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Original Article

Cone beam CT for determining breast cancer margin: an initial experience and its comparison with mammography and specimen radiograph

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Abstract: Purpose: To assess the ability of cone beam CT (CBCT) in determining the breast cancer margin using, to compare the results with mammography and specimen radiography, and to explore the clinical potential of CBCT for breast imaging. Methods: Specimens of 46 breast cancer patients were imaged by using a prototype CBCT system. Each patient underwent mammography, CBCT and X-ray of breast surgical specimen within 6 months. Images of mammography, breast surgical specimen radiography and CBCT were evaluated by an experienced radiologist. Indicators, such as: morphology, glitch, density, invasion, structural distortion and calcification, were observed. Result: There was no significant difference of the calcification, glitch and morphology among three methods. However, there was significant difference in indicators of breast tumor invasion among three methods. There was statistical significance in detecting invasions of breast cancer cells in peripheral tissues among three methods. Conclusion: CBCT shows no superiority over mammography and specimen radiography in determining tumor's outline and detecting calcification. On the other hand, CBCT demonstrates its advantage in determining the 3 dimensional position of a lesion which could be a potential clinical application in future practices of breast imaging.

Keywords: Breast cancer margin, breast imaging, specimen, cone-beam CT

Introduction

Breast cancer is the most common malignancy in women worldwide with more 370,000 deaths per year [1]. It is the second leading cause of cancer death among women with 20-59 years old [2]. People used to consider mammography reduce 30%-40% of mortality for breast cancer [3]. However, not all cancers can be detected with mammography screening films [4]. The sensitivity of mammography for cancer detection when used for screening is about 80%, ranging from 70.8% in the 40 to 44 year-old group to 84.5% for patients aged 75 to 89 years old. The concept of breast CT was first raised and studies in the 1970s [5]. Cone beam CT (CBCT) provides a three-dimensional (3D) breast image, which displays of the original structure of the human body more realistically. In our laboratory, we have dedicated to CBCT for many years [6, 7]. There are also other research institutes studying the CBCT for breast [8-10]. However, few clinical studies was reported due to these were technical researches. The specimen radiography was reliable in identifying clear tumor margins. Better results will be provided by digital mammographic equipment [11]. In this study accuracy of CBCT in displaying the breast cancer margins were evaluated and compared with the mammography and specimen radiography.

Material and methods

The clinical data

46 patients were examined according to protocols approved by the institutional review board; informed consent was obtained from each participant before surgical specimens acquiring and CBCT inspection. Breast specimens were scanned with a CBCT scanner immediately after surgery. CBCT image data sets (transverse, sagittal, coronal views) were compared with the diagnostic mammograms cranio-caudal and medio-lateral oblique views with additional views as required) and specimen radiography. Patients who ever had radiotherapy or

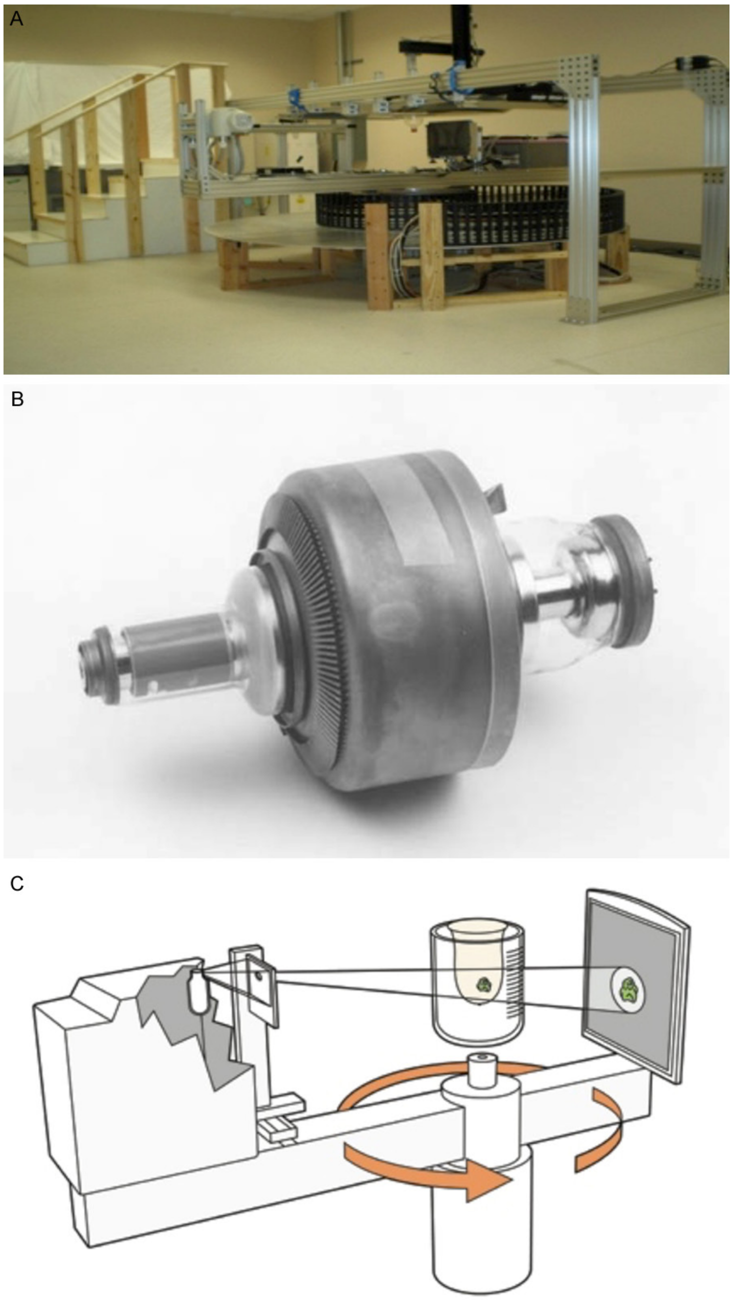

Figure 1. A. Experimental cone beam CT imaging system; B. The X-ray tube (G-1593/B180, Varian Medical System, and Salt Lake City, UT); C. The Breast Specimens placed in the center of the machine.

chemotherapy were excluded in order to keep the comparability of acquired images. Patients' data was collected from October 2006 to April 2013. All patients received mammography, CT, and pathologic examination within six months. All patients were female, with a mean age of 50.7 years old ranging from 29-95. Imaging indicators by CBCT in each patient were shown as follow: the boundary is clear (not); with (without) glitch; with (without) calcification; density of mass: low density, high density or gland density, the morphologically regular (irregular), the existence infiltration around the lesion (not).

Structure of CBCT

The general framework of breast CBCT was designed by Imaging Physics Laboratory from MD Anderson Cancer Center (**Figure 1A**). This is the improved third version of CBCT. The system consisted of an X-ray tube, a full field flat panel detector and a design motor-driven rotating table. The full field flat panel detector is 2923 complementary metal oxide semiconductor (CMOS) X-ray detector (Dexela company, England), which was a 14 bit digital output, 75 μm pixel pitch with 3888×3072 pixels and high-sensitivity and high-saturation modes, binning to 4×4 and high DQE scintillator options CsI 150 μm, CsI 600 μm, BNC input/output for X-ray generator triggering and Camera Link or Ethernet data connection. It employs state-of-the-art large-area CMOS image sensor technology and is supplied with a range of scintillator and interface options. The X-ray tube is G-1593I/B180, Varian Medical System, and Salt Lake City, UT. It is a 5.25" (133 mm) 125 kV, 1.1 MJ (1.5 MHU) maximum anode heat content, rotating anode insert. This metal center section insert is designed for radiography, cineradiography, digital and film screen angiography procedures. The insert features a 12° rhenium-tungsten facing on molybdenum with a graphite backed target and is available with nominal focal spots: 0.3-0.8-1.2 IEC 60336 (**Figure 1B**). The breast specimen was placed on the rotating table for full 360° rotation during the scan (**Figure 1C**). The diagram of the machine design was completed by our laboratory, the various components of the frame,

Table 1. BI-RADS Category and quantity and proportion of mammography

Type of category number	n (%)
0	6 (13.0%)
1	0 (0.0%)
2	0 (0.0%)
3	0 (0.0%)
4	4 (8.7%)
5	3 (6.5%)
6	33 (71.3%)
Total	46 (100%)

Notes: BI-RADS = Breast Imaging Reporting and Data System; n = case number.

Table 2. BI-RADS Category of glandular tissue types and the number of proportion

Type of category number	n (%)
Almost entirely fat	6 (13.0%)
Scattered	14 (30.4%)
Fibro glandular density	19 (41.3%)
Extremely dense	7 (15.2%)
Total	46 (100%)

Notes: BI-RADS = Breast Imaging Reporting and Data System; n = case number.

Table 3. Pathologic diagnoses and the number of proportion

Type	n (%)
DCIS	19 (41.3%)
IDC	9 (19.6%)
IDC+DCIS	6 (13.0%)
ILC	1 (2.2%)
LCIS	1 (2.2%)
ILC+LCIS	3 (6.5%)
ILC+DCIS	1 (2.2%)
IMC+DCIS	2 (4.3%)
DCIS+LCIS	1 (2.2%)
IDC+ILC	1 (2.2%)

Notes: n = case number; DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; LCIS = lobular carcinoma in situ; IMC = invasive mammary carcinoma.

table, gantry and other components were assembled by the members of the laboratory.

The distance between X-ray tube and specimens is 100 cm, and distance between X-ray tube and detectors is 125 cm. After breast specimen with a diameter of about 13 cm was put into a tapered plastic container (similar to a natural breast sagging state), the scanner was operated at 80 kVp [12] with a mean glandular dose of approximately 4-6 mGy and about 1R exposure level at the system iso-centerobtained by tube current-time. There were some studies of breast CT scan doses these years [12-14]. Vedantham S [13] reported a dedicated breast CT system that acquired nc projections over 2p for the circular scan. The addition of a line scan with equal spacing and constant X-ray beam quality (kVp and HVL), and mAs matched to the circular scan would result in increase of average glandular dose by scansof each source position along the line. Boone JM [12] reported the radiation dose of breast CT depended on X-ray technology related factors, such as kVp, mAs as well as output, and breast characteristics, such as diameter and types. Mettivier G [14] provided a method for scatter evaluation through Monte Carlo simulations, leading to a scatter correction procedure applied to measured projections via subtraction of the simulated scatter component. It presented an evaluation of this method through testsona mimic cylindrical orhemi-ellipsoidal breast with adiameter of 120 or 140 mm. The results indicated that this method was effective in reducing X-ray scattering, without increases of noise in CT images.

Statistical methods

Comparison between methods was done with χ^2 test. All statistical analyses were performed by using software SPSS 17.0. Kappa consistency test was conducted. When kappa value was between 0 and 1, the closer to 1, the more consistency between methods.

Result

There were 54 patients examined by all three methods, and only 46 patients accepted the study finally. Because one patient received an examination on one side of the breast with CBCT, while had a surgical on the opposite side; another three patients could not meet inclusion criteria due to poor qualities of CBCT images; and another three patients showed no cancer in pathology. In these 46 patients, women with mammography were evaluated by Breast Imaging Reporting and Data System (BI-RADS). The results were shown in **Tables 1** and **2**. **Table 1** shows the results of mammography BI-RADS

Table 4. Three kinds of ways to check basic descriptions of the breast cancer

Lesion		CBCT (n)	Mammography (n)	Specimen Radiology (n)	P
Calcification	Exist	25	28	22	P>0.05
	Un-exist	21	18	24	
Glitch	Exist	22	26	21	P>0.05
	Un-exist	24	20	25	
Boundary	Clear	10	22	21	P<0.05
	Fuzzy	36	24	25	
Morphological	Irregular	41	43	43	P>0.05
	Round	5	3	3	
Invasive	Exist	21	10	0	P<0.05
	Un-exist	25	36	46	

Notes: CBCT = Cone beam CT; n = case number.

grading. In **Table 1**, BI-RADS classifications of category 6 was found in 33 cases, with a total ratio of 71.3%; 6 cases in BI-RADS classification category 0 with a percentage of 13.0%; 4 cases in category 4 with a percentage of 8.7%; 3 cases in category 5 with a percentage of 6.5%; while there was no case in categories 2 and 3. **Table 2** shows the glandular tissue type, almost entirely fat glands were found in 6 cases (13%), scattered glands in 14 cases (30.4%); fibro glandular density glands in 19 cases (41.3%); extremely dense glans in 7 (15.2%). Pathological types were shown in **Table 3**, type ductal carcinoma in situ was found in 19 cases with a highest proportion of 41.3%; type invasive ductal carcinoma in 9 cases with a second highest proportion of 19.6%; while the rest types included invasive lobular carcinoma, lobular carcinoma in situ, invasive mammary carcinoma and other mixed types. According to some of the characteristics of breast mass margins, the following data was drawn in **Table 4**.

There were no significant differences in detecting calcification, glitch or morphology among three methods. There were significant differences in boundary and invasive performance among three methods. Calcification, glitch, and morphology had better consistency in CBCT than those in mammography and specimen radiography. Invasive characteristics of lesions could be displayed by diagnostic mammography better than CT.

One patient (**Figure 2**) showed a speculate mass in mammography and specimen radiography, which was not visible in CBCT. An infiltrated mass was seen at mammography and specimen radiography in another patient (**Figure 3**), while CBCT failed to show the invasive features of this mass. A regular mass was found in CBCT and specimen radiography another patient (**Figure 4**) but nothing in mammography.

A complete breast CBCT scan needed 40 seconds. One imagecan be obtained in every 1.2° rotation. After a 360° rotation, about 300 images can be obtained. Radiological artifacts could cause poor image qualities, therefore, some images were excluded due to interferences from artifacts of metal holder, but the rest images also had some artifacts without influencing diagnosis. Some laboratories [15, 16] dedicated to the research to remove the interference of metal artifacts. In this regard, a preliminary study has been down (**Figure 5**), Radiation artifact removal of metal and metal foreign body can be reduced because the metal artifact caused by diagnostic imaging errors, the following two figure in our laboratory and radiological removal of metal artifact after artifact before and after comparison, we can clearly see, removal of artifacts and metallic foreign body radiation image after observation of lesions can be more intuitive, but because it is artificial machine composite image, and the different between reality and this result still further explored, and we hope we will be able to restore the image to a maximum close to the real image.

Discussion

From these initial clinical results, some characteristics of breast cancer in CBCT scan were consistent with those in mammography, while some other characteristics of breast cancer in CBCT scan were significantly different from those in mammography. There were no significant differences of showing calcification, glitch and morphology between two methods, might because that characteristics of CBCT showing breast cancer were from initial clinical experiences and prototype of scanner, and specimen radiography were similar to mammography. Other characteristics of breast cancer in CBCT and specimen radiography were significantly different. But there was no significant difference of showing calcification among three methods. The margins of mass were shown

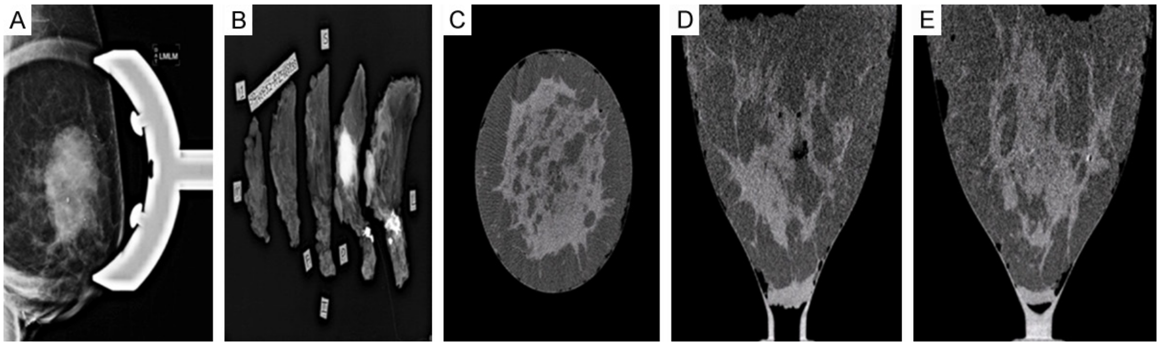

Figure 2. The glitch of a mass could be seen clearly in mammography (A) and specimen (B) but not in CT (C-E).

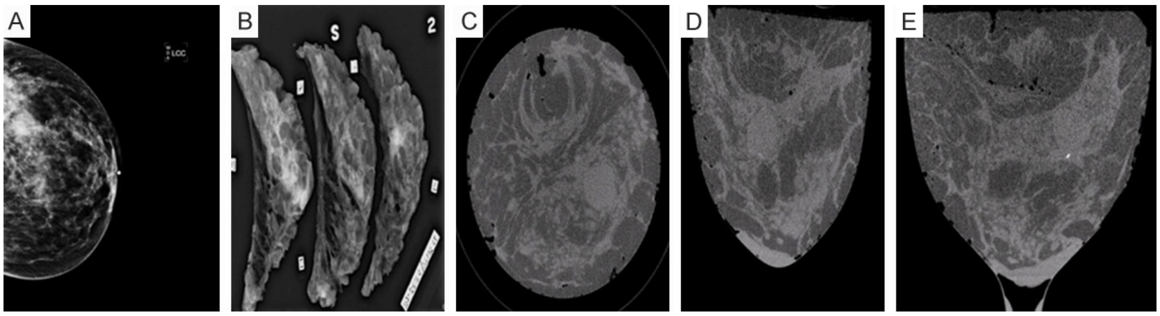

Figure 3. The invasion of a mass could be seen in mammography (A) and specimen (B) but not in CT (C-E).

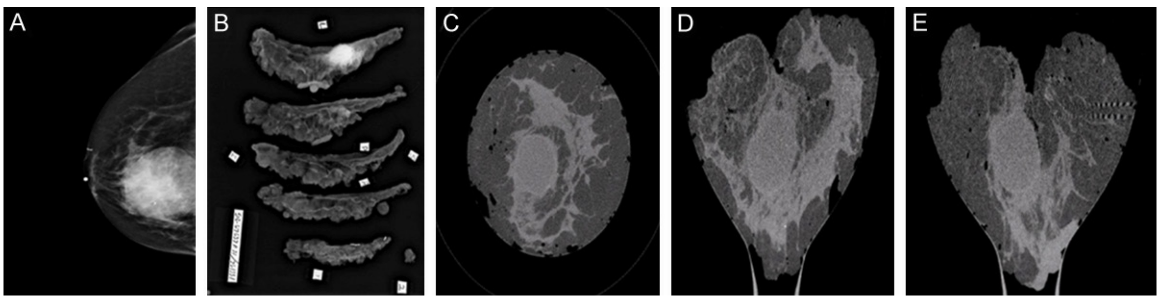

Figure 4. The regular morphological of s mass can be seen in specimen (B) and CT (C-E) but not in mammography (A).

more clearly in CBCT images and specimen radiographs than in mammograms, which might be caused that mammography was an overlap of two-dimensional images, thus margins were not well visualized in mammography. CBCT provided a 3D image. The specimen radiography was also tomography, which ruled out the problem of overlapping. As for the same large-scale invasions, images were more conspicuous in mammography and specimen radiography than in CBCT. Large-scale invasions were hardly visualized in CBCT images. This difference may be caused by high resolution and thin layer of CBCT, thus edema around the lesion was not easy to be shown. Density of the mass in three methods showed no difference. Mammography was a two-dimensional imaging. Patients needed to squeeze breast to get better images, but lesions were often overlapped. Thus, patients often were required multiple examinations, which could add patients burden of psychological and physiological without doubt.

Although the specimen radiography did not have overlapping problems, it is only used for a certain location with deviations. And CBCT scan was a good solution to this problem, which was a 3D imaging without overlapping problems and needs of squeezing breast. Squeezing

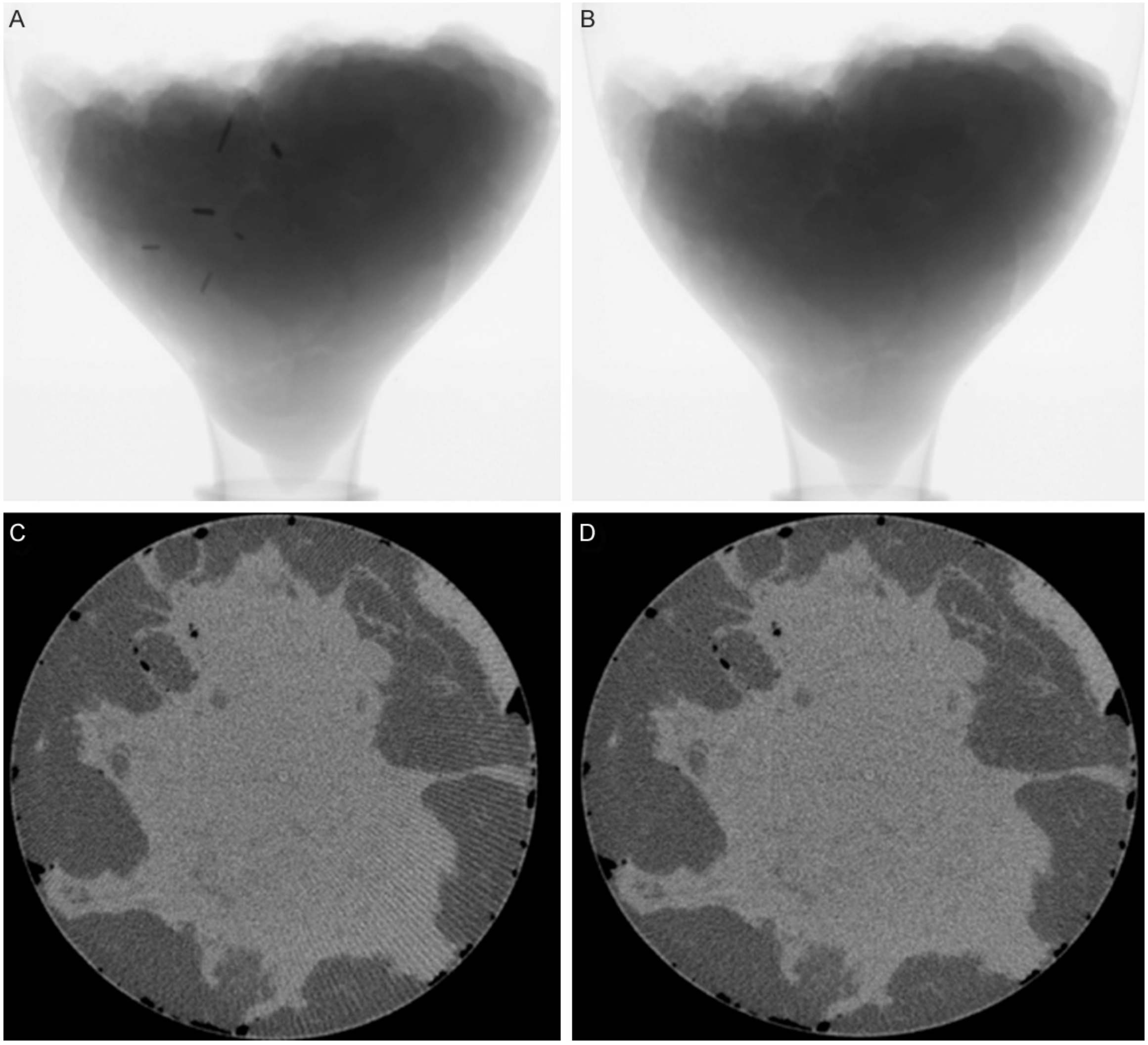

Figure 5. A. Is a radiology image of metal artifacts. B. Is the radiology image after the radioactive artifacts were removed. C. Is another radiology image of metal artifacts. D. Is the radiology image after the radioactive artifacts were removed.

breast caused patients' discomforts and burden of psychological and repetitive inspections of body. Such 3D images directly showed more exact locations in the next 3D positioning than conventional stereotactic mammography, and patients had less discomfort. Although these experiments were carried out with patients' gross specimen, without understanding the patients' feeling, there was a study [9] reported that breast CT scan was more comfort than mammography.

Breast CT can provide 3D images, which can be applied in future positioning biopsy or radiotherapy, radiofrequency ablation techniques, especially in localizing clinically non-palpable breast lesion more accurately and precisely. 3D stereotactic mammography was relatively more complicated with patients' heavier psychological burden, CT mammography or ultrasound could be much easier to achieve more accurate positioning with human solutions to meet better patients' clinical requests. At the same time, there were many interventional treatments requiring a complete image guidance, while CT has its space advantages which guided and controlled some of the clinical treatment programs such as radiofrequency ablation, or minimally invasive surgeries [17]. As with other researches, CBCT can be useful in screening breast cancer and applicable to the general population to improve visualization and characterization of calcification lesions. It was reported [17] that the most important barrier to adopt breast CT as a general screening method was visualization of calcification lesions. However, it was shown that breast calcifications in breast CBCT were not significantly different from those in mammography. If these conditions were right, this method was not better than mammography or calcified specimen radiography.

Some limitations existed in this study, diagnoses using breast CT were not done through double-blinded approaches, some patients were identified with breast cancer via breast biopsy before surgery, however recent study aimed to preliminary investigate the characteristics of CBCT showing margins of mass and calcifications. Breast CBCT has been studied in recent years in clinical examinations, but the limits on radiation dose resulting in high image noise. With existing parameters, qualities of these images were still not good. A preliminary study about removal of metal artifacts also showed relatively satisfactory results, but computers were artificially synthesized and the authenticity of the differences needs to be future studied. We hope to be closest to the real images.

In summary, although CBCT's ability of displaying border and calcification is not as good as those of mammography and specimen radiography, but it has unparalleled advantages of providing 3D images. Future stereotactic directions and minimally invasive surgeries should have relatively good developments, and there are more researchers working hard on this technique. The image noise is higher. In the first stage to study and compare CBCT with mammography, the CT image noise will be higher with the same or lower radiation dose of mammography. This limits the sharpness of images. If dose is increased, better images can be achieved. However the effects of high dose should be considered. Breast CT can be recommended as a feasible adjunct instead of a preferred method.

Disclosure of conflict of interest

None.

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