Original Article

Indeterminate breast lesions: Can contrast enhanced digital mammography change our decisions?

Samira Saraya*, Lamia Adel, Asmaa Mahmoud

Department of Radiodiagnosis, Faculty of Medicine, Cairo University, Cairo, Egypt

Abstract

Objective: To assess the efficiency of dual energy contrast enhanced mammography in the assessment of the indeterminate breast lesions (BI-RADS 3 and BI-RADS 4).

Materials and methods: 34 female having 39 indeterminate breast lesions (BI-RADS 3 and BI-RADS 4) by digital mammography were further examined by dual energy contrast enhanced mammography. Two images were acquired at low and high energy in MLO view after 2 min and in CC view at 4 min post iodinated contrast injection (1.5 ml/kg with flow of 4 ml/s). Images were processed to obtain subtracted images to enhance the areas of the contrast uptake.

Results: Results from pathology were detected for all cases. Contrast enhanced digital mammography showed specificity, sensitivity, PPV, NPV, FDR, FPR and accuracy of 93.75%, 91.3%, 88.2%, 95.4%, 11.7%, 8.6% and 92.3% respectively compared to full field digital mammography which were 68.75%, 69.5%, 61.1%, 76.1%, 38.8%, 30% and 69.2% respectively.

Conclusion: Contrast-enhanced digital mammography is a useful tool to be used for breast cancer detection especially in indeterminate lesions (BI-RADS 3 and 4).

1. Introduction

Mortality from breast cancer has been decreased (by about 30% since 1990) by using mammography as a screening tool for early detection of breast cancer especially in clinically occult disease [1], however its accuracy is limited in dense breasts where lesions identification is limited by surrounded fibro-glandular tissue [2] as well as in surgically manipulated breasts.

The tumor growth and its potential for metastasis depends upon the neo-angiogenesis where new vessels are abnormally formed causing leak and shunting of blood [3]. So imaging modalities using contrast media aid in detection of such lesions [4]. Digital subtraction mammography using an X-ray image intensifier system demonstrates contrast uptake in breast lesions where early strong uptake and early wash out denotes malignancy while less or no enhancement denotes benign lesions [4]. Initial clinical trial was done at 2010 using contrast enhanced breast CT as a modality for differentiating benign versus malignant lesions according to the strength of enhancement, however high radiation dose to breast and chest wall limits its use [5].

Contrast enhancing MRI has been used during the past decade depending on the morphologic and kinetic criteria of gadopentetate dimeglumine uptake in detection of malignant breast lesions, yet it has variable specificity and positive predictive value with more time-consumption and is more costly than mammography [3].

Recently contrast enhanced digital mammography (CEDM) is used as an advanced technique to detect the tumors neo-angiogenesis by using two techniques either the temporal subtraction technique with acquisition of high-energy images before and after contrast medium injection or the dual energy technique with acquisition of a pair of low and high-energy images only after contrast medium injection. The temporal subtraction technique is beneficial in analyzing the kinetic curve of enhancement of breast lesions, in a way similar to breast MRI. Although the dual energy technique lacks information about the kinetics of tumor enhancement, it allows the acquisition of multiple views of the same breast or bilateral examination being less sensitive to patient motion than temporal CEDM [6].

In our study we used the dual energy technique to assess whether dual energy contrast enhanced mammography is
Table 1
The results of both FFDM and CEDM examinations according to BIRADS classification.

<table>
<thead>
<tr>
<th>Number of lesions</th>
<th>FFDM</th>
<th>CEDM</th>
<th>Pathology results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>BIRADS 3</td>
<td>BIRADS 4</td>
<td>Malignant</td>
</tr>
<tr>
<td>1</td>
<td>BIRADS 3</td>
<td>BIRADS 3</td>
<td>Pre malignant</td>
</tr>
<tr>
<td>5</td>
<td>BIRADS 4</td>
<td>BIRADS 5</td>
<td>Malignant</td>
</tr>
<tr>
<td>2</td>
<td>BIRADS 4</td>
<td>BIRADS 4</td>
<td>Benign</td>
</tr>
<tr>
<td>5</td>
<td>BIRADS 4</td>
<td>BIRADS 3</td>
<td>Benign</td>
</tr>
<tr>
<td>16</td>
<td>BIRADS 3</td>
<td>BIRADS 3</td>
<td>Benign</td>
</tr>
<tr>
<td>6</td>
<td>BIRADS 4</td>
<td>BIRADS 4</td>
<td>3 malignant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 precancerous</td>
</tr>
</tbody>
</table>

*BIRADS: Breast imaging-reporting and data system.

Table 2
Statistical analysis results for both FFDM and CEDM.

<table>
<thead>
<tr>
<th></th>
<th>FFDM (%)</th>
<th>CEDM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>68.75</td>
<td>93.75</td>
</tr>
<tr>
<td>Specificity</td>
<td>69.5</td>
<td>91.3</td>
</tr>
<tr>
<td>PPV</td>
<td>61.1</td>
<td>88.2</td>
</tr>
<tr>
<td>NPV</td>
<td>76.1</td>
<td>95.4</td>
</tr>
<tr>
<td>FDR</td>
<td>38.8</td>
<td>11.7</td>
</tr>
<tr>
<td>FPR</td>
<td>30</td>
<td>8.6</td>
</tr>
<tr>
<td>Accuracy</td>
<td>69.2</td>
<td>92.3</td>
</tr>
</tbody>
</table>

*PPV: positive predictive value, NPV: negative predictive value, FDR: false discovery rate, FPR: false positive rate.

Fig. 1. 35 years old complaining of left breast axillary tail lump. A–D: FFDM of both breasts in MLO (A&B) and CC (C&D) views revealed left axillary tail dense ill-defined mass lesions of lobulated outline with few enlarged left axillary lymph nodes (arrowed). BIRADS 4, E–H: CEDM of both breasts in MLO (E&F) and CC (G&H) views revealed left axillary tail heterogeneous mass enhancement with partially ill-defined margins (arrowed), BIRADS 5, I–J: Complementary ultrasound showed slightly hypoechoic mass lesion of partially well-defined partially ill-defined mass lesion at left axillary tail with left enlarged axillary globular lymph nodes with muffled hilum. Pathology results: Invasive ductal carcinoma.
beneficial in the undetermined breast lesions diagnosis (BIRADS III and IV) where delayed diagnosis or unnecessary tissue core biopsy is to be avoided with the benefits of low dose exposure compared to CT as well as time and money saving compared to MRI.

2. Materials and methods

From December 2015 to March 2016, 34 females with age ranging from 35 to 72 years (mean age 53.5) were chosen from early detection cancer clinics. Pregnant patients and patients with history of previous allergic reaction to contrast agents or with renal failure were excluded. Written informed consents for performance of contrast enhanced digital mammography (CEDM) was signed by all patients. The study was approved by the ethics committee and the institutional review board.

Full field digital mammography exams were reported by two different expert radiologists blindly. To avoid any potential bias, images were reviewed independently and randomly with an intentional interval of 2 weeks between the two readings.

39 lesions were detected by full field digital mammography (FFDM). According to BI-RADS system, 21 of them were diagnosed as BI-RADS III lesions and 18 lesions were diagnosed as BI-RADS IV lesions.

All patients underwent CEDM, followed by tissue core biopsy.

All CEDM examinations were performed using a digital mammography machine (GE health care [Chalfont St. Giles, UK] allowing dual-energy CEDM acquisitions).

2.1. Patient preparation

An intravenous line was inserted into the antecubital vein of the arm contra lateral to the breast of concern. Light breast compression was used, which was strong enough to limit motion, but not to reduce blood flow. A single shot of 1.5 mL/body weight of non-ionic contrast medium (Iohexol (Omnipaque) 300; GE healthcare, USA) was given using a power injector (Vistron CT, Medrad), at a rate of 4 mL/s.

2.2. Image acquisition

During a single breast compression dual-energy CEDM was performed by acquiring a pair of low- and high-energy images after 2 min from the initiation of the contrast injection in the MLO view followed by another mammograms obtained after 4 min in the CC view. Specific image processing was performed in order to generate two subtracted images (one in the MLO and one in the CC view) where the areas that did not show contrast uptake will be efficiently removed from the images. Compression was done after contrast injection to minimize the motion artifact.
The total X-ray dose delivered to the patient depended on breast thickness and tissue composition where the maximum total radiograph dose of the procedure was slightly more than a standard digital mammogram (about 1.2 times).

The mean examination duration was approximately 10 min (ranging from 6 to 12 min).

Images were analyzed by the 2 radiologists for the lesions suspected to be BI-RADS 3 and BI-RADS 4 by FFDM to confirm their presence and morphology following the recommendations cited by ACR 2013 (with modifications done November 2015) [7] for masses (including the margin, shape and density), architecture distortion and asymmetry (whether focal or global) in addition to the presence or absence of enhancement.

2.3. Statistical analysis

IBM SPSS statistics [V.21.0, IBM Corp., USA, 2012] were used for data analysis.

3. Results

Our study included 34 female patients, with 39 lesions. All patients were chosen from early detection cancer clinics with BI-RADS category III and IV. FFDM and CEDM examinations were performed for all patients with the following results: (Table 1).
Sixteen lesions (41%) were diagnosed as BIRADS III by both FFDM and CEDM and 6 lesions (15.4%) were diagnosed by both modalities as BIRADS IV. Histopathological correlation confirmed these diagnoses.

Five lesions (12.8%) were reported as BIRADS IV by FFDM but they were downgraded to BIRADS III by CEDM and were pathologically proved as benign lesions.

Four lesions (10.25%) were identified as BIRADS III lesions by FFDM and their scores were upgraded to BIRADS IV by CEDM as they showed intense contrast uptake. They proved to be malignant on tissue core biopsy.

Another 5 lesions (12.8%) were upgraded from BIRADS IV by FFDM to BIRADS V by CEDM where 3 (7.7%) of them showed multiple satellite lesions and 2 (5.1%) of them showed enhancing axillary lymph nodes.

One lesion (2.6%) was diagnosed as BIRADS III by both modalities yet it was pathologically proven as precancerous ductal atypia. While another two lesions (5.1%) were reported as BIRADS IV by both modalities but tissue biopsy revealed benign nature (fibroadenoma with epithliosis, BIRADS 3).

According to the above results CEDM showed high sensitivity than FFDM (93.75% and 68.75% respectively) for the detection of breast cancer with specificity of 91.3% and 69.5% in the favor of CEDM. The PPV and the NVP for CEDM was 88.2% and 95.4% respectively compared to the FFDM which was 61.1% and 76.1% respectively. FDR and FPR for CEDM was 11.7% and 8.6% respectively while for FFDM they were 38.3% and 8.6% respectively. CEDM achieved accuracy of 92.3% in comparison to FFDM which scored 69.2% (Table 2).

4. Discussion

It is well established that the main modality for screening of breast cancer is mammography yet its accuracy is limited in dense breasts as the fibroglandular tissue reduce the detectability of the lesions [8], in addition malignant lesions and fibroglandular tissue have almost the same degree of X-ray absorption [4]. Tumor angiogenesis leads to lesions enhancement post a contrast medium injection leading to better cancer detection [9].

In review of the articles of the same subject they revealed that contrast-enhanced digital mammography proved to be more useful in the detection of the nature of the breast lesions compared to the FFDM. It also aids in the identification of the disease extent (multifocality and multicentricity) as well as in the axillary metastases. Furthermore, it is beneficial in the guidance of core needle biopsy or excision. When it is accessible it will be relatively less costly than the MR imaging technique [8].

In 2003 Roberta, et al. revealed in their initial clinical experience that eight of 10 patients showed enhancement at CEDM and were biopsy-proved cancers. In one case of ductal carcinoma...
in situ and one case of invasive ductal carcinoma, enhancement was not observed. No enhancement was seen in seven of 12 cases in which lesions were suspected of being malignant at initial imaging but were benign. Morphology generally correlated with the pathologic diagnosis [3].

According to Dromain et al. they reported that the average per-lesion sensitivity was significantly higher for mammography (MX) + ultrasound (US) + CEDM than for MX + US (0.78 vs. 0.71 using BI-RADS, p = 0.006). They mentioned that the clinical performance of all readers improved and that the average area under the ROC curve was significantly higher up for MX + US + CEDM than for MX + US (0.87 vs 0.83, p = 0.045). Even clarity of the lesions was as identical or superior on MX + CEDM than MX + US in 80% of cases [8]. In our study US was not included yet the diagnostic efficiency was higher for CEDM compared to FFDM.

Mokhtar and Mahmoud mentioned in 2014 that MX + CEDM sensitivity was higher compared to MX (97.7% vs. 93.2%) with almost equivalent specificity. In their study all of the 12 histologically proven multifocal lesions were identified by MX + CEDM in comparison to only 6 and 8 lesions were identified by MX and US respectively [9].

Kamal, et al. in 2015 showed that malignant breast lesions uptake of contrast was significant (p value ≤ 0.001) with an overall sensitivity and specificity of the CEDM being 88.99% and 83.33% respectively. In addition negative and positive probability ratios were 0.13 and 5.34 respectively [10].

According to our results and the previous studies results contrast-enhanced digital mammography proved to be more useful in the detection of the nature of the breast lesions compared to the FFDM. It also aids in the identification of the disease extent (multifocality and multicentricity) as well as in the axillary metastases. Furthermore, it is beneficial in the guidance of core needle biopsy or excision because in positive cases lesion identification is much easier in the post contrast images in the high density breasts so it helps more in exact localization either for biopsy or wire localization for excision (see Figs. 1-4).

5. Conclusion

Contrast-enhanced digital mammography is recommended to be used as one of the important diagnostic tools for breast cancer especially in indeterminate breast lesions.

Conflict of interest

All authors declared that they have no any competing interest.

References