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Assessment of the diagnostic accuracy of contrast-enhanced digital mammography in the differentiation between benign and malignant breast mass lesions

Hoda Ahmed
Radio-diagnosis, Al-Azhar university Assiut, Faculty of Medicine, Assiut , Egypt,
hodaradiology2012@gmail.com

yasser Ahmed
Radio-diagnosis, Faculty of Medicine, Al-Azhar university, Assiut, Egypt, yasser_abdelaal87@yahoo.com

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Radio-diagnosis

Assessment of the diagnostic accuracy of contrast-enhanced digital mammography in the differentiation between benign and malignant breast mass lesions

Hoda Abdel Kareem Ahmed, [1] MD, Yasser Abdel Aal [1] MD.

** Corresponding Author:*
Hoda Abdel Kareem Ahmed
hodaradiology2012@gmail.com

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[1]Radio-diagnosis Department, Faculty of Medicine (Assuit), Al-Azhar University, Egypt.

ABSTRACT

Background: It is important to find an accurate and cost-effective tool for early diagnosis of breast cancer which is the most common cancer in women worldwide. Contrast Enhanced Digital Mammography(CEDM) is an emerging modality in depicting abnormalities seen at screening mammography and it could demonstrate disease extension and help in detecting response to therapy.
Aim of the study: to evaluate the accuracy of CEDM in the diagnosis and differentiation between benign and malignant breast masses and mass like lesions.
Patients and Methods: This prospective study included 100 female patients with 154 breast lumps, their ages ranged from 30-75 years (Mean= 42±5.3) who referred with suspicious breast lump. An informed consent was obtained from all patients. All patients were subjected to local breast examination of both breast sides, renal function tests; Conventional mammography (CM), breast ultrasonography (U/S) and contrast enhanced digital mammography (CEDM). Diagnoses confirmed by biopsy and histopathology results that used as a gold standard.
Results: The 154 studied lesions found to be: 122 malignant neoplastic lesions (79.22%) and 32 benign lesions (20.78%) according to the histopathology results.CEDM was found to have higher sensitivity (97.56%), specificity (93.55%) and accuracy (96.75%) when compared to combined CM and U/S results that showed sensitivity (62.30%), specificity (68.75%) and accuracy (63.64%)
Conclusion: Contrast-enhanced digital mammography found to be a low cost effective diagnostic method in the differentiation between benign and malignant breast mass lesions that can improve diagnostic accuracy and increase cancer detection rate.

Keywords: *Contrast-enhanced digital mammography; diagnostic accuracy; benign; malignant: breast mass lesions..*

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide, and it is important to find an accurate and cost-effective tool for its early diagnosis [1]. Screen-film mammography had been proved for the reduction of breast cancer mortality; Since the early 2000s, It was progressively replaced by digital mammography (DM), which improved performance, especially in women under the age of 50 years and those with dense breasts [2]. Contrast-enhanced spectral mammography (CESM) utilizes a contrast agent to highlight areas of increased vascularization, such as those around and within tumors, using standard mammography equipment [3].

Contrast enhanced digital mammography (CEDM) combines digital mammography with the benefits of contrast imaging, using the high rates of blood vessel formation in tumors to distinguish between cancerous and healthy tissue [4]. The physiologic information provided by CEDM is similar to that is provided by breast MRI, without the added time or expense of conventional breast MRI protocols [5]. CEDM has a higher sensitivity for breast cancer detection compared with the sensitivities of full-field digital mammography (FFDM) alone and FFDM combined with ultrasound. For assessing tumor extent, its findings had a good correlation with the histopathology size, even in dense breasts [6-15].
The purpose of this work was to evaluate the accuracy of CEDM in the diagnosis and differentiation between

benign and malignant breast masses and mass like lesions.

PATIENTS AND METHODS

Patient's demographic data

This prospective study included 100 female patients with 154 breast lumps; their ages ranged from 30 to 75 years with a mean age=±42 years who referred to radio-diagnosis departments with a clinical diagnosis of a suspicious breast lump. Informed consent was obtained from all patients. Patients who had general contraindications for contrast media or who could not tolerate the mammography exam. were excluded from this study.

Inclusion criteria

All Patients with newly developed suspicious breast lump who did not have history of surgery or radiation therapy .

Exclusion criteria

Pregnant patients and patients with general contraindications for contrast media as well as those who could not tolerate the mammography examination .

All patients were subjected to local breast examination of both sides, renal function tests; Conventional mammography (CM), breast ultrasonography (U/S) & contrast-enhanced digital mammography (CEDM). Each detected lesion was specified according to the BI-RADS classification, localization, size (maximum diameter), and the distance between disease sites, which was used to determine whether surgery would involve conservation (multifocal disease) or mastectomy (multicentric disease) .

Conventional & Dual-energy CEDM technique

Conventional & CEDM were performed to all patients by using a digital mammography unit (Senographe 2000 D full-field digital mammography Essential GE Healthcare). First, craniocaudal (CC) and mediolateral oblique (MLO) views were obtained for all patients while additional views were taken if indicated (e.g. Lateral /Spot views). A cannula is inserted on the opposite side of the affected breast & I.V. iodinated contrast agent (omnipaque, 300 mg/ml) injected prior to patient positioning in a dose(1-1.5 ml/Kg).

Ultrasonography(U/S):- Detailed breath U/S exam. was done for both breasts and axilla by ultrasound machine (Logiq P5, GE Medical Systems) with 7.5–12 MHz using lineararray transducer. Also, all biopsies were taken under an U/S guide.

Dual-energy CEDM was performed by acquiring a pair of low- and high-energy images in quick succession during a single breast compression & after the initiation of contrast medium injection by 3 minutes, a set of bilateral imaging as followed: CC view of the unaffected breast followed by CC and MLO views of the affected breast; and then MLO view of the unaffected breast. Low-energy images were acquired at peak Kilovoltage (KV), 25-30, which is below the K-edge of iodine "33.2 KV" while high-energy images were acquired at 42-50 kV, which is above the K-edge of iodine, to perform a pair of low and high energy exposures in order to generate two subtracted images with contrast agent uptake information.

Image interpretation

All images were reviewed in consensus by two radiologists (HA and YA) with experience in breast imaging who were blinded to clinical data, and only concentrated on image findings and lesion characterization, including:- location, number, shape, borders, surrounding parenchyma, calcification if present and pattern of contrast enchantment. Focally enhanced lesions beyond normal background breast enhancement was considered as abnormal and the probability of malignancy using the BI-RADS system was applied for each lesion evaluation in all imaging techniques .

Biopsy with the histopathology results or clinical diagnosis after a conservative treatment & follow-up was taken as gold standard

Statistical analysis

Data entry and analysis was done using the program Statistical Package for the Social Sciences (SPSS). The technique results were studied using Student's t-test & Sensitivity, specificity; negative and positive predictive values (PPV) were assessed and compared. $P<0.05$ was considered statistically significant.

RESULTS

This study was carried on 100 patients with 154 breast lesions that according to the histopathology results proved to be:-122 malignant neoplastic lesions (79.22%), with 98invasive lesions & 24 lesions were non-invasive. While the remaining 32 lesions were benign (20.78%) with 16 fibro-adenomas & 9 lesions were granulomatous mastitis, (Table 1).

Conventional mammographic & U/S findings in studied breast lesions

Twenty-one benign lesion (21/32) showed well-defined margin (BI-RAD 2) that proved to be 16 fibroadenomas (FAL), 3 chronic abscesses and 2 fibro-adenolipoma while, 10 benign lesions (BI-RAD 3-4) showed poorly defined outlines that proved to be 9 granulomatous mastitis and 1 fat necrosis. The last benign lesion showed lobulated outlines that pathologically proved to be a phylloid(BI-RAD 3). However, 59/122 malignant lesions showed lobulated margins (BI-RAD 3-4) and 47/122 lesions (BI-RAD 4-5) showed ill-defined margin and the remaining 16 lesions showed speculated outlines (BI-RAD 5). Macro-calcification were detected in 17/35 beings lesions & micro-calcification seen in 69/122

malignant lesions while mixed calcifications were seen in 7maligant lesion & no calcification detected in the remaining 61 lesions, (Table 2) .

Distribution of lesions visible in CEDM

We made our study on 100 patients, 70 have single lesion that all were visible by sono-mammography (62 malignant and 8 benign lesions),while 59/62 lesions were visible by CEDM and 3 patientswith malignant lesions were not enhanced; 13 patients each had 2 contrast-enhanced lesions (18 malignant&8 benign). The remaining 17 patients, had more than 2 lesions (42 malignant & 16 benign lesions), (Table 3).

CEDM Imaging findings & enhancement pattern

We diagnosed 122 pathological lesions as malignant lesions, 78 lesions had heterogeneous mass enhancement while homogenous enhancement was seen in 12 masses, 2 lesions showed non-mass ductal enhancement, 14 lesions showed non-mass regional heterogeneous enhancement, non-mass segmental enhancement was seen in 6 lesions, heterogeneous mass enhancement with ductal enhancement seen in 5 masses, heterogeneous mass enhancement with foci of enhancement seen in 2 masses and 3 malignant lesions showed no enhancement and were not observed in CEDM (false negative). The 32 pathologically diagnosed benign lesions showed heterogeneous enhancement in 12 (7 granulomatous mastitis, 4 fibroadenoma & 1 phylloid lesion), homogenous seen enhancement in 12 fibroadenomas, ring enhancement seen in 8 lesions, 3 chronic abscesses, 2 granulomatous mastitis, 2 fibroadenolipoma and 1 fat necrosis), (Table 4).

Lesion outlines, borders and size in CEDM in correlation with pathological correlations

Out of the 154 detected lesions 35 diagnosed as benign lesions (32 lesions that showed well-defined margin but 3 lesions were with indistinct outlines). However, 119/154 lesions were diagnosed as malignant lesions, 59 lesions showed lobulated margins (58 malignant lesions & 1 was phylloid according to histopathology results), and 60 lesions showed ill-defined margin (59 lesions proved to be malignant and 1 was benign fat necrosis by histopathology. As regards the lesion sizes, they were ranged from 0.4 to 7 cm that did not reflected on radiologic diagnosis, with P-value= 0.4117 (not significant), (table 5).

Sensitivity, specificity, and accuracy of CEDM versus mammography combined with U/S for all studied lesions

CEDM was found to have higher sensitivity 97.56%, specificity 93.55) and accuracy 96.75% when compared to combined sono-mammography results that showed sensitivity 62.30%, specificity 68.75% and accuracy 63.64% , (Table 6, Figures 1-5).

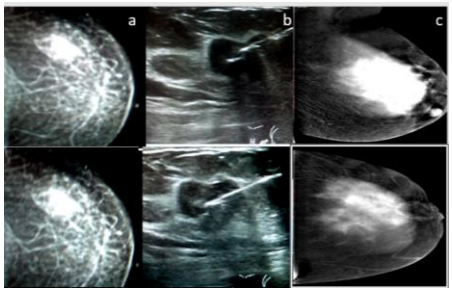

Fig 1: A 31 yes female Pt. (a) DM: revealed a non specific asymmetric densities at the UOQ. (b) U/S: showed a para-areolar cystic lesion with thick irregular walls and non-homogenous echoes(a&b: BIRAD 3-4). (c)CEDM: revealed a small well defined lesion with ring enhancement at the UOQ & areas of non-mass segmental enhancement suggesting inflammatory process with abscess formation (BIRAD 2). Aspiration & cytology:-Abscess

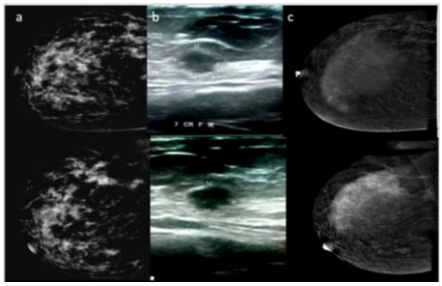

Fig 2: A 42 yes female Pt. (a) DM: revealed poorly defined dense lesions at UOQ (b) U/S: showed a poorly defined deep hypoechoic lesion with irregular outlines (a&b: BIRAD 3). c)CEDM: revealed non-mass heterogeneous regional enhancement with distortion of related tissue architectures echoes (BIRAD 4). Histopathology: Ductal Ca insitu with microscopic invasion.

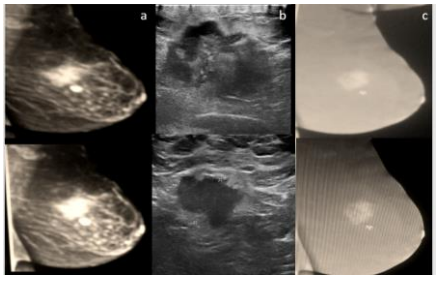

Fig 3: A 55 yes female Pt. (a) DM.: revealed diffuse edema with skin thickening and UOQ a small well defined dense lesion. (b) U/S: showed an ill-defined heterogeneous hypo-echoic lesion with intra-ductal extension (a&b: BIRAD 4). (c) CEDM: Revealed: an irregular moderate heterogeneous enhanced lesion with speculated outlines (BIRAD 5). Histopathology: Invasive ductal Ca.

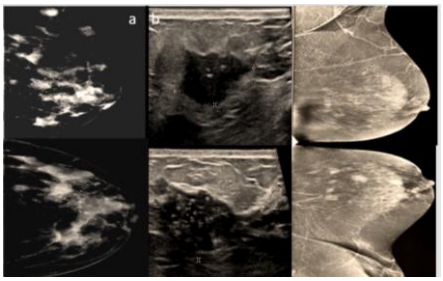

Fig 4: A 40 yes female Pt. (a)DM: reveled LOQ intermediately dense obscured lesions with clusters of mixed calcification. (b)U/S: showed multiple infiltrative hypoechoic lesions with micro-calcification and ductal extensions(a&b: multiple lesions with BIRAD 5). (c) CEDM: detected more lesions with irregular outlines and moderate/marked heterogeneous enhancement (Multicentric lesions with BIRAD 5). Histopathology: Multicentric IDC.

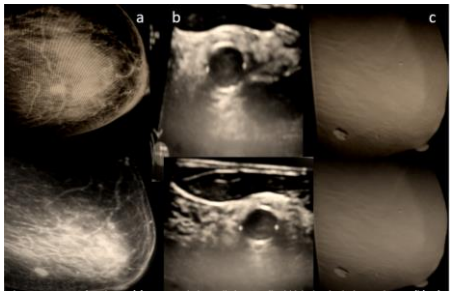

Fig 5: A 62 yes female Pt. (a) DM revealed a well circumscribed high density lesion at the LIC. (b) U/S showed a well-defined hypoechoic lesion (a&b: BIRAD 3). (c)CEDM revealed a well defined lesion with irregular outlines & diffuse intense homogenous enhancement (BIRAD 5). Histopathology: Metastatic neuro-endocrine Ca.

Lesion	**total**	**Pathological diagnosis**	**No**	**%**
Invasive (63.64%)	98	Invasive ductal Ca	76	62.3
		Invasive lobular Ca	10	8.2
		Mixed	7	5.73
		Metastatic	5	4.1
Non-Invasive (15.58%)	24	Intra-Ductal Ca	24	19.67
Benign (20.78%)	32	Fibroadenoma	16	50
		Granulom. mastitis	9	28.13
		Chronic abscess	3	9.4
		Fibroadenolipoma	2	12.5
		Phylloid	1	3.13
		Fat necrosis	1	3.13

Table 1: Final histopathology diagnosis of studied 154 breast lesions.

Lesion & BI-RAD score	**no.**	**borders**	**Calcification**
Fibroadeonoma(score2) Chronic abscesses (score2) Fibroadenolipoma (score2)	16 3 2	Well-defined	Macro/16 benign No/5 benign
Granulom. Mastietis (score 3-4) Fat necorsis. (BI-RAD 3-4)	9 1	poorly defined	 No/10 benign
Phylliod (BI-RAD 3) Malignant lesions(BI-RAD 3-4)	1 59	lobulated	Macro/1 phylloid Mixed/7 malignant Micro/8 malignant
Malignant lesions(BI-RAD 4-5)	47	Ill-defined	
Malignant lesions(Bi-RAd5)	16	Speculated	Micro/61malignant
Total=154 focal lesions	22 benign/69 border-line/63 malignant		

Table 2: CM & U/S findings in the studied breast lesions using BI-RAD scoring.

Multiplicity	**Pt.**	**lesion**	**Pathology**	**Non-Enhanced**	**+ve Enhanced**
Single	70	70	Benign(8)	0	8
			Malign.(62)	3	59
2 lesions	13	26	Benign(8)	0	8
			Malign.(18)	0	18
>2 lesions	17	58	Benign(16)	0	16
			Malign.(42)	0	42

Table 3: Distribution of lesions visible in CESM.

Lesions Pattern of enhancement	Total No.=154	Benign No=32	Malignant No=122
Heterogeneous	90(58.4%)	12(37.5%)	78(63.9%)
Homogenous	24(15.58%)	12(37.5%)	12(9.8%)
Ring enhanced	8(5.2%)	8(25%)	0 (0.0%)
Non-enhanced	3(1.94%)	0(0.0%)	3(2.5%)
Ductal enhancement	2(1.3%)	0(0.0%)	2(1.6%)
Segmental enhancement	6 (3.9%)	0 (0.0%)	6 (4.9%)
Regional heterogeneous	14 (9.09%)	0(0.0%)	14(11.5%)
Heterogen.mass +enhanced duct	5 (3.24%)	0 (0.0%)	5(4.1%)
Heterogen. mass +enhanced foci	2 (1.3%)	0 (0.0%)	2 (1.64%)

Table 4: Enhancement pattern of the studied 154 lesions in CEDM.

	Marginal wall			**Lobulated**			**Ill-defined**		
CEDM (151)	Lesion no=32	Benign	32	lesions no=59	benign	1	lesion no=60	benign	1
		Malign.	0		Malign	58		Malign.	59
3	No=3	Benign	-	non-enhancing with indistinct out-lines					
Size range	Benign lesion Malignant lesion		0.5-7 Cm 0.3-6.4 Cm				P-value= 0.4117 (not significant)		

Table 5: Lesion outlines, borders and size in CEDM in correlation with pathological results.

Modality	Sensitivity	Specificity	Accuracy	PPV	NPP
Sono-Mamog.	62.30%	68.75%	63.64%	88.37%	32.35%
CEDM	97.56%	93.55%	96.75%	98.36%	90.62

Table 6: Sensitivity, specificity and accuracy of CEDM for all studied lesions.

DISCUSSION

Breast cancer is the most common non-cutaneous malignancy in women [16]. Contrast-enhanced mammography is a promising new imaging modality that uses a dual-energy acquisition to provide both morphological and vascular assessments of breast lesions [17].

Our histopathology results revealed that 122/ 154 studied lesions were of malignant neoplastic etiology (79.22%) with most of them were of invasive criteria (98/122) while 32/154 were benign lesions (20.78%) with fibro-adenomas was the commonest (50%) diagnosis. These findings were matched with results of Basma AD et al 2017 who found that 37/53 studied lesions (69.8%) were malignant lesions with 31 invasive lesions & 16 lesions (30.1%) were benign with 7 fibroadenomas, that was the commonest benign lesions [18]. Also, Elżbieta Ł et al 2015 found that 81 out of 118 studied lesions (69%) were malignant with 72 invasive & 9 non-invasive cancers and 37 lesions (31%) were benign [19]. We use the standard mammography BI-RADS assessment for the probability of malignancy with histopathology results used as a gold standard for each lesion evaluation that was in agreement with Ahmed F el al 2018, who stated that all breast lesions were diagnosed pathologically by means of biopsy and BIRADS classification in an imaging modality [20] & Hannah P et al 2019 who said:- Although an independent BI-RADS lexicon does not yet exist for CEM, a BI-RADS categorization for CEM is identical to that used for standard mammography [5]. Screening mammography remains the only test for breast cancer that has been shown to reduce breast cancer mortality in randomized clinical trials as it is a rapid and low-cost test [21].

In this study, the combined conventional mammography & U/S findings could successfully diagnosed 21/32 benign lesions, BI-RAD 2 while 10 lesions were of suspicious etiology, BI-RAD 3-4 (border-line lesions) and only 1 phylloid lesion categorized as a BI-RAD 3 while it correctly diagnosed 68/122 as malignant lesions, 63 lesions, BI-RAD 4-5 and 5 lesions BI-RAD & 59/122 were border-line, BI-RAD 3-4. Calcification aid in the diagnosis as macro-calcification was detected in 17/35 beings lesions & micro-calcification seen in 69/122 malignant lesions.

Our results were in coincidence with Helal M et al 2017 results that revealed:- Mammography results that malignant lesions detected in 18/35 (51.4%) while benign lesions 17/35 (48.6%). Ultrasound revealed 27/35 (77.1%) lesions were malignant and 8/35 (22.9%) lesions benign [22] and Basma AD et al 2017 results that revealed conventional mammography findings of 16 benign lesions (32%) while 3 lesions (6%) had lobulated borders & Calcification seen only in 13 lesions (26%) [18]. On the other hand, Maxine S et al 2013 found that:- Conventional digital mammography depicted 42 (81%) of 52 index cancers [11].

This study results revealed that:- CEDM was found to have higher sensitivity (97.56%), specificity(93.55%) and accuracy(96.75%) when compared to combined CM & U/S results that showed lower sensitivity (62.30%), specificity(68.75%) and accuracy (63.64%), Our results were in agreement with Lee-Felker et al 2017 who concluded that:- Contrast-enhanced spectral mammography had a sensitivity of about (94%, 66/70 lesions and significantly high PPV (93%, 66/71 lesions and few false-positive findings (5/45) (P, .001 for all results) [15]. Also, Jochelson MS et al 2013 found that:- DE-CE digital mammography depicted 50 (96%) of 52 index tumors; conventional mammography depicted 42 (81%). There were 2 false-positive findings with DE CE digital mammography [11]. Also, Łuczyńska E et al 2015 results showed that histopathology confirmed 81/118 malignant lesions and 37 were benign & sensitivity was 100% with CESM, Accuracy was 79% and ROC curve areas based on BI-RADS were 0.83 for CESM [1] & Helal M et al 2017, concluded that:-CESM revealed 25/35 (71.4%) lesions were malignant & 10/35 (28.6%) lesions benign. Among 7 patients with multifocal/multi-centric histologically proven malignant lesions, all detected by CESM 7/7 cases (100%) versus 2/7 cases (28.6%) and 6/7 cases (85.7%) detected by mammography and ultrasound respectively. Based on, CESM had 95.2% sensitivity and 82.9% diagnostic accuracy [22-25].

CONCLUSION

Finally we concluded that contrast-enhanced digital mammography found to be a low cost effective diagnostic method in the differentiation between benign and malignant breast mass lesions that can improve diagnostic accuracy and increase cancer detection rate.

This study had some limitations & pitfalls as there is no basis for CEDM interpretation such as the B-RADS standard used in sono-mamography so inter individual diverge may affect the diagnosis. Non-automatic contrast injection or patients may develop allergic reaction to contrast medium could makes the enhancement pattern not optimal. Also, depending on enhancement pattern alone without respecting lesion morphology may lead to false positive and false negative results, as some benign lesions like inflammatory may show marked enhamcent and in the other hand some malignant lesions may not take obvious enhancements.

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