)]

Accurate diagnosis and characterization of breast lesions have an essential role in the management and improved prognosis of breast cancer**.** [(2)]

Breast asymmetries can be quite normal and are often secondary to variations in normal breast tissue. Nevertheless, in some cases, they may indicate an underlying serious pathology**.** [(3)] Breast asymmetries are one of the most challenging mammographic findings to evaluate and they often entail further assessment with additional mammography views and a targeted ultrasound study**.** [(4)]

Focal asymmetry is defined when the same features are observable on standard mammographic views occupying less than a single quadrant, but lacking convex margins and containing interspersed fat**.**[(5)] The incidence of asymmetric findings on mammograms varies, where focal asymmetry was reported in 0.87%**.**[(6)]

CESM is one of the relatively novel imaging modalities. It provides low energy images comparable to mammographic images and post- contrast recombined images to evaluate tumor neovascularity.

CESM allows better evaluation of calcifications by their visualization on low-energy images combined with enhancement criteria on the contrast enhanced recombined images**.** [(7)]

CEM is an alternative to US and MRI, and it can be used to obtain contrast material enhanced information and standard mammograms simultaneously. CEM examination is shorter than that of MRI, and the modalities have similar rates of sensitivity to detect lesions. CEM also costs less than MRI**.** [(8)]

Many studies have proved that CESM is superior to mammography in the identification of multiplicity, extent and size of malignant lesions especially in the dense breast parenchyma. [(3)]

Therefor the present study was conducted to investigate the potential benefits of using CESM in assessment of focal breast asymmetries detected on mammogram in 60 female patients over the course of one year.

Subjects and Methods

This study was case study & carried out to investigate the potential benefits of using intravenous contrast material with full-field digital mammography in facilitation of characterization of focal breast asymmetry.

In this study, 60 persons are examined.

The Scientific Research Statistics Committee has approved the conduct of the research in 11/2020.

The study was carried out in national cancer institute, the institute and patients were had no problems with this study.

I carried out cases by myself. These cases are examined from 9/2019 to 3/2020.

Statistical analysis

The collected data were coded, entered, presented, and analyzed by computer using a data base software program, Statistical Package for Social Science (SPSS) version 22 Chicago. Ill. USA)

Qualitative data were represented as frequencies and percentage.

For quantitative variables mean, standard deviation (SD), and (minimum-maximum) were computed.

Chi square (X2) test was used to detect relation between different qualitative variables.

Sensitivity, specificity, predictive value for positive (PVP), predictive value for negative (PVN), and accuracy were calculated at 95% CI to measure the validity.

The results were considered statistically significant and highly statistical significant when the significant probability (P value) was < 0.05* and <0.001** respectively.

Results:

The mean age of included patients was 50.8±8.93 years ranging from (37 to 74) years. About 66.7% of cases had lymph node enlargement. Only 6.7% of cases had nipple retraction. [Table 1]

CESM showed that two thirds of studied patients had mass enhanced lesions and the remaining one third had none mass enhanced lesions. About 50.0% of cases had micro-calcification with 6.7 % of cases had parenchymal infiltration. About 63.3% had heterogeneous pattern of enhancement and 56.7% had intense degree. [Table 2]

As shown in table 3, the majority of lesions were malignant (70.0%) with 71.4% of them were invasive duct carcinoma while benign lesions were only 30.0% with fibrocystic disease represented 44.4% of them.

Mammographic findings of mass lesions shows that 57.5% had micro calcification with 70.0 % of cases had heterogeneous pattern of infiltration and 65.0% had intense degree of enhancement. [Table 4]

Regarding histopathological results of mass lesions, the majority of lesions were malignant (82.5%) with 75.8% of them were invasive duct carcinoma while benign lesions were only 17.5% with fibrocystic disease and fibroadenoma represented 57.2% of them. [Table 5]

Table 6 shows that there was statistically significant difference (p<0.05*) between malignant and benign cases regarding calcification and lymph nodes enlargement with 66.6% of malignant masses had microcalcification versus 14.3% of benign lesions and 84.9% of malignant cases had lymph node enlargement versus 28.6% of benign cases.

Table (1): Demographic and clinical characteristics of the studied group (n=60).

Characteristics	Value	
Age (years):		
Mean± SD	50.8±8.93	
Range	(37-74)	
Items	No	%
Side:		
• **Left**	29	48.3
• **Right**	31	51.7
Lymph node involvement		
• **Yes**	40	66.7
• **No**	20	33.3
Lymph nodes		
• **Infra-mammary**	14	23.3
• **Axillary**	29	48.3
• **Supraclavicular**	4	6.7
• **Subpectoral**	3	5.0
Nipple retraction		
• **Yes**	4	6.7
• **No**	56	93.3

Table (2): mammographic finding of the studied lesions (n=60).

Variables	No.	%
Mass lesions	**40**	**66.7**
Non mass lesions	**20**	**33.3**
Calcification:		
No	**27**	**45.0**
Micro-calcification	**30**	**50.0**
Macro-calcification	**3**	**5.0**
Parenchyma infiltration		
Yes	**4**	**6.7**
No	**56**	**93.3**
Enhancement		
Homogenous	**21**	**35.0**
Heterogeneous	**38**	**63.3**
Ring	**1**	**1.7**
Degree of enhancement		
Faint	18	30.0
Moderate	8	13.3
Intense	34	56.7

Table (3): Histopathological results of the studied patients (n=60).

Variables	No.	%
Pathology results		
Benign	18	30.0
Malignant	42	70.0
Pathological types of benign lesions: (n=18)		
• **Simple cyst**	1	5.6
• **Fibrocystic disease of the breast**	8	44.4
• **Fibroadenoma**	5	27.8
• **Abscess**	3	16.6
• **Granulomatous mastitis**	1	5.6
Pathological types of malignant lesions (n=42)		
• **Ductal carcinoma insitu**	2	4.8
• **Invasive duct carcinoma**	30	71.4
• **Invasive Lobular Carcinoma**	10	23.8

Table (4): mammographic finding of mass lesions (n=40).

Variables	No.	%
Calcification:		
No	16	40.0
Micro-calcification	23	57.5
Macro-calcification	1	2.5
Shape of the mass:		
Rounded/oval	9	22.5
Irregular	31	77.5
Margin		
Well defined	12	30.0
Ill defined	28	70.0
Parenchyma infiltration		
Yes	4	10.0
No	36	90.0
Enhancement		
Homogenous	11	27.5
Heterogenous	28	70.0
Ring	1	2.5
Degree of enhancement		
Faint	9	22.5
moderate	5	12.5
Intense	26	65.0

Table (5): Histopathological results of the mass lesions (n=40).

Variables	No.	%
Pathology results		
Benign	**7**	**17.5**
Malignant	**33**	**82.5**
Pathological types of benign lesions: (n=7)		
• Simple cyst	**1**	**14.3**
• Fibrocystic disease of the breast	**2**	**28.6**
• Fibroadenoma	**2**	**28.6**
• Abscess	**1**	**14.3**
• Granulomatous mastitis	**1**	**14.3**
Pathological types of malignant lesions (n=33)		
• Ductal carcinoma insitu	2	6.1
• Invasive duct carcinoma	25	75.8
• Invasive Lobular Carcinoma	6	18.1

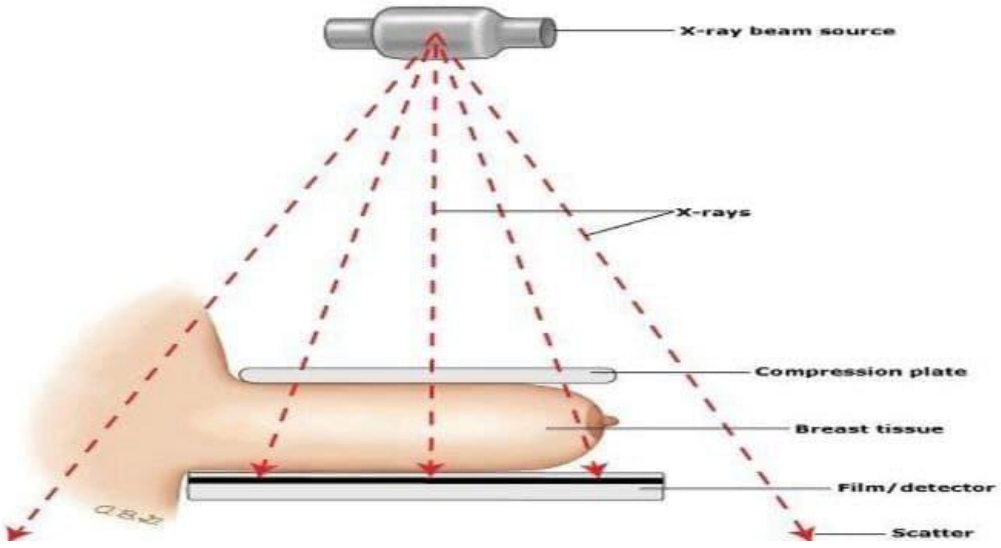

Fig. 1: Schematic diagram of a mammogram

Table (6): Comparing clinical and radiological findings by contrast mammography between malignant and benign mass lesions (n=40)

Variables	Benign (n=7)		Malignant (n=33)		
	No	%	No	%	P value
calcification:					
No	**6**	**85.7**	**10**	**30.3**	**0.025***
Micro-calcification	**1**	**14.3**	**22**	**66.6**	
Macro-calcification	**0**	**0.0**	**1**	**3.1**	
Skin infiltration					
Yes	**0**	**0.0**	**11**	**33.3**	**0.0145**
No	**7**	**100.0**	**22**	**66.7**	
Parenchyma infiltration					
Yes	**0**	**0.0**	**4**	**12.1**	**0.824**
No	**7**	**100.0**	**29**	**87.9**	
Lymph node involvement					
Yes	**2**	**28.6**	**28**	**84.9**	**0.002****
No	**5**	**71.4**	**5**	**15.1**	

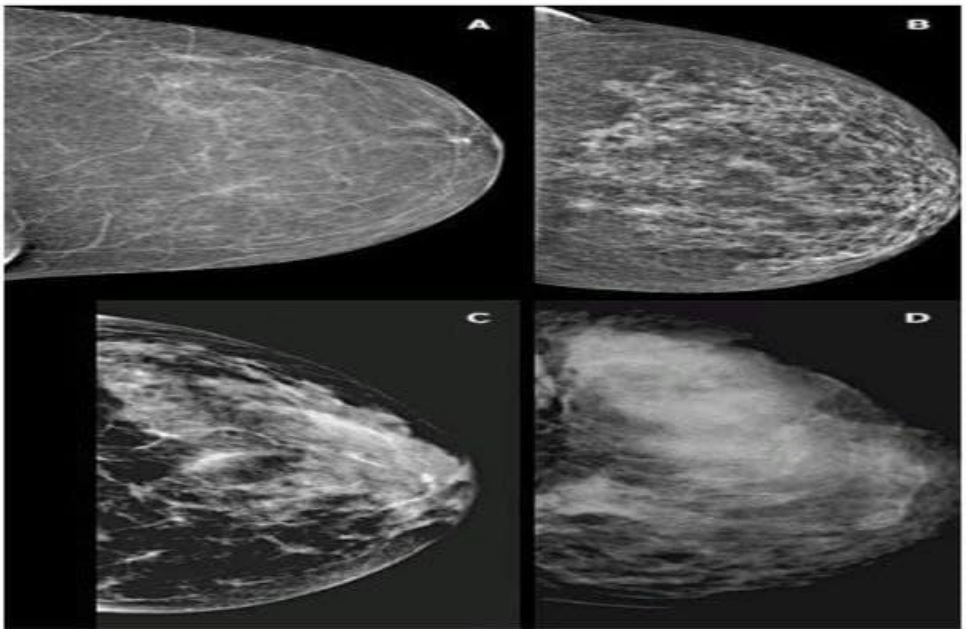

Fig. 2: Varying patterns of normal breast density using the standard BIRADS classification

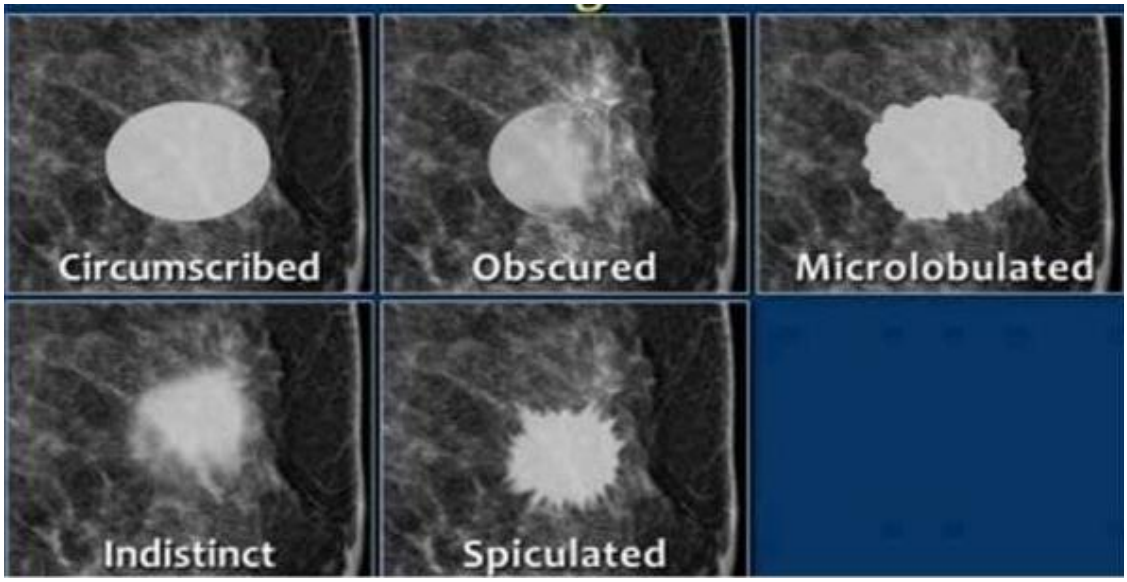

Fig.3: Mass margins (circumscribed, obscured, microlobulated, indistinct, and speculated). In general, these descriptors are arranged from least suspicious to most suggestive of Malignancy

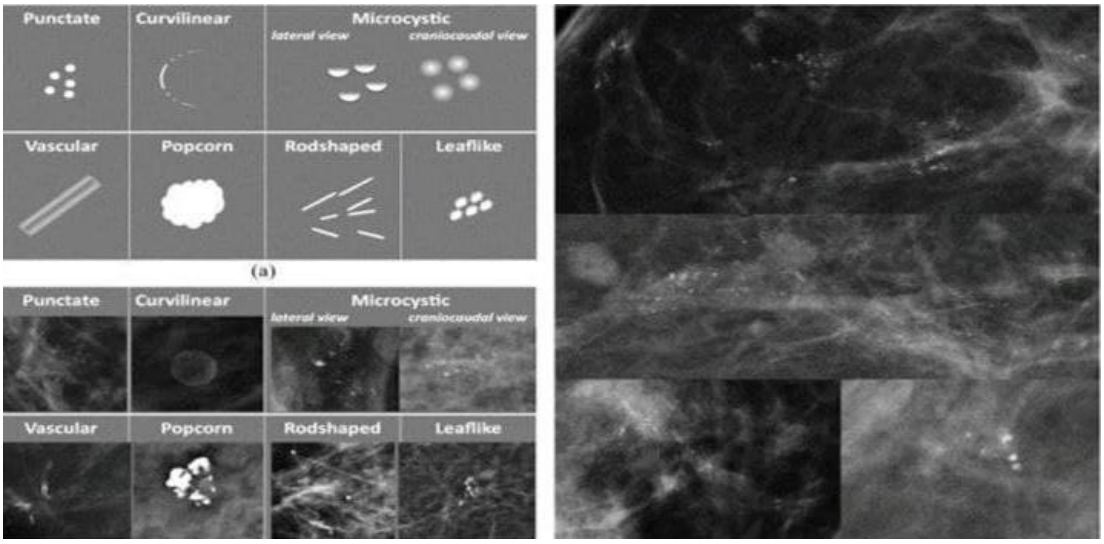

Fig.4: Patterns of calcification associated with a benign change; (b) examples of calcification associated with a benign change; and (c) examples of malignant calcification

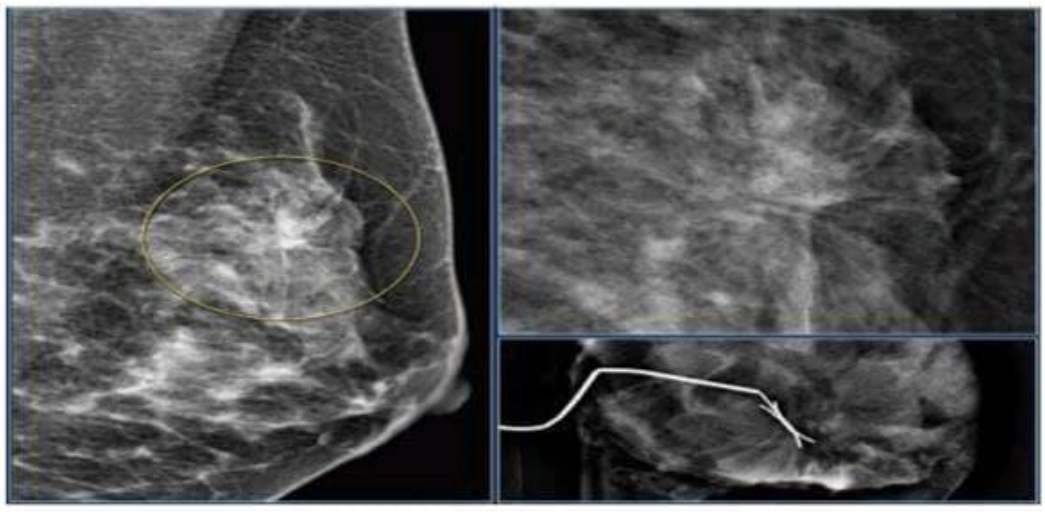

Fig. 5: Distortion of the normal breast architecture on oblique view (yellow circle) and magnification view

Discussion

CESM is a relatively new emerging imaging modality that provides better evaluation of breast masses by visualization of calcification depending on low-energy images combined with enhancement criteria on the contrast enhanced recombined images**.** [(8)]

Many studies reported that CESM is superior to mammography in the identification of multiplicity, extent and size of malignant lesions especially in the dense breast parenchyma**.** [(3)]

Therefor the present study was conducted to investigate the potential benefits of using CESM in assessment of focal breast asymmetries detected on mammogram in 60 female patients over the course of one year.

This study included 60 female patients with focal breast asymmetries detected on mammogram. Histopathology after ultrasound guided true cut biopsy was the standard reference for detecting lesions.

By the end of this study it was found that sensitivity of CESM 92.85%, specificity 88.9% with accuracy 91.66% in assessment of detected focal asymmetry. In mass enhanced lesions shape of the mass had the highest sensitivity 90.0% and specificity 85.7% with accuracy 90.0%. In non-mass lesions pattern of enhancement had the highest sensitivity 88.9%.

Regarding characteristics of studied participants, it was found that the mean age of included patients was 50.8±8.93 years ranging from (37 to 74) years. About 66.7% of cases had lymph node enlargement. Only 6.7% of cases had nipple retraction. CESM showed that two thirds of studied patients had mass enhanced lesions and the remaining one third had non mass enhanced lesions so all cases showed enhancement.

In agreement with an Egyptian study included 125 female patients had breast asymmetries on mammogram who presented for screening and diagnostic purposes, where the patients' mean ages were 48.87 years ranged from 25 to 81 years. Focal asymmetry was detected in 70.4% of cases and CESM showed that 56.8% of focal asymmetry cases had mass enhanced lesions, 34.1% had non-mass enhanced lesions and only 9% showed non-enhanced lesions. **(5)**

Regarding a study aimed to assess the value of CESM in characterization of breast asymmetries and if it should be incorporated in its diagnostic work-up among 380 patients where focal asymmetry detected in 60% of them with mean age of 47 years ranged from 29 to 69 years. Associated mammography findings as edema, skin thickening, parenchymal distortion and calcifications were seen in 29% cases. **(3)**

The age of women with known breast carcinoma was 49.6 years ranged from 25 to 74 years. (9)

Regarding histopathological results of studied patients, it was revealed that 70% of lesions were malignant with 71.4% of them were invasive duct carcinoma while benign lesions were only 30 % with fibrocystic disease represented 44.4% of them. About three fourth of mass enhanced lesions were malignant (82.5%). This indicated that focal asymmetries with enhancement are mainly in malignant lesions.

It is demonstrated that 26.1% of focal asymmetry cases were benign while 73.9% were malignant. Focal asymmetry showing mass enhancement was significantly correlated with malignancy, while non-enhancing focal asymmetry was correlated with benign pathology revealed that any enhancing asymmetry showing a mass or non-mass enhancement was significantly correlated with malignant pathology ($p \leq 0.001$). (5)

This aimed to assess the value of CESM in characterization of breast asymmetries among 380 patients revealed that

histopathology detected 23.2% benign lesions and 67.6% malignant lesions. (3)

It is showed that 57.4% of focal asymmetry cases were benign and 42.6% were malignant. Invasive duct carcinomas were the most encountered malignant tumour while adenosis and fibro-cystic changes were the most detected benign tumours. (10)

As regard morphological characteristics of enhanced malignant and benign lesions, in mass enhanced lesions there was highly statistically significant difference between benign and malignant lesions ($p<0.001$) regarding shape, margin, pattern and statistically significant ($p<0.05$) regarding degree of enhancement with the majority of malignant masses had irregular shape, ill-defined margin, heterogeneous intense enhancement. In non-mass enhanced lesions there was statistically significant difference between benign and malignant lesions ($p<0.05$) regarding enhancement pattern, degree of enhancement and distribution with the majority of malignant masses had heterogeneous intense enhancement with segmental distribution**.**

These results were supported by recent Egyptian study aimed to analyze the morphology and enhancement characteristics of breast lesions on CESM showes that in mass enhancement irregular mass shape, ill-defined or speculated margins, heterogeneous and intense internal enhancement all strongly correlated with a malignant pathology (p value ≤ 0.001). In non-mass enhancement intense and heterogeneous enhancement strongly correlated with a malignant pathology (p value≤ 0.001)**.** **(10)**

In consistence with presence of irregular shaped intensely enhancing mass lesions with ill-defined and speculated margins strongly correlated with malignant breast lesions**.** **(11)**

Regarding CESM findings and nature of lesions**,** it was found that there was highly statistically significant difference between benign and malignant breast lesions ($p <0.001$) regarding pattern and degree of enhancement with the majority of malignant masses had heterogeneous intense enhancement in contrast to benign lesions with the majority had homogenous pattern of enhancement and faint degree.

It is demonstrated that heterogeneous pattern of contrast uptake was characteristic for malignant mass lesions ($P \leq 0.001$). This could be explained by the fact that microvascular density plays a major role in

determining the heterogeneity of tumor enhancement. **(12)**

In the present study, it was showed that there was statistically significant difference ($p<0.05$) between malignant and benign cases regarding calcification and lymph nodes enlargement with 66.6% of malignant masses had microcalcification and 84.9% of malignant cases had lymph node enlargement.

It demonstrates that there was a significant correlation between focal asymmetry associated with distortion, suspicious calcification, skin/nipple changes and malignancy. Focal asymmetries with no other associated mammographic findings were significantly correlated with a benign pathology ($p \leq 0.001$). **(5)**

Regarding validity of CESM**,** it was found that CESM could predict 39 malignant lesions (true positive cases) out of 42 malignant lesions proven by histopathology with sensitivity 92.85% and can predict 16 benign lesions (true negative) out of 18 lesions proven by histopathology with specificity 88.9%. PVP and PVN were 95.1% and 84.42% respectively with accuracy 91.66%. CESM sensitivity increased to 93.9% in detection of mass enhanced lesions with accuracy92.5%. In non-mass enhanced CESM sensitivity decreased to 88.9% with accuracy 90% while its specificity was 90.9%.

In accordance with an Egyptian study to assess the value of CESM in characterization of breast asymmetries and if it should be incorporated in its diagnostic work-up found that CESM markedly improves the overall accuracy reaching 88.4% concluded that CESM is considered as a valuable complementary imaging tool considering the evaluation of breast asymmetries and should be incorporated in its diagnostic work-up in cases not resolved on an initial combined mammography and targeted ultrasound study especially in the presence of a heterogeneous dense breast parenchyma**.** **(3)**

CESM had a sensitivity of 89%, a specificity of 89%, PPV of 91%, NPV of 86% and a diagnostic accuracy of 89%. (13)

In an Egyptian study conducted to evaluate the clinical performance of CESM on asymmetries detected on a mammogram where 70.4% had focal asymmetry, CESM sensitivity, specificity, PVP and PVN were 100%, 55.88%, 85.85% and 100% respectively, with 15 false positive and no false negative findings concluded that focal asymmetries with other suspicious

mammographic findings were statistically significant for malignancy and CESM played an important role in delineating tumor size and extension. (5)

In 10th reference, it aimes to analyze the morphology and enhancement characteristics of breast lesions on CESM and to assess their impact on the differentiation between benign and malignant lesions demonstrated that CESM sensitivity was%, specificity 83.3%. PVP 85.8%, PVN 93.4% concluded that the assessment of the morphology and enhancement characteristics of breast lesions on CESM enhances the performance of digital mammography in the differentiation between benign and malignant breast lesions. (10)

CESM achieves sensitivity of 85%, specificity of 89%, PVP of 91%, PVN of 86% and a diagnostic accuracy of 89%. CESM showed slightly lower sensitivity and accuracy compared to MRI however because of being relative ease, available, cheap and acceptable by women, CEM can replace MRI as a problem-solving tool in the characterization of indeterminate breast lesions. (14)

The diagnoses based on CESM are slightly more reliable than those based on breast MRI. The sensitivity of CESM examination was 100%, higher than the 93% sensitivity of breast MRI ($p \leq 0.04$). The accuracy of the CESM exam (79%) was also higher than that of breast MRI (73%) in their study, but this difference was not statistically significant. PVN was 100% for CESM and only 65% for breast MRI ($p < 0.001$). (15)

It aims to determine feasibility of performing CESM and evaluate its performance compared with conventional digital mammography of histologically proven breast cancers as the gold standard which showed that the sensitivity increased to about 100% owing to CESM concluded that CESM was feasible and easily accomplished. It was used to detect known primary tumors at a rate comparable to that of MRI and higher than that of conventional digital mammography. (16, 17, 9)

Similarly, CESM, alone and in combination with mammogram, is as accurate as MRI but is superior to mammogram for lesion detection. Patients with dense breasts benefitted most from CESM with the smallest additional dose compared to mammogram. (18)

That conducts a comparative study between CESM and contrast enhanced MRI found that CESM showed slightly lower

sensitivity (88.89%) than breast MRI (96.3%) however specificity was higher in CESM (66.67%) than that of BMRI (33.33%) concluded that in spite of the lower sensitivity of the CESM compared to MRI, the CESM appeared to be a suitable, easy, more comfortable, low cost and fast alternative to MRI in early detection of breast cancer recurrence specially for patients with contraindications to MRI. [(19)] Similar observations were demonstrated that CESM sensitivity was 94.1% while MRI was 100% and CESM specificity 100% while MRI was 95.5%. [(20)]

Finally, CESM is a developing modality used for the workup and management of breast cancer and has high sensitivity and specificity that used as complementary to standard mammogram and can replace breast MRI.

Regarding the validity of morphology descriptors for prediction of breast lesions on CESM, in mass enhanced lesions it was found that the shape of the mass had the highest sensitivity 90.0% and specificity 85.7% with accuracy 90.0%. Enhancement pattern was 85.7% sensitive and 82.4% specific with the degree of enhancement had lesser sensitivity and specificity than the pattern. In non-mass enhanced lesions it was revealed that the pattern of enhancement had the highest sensitivity 88.9% while the pattern of distribution had the highest specificity 90.9% but the accuracy was highest regarding the pattern of enhancement 84.5%

By comparing the morphology descriptors, in mass enhanced lesions the highest level of performance was scored by tumor margin description (sensitivity and PVP: 96.3%, specificity and PVN: 83.3%). [(10)] In non-mass enhanced lesions degree of enhancement and distribution had the highest sensitivity 86.4% while pattern of enhancement and its degree showed the highest specificity (79.2%) concluded that the morphology descriptors of breast lesions on CESM are reliable in differentiating benign from malignant breast lesions with the exception of the ring pattern of contrast uptake.

Conclusion

CESM is valid and reliable tool in assessment of focal asymmetries. Enhancement and morphology characteristics are valuable in differentiation of benign and malignant breast lesions. It was found that sensitivity of CESM 92.85%, specificity 88.9% with accuracy 91.66% in assessment of detected focal asymmetry. In

mass enhanced lesions shape of the mass had the highest sensitivity 90.0% and specificity 85.7% with accuracy 90.0%. In non-mass lesions pattern of enhancement had the highest sensitivity 88.9%.

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