Quantification of contrast-enhanced digital breast tomosynthesis

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Abstract Digital breast tomosynthesis (DBT) is a technique in which tomographic images of the breast are reconstructed from X-ray projection images acquired over a limited angular range In contrast-enhanced DBT (CE-DBT) functional information is observed by administration of an X-ray contrast agent. To date, 13 patients have had CE-DBT in an ongoing clinical trial at the University of Pennsylvania. Using a simplified physiological model, a 0.5 cm thick breast lesion is expected to change X-ray transmission by approximately 5% for a 4 cm thick compressed breast. In this paper, we consider the technical requirements necessary to quantitatively analyze CE-DBT exams by investigating the effect of scatter, and patient motion on quantifying iodine uptake. These parameters were evaluated by means of experiments, analysis of clinical images, and theoretical modelling.

Keywords Digital breast tomosynthesis · Quantification · Contrast agent · Angiography

1 Introduction

Breast tumor growth and metastasis are accompanied by the development of new blood vessels [1]. These vessels typically are of poor quality, lacking a continuous intimae; thus, blood pools around tumors. An imaging technique using a vascular contrast agent should demonstrate and characterize the tumor and its vessels. Today, the best choice for imaging tumor vasculature is contrast enhanced magnetic resonance imaging (CE-MRI) with a gadolinium based contrast agent [2]. CE-MRI is, however, expensive and time consuming and is, therefore, unlikely to become widely available. We believe that contrast-enhanced digital breast tomosynthesis (CE-DBT) provides an attractive alternative to CE-MRI that will integrate the benefits of both CE mammography [3–5] and DBT [6], providing both functional information and improved breast cancer morphology by minimizing superimposition of nonadjacent breast tissues. Quantitative temporal analysis of contrast enhancement may further help to distinguish between benign and malignant lesions.

Contrast enhanced magnetic resonance imaging is performed using an iodinated contrast agent. Thus, the greatest subject contrast will occur by using X-rays with energies just above the K-edge of iodine. In the experiments described, we used logarithmic subtraction of high energy images acquired before and after administration of the contrast agent [3, 4] (Fig. 1). The signal intensities (SI) of the resulting images are proportional to the uptake of iodine. To date we have acquired 13 CE-DBT clinical cases using a modified GE 2000D at the University of Pennsylvania.

The uptake of iodine in the breast is very small and thus causes only small changes in X-ray transmission; typically less than 5%. This presents significant technical challenges if quantitative assessment of contrast agent uptake is desired. Technical factors that significantly influence quantitative analysis of CE-DBT exams are exposure

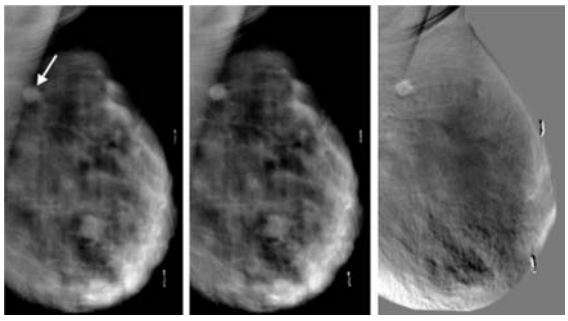


Fig. 1 MLO view of patient with invasive ductal carcinoma (*arrow*). Pre-contrast (*left*) and post-contrast (*center*) tomographic images are shown, as well as the tomographic subtraction image (*right*)

reproducibility, linearity of the detector as a function of position, scatter, patient motion and temporal stability of the detector. In this paper, we will discuss the influence of scatter and patient motion.

2 Clinical set-up

We have imaged 13 patients with temporal CE-DBT under an IRB-approved protocol. The breast is positioned in the MLO orientation and lightly compressed (5–7 dN). A pre-contrast tomosynthesis series is acquired. A series consists of 9 unique projections of the breast over a total angular range of ± 25°. The X-ray tube is manually positioned for each of the 9 exposures. One projection is acquired every 30 s. A high-energy X-ray spectrum is used (49 kVp, Rh target, 0.27 mm Cu filter). After the pre-contrast series, 1 ml/kg of Visipaque−320® (Amersham, Princeton, NJ, USA) is administered, followed by a 60-ml saline flush. One or two post-contrast series are acquired. The first post-contrast image is obtained 90 s after the start of contrast injection. The dose to the patient per tomosynthesis series is equal to a single mammographic view (≈ 2 mGy). Individual slices through the breast are reconstructed using a back-projection algorithm. An example of a reconstructed plane of the breast is shown in Fig. 1. Multiple tomographic images of the region containing the lesion are shown in Fig. 2, clearly showing a spiculated mass with rim enhancement.

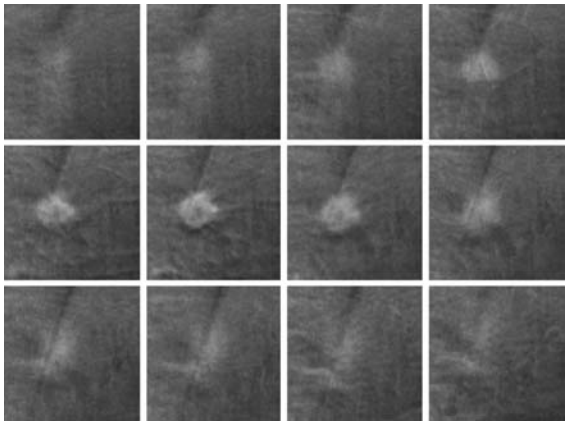


Fig. 2 Multiple reconstructed image planes, each separated by 5 mm, showing the region surrounding the lesion seen in Fig. 1

3 Simple physiologic model

We have developed a simple physiological model of breast tumors to estimate the maximum uptake of a breast lesion. This uptake provides a point of comparison when considering factors which can alter the quantitative measurement of iodine uptake. The model is based on the following assumptions: (1) the average adult has 5 l of blood that is completely recirculated in 1 min; (2) the time for an intravenous injection of contrast-agent is approximately 1 min, thus ensuring uniformmixing of the contrast-agent and blood; (3) the maximum extracellular concentration in the tumor is equal to the maximum intravascular concentration; and (4) the half-life of iodine in blood is long compared to the clinical exam time (~ 10 min). In our clinical trial, we used Visipaque-320® (320 mg iodine/ml iodixanol) injected at 1 ml/kg bodyweight. Using our simple model, a 70-ml injection would yield an iodine concentration of 4.5 mg/ml in the blood. Thus, a 0.5-cm thick tumor would have an aerial density of 2.2 mg/cm^2, which for a 4 cm 50/50 breast would result in an attenuation of 4.3% using the above spectrum.

4 Scatter

We perform CE-DBT without a grid. We have performed experiments to determine the effect of scatter on the quantification of iodine uptake. The magnitude of the scatter was determined using the scatter fraction, SF:

$$\mathrm{SF} = \frac{S}{S + P},$$

where S is scatter and P is primary radiation. SF was measured with Pb-disks with diameters from 3.9 to 11 mm. The signal intensities (SI) in the shadows of the Pb-disks and in an unperturbed ROI were measured. The logarithms of the measured SF as a function of Pb-disk diameter were plotted. The inverse logarithm at zero disk diameter was calculated using a linear fit through the measured values. These measurements were repeated as a function of position and breast equivalent thickness in 50% glandular–50% fatty (50/50) breast equivalent phantoms (CIRS, Norfolk, VA, USA). The phantoms were positioned so as to mimic the MLO position, including higher order scatter. A 49 kV Rh-spectrum with a 0.27 mm Cu filter was used.

Figure 3 illustrates SF profiles for 2, 4, 6 and 8 cm thick breast equivalent phantoms. The SF profiles are shown for Pb-disks placed parallel to the chest wall approximately 6.5 cm from the chest wall. As expected, the SF is higher for thicker breasts. For example, for a 20 mm 50/50 breast phantom, the SF at the center of the profile is 0.29, but it increases to 0.57 for the 80 mm phantom.

Failure to correct for scatter will result in an underestimation of the iodine concentration. We calculated that this underestimation will be approximately 28% for a 20 mm breast thickness, 40% for a 40 mm breast thickness, 47% for a 60 mm breast thickness and 54% for a 80 mm breast thickness. We have also considered the situation of imaging with a grid. This also results in underestimation of the iodine concentration. For example, a 40-mm breast thickness will result in an underestimation of 22%. This is relevant for both CE mammography and tomosynthesis systems using a grid.

5 Patient motion

In temporal subtraction, images from pre-and post-contrast series are subtracted. Any breast motion between series will result in artifacts. In our experiments with patients, the total acquisition time can exceed 10 min; thus, breast motion is inevitable. An analysis of clinical

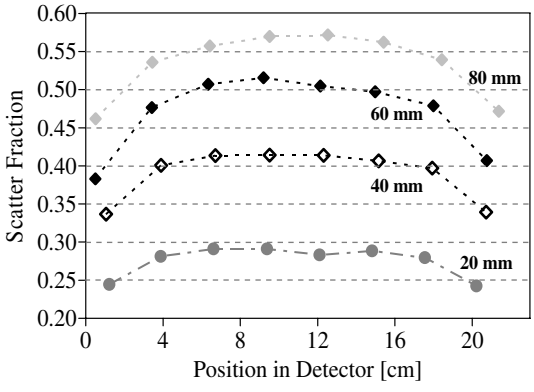
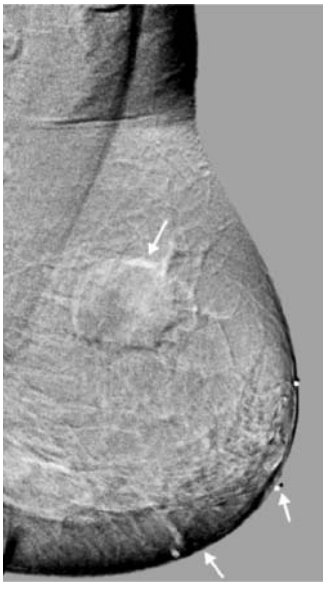


Fig. 3 *SF* as a function of breast thickness for Pb-disks positioned 6.5 cm from the chest wall for four breast thickness

CE-DBT images was used to estimate the effect of breast motion on the calculation of iodine uptake. In the patient images, ROIs were selected with uniform breast thickness. The absolute values of relative SI variations were calculated for displacements, Δx, varying from 1 to 128 pixels (0.1–12.8 mm). The SI as a function of the displacement was related to the equivalent iodine concentration using our model.

Measurements were applied to each of our clinical images. The measurements were performed for simulated displacements in the horizontal and vertical direction. Figure 4 shows the relative SI variations arising from various displacements. Even for a one pixel (0.1 mm) displacement, half of the pixel signal intensities vary by more than 0.7% and the maximum change is 4.7% (Fig. 4). A 4.7% SI variation would correspond to 2.3 mg/cm^2 iodine. That is greater then the concentration that we predicted with our simple physiological model for a 0.5 cm lesion.



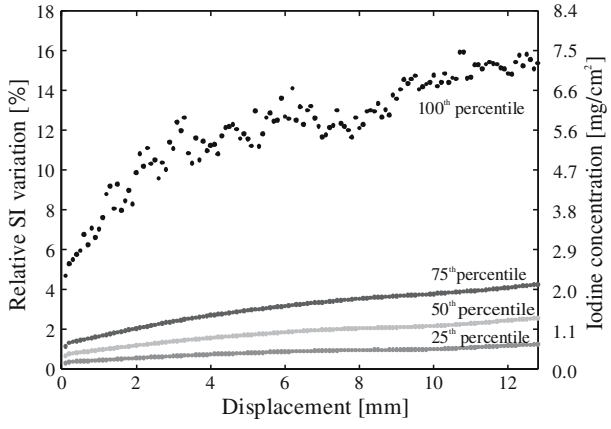


Fig. 4 *Upper part* Example pf patient movement (*arrows*). The image is the result of subtraction of a post-constrast projection image from apre-contrast projecting image. *Lower part* The relative SI and resulting iodine concentration arising from simulated motion. The percentiles refer to the fraction of pixels which maximally demonstrate a given SI variation

A clinical example of patient motion is also illustrated in Fig. 4. The image is the difference of a post-contrast projection image and a pre-contrast projection image. Two lead BBs were placed near the nipple of the patient. The arrows in the image demonstrate examples of patient motion. The lower BB shows a displacement of approximately 5 mm. We have found that the greatest motion in the breast generally occurs in the dependent (lower) portion of the breast.

6 Conclusions

Based on 13 patients, our experience suggests that 3D localization and vascular characteristics are demonstrable with CE-DBT. Thus far, when pre- and post-injection DBT images are compared, the maximum increase in attenuation occurs in the known breast lesion. These findings are similar to the qualitative vascular information obtained on the same patient with MR. Careful measurements and corrections for exposure variability, non-linearity of the detector, scatter, and temporal variations of the detector are necessary to estimate the actual concentration of iodine observed in CE-DBT. As an adjunct to digital mammography, CE-DBT offers the potential to visualize the vascular characteristics of breast lesions.

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