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Digital Breast Tomosynthesis guided Near Infrared Spectroscopy: Volumetric estimates of fibroglandular fraction and breast density from tomosynthesis reconstructions

Srinivasan Vedantham^{1,a}, Linxi Shi¹, Kelly E. Michaelsen², Venkataramanan Krishnaswamy², Brian W. Pogue², Steven P. Poplack^{3,b}, Andrew Karellas¹, and Keith D. Paulsen^{2,3}

¹ Department of Radiology, University of Massachusetts Medical School, Worcester, MA 01655, USA

² Thayer School of Engineering, Dartmouth College, Hanover, NH 03755, USA

³ Department of Radiology, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA

Abstract

A multimodality system combining a clinical prototype digital breast tomosynthesis with its imaging geometry modified to facilitate near-infrared spectroscopic imaging has been developed. The accuracy of parameters recovered from near-infrared spectroscopy is dependent on fibroglandular tissue content. Hence, in this study, volumetric estimates of fibroglandular tissue from tomosynthesis reconstructions were determined. A kernel-based fuzzy c-means algorithm was implemented to segment tomosynthesis reconstructed slices in order to estimate fibroglandular content and to provide anatomic priors for near-infrared spectroscopy. This algorithm was used to determine volumetric breast density (VBD), defined as the ratio of fibroglandular tissue volume to the total breast volume, expressed as percentage, from 62 tomosynthesis reconstructions of 34 study participants. For a subset of study participants who subsequently underwent mammography, VBD from mammography matched for subject, breast laterality and mammographic view was quantified using commercial software and statistically analyzed to determine if it differed from tomosynthesis. Summary statistics of the VBD from all study participants were compared with prior independent studies. The fibroglandular volume from

^a Corresponding author: Srinivasan Vedantham, PhD, Associate Professor of Radiology, University of Massachusetts Medical School, 55 Lake Avenue North, Room S2-835A, Worcester, MA 01655, Tel: (508) 856-1241, Fax: (508) 856-6363, srinivasan.vedantham@umassmed.edu.

^b Currently at Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO 63110, USA

Linxi.Shi2@umassmed.edu

Kelly.E.Michaelsen@dartmouth.edu

Venkataramanan.Krishnaswamy@dartmouth.edu

Brian.W.Pogue@dartmouth.edu

Poplacks@mir.wustl.edu

Andrew.Karellas@umassmed.edu

Keith.D.Paulsen@dartmouth.edu

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tomosynthesis and mammography were not statistically different ($p=0.211$, paired t-test). After accounting for the compressed breast thickness, which were different between tomosynthesis and mammography, the VBD from tomosynthesis was correlated with ($r=0.809$, $p<0.001$), did not statistically differ from ($p>0.99$, paired t-test), and was linearly related to, the VBD from mammography. Summary statistics of the VBD from tomosynthesis were not statistically different from prior studies using high-resolution dedicated breast computed tomography. The observation of correlation and linear association in VBD between mammography and tomosynthesis suggests that breast density associated risk measures determined for mammography are translatable to tomosynthesis. Accounting for compressed breast thickness is important when it differs between the two modalities. The fibroglandular volume from tomosynthesis reconstructions is similar to mammography indicating suitability for use during near-infrared spectroscopy.

Keywords

Breast [A01.236]; Spectroscopy; Near-Infrared [E01.370.350.750]; Mammography [E01.370.350.700.500]; Digital Breast Tomosynthesis; Breast Density

I. INTRODUCTION

Digital breast tomosynthesis (DBT) is a limited-angle x-ray tomographic technique that can reduce tissue superposition (Niklason et al., 1997, Suryanarayanan et al., 2000, Suryanarayanan et al., 2001). In DBT, multiple projection views of the compressed breast are acquired and reconstructed to provide quasi-three-dimensional (3D) image data. The reconstructed breast volumes are viewed along planes parallel to the detector and are often referred to as “slices” during interpretation. For clarity, the term “slice” in a DBT reconstructed volume is used to represent a plane parallel to the detector. Prospective clinical trials (Skaane et al., 2013, Ciatto et al., 2013) in screening populations have shown that DBT in combination with full-field digital mammography (FFDM) can significantly reduce false-positive rates and increase cancer detection, particularly for invasive disease. Retrospective observational studies (Rose et al., 2013, Friedewald et al., 2014) have also shown a significant decrease in false-positive rate with the combined DBT and FFDM screen. Several multi-reader multi-case retrospective studies (Rafferty et al., 2013, Wallis et al., 2012, Gennaro et al., 2013, Svahn et al., 2012) have shown that DBT improves performance measures, such as the area under the receiver operating characteristic curve (AUC). However, DBT provides only anatomical images.

Near Infrared Spectroscopy (NIRS) can measure several physiological parameters noninvasively such as hemoglobin concentration, oxygen saturation, water, and lipid content without the use of exogenous contrast agents. Malignant tumors are expected to exhibit higher hemoglobin concentration due to angiogenesis associated neovascularity, and lower oxygen saturation due to higher metabolism in cancers. NIRS alone exhibits poor spatial resolution. In the absence of any prior knowledge on tissue distribution, i.e., when NIRS is used as a stand-alone modality, its limited spatial resolution (>1 cm) resulted in an AUC for discriminating breast cancer from normal tissue of 0.67 (Poplack et al., 2007). For a subgroup of patients with lesions larger than 6 mm, the AUC improved to 0.88 (Poplack et

al., 2007). When anatomical priors are provided from another imaging modality, substantial improvements in NIRS spatial resolution have been reported enabling visualization of abnormalities in the millimeter range (Dehghani et al., 2003, Pogue et al., 2006, Fang et al., 2009) and increasing the accuracy of recovered optical properties (Brooksby et al., 2005, Brooksby et al., 2006, Carpenter et al., 2007).

The combination of DBT and NIRS in a single imaging platform would retain the benefits of DBT in terms of reduced false-positive rates and increased cancer detection, while improving discrimination of carcinoma from benign lesions through the addition of NIRS. The concept of integrating NIRS with DBT was first described by researchers from Massachusetts General Hospital (Li et al., 2003, Boverman et al., 2007, Fang et al., 2011). We are investigating the potential of DBT-guided NIRS using a simpler NIRS configuration (Vedantham et al., 2011, Krishnaswamy et al., 2012, Michaelsen et al., 2012, Michaelsen et al., 2014). In the study by Fang et al, hemoglobin concentration determined from NIRS was correlated with fibroglandular tissue content in the breast (Fang et al., 2011). Hence, in addition to providing spatial priors for NIRS image reconstruction, determining fibroglandular volume is important for estimating hemoglobin concentration, accurately. Thus, segmenting DBT reconstructions not only provides spatial priors for use during NIRS image reconstruction, but also determines fibroglandular content which improves the accuracy of hemoglobin concentration estimates from NIRS.

To achieve DBT segmentation, an algorithm previously described (Vedantham et al., 2011) has been refined to eliminate intermediate steps that did not alter the segmentation results. Relative to extracting spatial priors, DBT segmentations were discretized into 3-D meshes with tetrahedral elements for finite element method analyses (Mimics®, Materialise NV, Leuven, Belgium). Simulation studies showed that meshes with tetrahedral elements containing 30,000 nodes were sufficient for accurate NIRS parameter recovery without substantially increasing computation time (Michaelsen, 2014). Hence, the DBT segmentations were down-sampled to 20% prior to mesh generation, and yielded suitably resolved discretizations of approximately 35,000 nodes. The spacing between the nodes of the tetrahedral elements was approximately 0.25 cm, resulting in a volume of approximately 1.84 mm³. In this work, we focused on the other important task of determining fibroglandular volume from DBT using full-resolution data (*i.e.*, prior to down-sampling), and used these results as a framework for validating the DBT segmentation method.

Results from DBT segmentation offer other potential benefits as well, and could be used to estimate breast density quantitatively. Several studies (Saftlas et al., 1991, Boyd et al., 1995, Vachon et al., 2007, Greenwood et al., 2011) have suggested an association between breast density and breast cancer risk. A meta-analysis (McCormack and dos Santos Silva, 2006) observed that the relative risk was ~4.7 for women with >75% fibroglandular content compared to those with <5% fibroglandular content. Along with female sex, age and genetic or syndromic predisposition, breast density is amongst the most important cancer risk factors (Veronesi et al., 2005). Recognizing the significance of breast density as a risk factor and the fact that the sensitivity of mammography is lower for women with dense breasts (Kolb et al., 2002), some states in the USA now require that a woman undergoing screening mammography must be informed of her breast density.

Methods involving commercial and non-commercial software are available for determining breast density from FFDM. Given that at least one vendor has received regulatory approval from the United States Food and Drug Administration for the clinical use of a two-dimensional (2-D) synthetic mammogram (C-View™, Hologic Inc., Bedford, MA) generated from data acquired during DBT, one approach would be to estimate breast density from such a synthesized mammogram. However, the algorithm used for generating the synthesized mammogram is vendor-specific and may have an effect on the quantitative estimate. A few studies have reported on breast density associated measures from DBT. Bakic et al found that an area-based breast density (ABD) from the central projection of the DBT acquisition was correlated with the ABD from FFDM (Bakic et al., 2009). In a subsequent study, Kontos et al (Kontos et al., 2011) extracted six parenchymal texture features from the FFDM and from the central plane parallel to the detector (central slice) of the reconstructed DBT breast volumes. With respect to the ABD, texture features from the DBT central slice were better correlated than the texture features from FFDM. Tagliafico et al determined the average ABD from all DBT projections using two algorithms and observed that the ABDs from the DBT projections differed from FFDM (Tagliafico et al., 2012). A subsequent study compared the average ABD from all DBT projections, the average ABD from MRI on a per slice basis, and the ABD from FFDM, and noted that the estimate from FFDM significantly differed from DBT and MRI, while the estimates from DBT and MRI were similar (Tagliafico et al., 2013a). When ABD was computed on a per slice basis from DBT reconstructions and averaged, it also differed from the ABD from FFDM (Tagliafico et al., 2013b). A prospective case-control study with 1,100 subjects showed that breast cancer risk is more accurately predicted when volumetric estimates of breast density rather ABDs are used in conjunction with other known risk factors (Shepherd et al., 2011). Additionally, a recent study found that volumetric breast density (VBD) was more reliable than ABD (Alonzo-Proulx et al., 2015).

Hence, quantitatively determining the volumetric breast density (VBD) appears to be important, is readily accomplished with our DBT segmentation algorithm, and is another important aspect of this work. VBD is defined as the ratio of the fibroglandular volume to the total breast volume excluding the skin and was determined from the reconstructed breast volume. DBT reconstructions, rather than projections, were chosen for segmentation to facilitate widespread adaptation of the algorithm as the projection images may have manufacturer-specific formats. Currently available commercial software for determining VBD from DBT requires projection images. Also, an algorithm utilizing DBT reconstructions would facilitate retrospective clinical studies, as the projection images are often not archived. Hence, in this study we report on the quantitative estimates of fibroglandular volume and VBD determined using the developed algorithm (Vedantham et al., 2011) from DBT reconstructed breast volumes of women who participated in a clinical study of DBT-guided NIRS. A subset of study participants underwent routine annual (12-month) follow-up FFDM, subsequent to the DBT-guided NIRS exam. For these study participants, fibroglandular volume and VBD were determined using a US FDA-approved tool (Quantra™, Hologic Inc., Bedford, MA) for comparative analysis.

Thus, the study seeks to determine if the fibroglandular volume determined from DBT reconstructions is similar to estimates obtained from FFDM for the cohort of women who

underwent both DBT-guided NIRS and subsequent annual FFDM follow-up exams, and provides a form of validation of the DBT segmentation as a way of determining fibroglandular content. Since the DBT and FFDM data were acquired on two different imaging platforms with differing compressed breast thickness, the statistical association in VBD between DBT and FFDM was determined, and then VBD from all participants in the DBT-guided NIRS exams was compared with values from prior independent studies to investigate the reliability of the DBT segmentation method.

II. METHODS AND MATERIALS

II.a. Human Subjects

All study participants underwent the combined multimodality DBT-guided NIRS imaging in adherence to an Institutional Review Board (IRB)-approved, Hospital Insurance Portability and Accountability Act (HIPAA)-compliant protocol at the Breast Imaging Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH. Written informed consent was obtained from all study participants.

Cohort A corresponds to all study participants ($n = 34$) who underwent DBT-NIRS imaging (Figure 1). Fifteen of the study participants were assigned American College of Radiology (ACR) Breast-Imaging Reporting and Data System (BIRADS®) diagnostic assessment category 1 (“negative” or normal), and the remainder ($n = 19$) were assigned BIRADS® diagnostic assessment categories 4 or 5 that correspond to “suspicious finding” or “highly suggestive of malignancy”, respectively, and require tissue sampling (biopsy). In order to minimize the radiation dose to study participants, the number of views and orientations (craniocaudal, CC or mediolateral oblique, MLO) for each subject was limited to meet research objectives, such as evaluating the consistency in NIRS derived parameters for 2 views of the same breast, and determining differences between ipsilateral and contralateral breasts in the same view. A total of 41 CC-views and 21-MLO views of 41 breasts from these 34 study participants was available for analysis. None of the study participants underwent a MLO-view alone.

Quantra™ (Hologic Inc., Bedford, MA) requires DICOM “for processing” images from FFDM to compute VBD. As is customary at most institutions, the DICOM “for processing” images from FFDM acquired at the time of DBT-guided NIRS exam were not archived; only the DICOM “for presentation” images were saved. Hence, for a subset of study participants (cohort B: $n = 9$ subjects) that returned at 12 months following their DBT-guided NIRS exam for their annual mammogram (Selenia®, Hologic Inc., Bedford, MA), the DICOM “for processing” mammograms were used to determine VBD using Quantra™. For these 9 study participants, a total of 17 DBT reconstructions was acquired at the time of DBT-guided NIRS imaging: 6 unilateral 2-view (CC and MLO), 2 bilateral 1-view (CC alone), and 1 unilateral 1-view (CC alone) DBT-NIRS imaging. VBD estimates from mammograms acquired at matched laterality and orientation to the DBT reconstructions were used for comparative analysis. A schematic of the study groups is shown in Figure 1.

II.b. System Description and Imaging Protocol

The study utilized a prototype DBT system (Genesis, Hologic Inc., Bedford, MA) that was modified for NIRS imaging. Detailed description of the NIRS imaging component and its integration with the DBT system has been reported (Krishnaswamy et al., 2012). The prototype DBT unit uses concentric motion of x-ray tube and detector assembly with source-to-detector distance of 66 cm. The axis of rotation (AOR) is located 58.4 cm from the focal spot and 11 projections are acquired spanning an angular range of $\pm 7.5^\circ$ referenced to the AOR. In order to accommodate the NIRS detector panel, a 3.1 cm thick NIRS detector housing is positioned on top of the breast support. This addition results in a slight magnification for DBT imaging. Study participants underwent DBT-guided NIRS imaging with the breast supported on the NIRS detector housing. DBT and NIRS imaging was performed sequentially without altering patient positioning and compression. During DBT imaging, the NIRS detector panel was removed and the technique factors for acquisition were manually selected using manufacturer provided charts. After completion of the DBT acquisition, the NIRS detector panel was inserted within its housing and the NIR data was acquired using a raster scan of the breast. The acquired DBT projections were reconstructed using filtered back-projection (FBP) provided with the system to a nominal slice thickness of 1 mm and in-plane pixel size of approximately 100 μm . A photograph of the system along with the coordinates is shown in Figure 2. Thus, the reconstructed slices viewed by the radiologists correspond to (x, y) planes. The anonymized DBT reconstructions were transferred to the researchers at the University of Massachusetts Medical Center for segmentation and classification to generate anatomic priors for NIRS reconstruction. The segmented DBT reconstructions were used to compute the VBD from DBT.

II.c. Image preparation

Prior to segmenting the reconstructed DBT volume, several image preparation steps were necessary due to the use of an earlier-generation clinical prototype system. For a compressed breast thickness of CBT_T in mm, the DBT system reconstructed $\lceil CBT_T \rceil + 31$ slices, each 1 mm thick, where $\lceil CBT_T \rceil$ represents the compressed breast thickness rounded-up (ceiling function) to the nearest integer and the 31 slices correspond to the 31 mm thick NIRS detector housing positioned on top of the breast support. These 31 slices were removed prior to segmentation. The sequence of image processing steps is shown in Figure 3. On occasion, detector artifacts were observed in the reconstructed image volume (arrow 1 in Figure 3a, x - y plane). Also, the plastic screws of the NIRS detector housing were present within the DBT reconstructed field-of-view (FOV) located at the posterior and lateral edges of the image (arrow 2 in Figure 3a). These artifacts were removed from each slice by thresholding and area filtering (Figure 3b). If the plastic screw was within the reconstructed breast volume, which occurred often in MLO views, then the location corresponding to the screw was assigned the surrounding tissue type (often pectoralis muscle) post segmentation. The posterior edge of the NIRS detector housing also fell within the DBT FOV (arrow 3 in Figure 3b) and was manually identified and removed (Figure 3c). Since the posterior aspect of the breast seldom contains fibroglandular tissue, the breast region corresponding to Figure 3c was assigned as non-fibroglandular tissue (Figure 3d). The remainder of the breast region (Figure 3e) was used for segmentation. All of the aforementioned steps could be averted

with redesign of the NIRS housing panel to be outside the DBT imaging FOV, and with a more robust detector.

II.d. DBT segmentation

In reconstructed DBT breast volume, the skin along the breast periphery had higher intensity than adipose tissue due to its higher linear attenuation coefficient. To avoid classification of skin as fibroglandular tissue, the skin thickness (t_s , in mm) was determined as the average full-width at half-maximum of the gradient image computed along the medial-lateral direction from the central slice. The estimated t_s from the central slice was used to identify the skin layer (Figure 3f) followed by its removal through isotropic erosion in each slice (Figure 3g). The estimated skin layer thickness was rounded-up to the nearest integer ($\lceil t_s \rceil$), and $\lceil t_s \rceil$ slices in contact with the NIRS detector housing and compression paddle were removed from the breast volume. Thus, the breast volume used for segmentation excluded the skin. Upon completing these steps for all slices, the breast volume was preprocessed using an edge-preserving bilateral filter (Chen et al., 2007, Paris et al., 2009) with angular constraints (Vedantham et al., 2011) applied in the x - z planes. This result is not shown in Figure 3 as the slice used for interpretation corresponded to the x - y plane that is parallel to the detector, whereas the filter was applied in x - z planes.

After bilateral filtering the breast volume, an automated kernel-based fuzzy C-means (KFCM) clustering algorithm was used to segment the breast volume on a per-slice basis. Compared to the conventional fuzzy C-means (FCM) method, KFCM is more robust to noise and incomplete data (Wu and Yang, 2002, Zhang and Chen, 2003, Hathaway et al., 2005). The KFCM algorithm segmented the breast into two clusters: non-adipose (Figure 3h) and adipose (Figure 3i) tissues. If the pectoralis muscle was absent in the FOV (occurs only in CC views) then the segmented non-adipose tissue region was classified as fibroglandular tissue. Figure 3 is an example of such a case.

If the pectoralis muscle was present in the FOV and was separated from the fibroglandular region by adipose tissue, then a geographical area filter was applied to segment and classify the pectoralis muscle for expediency. In CC views, this geographical area filter was centered laterally and at the posterior aspect of the breast. In MLO views, the geographical area filter was positioned at the region corresponding to the axilla (Figure 4). The remainder of the non-adipose tissue region was classified as fibroglandular tissue. If the pectoralis muscle was connected to fibroglandular tissue (Figure 5), then a second iteration of KFCM was applied to the segmented non-adipose region to separate fibroglandular tissue from pectoralis muscle.

II.e. VBD computation

The voxel size in each reconstructed slice was dependent on its distance from the detector and this information was provided by the manufacturer. For each slice, the fibroglandular volume within that slice was estimated from the voxel size and the segmented fibroglandular region (example, Figure 3h). The fibroglandular volume for the entire breast was computed by summing the fibroglandular volume from each slice. For each slice, the breast volume within that slice was determined from the voxel size and by summing the segmented regions

corresponding to adipose and fibroglandular tissue (for example, regions corresponding to Figures 3d, 3h and 3i). When pectoralis muscle is present (for example, in Figures 4 and 5) then the segmented region corresponding to the pectoralis muscle was excluded from the breast volume estimate. The total breast volume was obtained by summing the breast volume from each slice. The VBD was determined as the ratio of fibroglandular volume for the entire breast to the total breast volume and was expressed in percentage. Thus, the VBD determined in this study excludes the skin and the pectoralis muscle, when present.

II.f. Statistical Methods

For cohort A, the VBD estimated from DBT reconstructions was compared with VBD from independent prior studies. For cohort B, the compressed breast thickness (CBT_M) recorded in the FFDM DICOM image headers as well as estimates of the total breast volume (TBV_M), the fibroglandular volume (GV_M), and the volumetric breast density (VBD_M) provided by Quantra were compared with the corresponding estimates from DBT, represented by the subscript “T”. Depending upon whether the data satisfied normality assumptions, appropriate parametric and nonparametric tests were used for statistical analysis. All data were analyzed either using SAS® (version 9.3, SAS Institute Inc., Cary, NC) or GraphPad Prism® (version 6.05, GraphPad Software, Inc., La Jolla, CA). All tests were two-tailed and effects associated with $p < 0.05$ were considered statistically significant.

III. RESULTS

III.a. Comparison between FFDM and DBT

For clarity, results of the paired comparison between FFDM and DBT that corresponds to cohort B are presented first, as this analysis permits validation of the method used to estimate VBD_T . Summary statistics of compressed breast thickness, fibroglandular volume, total breast volume and VBD from FFDM and DBT reconstructions are provided in Table 1. The difference between FFDM and DBT for each of these metrics satisfied the normality assumption ($p > 0.109$, Shapiro-Wilk's test).

After matching for study participant, breast laterality and view, the fibroglandular volume from FFDM (GV_M) provided by Quantra was statistically correlated (Pearson's $r = 0.498$, $p = 0.042$) with that from DBT (GV_T) determined using the algorithm. Paired t-test indicated that the GV_M and the GV_T were not statistically different ($p = 0.211$), with the GV_M being slightly larger than the GV_T (mean difference: 9.6 mm^3).

After matching for study participant, breast laterality and view, the compressed breast thickness recorded by FFDM (CBT_M) was not statistically correlated (Pearson's $r = 0.266$, $p = 0.302$) with that recorded by DBT after correcting for the 31 mm thick NIRS detector housing (CBT_T). Paired t-test indicated that the CBT_M statistically differed ($p = 0.014$) from the CBT_T , with the CBT_M being larger than the CBT_T (mean difference: 0.7 mm). Consequently, the total breast volume from FFDM (TBV_M) provided by Quantra also statistically differed ($p < 0.001$, paired t-test) from the total breast volume from DBT (TBV_T). The TBV_M was larger than the TBV_T (mean difference: 196.3 mm^3).

The volumetric breast density from FFDM (VBD_M) provided by Quantra was marginally correlated (Pearson's $r = 0.471$, $p = 0.056$) with that from DBT (VBD_T) determined using the algorithm. The VBD_M expressed in percent, was significantly different ($p = 0.028$, paired t-test) and lower than VBD_T (mean difference: -2.46%), as the TBV_M was different than TBV_T .

In order to account for the differing compressed breast thickness between the modalities (DBT and FFDM) and as a consequence the estimated total breast volume, multivariable linear regression was used to model the association between VBD_M and VBD_T , with step-wise selection of parameters that statistically differed between FFDM and DBT as possible covariates. Thus, the compressed breast thickness and the total breast volume from both FFDM and DBT were considered. Since linear regression is sensitive to outliers, studentized residuals and Cook's D were assessed, which identified 2 (out of 17) outliers and were excluded. These 2 outliers corresponded to DBT reconstructions with substantial detector artifacts that could not be completely corrected. With VBD_T as the outcome, step-wise selection resulted in a statistically significant model ($p = 0.008$, ANOVA) with VBD_M ($p = 0.004$), CBT_T ($p = 0.007$) and CBT_M ($p = 0.048$) as predictors. VBD_T was related to VBD_M as per equation (1):

$$VBD_T = a + bVBD_M + cCBT_T + dCBT_M \quad (1)$$

where, $a = -13.9649514$, $b = 0.7320357$, $c = 1.97264191$, and $d = 1.7686961$. However, the additive model given in equation (1) does not impose non-negativity constraint for VBD_T . Hence, linear regression using log-transformed variables was used to provide a multiplicative model that was statistically significant ($p = 0.0008$) and is shown in equation (2).

$$VBD_T = k_0 VBD_M (CBT_M)^{k_1} (CBT_T)^{k_2} \quad (2)$$

where, the fit parameters $k_0 = 5.8818068 \times 10^{-2}$, $k_1 = 1.1651628$ and $k_2 = 0.6454340$. All predictors were statistically significant ($p < 0.0132$). After adjusting for the compressed breast thickness (using equation 2), the model estimated VBD, represented as VBD_T , was determined. Figure 6 shows the plot of VBD_M provided by Quantra vs. VBD_T . VBD_T was statistically correlated with VBD_M (Pearson's $r = 0.843$, $p < 0.001$) and was not statistically different ($p = 0.9473$, paired t-test).

III.b. Comparison of VBD_T with independent prior studies

The VBD_T from all study participants (cohort A) for each breast were used for comparison with prior studies. A total of 41 CC-views and 21-MLO views of 41 breasts was available from these 34 study participants. For the 21 study participants who underwent CC and MLO views of the same breast during DBT-guided NIRS imaging, the VBD_T was analyzed to determine if a statistical difference occurred between the 2-views. The difference in VBD_T between CC and MLO views of the same breast satisfied the normality assumption ($p = 0.193$, Shapiro-Wilks test). Paired t-test indicated that the VBD_T from CC-view was not statistically different ($p = 0.243$) from MLO-view, and hence averaged. Summary statistics of the VBD_T from CC-views ($n = 41$ breasts), MLO-views ($n = 21$ breasts), all DBT

reconstructions ($n=62$), and the estimate for each breast ($n=41$ breasts) from all study participants (cohort A) are provided in Table 2. Summary statistics derived from VBD_T for each breast were compared with prior independent studies of VBD using fully 3-D, high-resolution dedicated breast CT (Nelson et al., 2008, Yaffe et al., 2009, Vedantham et al., 2012). The results from the analysis (unpaired t-test with Welch's correction) are summarized in Table 3. To account for the multiple comparisons, Sidak correction was applied, and hence, effects associated with $p < 0.017$ were considered statistically significant. The analysis indicated that the VBD_T from this study was not statistically different from prior independent studies reporting VBD from dedicated breast CT.

IV. DISCUSSION

The study did not observe a significant difference in fibroglandular volume between DBT and FFDM as most of the fibroglandular tissue was concentrated at the retro-areolar and central breast regions, which were included in the imaged FOV with both DBT and FFDM. This indicates suitability of the method for providing the fibroglandular volume during NIRS reconstruction. The study observed statistically significant differences in compressed breast thickness and total breast volume between DBT and FFDM, with the estimates being higher with FFDM. The thick detector assembly of the prototype DBT/NIRS system (~19 cm inclusive of NIRS detector housing) impeded proper positioning of the study participants. This restriction reduced inclusion of the posterior aspect of the breast in the imaged FOV and contributed to a reduction in compressed breast thickness and total breast volume. Consequently, the VBD_M was lower than the VBD_T . However, after accounting for the compressed breast thicknesses in DBT and FFDM, the VBD_T was correlated with, and linearly related to, VBD_M . Hence, breast density related risk estimates developed for mammography can be applied readily for VBD_T determined from DBT reconstructions using the method investigated. At present, most of the clinical knowledge is based on the combined DBT+FFDM exam, where projection data for DBT and the digital mammogram are acquired under the same compression. However, this result in approximate doubling of the radiation dose compared to DBT imaging alone (Sechopoulos et al., 2007, Feng and Sechopoulos, 2012, Vedantham et al., 2015). One approach to reduce the radiation dose is to replace the FFDM with the synthesized mammogram generated from data acquired for DBT. To our knowledge, no prior studies have demonstrated agreement in quantitative breast density between a synthesized mammogram and FFDM. Also, systems capable of DBT imaging alone have been developed (Wallis et al., 2012). While the VBD can be estimated from DBT projections, these images can be in vendor-specific format posing a challenge for widespread use. The method investigated here relies on DBT reconstructions and not projections, which would allow for retrospective studies investigating the association between quantitative breast density and risk factors with imaging performance. Hence, it is of clinical importance in addressing the current needs as well as facilitating retrospective studies.

Equation (2) can be written as: $VBD_T = k_0 VBD_M (CBT_M)^{k_1+k_2} \left(\frac{CBT_T}{CBT_M} \right)^{k_2}$. If the breast compression is maintained the same during DBT and FFDM acquisition, i.e., $CBT_T = CBT_M = CBT$ then equation (2) simplifies to: $VBD_T = k_0 VBD_M (CBT)^{k_1+k_2}$. Clinical systems

capable of DBT and mammographic acquisitions under the same compression are currently available and could provide a platform for future validation.

With regard to comparison with prior studies, the choice of dedicated breast CT needs clarification. Since we validated the VBD_T with FFDM, and dedicated breast CT provides higher resolution than breast MRI (Vedantham et al., 2014, O'Connell et al., 2014), VBD determined using breast CT was chosen for comparison. Also, both DBT and breast CT attempt to reconstruct the linear attenuation coefficients thus providing a direct comparison of a physical measure based breast density estimate. One study using breast MRI reported that the quantitative estimate of density was dependent on the image acquisition sequence (Tagliafico et al., 2014).

Additionally, the skin thickness (t_s) determined from DBT reconstructions was compared with prior independent studies using dedicated breast CT (Huang et al., 2008, Shi et al., 2013). The mean $\pm$ standard deviation of t_s determined from DBT was 1.78 ± 0.09 mm ($n=41$ breasts). Compared to the study by Huang et al. (Huang et al., 2008), the mean skin thickness statistically differed ($p < 0.001$) and on average the t_s from DBT was higher by 0.33 ± 0.04 mm. Compared to the study by Shi et al. (Shi et al., 2013), the t_s from DBT statistically differed ($p < 0.001$) and on average the t_s from DBT was higher by 0.34 ± 0.03 mm. Importantly, t_s estimated by x-ray imaging modalities includes the combined thickness of epidermis and dermis and excludes subcutaneous fat, as it is often indistinguishable from adipose tissue within the breast. A slight overestimation of t_s was expected with DBT, partly due to the curvature of the breast at its periphery and due to the nominal slice thickness of 1 mm.

In terms of developing an algorithm for segmenting and generating anatomic (structural) priors from DBT for use during NIRS reconstruction, these observations suggest that the fibroglandular volume determined from DBT reconstructions is similar to FFDM. Evaluation of concordance in radiologists' marking of fibroglandular regions with algorithm-segmented regions in the central DBT reconstructed slice using metrics such as dice ratio and overlap ratio are currently ongoing. We did not statistically analyze the association between radiologists' assignment of BI-RADS® breast density categories with the VBD, as data existed from only 34 study participants. Importantly, the BI-RADS density assignment is based on bilateral assessment and corresponds to the denser of the two breasts, if they differ. Since only 7 of the 34 study participants had undergone bilateral DBT-guided NIRS exams, we did not perform this analysis. Future work will investigate the association between BI-RADS density assignment and VBD from DBT.

In this study, we focused on the analysis of fibroglandular volume and VBD from DBT reconstructions obtained during DBT-guided NIRS imaging. Results from radiologists' interpretation of the combined DBT-guided NIRS exam and its association with pathological results and/or follow-up imaging exams are ongoing and will be reported in future.

CONCLUSIONS

The primary conclusion from this study is that the fibroglandular volume determined from DBT reconstructions was similar to that from FFDM, indicating the suitability of the segmentation algorithm for DBT-guided NIRS. Additional, key observations from this study were the linear association in VBD between DBT and FFDM, and the significant correlation between VBDs from DBT and FFDM, after accounting for compressed breast thickness. Hence, mammographic breast density based risk estimates are applicable to DBT. This finding is of clinical importance as DBT continues its transition to breast cancer screening. The observation that the summary statistics of VBD from DBT reconstructions was similar to prior studies using high-resolution dedicated breast CT indicates that the method described here could be suitable for population studies investigating the association between breast density, breast cancer risk, and imaging performance. The analysis also underscored the importance of accounting for compressed breast thickness when it differs between the two modalities.

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Figure 1.
Distribution of imaging views among study participants

Figure 2. Photographs of the developed DBT-guided NIRS system with the imaging coordinates labeled. The slices viewed by the radiologist correspond to x - y planes.

Figure 3.

Illustration of the steps used for segmenting DBT reconstructions. Prior to segmentation, each slice (A; x - y plane) was corrected for detector artifacts (arrow 1), if present, and plastic screws from the NIRS detector housing (arrow 2). These artifacts were removed from each slice by thresholding and area filtering (B). The posterior edge of the NIRS detector housing fell within the DBT field-of-view (arrow 3 in B) and was manually identified and removed (C). Post-segmentation, the removed region was added back as adipose tissue (D). After repeating this process for all slices, a bilateral filter was applied in x - z plane (not shown) to

provide the slice (E). The skin layer (F) was determined from the central slice and removed from each slice to provide the breast region excluding the skin (G). A kernel-based fuzzy c-means method was used to segment each slice into adipose (I) and non-adipose (H) regions.

Figure 4.

Illustration of the method used for segmenting pectoralis muscle when it is separated from fibroglandular region. After preprocessing with a bilateral filter, the skin layer from a slice (A) from MLO-view DBT reconstruction is removed to provide (B) for segmenting into adipose (C) and non-adipose (D) regions. A geographical area filter is applied to the non-adipose region to provide fibroglandular region (E) and pectoralis muscle (F). VBD computation excludes the skin and the pectoralis muscle.

Figure 5.

Illustration of the method used for segmenting pectoralis muscle when it is connected to the fibroglandular region. After preprocessing and skin removal, the slice (A) is segmented into adipose (not shown) and non-adipose (B) regions. A second iteration of KFCM is applied to the non-adipose region to segment fibroglandular tissue (not shown) and pectoralis muscle (C). VBD computation excludes the skin and the pectoralis muscle.

Figure 6. Scatter plot of the VBD from mammography and the VBD from DBT reconstructions after accounting for compressed breast thickness.

Table 1

Summary statistics and comparison of compressed breast thickness (*CBT*), fibroglandular volume (*GV*), total breast volume (*TBV*) and volumetric breast density (*VBD*) from FFDM (subscript 'M') and DBT (subscript 'T') reconstructions. The data were matched for study participant, breast laterality and view ($n=17$ DBT reconstructions). The paired data were statistically analyzed in terms of Pearson correlation coefficient (r) and paired t-tests.

Metric (units)	Mean	Standard Deviation	Minimum	1st Quartile	Median	3rd Quartile	Maximum
CBT_M (cm)	5.6	0.8	4.4	5.1	5.7	6.1	7.1
CBT_T (cm)	5.0	0.9	2.9	4.4	5.2	5.4	6.7
$CBT_M - CBT_T$ (cm)	$0.7 \pm 1.05, p=0.014; r=0.27, p=0.302$						
TBV_M (cm ³)	690.5	303.3	227.7	497.9	624.0	869.9	1241.1
TBV_T (cm ³)	507.6	185.2	241.8	357.5	516.9	669.2	841.4
$TBV_M - TBV_T$ (cm ³)	$196.3 \pm 163, p<0.001; r=0.89, p<0.001$						
GV_M (cm ³)	85.5	32.9	28.0	71.2	80.0	107.9	144.2
GV_T (cm ³)	75.9	27.2	28.8	61.6	79.1	95.9	118.3
$GV_M - GV_T$ (cm ³)	$9.65 \pm 30.5, p=0.211; r=0.498, p=0.042$						
VBD_M (%)	13.2	4.0	6.8	10.0	12.5	16.1	21.1
VBD_T (%)	15.7	4.2	9.6	13.0	14.9	16.1	27.6
$VBD_M - VBD_T$ (%)	$-2.46 \pm 4.19, p=0.028; r=0.471, p=0.056$						

Table 2

Summary statistics of VBD_T (in %) from all CC-views ($n=41$ breasts), all MLO-views ($n=21$ breasts), all views ($n=62$), and from all breasts ($n=41$).

	Mean	Standard Deviation	Minimum	1st Quartile	Median	3rd Quartile	Maximum
CC-views	17.04	4.40	9.75	14.31	16.11	19.38	27.8
MLO-views	15.30	5.21	7.59	11.94	13	18.7	24.75
All views	16.45	4.72	7.59	13	15.235	19.38	27.8
All breasts	16.62	4.29	9.75	13.72	15.34	19.33	27.8

Table 3

Comparison of VBD (in %) from this study using DBT reconstructions with prior studies using dedicated breast CT (Yaffe et al., 2009, Nelson et al., 2008, Vedantham et al., 2012). Summary data were compared using unpaired t-test with Welch's correction (2-tailed). To account for the multiple comparisons, Sidak correction was applied. Hence, effects associated with $p < 0.017$ were considered statistically significant. (SD – standard deviation).

	Mean $\pm$ SD	p -value	Difference between means
<i>Comparison of VBD (in %)</i>			
This study	16.6 $\pm$ 4.30		
Nelson et al., 2008	17.1 $\pm$ 15.2	0.769	0.48 $\pm$ 1.6
Yaffe et al. 2009 (Group A)	14.3 $\pm$ 10.3	0.022	-2.32 $\pm$ 1.0
Vedantham et al. 2012	15.8 $\pm$ 13.0	0.528	-0.82 $\pm$ 1.3