Original Article

Acta Radiologica
1–9

DOI: 10.1177/02841851221112562
journals.sagepub.com/home/acr
SAGE

Comparison of malignant calcification identification between breast cone-beam computed tomography and digital mammography

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Abstract

Background: Calcifications are important abnormal findings in breast imaging and help in the diagnosis of breast cancer.
Purpose: To compare breast cone-beam computed tomography (CBCT) with digital mammography (DM) in terms of the ability to identify malignant calcifications.
Material and Methods: In total, 115 paired examinations were performed utilizing breast CBCT and DM; 86 pathology-proven malignant lesions with calcifications detected on DM and 29 randomly selected breasts without calcifications were reviewed by three radiologists. The ability to detect calcifications was assessed on CBCT images. The characterization agreement of two imaging modalities was evaluated by the kappa coefficient. For breast CBCT images, the parameters for the display of calcifications were recorded. The Kruskal–Wallis test was used to compare the preferred slice thickness chosen by each of the three radiologists. The degree of calcification clarity was compared between two modalities using the Mann–Whitney *U*-test.
Results: The combined sensitivity and specificity of three radiologists in 85 DM-detected calcifications detection on breast CBCT images were 98.43% (251/255) and 98.85% (86/87), respectively. CBCT images showed substantial agreement with mammograms in terms of the characterization of calcifications morphology ($k = 0.703$; $P < 0.05$) and distribution ($k = 0.629$; $P < 0.05$). CBCT images with a slice thickness of 0.273 mm and three-dimensional maximum-intensity projection (3D-MIP) were more beneficial for calcifications identification. No statistically significant difference was found between standard DM views and CBCT images for three radiologists on calcification display clarity.
Conclusion: CBCT images were comparable to mammograms in calcification identification and may be sufficient for malignant calcifications detection and characterization.

Keywords
Calcifications, BI-RADS, digital mammography, cone-beam computed tomography

Date received: 26 October 2021; accepted: 21 June 2022

Introduction

Calcifications are one of the most common abnormal findings on mammography screening (1). The characteristics of calcifications on mammograms were defined in the 5th edition of the Breast Imaging Reporting and Data System (BI-RADS) published by the American College of Radiology (ACR) in 2013 (2). The specific morphology and distribution patterns of calcifications convey the risk of breast cancer, particularly changes in calcifications during follow-up (3,4). Moreover, the presence of calcifications and their characteristics have been proven to be strong indicators of the breast cancer molecular subtype (5).

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Digital mammography (DM) is considered the best technique for the identification and characterization of calcifications due to high spatial resolution. However, as a two-dimensional imaging modality, DM has unavoidable limitations, mainly including the masking effect caused by tissue overlapping.

A previous study has illustrated that calcifications can be demonstrated with equal or greater clarity using digital breast tomosynthesis (DBT) than DM (6,7), thus allowing for the improved interpretive analysis of detected calcifications. However, DBT is still a pseudo three-dimensional (3D) imaging modality based on DM in essence, accompanied by a limited angle, a limited slice thickness, and breast compression (8).

Commonly, as an insensitive imaging modality for the detection of calcifications (9), breast magnetic resonance imaging (MRI) is used to evaluate the vascularity of breast tumors to improve the positive predictive value after the administration of contrast agent (10,11). Moreover, women may be unable to undergo MRI examination because of pacemakers, non-titanium metallic implants, claustrophobia, high cost, or allergy to the gadolinium contrast agent (12–14).

Breast cone-beam computed tomography (CBCT) is an emerging 3D CT technology for breast imaging based on the principle of X-ray imaging (15–17). Prior studies have indicated the benefits and potential of CBCT in breast cancer imaging, including greater diagnostic accuracy and comfort than DM and comparable diagnostic sensitivity to MRI (18). These studies have demonstrated that breast CBCT effectively reduces the noise from overlapping structures and significantly improves the detectability of small lesions. Contrast-enhanced CBCT (CE-CBCT) provides tissue vascularity information that is not available from mammography, and many breast cancers have neovascularity that causes tumor enhancement after the injection of intravenous contrast material. Breast CBCT, including non-enhanced and enhanced images, combines the advantages of mammography in displaying calcifications and the ability of MRI to evaluate vascularity. Previous ex vivo studies have shown that breast CBCT has sufficiently high contrast and spatial resolution to detect calcifications as small as 231 μm at a dose of 7 mGy (19) and as small as 175 μm at a dose of 4 mGy (20). In addition, one study reported better performance than DM in simulated mass detection on breast CBCT images (21). As they are increasingly applied in clinics, the use for the detection and classification of calcifications on breast CBCT merits more research and attention.

To our knowledge, several studies have compared the clinical performance of breast CBCT and DM in the detection and diagnosis of breast cancer, but few studies have specifically addressed the display of calcifications. The aim of the present study was to focus only on the significance of breast CBCT, as a new breast imaging method, in the detection of calcifications and feature recognition. We considered DM as the reference standard of calcification detection and performed a retrospective analysis to assess the ability of calcifications detection and characteristic identification on breast CBCT images.

Material and Methods

Patients

From May 2012 to December 2019, the patients participated in a retrospective study that was approved by our institutional ethics committee and provided signed informed consent to admit the use of images in future research. The study coordinator, as well as a radiologist with >7 years of experience in breast imaging who was not involved in the subsequent imaging analysis, identified all patients with malignant calcifications on mammograms who underwent both pretreatment breast CBCT and mammography within seven days. The breasts were reviewed and included in this analysis. Some randomly selected DM-CBCT breast image pairs obtained during the same study period and identified without suspicious calcifications on both mammograms and CBCT images were added as the control group. The number of cases in the control group was determined by a ratio of 3:1 concerning the number of cases in the group with calcifications. A total of 86 breasts with mammographic calcifications and 29 breasts without calcifications on both mammograms and CBCT images were involved and organized as anonymous image sets at random for reading. The flow chart of patient selection is shown in Fig. 1.

Imaging examinations

DM was performed (Hologic, Selenia) and included standard craniocaudal (CC) and mediolateral oblique (MLO) views of the breasts, as well as additional magnified views of the suspicious lesion in some cases. All mammograms were acquired using Auto-Filter mode parameters.

Breast CBCT images were obtained with a CBCT system (KBCT-1000, Koning Corporation), which was approved by the U.S. Food and Drug Administration (FDA) in 2015. The X-ray tube voltage was set at a constant of 49 kVp. According to the breast size and density, the tube current was adjusted from 50 mA to 160 mA to obtain the optimal image quality at the lowest appropriate dose. In the present study, the tube current was in the range of 50–80 mA; accordingly, the radiation dose in one scan was 5.73 mGy for most breasts and 9.17 mGy for large breasts and breasts with dense fibroglandular tissue. During the scan, the patient was in a prone position, with one breast to be scanned hanging freely into the scanning field without compression at a time. To better observe the internal structure of the breast and the spatial distribution of calcifications, the projections

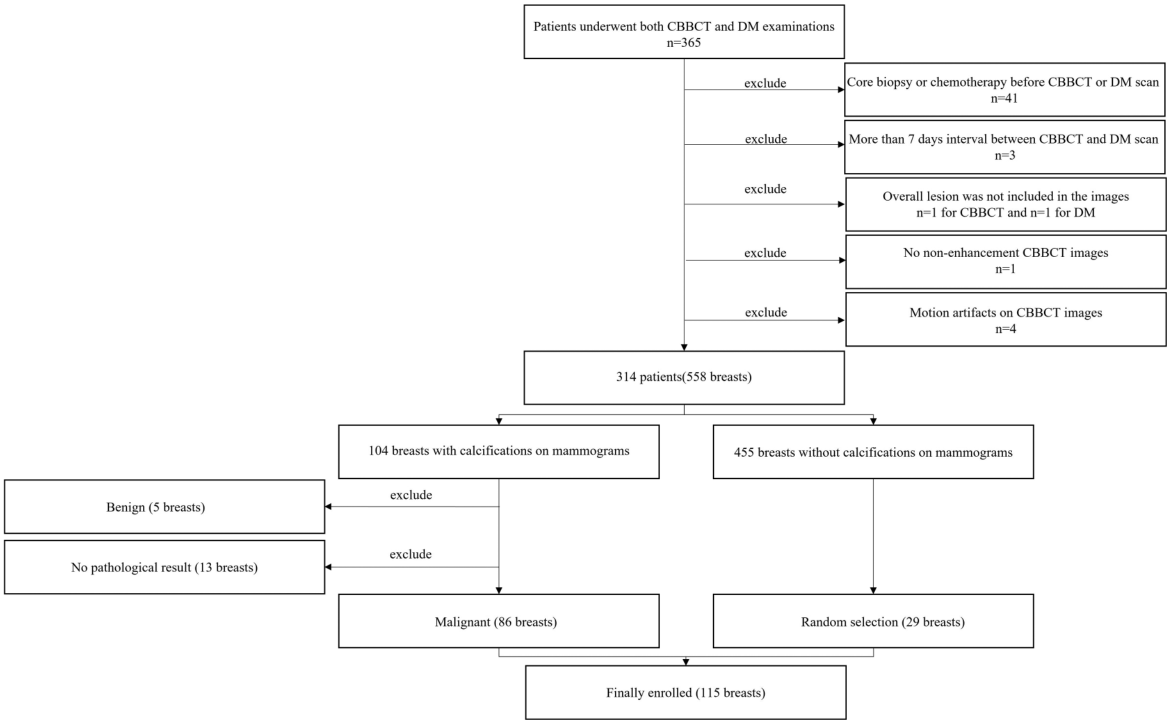

Fig. 1. Flow chart of patient selection.

were reconstructed with a skin-removed mode, that without the representation of the skin and in a voxel size of 0.273 mm^3. CE-CBCT images of the breast were not involved in this study.

Image analysis

The picture archiving and communicating system (PACS) and a high-resolution 5-MP monitor (Barco) were utilized to interpret all images, with mammograms displayed on standard and magnified views and breast CBCT images displayed on multiplanar reconstruction (MPR) images and three-dimensional maximum-intensity projection (3D-MIP). Three radiologists, with a range of 5–20 years of clinical experience in DM and 5–9 years of clinical experience in CBCT, blinded to patient history and any previous reports, read mammograms and CBCT images independently to identify the presence of calcifications in the breast. The performance of calcification detection on CBCT images was evaluated on the cases of DM-detected calcifications. The follow-up study was analyzed among the calcifications detectable on both imaging modalities by three radiologists. The characteristics of the calcifications were analyzed according to the BI-RADS descriptors, including an assessment of the morphology and distribution (2). A suspicious morphology was characterized as amorphous, coarse heterogeneous, fine pleomorphic, and fine linear or fine linear branching; the distribution could be assigned as diffuse, regional, grouped, linear, or segmental. The majority reports on morphology and distribution evaluation were generated from the consensus of three radiologists. For CBCT images, the slice thickness for calcifications displayed after MPR was adjusted by the radiologist, and the degree of calcification clarity was evaluated using the preferred thickness. The preferred thickness and whether the 3D-MIP was meaningful for displaying the spatial distribution were recorded. The score of calcifications clarity on mammograms was assessed with the standard views and magnified views, respectively. The two image sets (obtained by DM and CBCT) were read independently in sessions separated by at least four weeks.

Statistical analysis

Statistical analysis was performed with SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA), and the statistical significance level was $P = 0.05$. The performance of each radiologist in calcification detection on CBCT images was evaluated by sensitivity and specificity. The inter-observer agreement and the consistency between two imaging modalities on calcifications characteristics were evaluated by the kappa coefficient. Interpretation of the kappa coefficient was performed as characterized by Landis and Koch (22), with 0.21–0.40 denoting fair agreement, 0.41–0.60 indicating moderate agreement, 0.61–0.80 indicating substantial agreement, and 0.81–1.00 indicating almost perfect agreement. The Kruskal–Wallis test was used to compare the preferred slice thickness chosen by each of the three radiologists. A scale of 1–4 was used to indicate the degree of calcifications display clarity, ranging from poor to perfect. The degree of calcifications display clarity was compared between two modalities using the Mann–Whitney *U*-test.

Results

A total of 86 breasts from 86 patients (mean age = 48.95 ± 9.92 years) with mammographic calcifications and 29 breasts from 29 patients (mean age = 48.83 ± 7.00 years) without calcifications on both mammograms and CBCT images were involved in this study. There were no breasts with multiple calcification clusters.

Detection of calcifications

After three radiologists reviewed the image sets, one calcifications cluster was missed on DM. For the remaining 85 DM-detected calcifications, the combined sensitivity of the three radiologists was 98.43% (251/255), while the combined specificity was 98.85% (86/87) on breast CBCT images. The calcification detection performance of the individual radiologists is shown in Table 1. Eventually, 83 of 86 calcifications were identified on both imaging modalities by three radiologists. In 43 out of 83 breasts, additional magnified views of the suspicious lesion area were obtained.

Characterization of calcifications

The inter-observer agreement of calcification characterization calculated with a kappa test is shown in Table 2. As in the kappa values, it nearly had a substantial to almost perfect agreement ($P < 0.05$).

Table 1. Sensitivity and specificity of calcification detection on breast CBCT images.

	Radiologist 1	Radiologist 2	Radiologist 3
Sensitivity	98.82% (84/85)	97.65% (83/85)	98.82% (84/85)
Specificity	100% (29/29)	96.55% (28/29)	100% (29/29)

CBCT, cone-beam computed tomography.

Using the majority reports of the three radiologists, the consistency of the calcification characteristics was evaluated and compared between two imaging modalities. The CBCT images showed substantial agreement with the mammograms in terms of the calcification morphology ($\kappa = 0.703$; $P < 0.05$), and with slightly less agreement in terms of the calcification distribution ($\kappa = 0.629$; $P < 0.05$). The interpretations of calcification morphology and distribution for the two modalities are shown in Tables 3 and 4.

Display parameters on breast CBCT images

The set of 83 calcification clusters was used to analyze the appropriate display parameters, including the preferred selection of slice thickness and the 3D-MIP value evaluation in displaying the calcification morphology and spatial distribution. For most calcification clusters, a slice thickness of 0.273 mm on breast CBCT images was chosen as the preferred thickness for display by three radiologists (57.83% for radiologist 1, 48.19% for radiologist 2, and 45.78% for radiologist 3). The slice thicknesses chosen for different morphology types are shown in Table 5. There was no statistically significant difference in the preferred slice thickness chosen among the three radiologists. 3D-MIP was considered better than tomographic images for displaying the spatial distribution: 74.70% (62/83) for radiologist 1; 62.65% (52/83) for radiologist 2; and 72.29% (60/83) for radiologist 3. Regardless of the type of calcification spatial distribution, 3D-MIP was more meaningful for displaying the spatial distribution of calcifications clusters for all three radiologists (range = 63.46%–100% for radiologist 1, 50%–86.36% for radiologist 2, and 59.62%–100% for radiologist 3).

Clarity of calcifications

For the three radiologists, the display clarity of the calcifications was comparable between breast CBCT images and DM standard views, with no statistically significant difference for any radiologists ($P = 0.965$ for radiologist 1, $P = 0.107$ for radiologist 2, and $P = 0.447$ for radiologist 3) ($n = 83$). The interpretations of calcification clarity scores are shown in Table 6.

Table 2. Inter-observer agreement of calcifications characterization (kappa value, $p < 0.05$).

	DM		Breast CBCT	
	Morphology	Distribution	Morphology	Distribution
Radiologist 1 vs. radiologist 2	0.700	0.616	0.547	0.660
Radiologist 1 vs. radiologist 3	0.893	0.851	0.851	0.861
Radiologist 2 vs. radiologist 3	0.809	0.687	0.700	0.717

CBCT, cone-beam computed tomography; DM, digital mammography.

Table 3. Interpretations of calcifications morphology.

Calcifications morphology on breast CBCT images	Calcifications morphology on DM images				
	Amorphous	Coarse heterogeneous	Fine pleomorphic	Fine linear/ fine linear branching	Total
Amorphous	40	0	4	1	45
Coarse heterogeneous	0	0	1	0	1
Fine pleomorphic	3	0	25	2	30
Fine linear/ fine linear branching	0	0	3	4	7
Total	43	0	33	7	83

CBCT, cone-beam computed tomography; DM, digital mammography.

Table 4. Interpretations of calcifications distribution.

Calcifications distribution on breast CBCT images	Calcifications distribution on DM images					
	Diffuse	Regional	Grouped	Linear	Segmental	Total
Diffuse	0	0	0	0	0	0
Regional	1	2	0	0	0	3
Grouped	1	1	44	1	5	52
Linear	0	0	2	2	2	6
Segmental	0	1	2	1	18	22
Total	2	4	48	4	25	83

CBCT, cone-beam computed tomography; DM, digital mammography.

Table 5. Interpretations of slice thickness (in mm) chosen for different calcifications morphologies.

Calcifications morphology on breast CBCT images	Radiologist 1				Radiologist 2				Radiologist 3				*P* value
	0.273	0.5	1	2	0.273	0.5	1	2	0.273	0.5	1	2	
Amorphous	14	13	15	3	13	15	14	3	10	16	18	1	0.878
Coarse heterogeneous	1	0	0	0	1	0	0	0	1	0	0	0	-
Fine pleomorphic	27	3	0	0	21	7	2	0	22	7	1	0	0.125
Fine linear / fine linear branching	6	0	1	0	5	0	2	0	5	1	1	0	0.800
Total	48	16	16	3	40	22	18	3	38	24	20	1	0.447

CBCT, cone-beam computed tomography.

Table 6. Interpretations of calcifications clarity score.

	Radiologist 1	Radiologist 2	Radiologist 3
DM standard views	4 (2–4)	3 (2–4)	3 (2–4)
Breast CBCT images	3 (2–4)	3 (3–4)	3 (2–4)

Values are given as median (IQR).
CBCT, cone-beam computed tomography; DM, digital mammography; IQR, interquartile range.

Calcification clarity was compared among the standard and magnified views of the DM and breast CBCT images by Mann–Whitney *U*-test (n = 43) (Table 7). No statistically significant difference was found among the standard and magnified views of the DM and breast CBCT images for two of the three radiologists.

Discussion

Breast CBCT is a 3D imaging modality that images the entire breast with isotropic resolution and without compression, distortion, or overlapping (23,24). With the development of its clinical application, it is necessary to further clarify the characteristics of lesions on CBCT images. In this study, we found a good performance in the detection of calcifications and a performance comparable to DM in the characterization of calcifications on breast CBCT images. Moreover, MPR and 3D-MIP based on CBCT images provided more detailed information regarding calcification features.

It is the premise of the present study that the detection of calcifications on mammograms was considered as the inclusion criteria. The sensitivity and specificity of calcification detection on CBCT images were evaluated on the DM-detected calcifications. In addition, magnified views were performed on 43 breasts in our study, which pointed out the existence of suspicious lesions for radiologists when reviewing mammograms. Therefore, we did not compare the discrepancy between DM and CBCT in the detection of calcifications. Even so, it still showed good sensitivity and specificity for the detection of calcifications on breast CBCT images. In this study, two calcification clusters missed on CBCT images were identified as amorphous types on mammograms. Generally, the appearance of amorphous calcifications is not very clear on mammograms, especially when accompanied by dense parenchymal tissue or a high-density tumor background. Similarly, it is not very easy to identify this type of calcification on breast CBCT images. It is worth mentioning that even if calcifications cannot be detected clearly, the correct diagnosis could still be obtained by the combined evaluation of other features on breast CBCT images. Fig. 2 shows the mammograms in which a grouped amorphous calcification cluster was detected and the non-enhanced

Table 7. *P* value of Mann–Whitney *U*-test for evaluating the clarity discrepancy of calcifications.

	Radiologist 1	Radiologist 2	Radiologist 3
DM standard views vs. DM magnified views	0.305	0.003	0.242
DM standard views vs. breast CBCT images	0.852	0.509	0.766
DM magnified views vs. breast CBCT images	0.203	0.034	0.328

CBCT, cone-beam computed tomography; DM, digital mammography.

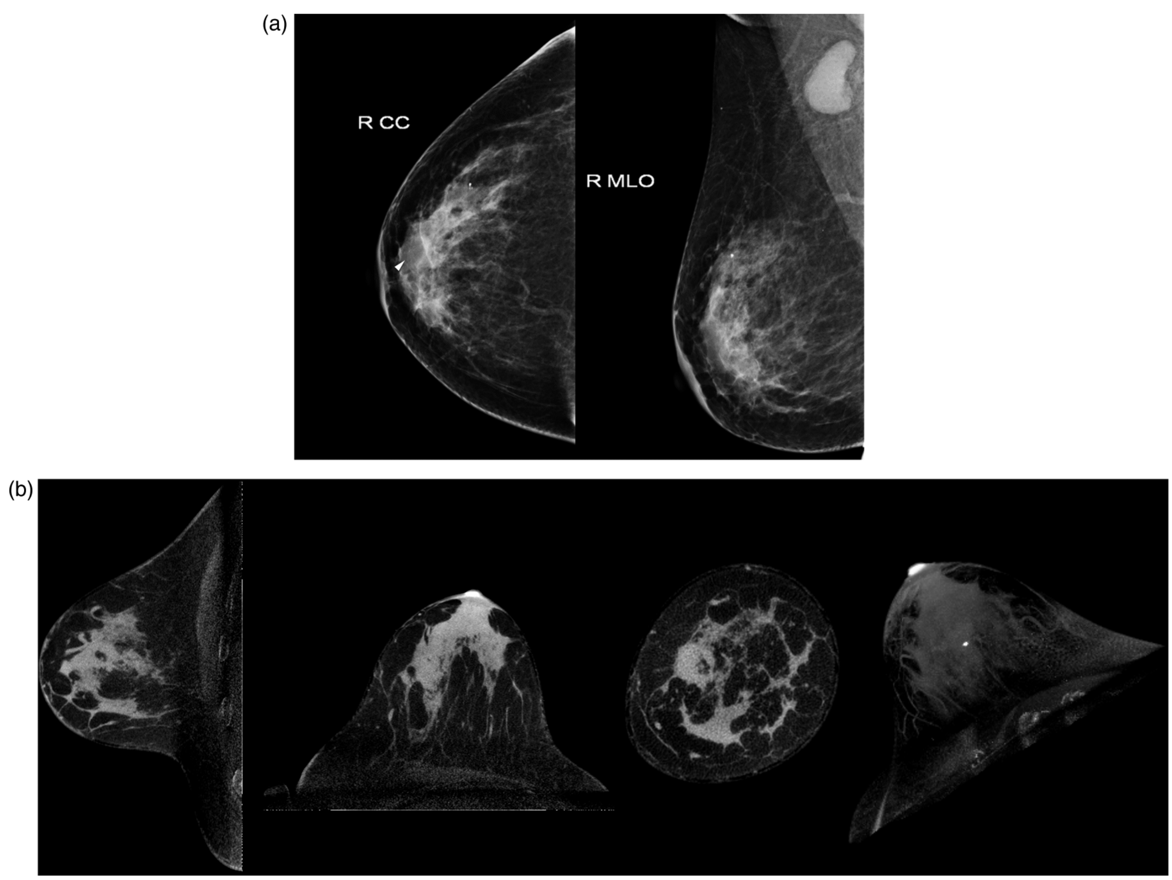

Fig. 2. Example of a grouped amorphous calcifications cluster missed on non-enhanced breast CBCT. (a) Craniocaudal and mediolateral oblique views of mammograms (white arrow points to the location of calcifications cluster in craniocaudal view); (b) sagittal, axial, and coronal views and 3D-MIP of non-enhanced CBCT images at a slice thickness of 0.273 mm. 3D-MIP, three-dimensional maximum-intensity projection; CBCT, cone-beam computed tomography.

CBCT images in which the cluster was missed. Conversely, the high-density, punctate shadows, which were present in dense breasts or accompanied by high-density lesions, were possibly mistaken for calcifications on interpretation of the breast CBCT image. In addition to the differences caused by different imaging principles, these errors were mainly caused by the lack of clear definitions of imaging findings on this new imaging method. It is suggested that we should not only prevent the missed diagnosis of calcifications but also avoid mistaking noise as calcifications, thus affecting the diagnostic accuracy.

The present study shows that DM and CBCT have substantial consistency in the morphology and spatial distribution classification of the calcifications. This high consistency also suggests that in a breast CBCT reading, we can refer to the definition of calcification features in BI-RADS. Among the four different types of suspicious morphologies suggesting calcifications, the consistency of the fine linear or fine linear branching morphologies between the two modalities was slightly poorer than that of the other types. Similarly, among the five different types of calcifications distributions, the consistency of linear calcifications distributions between the two modalities was slightly poorer than that of the other types. As the information was viewed as breast CBCT images obtained as slices, the perception of linear calcifications that were not encompassed in a single slice may have been reduced, and the observer may not have been able to perceive clusters of calcifications. However, the linear distribution of fine linear or fine linear branching calcifications has a high positive predictive value in the diagnosis of breast cancer (4), which suggests that more attention should be paid to the evaluation of this type of calcifications in clinical work.

Breast CBCT images were reviewed with a large amount of information, including axial, sagittal, and coronal views at the thinnest slice thickness of 0.273 mm, which required a great deal of time to read and could lead to radiologist fatigue. Therefore, it is important to select appropriate display parameters for the rapid and accurate detection and classification of calcifications. In our study, a slice thickness of 0.273 mm was considered as the preference to display the morphology of most calcification clusters. In addition, we found that increasing the slice thickness did not improve visualization of the distribution of calcification clusters, which was due to the inherent limitations

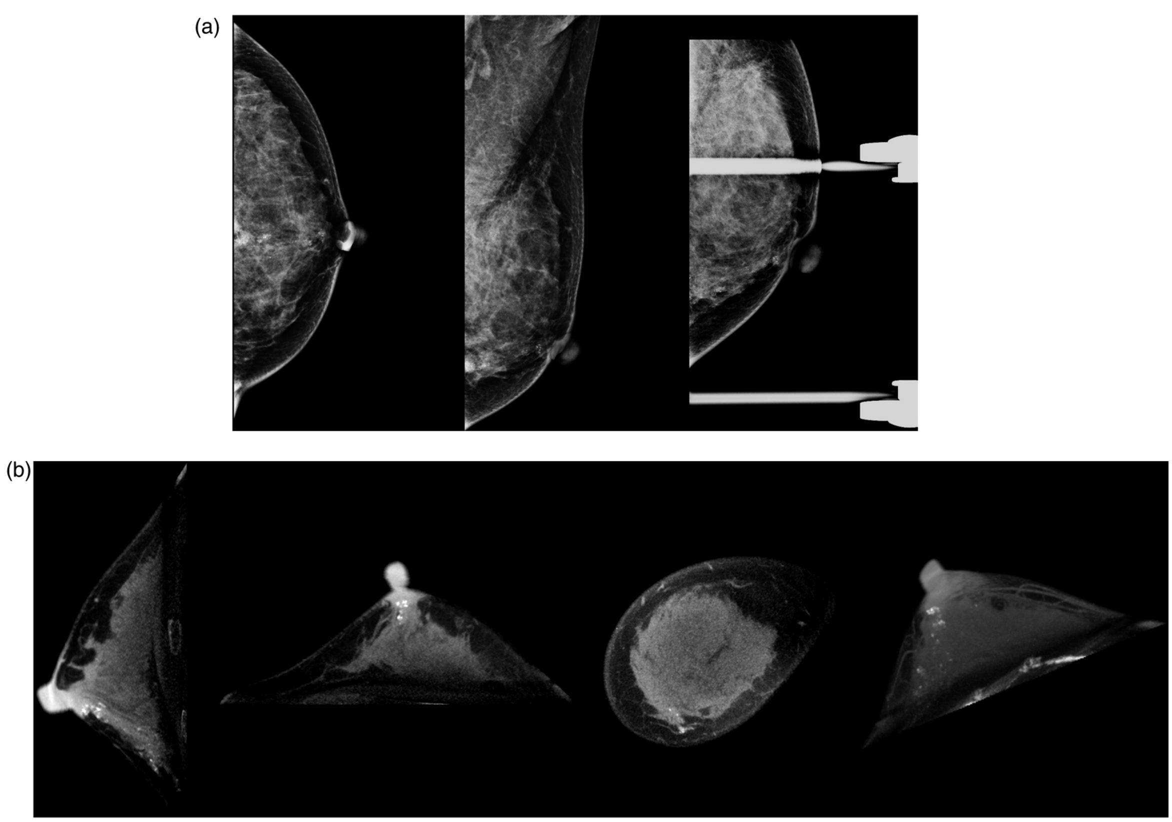

Fig. 3. Example of a segmental fine pleomorphic calcifications cluster detected on mammograms and breast CBCT images. (a) Craniocaudal, mediolateral oblique, and magnified views of mammograms; (b) sagittal, axial, and coronal views and 3D-MIP of non-enhanced CBCT images at a slice thickness of 1 mm (b). 3D-MIP, three-dimensional maximum-intensity projection; CBCT, cone-beam computed tomography.

of tomographic images in presenting spatial distributions. Moreover, increasing the slice thickness will render artifacts more serious, especially in the case of sharp calcifications, which will greatly increase the difficulty of observing the morphology. Although DM has been proven to be the best modality for characterizing calcification clusters, it cannot reflect the actual spatial distribution due to the two-dimensional imaging modality. Compared to mammograms, breast CBCT images may not be sufficient to directly display the spatial distribution of calcifications, but the use of 3D-MIP accounted for this deficiency here. 3D-MIP were considered more intuitive than tomographic images and mammograms regarding the display of the spatial distribution. Therefore, our study results indicate that the use of both a slice thickness of 0.273 mm and 3D-MIP was better for displaying both the morphology and distribution of calcification clusters. Fig. 3 shows mammograms and CBCT images of a breast with a segmental fine pleomorphic calcifications cluster.

Previous studies have suggested that combining magnification and compression may contribute to the better detection and diagnosis of calcifications (25). One of the main reasons is that the decrease in pixel size in DM-magnified views, including much more information per pixel, improved the delineation of the shape and contour of calcifications. On the other hand, magnified views with focal compression reduced tissue overlap. As complementary images were obtained for suspicious calcifications, magnified views can increase the specificity of the modality and prevent the unnecessary biopsy of benign lesions (26,27). Even so, in this comparison of calcification clarity, we also found there was no statistically significant difference among DM standard views, magnified views, and CBCT images on the evaluation of calcification clarity for two of the three radiologists.

To our knowledge, this is the first study to describe the presence of calcification clusters on CBCT images. In this study, we estimated the performance of CBCT in the display and classification of malignant calcifications. The main limitation of our study was that there was no discussion on the diagnostic efficiency of CBCT for calcifications, which is principally due to the lack of benign lesions with suspicious calcifications. Further study with more reviewers on the performance of breast CBCT for diagnosing calcifications based on a much larger and more complex study cohort is necessary. The other limitation was that there was no comparison between CBCT images and mammograms on the detection of calcifications, which is owing to the setting of inclusion criteria. In the future, we hope that the trial design could be adjusted to compare the detection of calcifications between mammograms and CBCT images more objectively.

In conclusion, according to the results of this study, CBCT was sensitive and specific enough in the detection of calcifications and comparable to DM in the characterization of calcifications. Breast CBCT images could provide sufficient information for suspicious calcifications, which would then be fully characterized by 3D-MIP and could lead to the improvement of breast cancer diagnosis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Key R&D Program of China, Tianjin Science and Technology Major Project (grant nos. 2017YFC0112600, 2017YFC0112601, and 19ZXDBSY00080).

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