Original Article
Strain elastography features in invasive breast cancer: relationship between stiffness and pathological factors

Ye Jin, Fenghua Li, Jing Du, Yifen Guo

Department of Ultrasound, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

Abstract: Our study aimed to investigate the relationship between stiffness and pathological factors in invasive breast cancer. We evaluated stiffness by strain elastography indicators of elasticity score and hardness percentage (HP) in tumors that histologically confirmed as invasive breast cancers. The relationship between stiffness and pathological factors including histologic type, histologic grade and molecular subtypes were analyzed, and the most influential factor was further determined by logistic regression analysis. Of 291 invasive breast cancers, 230 (79.0%) tumors were stiff according to elasticity score evaluation, and the average value of HP was (82.32±15.72)%. Based on the elasticity score result, the cutoff value of HP for hard tumors was 80.0% (sensitivity 90.1%, specificity 100.0%), lesions with inconsistent evaluation results by two indicators were almost grade III tumors (19/21). Differences in stiffness could be found in histologic grades (both P<0.001) and molecular subtypes (score P=0.003, HP P<0.001) but were not obvious in histological types (score P=0.034, HP P=0.131). Grade I or grade II (low grade) type tumors and luminal A type tumors were harder, while histologic grade was the only independent factor for tumor stiffness. The grade III group, which had a mean value of HP (65.68±18.02)%, was significantly softer than the low grade group (P<0.001). The cutoff value of HP for low grade tumors was 80.59% (sensitivity 88.2%, specificity 84.4%). Our study revealed a close relationship between tumor stiffness and the histologic grade of invasive breast cancer. Strain elastography may have potential applications to provide prognostic information for patients with breast cancer noninvasively.

Keywords: Elastography, stiffness, hardness percentage, breast cancer

Introduction

At present, strain elastography (SE) has become a valuable supplemental tool in breast diagnosis. SE has been performed successfully in the differentiation of benign and malignant breast lesions, and it could help to increase the specificity and accuracy of conventional ultrasound in assessing breast lesions [1, 2]. The basic principle of SE is the elasticity coefficient, which varies between different breast tissues in ascending order: adipose tissue, fibrosis, non-invasive ductal carcinoma and invasive ductal carcinoma (IDC) [3]. Malignant lesions are stiffer than benign ones. As outlined, breast cancers are histologically heterogeneous, pathological factors are important to breast tumors in classification, treatment and prognosis [4]. Basic research had revealed that tumor stiffness was associated with tumor progression [5], quantity of extracellular matrix collagens

plays an important part in the tumor stiffness [6]. Clinical research also indicated that tumor stiffness may match with disease progression [7]. With the increasing interest in prognostic importance of breast cancer, prognostic significance of SE findings will also be interested. Recently, several reports tried to identify pathological factors that affect the stiffness of breast cancer. Fleury et al. [8] analyzed false negative results by the elasticity score for cancers that presented as soft and found stiffness was influenced by histopathologic type, not by lesion size or patient age. Hayashi et al. [9] specifically evaluated tumor stiffness by the Fat Lesion Ratio in invasive breast cancer and found that lymph node involvement and tumor size, not the molecular subtype, were factors that affected stiffness. Later, Grajo et al. [10] only focused on the tumor grade by comparing maximum dimension of the tumor and found a difference between elasticity imaging/B-mode ratio and
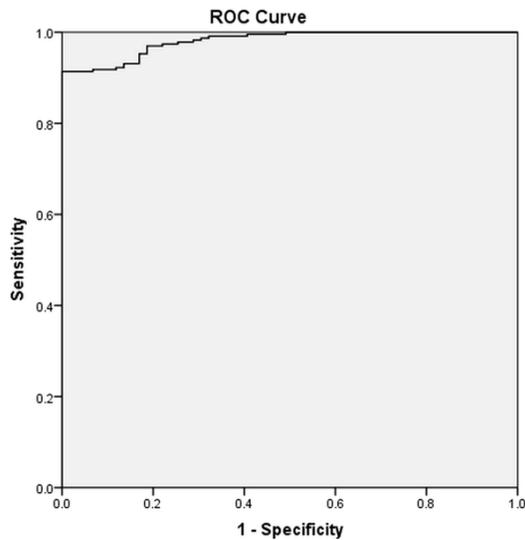
Figure 1. ROC curve for HP method to evaluate tumor stiffness based on elasticity score result.

histologic grade. However, the results above were inconsistent, and the independent pathological factor for tumor stiffness remains to be determined.

Therefore, the aim of our study was to investigated the relationship between tumor stiffness and pathological factors, including histologic type, histologic grade and molecular subtype Two indicators were used to evaluate tumor stiffness. One was the widely recognized evaluation indicator of elasticity score, which is a visual assessment based on the degree and distribution of strain in and surrounding the lesion; the other indicator was hardness percentage (HP), which could offer percentage value for the hardest part of the tumor, and it.was also reported a valuable evaluation indicator [11, 12].

Material and methods

Subjects

From February 2015 to June 2016, patients scheduled for surgery all underwent routine sonographic evaluation before the operation, and 352 patients with 356 lesions were histologically confirmed as invasive breast cancer after the operation. According to our research exclusion criteria, 30 patients who had received breast cancer-related treatments or had undergone biopsy for breast masses before examination, 2 patients with cancer of the accessory mamma at the axilla, and 33 lesions without

quality SE images (mostly too large) were excluded. The remaining 291 lesions in 287 women (age range, 24-85 years; mean age, 54.5±11.9 years) were enrolled in our study. This retrospective study was approved by the ethics committee of our hospital.

SE examinations

All SE examinations were performed by one radiologist who had 7 years of experience in breast ultrasound. Our study was performed using the MyLab™ Twice system (Esaote S.p.A., Genova, Italy) with a linear transducer (LA523, 4-13 MHz). The SE mode was started when optimal B-mode images were selected. According to the WFUMB Guidelines [13], the transducer was placed perpendicularly on the lesion with slight pressure and was kept still to acquire stable images. All images were stored in the machine.

Image analysis

Images were reviewed by two radiologists who were both blinded to patients' clinical data, and all evaluation results were made by consensus. The elasticity score was evaluated according to a five-point classification [14]. Score 1 was given when the whole lesion presented green, which indicated strain over the whole lesion; score 2 was given when the lesion presented as mostly green with a little blue, which indicated strain over most of the lesion with few areas spared; score 3 was given when the lesion presented as half green and half blue, which indicated strain in half of the lesion; score 4 was given when the lesion was predominantly blue, which indicated no strain or a little strain in the whole lesion; and score 5 was given when the whole lesion presented blue, which indicated no strain over the whole lesion or surrounding tissue. HP was analyzed by Elaxto software on the machine. When we traced the lesion on dual grayscale images, HP was auto calculated. In this study, the hardness level of HP was set at 20%, as the color scale of the machine had 5 colors ranging from blue, teal, green, yellow to red. Thus, all blue areas could be counted, which corresponded to the hardest areas in the tumor.

Histopathologic analysis

All pathologic analyses were performed after operation. Histologic types were determined by
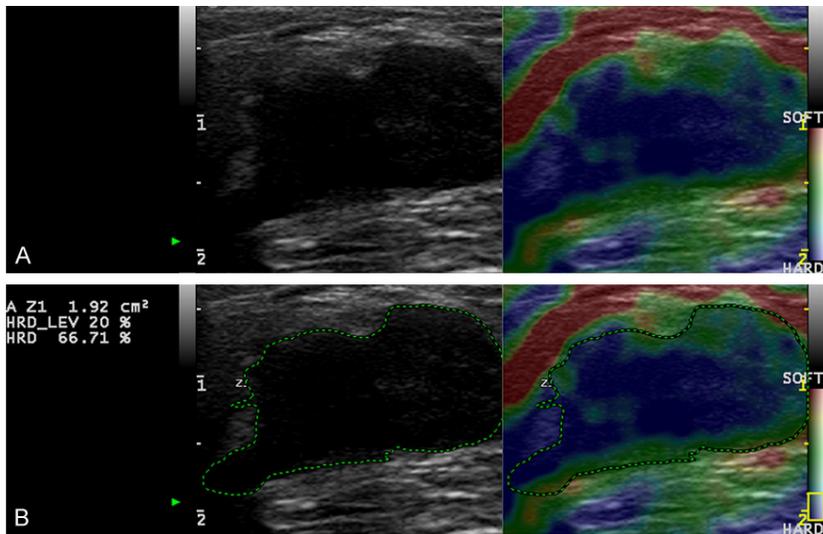
Figure 2. Images from a 42-year-old woman with grade III invasive ductal carcinoma. A. It is an irregular and markedly hypoechoic lesion, and seems hard with score 4 on elastography. B. The hardness percentage was only 66.71%.

Table 1. Stiffness of invasive breast cancer according to pathological factors

Pathological factors	N	Elasticity score			HP	
		2 or 3 n (%)	4 or 5 n (%)	P	Mean value (%)	P
Histologic type				0.034		0.131
Ductal	267	51 (19.1)	216 (80.9)		82.54±15.64	
Papillary	7	2 (28.6)	5 (71.4)		87.04±7.94	
Mucinous	10	4 (40.0)	6 (60.0)		79.06±7.53	
Lobular	5	3 (60.0)	2 (40.0)		66.12±25.78	
Medullary	1	1 (100.0)	0		51.16	
Tubular	1	0	1 (100.0)		91.86	
Histologic grade				<0.001		<0.001
Grade I	12	2 (16.7)	10 (83.3)		88.58±13.79	
Grade II	191	16 (8.4)	175 (91.6)		87.80±9.90	
Grade III	64	33 (51.6)	31 (48.4)		65.68±18.02	
Molecular subtype				0.003		<0.001
luminal A	51	1 (2.0)	50 (98.0)		90.69±6.69	
Luminal B1	126	28 (22.2)	98 (77.8)		81.86±17.22	
Luminal B2	39	9 (23.1)	30 (76.9)		82.25±16.26	
HER2	39	11 (28.2)	28 (71.8)		79.39±14.53	
TN	36	12 (33.3)	24 (66.7)		75.58±15.68	

Note: Luminal B1 = luminal B without HER2 overexpression. Luminal B2 = luminal B with HER2 overexpression.

the World Health Organization classification [15], and histologic grades were assessed by the Elston and Ellis grading system for IDC [16]. Immunohistochemical staining was performed to identify the expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki67. The ER and PR status were considered positive when nuclear staining was present in >10% [17]. The expression of HER2 was considered positive when the result of tumor cell membrane staining was 3+ or 2+ with amplification, which was further assessed by fluorescent in situ hybridization (FISH) analysis [18]. Molecular subtypes were defined by the St. Gallen criteria [19] : luminal A (ER and/or PR positive, HER2 negative, and Ki-67 LI <14%), luminal B without HER2 overexpression (luminal B HER2-, ER and/or PR positive, HER2 negative and Ki-67 LI ≥14%), luminal B with HER2 overexpression (luminal B HER2+, ER or/and PR positive and HER2 positive), HER2 (ER and PR negative and HER2 positive) and triple negative (TN) (ER, PR and HER-2 negative).

Statistical analysis

Tumors with scores of 1 to 3 were classified as soft lesions, and those with scores of 4 and 5 were classified as hard lesions. The chi-square test and Fisher's exact test were used in the comparison of the elasticity score between histological groups. The differences in continuous variable of HPs among pathologic subgroups were evaluated by the Mann-Whitney U-test or Kruskal-Wallis test. If statistical significance was found, the ANOVA
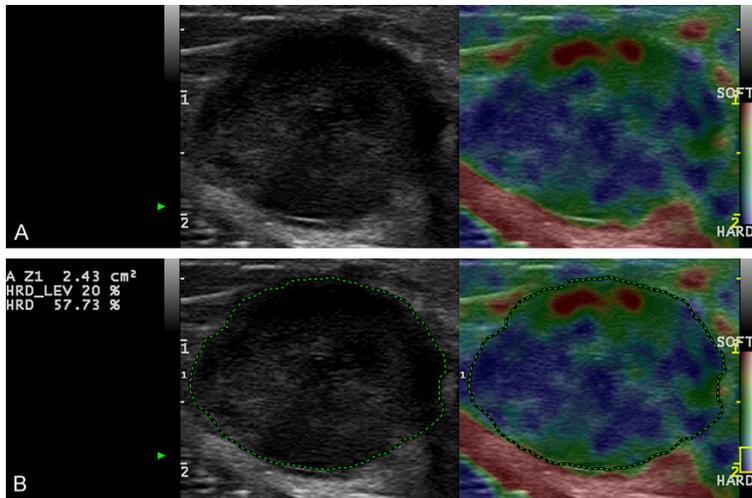
Figure 3. Images from a 34-year-old woman with a triple-negative, grade III invasive ductal carcinoma. A. The lesion is a hypoechoic round mass with a circumscribed margin and posterior acoustic enhancement. The elastography image depicts a green to blue colored lesion with a score of 3. B. The hardness percentage was 57.73%.
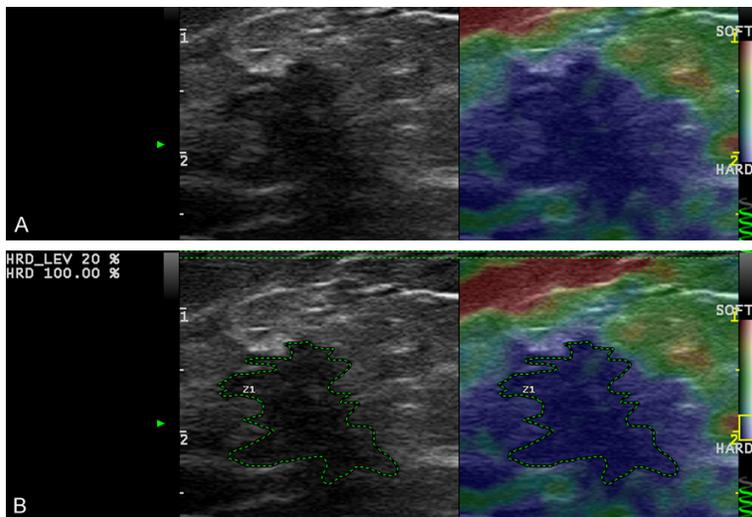

Figure 4. Images from a 40-year-old woman with a luminal A type, grade II invasive ductal carcinoma. A. It is an irregular, hypoechoic mass, and the elastography image depicts a focally blue colored lesion with a score of 5. B. The hardness percentage was 100%.

test was further used to assess the inter-group differences compared to each other. Finally, a logistic regression analysis was used to determine which pathologic factors were independently associated with tumor stiffness, and cutoff values of stiffness were made by ROC. All statistical analyses were performed with SPSS software (SPSS for Windows, Version 20.0; SPSS, Chicago, IL, USA), and P values less than 0.05 were considered statistically significant.

Results

Of 291 invasive breast cancers, 230 (79.0%) tumors were hard, 61 (21.0%) tumors were soft by elasticity score evaluation, no tumor was evaluated as score 1, and the average value of HP was (82.32±15.72)%. If using the elasticity score as a standard, the cutoff value of HP for hard tumors was 80.0% (sensitivity 90.1%, specificity 100.0%). Figure 1 shows the ROC curver. Besides, we found the inconsistent stiffness evaluation results by two methods were almost (19/21) grade III tumors (Figure 2).

When tumors were classified by histological factors, the SE appearances are shown in Table 1. There were 267 IDCs and 24 tumors of special types, and differences in stiffness according to histologic types were compared in subgroups with numbers over 5 (medullary and tubular types with only 1 tumor were not included), statistical significance was not found by HP (P=0.131), but the elasticity score showed a moderate correlation with histologic type (P=0.034). We found significant stiffness differences in histologic grades (both P< 0.001) and molecular subtypes (elasticity score P= 0.003, HP P<0.001). Of 267 IDCs, the grade III (high grade, Figure 3) group with a mean stiffness value of HP (65.68±18.02)% was significantly softer than the grade I or/and grade II (low grade, Figure 4) groups (P<0.001), and statistical significance was not found between the grade I and grade II group (P=0.502). Approximately 51.6% (33/64) of grade III IDCs were soft according to elasticity score evaluation, and there was no tumor with a score of 5 in this group. Among molecular subtypes, the Luminal A tumors (Figure 4) had the highest

Table 2. Influence of pathologic factors on the stiffness of invasive breast cancer

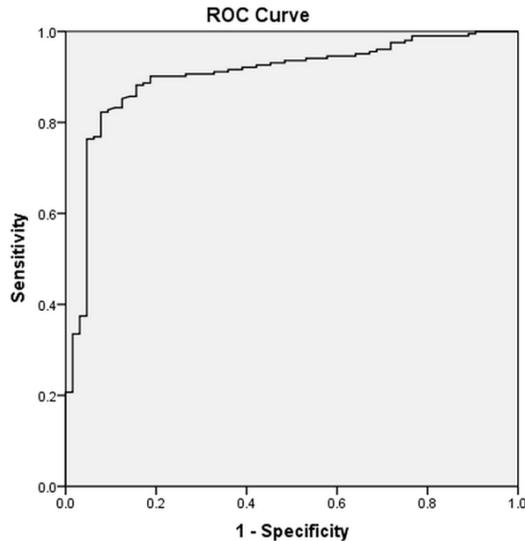| Pathological factors	Odds Ratio	95% Confidence Interval	P
Histological grade	10.07	4.71-21.53	<0.001
Molecular subtypes	0.93	0.70-1.24	0.625

Figure 5. ROC curve for HP method in differentiating low from high grade of invasive ductal carcinomas.

average stiffness value of HP (90.69±6.69)% than the other subtypes, especially compared with the Her2 (P=0.006) or TN tumors (P< 0.001, **Figure 3**). Almost all luminal A tumors were hard according to elasticity score evaluation. Only 1 tumor was soft with a score of 3, and the histological type was mucinous carcinoma.

Regression analysis in **Table 2** indicated that histologic grade was the only independent pathologic determinant of tumor stiffness (P<0.001), and the influence of molecular subtype on tumor stiffness values was not statistically significant (P=0.625). The cutoff value of HP for low-grade IDC was 80.59% with a sensitivity of 88.2% and specificity of 84.4% (**Figure 5**).

Discussion

Recently, SE has become widely available and has shown great diagnostic performance in breast cancer. Our results show that most invasive breast cancers, including 60% mucinous carcinoma and 66.7% TN type tumors, which usually mimicked a benign appearance on conventional ultrasound, exhibited high stiffness. SE may therefore more easily identify invasive breast cancer by tumor stiffness. It was said that malignant breast lesion usually had an obvious desmoplastic reaction or short doubling time, which could make it stiffer than a benign lesion [20]. When taking histological factors into account, we found differences in stiffness with histologic grades and molecular subtypes. The result was consistent with previous studies [8, 21]. High stiffness was noted in low grade IDC and Luminal A tumors This may be because tumors with a lower invasive behavior usually grow slowly and have enough time to develop a desmoplastic reaction [22], which plays an important role in changing tumor stiffness by the components of fibrosis and extracellular matrix protein [23, 24]. Respectively, high-grade IDC and TN in our study were less stiff, and they were recognized as more aggressive tumors with higher cellularity and grew rapidly, which would lead to more internal necrosis and less fibrosis [25]. Our results made sense considering findings by Chamming et al. [26], who reported that stiffness showed a positive correlation with the fibrosis and a negative correlation with tumor cells and necrosis. However, regression analysis indicated that histologic grade was the only independent factor for tumor stiffness, and molecular subtype may be a dependent factor influencing elasticity, stiffness measurement couldn't be used to determine molecular subtype, which was in line with Chang et al. [27]. Furthermore, we found tumors with HP over 80.59% or hard tumors evaluated by elasticity score, were probably low grade tumors. The ability to predict the grade of invasive breast cancer by SE may have clinical significance in making a preliminary prognostic evaluation. The stiffer of the tumor is, the greater of the chance to be related to low-grade carcinoma, with a relative good prognosis.

Though our study found no statistically significant stiffness difference between histologic types, there was a tendency that ductal and papillary carcinomas were relatively hard. What's more, tubular carcinoma in our study also presented with high stiffness, it was recognized as a hard tumor with abundant of fibrous in stroma by basic research [28]. While, it was

not analyzed, more samples may be needed to validate this observation. Nevertheless, our observation suggests that hard tumors may have good prognosis, because those types were all well differentiated tumors.

In addition, we selected two indicators, the elasticity score and HP, to evaluate tumor stiffness. The elasticity score is convenient, but it is a subjective evaluation and offers only a visual assessment of stiffness. Tumors with a highly heterogeneous appearance on SE made the evaluation between score 4 and score 3 difficult [29]. Thus, its combination with HP may facilitate a more accurate, objective evaluation. Meanwhile, we found that the inconsistent stiffness evaluation results by two methods also made sense for aggressive tumors, especially high-grade IDC. According to the principal HP over 80.0% for hard tumors, we found tumors with opposite stiffness evaluation results by elasticity score were almost grade III IDC (90.5%). They usually had an indistinct edge, and the hard part on the color map showed chunks of blue, which made the eye-based elasticity score overrate stiffness. The hard part may be a complicated combination of increased cellularity, microvessel density and fibrosis [30], HER2 was also reported to correlate with a high intracellular sensitivity to stiffness, and the effect was matrix stiffness-dependent [31]. The soft part of the tumor may be the necrotic area, which did not present special characteristics on conventional ultrasound. This finding may have a potential application to identify grade III IDC in clinical practice. When a tumor appears hard at first, but the low value of HP suggests that the mass is not as hard as it appears, a high-grade tumor should be suspected. This was particularly useful because high-grade tumors have been found to be less characteristic on conventional ultrasound. SE may thus be complementary in identifying breast cancer.

There were several limitations in this study. First, though many series of histological types were included, the numbers of special types were too small. A larger cohort may be needed to obtain a more stable statistical model. Second, the intraobserver variation was not analyzed, but two stiffness evaluation methods were used to control the influence of measurement error. Moreover, another limitation was that we analyzed different breast cancers con-sidering stiffness features alone, which might be insufficient. Though it was not the aim of our study, SE combined with conventional ultrasound may do more to help predict the pathological characteristics of breast cancer, which requires further research.

In conclusion, tumor stiffness was related to histological factors, but histologic grade was the only independent factor for tumor stiffness. SE may have the potential ability to discriminate tumor grade and predict clinical outcome non-invasively for patients with breast cancer.

Disclosure of conflict of interest

None.

Address correspondence to: Fenghua Li, Ren Ji Hospital, No.1630 Dong Fang Road, Shanghai, China. Tel: +86-021-68383396; E-mail: fenghua-li@163.com

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