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# Contrast ultrasound versus ultrasound elastography for diagnosis of breast lumps

## A cross-sectional study

Wei Zhao, MD, Kaituo Yan, MD, Yingying Liu, MD, Zaibin Zhang, MD*

**Abstract**

Chinese women have dense and small breasts. Therefore, in China, contrast ultrasound and ultrasound elastography are commonly used for detection of the breast lumps. Purpose of the study was to compare the sensitivity and accuracy of ultrasound elastography with contrast ultrasound for the diagnosis of the breast lumps.

A total of 1000 women with a damp in breast mass, breast pain, nipple discharge, and/or breast skin discharge were subjected to contrast ultrasound and ultrasound elastography. Women were subjected to stereotactic vacuum-assisted biopsy under B-mode ultrasonography (n=750). The ultrasound examinations were graded on a 5-points scale method. Data were subjected to the Chi-square Independence test at 99% of confidence level.

Ultrasound elastography was detected the same numbers of benign lesions (648 vs 651, $P=.88$), malignant lesions (90 vs 99, $P=.53$), and false positive lesions (5 vs 0, $P=.07$) as those detected by biopsies. However, diagnostic parameters for contrast ultrasound had a significant difference with those detected by biopsies ($P<.0001$ for all). For contrast ultrasound and ultrasound elastography, the working area to detect deformation in the image of the breast lesions at least 1 time were 0% to 45% and 5% to 100%.

Ultrasound elastography is the most reliable diagnostic method for detection of the breast lumps.

**Abbreviations:** DCIS = ductal carcinoma in situ, STARD = the standard for reporting diagnostic accuracy studies.

**Keywords:** benign, breast cancer, contrast ultrasound, malignant, ultrasound elastography

## 1. Introduction

In today's time, within Chinese women, breast lumps are common,[1] breast cancer rates are higher than Caucasian women,[2] and it is the fourth leading cause of death in China PR.[3] Diagnosis of breast cancer is important for early treatment.[4] A biopsy is the "gold standard" method for detection of the breast lumps but it is an invasive method and has a high cost for diagnosis.[5] Mammography has been adopted technique for diagnosis of the breast lumps[6] but Chinese women have dense and small breasts (Fig. 1)[7] but mammography has less accuracy in the dense breast.[6] Also, breast cancer could be developed in Chinese women at the age of 45 to 55 years, which is younger (about 10–20 years) than that in Caucasian women[1,8] and mammography is a less sensitive tool for detection of the breast lumps in younger women than older women.[9,10] However, ultrasound images are not affected by age.[6] Therefore, in China, contrast ultrasound, ultrasound elastography, B-mode ultrasound, color-Doppler ultrasound, and spectral Doppler ultrasound are used diagnostic methods for detection of the breast lumps.[4] Also, diffusion-weighted magnetic resonance imaging is a noninvasive and nonionizing technique, has the short examination time, does not require the administration of contrast agent, and has the ability to assess the tumor fully[11] but has difficulties in differentiation of malignant and benign lesions (overlap of apparent diffusion coefficient values between benign and malignant proliferative lesions) and detection <1 cm breast lumps.[12] Contrast ultrasound has a high scope than B-mode ultrasound[13] and has reported high diagnostic accuracy for liver sarcoma than contrast magnetic resonance imaging or contrast computed tomography[14] but in breast cancer, its superiority is not well-established. Ultrasound elastography is the "fourth revolution" modern technology in ultrasound[15] and breast lump is judged on the base of the hardness of the tissues.[4]

The objective of the study was to compare the sensitivity and accuracy of ultrasound elastography with contrast ultrasound for the diagnosis of the breast lump in Chinese ladies considering the results of histopathology as "gold standard."

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The datasets used and analyzed during the present study available from the corresponding author on reasonable request.

The authors declared that he has no conflict of interest or any the other competing interest regarding results and/or discussion reported in the research.

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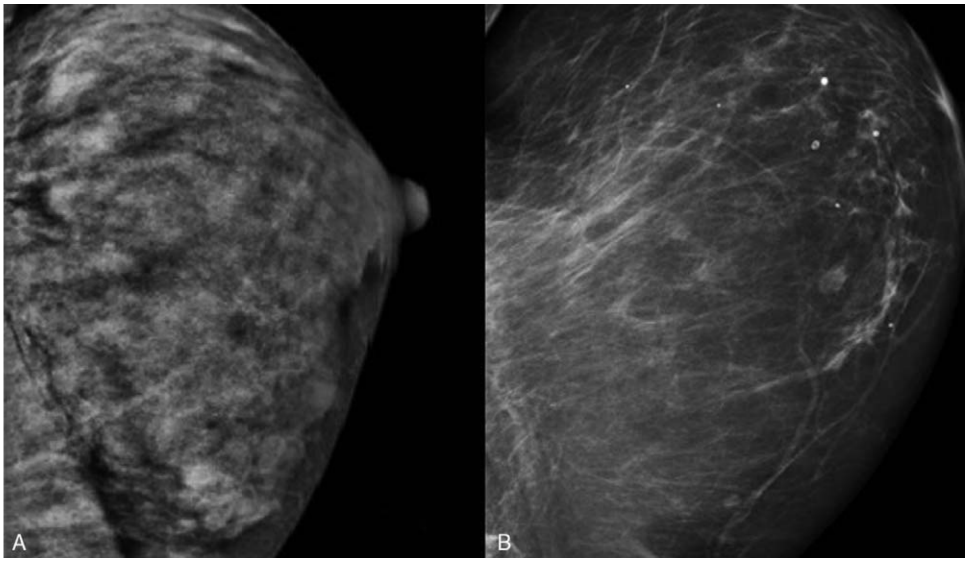


**Figure 1.** Mammography of the breast. (A) Breast of a Chinese woman. (B) Breast of Caucasian woman.

## 2. Patients and methods

### 2.1. Ethics approval and consent to the participant

The study protocol (YCH/CL/14/14 dated 14 May 2014) had been granted by the Weifang Yidu Central Hospital review board. An informed consent form regarding anesthesia, pathology, radiology, and publication of the study in all formats (hard and electronics) irrespective of time and language had been signed by enrolled patients or their relatives (legally authorized person). The study had adhered to the law of China, the standard for reporting diagnostic accuracy studies (STARD), and 2008 Helsinki Declaration.

### 2.2. Reagents

The contrast agent (Sono Vue) was purchased from Bracco Imaging B.V., Geneva, Switzerland. Levobupivacaine was purchased from Neon Laboratory India Ltd. Normal saline was purchased from Baxter (Crow Wing County, MN). Formalin, glycerin, hematoxylin, and eosin were purchased from Sigma-Aldrich (St. Louis, Missouri).

### 2.3. Inclusion criteria

Women with a damp in breast mass, breast pain, nipple discharge, and/or breast skin discharge were included in the study.

### 2.4. Exclusion criteria

Women with confirmed breast cancer by biopsy following histopathology and those who had faced negative clinical, pathological, and sonographic examinations in past 9-months were excluded from the study.

### 2.5. Ultrasound elastography and contrast ultrasound

Women were instructed for a supine and lateral position. Ultrasound was performed for vertical and horizontal sections of the breast using ultrasound equipment with 18L6 HD Transducer (ACUSON S2000 ABVS, Siemens Healthineers, Munich, Germany). The frequency of the probe was 35 MHz, strain elastography was performed, and real-time images were evaluated. In the same position, the contrast (59 $\mu$G in 5 mL normal saline) was injected to the antecubital vein by cannula (20G, BD, CA) and breast images were developed by the same ultrasound equipment. Ultrasonography was performed by ultra-sonographers (minimum 3 years' experience) of the institute.

### 2.6. Image analysis

All images were analyzed using software sUSBA (Siemens Healthineers) by ultra-sonographers (blinded regarding pathological findings) with 5 years of experience in breast ultrasonographic image analysis. The interpretations of colors were as green: the average hardness, blue: softer than the average hardness, and red: more rigid than the average hardness. The images (Fig. 2) reported in ultrasound elastography were interpreted and graded on a 5-point scale as per Table 1.[16] If the ratio of an elasticity imaging to B-mode was 1 or more than 1, lesions were graded as malignant and if that ratio was less than 1 lesions were graded as benign.[17]

The images (Fig. 3) reported in contrast ultrasound were interpreted and graded on a 5-point scale as per Table 2.[18] If greater and longer signal enhancement of contrast agent was found, lesions were graded as malignant and if fair signal enhancement of contrast agent was found, lesions were graded as benign.[19]

### 2.7. Biopsy

After ultrasonography, the patients who had been recommended for biopsies were subjected to stereotactic vacuum-assisted biopsy under B-mode ultrasonography. 0.25% levobupivacaine in normal saline was infiltrated over breast skin and 9G needle (BD) was inserted into the breast. Two cores were collected in the formalin by a physician (a minimum of 3 years of experience). The biopsy cavity was infiltrated with normal saline.[5] The samples of biopsies were sent to a laboratory for further study.


**Figure 2.** Schematic representation of ultrasound elastography images. Green: the average hardness, blue: softer than the average hardness, red: more rigid than the average hardness. 0: no deformation, 1: the central part was not deformed and the edges were deformed, 2: the central part was deformed and the edges were not deformed, 3: the lesion was deformed except surrounding, 4: the lesion was deformed including surrounding.

**Table 1**

**Ultrasound elastography images interpretation.**

| Observation | Score | Interpretation |
|---|---|---|
| All lesion was green | 0 | No deformation |
| Central part green and surrounding was blue | 1 | The central part was not deformed and the edges were deformed |
| Central part blue and surrounding was green | 2 | The central part was deformed and the edges were not deformed |
| The whole lesion was blue but surrounding was not included | 3 | The lesion was deformed except surrounding |
| The whole lesion was blue and surrounding was also blue | 4 | The lesion was deformed including surrounding |

Green: the average hardness,
Blue: softer than the average hardness,
Red: more rigid than the average hardness.
All images were analyzed by ultra-sonographers (blinded regarding pathological findings) with 5 years of experience in breast ultrasonographic image analysis.

Histopathology was performed by a pathologist (minimum of 3 years of experience) under the hematoxylin-eosin stain and examined under a light microscope (Olympus, Beijing China). Based on the histological examinations, the lesions were classified as benign or malignant. The malignant lesion was further graded as ductal carcinoma in situ (DCIS), nonscirrhous type invasive ductal carcinoma, and invasive ductal carcinoma. The benign lesions were further graded as included fibroadenoma, intraductal papilloma, and aberrations without fibroadenoma of normal development and involution (eg, sclerosing adenosis, lobular hyperplasia, and duct papillomatosis).[16]

### 2.8. Beneficial score analysis

Decision curve analysis was applied to get a beneficial score analysis for adopted diagnostic modalities for detection of the breast lumps as per Eq. 1 and 2[20]:

$$\text{Beneficial score} = \frac{\text{accurate positive lesions detected}}{\text{numbers of women subjected}} - \left(\frac{\text{false positive lesions detected}}{\text{number of women subjected}} \times \text{risk of overdiagnosis}\right) \quad (1)$$

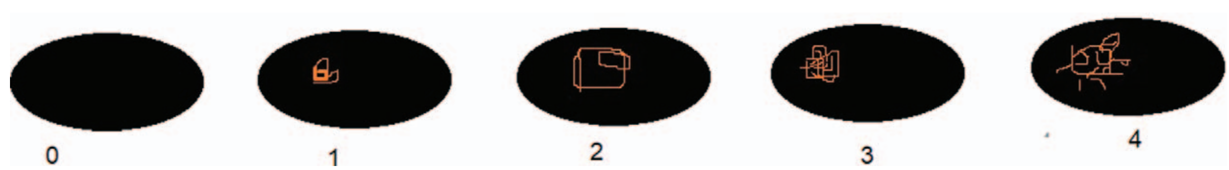


**Figure 3.** Schematic representation of contrast ultrasound images. Black: the breast tissue. Brown: contrast enhancement. 0: no deformation, 1: the central part was not deformed and the edges were deformed, 2: the central part was deformed and the edges were not deformed, 3: the lesion was deformed except surrounding, 4: the lesion was deformed including surrounding.

**Table 2**

**Contrast ultrasound images interpretation.**

| Observation | Score | Interpretation |
|---|---|---|
| No enhancement in the lesion | 0 | No deformation |
| Iso-and synchronous enhancement of the lesion without a clear outline in the image | 1 | The central part was not deformed and the edges were deformed |
| Homogeneous ring-like enhancement of the lesion with a clear outline in the image | 2 | The central part was deformed and the edges were not deformed |
| Heterogeneous enhancement of the lesion with a clear outline in the image without a perfusion defect and crab claw-like enhancement | 3 | The lesion was deformed except surrounding |
| Heterogeneous enhancement of the lesion with a clear outline in the image with a perfusion defect and crab claw-like enhancement | 4 | The lesion was deformed including surrounding |

All images were analyzed by ultra-sonographers (blinded regarding pathological findings) with 5 years of experience in breast ultrasonographic image analysis.

$$\text{Risk of overdiagnosis} = \frac{\text{level of diagnostic confidence above which mastectomy was performed}}{4 - \text{level of diagnostic confidence above which mastectomy was performed}} \quad (2)$$

### *2.9. Statistical analysis*

Data were subjected to the Chi-square Independence test.[6] InStat, version Window, GraphPad Indiana, San Diageo, CA was used for statistical analysis purposes. All data were considered significant at 99% of confidence level.

## 3. Results

### *3.1. Study participation*

From May 16, 2014 to May 14, 2018, a total of 1087 women with a damp in breast mass, breast pain, nipple discharge, and/or breast skin discharge were available at an outpatient setting of the Weifang Yidu Central Hospital, China and the referring hospitals. Among them, 35 women had confirmed breast cancer by biopsies and 52 women had negative clinical, pathological, and sonographic examinations in past 9-months. Therefore, they were excluded from the analysis. A total of 1000 women were included in the cross-sectional study. STARD flow diagram of the study is presented in Figure 4.

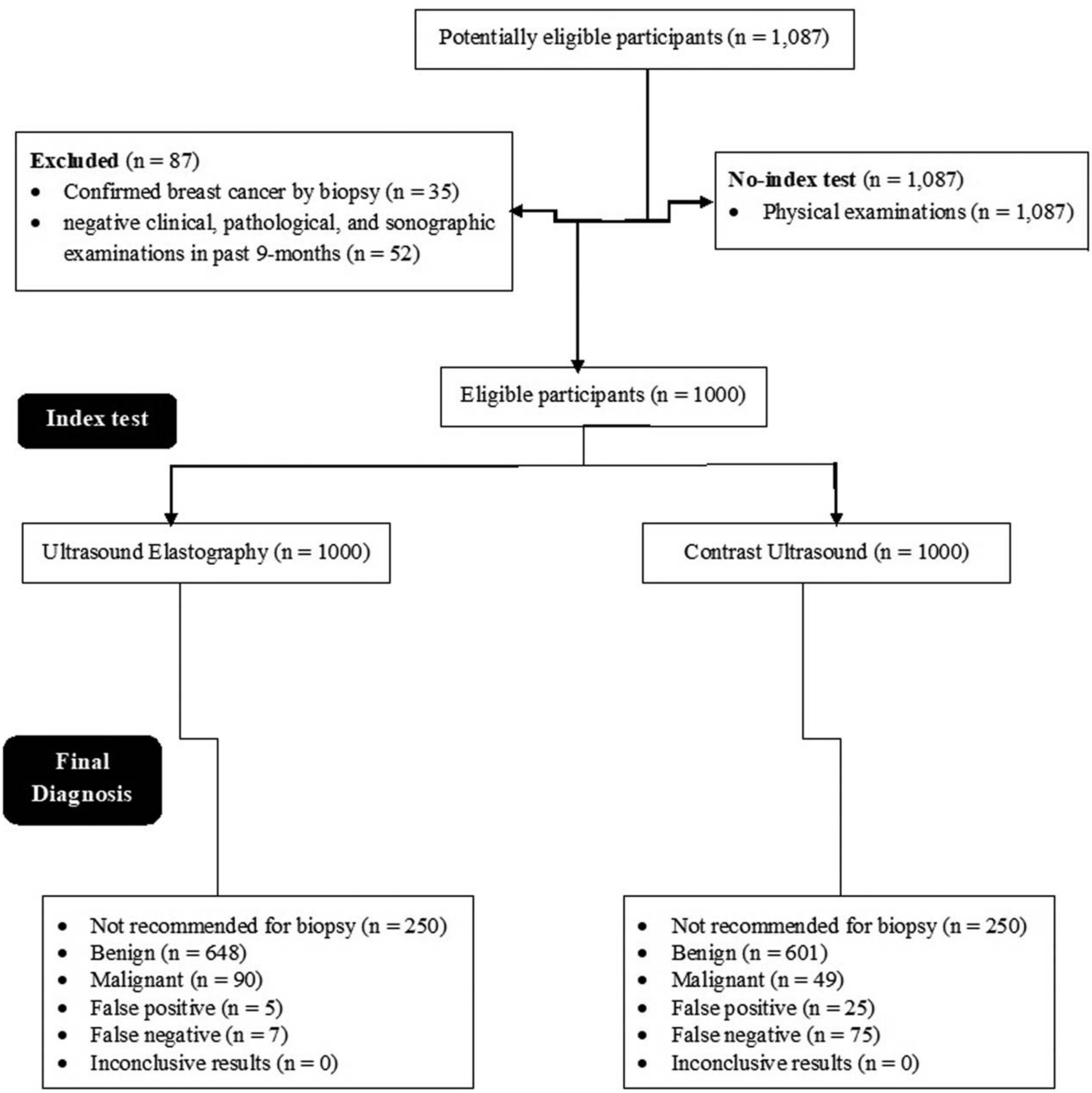


**Figure 4.** STARD flow diagram of the study. STARD = standard for reporting diagnostic accuracy studies.

**Table 3**

**Demographic and social characteristics of enrolled patients.**

| Characters | Populations |
|---|---|
| **Sample size (numbers of patients included in the study)** | **1000** |
| Age, yr | |
| Minimum | 45 |
| Maximum | 75 |
| Mean ± SD | 54.55 ± 8.71 |
| Body mass index, kg/m$^2$ | 23.52 ± 3.45 |
| Menopausal status | |
| Premenopausal | 731 (73) |
| Postmenopausal | 269 (27) |
| The family history of breast cancer | |
| No | 912 (91) |
| Yes | 88 (9) |
| Occupation | |
| Housewife | 734 (73) |
| Mental/manual worker | 266 (27) |
| Education | |
| Undergraduate | 351 (35) |
| Graduate | 552 (55) |
| More than graduate | 97 (10) |
| Marital status | |
| Married | 851 (85) |
| Divorced | 61 (6) |
| Single | 88 (9) |
| Smoker | |
| No | 811 (81) |
| Previous | 108 (11) |
| Current | 81 (8) |
| Alcohol consumption | |
| No | 801 (80) |
| Previous | 112 (11) |
| Current | 87 (9) |

Constant variables were represented as a number (percentage). Continuous variables were represented as mean ± SD.
All women are of PR China origin.
SD = standard deviation.

### 3.2. The demographic characteristics

Forty-five years to 75 years aged women were included in the study. Seventy-three percent of women were premenopausal, only 9% of women had a family history of breast cancer. Seventy-three percent of women were housewives, while 27% of women were workers. The other demographic characteristics of enrolled patients are reported in Table 3.

### 3.3. Biopsies

Ultrasound elastography and contrast ultrasound were recommended biopsies in 750 women and biopsies of only these women were performed. Therefore, biopsies data of 750 women had taken into statistical analysis. Histopathological findings had provided information for the type of breast cancer (Fig. 5). There was a very low case of the invasive tumor but a lot of patients with DCIS (Table 4).

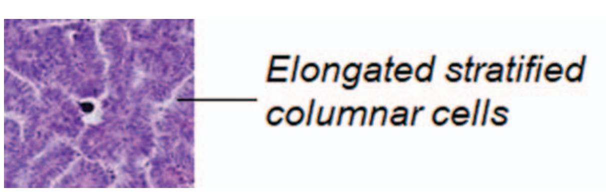


**Figure 5.** Histology of breast lesion.

**Table 4**

**Histopathological findings.**

| Lesions type | Population |
|---|---|
| **Sample size** | **750** |
| Benign | |
| Fibroadenoma | 431 (57) |
| Intraductal papilloma | 112 (15) |
| Aberrations without fibroadenoma of normal development and involution | 108 (14) |
| Malignant | |
| Ductal carcinoma in situ | 79 (11) |
| Nonscirrhous type invasive ductal carcinoma | 12 (2) |
| Invasive ductal carcinoma | 8 (1) |

Data were represented as number (percentage).
Histopathology was performed by a pathologist (minimum of 3 years of experience) under the hematoxylin-eosin stain.

### 3.4. Ultrasound elastography and contrast ultrasound

Ultrasound elastography was detected the same numbers of benign lesions (648 vs 651, $P = .88$) and malignant lesions (90 vs 99, $P = .53$) as those detected by biopsies. Also, ultrasound elastography had no significant difference in false positive lesions (5 vs 0, $P = .07$), false negative lesions (7 vs 0, $P = .02$), and sensitivity (0.9907 vs 1, $P = .02$) compared to biopsies results. However, diagnostic parameters for contrast ultrasound had a significant difference with those detected by biopsies ($P < .0001$ for all). The accuracy for detection of the breast lumps was in the order of biopsy > ultrasound elastography > contrast ultrasound (Table 5).

Prediction for lesions according to image analysis also had a significant difference between ultrasound elastography and contrast ultrasound ($P = .002$, Table 6).

### 3.5. Beneficial score analysis

The working area for contrast ultrasound to detect deformation in the image of the lesion at least 1 time was 0% to 45% (limited to heterogeneous and homogeneous ring-like enhancement of the lesion) and over 45% of the working area (for iso- and synchronous enhancement of the lesion without a clear outline in the image) there were chances of overdiagnosis. While the working area for ultrasound elastography to detect deformation in the image of the lesion at least 1 time was 5% to 100% (all types of deformation). There was the least risk of overdiagnosis for ultrasound elastography. The cysts detection had a high working area for ultrasound elastography and did not require to perform biopsies (Fig. 6).

## 4. Discussion

### 4.1. Ultrasound diagnosis

The study was a 5-point grading system that put contrast ultrasound and ultrasound elastography on 1 benchmark and reported that both were successful in the diagnosis of the benign and malignant breast lumps in ladies including premenopausal women (73%). Early diagnosis of women with the breast lump (small than 2 mm) is increased the survival rates of them.[17]

**Table 5**

**Diagnostic parameters for adopted modalities.**

| Type of lesions | Diagnostic modalities | | | | |
|---|---|---|---|---|---|
| Sample size | Biopsy 750 | Ultrasound elastography 1000 | Comparisons between biopsy and ultrasound elastography *P*-value | Contrast ultrasound 1000 | Comparisons between biopsy and contrast ultrasound *P*-value |
| Not recommended for biopsy | – | 250 (25) | N/D | 250 (25) | N/D |
| Benign | 651 (87) | 648 (64.8)* | .88 | 601 (60) | .007 |
| Malignant | 99 (13) | 90 (9)* | .53 | 49 (5) | <.0001 |
| Sensitivity | 1 | 0.997* | .02 | 0.9 | <.0001 |
| Accuracy | 1 | 0.984 | .001 | 0.8667 | <.0001 |
| False positive | 0 | 5 (0.5)* | .07 | 25 (3) | <.0001 |
| False negative | 0 | 7 (0.7)* | .02 | 75 (7) | <.0001 |

Data were represented as number (percentage).
The Chi-square Independence test was used for statistical analysis.
A $P<.01$ was considered significant.
All images were analyzed by ultra-sonographers (blinded regarding pathological findings) with 5 years of experience in breast ultrasonographic image analysis.
If the ratio of an elasticity imaging to B-mode was 1 or more than 1, lesions were graded as malignant and if those ratios were less than 1 lesions were graded as benign.
If greater and longer signal enhancement of contrast agent was found, lesions were graded as malignant and if fair signal enhancement of contrast agent was found, lesions were graded as benign.
False positive: deformation was reported in ultrasound but was not reported in the biopsy.
False negative: deformation was not reported in the ultrasound but was reported in the biopsy.
N/D = not derived.
* Not significant with biopsy result.

Ultrasound is effective than mammography in Chinese premenopausal women.[3] The study recommended ultrasound instead of mammography in Chinese women for the possible breast lump detection.

### 4.2. Diagnostic parameters

Compared to biopsies, ultrasound elastography had not significant false positive lesions while contrast ultrasound had higher numbers of false positive lesions ($P<.0001$). The results of the study were in line with the available study[4] but not consistent with a preliminary report.[18] The possible justification for higher false positive lesions of contrast ultrasound was that the blood supply in the microvessels of the breast is responsible for the false positive image in contrast ultrasound.[21] Also, compared to biopsies, ultrasound elastography is a fast diagnostic method.[17] Among diagnostic modalities, ultrasound elastography method is a superior method for the detection of breast cancer.

Compared to biopsies, ultrasound elastography had 0.9907 and contrast ultrasound had 0.9 sensitivities. The results of the study were consistent with the prospective study.[17] Contrast ultrasound has difficulties in identifying breast lumps less than 2 mm in size.[13] Ultrasound elastography imaging has high sensitivity in characterizing breast lumps and contrast ultrasound underestimates breast lumps in Chinese women.

### 4.3. Beneficial score analysis

Beneficial score analysis had a high working area for ultrasound elastography and low risk of overdiagnosis than contrast ultrasound especially to detect iso- and synchronous enhancement of the lesion. The results of the study were in line with the present study.[17] Annual follow-up is required for contrast ultrasound,[22] which leads to overdiagnosis of the breast for lump detection. In respect to the risk of overdiagnosis, ultrasound elastography is the safest option for diagnosis of breast lumps.

**Table 6**

**Ultrasound findings.**

| Score | Diagnostic modalities | | Comparisons between diagnostic modalities |
|---|---|---|---|
| Sample size | Ultrasound elastography 1000 | Contrast ultrasound 1000 | *P*-value |
| 0 | 250 (25) | 250 (25) | |
| 1 | 399 (40) | 458 (46) | |
| 2 | 154 (15) | 144 (14) | .002 |
| 3 | 107 (11) | 99 (10) | |
| 4 | 90 (9) | 49 (5) | |

Data were represented as a number (percentage).
0: No deformation,
1: Central part was not deformed and the edges were deformed,
2: Central part was deformed and the edges were not deformed,
3: The lesion was deformed except surrounding,
4: The lesion was deformed including surrounding.
The Chi-square independence test was used for statistical analysis.
All images were analyzed by ultra-sonographers (blinded regarding pathological findings) with 5 years of experience in breast ultrasonographic image analysis.
A $P<.01$ was considered significant.

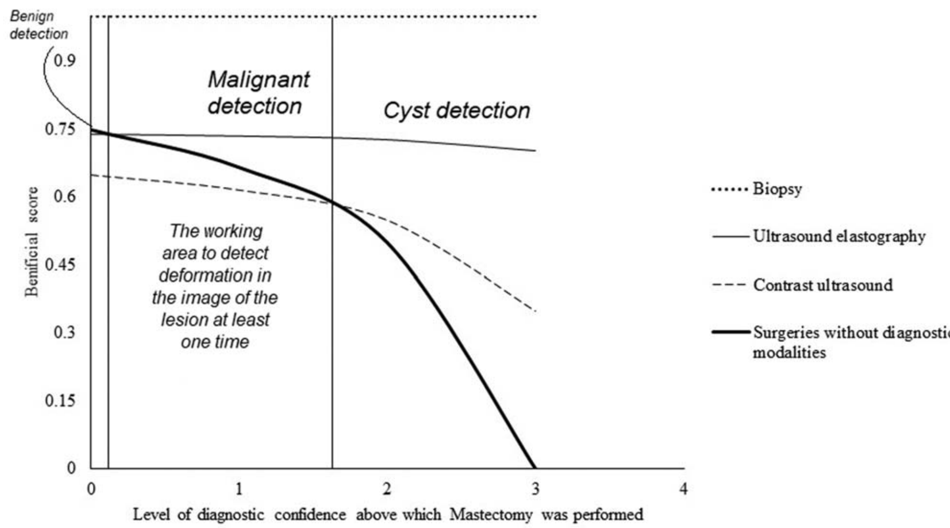


**Figure 6.** Beneficial score analysis for adopted modalities. Surgeries without diagnostic modalities were used for comparison purpose only. The beneficial score was true positive ratio respect to the risk of overdiagnosis and false negative ratio. Ultrasonography was performed by ultra-sonographers (minimum 3 yr experience) of the institute.

### 4.4. Limitations

In the limitations of the study, for examples, biopsies were performed for 750 women only. The cause for the discharge of the breast skin or the nipple was not evaluated for remaining women (n=250). There were 5 lesions were found false positive in ultrasound elastography in respect to biopsies results. The possible justification for that elastography of normal lesions and benign lesions are almost the same in the case of the dense breast.[17] Contrast ultrasonography has high accuracy in the case of malignant breast cancer because malignant lesions are inflammatory lesions[23] but the study was no evaluated diagnostic parameters for false negative results in details. The possible reason for that the chances of a malignant tumor are less than the benign tumor in the breast cancer screening.[24] Ultrasound elastography has the limitation of detection of DCIS,[17,25] for example, the ratio of an elasticity imaging to B-mode was found 1 or less in case of DCIS. Also, ultrasound is not completely reliable and controversial for the detection of nodal metastases of breast cancer.[26]

## 5. Conclusion

The 5-point graded cross-sectional study on ultrasound concluded that ultrasound elastography is the most reliable method for detection of the breast lumps than contrast ultrasound.

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## Author contributions

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**Supervision:** Yingying Liu.
**Writing – original draft:** Zaibin Zhang.
**Writing – review and editing:** Zaibin Zhang.
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