Comparison of ultrasound and digital mammography plus tomosynthesis in determining benign and malignant breast lesions using pathology as a gold standard, in 102 Chinese women

Lei Yang MD,
Chunwu Zhou MD

Department of Radiology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Keywords: Tomosynthesis - Digital mammography - Ultrasonography - Breast tumor size - Breast density

Corresponding author:
Dr. Chunwu Zhou
Department of Radiology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
No.17, Pan Jia Yuan Nan-li, PO Box 2258, Beijing 100021, China
Tel: +86-10-87788550, Fax: +86-10-87788550
cjr.zhouchunwu@vip.163.com

Received:
22 November 2018
Accepted revised :
25 January 2019

Abstract

Objective: This study was to evaluate performance characteristics of ultrasonography (US) and a combined two-and three-dimensional (2D+3D) digital mammography in identifying breast tumors in Chinese women. **Subjects and Methods:** One hundred and two women with suspected breast tumors were examined using diagnostic imaging techniques of US and a combined 2D+3D imaging protocol. Detection of breast tumors in women with and without dense breasts was validated according to the features of image-detected breast tumors which were proven by histological exam in this study cohort. **Results:** Breast US was superior to 2D+3D imaging in assessing benign lesions ($P<0.01$). The diagnostic measure on 2D+3D mammography was more accurate than the US exam in breast cancer detection. Furthermore, 2D+3D imaging was more sensitive than US in identifying malignant lesions in size of ≤1cm and in relatively high breast density ($P<0.01$ or 0.05). Breast US showed a better correlation with the sizes of benign tumor as compared to 2D+3D imaging with correlation coefficients of 0.930 and 0.920. Conversely, 2D+3D imaging showed a better correlation with the sizes of malignant tumors as compared to US with correlation coefficients of 0.951 and 0.815. Additionally, presence of microcalcifications on mammography significantly increased in breast cancers as compared to benign tumors ($P<0.001$). **Conclusion:** Breast US and 2D+3D mammography imaging play an additive role in identifying breast tumors. Intervention of the 2D+3D imaging technique helps recognize appearance and characteristics of breast lesions particularly in the women with a lesion measure of ≤1cm and those with dense breasts or breast microcalcifications.

Hell J Nucl Med 2019; 22(1): 36-42 *Epub ahead of print: 7 March 2019* *Published online: 5 April 2019*

Introduction

Both breast ultrasonography (US) and 2D digital mammography screening are routine examinations for patients suspected of having a breast tumor [1, 2]. Breast US is an important diagnostic adjunct to mammography in detecting a solid mass or an area of architectural distortion and identifying a cystic mass [3-5]. The benefit of this approach to evaluating suspicious lesion as either benign or malignant has been presented in a series of 2020 patients who underwent clinical exam, mammography, and breast US [6]. In contrast, the rate at which lesions discovered by US screening are shown to be breast cancer is actually very low particularly for women with dense breast tissue [7].

Mammography is a proven technique for both diagnosis and screening of breast cancer [8, 9]. However, the appearance of overlapping tissue on mammograms poses a significant obstacle to interpretation in women with dense breasts, which remains a limitation of conventional mammography [9, 10]. Some studies have indicated that breast cancers have the same density as surrounding tissue, and can be obscured by overlapping tissue [11, 12]. With tumors potentially obscured by overlapping tissue in 2-D conventional mammography, digital breast tomosynthesis (DBT), a 3D image-segmented evaluation procedure, can be expected to ameliorate this problem by reducing or eliminating tissue overlap [11, 13]. However, whether or not the digital mammography as a screening method is superior to the breast US exam is still a subject of debate.

Our study aimed to investigate the diagnostic performance US and 2D+3D imaging for evaluation of women with suspected breast lesions using histological examination as the gold standard. Our results indicate clinical values of the two approaches with utility in identifying breast lesions in the study cohort.

Subjects and Methods

Patients and inclusion criteria

According to complete recordings, 102 women were randomly recruited into two groups of the breast US exam and a combined 2D+3D imaging from July 2014-September 2014. Age distribution (years) of these patients is shown in table 1. Population proportions of patients in age included 17.6% of ≤40, 37.4% of ≤50 and 45% of >50, respectively.

Major inclusion criteria were 1) Women suspected of having a breast tumor after a clinical exam (a palpable mass or breast lumps); 2) Ability to complete examinations; 3) Age ≥ 25 years old with recent breast US exam at our hospital; 4) No breastfeeding or lactating; 5) No clinical history of breast surgery and chemotherapy; 6) Histopathologically diagnosis as breast tumors in all patients studied.

The study has been approved by the Ethics Committee of the Peking Union Medical College. For this retrospective study, the requirement of informed consent was waived.

Image acquisition

All women received an X-rays exam of breast (Selenia, Dimensions mammography system, Hologic, Bedford, MA USA) using "combo mode" (a protocol where both 3D and 2D images acquired in the same breast compression, with the second acquisition following the first immediately). These patients acquired standard bilateral two-view tomosynthesis images of both breasts, and typically these images were taken from two angles including a medio-lateral view and a cranio-caudal view. Overall scanning time was less than 5 seconds. 15 low-dose projection images were obtained over a 15° arc (±7.5°) kVp (25 to 49kVp.). The maximum X-rays tube current was 200mA. Reconstruction time for images was 2-5 seconds while the image pixel size of about 100 microns. The 2D pixel size was 70 microns. Ultrasonography imaging of breast was also performed by using a GE-Volution 730 system for all patients within 2 weeks prior to surgery.

Image interpretation and analysis

Image interpretation was performed using remote sensing imagery. Identification and measurement of a breast lesion in an image was executed manually or visually. In evaluation of diagnostic US imaging, malignant breast masses are commonly hypoechoic lesions with ill-defined borders. Typically, a malignant lesion presents as a hypoechoic nodular lesion, which is taller than broader and has spiculated margins, posterior acoustic shadowing and microcalcifications [14]. In term of the X-rays image, a lesion on a digital mammogram usually appears as brighter than the surrounding tissue. This is because the diseased tissue that is denser than fat stops more X-rays photons, hence they appear brighter.

Lesions on sonography and mammography were analyzed prior to histologic confirmation of the lesions. Briefly, the largest tumor diameter was chosen as the sizing reference in each case. The imaging lesion size of a breast mass was calculated according to the measurement of longest axis of a lesion. The architectural distortion and asymmetries on a mammogram was measured according to approximation of its greatest linear dimension, clustered microcalcifications were observed according to calcium particles of various size and shape measuring between 0.1 to 1mm in diameter and numbering more than four to five per cubic centimeter.

As with any breast imaging, breast US and mammography depend on the level of skill and experience of the clinical worker interpreting the images. In this study, diagnostic evaluation of breast lesions was implemented by two radiologists who had experience with US and DBT image interpretation.

Assessment of breast lesion and density scale

Risk assessment of breast lesions was carried out according to the Breast Imaging-Reporting and Data system (BI-RADS) standard [15, 16]. Each lesion defined by BI-RADS was categorized as: 1 (negative), 2 (benign finding), 3 (probably benign, ≤2%, probability of malignancy and 6 months follow-up recommended), 4a (2%-10% probability of malignancy and biopsy recommended), 4b (10%-50% probability of malignancy), 4c (50%-95% probability of malignancy), 5 (≥95% suggestive of malignancy). In general, BI-RADS 1-3 were classified as benign findings or probably benign, whereas BI-RADS 4(a, b, c) and 5 were considered as suspicious abnormality or highly suspicious of malignancy since the presence of each lesion was different in these data sets gathered using the 2D+3D imaging techniques, a high value was taken as the final diagnosis of the breast lesion. To validate diagnostic accuracy of breast imaging, a histologic diagnosis of breast cancer was offered mainly by needle biopsy according to golden standard for cancer diagnosis.

Mammographic density, a risk factor for breast cancer, was classified using a 4-level density scale according to the criteria of the American College of Radiology's (ACR) Breast Imaging Reporting and Data System [17], Qualitative classification of breast density was assigned as ACRa (Almost entirely fatty), ACRb (Scattered areas of fibroglandular density), ACRc (Heterogeneously dense), ACRd (Extremely dense). Categories ACRc and ACRd were considered dense since they had a lower sensitivity of mammography than ACRa and ACRb.

ROC curve analysis

A receiver operating characteristic (ROC) curve is created by plotting the true positive rate against the false positive rate at various threshold settings, which is expressed as a graph of sensitivity (y-axis) versus 1-specificity (x-axis). Maximizing sensitivity and specificity correspond to some large y and to a small x value on the curve, respectively. An important measure of the accuracy of the clinical test is the area under the curve (AUC). If this area equals to 1.0, then the ROC curve consists of two straight lines shown as one vertical from 0,0 to 0,1 and the next horizontal from 0,1 to 1,1. This test is identified as 100% accurate because both the sensitivity and specificity are 1.0. The closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test [18].

The diagonal line from 0,0 to 1,1 (y=x) represents the strategy of randomly guessing a class. If a classifier randomly guesses the positive class half the time, it can be expected to get half the positives and half the negatives correct; this yields

the point (0.5, 0.5) in the ROC space and the ROC area for this line is 0.5 [19]. A diagonal line from lower left to upper right traces the curve for a perfectly useless test. A test with perfect discrimination should have a ROC curve that passes through the upper left corner. In this study, the optimal cut-off point for the predictors of US and 2D+3D imaging from breast tumors was selected on the ROC curve moving from the vicinity of the upper left corner over toward the upper right corner. The AUC is expressed as a percentage of randomly drawn pairs for which this is true.

The 95% confidence interval (CI) is the interval in which the true (population) area under the ROC curve lies with 95% confidence. The significance level or P-value is the probability that the observed AUC is found when the true area under the curve is 0.5. If a P value is less than 0.05 then it can be concluded that the area is significantly different from 0.5 and that therefore there is evidence that the test does have an ability to distinguish between the two approaches.

Statistical analysis

Statistical analysis was performed using MedCalc 13.0 (Ostend, Belgium). A ROC curve was used to analyze diagnostic accuracy of breast US and 2D+3D imaging. Spearman's correlation coefficient was calculated to observe the relationship between clinical performance of US and 2D+3D imaging data based on the pathological findings. Inter-rater reliability for the two readers was computed using Cohen's kappa coefficients. The chi-square test (χ^2) was conducted to analyze the significance of population distribution for the women with microcalcifications, as well as to compare the diagnostic accuracy between the breast US and 2D+3D imaging. A P value of <0.05 was considered significant.

Results

Patient characteristics

In this retrospective study, 52 postmenopausal women (51%) and 97 patients (95.1%) with no family history of breast cancer were found in the 102 cases. Additionally, there were 38 (37.2%) and 36 (35.3%) patients classified as ACRc and ACRd. However, there were 1 (1%) and 27 (26.5) patients were diagnosed as ACRa and ACRb, respectively. In contrast, population proportion for the women with high breast densities was larger than those with low densities in the investigated cohort. Thirty-two (31.4%) women presented with breast lesions in the upper-outer quadrant of the right breast and 25 (24.5%) were in the upper-outer quadrant of the left breast, which were most positions visible on breast lesions. 71 (69.6%) in 102 cases only showed a breast mass as one of the pathological features of the tumors. Of 102 patients, a breast cancer was confirmed in 75 cases and a benign tumor in 27 cases pathologically (Table 1).

Lesion measurement

In a total of 102 women with suspected breast tumors, 83 and 100 cases with breast lesions were detected by US and 2D+3D imaging, respectively. In 27 women with a benign lesion, there was a positive relationship between the US or 2D+3D imaging data and the pathological finding with correlation coefficients of 0.93 and 0.92, respectively (Figure 1). In 75 women with malignant lesions, the correlation coefficient (0.951) for the 2D+3D imaging was higher than the US exam (0.815). In calculation of the Kappa statistic, the inter-rater reliability coefficients for the 2D+3D imaging and the US exam were estimated as 0.627 and 0.633 in the study cohort, respectively.

In the predefined subgroups regarding lesion sizes, the performance of 2D+3D imaging for detection of breast cancer was significantly better than US alone particularly for the lesion size of ≤1.0cm (difference between areas, 0.400; 95% CI from 0.127 to 0.673; P=0.0041). In women with ARCc+ ARCd breast density, the diagnostic accuracy of 2D+3D imaging for breast cancer was more sensitive than the US exam in the observed cohorts (difference between areas, 0.124; 95% CI from 0.0212 to 0.226; P=0.0180) (Table 2). In the Kappa statistic, the inter-rater reliability coefficients for the 2D+3D and the US exams were estimated 0.643 and 0.635 in the analysis of BI-RADS categories, respectively.

Table 1. *Patient characteristics.*

Number of patients	102
Age	
≤40	18 (17.6%)
>40 and ≤50	38 (37.3%)
>50	46 (45.0%)
Menopause status	
Premenopausal/Perimenopausal	50 (48.9%)
Postmenopausal	52 (51.1%)
Family history of breast cancer	5 (4.9%)
Breast density	
ACRa	1 (1.0%)
ACRb	27 (26.5%)
ACRc	38 (37.2%)
ACRd	36 (35.3%)
Pathology type	
Cancer	75 (73.5%)
Benign lesion	27 (26.5%)

Observation of lesion sizes

Tumor size in breast cancer influences therapeutic decisions. To establish an imaging method corresponding with the histological result, this test was performed with evaluating sizing of primary breast lesion using digital mammography and US. Our results are shown in Figure 2. A breast mass at a diameter of <1.0cm was clearly detected only by 3D imaging but not another two techniques (Figure 2A). How-

ever, a breast lesion at a diameter of >1.0cm was observed using US and 2D+3D imaging (Figure 2B). Digital mammography showed the solid mass with irregular shape, indistinct and angular margins. In the US exam, the boundaries of the breast lesion were not clear and the internal echoes of the lesion were not uniform. Histopathology revealed invasive ductal carcinoma.

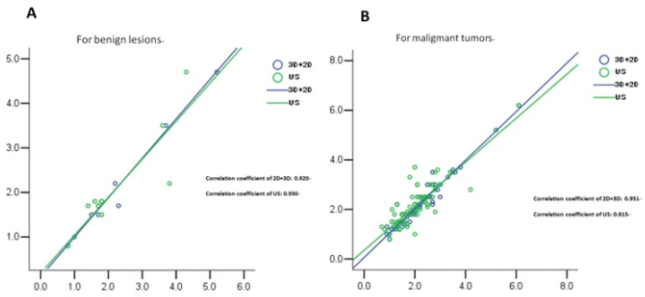

Figure 1. The Spearman correlation between the lesion size and the histological result of benign (A) and malignant (B) lesions was observed in women receiving 2D+3D and US screening, respectively. In 27 women with benign lesions, correlation coefficient of the US exam was larger than that of 2D+3D imaging. In 75 patients with breast cancer, correlation coefficient of 2D+3D imaging is larger than that of the US exam.

Table 2. *Diagnostic accuracy measure.*

Diagnostic accuracy	Area under the curve	95% Confidence interval
Benign lesions		
2D+3D	0.639	0.537-0.731
Ultrasound	0.834	0.747-0.900
Difference between areas	0.196	0.057-0.333
P value	0.005	
Malignant lesions		
2D+3D	0.940	0.875-0.977
Ultrasound	0.821	0.732-0.890
Difference between areas	0.119	0.034-0.205
P value	0.006	
Malignant lesions (≤1cm)		
2D+3D	0.900	0.637-0.993
Ultrasound	0.500	0.239-0.761
Difference between areas	0.400	0.127-0.673
P value	0.004	
Malignant lesions (1-2cm)		
2D+3D	0.932	0.821-0.985
Ultrasound	0.801	0.661-0.902
Difference between areas	0.131	-0.002 to 0.263
P value	0.053	
Malignant lesions (>2cm)		
2D+3D	0.955	0.835-0.995
Ultrasound	0.902	0.763-0.973
Difference between areas	0.053	-0.115 to 0.222
P value	0.537	
ACRa+ACRb breast density		
2D+3D	1.000	0.877-1.000
Ultrasound	0.894	0.719-0.978
Difference between areas	0.106	-0.063-0.275
P value	0.220	
ACRc+ACRd breast density		
2D+3D	0.915	0.827-0.967
Ultrasound	0.792	0.681-0.877
Difference between areas	0.124	0.021-0.226
P value	0.018	

Statistical significance considered when P<0.05.

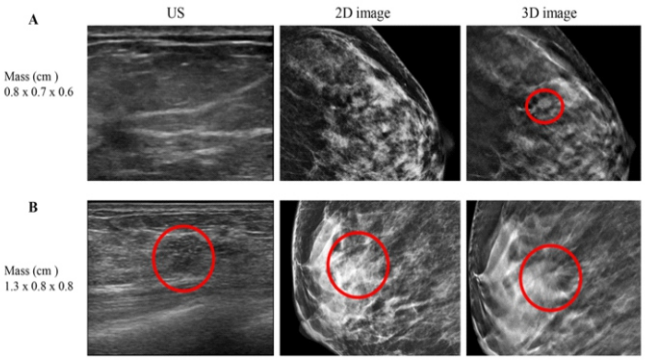

Figure 2. Breast lesions in a size of <1.0cm (A) and ≥1.0cm (B) were measured using US and 2D+3D imaging, respectively. The breast lesion (red circle) at a smaller size was seen only by 3D imaging. Digital mammography showed the solid mass with irregular shape, indistinct and angular margins. In the US exam, the boundaries of the lesion were not clear with no uniform internal echoes. Histopathology revealed invasive ductal carcinoma.

Observation of lesion in dense breasts

Patients with dense breasts represent a diagnostic dilemma. In addition to the increased density resulting in malignancies being obscured, patients with dense breasts have increased incidence of breast cancer. Since mammography has been shown to have a decrease in sensitivity in dense breasts, additional imaging modalities need to be investigated to improve the diagnostic accuracy of imaging in breast cancer. Our results are shown in Figure 3. Though breast lesions (ACRc and ACRd) were detected using US and 2D+3D imaging, 3D imaging was more visible than another two approaches in identifying features of the lesions. DBT showed small calcium deposits in the breast mass (Figure 3A) and burrs on edge of the mass (Figure 3B). Ultrasonography only displayed a hypo-anechoic breast mass with non-uniform

internal echoes. This mass presented with irregular shape and margins, and subtle acoustic shadowing at the edges of the lesion. Histopathology revealed invasive ductal carcinoma.

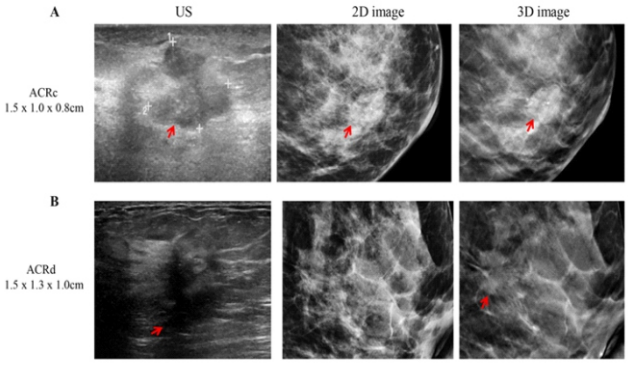

Figure 3. Breast lesions were measured in dense breasts classified as ACRc (A) and ACRd (B) using US and 2D+3D, respectively. Though breast lesions (red arrows) were detected using US and 2D/3D imaging, 3D imaging was more visible than another two approaches in identifying features of the lesions. Breast US showed a hypo-anechoic mass with irregular margins and subtle acoustic shadowing at the edges of the lesion. Histopathology revealed invasive ductal carcinoma.

Observation of microcalcifications

White dots on the 2D+3D images were observed in women with biopsy-proven breast tumors and population proportion for the women with microcalcifications is shown in Figure 4. In benign lesions (n=27), there were no women with breast microcalcifications seen on the 2D+3D images. The women with malignant lesions were shown with breast microcalcifications in 29 of 75 cases (38.7%). The chi-square test (χ^2) showed that there was a significant difference in the presence of microcalcifications between the patients with malignant and benign breast tumors (P<0.001).

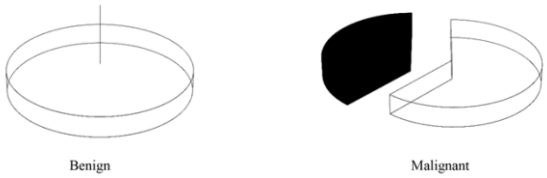

Figure 4. Microcalcifications in breasts were detected using 2D+3D imaging. Population proportions for patients with (black) and without (white) microcalcifications were expressed as a percentage of the women with benign (n=27) and malignant tumors (n=75). A χ^2 test showed that there was a statistical significance in the presence of microcalcification between the women with malignant and benign tumors (P<0.001).

Assessment of diagnostic accuracy

The sensitivity and specificity of the 2D+3D imaging were 97.3% and 88.9%, respectively. The sensitivity and specificity of the US were 96.0% and 59.3%, respectively. In a ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (specificity) for different cut-off points. The area under the ROC curve is a reflection of how good the test is at identifying risk of mortality. In comparison with the diagonal line, the two curves started in the same way from lower left corner, went straight up to the upper left corner, and then to the upper right corner on the ROC analysis. The shape of the 2D+3D curve for diagnostic accuracy of breast lesions corresponded to a leftward movement in the ROC curve analysis and displayed different changes in the area under the curve as compared to the US curve. The results are shown in Figure 5. In breast lesions detected by 2D+3D imaging, no benign cases were catalogued as BI-RADS 4c or 5. Most of the women with breast cancer diagnosed by the imaging were defined as BI-RADS 5 in 34 of 75 cases (33%) as compared to the US approach in 15 of 75 cases (20%). The diagnostic accuracy of breast US for women with benign lesions was higher than the 2D+3D technique (difference between areas, 0.196; 95% CI from 0.0576 to 0.333; P=0.0055). However, the accuracy of 2D+3D imaging for women with breast cancer was significantly higher than the US exam (difference between areas, 0.119; 95% CI from 0.0340 to 0.205; P=0.0061).

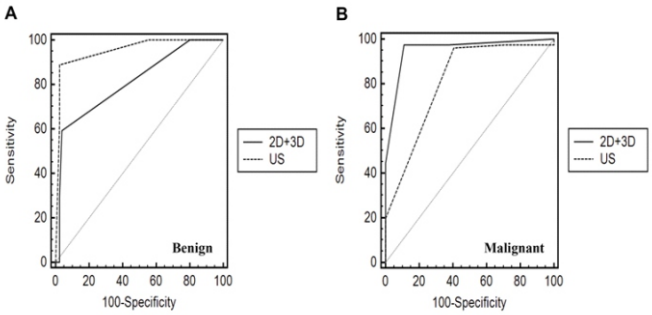

Figure 5. The ROC graph for diagnostic evaluation. Diagnostic accuracy of benign (A) and malignant (B) lesions was examined according to the changes in the area under the ROC curve (AUC). In contrast, the ROC space for the US exam was larger than 2D+3D imaging in diagnostic evaluation of benign tumors. However, the ROC space for 2D+3D imaging was larger than the US exam in evaluation of malignant tumors (11). All tests displayed significant differences in the AUC values as compared to 0.5 (P<0.01).

Discussion

In 102 women suspected of having a breast tumor, the US exam was superior to 2D+3D imaging in assessing benign breast lesions. However, the combined digital mammography with tomosynthesis was more effective than US in breast cancer detection. These results indicated that both approaches can play an additive role in helping to identify the nature of breast lesions. It has been reported that US alone is not a good breast cancer screening tool because of many false positive and false negative results [20, 21]. Therefore it's reasonable to consider that it may be used as a follow-up test after an abnormal finding on clinical breast exam [4]. Intervention of the 2D+3D imaging technique offered an obvious advantage over US in breast cancer screening, suggesting that the combined imaging increased the sensitivity for detecting cancer and was more conclusive than US in identifying malignant breast lesions. Since screening mammography with DBT improves accuracy and reduces false

positive rates in women with breast diseases [22], it's conceivable that 2D+3D imaging would help to avoid unnecessary repeat biopsies that lead to pain and scarring.

The breast tumor size predicted by imaging modality is one of the important factors for subsequent surgical intervention since tumor size may influence patients' status [22-25]. Our data showed that combined 2D with 3D mammography but not US alone detected a malignant breast mass with the ill-defined margin less than 1.0cm in diameter, suggesting that 2D+3D imaging allowed reliable identification and characterization of breast lesions in small size. The breast US exam quite require the sonographer's skill level in exactly finding the diameter of a lesion because many cancers are vertical tumors (taller-than-wide breast mass) in which posterior acoustic shadows obscure the posterior border [26]. Given that tumor size is strongly related to prognosis [27], it's reasonable to speculate that the combined 2D+3D mammography exam potentially provided a precious choice for women of being cured by surgery. In further analysis, the radiographic effect mainly came from the 3D mammography exam since the breast lesions less than 1.0cm in diameter were not visible in either US or 2D imaging. Digital breast tomosynthesis is an advanced form of breast imaging that aids in the early detection and diagnosis of breast disease through using computer reconstructions to create 3D images of the breasts [11]. It's very likely that the computer-reconstructed radiographic images allowed visual review of thin breast sections and offered the potential to unmask cancers obscured by normal tissue located above and below the lesion [28].

The growing use of full field digital mammography has led to significant improvement of sensitivity in women with dense breasts secondary to improved contrast sensitivity [9]. Unfortunately, digital mammography is still limited by the overlapping breast tissue. It has been reported that population proportion of Asian women with dense breasts are higher than Western women [29]. Our data showed that there were 38 (37.2%) and 36 (35.3%) women classified as ACRc and ACRd in the 102 patients, suggesting that dense breast tissue was a risk factor for developing breast lesion. Since US was superior to 2D imaging in detecting a lesion in dense breast tissue, it was necessary to point out that notification of breast density should be given with sonographic results so that women with dense breasts would be aware of the implications, and could pursue supplemental screening beyond US and 2D screening. Digital breast tomosynthesis was more visible and precise than another two technologies in identifying characteristics of a malignant lesion in dense breast tissue, led us to conclude that adding 3D mammography to regular screening would find more cancers in dense breasts. Digital breast tomosynthesis, a new X-rays technology, is used for helping to solve the overlapping tissue problem since it produces a series of images with multiple low-dose tomographic images acquired in an arch [30]. These images are reconstructed and allow for visualization of the breast in multiple contiguous slices [31]. The benefits of DBT in screening sensitivity and diagnostic evaluation not only solve the overlapping tissue problem but also improve the characterizations of different lesion types [32, 33]. Relative to US, all-digital screening is not cost-effective. However, age-targeted digital screening appears cost-effective in select population subgroups particularly among women who have dense breast tissue or surgical biopsies [34]. Additionally, using DBT screening has a potential economic value in reducing the number of women recalled for additional follow-up imaging and diagnostic testing services but also facilitating early diagnosis of breast cancer when treatment costs are less [35].

It has been reported that mammary microcalcifications can be the early and only presenting sign of breast cancer and they appear in one-third of invasive carcinomas [36, 37]. Our results showed that microcalcifications on the 2D+3D images were detectable in 29 of 75 cases (38.7%) only with breast cancers, suggesting that the presence of microcalcifications are much more likely to be malignant with a biopsy necessary of the breast lesions. Although microcalcifications are also associated with benign conditions such as secretory diseases and fat necrosis, around 40% of breast cancers present with microcalcifications and frequently, serve as the only mammographic features indicating the presence of a malignant tumor [38]. Thus, mammographic findings in microcalcifications associated with breast tumors can be stratified by suspicion for malignancy, and the BI-RADS categories would be helpful in alerting the referring physicians, the pathologists, and surgeons to the underlying risk of malignancy [39]. Additionally, it has been reported that breast cancers presenting with microcalcifications are often associated with lymph node invasion [40]. The condition of axillary lymph nodes in breast cancer is of great importance for deciding appropriate treatment and staging as well as predicting the long-term survival [41]. Although etiology of microcalcification on breast cancer metastasis is not clear, it's likely that the change in chemical composition of the microcalcification is related to a malignant aggression [42].

In this study, the diagnostic accuracy of breast US was higher than 2D+3D in making diagnosis of benign lesions. This was caused due to the probabilities that some benign lesions were associated with smooth border appearing on cystis, intraductal papilloma, small fibrosum adenoma, adenosis tumor, lipoma and fat necrosis. These would be difficult to be recognized on the 2D+3D images, but were able to be diagnosed clearly by US because of their distinctive shapes and echoes. Ultrasound imaging is not really any more expensive than digital mammography, and in many ways it is more convenient. However, almost all suspicious ultrasound findings are inconclusive in women with high breast density. Since it's difficult to diagnose benign lesions with irregular borders which occurred in cancers, the US exam may incur false positives with an unnecessary biopsy [43-47].

I*n conclusion*, this study indicates that the US exam and 2D+3D mammography play an additive role in identifying breast lesions. Intervention of 3D mammography serves as a diagnostic technique with utility in detecting breast cancers particularly in Chinese women with the tumor diameter of ≤1.0cm and those with either dense breasts or breast microcalcifications.

The authors declare that they have no conflicts of interest.

Funding

This study has received funding by the National Natural Science Foundation of China (grant numbers 81671829 and 81671757), the CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2016-I2M-1-001).

Bibliography

1. Madjar H. Role of Breast Ultrasound for the Detection and Differentiation of Breast Lesions. *Breast Care* 2010; 5(2): 109-14.
2. Ji SC, Han BK, Ko EY et al. Comparison between two-dimensional synthetic mammography reconstructed from digital breast tomosynthesis and full-field digital mammography for the detection of T1 breast cancer. *Eur Radiol* 2016; 26(8): 2538-46.
3. Harvey JA, Nicholson BT, Lorusso AP et al. Short-Term Follow-Up of Palpable Breast Lesions With Benign Imaging Features: Evaluation of 375 Lesions in 320 Women. *Am J Roentgenol* 2009; 193(6): 1723-30.
4. Flobbe K, Bosch AM, Kessels AGH et al. The Additional Diagnostic Value of Ultrasonography in the Diagnosis of Breast Cancer. *Arch Int Med* 2003; 163(10): 1194.
5. Soo MS, Rosen EL, Baker JA et al. Negative predictive value of sonography with mammography in patients with palpable breast lesions. *Am J Roentgenol* 2001; 177(5): 1167-70.
6. Leichter I, Buchbinder S, Bamberger P et al. Quantitative charcterization of mass lesions on digitized mammograms for computer-assisted diagnosis. *Invest Radiol* 2000; 35(6): 366-72.
7. Melnikow J, Fenton JJ, Whitlock EP et al. Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Service Task Force. A*nn Intern Med* 2016; 164(4): 268.
8. Karellas A, Vedantham S. Breast cancer imaging: a perspective for the next decade. *Med Phys* 2008; 35(11): 4878-97.
9. Pisano ED, Gatsonis C, Hendrick E et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005; 353(17): 1773-83.
10. Bick U, Diekmann F. Digital mammography: what do we and what don't we know? *Eur Radiol* 2007; 17(8): 1931-42.
11. Helvie MA. Digital mammography imaging: breast tomosynthesis and advanced applications. *Radiol Clin North Am* 2010; 48(5): 917-29.
12. Bae MS, Moon WK, Chang JM et al. Breast cancer detected with screening US: reasons for nondetection at mammography. *Radiology* 2014; 270(2): 369-77.
13. Park JM, Franken EA, Jr., Garg M et al. Breast tomosynthesis: present considerations and future applications. *Radiographics* 2007; 27: S231-40.
14. Stavros AT. Benign solid nodules: Specific pathologic diagnosis. *Breast Ultrasound* 2004; 13: 528-96.
15. Obenauer S, Hermann KP, Grabbe E. Applications and literature review of the BI-RADS classification. *Eur Radiol* 2005; 15(5): 1027-36.
16. Spak DA, Plaxco JS, Santiago L et al. BI-RADS((R)) fifth edition: A summary of changes. *Diagn Interv Imaging* 2017; 98(3): 179-90.
17. D'Orsi C, Sickles E, Mendelson E et al. ACR BI-RADS® Atlas. *Breast Imaging Reporting and Data System*. 5th edn 2013.
18. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem* 1993; 39(4): 561-77.
19. Fawcett T. An introduction to ROC analysis. *Pattern Recogn Let*t 2006; 27(8): 861-74.
20. Berg WA, Zhang Z, Lehrer D et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. *JAMA* 2012; 307(13): 1394-404.
21. Gartlehner G, Thaler K, Chapman A et al. Mammography in combination with breast ultrasonography versus mammography for breast cancer screening in women at average risk. *Cochrane Database Syst Rev* 2013; 4: Cd009632.
22. Fornvik D, Zackrisson S, Ljungberg O et al. Breast tomosynthesis: Accuracy of tumor measurement compared with digital mammography and ultrasonography. *Acta Radiolog* 2010; 51(3): 240-7.
23. Edge SB. AJCC Cancer Staging Manual. JAMA 2002; 304(15): 1726-7.
24. Downes KJ, Glatt BS, Kanchwala SK et al. Skin-sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high-risk breast carcinoma. *Cancer* 2005; 103(5): 906-13.
25. Luparia A, Mariscotti G, Durando M et al. Accuracy of tumour size assessment in the preoperative staging of breast cancer: comparison of digital mammography, tomosynthesis, ultrasound and MRI. *Radiol Med* 2013; 118(7): 1119-36.
26. Dummin LJ, Cox M, Plant L. Prediction of breast tumor size by mammography and sonography-A breast screen experience. *Breast* 2007; 16(1): 38-46.
27. Narod SA. Tumour size predicts long-term survival among women with lymph node-positive breast cancer. *Curr Oncol (Toronto, Ont)* 2012; 19(5): 249-53.
28. Gong X, Glick SJ, Liu B et al. A computer simulation study comparing lesion detection accuracy with digital mammography, breast tomosynthesis, and cone-beam CT breast imaging. *Med Phys* 2006; 33(4): 1041-52.
29. Calderon-Garciduenas AL, Sanabria-Mondragon M, Hernandez-Beltran L et al. Mammographic breast density patterns in asymptomatic Mexican women. *Radiol Res Pract* 2012; 2012: 127485.
30. Good WF, Abrams GS, Catullo VJ et al. Digital breast tomosynthesis: a pilot observer study. *Am J Roentgenol* 2008; 190(4): 865-9.
31. Gur D, Zuley ML, Anello MI et al. Dose reduction in digital breast tomosynthesis (DBT) screening using synthetically reconstructed projection images: an observer performance study. *Acad Radiol* 2012; 19(2): 166-71.
32. Gennaro G, Toledano A, di Maggio C et al. Digital breast tomosynthesis versus digital mammography: a clinical performance study. *Eur Radiol* 2010; 20(7): 1545-53.
33. Andersson I, Ikeda DM, Zackrisson S et al. Breast tomosynthesis and digital mammography: a comparison of breast cancer visibility and BIRADS classification in a population of cancers with subtle mammographic findings. *Eur Radiol* 2008; 18(12): 2817-25.
34. Lee CI, Cevik M, Alagoz O et al. Comparative effectiveness of combined digital mammography and tomosynthesis screening for women with dense breasts. *Radiology* 2015; 274(3): 772-80.
35. Miller JD, Bonafede MM, Herschorn SD et al. Value Analysis of Digital Breast Tomosynthesis for Breast Cancer Screening in a US Medicaid Population. *J Am Coll Radiol* 2017; 14(4): 467-74.e5.
36. Castellaro AM, Tonda A, Cejas HH et al. Oxalate induces breast cancer. *BMC Cancer* 2015; 15: 761.
37. Stomper PC, Winston JS, Proulx GM et al. Mammographic detection and staging of ductal carcinoma in situ: Mammographic-pathological correlation. *Semin Breast Dis* 2000; 3(1): 26-41.
38. Castronovo V, Bellahcene A. Evidence that breast cancer associated microcalcifications are mineralized malignant cells. *Int J Oncol* 1998; 12 (2): 305-8.
39. Sanders MA, Roland L, Sahoo S. Clinical implications of subcategorizing BI-RADS 4 breast lesions associated with microcalcification: a radiology-pathology correlation study. *Breast J* 2010; 16(1): 28-31.
40. Holme TC, Reis MM, Thompson A et al. Is mammographic microcalcification of biological significance? *Eur J Surg Oncol* 1993; 19(3): 250-3.
41. Cen D, Xu L, Zhang S et al. BI-RADS 3-5 microcalcifications: prediction of lymph node metastasis of breast cancer. *Oncotarget* 2017; 8(18): 301-90-8.
42. Baker R, Rogers KD, Shepherd N et al. New relationships between breast microcalcifications and cancer. *Br J Cancer* 2010; 103(7): 1034-9.
43. Nothacker M, Duda V, Hahn M et al. Early detection of breast cancer: benefits and risks of supplemental breast ultrasound in asymptomatic women with mammographically dense breast tissue. A systematic review. *BMC Cancer* 2009; 9: 335.
44. Ozülker T, Ozülker F, Ozpaçaci T et al. The efficacy of ^{99m}Tc-MIBI scintimammography in the evaluation of breast lesions and axillary involvement: a comparison with X-rays mammography, ultrasonography and magnetic resonance imaging. *Hell J Nucl Med* 2010; 13(2):144-9.
45. Lyra M, Vamvakas I, Gavriilelli M, Chatzigiannis C. Absorption dose in scintimammography and in X-rays mammography. *Hell J Nucl Med* 2010; 13(1): 81-7.
46. Lyra M, Vamvakas I. Dosimetry in scintimammography by ^{99m}Tc-MIBI, ^{99m}Tc-tetrofosmin, ^{99m}Tc-(V)DMSA and ^{201}TlCl compared with X-rays mammography. *Hell J Nucl Med* 2009; 12(2): 184-8.
47. Chen Q, Xie Q, Zhao M et al. Diagnostic value of ^{99m}Tc-3PRGD2 scintimammography for differentiation of malignant from benign breast lesions: Comparison of visual and semi-quantitative analysis. *Hell J Nucl Med* 2015; 18(3): 193-8.