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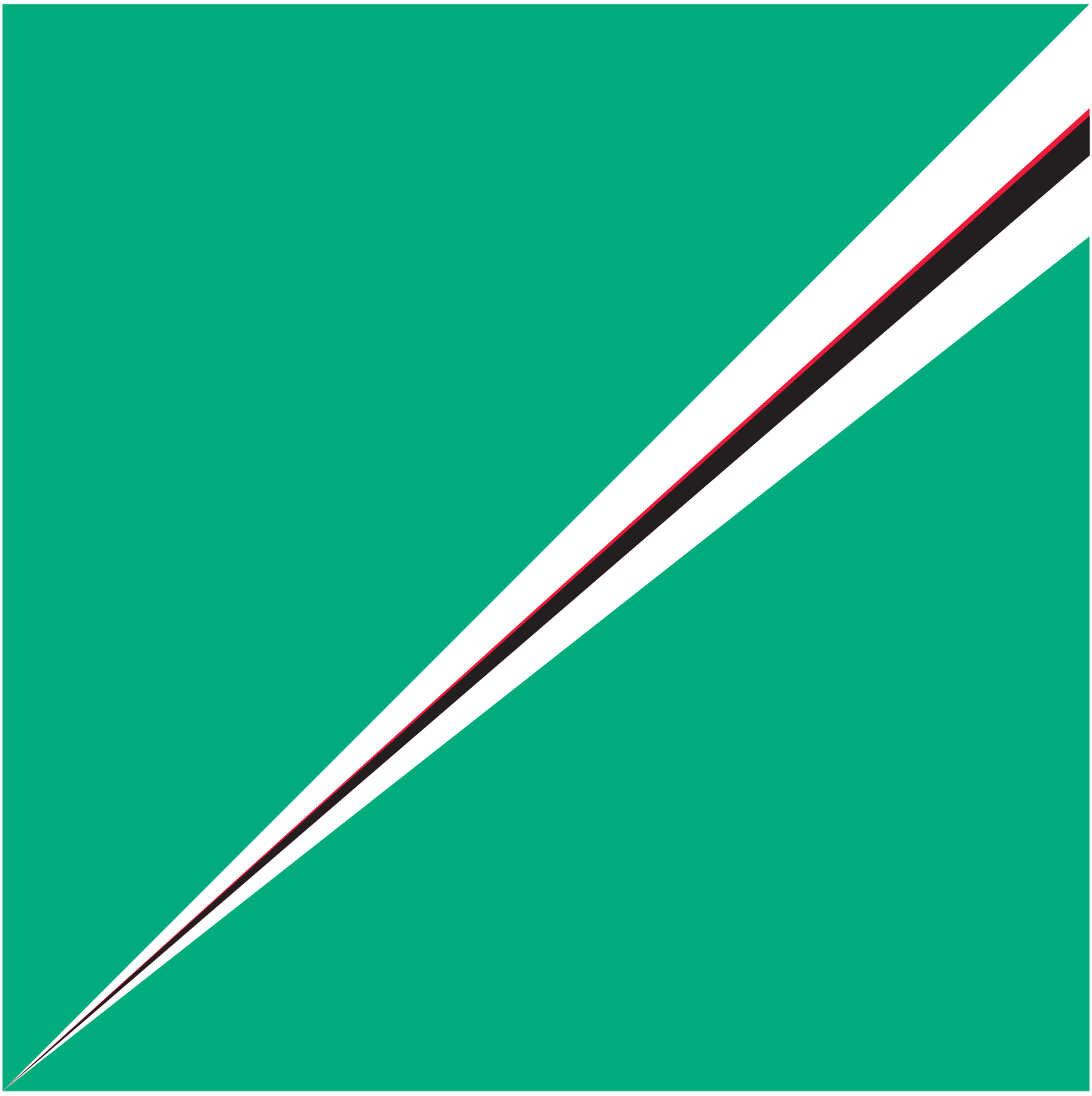
富士フイルム研究報告



## PURPOSE OF PUBLICATION

This publication is issued in order to introduce the results of research and development carried out in the laboratories of FUJIFILM Corporation and its subsidiaries. This collection includes the papers, which are newly written or have already been published in various science and technology journals, regarding our noteworthy new products and novel technologies.

## 刊 行 の 趣 旨

富士フイルム株式会社および関連会社が行なった研究開発活動の成果を紹介するために，本誌を発行する。多くの事業分野から特筆すべき新製品およびそれらに盛り込まれた技術をとりあげ，本誌に投稿された書き下ろし論文と，科学技術誌等に掲載された論文の転載により解説する。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# Foreword

**Teiichi Goto**
**Director, Senior Vice President**
**FUJIFILM Corporation**

The healthcare business of Fujifilm is striving to further enhance the quality of life of people worldwide by leveraging the group's extensive range of products, service and technology accumulated to date as a comprehensive healthcare company encompassing wide-ranging business relating to people's health, from diagnosis, treatment and prevention.

The starting point of the business of the "diagnosis" field goes back to the launch of "X-ray film" in 1936 soon after the company foundation. Ever since, the company continues to expand the domain of "diagnosis" with medical equipment including digital X-ray diagnostic imaging system "FCR", "FUJIFILM DR", endoscope system, in-vitro diagnostic system and ultrasound diagnostic equipment as well as "SYNAPSE" the medical-use picture archiving and communications systems (PACS)" and radioactive diagnostic agent.

To make a leap forward in the "treatment" field, we acquired Toyama Chemical Co., Ltd., a drug developing company with strength in infectious disease and anti-inflammation in 2008 and made a full-scale entry into the treatment field.

In the "diagnosis" field, Fujifilm released FCR5000M, a digital X-ray diagnostic imaging system (mammography devices) for breast cancer screening in 2000. Breast cancer is the number one cancer of women but is a disease that can be cured with high probability with early detection. Various types of diagnostic equipment have been developed for breast cancer examination, but it is only the mammography system that has proved to reduce the death rate through screening. Our company is continuing to add new proprietary technology to the breast X-ray diagnosis system to realize high-resolution and minimally invasive screening. We have been putting special effort in the development of mammography in the overall medical systems business as we aspire to contribute to the society with early detection of breast cancer.

Fujifilm released its first DR type digital mammography system "AMULET" in October 2008, "AMULET f/s" in 2011 and "AMULET Innovality" in 2013. To commemorate the AMULET series achieving accumulated sales of over 4000 units, the 63rd issue of FUJIFILM RESEARCH & DEVELOPMENT will be featuring "AMULET Innovality."

The mammography system of our company combines material synthesis technology, image generation technology and image processing technology at the most advanced level. The tomosynthesis function which significantly improved the acquiring ability of images of tumors or other lesion is a function achieved from our proprietary image technology. This issue covers the clinical effect and associated technology of the tomosynthesis function.

Ever since our company first digitalized the X-ray image in the world, we have been pursuing technology that can only be made possible by digitalization. We will continue to address the changes in the market with agility and utilize AI and ICT technology for our product portfolio in the mammography field to continuously develop and create new value to protect the daily happiness and wellbeing of all women and their beloved ones.

# Preface

This special issue, No.63, 2019, features mammography. Mammography is a breast-specific X-ray, and is one of the most successful diagnostic imaging methods, that is essential for early detection of breast cancer.

In this issue, the highlight is the technology behind the digital mammography system - AMULET Innovality, ASPIRE Cristalle is the trade name of AMULET Innovality in the United States (product name FDR MS-3500) - developed by Fujifilm, that achieved both a good breast cancer diagnostic and clinical performance.

Following the latest report on breast cancer diagnostic performances, we asked Dr. Endo, the director of the Japan Central Organization on Quality Assurance of Breast Cancer Screening, to write an article which is titled, *Comparison of Diagnostic Performance of Low Dose Tomosynthesis plus Synthesized Mammography versus Digital Mammography*. The article discusses the combinational diagnostic performance of a tomographic image and synthetic 2D image. The tomographic image obtained by tomosynthesis to find obscure lesions hidden in the mammary gland, that are difficult to diagnose with conventional 2D mammography. The synthetic 2D image generated from tomosynthesis with a reduced radiation dose.

The feature of the issue is then introduced, AMULET Innovality in *Development of Digital Mammography System "AMULET Innovality" for Examining Breast Cancer* (FUJIFILM RESEARCH & DEVELOPMENT No. 59).

A technical description of AMULET Innovality's X-ray detector, which is particularly important in digital mammography systems, is introduced, consisting of *A newly developed a-Se mammography flat panel detector with high-sensitivity and low image artifact* (Proceeding of SPIE, Medical Imaging 2013: Physics of Medical Imaging, 8668, 86685V).

In addition, to the feature on AMULET Innovality's Dual-mode tomosynthesis, we also provide their technical explanation in the article, *Fujifilm's Innovative Mammography "AMULET Innovality" Provides Optimal Tomosynthesis-Imaging for Diagnosis and Screening* (FUJIFILM RESEARCH & DEVELOPMENT No.62), and the systems clinical efficacy in *Detectability comparison of modes in dual-mode digital breast tomosynthesis* (Breast Cancer. 2017 May;24(3):442-450).

Lastly, the reconstruction techniques that are applied to the super-resolution, and iterative methods, all of which are features of the AMULET Innovality tomosynthesis images, are introduced in *Improved Tomosynthesis Reconstruction using Super-resolution and Iterative Techniques* (FUJIFILM RESEARCH & DEVELOPMENT No. 61), and the clinical efficacy of this reconstruction technology is discussed in *Diagnostic performance of digital breast tomosynthesis and full-field digital mammography with new reconstruction and new processing for dose reduction* (Breast Cancer. 2018 Mar; 25(2):159-166).

We hope that this issue will give you an insight into the clinical efficacy of mammography and an understanding of the AMULET Innovality system.

# FUJIFILM RESEARCH & DEVELOPMENT

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### Original



### Reprints



* Co-researcher outside FUJIFILM Corporation

# 巻頭言

富士フイルム株式会社
取締役・常務執行役員
後藤 禎一

富士フイルムの医療ビジネスは，人々の健康に関わる「診断」から「治療」，「予防」の領域まで，健康の維持・回復を横断的に手掛けることのできる幅広い技術と視野を持った「トータルヘルスケアカンパニー」として，グループの持つ製品・サービス・これまで蓄積してきた技術を生かし，「人々の生活の質のさらなる向上」に取り組んでいます。

「診断」領域のビジネスの原点は，創業間もない 1936 年の「X 線フィルム」の発売にまでさかのぼります。その後，世界で初めて X 線画像のデジタル化を実現した，デジタル X 線画像診断システム「FCR」をはじめ，「FUJIFILM DR」，内視鏡システム，血液診断システム，超音波画像診断システムなどの医療機器や，医用画像情報ネットワークシステム「SYNAPSE」や放射性診断薬など，「診断」は領域を次々と拡大しております。

さらに「治療」領域に対し，一層の飛躍を図るため，2008 年に感染症・抗炎症などに強みを持つ創薬メーカーである富山化学工業をグループに迎え，医薬品事業に本格参入しました。

「診断」領域において，当社は，女性のがんで罹患率の第 1 位である乳がん検査用のデジタル X 線画像診断装置（マンモグラフィ装置）として 2000 年に FCR5000MA を市場導入しました。乳がんは，早期発見で治癒する確率が非常に高い疾患です。乳がん検査用にはさまざまな診断機器が開発されていますが，検診による死亡率低下の効果が認められている唯一の検査がマンモグラフィ検査です。当社は乳房 X 線診断装置に，独自の新しい技術を搭載し続けることで，高精細かつ低侵襲な検査を実現し，早期乳がんの発見で社会に貢献する事を目標に，当社のメディカルシステム事業の中でも力を入れて開発を進めてまいりました。

2008 年 10 月に当社初の DR 方式のデジタルマンモグラフィ装置である「AMULET」，2011 年に「AMULET f/s」，さらに 2013 年に「AMULET Innovality」を販売開始しました。今回，AMULET シリーズ累計で 4000 台を突破したことを記念し，富士フイルム研究報告 63 号は，「AMULET Innovality」の特集号として発刊することといたしました。

当社のマンモグラフィ装置は，当社の強みである独自の材料合成技術，画像生成技術，画像処理技術を最高レベルで結集させた装置です。腫瘤などの病変画像の描出能を大幅に向上させた Tomosynthesis 機能は独自の画像技術から実現した機能です。本研究報告では Tomosynthesis 機能による臨床効果と関連技術についてまとめました。

当社は，X 線画像を世界で初めてデジタル化して以来，デジタルならではの技術を追求してきました。今後も，市場の変化に素早く対応し，当社が保有する製品群に AI・ICT 技術を活用し，マンモグラフィ領域においても一人でも多くの女性とその方の周囲の大切な方（家族，友人，恋人）の日常の幸せを守るために継続的に新しい価値を創出し，開発し続けてまいります。

# はじめに

富士フイルム研究報告 No.63 は「マンモグラフィ」の特集です。マンモグラフィとは乳房専用の X 線撮影のことで，乳がんの早期発見に欠かすことのできない，最も有効な画像診断方法のひとつです。

今号では，富士フイルムが開発したデジタルマンモグラフィシステム「AMULET Innovality」（米国製品名 ASPIRE Cristalle, 販売名 FDR MS-3500）の乳がん診断性能と臨床性能を達成するために搭載されている技術について取り上げたいと思います。

はじめに，最新の乳がん診断の性能に関して、日本乳がん検診精度管理中央機構の理事長である遠藤登喜子先生に『低線量トモシンセシス＋合成マンモグラフィと従来マンモグラフィとの診断性能比較』と題して書き下ろしていただきました。この論文では、断層像と合成 2D の組み合わせの診断性能を報告しています。断層像はトモシンセシス撮影から得られ、従来のマンモグラフィ撮影で診断が難しい乳腺内に隠れて見にくい病変を見つけ出すことが期待されます。合成 2D は断層像から合成され、被ばく低減のために使われることが期待されます。

続いて，AMULET Innovality そのものの特徴として AMULET Innovality 本体の開発内容を『乳がん検査用デジタル X 線撮影装置「AMULET Innovality」の開発』（富士フイルム研究報告 No.59 より転載，本誌 14 ページ）で紹介します。

デジタルマンモグラフィシステムで特に重要な X 線検出に対して，AMULET Innovality の X 線検出器の技術的な解説を『AMULET Innovality 向け六角形画素 FPD の開発』（Proceeding of SPIE より転載，本誌 17 ページ）で紹介します。

さらに，AMULET Innovality のトモシンセシス撮影の特徴である Dual-mode Tomosynthesis について，その技術的な解説を『診断と検診のそれぞれに最適なトモシンセシス撮影ができる富士フイルムのイノベーティブ・マンモグラフィ「AMULET Innovality」』（富士フイルム研究報告 No.62 より転載。本誌 44 ページ）で紹介し，その臨床効果を『デュアルモードトモシンセシスの検出性能の比較』（Breast Cancer より転載，本誌 26 ページ）で紹介します。

AMULET Innovality のトモシンセシス撮影で得られた画像の特徴である超解像と逐次法を応用した再構成技術を『超解像と逐次法を応用したトモシンセシス再構成技術の開発』（富士フイルム研究報告 No.61 より転載, 本誌 59 ページ）で紹介し, この再構成技術の臨床効果を『線量低減を目的とした新しい再構成のトモシンセシスおよび新しい画像処理のマンモグラフィの診断性能』（Breast Cancer より転載，本誌 65 ページ）で紹介します。

本特集が皆様にとってマンモグラフィそのものの有効性や AMULET Innovality の理解への端緒となれば幸いです。

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## 原　著



## 転　載



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

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## Abstract

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.

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## 1. Introduction

The usefulness of digital breast tomosynthesis (DBT) for both diagnosis and screening has been reported [1-8]. 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 [9-12]. 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 $cm^2$) 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™; 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[17] was 1.5mGy. 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[18] 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[19] score of 1, 2, 3-1, 3-2, 4, or 5, adapted from a forced Breast Imaging Reporting and Data System (BI-RADS®) categorization[20], 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 1 Details of cases for each cohort

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

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

[a] FAD = focal asymmetric density, DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma

[b] Numbers are lesion sizes in millimeters

Table 2 Radiologist experience and diagnostic performance for radiologists in the cohort of DBT at 90% dose of FFDM

| | | Sensitivity | | Specificity | | AUC | |
|---|---|---|---|---|---|---|---|
| Radiologist | Years of experience[a] | DBT plus SM | FFDM | DBT plus SM | FFDM | DBT plus SM | FFDM |
| 1 | 18 | 71.4% | 66.7% | 92.4% | 95.5% | 86.2% | 84.1% |
| 2 | 14 | 66.7% | 88.1% | 77.3% | 87.9% | 76.6% | 90.7% |
| 3 | 26 | 90.5% | 95.2% | 92.4% | 87.9% | 86.9% | 93.9% |
| 4 | 18 | 78.6% | 88.1% | 81.8% | 83.3% | 83.4% | 87.7% |
| 5 | 16 | 76.2% | 83.3% | 81.8% | 86.4% | 83.7% | 87.3% |
| 6 | 21 | 73.8% | 73.8% | 80.3% | 89.4% | 81.5% | 84.2% |
| 7 | 7 | 66.7% | 66.7% | 87.9% | 92.4% | 85.2% | 80.9% |
| 8 | 33 | 85.7% | 85.7% | 74.2% | 72.7% | 85.8% | 84.7% |
| Mean | 19 | 76.2% | 81.0% | 83.5% | 86.9% | 83.6% | 86.7% |
| Median | 18 | 75.0% | 84.5% | 81.8% | 87.9% | 84.4% | 86.0% |
| Range | 7-33 | 66.7%-90.5% | 66.7%-95.2% | 74.2%-92.4% | 72.7%-95.5% | 76.6%-86.9% | 80.9%-93.9% |

Note.—DBT = digital breast tomosynthesis, FFDM = full-field digital mammography, SM = synthesized mammography, AUC = area under the receiver operating characteristic curve.

[a]Years of experience in interpreting mammograms.

Table 3 Diagnostic performance for radiologists in the cohorts of DBT at 75% and 55% dose of FFDM

| | Sensitivity | | | Specificity | | | AUC | | |
|---|---|---|---|---|---|---|---|---|---|
| Radiologist | DBT (75%) plus SM | DBT (55%) plus SM | FFDM | DBT (75%) plus SM | DBT (55%) plus SM | FFDM | DBT (75%) plus SM | DBT (55%) plus SM | FFDM |
| 1 | 85.1% | 83.3% | 83.3% | 90.6% | 90.4% | 94.2% | 89.8% | 89.9% | 87.9% |
| 2 | 89.4% | 77.1% | 72.9% | 86.8% | 88.5% | 92.3% | 89.9% | 86.2% | 91.6% |
| 3 | 76.6% | 72.9% | 75.0% | 94.3% | 92.3% | 92.3% | 91.8% | 84.3% | 86.7% |
| 4 | 80.9% | 75.0% | 85.4% | 94.3% | 90.4% | 92.3% | 88.6% | 86.2% | 91.6% |
| 5 | 80.9% | 79.2% | 79.2% | 94.3% | 82.7% | 88.5% | 90.1% | 87.8% | 88.1% |
| 6 | 87.2% | 83.3% | 77.1% | 79.2% | 84.6% | 90.4% | 92.8% | 93.3% | 90.0% |
| 7 | 78.7% | 75.0% | 75.0% | 92.5% | 90.4% | 84.6% | 87.6% | 92.8% | 86.9% |
| 8 | 85.1% | 70.8% | 79.2% | 83.0% | 86.5% | 86.5% | 91.3% | 83.5% | 87.0% |
| Mean | 83.0% | 77.1% | 78.4% | 89.4% | 88.2% | 90.1% | 90.2% | 88.0% | 88.7% |
| Median | 83.0% | 76.0% | 78.1% | 91.5% | 89.4% | 91.3% | 90.0% | 87.0% | 88.0% |
| Range | 76.6%-89.4% | 70.8%-83.3% | 72.9%-85.4% | 79.2%-94.3% | 82.7%-92.3% | 84.6%-94.2% | 87.6%-92.8% | 83.5%-93.3% | 86.7%-91.6% |

Note.—DBT = digital breast tomosynthesis, FFDM = full-field digital mammography, SM = synthesized mammography, AUC = area under the receiver operating characteristic curve.

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

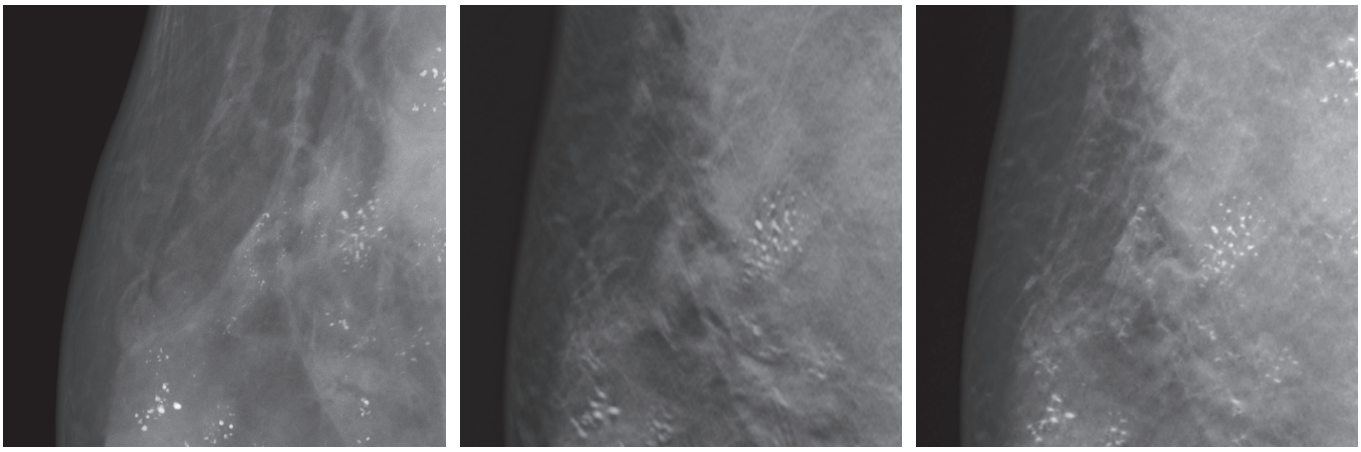
### 3.1 Cancer and Other Cases

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.

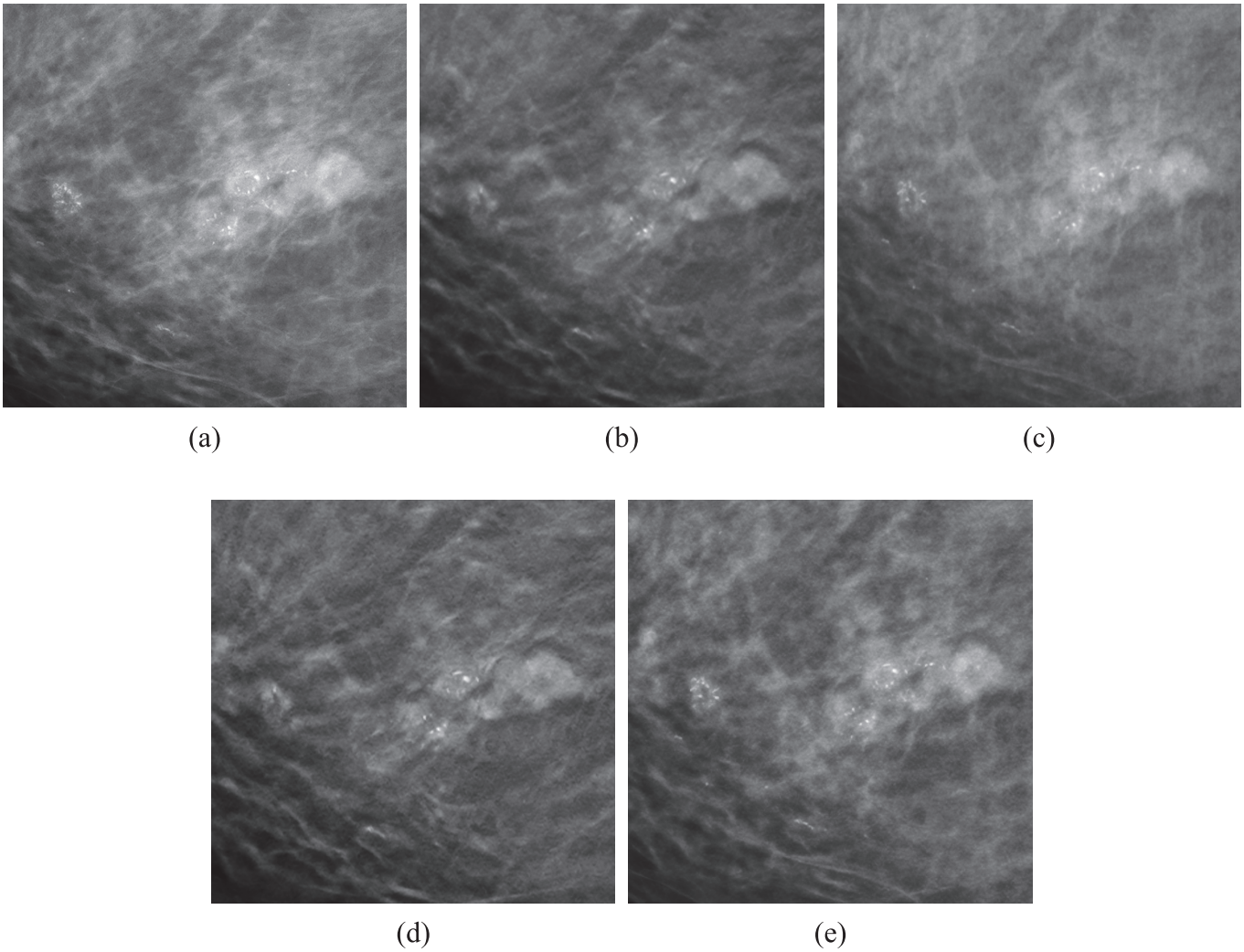
### 3.2 AGD

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



(a) (b) (c)

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.



(a) (b) (c)

(d) (e)

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 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 Skaane et al. [6,9], diagnostic by Gennaro et al. [21], 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 Skaane 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.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## References


1) Poplack, Steven P.; Tosteson, Tor D.; Kogel, Christine A.; Nagy, Helene M. Digital breast tomosynthesis: initial experience in 98 women with abnormal digital screening mammography. American Journal of Roentgenology. 2007, 189(3), p.616-623.
2) Gur, David; Abrams, Gordon S.; Chough, Denise M.; Ganott, Marie A.; Hakim, Christiane M.; Perrin, Ronald L. et al. Digital Breast Tomosynthesis: Observer Performance Study. American Journal of Roentgenology. 2009, 193(2), p.586-691.
3) Spangler, M. Lee; Zuley, Margarita L.; Sumkin, Jules H.; Abrams, Gordan; Ganott, Marie A.; Hakim, Christiane et al. Detection and Classification of Calcifications on Digital Breast Tomosynthesis and 2D Digital Mammography: A Comparison. American Journal of Roentgenology. 2011, 196(2), p.320-324.
4) Bernardi, Daniela; Ciatto, Stefano; Pellegrini, Marco; Tuttobene, Paolina; Fanto', Carmine; Valentini, Marvi et al. Prospective Study of Breast Tomosynthesis as a Triage to Assessment in Screening. Breast Cancer Research and Treatment. 2012, 133(1), p.267-271.
5) Skaane, Per; Gullien, Randi; Bjørndal, Hilde; Eben, Ellen B.; Ekseth, Ulrika; Haakenaasen, Unni et al. Digital Breast Tomosynthesis (DBT): Initial Experience in a Clinical Setting. Acta Radiologica. 2012, 53(5), p.524-529.
6) Skaane, Per; Bandos, Andriy I.; Gullien, Randi; Eben, Ellen B.; Ekseth, Ulrika; Haakenaasen, Unni et al. Comparison of Digital Mammography Alone and Digital Mammography Plus Tomosynthesis in a Population-based Screening Program. Radiology. 2013, 267(1), p.47-56.
7) Rafferty, Elizabeth A.; Park, Jeong Mi; Philpotts, Liane E.; Poplack, Steven P.; Sumkin, Jules H.; Halpern, Elkan F. et al. Assessing Radiologist Performance using Combined Digital Mammography and Breast Tomosynthesis Compared with Digital Mammography Alone: Results of a Multicenter, Multireader Trial. Radiology. 2013, 266(1), p.104-113.
8) Vedantham, Srinivasan; Karellas, Andrew; Vijayaraghavan, Gopal R.; Kopans, Daniel B. Digital Breast Tomosynthesis: State of the Art. Radiology. 2015, 277(3), p.663-684.
9) Skaane, Per; Bandos, Andriy I.; Eben, Ellen B.; Jebsen, Ingvild N.; Krager, Mona; Haakenaasen, Unni et al. Two-view Digital Breast Tomosynthesis Screening with Synthetically Reconstructed Projection Images: Comparison with Digital Breast Tomosynthesis with Full-field Digital Mammographic Images. 2014, Radiology 271(3), p.655-663.
10) Zuley, Margarita L.; Guo, Ben; Catullo, Victor J.; Chough, Denise M.; Kelly, Amy E.; Lu, Amy H. et al. Comparison of Two-dimensional Synthesized Mammograms versus Original Digital Mammograms Alone and in Combination with Tomosynthesis Images. Radiology 271(3):664-671.
11) Olgar, T; Kahn, T; Gosch, D. Average Glandular Dose in Digital Mammography and Breast Tomosynthesis. Fortschr Röntgenstr. 2012, 184(10), p.911-918.

12) Sechopoulos, Ioannis. A Review of Breast Tomosynthesis. Part I. The Image Acquisition Process. Medical Physics. 2013, 40(1), 014301.
13) Nuyts, John; De Man, Bruno; Dupont, Patrick; Defrise, Michel; Suetens, Paul; Mortelmans, Luc. Iterative Reconstruction for Helical CT: a Simulation Study. Physics in Medicine & Biology. 1998, 43(4), p.729-737.
14) Fukuda, Wataru; Morita, Junya; Yamada, Masahiko. Improved Tomosynthesis Reconstruction using Super-resolution and Iterative Techniques. FUJIFILM RESEARCH & DEVELOPMENT. 2016, 61, p.1-7.
15) Fukuda, Wataru; Morita, Junya; Yamada, Masahiko. Improved Tomosynthesis Reconstruction using Super-resolution and Iterative Techniques. FUJIFILM RESEARCH & DEVELOPMENT. 2016, 61, p.1-7, http://www.fujifilm.com/about/research/report/061/, (accessed 2016-09-26).
16) Fukuda, Wataru. Evelopment of Newly 3D-mammography with Super-resolution and Iterative Tomosynthesis Reconstruction(Chikuji-chokaizo-saikousei Ni Yoru Atarashii 3D Mammography No Kaihatsu in Japanese). JIRA Technical Report. 2016, 26(2), p.20-21.
17) Van Engen, R.; Van Wouldenberg, S.; Bosmans, H.; Young, K.; Thjissen, M. "European Protocol for the Quality Control of the Physical Aspects of Mammography Screening-screen-film Mammography". European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis. 4th ed, Luxembourg, European Communities, 2006. p.61-104, 92-79-01258-4.
18) Kak, Avinash C.; Slaney, Malcolm. Principles of Computerized Tomographic Imaging. IEEE Press, 1988, 329p., 0879421983.
19) "Record of Findings(Syoken no kisai in Japanese)". Japan Radiological Society, Japanese Society of Radiological Technology. Mammography Guideline. 3rd Supplemental ed., Igaku Shoin, 2014, p.61-68, 978-4-260-01965-1.
20) ACR BI-RADS Atlas. 5th ed., Reston, Va, American College of Radiology, 2013, 978-1-55903-016-8.
21) Gennaro, Gisella; Hendrick, R. Edward; Ruppel, Patricia; Chersevani, Roberta; di Maggio, Cosimo; La Grassa, Manuela et al. Performance Comparison of Single-view Digital Breast Tomosynthesis Plus Single-view Digital Mammography with Two-view Digital Mammography. European radiology. 2013, 23(3), P.664-672.
22) Svahn, T; Andersson, I; Chakraborty, D; Svensson, S; Ikeda, D; Förnvik, D. et al. The Diagnostic Accuracy of Dual-view Digital Mammography, Single-view Breast Tomosynthesis and a Dual-view Combination of Breast Tomosynthesis and Digital Mammography in a Free-response Observer Performance Study. Radiation Protection Dosimetry. 2010, 139(1-3), p.113-117.
23) Gennaro, Gisella; Hendrick, R. Edward; Toledano, Alicia; Paquelet, Jean R.; Bezzon, Elisabetta; Chersevani, Roberta et al. Combination of One-view Digital Breast Tomosynthesis with One-view Digital Mammography Versus Standard Two-view Digital Mammography: per Lesion Analysis. European Radiology. 2013, 23(8), p.2087-2094.
24) Wallis, Matthew G.; Moa, Elin; Zanca, Federica; Leifland, Karin; Danielsson, Mats. Two-View and Single-View Tomosynthesis Versus Full-Field Digital Mammography: High-Resolution X-Ray Imaging Observer Study. Radiology. 2012, 262(3), p.788-796.
25) Warren, Lucy M.; Given-Wilson, Rosalind M.; Wallis, Matthew G.; Cooke, Julie; Halling-Brown, Mark D.; Mackenzie, Alistair et al. The Effect of Image Processing on the Detection of Cancers in Digital Mammography. American Journal of Roentgenology. 2014, 203(2), p.387-393.
26) Gennaro, Gisella; Toledano, Alicia; di Maggio, Cosimo; Baldan, Enrica; Bezzon, Elisabetta; La Grassa, Manuela et al. Digital Breast Tomosynthesis Versus Digital Mammography: a Clinical Performance Study. European Radiology. 2010, 20(7), p.1545-1553.
27) Sechopoulos, Ioannis; A Review of Breast Tomosynthesis. Part II. Image Reconstruction, Processing and Analysis, and Advanced Applications. Medical Physics. 40(1), 014302.
28) Rafferty, Elizabeth A.; Park, Jeong Mi; Philpotts, Liane E.; Poplack, Steven P.; Sumkin, Jules H.; Halpern, Elkan F. et al. Diagnostic Accuracy and Recall Rates for Digital Mammography and Digital Mammography Combined with One-view and Two-view Tomosynthesis: Results of an Enriched Reader Study. American Journal of Roentgenology. 2014, 202(2), p.273-281.
29) Svahn, T. M.; Chakraborty, D. P.; Ikeda, D.; Zackrisson, S.; Do, Y.; Mattsson, et al. Breast Tomosynthesis and Digital Mammography: a Comparison of Diagnostic Accuracy. British Institute of Radiology. 2012, 85(1019), e1074-e1082.

## Trademarks

## Editorial Note

So far, FUJIFILM RESEARCH & DEVELOPMENT have comprehensively covered themes on a wide range of technical fields of FUJIFILM. In this special issue No.63, theme is “mammography”. We decided to focus on one technology and systematically take up the individual elements that make up that technology. We would be extremely delighted if this report will provide you an opportunity to deepen your understanding.

Hiroyuki Yoneyama
Editorial Staff

## 編 集 後 記

富士フイルム研究報告は，これまで富士フイルムが有する幅広い技術分野を網羅的に取り上げてきましたが，第 63 号はこれまでと趣向を変え，マンモグラフィーに関する技術の特集号として発行することといたしました。一つの技術に絞り，それを構成する要素を体系的に取り上げることで，当社の技術をご理解いただく一助となれば幸いです。

（編集人　米山　博之）





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