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Contrast-enhanced spectral mammography: Impact of the qualitative morphology descriptors on the diagnosis of breast lesions

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ABSTRACT

Objective: To analyze the morphology and enhancement characteristics of breast lesions on contrast-enhanced spectral mammography (CESM) and to assess their impact on the differentiation between benign and malignant lesions.
Materials and method: This ethics committee approved study included 168 consecutive patients with 211 breast lesions over 18 months. Lesions classified as non-enhancing and enhancing and then the latter group was subdivided into mass and non-mass. Mass lesions descriptors included: shape, margins, pattern and degree of internal enhancement. Non-mass lesions descriptors included: distribution, pattern and degree of internal enhancement. The impact of each descriptor on diagnosis individually assessed using Chi test and the validity compared in both benign and malignant lesions. The overall performance of CESM were also calculated.
Results: The study included 102 benign (48.3%) and 109 malignant (51.7%) lesions. Enhancement was encountered in 145/211 (68.7%) lesions. They further classified into enhancing mass (99/145, 68.3%) and non-mass lesions (46/145, 31.7%). Contrast uptake was significantly more frequent in malignant breast lesions (p value $\leq$0.001). Irregular mass lesions with intense and heterogeneous enhancement patterns correlated with a malignant pathology (p value $\leq$0.001). CESM showed an overall sensitivity of 88.99% and specificity of 83.33%. The positive and negative likelihood ratios were 5.34 and 0.13 respectively.
Conclusion: 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.

1. Introduction

Up-to-date, mammography appears to be the most consistent method for the early detection of breast cancer; yet, it has both limited sensitivity and specificity in the detection and diagnosis of breast lesions, especially in dense breasts. Moreover the full extent of the disease may not be clearly depicted. In reference to this, mammography misses about 20% of invasive breast cancers [1,2].

The use of an intravenous injected iodinated contrast agent could help increase the sensitivity of digital mammography by adding information on tumor angiogenesis. The contrast agent can be used to highlight areas of unusual blood flow. Two approaches have been made for clinical implementation of contrast-enhanced mammography, namely; single-energy (SE) and dual-energy (DE) imaging. In each technique, pairs of mammograms are acquired, which are then subtracted in order to cancel the appearance of healthy breast tissue and thus permit the sensitive detection and specific characterization of lesions [3].

In the single energy or temporal subtraction technique high-energy images are acquired before and after contrast medium injection while in the dual energy technique the acquisition of a pair of low and high-energy images occurs only after contrast medium injection. The dual energy technique does not provide information

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about the kinetics of tumor enhancement but allows the acquisition of multiple views of the same breast or bilateral examination and is less sensitive to patient motion than the temporal technique. This feature allows for better morphology assessment [4].

At present, there are no standardized interpretation criteria for the evaluation of breast lesions on CESM. The different patterns of contrast uptake and the morphology descriptors of enhancing lesions which allow characterization of benign and malignant breast lesions on CESM are still a subject of research.

In this study, the enhancement characteristics and morphology descriptors of breast lesions on contrast-enhanced spectral mammography (CESM) are analyzed to assess their impact on the differentiation between benign and malignant breast lesions.

2. Materials and methods

2.1. Patients

This study is a retrospective analysis that included 168 consecutive patients with 211 breast lesions in the period from January 2012 to June 2013. The study was approved by the Scientific Research Review Board of the Radiology Department, and waiver of informed consent was applied for the used data of the included cases.

Indication of contrast injection was to (i) further evaluate heterogeneous dense breast parenchyma (27/211; 12.8%) or (ii) clarify already identified mammography abnormalities (184/211; 87.2%) namely mass lesions, areas of parenchyma distortion, focal asymmetries or suspicious microcalcifications.

Patients with renal impairment, pregnant patients and those giving history of allergy to contrast media were excluded from the study.

Reference standard was histopathology after core or surgical biopsy, as well as follow-up (for 1year) of lesions classified as benign.

2.2. Digital mammography system

Dual energy contrast-enhanced spectral mammography (CESM) was performed using Senographe Essential; (Seno DS; GE, Buc, France) that is adapted to obtain low and high-energy images for each mammography view. The low-energy image is comparable to the standard mammography image and the high-energy image shows the contrast-enhanced areas.

2.3. Technique of examination

The examination consists of an intravenous injection of an iodinated contrast agent (iohexol, 300 mg I/ml) at a dose of 1.5 ml/kg through a catheter introduced in the ante-cubital vein before application of compression to avoid interference with the normal vascular dynamics of the breast. This is followed by a 2-min wait before a mammography exam is performed in exactly the same positions as the standard examination. Low- and high-energy images are consecutively acquired in each view during a single compression to minimize motion artifact. Low-energy images were acquired at peak kilovoltage values ranging from 26 to 31 kVp, which is below the k-edge of iodine. High-energy images were acquired at 45–49 kVp, which is above the k-edge of iodine. Iodine-enhanced images are calculated by weighted logarithmic subtraction of the two images through appropriate image processing and thus the visibility of the parenchyma is reduced and contrast-enhanced images are generated.

2.4. Image analysis

Mammograms were analyzed according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon designed by the American College of Radiology [5].

Analysis was performed by independent double reading using two different radiologists for each of the standard mammograms and CESM images. Readers were blinded about each other analysis, the pathology reports and follow up outcome.

Regarding CESM images; the presence or absence of contrast enhancement was assessed on the subtraction images. The assessment of the low-energy images was also essential to identify non-enhancing suspicious clusters of microcalcifications, areas of parenchymal distortion, focal asymmetries and to evaluate the morphologic features of non-enhancing mass lesions.

Lesions were classified as enhancing and non-enhancing. Enhancing lesions were further classified as mass versus non-mass.

A mass lesion was described when a three dimensional space-occupying lesion $\geq$5 mm was seen in both mammography views. Mass lesions morphology descriptors included: mass shape (oval, rounded or irregular), margins (well-defined, ill-defined or spiculated), internal enhancement pattern (homogeneous, heterogeneous or ring) and degree of enhancement.

Non-mass enhancement was described when the enhancement was an area with no space-occupying or 3D volume effect. Non-mass lesions morphology descriptors included: distribution of enhancement, internal enhancement pattern and degree of enhancement.

2.5. Statistical analysis

Data were statistically described in terms of frequencies and percentages. The impact of the individual morphology descriptors on the diagnosis of breast lesions was assessed using Chi square (χ^2) test. The validity of each descriptor was compared in both benign and malignant lesions. p values less than 0.05 were considered statistically significant. The positive and negative predictive values and the likelihood ratios (LR) were calculated using the sensitivity and specificity to assess each morphology descriptor individually. A LR greater than 1 indicates a strong association with a diagnosis of malignancy. A LR less than 1 indicates a strong association with the absence of malignancy. Likelihood ratios that lie close to 1 indicate little practical significance. After validating the impact of these signs in differentiating benign from malignant breast lesions, the overall performance of CESM was evaluated.

3. Results

3.1. Classification of lesions

The study included 211 breast lesions: 102/211 (48.3%) benign and 109/211 (51.7%) malignant. The reference standard was histopathology of core or surgical biopsy specimens in 128/211 (60.7%) lesions and a scheduled follow-up study for 1 year in 83/211 (28.9%) lesions that showed typical benign morphology descriptors.

Malignant lesions included: 81/211 (38.4%) invasive duct carcinomas (IDC), 4/211 (1.95%) invasive lobular carcinomas (ILC), 14/211 (6.6%) mixed invasive duct and lobular carcinoma, 2/211 (0.95%) mucinous carcinomas, 2/211 (0.95%) primary non-Hodgkin's lymphoma, 3/211 (1.4%) DCIS, and 3/211 (1.4%) metastatic lesions to the breast.

Benign lesions included: 21/211 (10%) fibro-adenomas, 45/211 (21.3%) adenosis and fibro-cystic changes, 23/211(10. 9%) benign post operative breast changes; 6/211 (2.8%) abscess cavities and infected cysts, 4/211(1.9%) intra-mammary lymph nodes in atypical

sites, 1/211 (0.5%) intra-ductal papilloma, and 2/211 (0.95%) cases with duct hyperplasia and atypia.

3.2. Initial standard digital mammography results

The breast density was predominantly fatty in 67/168 (39.9%) mammograms and predominantly fibroglandular in 101/168 (60.1%) mammograms. Initial DM identified abnormalities are listed in Table 1.

Table 1
Shows the initial standard DM identified abnormalities in correlation to their final diagnosis.

Mammography findings	Benign		Malignant		Total	
Mass lesions	37	36.3%	57	53.2%	95	45%
Focal asymmetry	31	30.4%	23	21.1%	54	25.6%
Distorted parenchyma	11	10.8%	11	10.1	22	10.4%
Indeterminate microcalcifications	4	3.9%	9	8.3%	13	6.2%
Heterogeneous dense breast	19	18.6%	8	7.3%	27	12.8%
Total	102	100%	109	100%	211	100%

3.3. Presence or absence of contrast uptake

Enhancement was observed in 145/211 lesions (68.7%): 42/145 (29%) benign and 103/145 (71%) malignant lesions (p value $\leq$0.001). No enhancement was noted in 66/211 lesions (31.3%): 60/66 (90.9%) benign and 6/66 (9.1%) malignant lesions (p value $\leq$0.001) (Fig. 1).

No enhancement was identified in 6/109 (5.5%) malignant breast lesions namely one duct carcinomas in situ (DCIS), two mucinous carcinomas, 2 IDC and one metastatic lesion to the breast (Fig. 2). On the other hand, enhancement was noted in 42/102 (41.7%) benign lesions namely four abscess cavities, three infected cysts, twenty mammary adenosis, eight fibroadenomas and four operative beds, one intraduct papilloma and 2 duct hyperplasia with atypia (Fig. 3).

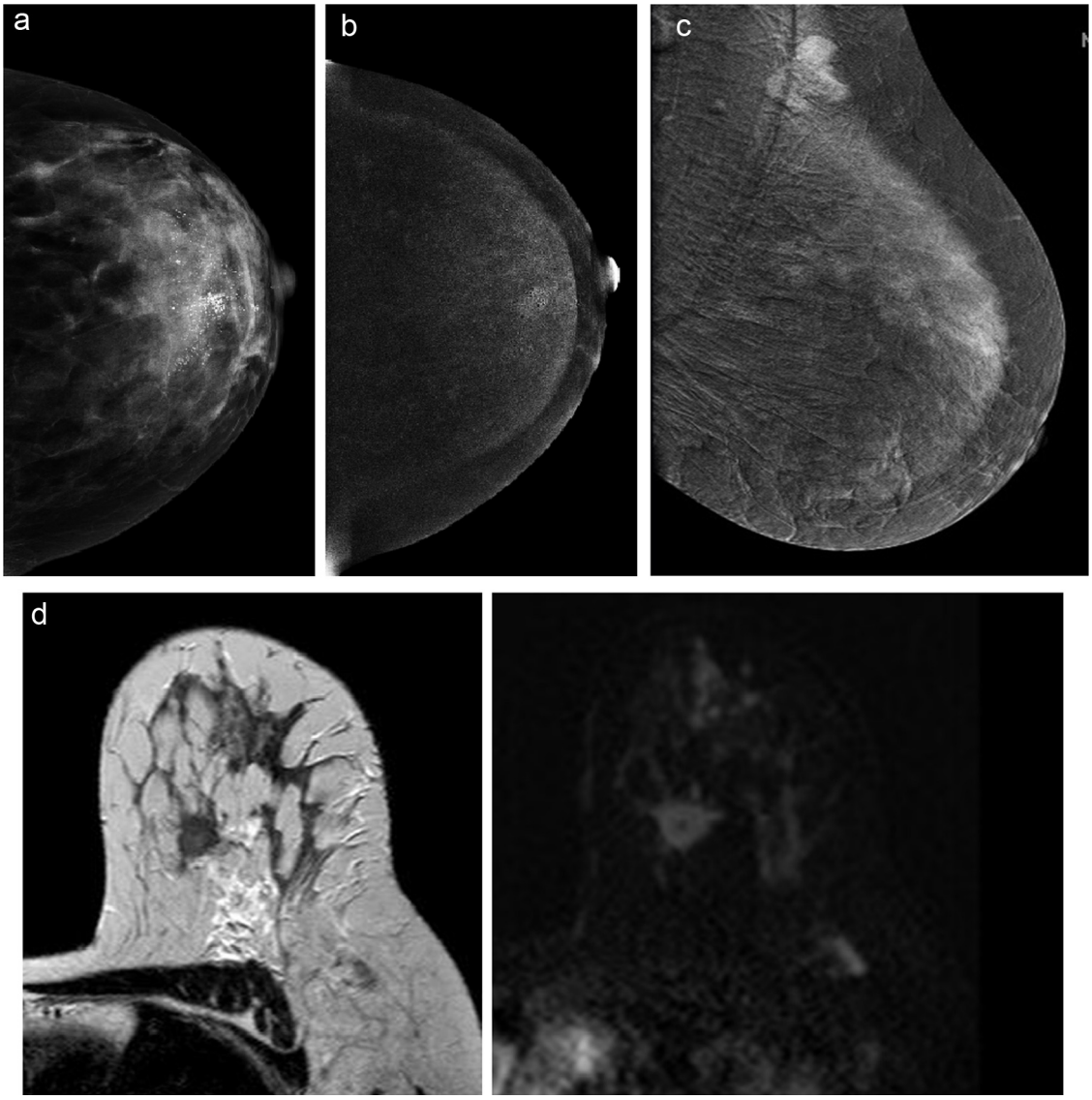

Fig. 1. Two different cases with non-enhancing malignant lesions on CESM: DCIS (a and b) and IDC (c and d). (a) CESM low-energy cranio-caudal images showing retro-areolar clusters of microcalcifications in a histopathology proved case with DCIS. (b) No contrast uptake is noted on the corresponding CESM subtraction images. (c) CESM subtraction medio-lateral oblique images showing enhanced pathological left axillary nodes and faint back ground parenchymal enhancement. (d) T2 and subtraction contrast-enhanced MRI images showing a deeply seated left breast carcinoma exhibiting ring enhancement that was not identified on CESM subtraction images.

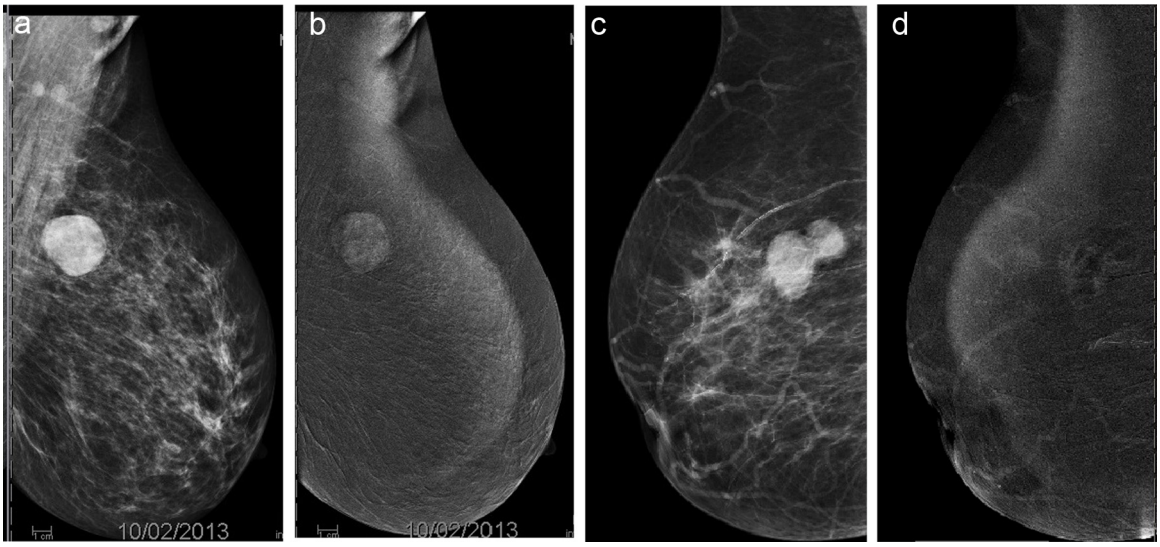

Fig. 2. Two different cases with fibro adenomas: enhancing fibro adenoma: (a and b) and non-enhancing fibro adenoma (c and d). (a) Digital mammography medio-lateral oblique view of the left breast shows an upper outer quadrant rounded fibroadenoma. (b) CESM subtraction images shows faint, homogeneous enhancement of the fibroadenoma with well-defined margins. (c) Digital mammography, medio-lateral view of the right breast showing an upper outer quadrant macro-lobulated fibroadenoma. (d) CESM subtraction image shows no significant corresponding contrast uptake.

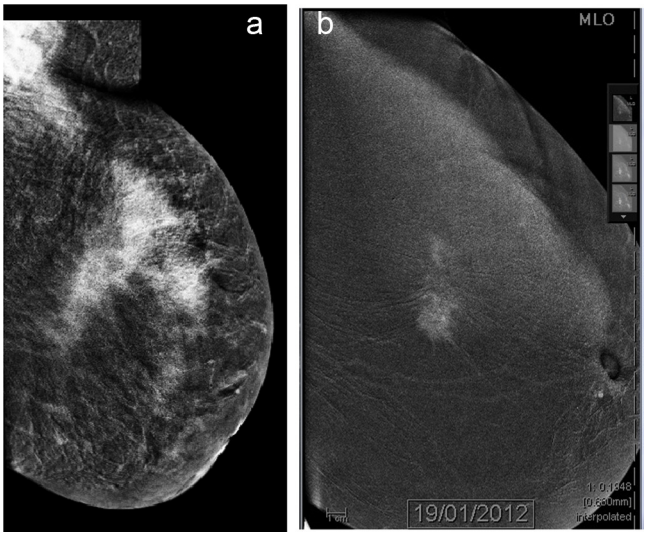

Fig. 3. CESM images in 2 different cases showing intense heterogeneous enhancement in an irregular shaped mass lesion with spiculated and ill-defined margins: (a) locally advanced IDC. (b) IDC grade 2.

3.4. Mass versus non-mass enhancement

Enhancing breast lesions were further described as enhancing mass lesions (99/145, 68.3%%) and enhancing non-mass lesions (46/145, 31.7%) (Fig. 1).

3.5. Morphology descriptors of enhancing mass lesions

Mass enhancement (99/145) morphology descriptors are shown in Table 2. Irregular mass shape, ill defined or speculated margins, heterogeneous and intense internal enhancement all strongly correlated with a malignant pathology (p value $\leq$0.001) (Fig. 4). Ring pattern of contrast uptake was reported in 17 cases: 10/17 (58.8%) benign lesions and 7/17 (41.2%) malignant lesions. These are 6 abscess cavities/infected cysts, 4 operative bed infected seromas, 2 cases of lymphoma and 6 IDCs (Fig. 5).

Table 2
Analysis of the morphology descriptors of 99 enhancing mass lesions.

	Benign (18/99)		Malignant (81/99)		P value
• **Mass shape**					
- Round/oval	14/18	77.8%	17/81	20.9%	≤0.001*
- Irregular	4/18	22.2%	64/81	79.1%	
• **Enhancement patterns**					
- Homogeneous	6/18	33.3%	18/81	22.2%	≤0.001*
- Heterogeneous	2/18	11.1%	56/81	69.1%	
- Ring pattern	10/18	55.6%	7/81	8.7%	
• **Degree of enhancement**					
- Faint	15/18	83.3%	18/81	22.2%	≤0.001*
- Intense	3/18	16.7%	63/81	77.8%	
• **Margins**					
- Well-defined	15/18	83.3%	3/81	3.7%	≤0.001*
- Ill-defined	2/18	11.1%	54/81	66.7%	
- Spiculated	1/18	5.6%	24/81	29.6%	

* P value $\leq$ 0.05 is considered significant.

3.6. Morphology descriptors of enhancing non-mass lesions

Non-mass enhancement (46/145) morphology descriptors are shown in Table 3. Ductal, segmental or regional distribution showing focal or clumped, intense and heterogeneous enhancement strongly correlated with a malignant pathology (p value $\leq$0.001) (Fig. 5).

3.7. Level of performance of the individual diagnostic criteria

The sensitivity, specificity, positive and negative predictive values of each individual mass and non-mass morphology descriptor are shown in Tables 4 and 5.

3.8. Overall performance of CESM

The overall performance of CESM was finally assessed in correlation to the validity and reliability of these diagnostic criteria. The calculated values are: sensitivity 94.5%, specificity 83.3%. PPV 85.8%, NPV 93.4%, LR+ 5.67 and LR− 0.07.

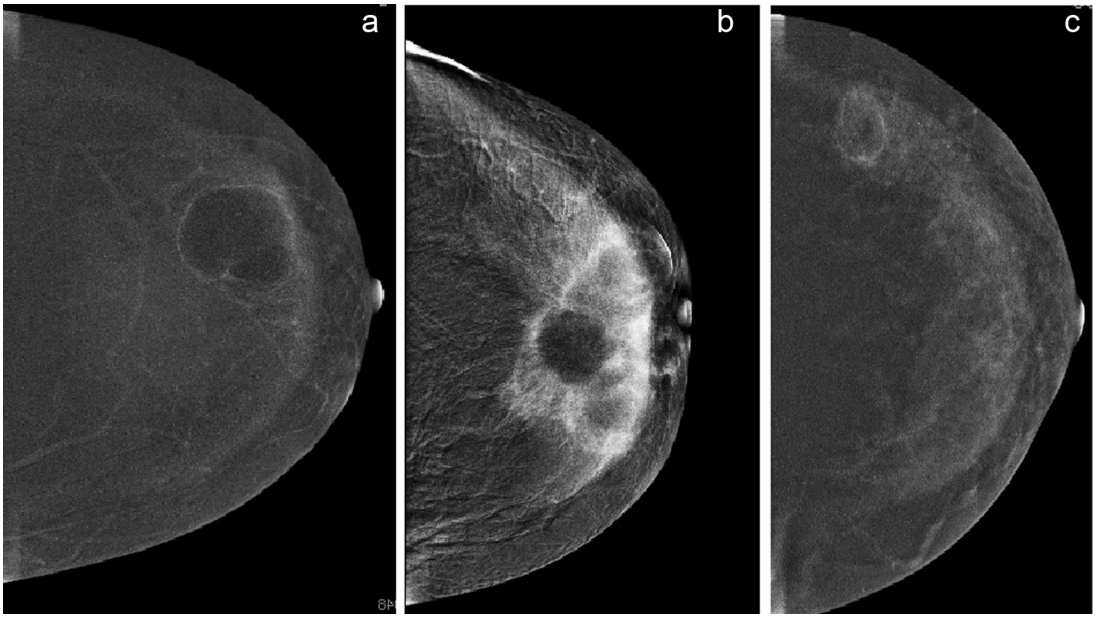

Fig. 4. CESM images in three different cases showing ring-pattern of contrast uptake. (a) Infected cyst with fine ring enhancement. (b) Abscess cavity with markedly enhancing surrounding reactionary parenchyma. (c) IDC showing ring enhancement.

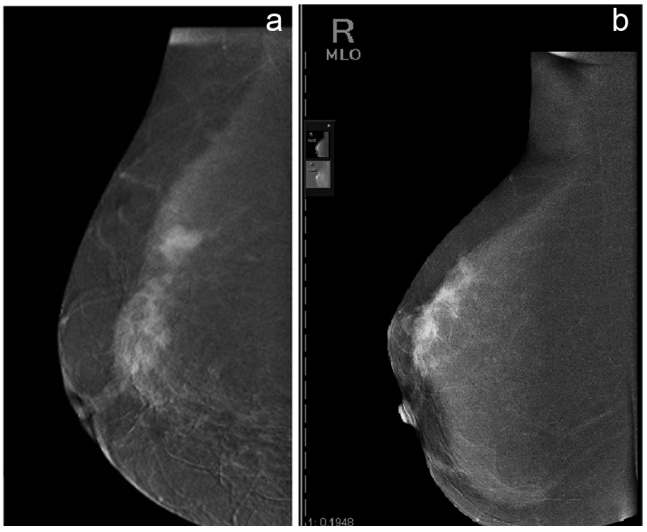

Fig. 5. CESM images in two different cases showing non-mass (a) ductal and (b) segmental enhancement.

Table 3
Analysis of the morphology descriptors of 46 enhancing non mass lesions.

	Benign (24/46)		Malignant (22/46)		*P* value
• **Enhancement patterns**					
- Homogeneous	19/24	79.2%	4/22	18.2%	≤0.001*
- Heterogeneous	5/24	20.8%	18/22	81.8%	
• **Degree of enhancement**					
- Faint	19/24	79.2%	3/22	13.6%	≤0.001*
- Intense	5/24	20.8%	19/22	86.4%	
• **Distribution**					
- Diffuse/patchy/nodular	17/24	70.9%	3/22	13.6%	≤0.001*
- Ductal/Segmental/regional	4/24	16.6%	13/22	59.1%	
- Focal	1/24	4.2%	2/22	9.1%	
- Clumped	2/24	8.3%	4/22	18.2%	

* *P* value ≤ 0.05 is considered significant.

4. Discussion

In 2001, Lewin et al. discussed a dual-energy approach to contrast digital mammography based on a weighted subtraction of two images; one below and the other above the K edge of iodine [6,7].

The morphology enhancement characteristics of benign and malignant breast lesions on dual-energy CESM are still under investigation. In this manuscript we assessed the enhancement characteristic and morphology descriptors of breast lesions on CESM and their impact on differentiating benign from malignant breast lesions.

The first step was to validate whether the absence of contrast uptake would exclude a malignant pathology or not. According to the study performed by Jong et al., enhancement was reported in 89% (8/9) invasive cancers and 42% (5/12) benign lesions [1]. We reported a significantly lower incidence of non-enhancing malignant (6/109, 5.5%) than benign (60/102, 41%) lesions (p value ≤0.001), from this we emphasize on the fact that we should never discard considering biopsy in the presence of mammography or ultrasound suspicious findings. Previous studies verified that non enhancing malignant lesions on CE-MRI may be attributed to technical reasons, missed enhancement due to background enhancement or factors related to the intrinsic properties of tumors; for example: small tumor size, lack of invasive component and lack of surrounding angiogenesis which allows increased microvessel permeability [8–10].

According to Fallenberg et al., 2014, CESM offers promise, seemingly providing information comparable to MRI [11]. Therefore, inspired by the ACR MRI BI-RADS lexicon morphology descriptors, we classified enhancing lesions into mass and non-mass. Analysis of the morphology descriptors of enhancing breast lesions was expected to yield a high diagnostic accuracy in discriminating benign from malignant breast pathologies. For mass lesions, the mass shape, outline, internal enhancement pattern and degree of contrast uptake were analyzed. For non-mass lesions, we assessed the internal enhancement pattern, the degree and distribution of enhancement.

As described in previous studies that discussed the morphology descriptors of malignant breast lesions on MRI, the presence of irregular shaped intensely enhancing mass lesions with ill defined

Table 4
The level of performance of the individual morphology descriptors in 99 enhancing mass lesions.

	Mass shape		Enhancement patterns		Degree of enhancement		Margins	
		95% CI		95% CI		95% CI		95% CI
Sensitivity	79%	0.689–0.865	75.7%	0.648–0.84	77.8%	0.676–0.855	96.3%	0.897–0.987
Specificity	77.8%	0.549–0.91	75%	0.409–0.929	83.3%	0.608–0.942	83.3%	0.698–0.942
PPV	94.1%	0.858–0.977	96.6%	0.883–0.99	95.5%	0.875–0.948	96.3%	0.897–0.987
NPV	45.2%	0.292–0.622	25%	0.12–0.449	45.5%	0.298–0.62	83.3%	0.698–0.942
LR+	3.556	1.487–8.5	3.027	0.905–10.122	4.667	1.65–13.197	5.778	2.055–16.247
LR−	0.27	0.165–0.44	0.324	0.184–0.572	0.267	0.169–0.421	0.044	0.014–0.138

Table 5
The level of performance of the individual morphology descriptors in 46 enhancing non-mass lesions.

	Enhancement pattern		Degree of Enhancement		Distribution	
		95% CI		95% CI		95% CI
Sensitivity	81.8%	0.615–0.927	86.4%	0.6667–0.953	86.4%	0.667–0.953
Specificity	79.2%	0.595–0.908	79.2%	0.595–0.908	73.9%	0.535–0.875
PPV	78.3%	0.581–0.903	79.2%	0.6667–0.953	76%	0.566–0.885
NPV	82.6%	0.629–0.93	86.4%	0.595–0.908	85%	0.64–0.948
LR+	3.927	1.757–8.779	4.145	1.868–9.202	3.311	1.631–6.718
LR−	0.23	0.092–0.57	0.172	0.059–0.503	0.184	0.063–0.543

and speculated margins strongly correlated with malignant breast lesions [8,12–14]. A strong correlation of the mentioned descriptors and malignant mass lesions was further confirmed in the current study ($\leq$0.001). By comparing the morphology descriptors, the highest level of performance was scored by tumor margin description (sensitivity and PPV: 96.3%, specificity and NPV: 83.3%, LR+: 5.778 and LR−: 0.004).

The internal enhancement patterns of mass lesions were classified into homogeneous, heterogeneous and ring-pattern. Heterogeneous pattern of contrast uptake was characteristic for malignant mass lesions ($\leq$0.001). This could be explained by the fact that microvascular density plays a major role in determining the heterogeneity of tumor enhancement [9,12].

According to Schnall et al., ring like enhancement highly correlates with cancer diagnosis on MRI examinations (PPV, 84%). One advantage of MRI is that on reviewing the T2 images, abscess cavities and infected cysts can be confidently excluded [9]. The absence of this advantage with CESM, ring enhancement was not considered a reliable indicator of the nature of mass lesions in this study.

The characterization of non-mass enhancing lesions on CESM images was more intricate than mass lesions due to the lack of adequate discriminating criteria and ill-defined margins. According to a study performed by Wilhelm et al. [15], to evaluate the malignancy rates for non-mass enhancement on breast MRI, it is difficult to establish guidelines for management of non-mass enhancement. They recorded the highest PPV for segmental and clumped enhancement. Heterogeneous and intense non mass enhancement (p value $\leq$0.001) taking a ductal, segmental or clumpded pattern (p value $\leq$0.003) were all strongly indicative of a malignant pathology in the current study.

The overall performance indicators of CESM according to the above analyzed morphology descriptors were measured. The calculated values are; sensitivity: 94.5%, specificity: 83.3%, PPV: 85.8%, NPV: 93.4%, LR+: 5.67 and LR−: 0.07 as compared to those calculated for the initial standard DM; sensitivity: 81.9%, specificity: 41.8%, PPV: 69%, NPV: 59.4%, LR+: 1.407 and LR−: 0.432.

The study still had several limitations. The number of patients enrolled in the study is considered relatively low and not all the pathological entities were included. Many of the assessment criteria are subjective and are thus subject to personal assessment variation. The comparison with Digital Mammography is not a fair comparison based on the selection inclusion criteria.

In conclusion, 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. The relative high reported predictive values of CESM in this study as compared to those reported of mammography makes it suitable to be integrated in the diagnostic work up of patients with breast-related problems that may not be adequately addressed with standard digital mammography.

Conflict of interest

The authors have no conflict of interest to declare.

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