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CE-DBT was performed in the medial lateral oblique view with a DBT system, modified under IRB approval to allow high-energy (HE) image acquisition with a 0.25 mm Cu filter. Image acquisition occurred via both temporal and dual-energy subtraction CE-DBT.
Between the precontrast and postcontrast DBT image sets, a single bolus of iodinated contrast agent (1.0 ml/kg) was administered, followed by a 60 ml saline flush. The contrast agent and saline were administrated manually at a rate of ~2 ml/second.

Images were reconstructed using filtered-backprojection in 1-mm increments and transmitted to a clinical PACS workstation.

Dual-energy CE-DBT is shown to be clinically feasible. In our index case, dual-energy technique was able to demonstrate morphology and kinetics information about the known malignancy. This information is qualitatively concordant with that of CE-MRI. In comparison with the temporal subtraction CE-DBT technique, dual-energy CE-DBT appears less susceptible to motion artifacts.

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Not Applicable, Not Applicable
We do not oppose any specific reviewers.
Dual-Energy Contrast-Enhanced Digital Breast Tomosynthesis – A Feasibility Study

RUNNING TITLE: Feasibility of Dual-Energy Contrast-Enhanced Digital Breast Tomosynthesis

Category: SHORT COMMUNICATIONS

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Key Words – Breast imaging, neoangiogenesis, contrast-enhanced digital breast tomosynthesis – dual energy – temporal subtraction
Introduction

Breast tumor growth and metastasis are accompanied by the development of new blood vessels that have an abnormally increased permeability [1]. As a result, the absorption of vascular contrast agents is often different in malignant breast tissue than in benign and normal tissues. Today, contrast enhanced magnetic resonance imaging (CE-MRI), which uses a gadolinium chelate as a vascular contrast agent, is the standard for vascular imaging of breast cancers [2-7]. Breast lesion characterization with CE-MRI relies on a combination of the analysis of the morphological features of the lesion as well as the vascular enhancement kinetics.

Preliminary studies have demonstrated that contrast-enhanced digital breast tomosynthesis (CE-DBT) using an iodinated vascular contrast agent has the potential to demonstrate morphology and vascular enhancement information concordant with that of CE-MRI [8]. As the clinical uses of CE-MRI continue to expand, investigation into a potential alternative such as CE-DBT (which is projected to be less costly and more widely available than MRI) may also increase in importance.

A temporal subtraction CE-DBT technique has been reported, where one pre- and one or more post-contrast tomosynthesis time-points are acquired using a spectrum predominantly above the K-edge of iodine (32.3 keV) [9-12]. Pre- and post-contrast image series are then logarithmically subtracted yielding iodine-enhanced images.

Another contrast-enhanced x-ray breast imaging technique that has been reported is dual-energy subtraction. This has been reported in the context of digital mammography (DM), where post-contrast images are acquired in pairs at energies that closely bracket the K-absorption edge of iodine [13-16]. At each time point, iodine-enhanced images are calculated by weighted logarithmic subtraction of the low- and high-energy (LE and HE) images.
The objective of this study is to assess the feasibility of applying a dual energy subtraction technique to CE-DBT. In addition, we sought to compare the quality of the images obtained with a dual energy CE-DBT technique with those obtained via temporal subtraction CE-DBT.

**Materials and Methods**

**Eligibility Criteria**

IRB approval was obtained for a pilot project to assess the clinical feasibility of temporal and dual energy subtraction CE-DBT. The CE-DBT pilot study was part of a National Cancer Institute-funded grant (NIH P01 CA85484-01A2) evaluating multimodality breast imaging. A patient with a known malignancy (status post ultrasound-guided core biopsy with clip placement) was imaged with both CE-DBT techniques and with CE-MRI. We present the findings from this index patient.

**Imaging Protocol**

Temporal and dual energy subtraction CE-DBT imaging were performed with a General Electric Senographe DS DBT system (GE Medical Systems, Chalfont St. Giles, U.K.). The system was modified under IRB approval to allow HE image acquisition by adding a 0.25 mm Cu filter (Alfa Aesar, Ward Hill, MA) to the x-ray beam path. The affected breast of each patient underwent CE-DBT using a single breast compression in the mediolateral oblique (MLO) view, with the patient remaining seated for the duration of the exam. The DBT prototype used in this study did not have the ability to record compression force; light to moderate compression was applied to immobilize the breast and to reduce the dose latitude and scatter. The timing of the DBT image sequence is shown in Figure 1. First, a pre-contrast HE DBT projection image series was acquired. After contrast agent administration, HE and LE DBT projection image series were acquired twice. The technical parameters for the HE and LE image series for this patient with a breast thickness of 5 cm in compression are specified in Table 1. The technique was optimized as a compromise between iodine enhancement, the heating and cooling capacity of the x-ray tube, the patient radiation dose and the speed of the image read-out.
Each DBT projection series consists of seven images acquired in 6.7-degree increments over a 40-degree arc and the tube motion is motorized from head to toe; between each image series there is a need to reset the x-ray tube to the original start position.

The contrast agent was Visipaque-320® (320 mg I/ml iodixanol, Amersham, Princeton, NJ) with a dosage of 1.0 ml/kg bodyweight. The contrast agent injection was followed by a 60 ml saline flush. The contrast agent and saline were administrated manually at a rate of ~2 ml/second.

The total procedure time was 8 minutes. The HE pre-contrast series took approximately 0.27 minutes to acquire. The total injection time (contrast agent + saline flush) was approximately 1 minute given this patient’s weight (85 kg). The first post-contrast HE series was initiated 1.5 minutes after the start of contrast agent injection, the first post-contrast LE series was initiated 2.9 minutes after the start of the injection, the second post-contrast HE series was at 4.4 minutes after the start of the injection, and the second post-contrast LE series, was initiated 5.85 minutes after the start of the injection. The time delay between the post-contrast series was limited by the image read-out time of the x-ray detector.

The total mean glandular dose (MGD) was 6.48mSv for this patient with a breast thickness of 5 cm in compression; this is comparable to the dose of two conventional mammographic views. MGD were calculated using a model published by Boone [17]. This model requires knowledge of the breast entrance dose and the spectrum incident on the breast. Breast entrance doses were calculated based on air kerma measured free-in-air measured with an air ionization chamber (Radcal MDH1515, Radcal Corporation, Monrovia, CA). We simulated the input spectrum necessary for this calculation using a validated extrapolation of Boone’s model for high-energy mammographic spectra [12, 18]. MGD were calculated assuming breasts with a 50% glandular – 50% adipose equivalency.
Image processing
Temporal and dual energy subtraction iodine-enhanced images were produced from the recorded projection images; these images are corrected for detector non-uniformity; the data are linear with detector dose. Temporal subtraction projection series were obtained at two time points (Figure 1.). At each time point a logarithmic subtraction was performed between the HE pre-contrast series and the respective HE post-contrast image series.

Dual energy subtraction projection series were generated at three time points (Figure 1). The second dual energy series is a result of using the first LE image series twice, once as a LE mask for the first dual energy timepoint, and again as the LE mask for the second dual energy timepoint. At each time point, a weighted logarithmic subtraction was applied to the HE and LE image series. For the breast in this case, a constant weighting factor, \( w_t \), was applied; \( w_t \) was optimized for the region of the breast with constant compressed thickness [16]. The optimal \( w_t \) value was determined by varying \( w_t \) in the logarithmic subtraction from 0 to 1 in steps of 0.01 in a region with uniform compressed breast thickness; \( w_t = 0.21 \) resulted in the minimum breast tissue background variance.

Tomographic reconstruction
Each subtracted projection image series was reconstructed using a custom filtered-backprojection algorithm [19]. This reconstruction algorithm was also applied to the final LE image series to provide a 3D image of the breast anatomy. A 20.5×20.5×T cm\(^3\) volume of interest was reconstructed in each instance, where T is equal to the thickness of the breast as measured by the compression device and recorded in the source image DICOM header. The images were reconstructed in planes parallel to the detector in 1-mm increments, images were reconstructed with an in-plane voxel pitch of 220 µm. Each reconstructed image series was written as DICOM CT object to the PACS.

Image Display
The DBT and MRI images were displayed with Efilm (V1.5.3; Merge Healthcare, Milwaukee, WI) at full resolution on two 21” 1200×1600 grayscale monitors (Siemens SMM-21125P, Karlsruhe, Germany) in stack mode. Monitor luminance was calibrated to the DICOM GSDF using the AAPM TG18 protocol [20].

**Results**
The patient in our feasibility study had undergone ultrasound-guided core biopsy with clip placement in the right upper outer quadrant breast lesion, with pathology results of poorly differentiated invasive ductal carcinoma. Suspicious rim enhancement was demonstrated on both CE-DBT techniques. This enhancement was qualitatively concordant with that demonstrated on CE-MRI in the same patient (Figure 2).

All images show consistent lesion morphology (Figures 2, 3 and 4). Using the clip from prior core biopsy as an internal marker for motion artifact, the dual-energy images had less motion artifact than the temporal subtraction images (Figures 3 and 4). Given less motion artifact, the internal enhancing architecture of the tumor is sharper on the dual-energy images when compared with the temporal subtraction images.

**Discussion**
Malignant breast lesions often have an altered microenvironment which results in neoangiogenesis [1]. This feature of their biology can differentiate them on imaging from benign breast tissue via the way in which intravenous contrast agent is handled. Currently, CE-MRI and gadolinium are used to obtain breast lesion morphology and vascular enhancement information [2, 3, 5, 6]. Recently, CE-DBT has been reported to be a potential alternative method of imaging malignant breast lesion morphology and vascular enhancement patterns [8]. A temporal subtraction CE-DBT technique has been described previously [8-11]. In this study, we report the application of a dual-energy subtraction
CE-DBT technique.

In this feasibility study, DBT image series were obtainable via the methods described. The dual energy CE-DBT images demonstrate gross lesion morphology as well as enhancement information. In comparison with CE-MRI in the same patient, qualitatively concordant information was obtained from the dual energy CE-DBT images.

Temporal subtraction CE-DBT images were also obtained in this case. When compared, less motion artifact is present on the dual energy images. This is likely the consequence of the smaller time delay between the respective pairs of DBT series used to generate the dual energy images relative to the time that elapsed between the pre-contrast DBT series and each post-contrast DBT series used for the temporal subtraction images. This is one of the theoretical advantages of dual energy subtraction contrast-enhanced x-ray imaging of the breast [13-16].

In addition, data from an intermediate timepoint was available from the dual energy sequences, as the first post-contrast LE set could be used with the HE data set acquired either immediately before or after it. This extra kinetic information is not available from the temporal subtraction method, and illustrates another theoretical advantage of a dual energy CE-DBT technique.

**Future directions**

In theory, another potential advantage of dual energy CE-DBT is that the protocol would allow for a delayed post-contrast DBT pair of the contralateral breast. With a pure temporal subtraction CE-DBT technique, this contralateral imaging is not possible. As synchronous contralateral cancers do occur, information about the contralateral breast can be useful clinically.
Additional investigation into minimizing motion artifacts, either a priori or via post-processing, remains to be done. This can be said of both dual energy and temporal subtraction CE-DBT techniques. For example, as currently described, the dual energy CE-DBT technique is not optimized to minimize patient motion as the time between the acquisition of the HE and LE image series at a single time-point is 1.4 to 1.5 minutes. At this time, this delay is necessary to allow for the read-out of each tomosynthesis series. Data series acquisition time can be reduced by developing a dedicated CE-DBT system with rapid image read-out and whereby either interleaved LE and HE exposures are acquired in rapid succession within one x-ray tube sweep. Decreasing the time delay between the acquisitions in dual energy CE-DBT will not only reduce motion artifacts but also improve the temporal resolution.

Image post-processing of the dual energy CE-DBT images also requires further optimization. With dual energy CE-DBT, the background breast parenchyma is partially visualized even on the subtraction images. In this case, we applied a constant $w_0$ for the compressed breast in order to cancel background breast tissue with the goal of increasing enhancement conspicuity. A breast in compression is not of a uniform thickness, however, and the optimal $w_0$ is breast thickness dependent [21]. Thus, to optimally cancel background breast tissue, smaller $w_0$ values should be applied at the periphery of the breast than in the center. Quantification of the breast thickness as a function of position at the periphery of the breast is required to fine-tune $w_0$. This could be obtained by incorporating a correction for x-ray field non-uniformities caused by the heel-effect, beam hardening, scatter, and inverse square law in the source projection images.

Furthermore, power injection instead of manual injection of contrast agent should be used. With power injection, the rate of contrast administration could be doubled. Thus, the first post-contrast
image series could be acquired earlier. This would potentially decrease patient motion as well as improve temporal resolution.

**Conclusion**

In this study, dual-energy CE-DBT is shown to be a clinically feasible technique. In our index case, dual-energy technique was able to demonstrate morphology and kinetics information about the known malignancy. Though this is not a clinical study, this information was qualitatively concordant with that of CE-MRI. In comparison with the temporal subtraction CE-DBT technique, dual-energy CE-DBT appears less susceptible to motion artifacts. Future directions include further investigation into dual-energy CE-DBT, and comparison or possibly fusion of this with temporal subtraction CE-DBT.
References
**Figure 1.**
Illustration of the imaging sequence and timing of acquisition. The affected breast is compressed, then a HE pre-contrast tomosynthesis image series is acquired. After injection, two HE/LE tomosynthesis image series are acquired. After image processing and tomographic reconstruction temporal subtraction CE-DBT images at 2 time points (Temp1 and Temp2) and dual energy (DE) CE-DBT images at 3 time points (DE1, DE2 and DE3), were available.

**Figure 2.**
CE-MRI slice (A.) and DBT slice (B.) at similar planes demonstrate comparable morphologic information about the malignant lesion (arrow).

**Figure 3.**
Dual energy (DE) CE-DBT image at the first time point (A.), which demonstrates the malignancy (arrow). The malignant lesion and its rim enhancement are highlighted in the zoomed images at each of the three dual energy time points (B., C., and D.)

**Figure 4.**
Temporal subtraction CE-DBT image at the first time point (A.), which also demonstrates the malignancy (arrow). The malignant lesion and its rim enhancement are highlighted in the zoomed images at each of the two temporal subtraction time points (B. and C.) Note the motion artifacts in the temporal subtraction CE-DBT images; a clip inside the lesion shows a displacement of approximately 2 mm.
Table 1. Technical parameters used to acquire the high energy (HE) and low energy (LE) DBT projection image series. The mean glandular dose (MGD) is specified for a 5 cm thick 50% glandular – 50% adipose breast.
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Technical parameters used to acquire the high energy (HE) and low energy (LE) DBT projection image series. The mean glandular dose (MGD) is specified for a 5 cm thick 50% glandular – 50% adipose breast.

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<th>MGD [mSv]</th>
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