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Quantitative and Qualitative Evaluation of Breast Cancer Prognosis: A Sonographic Elastography Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CE 1 Yue You
BD 1 Yu Song
EF 1 Songxiu Li
EF 2 Zhenhai Ma
AEG 1 Huaying Bo

1 Department of Ultrasound, The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, P.R. China
2 Department of Breast Surgery, The Second Affiliated Hospital of Dalian Medical University, Dalian, Liaoning, P.R. China

Corresponding Author: Huaying Bo, e-mail: bohuaying@outlook.com
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Background: Breast cancer is one of the most commonly diagnosed cancers in women worldwide, and sonographic elastography has previously demonstrated good performance in detecting breast malignancies. However, the exact relationship between elastographic measures and clinical prognostic factors is still not well understood. Thus, the aim of this study was to evaluate any associations between major clinical prognostic factors and strain elastography and to validate the diagnostic value of elastography in breast cancer.

Material/Methods: A total of 373 subjects with breast masses, of which 196 were benign and 177 were malignant, were included in the study. All subjects underwent routine ultrasound examination and strain elastography before biopsy. The elastographic measures – strain ratio (SR) for qualitative measures and Tsukuba score (TS) for quantitative measures – were obtained and compared with prognostic factors, including nuclear grade, lymph node status, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 (HER-2). The SR demonstrated the best diagnostic performance in differentiation between malignant and benign lesions.

Results: With the best cut-off value at 2.42, the SR achieved a sensitivity of 96.0% and specificity of 98.5%. Moreover, higher SRs and TSs were associated with breast lesions with a high nuclear grade and lymph node metastasis and with being ER-negative, PR-negative, and HER-2 negative.

Conclusions: Elastography is a useful imaging technique in differentiating benign breast masses from malignant ones. The strong relationship between prognostic factors and elastographic measures also demonstrated its excellent performance in predicting the prognosis of breast malignancies.

MeSH Keywords: Breast Neoplasms • Elasticity Imaging Techniques • Ultrasonography, Doppler

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Background

Threatening the health of more than 2.1 million women in both developed and developing regions each year, breast cancer is the major cause of cancer-related deaths among women. Despite the serious situation that we are now facing, screening and improved treatment have helped clinical practitioners significantly increase the overall survival of women with breast cancer. Among the methods used in clinical practice for the evaluation of breast lesions, non-invasive preoperative diagnostic techniques are more favorable than other intra-operative examinations since healthcare resources can be optimized and surgery can be tailored to avoid unnecessary morbidity [1]. Various screening and follow-up examinations, like annual mammography, ultrasound, computed tomography, and magnetic resonance imaging (MRI), are recommended by different guidelines [2]. Imaging has always played an indispensable role in tumor staging, treatment planning, treatment response assessing, and detecting recurrent disease.

Due to its low cost and feasible implementation, in developing regions ultrasound is used more in breast cancer detection, image-guided biopsy, and lymph node diagnosis compared to mammography and MRI [3]. In further consideration of the factors of radiation safety, sonography has its own unique advantages over mammography. A negative predictive value of 99.5% [4] was demonstrated by traditional 2D ultrasound in distinguishing benign solid lesions. However, the vague differentiation between benign and malignant lesions is insufficient for the prediction of disease prognosis. Even patients with malignant tumors have different clinical outcomes. This makes the qualitative nature of conventional ultrasound not informative enough for disease evaluation [5]. Thus, the application of a novel technique that can both qualitatively and quantitatively evaluate the tissue characteristics could improve the prognostic accuracy.

Elastography was first introduced in the 1990s as a new branch of ultrasound technology. Elastography can both sensitively and non-invasively assess the stiffness and mechanical properties [6] of targeted tissues. Usually, there are 2 ways to assess the stiffness of the tissue: strain elastography and shear-wave elastography [7]. By compressing the tissue, a quasi-static method of elastography induces a color-coded map of the strain ratio (SR) and this map is used to visualize the tissue stiffness of the examined areas. Moreover, to qualitatively classify breast lesions, the Tsukuba elasticity score (TS) was also introduced by Itoh et al. [8] and applied in different studies. With changed elasticity in soft tissues, specific pathological processes can be detected by elastography, thus enabling the differentiation of solid tumors from normal tissues. Potential clinical applications, like assessing the severity of liver fibrosis and differentiating breast lesions [9], thyroid nodules, and prostate abnormalities, are proposed by the guidelines published by the European Federation for Ultrasound in Medicine and Biology [10]. In obstetrics and gynecology, possible uses of elastography include the prediction of preterm delivery [11,12], successful labor induction [13,14], and differentiation between benign and malignant masses. It has also been found that elastography can be used as a complementary tool to conventional ultrasound to avoid unnecessary benign biopsies [15]. Considering that breast cancer can differentiate benign breast lesions and malignant tumors, changes in tissue elasticity might reflect disease outcome. Thus, the purposes of our present study are to: 1) study the diagnostic performance of strain elastography in distinguishing malignant breast tumors and benign ones, and 2) to assess the association between SR and various prognostic factors to determine the prognostic value of SR in breast cancer.

Material and Methods

Participants

This cross-sectional study was conducted at the Department of Ultrasound, the Second Affiliated Hospital of Dalian Medical University, from December 2014 to January 2018. The study protocol was approved by the local institutional review board and written informed consent was obtained from the subjects.

We retrospectively assessed 516 female patients with breast masses who had undergone routine B-mode ultrasound examination. All patients underwent a detailed history check and complete general and gynecological examination before the histopathological diagnosis was obtained via core needle biopsy or excision surgery. Patients with inflammatory cancers or who were receiving ongoing chemotherapy without a histopathological confirmation of the lesion were excluded. Patients with tumorous lesions smaller than 5 mm in diameter were excluded to avoid unreliable delineation of the tumor by MRI. Eventually, 143 patients were excluded and 373 patients were included in our study.

Histological analysis

Histological analysis was performed on tissues obtained by core needle biopsy and excision surgery on the day following ultrasound examination to confirm the final diagnosis (pathologists were blind to sonographic and elastographic findings). The nuclear grade (1 for differentiated, 2 for moderately differentiated, and 3 for poorly differentiated) was determined from formalin-fixed paraffin-embedded tumor tissue sections and stained with hematoxylin and eosin. Immunohistochemistry was performed on paraffin-embedded material using primary antibodies against estrogen receptor (ER), progesterone

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receptor (PR), and human epidermal growth factor 2 (HER-2). The ER and PR expressions were scored as positive or negative with a nuclear immunostaining cut-off of 10% [16]. The HER-2 expression was defined as positive when membrane immunostaining was scored 3+ or when HER-2 gene amplification was demonstrated with a score of 2+. Lymph node information was obtained by sentinel lymph node (SLN) resection followed by immediate lymph node dissection. A positive finding was determined by the presence of metastasis.

Eventually, the prognostic markers considered in the current study were nuclear grade, lymph node status, and molecular markers, including ER, PR, and HER-2.

Elastogram acquisition and analysis

On the day of admission to the hospital, all subjects underwent a sonographic elastography examination to assess breast lesion stiffness. All sonographic and elastographic examinations were performed by the same examiners (You and Song), who had 10 years of experience in breast imaging. A digital sonography scanner (Hitachi HI VISION Preirus, Hitachi Medical Systems Europe Holding AG, Zug, Switzerland, equipped with a 4.0–9.0 MHz multifrequency probe) with real-time tissue elastography software was used for both B-mode ultrasound and elastography. During strain elastography, patients were asked to breathe normally and the elastographic images of the breast were generated by applying minimal vibration or significant compression to the skin above the targeted breast lesion. To avoid insufficient or excessive pressure on the tissue, the obtained elastogram images with either homogeneous color mapping within the region of interest (ROI) or a pressure indicator ranging between 3 and 4 were considered optimal. The ROIs were set to include subcutaneous fat, the superficial portion of the pectoral muscle, both targeted lesions, and the surrounding normal tissue. Elastograms were classified according to the TS scoring system on a scale from 1 to 5. A TS of 1 or 2 indicates a benign lesion and a TS of 3 is probably a benign lesion, whereas a TS of 4 or 5 indicates a malignant lesion [17]. The SR, which is defined as the fat-to-mass strain ratio, was then automatically calculated by the morphometry algorithm. The ROI A was located entirely within the lesion at the maximum diameter and the ROI B was selected to include the subcutaneous fat tissue and exclude the lesion. The SR measurements were performed at least 3 times by 2 independent observers and were based on different static images. The average SRs were recorded as the final results.

Statistical analysis

For continuous variables, the Kolmogorov-Smirnov test was performed. For comparisons between breast cancer and different types of benign lesions, the *t* test was used. In addition, the receiver operating characteristics (ROC) curve was fitted and the area under the ROC curve (AUC) with a 95% CI was determined to find the cut-off SR value for differentiating between benign and malignant breast masses. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

The relationships between the SR value and prognostic factors were calculated using the *t* test with Bonferroni correction. We compared the SR and TS values of nuclear grade 1 versus nuclear grades 2 and 3, lymph node-positive versus lymph node-negative, ER-positive versus ER-negative, PR-positive versus PR-negative, and HER-2 positive versus HER-2 negative. For all statistical analyses, the level of significance was set at $p<0.05$, and SPSS 22.0 (SPSS, Chicago, IL) was used.

Results

A total of 373 women (mean age: 50.2±11.2 years) with breast lesions were included in the study. Out of these 373 subjects, 196 had benign lesions (Figure 1) and 177 had malignant lesions (Figure 2) based on the pathological results. Detailed demographics and pathological types of the lesions are summarized in Table 1.

When we analyzed the TS and SR values of the malignant and benign breast lesions, we found that malignant lesions usually had a higher TS ($p<0.001$) and SR ($p<0.001$) than benign lesions (Table 1). The SR demonstrated significantly better performance than the TS in distinguishing malignant lesions from benign ones, as the ROC curve shows in Figure 3. The AUCs for the TS and SR were 0.902 and 0.995, respectively. With the best cut-off SR value at 2.42, strain elastography achieved a sensitivity of 96.0%, a specificity of 98.5%, a positive predictive value of 98.3%, and a negative predictive value of 96.5% in differentiation. Meanwhile, with the best cut-off value at 2.5, the TS yielded a sensitivity of 93.8%, a specificity of 80.6%, a positive predictive value of 81.4%, and a negative predictive value of 93.5% in differentiation between benign and malignant tumors.

We next examined the relationship between elasticity measurements and independent tumor prognostic factors. We obtained tumor prognostic factors like nuclear grade, lymph node status, and molecular markers, including the ER, PR, and HER-2. Our analysis revealed significant associations between the SR and TS values versus all prognostic factors. In those patients with malignant breast lesions, univariate analysis demonstrated significantly higher SR and TS values for high nuclear grade (grade 2 and 3), lymph node-positive, ER-negative, PR-negative, and HER-2 negative lesions. Detailed SR and TS values for patients with different prognostic factors are shown in Table 2.

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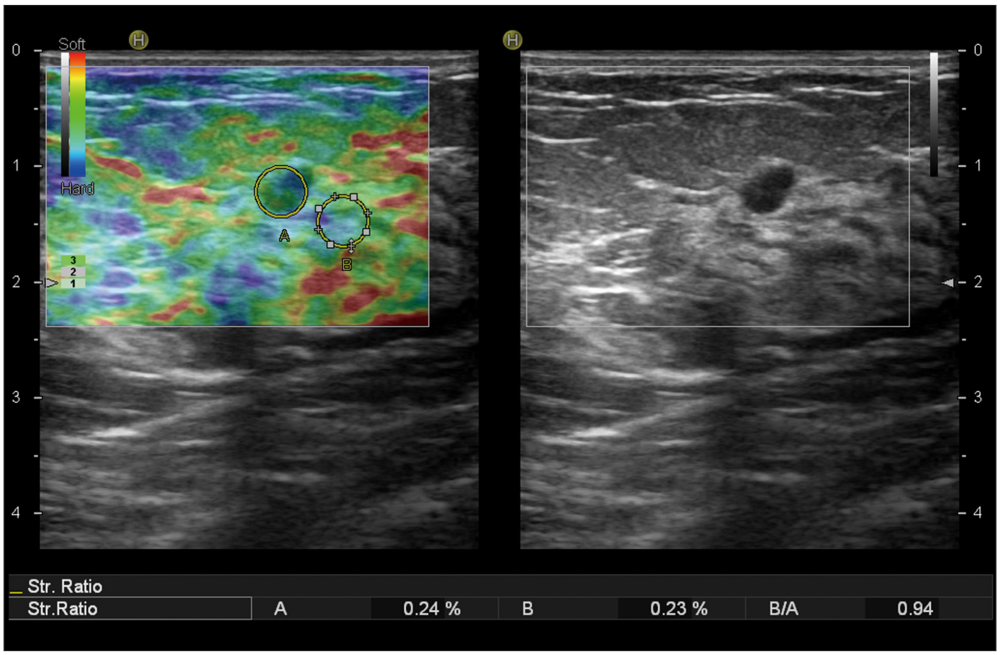

Figure 1. Sonographic elastography image of a 50-year-old woman with a breast mass confirmed to be fibroadenoma. The left image shows the elastography mode while the right shows the routine B-mode sonography. The 2 circles represent the regions of interest (ROI), which were used for the calculation of strain ratio (SR). ROI A was located entirely within the lesion at maximum diameter and ROI B was selected to include the subcutaneous fat tissue and exclude the lesion. This lesion was qualitatively scored with a TS value of 1 and quantitatively with an SR value of 0.94.

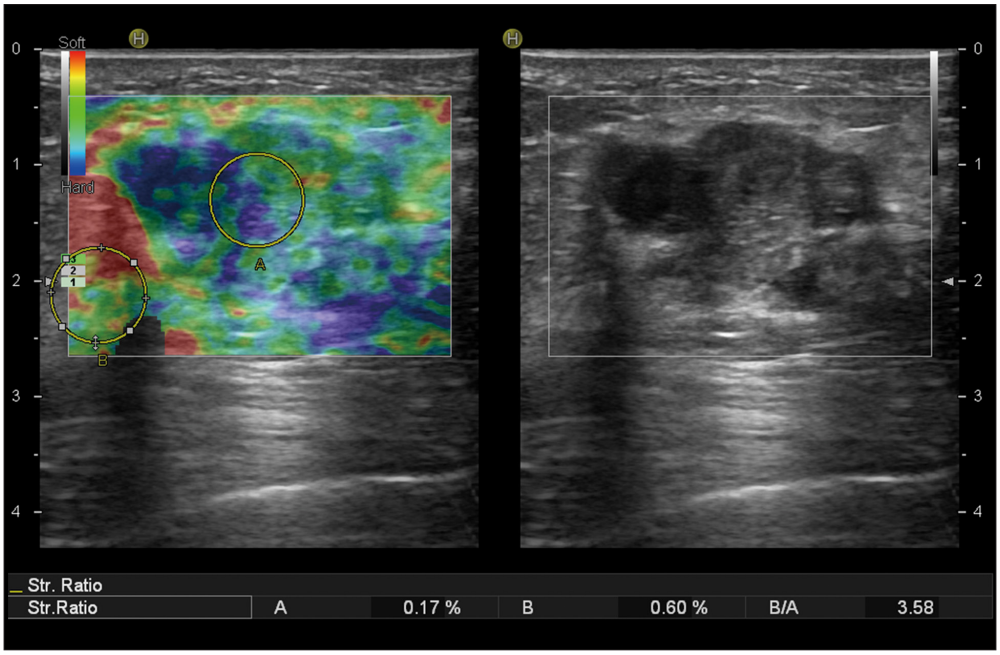

Figure 2. Sonographic elastography image of a 60-year-old woman with a left breast mass confirmed to be an infiltrating ductal carcinoma. The histologic grade was 2, with axillary lymph node metastasis. Immunohistochemical staining was positive for ER and HER-2 expression, and negative for PR. The left image shows the elastography mode while the right shows the routine B-mode sonography. The 2 circles represent the regions of interest (ROI), which were used for the calculation of strain ratio (SR). ROI A was located entirely within the lesion at maximum diameter and ROI B was selected to include the subcutaneous fat tissue and exclude the lesion. This lesion was qualitatively scored with a TS value of 3 and quantitatively with an SR value of 3.58.

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Table 1. Patient demographics, histopathological diagnosis, and imaging biomarkers for patients with benign and malignant breast lesions (n=373).

Characteristics	Benign (n=196)	Malignant (n=177)	P value
Age (years)	49.9±11.5	50.6±10.9	0.54
Final diagnosis; n (%)			
Fibrocystic changes	9 (4.6)	–	–
Plasma cell mastitis	39 (19.9)	–	–
Intraductal papilloma	23 (11.7)	–	
Fibroadenoma	57 (33.3)	–	
Mastopathy	48 (25.1)	–	
Sclerosing mastopathy	20 (10.0)	–	
Infiltrating ductal carcinoma	–	76 (42.9)	
Malignant phyllodes tumor	–	20 (11.3)	
Mucinous carcinoma	–	16 (9.0)	
Invasive lobular carcinoma	–	65 (36.7)	
TS	1.86±0.98	3.63±0.77	<0.001**
SR	1.67±0.51	4.8±2.55	<0.001**

** p<0.001.

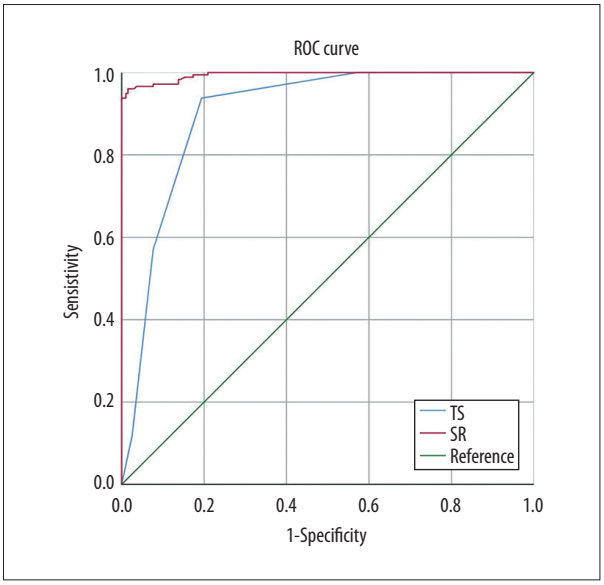

Figure 3. Receiver operating characteristic curve (ROC) for strain ratio (SR) and a Tsukuba score (TS) in differentiation between benign and malignant breast lesions. The diagonal line is the line of no-discrimination.

Discussion

To the best of our knowledge, this is the first large-population study conducted with subjects of Chinese ethnicity to evaluate the efficacy of strain elastography in predicting breast cancer outcome. In general, our study confirmed that sonographic elastography has good diagnostic and prognostic performance for clinical and imaging evaluations of suspected local breast lesions. Our results showed that malignant breast lesions had higher lesion elasticity, as indicated by higher SR and TS values, than that of benign lesions. Our data showed a sensitivity of 96.0% and specificity of 98.5% when using the SR to classify breast lesions. When we further compared those elasticity measurements between patients with better and worse prognostic factors, we found that patients with relatively worse clinical outcomes demonstrated significantly higher SR and TS values.

We first validated the diagnostic value of elastography. For daily clinical assessment of suspected breast lesions, traditional B-mode ultrasound is an essential tool in the gross evaluation of the morphology, orientation, internal structure, and margins of lesions [18]. However, the traditional B-mode ultrasound technique is prone to give false results [19] due to the moderate sensitivity and specificity of this method. Elastography, which is more comprehensive in terms of assessing differences in stiffness between different tissue types, thus potentially improves the accuracy of breast cancer diagnosis [6]. Previous studies showed that increased stiffness of targeted tissue on an elastography scan usually indicates the presence of neoplastic cells [18]. For instance, an *ex vivo* investigation of breast tissue samples showed that normal breast fat and fibroglandular tissue usually present with similar elasticity, while fibroadenomas

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Table 2. Associations between prognostic factors and SR measurements for patients with malignant breast lesions (n=177).

Prognostic factors	No. of cases (n=177)	SR		TS	
		Mean±SD	P value	Mean±SD	P value
Nuclear grade	1 (n=160)	1.85±0.09	<0.001	1.18±0.12	<0.001
	2+3 (n=147)	1.56±0.11		0.87±0.08	
Lymph node status	Positive (n=120)	5.31±2.75	<0.001	3.80±0.75	<0.001
	Negative (n=57)	3.73±1.67		3.26±0.69	
ER	Positive (n=42)	3.53±1.23	<0.001	3.26±0.54	<0.001
	Negative (n=135)	5.20±2.73		3.74±0.80	
PR	Positive (n=39)	3.45±1.85	<0.001	3.10±0.72	<0.001
	Negative (n=138)	5.19±2.61		3.78±0.73	
HER-2	Positive (n=43)	3.48±1.64	<0.001	3.14±0.64	<0.001
	Negative (n=134)	5.23±2.66		3.78±0.75	

were twice as stiff as fat tissue [20]. Fibrocystic disease and malignant tumors showed a 3- to 6-fold increase in stiffness, while invasive ductal carcinoma could achieve up to a 13-fold increase in stiffness compared to fibroglandular tissue [20]. Thus, to measure the tissue stiffness both qualitatively and quantitatively, different indices were proposed. The most frequently used quantitative measurement is SR, which is quantified by the fat-to-lesion ratio in breast imaging. The qualitative method usually refers to a 5-point scoring system introduced by Itoh et al. [8]. The scoring system proposed that a score of 1 refers to deformability of the entire lesion; a score of 2 refers to deformability of majority of the lesion shows small, stiff areas; a score of 3 refers to stiff tissue in the center surrounded by deformability; a score of 4 refers to the entire lesion is stiff; while a score of 5 refers to both the lesion and the surrounding tissue are stiff. Eventually, sensitivities ranging from 75% to 93% and specificities up to 93% could be observed when using elastography to detect breast malignancies [21–23]. Our results are in line with previous studies and show that the SR is more feasible than the TS in clinical settings. However, when compared with traditional B-mode ultrasound, elastography does not contribute much to the sensitivity of assessing breast malignancy but it still improved the specificity and accuracy of predicting malignancy in the breast, especially in BI-RADS US-3 lesions [21]. So far, no consensus has been reached in terms of the absolute threshold needed to distinguish benign and malignant lesions. This might be due to the subjective nature of elastography. Although different values were proposed by different studies, some authors suggested that using a fixed value to categorize lesion type should always be avoided [24,25].

The major contribution of the present study lies in the prognostic value of elastography. Breast cancer is one of the most commonly diagnosed cancers in women worldwide, and various examinations have demonstrated promising performance for the detection, diagnosis, and prognostic evaluation of breast cancer [26]. Considering that personalized and targeted therapeutic approaches are largely dependent on accurate tumor characterization, both in terms of histological composition and biological aggressiveness, a non-invasive method capable of providing all the prognostic features is superior other techniques. Traditional prognostic factors for breast cancer include histology, stage (size and axillary node involvement), tumor grading, heredity, obesity, smoking, and molecular markers [27]. Among these factors, molecular markers like ER, PR, and HER-2 status have been recently and widely used as indicators to guide adjuvant therapy and predict long-term outcomes [28]. Since ultrasound examinations are less expensive and more available in developing countries compared to the Oncotype DX, the development of sonographic biomarkers for breast cancers has been conducted by many researchers. From the above results demonstrating that malignant breast lesions had higher SRs and TSs, we would expect that lesions with higher stiffness, which might be due to higher proliferation and cellularity, would be correlated with higher aggressiveness in general. Cellularity is an important indicator of tumor malignancy and prognosis. Since increased cellular density of a high-grade tumor is associated with higher tissue stiffness, tumor cellularity is associated with the tumor SR. This theory is in line with the findings of a study by Lee et al. that used shear-wave elastographic features to prove that histological grade 3 tumors had higher stiffness than other grades due to higher tumor cellularity. In our study, SR and TS both demonstrated very good performance in predicting the clinical outcomes of breast cancer. However, the exact relationships between tissue stiffness and well-known prognostic factors are still not well understood. Durhan et al. [29] published

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controversial results stating that lower SR values were associated with a higher histological grade, while our results demonstrated a statistically significant association between a higher nuclear grade and higher SR value. Although the prognosis of malignant tumors does not exclusively depend on cancer cells, the histopathological characteristics of the tumor, especially tumor grade, still have a strong correlation with tumor progression. Meanwhile, our results showed that patients with detected lymph node metastasis had a significantly higher SR in the primary breast tumor. This is in line with other imaging studies [30,31] that commonly suggested that higher cellularity is an indicator of higher aggressiveness and metastatic potential. Overexpression of the HER-2 accelerates cell growth, thus contributing to the carcinogenesis of cells. Consequently, HER-2-positive cells have more malignant phenotypes than do HER-2 negative cells, which is usually linked with cell proliferation, invasion, and metastasis. However, the present study showed a higher SR value in HER-2-negative breast cancer than in HER-2-positive breast cancer. This lower SR we observed in HER-2 positive lesions might be associated with lower fibrosis and higher necrosis. We also observed a higher SR and TS in ER- and PR-negative lesions, whereas most studies did not observe any significant association between them. Thus, the correlation of SR with other prognostic factors like ER, PR, and HER-2 is less consistent to date and may vary in different populations. Further large-population studies may be needed to determine the relationship between elastographic measures and these prognostic factors.

There are several limitations to the present study, including the lack of comparison between traditional B-mode ultrasound and elastography. Although extensive studies have already been done in this area, additional information regarding this issue could have made our study more comprehensive. Second, the study was performed in populations with clear pathological results, which may have yielded selection bias in our population. Finally, we were not able to evaluate the inter- and intra-observer variability of elastography. We will address this issue in our future research to further assess the reliability of this technique.

Conclusions

Strain elastography demonstrated excellent performance in differentiating malignant breast lesions from benign ones. More importantly, both the SR and TS were significantly associated with clinical prognostic factors, suggesting elastrographic features could potentially be used to predict breast cancer outcomes.

Conflict of interest

None.

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