Comparison of Diagnostic Performance of Low Dose Tomosynthesis plus Synthesized Mammography versus Digital Mammography

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AIM: To compare diagnostic performance of reduced-dose digital breast tomosynthesis plus synthesized mammography versus full-field digital mammography.

MATERIALS AND METHODS: Two hundred ninety-nine participants were recruited from April 2014 to July 2015 consecutively. One hundred fifty women were imaged with digital breast tomosynthesis at 90% dose setting of full-field digital mammography and 149 women were imaged with digital breast tomosynthesis at 75% dose setting of full-field digital mammography. Images of 54 and 50 women were used for this study. Digital breast tomosynthesis at 90% were reconstructed by a filtered back projection and digital breast tomosynthesis at 75% were reconstructed by an iterative method. Eight radiologists provided Japanese categorizations and probability of malignancy independently. Diagnostic performance was assessed by comparing sensitivity, specificity and area under the receiver operating characteristic curve. Two-sided P values were calculated.

RESULTS: Diagnostic performance of digital breast tomosynthesis plus synthesized mammography versus full-field digital mammography was not significantly different in either 90% or 75% dose of full-field digital mammography (area under the receiver operating characteristic curve 83.6% vs. 86.7%, P=0.185, 95% confidence Interval -0.078, 0.018 and 90.2% vs. 88.7%, P=0.167, 95% confidence Interval -0.008, 0.038).

CONCLUSION: In this enriched study population, diagnostic performance of digital breast tomosynthesis, whether reconstructed either by a filtered back projection or an iterative method, plus synthesized mammography at lower-dose than full-field digital mammography was not inferior to full-field digital mammography.

Original paper (Received May 8, 2019)
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Abstract

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1. Introduction

The usefulness of digital breast tomosynthesis (DBT) for both diagnosis and screening has been reported \(^1,^4\). The main feature of DBT is the addition of depth information which makes breast anatomy and findings easier to understand and identify compared to full-field digital mammography (FFDM). However, FFDM is superior to DBT in that DBT may not image microcalcifications as well and maintaining the availability of the established gold standard, FFDM, may provide a safety margin. For this reason, DBT has been added in combination with FFDM.

Synthesized mammography (SM), which produces projection-like two-dimensional images from the information acquired during a DBT acquisition, has been developed. Hence, the need for adding FFDM in addition to DBT could potentially be eliminated if the satisfactory diagnostic performance of SM could be demonstrated.

According to Skaane et al. \(^9\), the radiation exposure in DBT is about 23% higher than in FFDM, and furthermore when DBT is combined with FFDM, the radiation exposure is increased to more than double \(^8,^{12}\). The problem to be solved for dose reduction with DBT is to improve the quality of DBT. The recent progress in image processing is remarkable. Iterative reconstruction algorithms depicting the shape of the microcalcifications more clearly have been developed \(^13-16\). We explored using iterative reconstruction algorithms to allow lowering the dose of DBT.

The purpose of this study was to compare the diagnostic performance of reduced-dose DBT, reconstructed with an iterative method, plus SM versus FFDM.

2. Materials and methods

An institutional review board approved this study and written informed consent was provided by all participants.

2.1 Study population

Two hundred ninety-nine women (mean age, 54.7; range, 30-86) presenting for screening or diagnostic mammography from April 2014 through July 2015 were enrolled consecutively in this study. Women with previous mastectomy and with breast size not fitting the detector size (24 × 30 cm²) were not enrolled. All women were imaged with both DBT and FFDM: 150 women with a DBT dose setting of 90% that of FFDM (DBT90) and 149 women with a DBT dose setting of 75% that of FFDM (DBT75). All cases had complete imaging data sets and passed quality control review (optical density, contrast, graininess, sharpness, artefact and positioning) and were eligible for analysis; no cases were excluded. All eligible cases with documented malignancy were included in this study (42 women in the cohort of DBT90 and 47 in the cohort of DBT75). Noncancer cases were selected randomly from the eligible cases. The number of cases was chosen by power analysis, making the number of cancer and noncancer approximately the same, and considering reading fatigue of the reader. The resulting number of cases was 108 (mean age, 51; range, 30-85) for the cohort of DBT90 and 100 (mean age, 58; range, 37-86) for the cohort of DBT75.

2.2 Image acquisition protocol

We imaged craniocaudal and mediolateral oblique projections of both breasts of participants with DBT and FFDM with a commercially available system (AMULET Innovality\textsuperscript{TM}; FUJIFILM, Tokyo, Japan). DBT and FFDM images were acquired in a single compression, and consequently with the same positioning.

In DBT, 15 projection images were acquired over 15 degrees’ tube motion and reconstructed with 1 mm thick slices. The anode/filter combination and kVp for DBT and FFDM and the total mAs of FFDM exposure were defined as a function of compressed breast thickness. The exposure setting for FFDM was H-mode in AMULET Innovality. The average glandular dose (AGD) to the standard breast as defined in European guidelines for quality assurance in breast cancer screening and diagnosis fourth edition\(^7\) was 1.5 mGy. The total mAs of DBT was set in accordance with the study design; DBT90 and DBT75.

The DBT images acquired at DBT90 and DBT75 were reconstructed by filtered back projection\(^9\) and an iterative method\(^13,15\), respectively. In addition, to investigate the further possibility of reducing dose, DBT images at a DBT dose setting of 55% that of FFDM (DBT55) with the iterative method were created by using 11 of the 15 projection images of DBT at DBT75.

2.3 Image interpretation protocol

Eight radiologists with 2-3 years of experience in DBT interpretation and 7-33 (mean, 19) years of experience in mammographic interpretation and who currently interpret DBT and FFDM in clinical practice interpreted the images in this study.

Readers first scored FFDM, then they scored DBT plus SM of the same case after more than 30 days of wash-out. Readers were blinded as to which image of DBT was DBT90, DBT75 or DBT55 during this assessment. Readers interpreted all cases independently. The readers provided a Japanese categorization\(^9\) score of 1, 2, 3-1, 3-2, 4, or 5, adapted from a forced Breast Imaging Reporting and Data System (BI-RADS\textsuperscript{®}) categorization\(^9\), with the following categories: 1, negative; 2, benign; 3, probably benign; 4, suspicious; and 5, highly suggestive of malignancy. Score of 3-1 is probably benign and 3-2 is benign, but malignancy can’t be ruled out.
The Japanese categorization is used for daily practice widely in Japan. Readers also provided a probability of malignancy score ranging from 0%-100% for each case.

2.4 Data analysis

Cases with biopsy-proven malignant disease results were considered positive. Cases with concordant benign biopsy results and women not undergoing biopsy with no evidence of breast malignancy after one year of clinical follow-up were considered negative. Details of cases were provided by the hospital where the breast physicians made their final assessments based on the results of interviews, clinical breast examination, mammography, ultrasonography, MRI, and biopsy if needed.

Japanese categorization scores were used to calculate diagnostic sensitivity and specificity. Probability of malignancy scores were used to calculate area under the receiver operating characteristic curve (AUC). AUC was measured by using multiple-reader multiple-case receiver operating characteristic analysis.

The study was prospectively designed to test the null hypotheses of inferior sensitivity, specificity and AUC for DBT plus SM vs. FFDM. Diagnostic sensitivity and specificity were compared using a Japanese categorization.

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>All</th>
<th>DBT cohort at 90% dose setting of FFDM</th>
<th>DBT cohort at 75% dose setting of FFDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of cases</td>
<td>208 (100%)</td>
<td>108 (100%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>Mammographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>69 (33.2%)</td>
<td>41 (38%)</td>
<td>28 (28%)</td>
</tr>
<tr>
<td>Micro-calcification</td>
<td>97 (46.6%)</td>
<td>42 (38.9%)</td>
<td>55 (55%)</td>
</tr>
<tr>
<td>Mass</td>
<td>68 (32.7%)</td>
<td>30 (27.8%)</td>
<td>38 (38%)</td>
</tr>
<tr>
<td>Distortion</td>
<td>15 (7.2%)</td>
<td>9 (7.4%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>FAD</td>
<td>20 (9.6%)</td>
<td>13 (12%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Breast density score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a (Almost entirely fat)</td>
<td>4 (1.9%)</td>
<td>2 (1.9%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>b (Scattered fibroglandular tissue)</td>
<td>98 (47.1%)</td>
<td>48 (44.4%)</td>
<td>50 (50%)</td>
</tr>
<tr>
<td>c (Heterogeneous fibroglandular tissue)</td>
<td>94 (45.2%)</td>
<td>50 (46.3%)</td>
<td>44 (44%)</td>
</tr>
<tr>
<td>d (Extreme fibroglandular tissue)</td>
<td>12 (5.8%)</td>
<td>8 (7.4%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Total no. of cancers</td>
<td>89 (42.8%)</td>
<td>42 (38.9%)</td>
<td>47 (47%)</td>
</tr>
<tr>
<td>Invasive cancers with or without DCIS</td>
<td>74 (35.6%)</td>
<td>36 (33.3%)</td>
<td>38 (38%)</td>
</tr>
<tr>
<td>Lesion size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean*</td>
<td>19.3</td>
<td>17.9</td>
<td>20.1</td>
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<tr>
<td>Median*</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Range*</td>
<td>3 - 80</td>
<td>7 - 80</td>
<td>3 - 70</td>
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<tr>
<td>Standard deviation*</td>
<td>17.9</td>
<td>20.8</td>
<td>16.4</td>
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<tr>
<td>Histologic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDC</td>
<td>50 (24%)</td>
<td>27 (25%)</td>
<td>23 (23%)</td>
</tr>
<tr>
<td>ILC</td>
<td>6 (2.9%)</td>
<td>4 (3.7%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Tubular</td>
<td>8 (3.8%)</td>
<td>1 (0.9%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>3 (1.4%)</td>
<td>1 (0.9%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>7 (3.4%)</td>
<td>3 (2.8%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>14 (7.2%)</td>
<td>6 (5.6%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Lobular carcinoma in situ</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Total no. of non-cancer cases</td>
<td>119 (57.2%)</td>
<td>66 (61.1%)</td>
<td>53 (53%)</td>
</tr>
</tbody>
</table>

Note. —DBT = digital breast tomosynthesis, FFDM = full-field digital mammography.

* FAD = focal asymmetric density, DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma

* Numbers are lesion sizes in millimeters

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score of 3-2, 4 or 5 considered as positive and 1, 2, or 3-1 as negative. The paired t-test was used for comparisons across all readers’ scores. Two-sided P values were calculated using R statistical analysis software, version 3.1.2 (The R Foundation for Statistical Computing; Vienna, Austria; URL: https://www.R-project.org/); P < 0.05 was considered to indicate a significant difference.

### 3. Results

#### 3.1 Cancer and Other Cases

Total number of cancer cases was 89.

Of the malignant cases, 6 and 8 cases for the DBT cohorts at DBT90 and DBT75, respectively were ductal carcinoma in situ alone and a case at DBT75 was lobular carcinoma in situ alone; the remainder were invasive or combined invasive and in situ cancers. For invasive cancers the median size was 15 mm for both DBT at DBT90 (n= 36) and DBT75 (n= 38), respectively. Table 1 shows the details of cases used for this study.

### 3.2 AGD

The AGD of FFDM for a single mammographic view for DBT cohort at DBT90 and DBT75 was 1.67 mGy (mean) ± 0.49 (standard deviation) (range, 0.71-3.51) and 1.72 mGy ± 0.48 (0.65-4.16), respectively. The AGD of DBT for a single mammographic view for DBT cohort at DBT90 and DBT75...
Fig. 1 Mediolateral oblique view of right breast in 43-year-old woman; (a) full-field digital mammography (mean glandular dose: 1.58mGy), (b) digital breast tomosynthesis (1.44mGy) and (c) synthesized mammography for DBT at 90% dose setting of FFDM. Invasive ductal carcinoma was diagnosed at histologic examination.

Fig. 2 Mediolateral oblique view of right breast in 61-year-old woman; (a) full-field digital mammography (mean glandular dose: 1.31mGy), (b) digital breast tomosynthesis (1.00mGy) and (c) synthesized mammography for DBT at 75% dose setting of FFDM and (d) digital breast tomosynthesis (0.73mGy) and (e) synthesized mammography for DBT at 55% dose setting of FFDM. Invasive ductal carcinoma was diagnosed at histologic examination.
was 1.54 mGy ± 0.34 (0.95-3.19) and 1.25 mGy ± 0.30 (0.87-2.70), respectively. The ratio of the mean AGD of DBT and FFDM to the AGD of the DBT cohorts at DBT90 and DBT75 was 0.922 and 0.727, respectively. The ratio for DBT cohort at DBT55 was 0.533.

3.3 Radiologist Performance
Table 2 and 3 show the details of sensitivity, specificity and AUC of DBT plus SM and FFDM for DBT cohort at DBT90, DBT75 and DBT55. Examples images of DBT (one of the slices), SM and FFDM for DBT at DBT90, DBT75 and DBT55 are shown in Fig. 1 and 2.

3.4 Sensitivity
The sensitivity of DBT plus SM and FFDM for the DBT cohort at DBT90 was 76.2% (mean) (range, 66.7%-90.5%) and 81.0% (66.7%-95.2%), respectively. The sensitivity of DBT plus SM and FFDM and FFDM for the DBT cohort at DBT75 was 83.0% (76.6%-89.4%) and 78.4% (72.9%-85.4%), respectively. In addition, the sensitivity of DBT plus SM for the DBT cohort at DBT55 was 76.0% (70.8%-83.3%). The differences in sensitivity between DBT plus SM and FFDM for the DBT cohort at DBT90, DBT75 and DBT55 were -4.8% (95% confidence interval [CI]: -0.115, 0.020; P=0.142), 4.6% (95% CI: -0.007, 0.099; P=0.079), and -1.3% (95% CI: -0.060, 0.034; P=0.533), respectively, and all of the differences was not significant.

3.5 Specificity
The specificity of DBT plus SM and FFDM for the DBT cohort at DBT90 was 83.5% (74.2%-92.4%) and 86.9% (72.7%-95.5%), respectively. The specificity of DBT plus SM and FFDM and FFDM for the DBT cohort at DBT75 was 89.4% (79.2%-94.3%) and 90.1% (84.6%-94.2%), respectively. In addition, the specificity of DBT plus SM for the DBT cohort at DBT55 was 88.2% (82.7%-92.3%). The differences in specificity between DBT plus SM and FFDM for the DBT cohort at DBT90, DBT75 and DBT55 were -3.4% (95% CI: -0.076, 0.007; P=0.095), -0.8% (95% CI: -0.060, 0.045; P=0.743), and -1.9% (95% CI: -0.051, 0.013; P=0.203), respectively, and all of the differences was not significant.

3.6 AUC
The AUC of DBT plus SM and FFDM for the DBT cohort at DBT90 were 83.6% (76.6%-86.9%) and 86.7% (80.9%-93.9%), respectively. The AUC of DBT plus SM and FFDM for the DBT cohort at DBT75 were 90.2% (87.6%-92.8%) and 88.7% (86.7%-91.6%), respectively. In addition, the AUC of DBT plus SM for the DBT cohort at DBT55 were 88.0% (83.5%-93.3%). The differences in AUC between DBT plus SM and FFDM for the DBT cohort at DBT90, DBT75 and DBT55 were -3.0% (95% CI: -0.078, 0.018; P=0.185), 1.5% (95% CI: -0.008, 0.038; P=0.167), and -0.7% (95% CI: -0.042, 0.027; P=0.638), respectively, and all of the differences was not significant.

4. Discussion
Many studies have demonstrated that by adding DBT to FFDM, diagnostic performance improves above that of FFDM alone. The study populations in those studies were screening by Skanne et al. 6,9, diagnostic by Gennaro et al. 7, and both by Rafferty et al. 7. Diagnostic performance improves with the addition of DBT to FFDM by reducing the impact of overlapping structures in the breast. Although various attempts have been made to reduce the dose increase accompanying the addition of DBT to FFDM, such as one-view DBT 22, a mixture of craniocaudal FFDM with mediolateral oblique DBT 23, and DBT without FFDM 24, none of these solutions to the increased dose have yet achieved wide acceptance.

On the other hand, Warren et al. demonstrated that image processing has a significant impact on image quality 25. Furthermore, Fukuda et al. developed image processing for DBT 14. We applied this image processing technique to DBT in combination with SM and we obtained diagnostic performance not inferior to that of conventional FFDM and with dose lower than that of conventional FFDM. We believe that our results of finding no significant difference in the AUC, sensitivity, and specificity of DBT plus SM at 90%, 75% and 55% the dose setting of FFDM in this study are reasonable and are consistent with the works of Skanne et al. 9 and Gennaro et al. 26 in terms of the diagnostic performance of DBT plus SM versus FFDM. More importantly, the AGD of DBT plus SM in this study was less than that of FFDM, even though there was no significant difference in diagnostic performance in comparison with FFDM. We attribute the reason to the positive difference the reconstruction algorithm we used made. Generally, the image quality of DBT reconstructed by an iterative method is better than that by reconstructed by filtered back projection 27.

In our study, dose reduction was our top priority. If the dose of DBT were to be increased to be the same as conventional FFDM, image quality improvement could be expected, and so we believe that the diagnostic performance would also be improved. There was a cancer that 3 out of 8 radiologists were missed in our study, the size of the mass was 4 mm and the breast density was extremely dense. We believe that detection could be possible by increasing the dose.

Our study has several limitations. First, since the study population includes both diagnostic and screening cases, we explored the possibility that a high number of large cancers were included, and that might be a factor in the
non-inferior performance. However, on investigation, we found the cancer sizes were almost the same size as other similar studies \(^6,7,28\), and so we believe the influence of cancer size in this study is small.

Secondly, while the follow-up interval for benign cases and biopsy-proven benign cases would preferably be two years, the follow-up in our study was one year, and the same interval as in a similar study \(^29\).

A third limitation of our study is the sufficiency of investigating the reducible dose levels. We chose the dose levels in this study from the results of our preliminary investigation using whole breast specimens. Although we are not able to separate the AGD and diagnostic performance differences between the filtered back projection and iterative methods, we were able to determine the diagnostic performance of two combinations of dose and reconstruction algorithms: DBT plus SM with filtered back projection at 90% dose setting of FFDM and DBT plus SM with an iterative method at 75% dose setting of FFDM.

The last limitation of our study is that it was conducted at a single site. Although we confirmed the diagnostic performance of DBT plus SM for the population and conditions at our site, further study with more subjects from multiple sites is necessary to generalize this result.

Future work is further evaluation of the diagnostic performance for DBT plus SM at the 55% dose setting of FFDM is necessary because this highest dose reduction was partly simulated rather than entirely through exposure reduction.

5. Conclusion

In this enriched study population, diagnostic performance of digital breast tomosynthesis, whether reconstructed either by a filtered back projection or an iterative method, plus synthesized mammography at lower-dose than full-field digital mammography was not inferior to full-field digital mammography.

Acknowledgements

The authors would like to thank N. Tsunoda, Y. Nishino, R. Yokoi, and Y. Araki of the National Hospital Organization Higashi Nagoya National Hospital; Y. Ota, A. Kato, S. Moritani, M. Hasegawa, T. Kuroishi, T. Hayashi, M. Yasue, T. Takizaki, A. Ando, Y. Horikawa, W. Hayashi, K. Yonezawa, H. Sasada, E. Matsuda, N. Yamaguchi, O. Esaki, and Y. Hirofuji of the National Hospital Organization Nagoya Medical Center; M. Tawara of the National Hospital Organization Kanazawa Medical Center for the breast cancer examination and helpful discussion and scientific debate, and R.A. Uzenoff of FUJIFILM Medical Systems U.S.A., Inc. for the English language review.

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