Contrast-enhanced dual-energy digital mammography in the evaluation of breast cancer

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Abstract

Introduction: The purpose of this study is to detect the diagnostic accuracy of dual-energy contrast-enhanced digital mammography (CEDM) in the diagnosis of breast cancer. Methods: Twenty-one females with pathologically proven breast cancer underwent CEDM, prior to their scheduled surgeries. BI-RADS scores were evaluated for all lesions. Written consent was obtained from all patients prior to the studies.

Results: Contrast-enhanced digital mammography (CEDM) showed focal enhancement in 19 patients. The kinetic curves of enhancement were classified as type 2 in 13 patients and type 3 in six patients. For the two false negative cases, no enhancement was noted on CEDM.

Conclusions: Dual-energy contrast-enhanced digital mammography improves the diagnostic accuracy of full field digital mammography in the detection of breast cancer.

1. Introduction

Full-field digital mammography (FFDM) enables high-quality breast images with higher-contrast resolution, improved dynamic range, and rapid processing of data and images compared with conventional mammography. FFDM has been shown to provide increased accuracy in screening pre- or peri-menopausal women, women younger than 50, and women with dense breasts. Moreover, FFDM offers the possibility of developing new and advanced applications for breast imaging. Contrast-enhanced digital mammography (CEDM) with injection of an iodinated contrast agent is one of them (1).

During the past few years, many methods for imaging angiogenesis in vivo have been developed. Digital subtraction angiography of the breast has been performed using a radiograph image intensifier system (2,3). Subtracted images of malignant tumors showed rapid and strong enhancement followed by a washout, whereas benign tumors showed less or no enhancement. At present, contrast medium is used with both CT and MRI techniques to explore angiogenesis in breast carcinoma.
Iodinated contrast-enhanced conventional CT was shown to be useful for detecting breast carcinoma. However, conventional CT results in a high-radiation dose to the breast and chest wall. Recent studies on dedicated breast CT with radiation doses similar to or slightly higher than those of two-view mammography have shown that malignant lesions were significantly more conspicuous at contrast-enhanced breast CT than at mammography (4,5). Breast MRI using gadolinium-based contrast agents is currently considered the most sensitive imaging technique for the detection of breast carcinoma, and multiple indications have been established for breast MRI (6). However, breast MRI has a variable specificity and positive predictive value and is more time-consuming and more expensive than mammography (7,8).

Investigational clinical results on CEDM have been published during the last few years, suggesting that the technique may be a useful adjunct to FFDM with lesion contrast uptake information (9,10). Two CEDM examination techniques have been investigated: temporal subtraction and dual-energy. The study by Lewin and colleagues (9) is the only published preliminary clinical experience using dual-energy CEDM. The authors showed the technical and clinical feasibilities of this technique and reported a high sensitivity and specificity for the detection of breast carcinoma.

2. Materials and methods

2.1. Patients

From August 2011 to May 2013, twenty-one females with pathologically proven breast cancer were included in the study. All patients provided written informed consents for performance of FFDM and CEDM. The study was approved by the ethics committee and the institutional review board. Exclusion criteria were pregnancy or possible pregnancy, or a history of allergic reaction to an iodinated contrast agent.

The patients had a mean age ± standard deviation (SD) of 53 ± 9 years. Suspicious breast lesions included palpable masses in six patients, mammographic densities in eleven patients (eight with spiculated masses and three with asymmetrical breast densities), and sonographic masses in thirteen patients. Breast densities were classified as BI-RADS category 2 in nine patients, and category 3 in twelve patients.

The masses were pathologically proven as breast cancer by histopathological analysis of excised specimens.

2.2. Dual-energy CEDM examinations

All CEDM examinations were performed within 7 days before breast surgery with a digital mammography machine (Selenia, Hologic Dimensions, Bedford, USA) which allowed dual-energy CEDM acquisitions. Dual-energy CEDM was performed by acquiring a pair of low- and high-energy images in quick succession during a single breast compression.

Patients were comfortably settled to avoid motion. A catheter was inserted into the antecubital vein of the arm contralateral to the breast of concern. Light breast compression was used for all images, which was strong enough to limit motion, but not to reduce blood flow. A single mask mammogram was first taken. 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 3 mL/s. The first contrast-enhanced mammogram was obtained 30 s after starting the injection, and subsequent mammograms were obtained after 90, 150, 240, 330, and 420 s. Therefore, a total of seven mammograms including six contrast-enhanced mammograms were obtained for each patient. The total X-ray dose delivered to the patient depended on breast thickness and tissue composition.

The mean examination duration was approximately 15 min (ranging from 12 to 25 min). The maximum total radiograph dose of the procedure ranged between 1 and 4 mGy, which is similar to a conventional single-view mammogram.

2.3. Image analysis

The displayed images show the regions of contrast uptake while canceling non-enhancing anatomic noise in the background. Image processing included logarithmic subtraction and the analysis of enhancement kinetic curves. The maximum diameter of the tumor measured on subtracted contrast-enhanced digital mammography images was recorded. Regions of interest were placed at areas of early enhancement and adjacent breast tissue to analyze the uptake and the washout of the contrast agent. To minimize the effect of breast thickness on density values, the region of interest for the lesion and the healthy breast tissue had the same size and were located at the same distance from the posterior aspect of the breast.

Values of differential contrast enhancement between lesions and healthy breast tissues were then plotted versus time. The time-intensity curves were classified into three types based on the wash-in and washout of contrast medium: type 1, gradually increasing enhancement, type 2, early enhancement followed by plateau and type 3, early enhancement followed by washout (Fig. 1). The enhancement was considered early if the peak of enhancement was before 1 min 30 s.

For FFDM examination, the two CC and MLO images were reviewed without any additional views.

2.4. Statistical analysis methods

Comparisons of sensitivity and specificity of FFDM and CEDM were done using McNemar’s chi-squared test, and comparison of false-positive and false-negative marks per case used the Wilcoxon signed rank test. Statistical tests were performed at a significance level of 0.05.

Fig. 1 Schematic drawing of the time-signal intensity curve types.
3. Results

Results for the patients are summarized in Table 1. Contrast-enhanced digital mammography (CEDM) showed focal enhancement in 19 patients. The median maximum diameter of the lesions measured on the subtracted image at 90 s after injection was 10 mm, ranging from 6 to 20 mm. The kinetic curves of enhancement were classified as type 2 in 13 patients and type 3 in six patients.

Morphologically, in three of the malignancies, a rim-like appearance was observed on CEDM. Inhomogeneous enhancement with spiculated outline was seen in two cases (Fig. 2) and regional enhancement with no mass in one case (Fig. 3). The other malignancies presented as irregular and poorly defined masses (Fig. 4). For the two false negative cases, no enhancement was noted on CEDM.

Histopathological analysis of surgical specimens is summarized in Table 1. It shows malignant tumors in all patients, including 13 invasive ductal carcinomas (IDC), three invasive lobular carcinoma (ILC), and five ductal carcinoma in situ (DCIS) with micro invasion, including the two false negative cases. The median maximum diameter of lesions measured at histology was 13 mm (range, 4–28 mm).

The comparison between contrast-enhanced digital mammography and histopathological results showed 19 true-positives and two false-negatives for contrast-enhanced digital mammography. Consequently, the sensitivity of CEDM for detecting breast carcinomas was 90%. A good correlation was found between the size of lesions measured on contrast-enhanced digital mammography images and those measured on histological sections, with a coefficient of correlation of 93%.

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Table 1 Radiological findings in the patient population.

<table>
<thead>
<tr>
<th>Clinically palpable</th>
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<tr>
<td>Type of Findings on FFDM</td>
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<tr>
<td>Mass</td>
<td>10</td>
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<tr>
<td>Asymmetry</td>
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<td>Micro calcification</td>
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<td>Breast density</td>
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<td>Dense</td>
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<td>ACR 1 and 2</td>
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<td>Ultrasound Detected Mass</td>
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<td>Types of Enhancement on CEDM</td>
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<td>Rim-like</td>
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<td>Spiculated</td>
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<td>Types of enhancement curves</td>
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<td>Type 3</td>
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<td>Histopathological Analysis</td>
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<td>IDC</td>
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<td>ILC</td>
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Fig. 2 Invasive ductal carcinoma in a 53-year old female. (A) CEDM, mediolateral image depicts an irregular, poorly defined, mass in the lower quadrant of the breast (arrows). (B) The left mediolateral oblique view mammogram shows a dense breast with no definite abnormalities.

Fig. 3 Invasive lobular carcinoma in a 61-year old female. (A) The left mediolateral oblique mammogram shows no obvious lesion in the breast. (B) CEDM, mediolateral oblique image clearly depicts non-mass regional enhancement in the inferior quadrant (arrowheads).
Contrast-enhanced digital mammography (CEDM) is a breast imaging technique that aims at demonstrating breast carcinoma angiogenesis. Encouraging results have been published during the last few years on CEDM as an adjunct to mammography (11–12).

Enhanced CEDM is similar in concept to enhanced breast MR imaging and could potentially be applicable in situations in which MR imaging is currently used. Such situations include detection of a primary breast cancer in a woman with a positive axillary lymph node and determination of the extent of disease in cases of known cancer, as well as problem solving in cases of mammographic findings that were not depicted in US scans (9). Some of the limitations of contrast-enhanced digital mammography in breast imaging compared with MRI are irradiation of the breast, lower contrast resolution, and the use of iodinated contrast material. However, the technique is weakly irradiating, easily implemented, inexpensive, fast, and practical (13).

The use of iodinated contrast agents, however, is not completely devoid of risk. Most adverse side effects are minor and have decreased considerably with the use of low-osmolality contrast media. Still, life-threatening reactions, though rare, can occur in the absence of any specific risk factors and with any type of contrast media. All personnel (nurses, technologists, and radiologists) who administer contrast media must be fully prepared to treat even the most severe reactions, and adequate equipment and supplies must be available in the mammography suite (13).

Enhancement kinetics, also used for differentiating benign from malignant lesions at MR imaging, can be determined at CEDM with serial imaging (14). Because whole-breast images can be acquired more rapidly than with most MR imaging sequences, kinetic information could be determined with greater precision (9). In this study, the mentioned enhancement curves were used for the diagnosis of breast malignancy with CEDM.

Using a temporal CEDM technique, both benign and malignant breast tumors have shown progressive enhancement with poor capability of differentiation between them. Unlike the temporal subtraction technique, dual-energy CEDM enables differential diagnosis of benign and malignant breast tumors based on differences in tumor kinetics. It also has the potential of performing bilateral examinations with only one contrast agent injection and allows shorter acquisition duration than temporal subtraction techniques and does not require extended breast compression. This could result in better acceptance from patients and fewer technical problems (10). In this study, all CEDM examinations were performed by using a temporal energy technique.

Dromain et al. (10) in their study chose the craniocaudal projection rather than the mediolateral oblique projection to minimize motion artifacts. However, they reported that the craniocaudal position was questionable because it did not allow much breast tissue to be visualized as does the mediolateral oblique view and recommended that in the future, the procedure for contrast-enhanced digital mammography would include craniocaudal projections with the introduction of an additional mediolateral oblique view at the end of the examination (one image acquisition at 5 min). Lewin et al. (9) in their study on CEDM performed the study in mediolateral oblique view, which was what we did for all our patients for better coverage of the breast tissue. We did not have problems with motion artifacts.

Contrast-enhanced digital mammography results reported in this study were independent of the histological type of carcinoma, which was supported by (14) who suggested that the rate of contrast medium enhancement is not related to the histological type of the tumor and that enhancement is related not only to the number of vessels, but also to functional parameters such as vessel permeability, particularly when using a contrast agent that is migrating to the extra cellular fluid space.

A typical contrast MRI curve for malignancy (15,16) with rapid enhancement followed by a decrease during the delayed phase was observed in only six of the 21 malignant lesions of this study. These differences between kinetic curves observed using dynamic contrast-enhanced digital mammography and MRI are probably because of the breast compression, even low breast compression, which may alter blood flow, according to Lewin et al. (13).

Histolopathological analysis of the two tumors with no enhancement on CEDM of our study (false negative for malignancy) showed no tumoral necrosis. Both cases had ductal carcinoma in situ with micro invasion, seen on digital mammography as suspicious clustered micro calcification.

The sensitivity of CEDM for detecting breast carcinomas was 90% in our study, which matched the results of Lewin et al. (9) and Dromain et al. (10) who mentioned that the
sensitivity of CEDM in their studies was 92% and 80%, respectively.

The results of this study suggest that dual-energy contrast-enhanced digital mammography improves the diagnostic accuracy of full field digital mammography in the detection of breast cancer. In the near future, contrast-enhanced digital mammography will probably have the benefit of other digital mammography improvements such as tomosynthesis (17).

Conflict of interest

None declared.

References