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Role of Contrast-Enhanced Spectral Mammography in Characterization of Suspicious Breast Microcalcification

FATMA M. AWAD, M.D.*; HAGAR SAAD ELDIN ALSHENNAWY, M.Sc.*;
SHERIF OMAR, M.D.** and SHERIHAN FAKHRY, M.D.*

The Departments of Radiology and General Surgery**, Faculty of Medicine, Cairo University*

Abstract

Background: One of the earliest signs of non-palpable breast cancer is microcalcification, which is usually associated with ductal carcinoma in situ (DCIS). Contrast-enhanced spectral mammography (CESM) combines the advantage of mammography in detecting early malignancy in the form of microcalcification, with additional information on lesion characterization, extent and vascularity, which are crucial for surgical management.

Aim of Study: Evaluation of the role of contrast-enhanced spectral mammography (CESM) in characterization of suspicious breast micro calcification, its diagnostic accuracy and its effect on surgical management.

Patients and Methods: This is an observational; case control study that included 31 female patients with suspicious microcalcification, as detected on mammography, categorized as BI-RADS 4 or 5. CESM was performed for all patients. Detailed analysis of the low-energy images for microcalcifications morphology, distributionand degree of enhancement was done. On recombined CESM images,the presence of enhancing lesions (mass or non-mass enhancement), their distributionand patterns of enhancement were also analyzed.

Results: This study comprised 31 female patients with suspicious breast microcalcifications on mammography. Among the studied cases, 6/31 (19.4%) cases were benign, while 25/31 (80.6%) cases were malignant. According to CESM, 5/31 (16.1%) cases were probably benign category (BIRADS 2), as they showed no enhancement. Conversely, 26/31 (83.9%) cases were (BIRADS 5) category, out of which one case (3.8%) was pathologically-proven to be benign (False positive).

Conclusion: Contrast-enhanced spectral mammography (CESM) is highly accurate in the detection and characterization of breast microcalcification.

Key Words: *CESM – Breast microcalcification – Ductal carcinoma in situ (DCIS) – Breast conservative surgery (BCS).*

Correspondence to: Dr. Fatma M. Awad, The Department of Radiology, Faculty of Medicine, Cairo University

Introduction

BREAST cancer is the most common cancer in females over the age of 20 **[1]**. One of the earliest signs of non-palpable breast cancer is micro calcification, which is usually associated with ductal carcinoma in situ (DCIS), but can also be present in invasive cancers. In screening program, a significant percentage of women may be recalled with micro calcification as the only sign of cancer **[2]**.

Mammography is used worldwide for breast screening, as it's the only radiological technique capable of detection of microcalcificaton **[3]**.

The assessment of disease extent in patients with DCIS or non-palpable invasive breast cancer is challenging. Contrast-enhanced spectral mammography (CESM) combines the advantage of mammography in detecting early malignancy in the form of microcalcification, with additional information on lesion characterization, extent and vascularity, which are crucial for surgical management **[4,5]**.

Aim of work:

Evaluation of the role of contrast-enhanced spectral mammography (CESM) in characterization of suspicious breast micro calcification, its diagnostic accuracy and its effect on surgical management.

Patients and Methods

Patient selection:

This is an observational; case control study that included 31 female patients with suspicious microcalcification, as detected on mammographic examination, who were referred from the surgery department for further characterization and management planning. Their ages ranged between 31 and 73

years (mean age 52.19 ± SD). It was carried out in the Women's Imaging Unit, Radiology Department, Cairo University, in the period between January 2019 and June 2021. The study was approved by the faculty of medicine ethical committee. An informed consent was taken from all the patients included in this study after explaining the procedure in details and possible risks.

Inclusion criteria:

Patients with suspicious microcalcifications detected on mammography and were categorized as BI-RADS 4 or 5.

Exclusion criteria:

- Contraindication to mammography, e.g., pregnant women.
- Patients who had a contraindication to intravenous contrast administration, e.g., patients with renal impairment, allergic patients, or those known to have a history of anaphylactic reaction to contrast media.
- Patients with typically benign calcifications.

Contrast-Enhanced Spectral Mammography (CESM):

CESM was performed using Senographe Essential, GE healthcare Full Field Digital Mammography machine. Intravenous injection of 1.5mL/Kg bodyweight of the non-ionic contrast medium (Omnipaque 300; Nycomed, Roskilde, Denmark) was performed manually, with an injection rate of 3mL/s.

Preparation and technique:

- Renal function tests were done for each patient, to ensure normal renal function prior to contrast injection.
- A catheter was inserted into the antecubital vein of the arm contra-lateral to the breast of concern.
- The contrast agent was injected.
- Two minutes after the initiation of contrast administration, the breast was compressed in the cranio-caudal (CC) view, and a low- and high-energy pair of images were acquired within 20 seconds of one another.
- The breast was compressed then in the mediolateral oblique (MLO) view, and a new low- and high-energy pair of exposures were acquired 4 minutes after the initiation of contrast administration.
- A combination of low-energy and high-energy images through a specific image processing were performed in order to generate two subtracted images with contrast agent uptake information (one in the CC and one in the MLO views).
- The breast was lightly compressed for the duration of the examination, with enough pressure to limit anatomic motion but not to significantly reduce blood flow.

Image analysis:

Until the time of conducting this study, there was no standardized BIRADS lexicon to CESM, so the MRI BIRADS atlas 2013 morphology descriptors [6] was used to determine the BIRADS category for each lesion.

On low energy images, the morphology and distributionof microcalcification were detected. In case of a mass, it was further assessed, based on mammography BIRADS lexicon, for its shape, margin and density. The presence of asymmetry or architectural distortion was also recorded.

On recombined subtracted images,the presence or absence of enhancing lesions was recorded. Enhancing lesions were then classified as mass or non-mass. When an enhancing mass lesion was detected, it was further assessed for itspattern of enhancement (homogenous, heterogeneous or ring enhancement). When non-mass enhancement was detected, it was further assessed for distribution (focal, linear, segmental, regional, multiregional or diffuse) and pattern of internal enhancement (homogeneous, heterogeneous, clustered and clumped).

Histopathological analysis:

Core-needle biopsies were done for all lesions and the results were used as the gold standard for characterization of microcalcification.

Statistical analysis:

Data were statistically described in terms of sensitivity. Statistical analysis was done using IBM SPSS Statistics program" version 22". Chi square (X^2) test was used to describe the impact of different morphological characters of the lesions on the diagnosis of them. All the statistical tests were done at .001 level of significance.

Results

This study comprised 31 female patients with suspicious breast microcalcifications on mammography. Among the studied cases, 6/31 (19.4%) cases were benign, while 25/31(80.6%) cases were malignant. According to the final histopathological diagnoses, the most common benign pathology was fibrocystic mammary changes which was encountered in 3/6 (50%) cases. On the other hand, the most common malignant pathology was invasive duct carcinoma which was encountered in

12/25 (48%), and is associated with DCIS in 3/25 (12%) cases, as emphasized in Table (1).

Table (1): Histopathological findings among the included patients.

	Count	%from total cases
Malignant cases:		
Pure Ductal carcinoma in situ	9	29%
Invasive duct carcinoma	12	38.7%
DCIS and IDC	3	9.7%
Paget disease and DCIS	1	3.2%
Benign cases:		
Fibrocystic changes	3	9.7%
Duct ectasia	1	3.2%
Fibroadenoma	1	3.2%
Complicated cyst	1	3.2%

Regarding breast density, 18/31 (58.1%) cases were ACR b, while 13/31 (41.9%) caseswere ACR c and d.

The majority of cases included in this study presented with fine pleomorphic microcalcification (17/31 cases, 54.8%) followed by amorphous microcalcification (8/31 cases, 25.8%), as illustrated in Table (2).

In 6/31 (19.3%) cases, the histopathological results were of benign disorders. Out of these benign cases, amorphous microcalcification was noted in 3/6 cases (50%), while 2/6 (33.3%) cases showed fine pleomorphic microcalcification and 1/6 (16.7%) case showed fine linear microcalcification.

Table (2): Morphology of suspicious microcalcification as depicted in mammography.

Morphology	Count	%
Coarse heterogeneous	3	9.7
Fine pleomorphic	17	54.8
Fine linear	3	9.7
Amorphous	8	25.8

Regional and grouped distribution of microcalcification were equally encountered (10/31 cases for each, 32.3%). Also, diffuse and segmental microcalcifications were equally encountered being depicted in 4/31 (12.9%) cases for each, as illustrated in Table (3).

Table (3): Distribution of suspicious microcalcification as depicted in mammography.

Distribution	Count	%
Diffuse	4	12.9
Regional	10	32.3
Grouped	10	32.3
Linear	3	9.6
Segmental	4	12.9

In this study, masses were noted in 18/31 (58.1%) cases out of which 17/18 (94.4%) cases were irregular in shape with non-circumscribed or spiculated margins. There were no depicted masses in 13/31 cases (45.2%). The most commonly encountered non mass abnormality was architectural distortion which was found in 6/31 (19.4%) cases as emphasized in Table (4).

Table (4): Lesion morphology associated with suspicious microcalcification.

	Count	%
MASS (n:18):		
Margin:	18	58
Non circumscribed	8	44.4
Circumscribed	1	5.6
Spiculated	9	50.0
Shape:		
Oval	0	0
Rounded	1	5.6
Irregular	17	94.4
NON-MASS (n:13):		
Parenchymal distortion and asymmetry	6	19.4

Five cases (16.1%) showed no enhancement, while 26 cases (83.9%) showed enhancement; whether mass enhancement only (1/31, 3.2%), non-mass enhancement only (8/31, 25.8%) or mixed mass and non-mass enhancement (17/31, 54.8%). Five of the latter cases (16.1%) had areas of non-mass enhancement and microcalcification away from the enhancing masses (Table 5).

Table (5): CESM findings of the lesions.

	Count	Column N %
Mass:		
Pattern:		
Homogenous	2	11.1
Heterogenous	15	83.3
Rim	1	5.6
Non-Mass:		
Pattern:		
Heterogenous	20	80
Clumped	5	20
Distribution:		
Focal	7	28
Linear	1	4
Regional	9	36
Multiple Regional	4	16
Segmental	3	12
Diffuse	1	4

According to CESM, 5/31 (16.1%) cases were benign category (BIRADS 2), as they showed no enhancement. All of these lesions were pathologically-proven to be benign according to the histopathological results.

Conversely, 26/31 (83.9%) cases were assigned (BIRADS 5) category, out of which one case (3.8%) was pathologically-proven to be benign (Table 6).

The sensitivity, specificity, and accuracy were 100%, 83.33%, and 96.77% respectively with negative predictive value of 100%, as emphasized in Table (7).

According to this study, we found no significant correlation between the degree of the enhancement and the morphology of microcalcification with estimated *p*-value 0.96, as shown in Table (8).

Table (6): Diagnostic performance of CESM as compared to the final pathology.

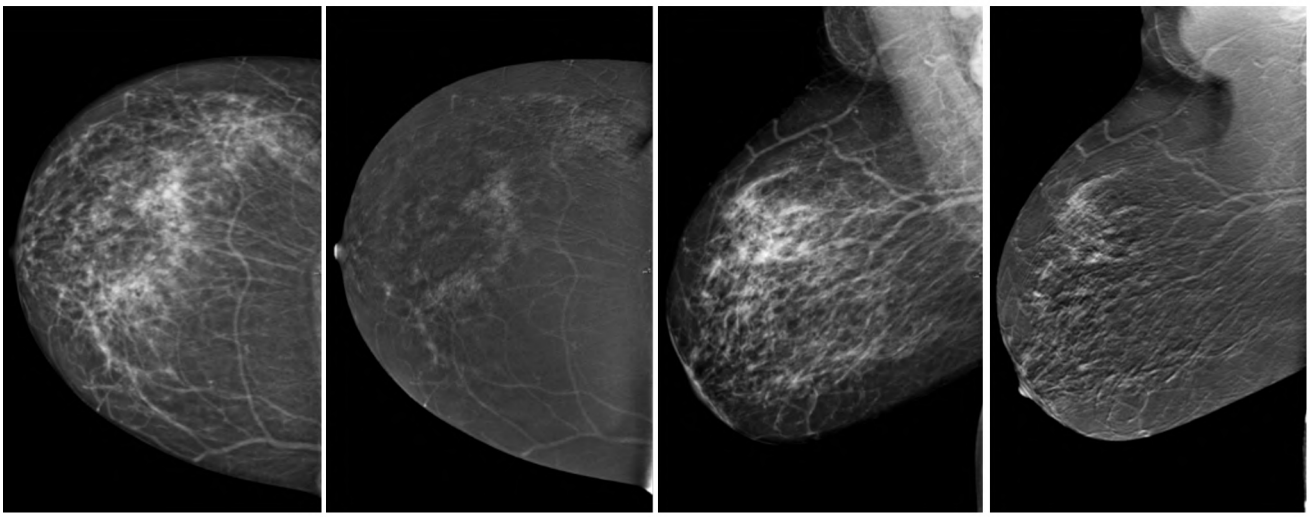
	Pathology				*p*-value
	Malignant		Benign		
	Count	%	Count	%	
(CESM):					
Malignant	25	80.8	1	16.7	0.004
Benign	0	19.2	5	83.3	

Table (7): Diagnostic indices of CESM in the evaluation of microcalcification.

Statistic	Value	95% CI
Sensitivity	100.00%	86.28% to 100.00%
Specificity	83.33%	35.88% to 99.58%
Positive Likelihood Ratio	6.00	1.00 to 35.91
Negative Likelihood Ratio	0.00	
Positive Predictive Value (*)	96.15%	80.68% to 99.34%
Negative Predictive Value (*)	100.00%	
Accuracy (*)	96.77%	83.30% to 99.92%

Table (8): Correlation between degree of enhancement with morphology of microcalcifications.

	No		Minimal		Mild		Moderate		Marked		*p*-value
	Count	%	Count	%	Count	%	Count	%	Count	%	
Calcification morphology on Mammography:											
Benign	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0.960
Amorphous	2	20.0	1	33.3	0	0.0	3	37.5	2	11.1	
Coarse heterogenous	0	0.0	1	0.0	1	20.0	0	0.0	1	11.1	
Fine pleomorphic	2	40.0	1	33.3	4	60.0	4	37.5	6	33.3	
Fine linear	1	20.0	0	0.0	0	0.0	1	12.5	1	11.1	



(A) (B) (C) (D)

Fig. (1): 61-year-old female patient with right mastalgia. Mammography (A; CC view-C; MLO view): Right UOQ focal asymmetry along with multiple clusters of suspicious pleomorphic microcalcification. CESM (B-D): Right UOQ heterogeneous regional non-mass enhancement. Histopathological diagnosis: Ductal carcinoma in situ (DCIS) with comedo necrosis.

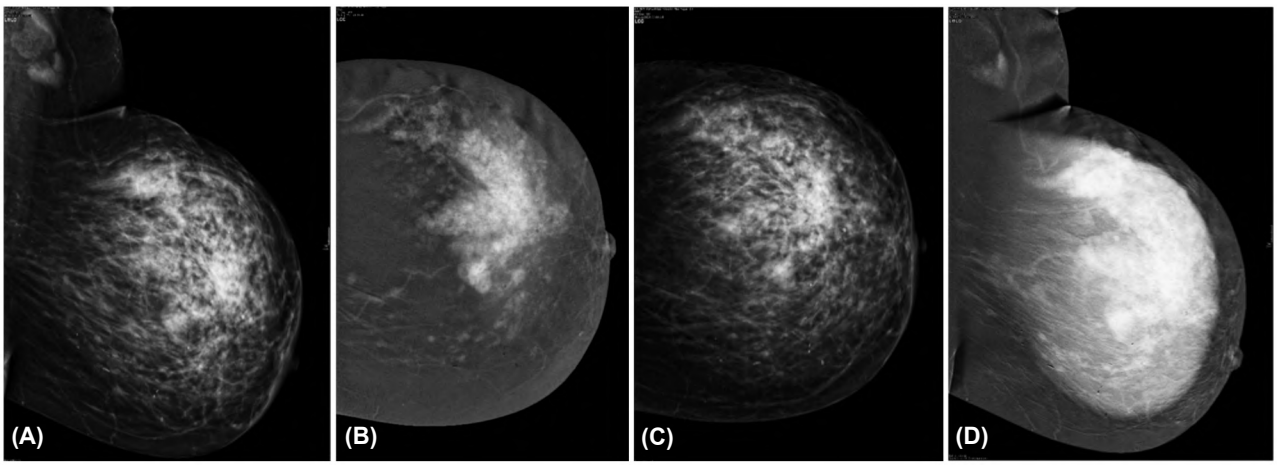


Fig. (2): 66-year-old female patient with left mastalgia and breast swelling. Mammography (A; MLO view-C; CC view): Left parenchymal distortion with scattered pleomorphic microcalcification. CESM (B-D): Intense non -mass enhancement of heterogenous and clumped patterns occupying the whole breast. Histopathological diagnosis: Invasive duct carcinoma, Grade II with DCIS.

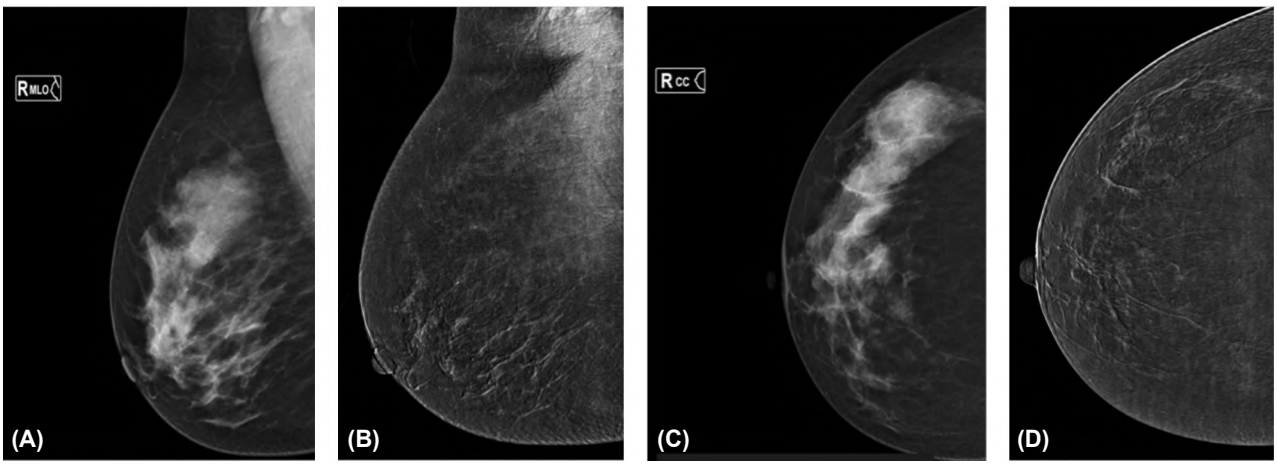


Fig. (3): 51-year-old female patient with right mastalgia and positive family history of breast malignancy,Mammography (A; MLO view-C; CC view): Right 10-11 o'clocks, ill-defined dense area showing internal clustered microcalcification. CESM (B-D): No enhancing lesions. Histopathological diagnosis:Fibrocystic changes, with no evidence of malignancy.

Discussion

Microcalcification comprises up to 31% of lesions diagnosedon screening mammography. Ductal carcinoma in situ (DCIS) often presents with microcalcification on mammography (79% of cases) Careful evaluation of mammographically-detected microcalcification is essential, because not all microcalcification are associated with in -situ or malignant disease [2].

Contrast-enhanced digital mammography (CEDM) shows a great potential in characterization of breast lesions and detection of tumor neovascularity [7].

This study encompassed 31 female patients aged between 31 and 73 years (mean age; 52.19 years) with suspicious breast microcalcification (BIRADS 4 and 5) categories. The final histopathological diagnoses for these cases were 25/31 cases (80.6%) malignant and 6/31 (19.4%) were benign.

In our study, the sensitivity of contrast-enhanced spectral mammography (CESM) in detecting malignant lesions was 100% and specificity 83.3%, with overall diagnostic accuracy of 96.77%. In a study of Cheung et al., [8], the sensitivity of CESM in predicting malignancy presented by suspicious microcalcification was 89%, while in another study done by Houben et al., [4], the sensitivity of CESM was 93.8%. The high sensitivity of CESM in our study may be attributed to that we considered that the sole indicator of benignity was lack of contrast enhancement.

The sensitivity of CESM has been reported as 93-100%, being significantly higher compared to

that of mammography and ultrasound alone **[9]**. In this study, CESM succeeded in the characterization of breast micro calcification into benign and malignant, with high diagnostic accuracy (96.8%) compared to mammography alone were all the microcalcificaton was considered suspicious.

Our results are also in accordance with Helal et al., **[10]** and Jochelson et al., **[11]** who reported higher sensitivity, specificity, and accuracy of CESM over digital mammography.

In this study, 8/31 cases (25.8%) presented by amorphous microcalcification, out of which 5 cases (62.5%) were malignant and 3 cases (37.5%) were benign, which is in accordance with Hernández et al., **[12]** who mentioned thatamorphous microcalcification, though considered suspicious, may be encountered with fibrocystic mammary changes, especially if diffuse and bilateral.

On the other hand, fine pleomorphic microcalcification was mostly associated with malignancy. It was seen in 17/31 cases (54.8%) in our study, out of which 2/17 cases (11.7%) only were benign. According to a study by Bent et al., **[13]**, about 41% of cases that presented by fine pleomorphic and linear microcalcifications had malignant lesions.

The limitation of this study was the small sample size and that some of the cases of microcalcification were associated with breast masses, which aided CESM in the characterization of the microcalcification.

Conclusion:

Contrast-enhanced spectral mammography (CESM) is highly accurate in the detection and characterization of breast microcalcification.

References

1- NASEEM M., MURRAY J., HILTON J.F., et al.: Mammographic microcalcifications and breast cancer tumorigenesis: A radiologic-pathologic analysis. BMC Cancer, 15: 307, 2015.

2- MORDANG J.J., et al.: The importance of early detection of calcifications associated with breast cancer in screening. Breast cancer research and treatment, 167.2: 451-458, 2018.

3- CHENG, HENG-DA, et al.: Computer-aided detection and classification of microcalcifications in mammograms: A survey, 36.12: 2967-2991, 2003.

4- HOUBEN, IVO P.L., et al.: Contrast-enhanced spectral mammography in the evaluation of breast suspicious calcifications: Diagnostic accuracy and impact on surgical management. Acta. Radiologica, 60.9: 1110-1117, 2019.

5- LEE J., JUNG J.H., KIM W.W., et al.: Efficacy of breast MRI for surgical decision in patients with breast cancer: Ductal carcinoma in situ versus invasive ductal carcinoma. BMC Cancer, 20: 934, 2020.

6- American College of Radiology. Breast imaging reporting and data system (BI-RADS). 4th ed. Reston, Va: American Collegeof Radiology, 2003.

7- PATEL B.K., LOBBES M.B.I. and LEWIN J.: Contrast Enhanced Spectral Mammography: A Review. Semin Ultrasound CT MR, 39 (1): 70-79, 2018.

8- CHEUNG Y.C., TSAI H.P., LO Y.F., UENG S.H., HUANG P.C. and CHEN S.C.: Clinical utility of dual-energy contrast-enhanced spectral mammography for breast microcalcifications without associated mass: A preliminary analysis. European Radiology, 26: 1082-1089, 2016.

9- FALLENBERG E.M., DROMAIN C., DIEKMANN F., et al.: Contrast-enhanced spectral mammography: Does mammography provide additional clinical benefits or can some radiation exposure be avoided? Breast Cancer Res. Treat., 146 (2): 371-381, 2014.

10- HELAL M.H., MANSOUR S.M., AHMED H.A., ABDEL GHANY A.F., KAMEL O.F. and ELKHOLY N.G.: The role of contrast-enhanced spectral mammography in the evaluation of the postoperative breast cancer. Clinical Radiology, 74 (10): 771-781, 2019.

11- JOCHELSON M.S. and LOBBES M.B.: Contrast-enhanced mammography: State of the art. Radiology. Apr., 299 (1): 36-48, 2021.

12- HERNÁNDEZ L., DÍAZ G.M., POSADA C. and LLANO-SIERRA A.: Magnetic resonance imaging in diagnosis of indeterminate breast (BIRADS 3 & 4A) in a general population. Insights into imaging, 149 (12), 2021.

13- BENT C.K., BASSETT L.W., D'ORSI C.J. and SAYRE J.W.: The Positive Predictive Value of BI-RADS Microcalcification: Descriptors and Final Assessment Categories. Women's Imaging, 194 (5), 2010.

دور التصوير الأشعاعى للثدى بالصبغة فى توصيف التكلس الدقيق المشكوك فيه للثدى

الخلفية : يُعد التكلس الدقيق من العلامات المبكرة لسرطان الثدى، والذى يرتبط عادة بسرطان الأقنية الموضعى (DCIS). يجمع التصوير الاشعاعى للثدى بالصبغة (CESM) بين ميزة التصوير الاشعاعى للثدى فى الكشف عن الأورام الخبيثة المبكرة فى شكل تكلس، مع معلومات إضافية حول توصيف الآفة ومدى انتشارها والأوعية الدموية المغذية لها، والتى تعتبر ضرورية للإدارة الجراحية.

الهدف : تقييم دور التصوير الاشعاعى للثدى بالصبغة (CESM) فى توصيف التكلس الدقيق للثدى ودقته التشخيصية وتأثيره على التخطيط الجراحى.

المرضى والطرق : اشتملت هذه الدراسة على ٣١ مريضة مصابة بتكلس دقيق مشكوك فيه، فى التصوير الاشعاعى للثدى، مصنفة على أنها BI-RADS 4 أو ٥، تم إجراء CESM لجميع المرضى. تم إجراء تحليل مفصل للصور منخفضة الطاقة للتشكيلات الدقيقة وتوزيعها، والصور المعاد تجميعها، لوجود آفات محسنة بالصبغة (كتل أو غير الكتل) وتوزيعها وأنماط التعزيز.

النتائج : ضمت هذه الدراسة ٣١ مريضة مصابات بتكلسات صغيرة فى الثدى فى التصوير الاشعاعى للثدى. ومن بين الحالات المدروسة، كانت ٣١/٦ (١٩.٤٪) حميدة، فى حين كانت ٣١/٢٥ (٨٠.٦٪) حالات خبيثة. وفقاً لـ CESM، كانت ٣١/٥ (١٦.١٪) من الحالات حميدة (2 BI-RADS)، حيث لم تظهر أى تحسن. على العكس من ذلك، كانت ٣١/٢٦ (٨٣.٩٪) من الحالات (BI-RADS 5)، منها حالة واحدة (٣.٨٪) ثبت أنها حميدة (إيجابية كاذبة).

الاستنتاج : يعتبر التصوير الاشعاعى للثدى بالصبغة (CESM) دقيقاً للغاية فى اكتشاف وتوصيف التكلس الد قيق للثدى.