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FULL PAPER

Contrast enhanced dual energy spectral mammogram, an emerging addendum in breast imaging

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Objective: To assess the role of contrast-enhanced dual-energy spectral mammogram (CEDM) as a problem-solving tool in equivocal cases.

Methods: 44 consenting females with equivocal findings on full-field digital mammogram underwent CEDM. All the images were interpreted by two radiologists independently. Confidence of presence was plotted on a three-point Likert scale and probability of cancer was assigned on Breast Imaging Reporting and Data System scoring. Histopathology was taken as the gold standard. Statistical analyses of all variables were performed.

Results: 44 breast lesions were included in the study, among which 77.3% lesions were malignant or precancerous and 22.7% lesions were benign or inconclusive. 20% of lesions were identified only on CEDM. True extent of the lesion was made out in 15.9% of cases, multifocality

was established in 9.1% of cases and ductal extension was demonstrated in 6.8% of cases. Statistical significance for CEDM was p -value <0.05 . Interobserver kappa value was 0.837.

Conclusion: CEDM has a useful role in identifying occult lesions in dense breasts and in triaging lesions. In a mammographically visible lesion, CEDM characterizes the lesion, affirms the finding and better demonstrates response to treatment. Hence, we conclude that CEDM is a useful complementary tool to standard mammogram.

Advances in knowledge: CEDM can detect and demonstrate lesions even in dense breasts with the advantage of feasibility of stereotactic biopsy in the same setting. Hence, it has the potential to be a screening modality with need for further studies and validation.

INTRODUCTION

The currently utilized full-field digital mammography (FFDM) is a well-established, cost-effective screening modality in the detection of breast pathologies. Despite being a well-accepted technique, it has certain limitations, especially in cases of dense breasts and in lesions which are identified on only one view. Mammography can miss 20% of lesions in dense breasts.^{1,2} The sensitivity of mammogram decreases from 98% for fatty breasts to 48% for dense breasts.³ While almost all cancers are visible in fatty breasts on mammogram, only half may be visualized in dense breasts.³ Even though ultrasound is a commonly used complementary tool and is part of standard of care, it has certain limitations especially in cases with dense breasts. It is very subjective and it is impractical to obtain a second opinion on already obtained images. Since it is operator dependent, it may not be reproducible in all cases.⁴

The essence of screening the breast through various modalities is to detect malignant lesions, which are well

known to have tumour angiogenesis. Hence, various imaging techniques such as CT and MRI, which could demonstrate neovascularization in breast lesions, were incorporated into breast imaging. CT has the disadvantage of high radiation.^{5,6} Breast MRI is a valuable imaging tool which allows identification of otherwise occult breast diseases.⁷ MRI is contraindicated in patients with pacemakers, in those with metallic implants and is not possible in patients with claustrophobia. Above all, if a lesion is detected on MRI, performing a biopsy under MRI guidance is a cumbersome procedure.

In order to overcome these practical difficulties, a newer technological advancement in the field of FFDM called contrast-enhanced digital mammography has come into place. This is an advanced application which uses the property of tumoral angiogenesis. There are two techniques utilizing contrast in mammography: the first is temporal subtraction technique, in which a mask image and a series of post-contrast images are obtained and then the subtracted images are used for analysis. The limitation is

that it is difficult to get artefact-free subtracted images, since it is difficult to keep the breast motionless for several minutes.⁸ The second technique is contrast-enhanced dual-energy spectral mammogram (CEDM) which utilizes a pair of high- and low-energy images with the advantage that it is relatively less sensitive to motion artefact.⁸ As per limited available data on this technique, CEDM can provide additional information and improve cancer diagnosis.⁹ Studies have demonstrated that low-energy contrast-enhanced images are equivalent or rather not inferior to FFDM images and thereby can replace FFDM and reduce the radiation dose.^{10–13} Since there exists sparse literature on CEDM, there is need for further studies to evaluate and validate its utility. The goal of our study was to assess the diagnostic role of CEDM in patients with equivocal findings on FFDM.

METHODS AND MATERIALS

After obtaining institutional review board approval, 44 consenting females satisfying inclusion and exclusion criteria were consecutively included in the study and underwent two-view CEDM using our digital mammography system (GE Medical systems S.C.S., France, Senographe Essential). Inclusion criteria: patients with equivocal findings on FFDM and those who needed additional investigations to confirm the diagnosis on FFDM; exclusion criteria: history of allergy to contrast, patients who were pregnant and those with abnormal renal function parameters. Lesions without histopathological correlation were also excluded from the study.

Method

During every CEDM examination, 1.5 ml kg^{-1} of non-ionic contrast medium was injected using Liebal-Flarsheim pressure injector at the rate of 3 ml s^{-1} . The contrast medium used in our study was Iomeron 350 mg ml^{-1} . Initiation of contrast injection was taken as 0 s. Following the cessation of contrast injection, the patient was positioned for the right craniocaudal view and a pair of low- and high-energy images was obtained at 2 min. This was followed by positioning and acquiring images in the left craniocaudal view, right mediolateral oblique view and left mediolateral oblique view consecutively, as represented by the schematic diagram. All images were obtained within the 5–7-min cut-off time, as noted in various clinical studies.¹⁴

Each projection had a pair of low- and high-energy exposures, which were combined to obtain a recombined image. Low-energy images utilized Rh/Rh target/filter combination at peak kilovoltage spectrum ranging from 26–30 kVp. Since this peak kilovoltage spectrum is below the *k*-edge of iodine, the low-energy exposure resembles an FFDM and gives morphological information.¹¹ In order to demonstrate iodine uptake areas, high-energy exposure is required. The high-energy images were obtained using Rh/Cu target/filter combination and with tube voltages in the range of 45–49 kVp. Exposure at high energy is possible by shaping the X-ray spectrum to have energies above the *k*-edge of iodine (33.2 Kev) by adding a copper filter.¹⁵ These high-energy images are not used for diagnostic purposes, but are used in post-processing to create the recombined image.¹¹ To create a combined dual-energy image, subtraction

logarithm of the low-energy image from that of the high-energy image was performed.¹⁶ The resultant recombined image enhances contrast uptake areas and gives functional information.

All the images were analyzed on a BARCO (Barco N.V., Kortrijk, Belgium) coronis monitor having resolution of 5 MP. Options of zoom and pan were made available on these monitors.

Analysis of the recombined images was based on contrast intensity and morphology. Lesions which had spiculated margins, irregular margins, irregular shape and heterogeneous enhancement were taken as predictive of malignancy. Images were blinded of their history and histopathological results. Lesions which had histopathological correlation were alone included in the study. Images were interpreted by two qualified radiologists having experience in the field of breast imaging, independently in two steps, right after each other in a single setting. The first step included interpretation of FFDM alone and the second step included CEDM. Interpretation in each step includes analysis of two components: first is confidence of the presence of lesion; this was plotted in a three-point Likert scale (1—not seen, 2—faintly seen and 3—seen). The second was probability of cancer; this was obtained by assigning Breast Imaging Reporting and Data System (BIRADS) scoring to the lesions (BIRADS 1–5; scorings 0 and 6 were not allowed as in various clinical studies).¹⁷ Histopathology was obtained as either excision biopsy/trucut core biopsy/Fine needle aspiration cytology (FNAC).

Statistical analysis

Statistical analysis of three-point Likert scale and BIRADS scoring of all patients was performed taking by histopathology as gold standard. Frequency table was obtained for all the variables. Confidence of presence in terms of three-point Likert scale on FFDM and CEDM was plotted for both observers independently. Pearson χ^2 test was performed by taking histopathology as gold standard, and *p*-value was obtained. Probability of malignancy in terms of BIRADS score on FFDM and CEDM was plotted for both observers, following which χ^2 test was performed and *p*-value obtained. Sensitivity and specificity were obtained for both confidence of presence and probability of malignancy. Receiver-operating characteristic (ROC) curve for three-point Likert scale and probability of malignancy on FFDM and CEDM was obtained for both observers. Finally, the interobserver variation was analyzed to prove consistency. Mean and standard deviation of radiation dose was obtained.

RESULTS

In 44 patients, even though more than 44 lesions were present, only those 44 lesions with histopathological diagnosis were included for analysis. In this study, predominant subjects had a dense breast (Table 1). 30 lesions were malignant, 3 lesions were precancerous, 8 lesions were benign and 2 lesions came out to have scanty tissue; however, on follow-up, Histopathological examination (HPE) showed benign lesions (Table 2). One patient had conservative management for malignancy and was on follow-up (this history was blinded to the observers). 20% of

Table 1. Breast density in the study group

Breast density, American College of Radiology (ACR)	Number of patients
Scattered fibroglandular parenchyma	3
Heterogeneously dense fibroglandular parenchyma	32
Homogeneously dense fibroglandular parenchyma	9

lesions were identified only on CEDM. For the purpose of cross-tabulation, malignant and precancerous lesions were taken as positive, contributing to 77.3% of the total, and benign lesions were taken as negative, contributing to 22.7% of the total. For correlation of mammographic findings on a three-point Likert scale with histopathology, lesions not seen (Point 1) were taken as negative and lesions faintly seen (Point 2) and seen (Point 3) were taken as positive. For the purpose of cross-tabulation with histopathology, BIRADS 1, 2 and 3 were taken as negative and BIRADS 4 and 5 were taken as positive. Histopathology was taken as gold standard (trucut core biopsy/FNAC in 37 patients and excision biopsy/mastectomy in 7 patients).

Interpretation of images by Observer 1 and Observer 2 was carried out independently. On FFDM, the confidence of the presence of a lesion was given points on a three-point scale and frequency table was obtained. Accordingly, for Observer 1, among 44 breast lesions, 59.1% lesions were seen, 18.2% lesions were faintly seen and 22.7% lesions were not seen. For Observer 2, 54.5% lesions were seen, 29.5% lesions were faintly seen and 16% lesions were not seen. Sensitivity for confidence of the presence of lesion on FFDM for Observer 1 was 76.5%; specificity was 20% with an insignificant statistical p -value of 0.594. For Observer 2, sensitivity was 85% and specificity was 20% with an insignificant statistical p -value of 0.509. On CEDM, when the images were evaluated, sensitivity and specificity increased to 97% and 40%, respectively, for Observer 1, having a statistically significant p -value of 0.007, and for Observer 2, sensitivity and specificity increased to 97% and 30%, respectively, having a statistically significant p -value of 0.032. The ROC curves for Observers 1 and 2 on FFDM had an area of 0.482 and 0.526, respectively; however, on CEDM images, they had an area of 0.685 and 0.635, respectively.

For assessing probability of malignancy, each lesion was assigned BIRADS 1–5; BIRADS 0 and 6 were not allowed as followed in various clinical studies.¹⁷ Accordingly, BIRADS on FFDM for Observer 1 had 74% sensitivity and 70% specificity with a statistically significant p -value of 0.017. For Observer 2, sensitivity was 68% and specificity was 80% with a statistically significant p -value of 0.010. When both readers were asked to analyze CEDM images, sensitivity and specificity for both Observers 1 and 2 were 82% and 80%, respectively, with a significant p -value of 0.001. The ROC curves for Observers 1 and 2 on FFDM had an area of 0.718 and 0.738, respectively; however, on CEDM images, both had an area of 0.812 (Figure 1).

When interobserver variation was compared, the resultant kappa value for Observers 1 and 2 for three-point Likert scale on CEDM was 0.835, suggestive of consistency.

The true extent of the lesion was made out in 15.9% of cases, multifocality was established in 9.1% of cases and ductal extension was demonstrated in 6.8% of cases.

In our study, the average glandular dose per view of CEDM procedure had a mean value of 2.4 mGy with standard deviation of 0.33. The minimum and maximum average glandular doses delivered were 1.7 and 3.05 mGy depending on breast density. The entrance surface dose per view of CEDM had a mean value of 6.04 mGy with standard deviation of 1.58. The minimum and maximum entrance surface doses were 3.95 and 11.30 mGy.

DISCUSSION

Contrast-enhanced mammogram is an advanced application in already established FFDM. It acts as a simple tool in cases where additional information is needed. It utilizes the property of unusual blood flow patterns in suspicious lesions and hence iodinated contrast uptake in such lesions. A well-accepted advantage of dual-energy contrast mammography is that it is less sensitive to motion artefacts, since the time between low- and high-energy exposures is very low.⁸ Along with FFDM, contrast-enhanced mammogram can be a complete assessment tool, since at the end of study, there are no questionable findings. It is a fast imaging technique which is reproducible, demonstrable and has consistent findings. Since the procedure is the same as mammogram, special training for technologist is not required. A major advantage is that a lesion detected on contrast-enhanced MRI can be biopsied only on MRI. If the lesion is picked up on contrast-enhanced study, in the same machine and in the same setting, stereotactic biopsy can be performed with ease.

In our experience, in patients with dense breasts, contrast-enhanced mammogram could demonstrate the presence of

Table 2. Histopathology of study group

Histopathology	Number of patients
Infiltrating ductal carcinoma	29—newly detected 1—on follow-up
Invasive lobular carcinoma	1
Atypical ductal carcinoma	1
Apocrine metaplasia	1
Papillary neoplasm	1
Fibroadenoma	8
Complicated cysts	2

Figure 1. Receiver-operating characteristic (ROC) curves of the Breast Imaging Reporting and Data System impression on full-field digital mammography (FFDM) vs contrast-enhanced dual-energy spectral mammogram (CEDM) for (a) Observer 1 and (b) Observer 2.

enhancing lesions which were occult on FFDM. In a partially circumscribed lesion on FFDM, contrast-enhanced mammogram could delineate the entire margin. When there was subtle microcalcification without mammographically visible underlying lesion, contrast-enhanced mammogram could

demonstrate margins of the lesion, hence avoiding unnecessary follow-up and preventing delay in diagnosis. If subtle architectural distortion seen on mammography, underlying lesion was demonstrated on CEDM (Figure 2). In patients with multiple lesions in both breasts, FNAC/biopsy is not practical for all the

Figure 2. (a) On full field digital mammogram, a subtle architectural distortion seen along the plane of nipple; (b) On contrast enhanced dual energy mammogram, a spiculated enhancing lesion seen. HPE, invasive lobular carcinoma.

lesions; hence, in such cases, only lesions with abnormal contrast uptake on CEDM were chosen among the other non-enhancing ones for histopathological evaluation and thus triaging lesions. Retroareolar lesions are more likely to be masked, since breast tissue is denser in this region; hence, in such cases, CEDM could demonstrate the underlying lesion.

In BIRADS 3, contrast-enhanced mammogram had a role in upgrading or downgrading. On ultrasound, it is easier to differentiate a cyst from a solid fibroadenoma, but doubt arises when there are dense inspissated contents within a cyst and hence, the diagnosis is questionable between cyst and fibroadenoma. In our experience, on CEDM, cysts appeared as lucent lesions or peripherally enhancing lesions or as faintly enhancing lesions, while most of the fibroadenomas did not enhance (Figure 3) or if they did, they showed faint homogeneous contrast enhancement. Hence, when a BIRADS 3 lesion (assigned in a previous study) showed peripheral enhancement, it was downgraded to a BIRADS 2 cyst, which in turn was confirmed on FNAC. On the other hand, when a BIRADS 3 lesion showed heterogeneous contrast uptake, BIRADS 4 category was assigned and was confirmed on biopsy.

On a mammographically detected lesion, ductal extension was better demonstrated on CEDM (Figure 4a,b). If a spiculated lesion was visible on mammography, multifocality was established on CEDM (Figure 4c,d). In case of patients on neo-adjuvant chemotherapy, reduction in size of the enhancing

lesion and hence response to chemotherapy was well demonstrated (Figure 5).

Dromain et al¹⁷ performed an extensive study on 110 patients with 148 breast lesions, who underwent two-view dual-energy CEDM in addition to mammogram and ultrasound. It was a multicentre study, analyzed by six radiologists in terms of confidence of the presence and probability of cancer similar to that in our study. They confirmed the superior diagnostic accuracy of contrast-enhanced mammogram with sensitivity of 93%.

Luczyńska et al¹³ performed a study on 152 consecutive patients with 173 breast lesions diagnosed on conventional mammogram or contrast-enhanced mammogram and concluded that contrast-enhanced mammogram may have improved sensitivity and specificity of breast cancer detection.

Both the reports were consistent with our findings of 97% sensitivity for CEDM when compared with that of FFDM.

ElSaid et al¹⁸ performed a prospective study on 34 female patients with breast oedema and concluded that dual-energy contrast-enhanced digital mammography is capable of demonstrating lesions that are not visible in standard mammography and serves as a promising means of follow-up of cases. In our study, only one patient had oedematous breast; post-treatment, in that case, response to treatment was better demonstrated on CEDM in line with the study performed by ElSaid et al.¹⁸

Figure 3. (a) A craniocaudal view of the breast is showing a benign well-circumscribed lesion (earlier biopsy proven as fibroadenoma) in the inner quadrant on full-field digital mammography. (b) On contrast-enhanced dual-energy spectral mammogram, there is no contrast enhancement within the fibroadenoma; however, an oblong-shaped enhancing lesion is demonstrated in the retroareolar region, which is obscured by dense glandular tissue. HPE, malignant papillary lesion.

Figure 4. (a) Multiple spiculated radiodense lesions with malignant calcifications in the outer quadrant on full-field digital mammography (FFDM); (b) in addition, ductal extent is better seen on contrast-enhanced dual-energy spectral mammogram (CEDM); (c) a spiculated radiodense lesion is in the inner quadrant on FFDM; (d) multifocal enhancing spiculated lesions on CEDM.

Figure 5. A heterogeneously dense breast on (a) pre-chemotherapy full-field digital mammography (FFDM) and (b) post-chemotherapy FFDM; (c) a heterogeneously enhancing lesion on contrast-enhanced dual-energy spectral mammogram pre-chemotherapy; (d) reduction in size and intensity of lesion post-chemotherapy.

Limitations in our study

Since there is use of iodinated contrast in the procedure, patients having deranged renal function parameters and those allergic to contrast cannot undergo this procedure. All the cases in our study had previous FFDM, based on which, patients who required additional contrast imaging were decided. In this way, the

radiation dose was higher than that of standard mammogram. However, with further validation, the low-energy exposure can replace FFDM so that only CEDM can be performed in patients at high risk, thereby reducing the radiation dose delivered, as reported in few recently published studies.¹¹ Kinetics of tumour enhancement obtained on contrast-enhanced mammogram is

a field having a learning curve with potential to further increase the sensitivity and specificity of the study.

CONCLUSION

Contrast-enhanced dual-energy mammogram has a useful role in identifying occult lesions in dense breasts and in triaging lesions. In a mammographically visible lesion, contrast-enhanced dual-energy mammogram characterizes the lesion, affirms the finding and

better demonstrates response to treatment. Hence, we conclude that contrast-enhanced dual-energy mammogram is a useful complementary tool to standard mammogram.

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