

## Original article

# Advantage of digital breast tomosynthesis combined with standard digital mammography over standard digital mammography alone in surveillance for local recurrent breast cancer in patients with breast conservative treatment

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**Background:** Although breast conserving therapy (BCT) offers more advantages in addition to the competitive survival rate over the traditional treatment of mastectomy, post-BCT surveillance for cancer recurrence remains challenging.

**Objectives:** The purpose of this study was to compare rates of indeterminate findings of standard digital mammography (DM) plus digital breast tomosynthesis (DBT) and DM alone in patients who had undergone BCT at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

**Methods:** We retrospectively enrolled 150 post-BCT patients who had regular follow-up visits for cancer surveillance by radiological imaging at least for two years at the hospital from January 1, 2013 to December 31, 2014. Rates of indeterminate findings were estimated and then compared between the group of DM plus DBT and the other group of DM alone at 6-month, 12-month, 18-month and 24-month follow-up visits.

**Results:** The average age of the enrolled patients was 54 years, ranging from 33 to 86 years. The majority of them had not received intraoperative radiation therapy (IORT). Of those 150 patients, 31 patients (20.7%) had indeterminate findings on DM. These indeterminate findings were clarified by DBT. It was found that all asymmetrical density lesions on DM were able to be clarified by DBT ( $P < 0.001$ ). On the contrary, a significant number of additional mass lesion were detected by DBT at 6-month follow-up visits ( $P = 0.031$ ).

**Conclusion:** The addition of DBT to DM significantly lowered rates of the indeterminate finding of asymmetrical density for surveillance in post-BCT patients.

**Keywords:** Breast cancer, breast conservative treatment, digital breast tomosynthesis, digital mammography, intraoperative radiation therapy.

Breast cancer is one of the most common cancers globally. It is also the leading cause of cancer-related death in women. Breast cancer is also the most common cancer of women in Thailand. According to hospital-based cancer registry annual report in 2017, there are 780 new cases of breast cancer in women (incident rate about 35 cases per 1,000 people), followed by cervical cancer and colorectal cancer.<sup>(1)</sup> The combination of early detection and effective

treatment significantly reduce the mortality rate of breast cancer. Long-term appropriate surveillance programs are necessary for both screening and follow up.

Multiple observational studies show that patients treated with breast conservative treatment (BCT) had better survival rate or equal than those treated with mastectomy for early stage breast cancer.<sup>(2-4)</sup> BCT consists of breast conserving surgery, axillary lymph node assessment and radiotherapy. Intraoperative radiation therapy (IORT) combines with surgery were performed in some cases, especially for patients in early stage breast cancer without any metastasis.<sup>(5-7)</sup> Some prior studies found that the IORT group demonstrated a higher incidence of fat necrosis and parenchymal scarring over a following

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time on mammogram. <sup>(8-9)</sup> However, some studies were show no statistically significant difference between the IORT and whole breast irradiation groups in the incidence of architectural distortion, dystrophic calcifications, skin retraction, or mass density. <sup>(10)</sup>

Digital mammography (DM) is a quick, economy and non-invasive study with low doses radiation exposure. However, there are two major limitations. First, low sensitivity (poor visibility of the lesion) occasionally caused by dense glandular tissue located above and/or below an interested lesion. <sup>(11-13)</sup> Second, low specificity in some circumstances. <sup>(11-13)</sup> For example, two or more normal features that are only vertically separated can appear to be the projection of a lesion of interest.

Digital breast tomosynthesis (DBT) is an imaging technique that acquires mammographic projections at different angles in an arc over the breast, which are reconstructed into a series of thin-slice images to provide three-dimensional (3D) information through the whole breast. The potential benefits of DBT include reducing the diagnostic challenges associated with superimposed breast tissues and allowing better visualization of the individual planes of breast tissue. <sup>(11-13)</sup> As a consequence of these benefits, sensitivity and specificity of breast cancer detection are increased. A major concern for DBT is increasing of patient's radiation exposure, however a minimally higher dose may be acceptable.

Advantage of combine DBT with DM is clearly known in screening populations, <sup>(14-16)</sup> however the benefit in breast conservative surveillance is not well established. At King Chulalongkorn Memorial Hospital, both DM and DBT were routinely performed for surveillance after BCT. There is insufficient evidence to show that combined DM and DBT are superior to DM alone. We retrospectively reviewed to prove that the addition of DBT to DM can significantly reduce the rates of indeterminate findings for surveillance in breast conservative patients with or without IORT compared to DM alone at King Chulalongkorn Memorial Hospital. This may reduce unnecessary follow up studies, repeat mammography and/or biopsies.

## Materials and methods

### *Patients*

From our radiological and clinical databases, we retrospectively identified 150 female patients who had undergone BCT with or without intraoperative radiotherapy (IORT) and regularly follow-up imaging

after BCT including both DM and DBT as routine surveillance at least two years in King Chulalongkorn Memorial Hospital between January 1, 2013 and December 31, 2014. In a total of 150 cases, 2 cases were confirmed diagnosis by tissue pathology (one benign and one malignancy), 16 cases were confirmed by ultrasonography and 132 cases were confirmed by negative follow up data for two years. The study was approved by the research ethics committee of Faculty of Medicine at our training center.

### *Imaging technique and interpretation*

Routine mammogram and digital breast tomosynthesis were performed by using standard mediolateral oblique (MLO) views and craniocaudal (CC) views, using Selenia Dimensions Mammography System, Hologic, Massachusetts, USA. The researcher and a breast radiologist interpreted digital mammography and then additional digital breast tomosynthesis in the same date for each patient with consensus imaging interpretation.

### *Data collection*

Hospital electronic medical records and synapses were searched for 150 female patients who underwent breast conservative treatment and performed both DM and DBT as routine surveillance at least two years at King Chulalongkorn Memorial Hospital between January 1, 2013 and December 31, 2014. We also reviewed patient ages, breast density, breast cancer pathology and treatment, histopathology and treatment modality (with or without IORT), and radiographic follow-up data for at least two years after BCT.

Patients who were not fulfilled criteria, including poor image quality and patients with no evidence to confirm diagnosis or loss to follow-up were excluded from our study.

The DM and DBT images of post-treatment breasts were retrospectively reviewed for each patient by consensus imaging interpretation of the 5 - year experience breast radiologist and the researcher with blinded final diagnosis. Lesion characteristics including asymmetrical density, architectural distortion, microcalcification and mass were recorded. Lesions those need additional imaging studies for clarification were defined as an indeterminate finding. The consensus of all imaging findings was retrospectively compared with the gold standards, which are tissue pathology and/or ultrasonography and/or negative 2 - year follow-up data.

**Statistical analysis**

Descriptive statistics was used for demographic data including number (percentage), mean and standard deviation. McNemar’s test was performed for comparing lesion characteristics between DM plus DBT and DM alone. Comparing lesion characteristics during follow-up in each group was analyzed using Cochran’s Q test. Statistical analysis was performed by using the Statistical Package for Social Sciences software (SPSS) version 15.0. Results were considered statistically significant if *P* - value was less than 0.05.

**Results**

A total of one hundred fifty female patients who had undergone breast conservative treatment and surveillance with both DM and DBT were enrolled. The average age of the enrolled patients was 54 years, ranging from 33 to 86 years.

Histopathology of breast cancers were invasive carcinoma for one hundred twenty-four patients (82.7%) and ductal carcinoma in situ in twenty-six patients (17.3%). Breast density of almost cases was heterogeneously dense breast (90.7%). Twenty-one patients (14.0%) have been treated with intraoperative

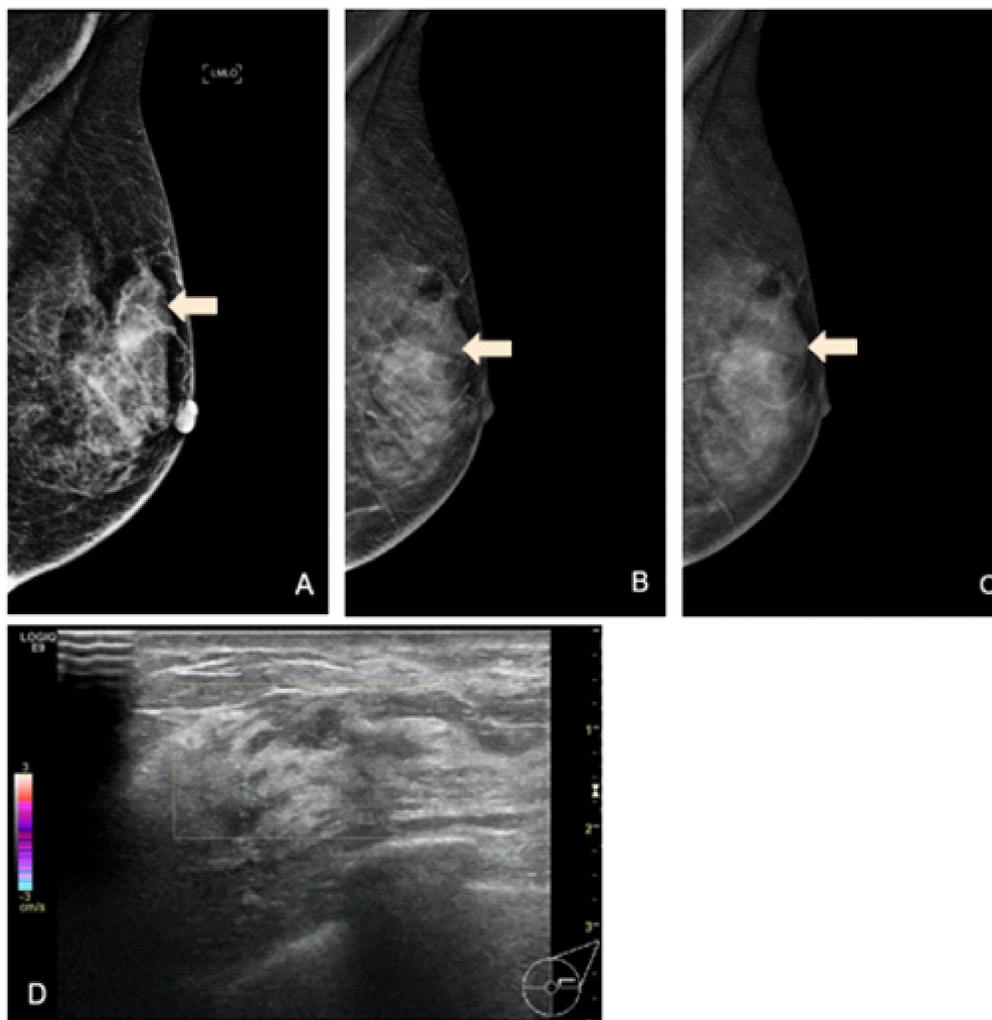
radiation therapy. Demographic characteristics are shown in (Table 1).

Of those 150 patients, 31 patients (20.7%) had indeterminate findings on DM. These indeterminate findings were clarified by DBT.

At 6, 12, 18 and 24 months follow-up data, there were 116, 171, 129 and 149 breast lesions were detected on DM, respectively. The majority of lesions were architectural distortions; 85 (96.6%), 126 (96.2%), 90 (94.7%) and 108 (95.6%) lesions by follow up at 6, 12, 18 and 24 months, respectively. BCT scar were subsequently confirmed by ultrasonography in all of these architectural distortions. All asymmetrical density lesions were clarified by using DBT and became either normal fibroglandular tissue (Figure 1) or well-circumscribed mass (Figure 2). Detection of mass lesion at a 6-month follow-up visit is higher in DBT plus DM than in DM alone. Most of them show as post-operative seroma or hematoma by ultrasonography. There was no difference between DM alone and DM plus DBT for detected architectural distortion and microcalcification. Table 2 shows the number of lesions by lesion characteristics at 6, 12, 18 and 24 months follow-up.

**Table 1.** Demographic characteristics.

Patient characteristics	n = 150 (%)
<b>Age (years) – Mean (SD)</b>	54 (11.0)
<40	18 (12.0)
40 - 49	33 (22.0)
50 - 59	51 (34.0)
60 - 69	36 (24.0)
>70	12 (8.0)
<b>Pathology</b>	
Invasive carcinoma	124 (82.7)
Ductal carcinoma in situ	26 (17.3)
<b>Laterality</b>	
Right	75 (50.0)
Left	75 (50.0)
<b>Breast density</b>	
Predominantly fatty	1 (0.7)
Scattered fibroglandular	8 (5.3)
Heterogeneously dense	136 (90.7)
Extremely dense	5 (3.3)
<b>Intraoperative radiation therapy</b>	
No	129 (86.0)
Yes	21 (14.0)



**Figure 1.** A 67-year-old female patient who had undergone BCT at left upper outer quadrant for surveillance at 6 months, (A) DM left MLO view shows suspicious asymmetrical density and architectural distortion at left upper outer quadrant (arrow). (B and C) DBT left MLO views show only normal fibroglandular tissue at left upper outer quadrant (arrows). (D) Ultrasonography of left breast shows irregular hypoechoic lesion and prominent ducts at left upper outer quadrant, no mass is demonstrated. Finally, it is post-treatment change confirmed by radiologically stable for the 2-year follow-up with mammography and ultrasonography.

It has confirmed that DM and DBT had a significantly lowered rates of the indeterminate finding of asymmetrical density for surveillance in post-BCT patients compared to DM alone at all of follow up times (at 6 months 0.0% vs. 15.9%  $P < 0.001$ , at 12 months 0.0% vs. 12.2%  $P < 0.001$ , at 18 months 0.0% vs. 13.7%  $P < 0.001$  and at 24 months 0.0% vs. 11.5%  $P < 0.001$ ). Nevertheless, DBT and DM also increases sensitivity in mass detection at 6 months follow up (9.1% vs. 2.3%  $P = 0.031$ ).

The study also demonstrates the improvement of asymmetrical density interpreted in post BCT without IORT group at all range of follow up times (at 6 months 0.0% vs. 17.9%  $P < 0.001$ , at 12 months 0.0% vs. 11.7%  $P < 0.001$ , at 18 months 0.0% vs. 13.3%

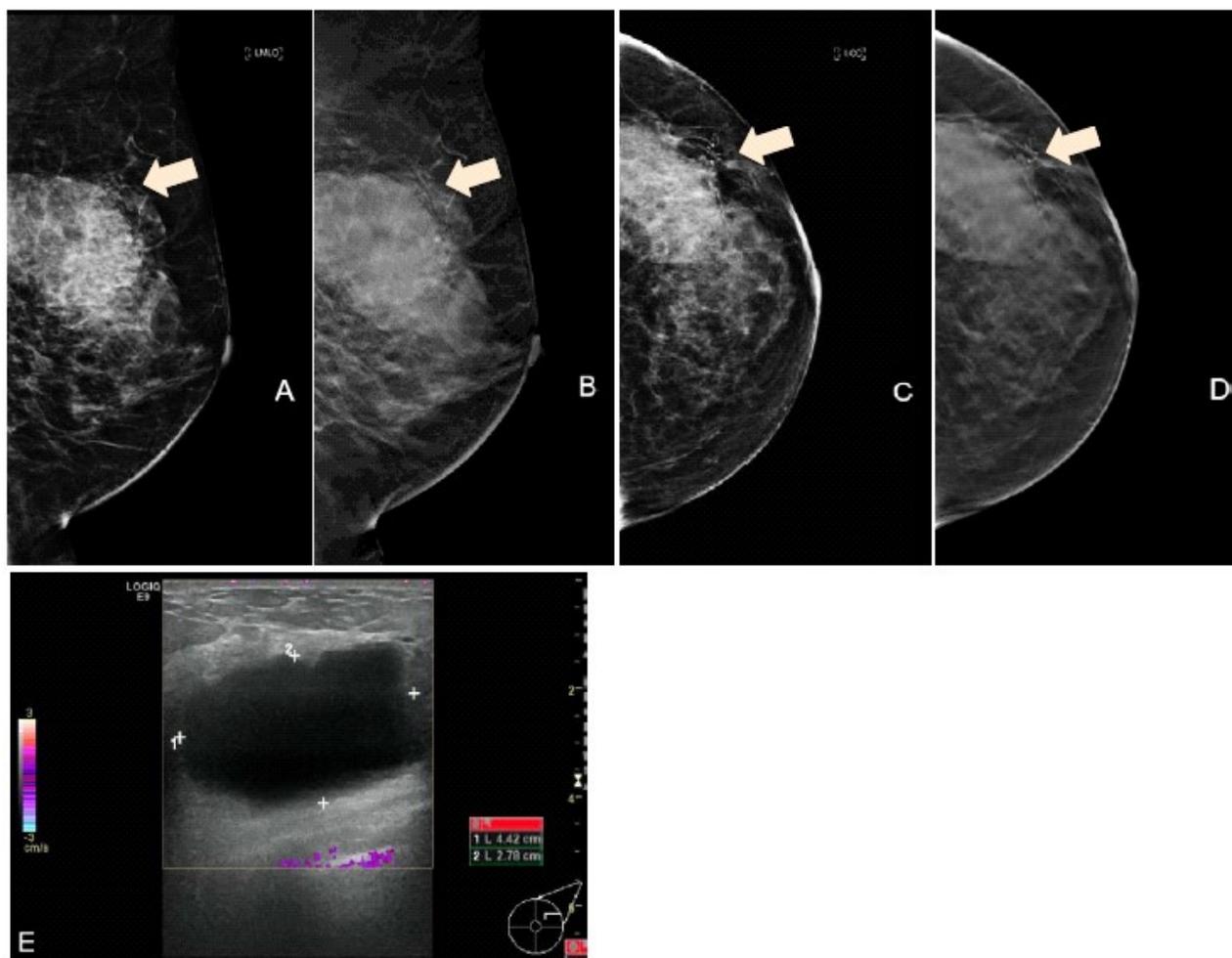
$P = 0.002$  and at 24 months 0.0% vs. 10.8%  $P = 0.002$ ).

One hundred and twenty-nine of 150 patients were treated with breast conserving surgery without IORT, 27 patients (20.9%) had indeterminate findings on DM that were clarified by using DBT. The most common lesions were architectural distortion. There was no difference in most common lesions detected between with IORT and without IORT group. All of asymmetrical density lesions were clarified by using DBT in both with IORT and without IORT group. Asymmetrical density lesions were seen in IORT group more than without IORT group except at 6 months follow up. Table 3 shows these lesions by type.

There are only 36 patients who had follow-up studies every six months for two years. Number of microcalcification lesions found at 6, 12, 18 and 24 months follow-up are 5, 8, 9 and 10 cases, respectively in both DM and DM plus DBT groups. There is a statistic significantly in the increasing microcalcifications detected at least once over a follow up times in both DM alone and DM plus DBT groups ( $P = 0.015$ ) while asymmetrical density, architectural distortion and mass detected are not

significant difference during 2 years study. (Table 4) shows number of lesions by follow up times.

Only one patient had biopsy-confirmed malignant lesions (invasive ductal carcinoma) and this lesion was detected on DM as an asymmetrical density but DBT clarified as a mass (Figure 3). Another patient had a biopsy which is not malignancy (foreign body granuloma). An abnormal microcalcification was identified on both DBT and DM in this patient.



**Figure 2.** A 56-year-old female patient who had undergone BCT at left upper outer quadrant for surveillance at 6 months, (A and C) DM left MLO and left CC views show suspicious asymmetrical density and architectural distortion at left upper outer quadrant (arrows). (B and D) DBT left MLO and left CC views show well-circumscribed isodense mass at left upper outer quadrant (arrows). (E) Ultrasonography of left breast shows a 2.8 x 4.4 cm cystic lesion without internal vascularity at left upper outer quadrant, probably seroma or hematoma.

**Table 2.** Number of lesions detected on DM and DBT plus DM in all post BCT breasts at 6, 12, 18 and 24 months follow-up, by lesion characteristics.

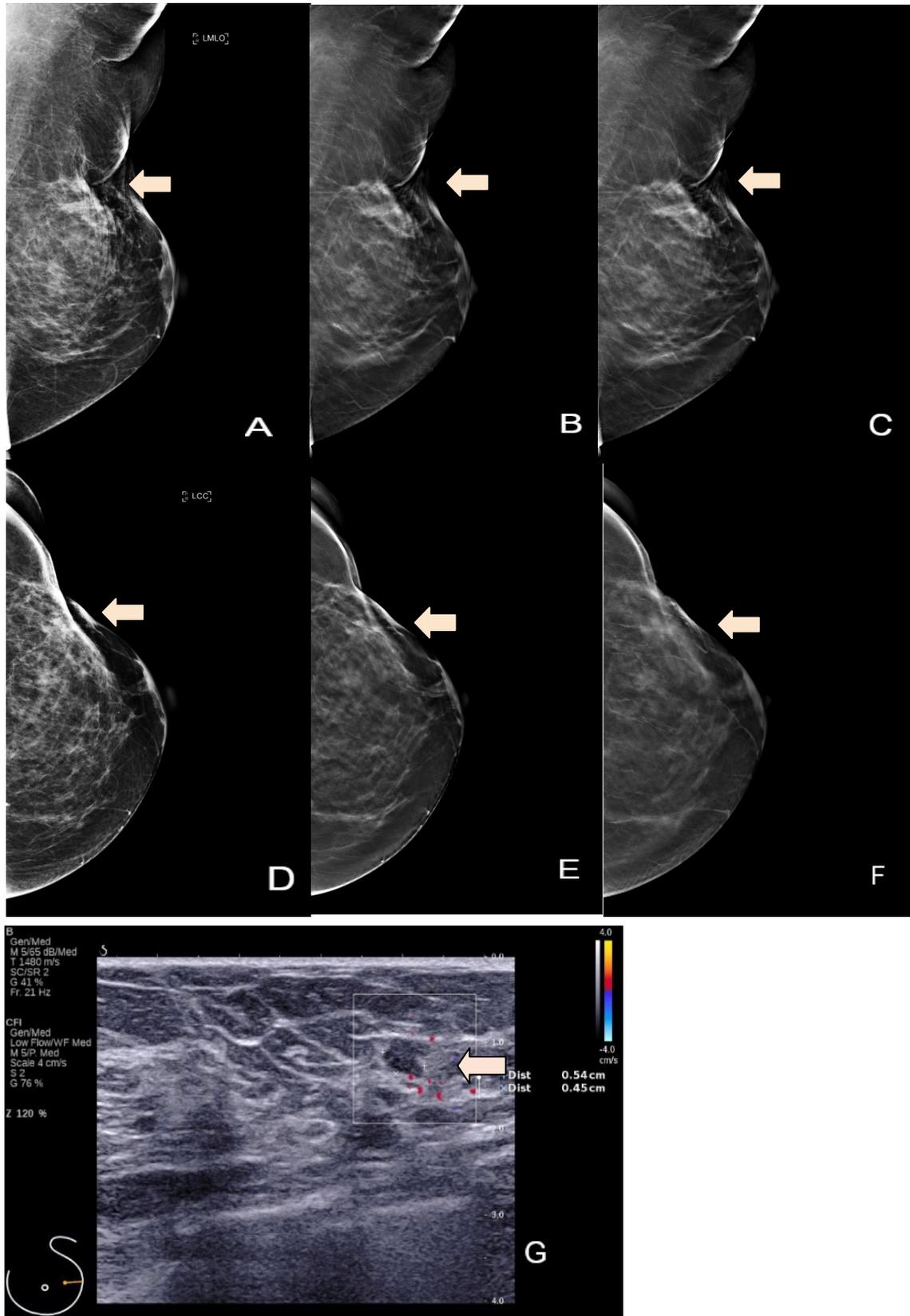
Lesion characteristics	DM (%)	DM + DBT (%)	<i>P</i> - value
<b>At 6 months (n = 88)</b>			
Asymmetrical density	14 (15.9)	0 (0.0)	<0.001
Architectural distortion	85 (96.6)	85 (96.6)	1.000
Microcalcification	15 (17.0)	15 (17.0)	1.000
Mass lesion	2 (2.3)	8 (9.1)	0.031
<b>At 12 months (n = 131)</b>			
Asymmetrical density	16 (12.2)	0 (0.0)	<0.001
Architectural distortion	126 (96.2)	126 (96.2)	1.000
Microcalcification	20 (15.3)	20 (15.3)	1.000
Mass lesion	9 (6.9)	13 (9.9)	0.219
<b>At 18 months (n = 95)</b>			
Asymmetrical density	13 (13.7)	0 (0.0)	<0.001
Architectural distortion	90 (94.7)	88 (92.6)	1.000
Microcalcification	20 (21.1)	20 (21.1)	1.000
Mass lesion	6 (6.3)	11 (11.6)	0.063
<b>At 24 months (n = 113)</b>			
Asymmetrical density	13 (11.5)	0 (0.0)	<0.001
Architectural distortion	108 (95.6)	108 (95.6)	1.000
Microcalcification	23 (20.4)	23 (20.4)	1.000
Mass lesion	5 (4.4)	8 (7.1)	0.25

DM = digital mammography; DBT = digital breast tomosynthesis

**Table 3.** Number of lesions detected on DM and DBT plus DM in all post BCT breasts with IORT and without IORT at 6, 12, 18 and 24 months follow-up, by lesion characteristics.

Lesion characteristics	IORT		<i>P</i> - value	IORT		<i>P</i> - value
	No	Yes		No	Yes	
	DM (%)	DM + DBT (%)		DM (%)	DM + DBT (%)	
<b>At 6 months</b>						
	<b>(n = 67)</b>			<b>(n = 21)</b>		
Asymmetrical density	12 (17.9)	0 (0.0)	<0.001	2 (9.5)	0 (0.0)	0.5
Architectural distortion	65 (97.0)	65 (97.0)	1.0	20 (95.2)	20 (95.2)	1.0
Microcalcification	12 (17.9)	12 (17.9)	1.0	3 (14.3)	3 (14.3)	1.0
Mass lesion	1 (1.5)	5 (7.5)	0.125	1 (4.8)	3 (14.3)	0.5
<b>At 12 months</b>						
	<b>(n = 111)</b>			<b>(n = 20)</b>		
Asymmetrical density	13 (11.7)	0 (0.0)	<0.001	3 (15.0)	0 (0.0)	0.25
Architectural distortion	108 (97.3)	108 (97.3)	1.0	18 (90.0)	18 (90.0)	1.0
Microcalcification	15 (13.5)	15 (13.5)	1.0	5 (25.0)	5 (25.0)	1.0
Mass lesion	6 (5.4)	9 (8.1)	0.375	3 (15.0)	4 (20.0)	1.0
<b>At 18 months</b>						
	<b>(n = 75)</b>			<b>(n = 20)</b>		
Asymmetrical density	10 (13.3)	0 (0.0)	0.002	3 (15.0)	0 (0.0)	0.25
Architectural distortion	71 (94.7)	70 (93.3)	1.0	19 (95.0)	18 (90.0)	1.0
Microcalcification	14 (18.7)	14 (18.7)	1.0	6 (30.0)	6 (30.0)	1.0
Mass lesion	3 (4.0)	6 (8.0)	0.25	3 (15.0)	5 (25.0)	0.5
<b>At 24 months</b>						
	<b>(n = 93)</b>			<b>(n = 20)</b>		
Asymmetrical density	10 (10.8)	0 (0.0)	0.002	3 (15.0)	0 (0.0)	0.25
Architectural distortion	90 (96.8)	90 (96.8)	1.0	18 (90.0)	18 (90.0)	1.0
Microcalcification	18 (19.4)	18 (19.4)	1.0	5 (25.0)	5 (25.0)	1.0
Mass lesion	4 (4.3)	5 (5.4)	1.0	1 (5.0)	3 (15.0)	0.5

DM = digital mammography; DBT = digital breast tomosynthesis; IORT = intraoperative radiation therapy



**Figure 3.** A 67-year-old female patient who had undergone BCT at left upper outer quadrant (pathology = invasive ductal carcinoma grade 2 with extensive ductal carcinoma in situ) for surveillance at 6 months, (A and D) DM left MLO and left CC views show suspicious asymmetrical density and architectural distortion at left outer mid part (arrows). (B, C, E and F) DBT left MLO and left CC views show irregular shape mass with indistinct margin at left outer mid part (arrows). (E) Ultrasonography of left breast shows a 4.5 x 5.4-mm well-defined lobulated hypoechoic nodule without definite internal vascularity at left outer mid part, suspicious lesion for recurrence. Then she went to re-excision (pathology = invasive ductal carcinoma grade 3 with 10.0% ductal carcinoma in situ).

**Table 4.** Number of lesions in each lesion characteristic by 6, 12, 18 and 24 months follow-up.

	DM (n = 36)		DM + DBT (n = 36)	
	Lesions (n) (%)	P-value	Lesions (n) (%)	P-value
<b>Asymmetrical density</b>		0.861		
6 months	6 (16.7)		0 (0.0)	
12 months	6 (16.7)		0 (0.0)	
18 months	5 (13.9)		0 (0.0)	
24 months	5 (13.9)		0 (0.0)	
<b>Architectural distortion</b>		0.194		0.392
6 months	34 (94.4)		34 (94.4)	
12 months	33 (91.7)		33 (91.7)	
18 months	35 (97.2)		33 (91.7)	
24 months	33 (91.7)		33 (91.7)	
<b>Microcalcification</b>		0.015		0.015
6 months	5 (13.9)		5 (13.9)	
12 months	8 (22.2)		8 (22.2)	
18 months	9 (25.0)		9 (25.0)	
24 months	10 (27.8)		10 (27.8)	
<b>Mass lesion</b>		0.187		0.468
6 months	2 (5.6)		5 (13.9)	
12 months	4 (11.1)		6 (16.7)	
18 months	4 (11.1)		6 (16.7)	
24 months	2 (5.6)		4 (11.1)	

DM = digital mammography; DBT = digital breast tomosynthesis

## Discussion

Several recent studies have reported benefits of combined DBT and DM over DM alone for reducing indeterminate findings and increasing cancer detection rates. (4 - 17) However, most of the studies are performed in screening program. (14-16) We design a retrospective study to evaluate benefit of additional DBT to DM for surveillance in breast cancer patients who had undergone BCT with or without IORT treatment. Several changes in post BCT breasts e.g. masses, fluid collection, increased breast density, skin thickening, architectural distortion and calcifications may reduce sensitivity rate of recurrence tumor detection by limiting compressibility of the breast and obscure tumor recurrence. (18 - 19)

Although the percentage of lesion characteristics between DM alone and DM plus DBT were different, this study fails to demonstrate with statistical significance due to a small sample size in each subgroup of IORT. There was no significant difference of mass lesion between 6 months follow up in both IORT group and no IORT group.

DBT and DM increases sensitivity in mass detection at 6 months follow up. This may explain by mass-like lesion (post-operative seroma/hematoma)

which frequently found early in post-operation and usually resolved later.

There is a statistical significance in the increasing microcalcification detected while asymmetrical density, architectural distortion and mass detected are not increasing during 2-years follow-up. The possible reason of this finding is dystrophic calcification which usually found after radiation.

Our study demonstrates no significant difference in cancer detection rates between DM alone and DBT with DM because only one case of recurrence cancer from enrolled 150 patients in this study.

There are some limitations to the study. First, as it is a retrospective study some patients did not complete follow-up imaging at 6, 12, 18 and 24 months after BCT. Therefore, number of cases in each period of follow-up time were not the same. The study found that most of patients were followed-up at 12 and 24 months. Second, this study was done in a single center.

## Conclusion

The addition of DBT to DM significantly lowered rates of the indeterminate finding of asymmetrical density for surveillance in post-BCT patients.

### Conflict of interest

The authors, hereby, declare no conflict of interest.

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