Strain histograms used for differential diagnosis of breast masses according to hardness percentage

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Abstract

To evaluate the diagnostic performance of percentage of hard component (PHC) versus strain ratio (SR) in focal breast lesion diagnosis. Ultrasonography and elastography images of 245 malignant and 255 benign breast lesions were obtained and analyzed according to the Breast Imaging-Reporting and Data System of the American College of Radiology. PHC and SR were measured for each lesion and receiver operating characteristic (ROC) curve analysis was performed to evaluate and compare the diagnostic performance of conventional ultrasound (CU) only, PHC with CU, and SR with CU.

Mean PHC differed significantly between malignant (90.46±13.29) and benign (62.03±25.61) lesions. Mean SR differed significantly between malignant (4.61±1.75) and benign (2.34±1.80) lesions. ROC curve threshold values were 82.45 for PHC and 2.69 for SR. The area under the curve values for CU, SR with CU, and PHC with CU were 0.956, 0.960, and 0.956, respectively, with no significant differences among them (P<.05).

PHC was comparable to SR for differentiating malignant from benign breast masses and may be an auxiliary tool for breast lesion stiffness evaluation. ROC data for CU, SR with CU, and PHC with CU were statistically similar.

Abbreviations: CU = conventional ultrasound, PHC = percentage of hard component, ROC = receiver operating characteristic.

Keywords: breast neoplasm, percentage of hard component, quasi-static elastography, strain ratio, ultrasound

Key Points

- PHC is a new tool of SE to evaluate the stiffness of lesions in breasts.
- PHC does not need reference tissue, and its diagnostic accuracy is higher than SR.
- PHC is a convenient and easy-to-learn method.

1. Introduction

Biological tissues possess a specific inherent elasticity that can be altered by pathophysiological processes, such as tumor development.\textsuperscript{[1]} Elastography is a noninvasive ultrasound imaging technique that enables visualization and measurement of intrinsic tissue stiffness. This method provides an estimation of tissue elasticity by measuring the degree of distortion that occurs with the application of an external force and it is more objective than palpation.\textsuperscript{[2]} Generally, breast lesions with a smaller displacement are characteristic of harder tissues that tend to be malignant.

Previous studies have reported that elastography has the potential to improve differentiation of benign and malignant masses.\textsuperscript{[3,4]} There are 2 widely employed strain elastography evaluation methods: a scoring system and evaluation of strain ratio (SR). Regarding the former, there are different standards that have been used to score lesions.\textsuperscript{[5–7]} For example, the Tsukuba elastography scoring system\textsuperscript{[6]} provides a pseudo-color lesion map representing stiffness detected in a focal tissue, with scores of 1 to 3 indicating a benign lesion and scores of 4 and 5 indicating a malignant lesion. However, lesion scoring can be biased by multiple subjective factors.\textsuperscript{[8]} Meanwhile, SR calculation is based on determining the average deformation of a lesion relative to that of adjacent normal tissue. It has been proposed that SR evaluation, which can be semiquantitative,\textsuperscript{[7]} may provide better differentiation between benign and malignant lesions.\textsuperscript{[3]}

Some authors have proposed that subjective bias can be controlled by using SR. However, selection of type, position, and area of a tissue to serve as a reference may be a challenge given the potential for surrounding tissue to be inhomogeneous. The selection and position of a reference normal tissue have been inconsistent in previous studies.\textsuperscript{[8,9]}

We propose that information regarding the internal hardness of lesions may be useful for obtaining a less biased differential
diagnosis. To test this hypothesis, we divided the internal strain of a lesion series into 100 hardness values ranging from hard to soft. We selected the top 33% (from hard to soft) of hardness values to define the hard component of each lesion and employed this rubric to evaluate breast lesion stiffness. The notion of using the percentage of the hard component (PHC) of a lesion to differentiate malignant from benign lesions is emergent. Notwithstanding, previous studies have shown that calculations of lesion elastic strain made with neural networks, computer-aided diagnostic systems, and off-line software are precise.

The focus of the present study was to evaluate prospectively the utility of PHC in the differential diagnosis of malignant versus benign breast lesions in a clinical setting, and to compare these results with SR data. The secondary aim was to evaluate whether an evaluation of both PHC and SR in combination with conventional ultrasound (CU) can provide better diagnostic efficacy than CU alone for breast cancer.

2. Materials and methods

2.1. Study patients

Between December 2015 and September 2017, 500 breast lesions were detected among 696 lesions that were examined in 612 female patients (mean age, 45.16 ± 12.54 years; range, 15–81 years) at our breast center. These patients underwent both CU and quasistatic elasticity imaging. Excision by surgery or with the Mammotome system (Mammotome EX, Johnson and Johnson Company, New Brunswick, New Jersey) confirmed the histological nature of the lesions. Lesions were excluded if they were confirmed to be malignant by cytology before examination (n = 14), if a histopathological diagnosis was absent (n = 78), if subcutaneous lipomas were present (n = 9), or if the elastogram performed was unsatisfactory (ie, sampling frame did not cover the lesion completely/insufficient intralesion color, poor contrast with surrounding tissue, or color instability wherein no 3-s period of no flickering could be captured) according to our previous research (n = 95). This study was approved by the Institutional Ethics Committee of the local Hospital and all enrolled patients provided informed consent acquired by oral notification before undergoing imaging.

2.2. Image and data acquisition

Imaging was performed with a commercially available scanner (MyLab Twice eHD, Esaote, Genoa, Italy) equipped with a high-frequency linear transducer (LA523, 4–13 MHz). Both CU and elastographic analyses were conducted by 2 radiologists with more than 8 years of experience in the field of breast CU and elastography. The radiologists were blinded to the results of other studies and evaluated all of the images together. Each breast evaluation was performed 2 weeks before a surgical procedure.

Elastography was performed immediately after the collection of CU data with the patient in a supine position using elaXto software. Briefly, the transducer was positioned perpendicular to the skin for the application of light compression. To obtain optimal elastography images, the real-time elaXto-spring tool (indicated with a yellow arrow in Fig. 1) was employed to help the operator achieve an accurate elastography representation by adjusting the pressure and frequency of compression. In Figure 1, representative images are presented as a grayscale ultrasound image on the left and an elastographic image on the right. An elastic sampling frame was selected for each elastography acquisition with the superior margin including subcutaneous fat and the inferior margin including pectoral muscle. Tissue hardness is represented as a color-coded map in the elastographic images, with increasing hardness presented as an ascending color scheme of red, green, and blue.

Calculation of SR was based on a comparison of the average strain measured in a lesion with the strain measured in a corresponding superficial adipose tissue. The average strain for each lesion was determined by manually drawing an inner margin (labeled Z1). Subsequently, the average strain for adjacent fatty breast tissue was selected and labeled Z2. Proprietary software on the ultrasound machine calculated SR values automatically based on these Z2/Z1 ratios (shown in “a” of Figs. 2–4); these values represent the stiffness property of the lesions examined.

Elasto histogram analysis was used to evaluate the value of determining lesion internal hardness for differential diagnosis (Fig. 1). Briefly, the internal strain of each lesion was divided into 100 parts (each 1% of the hardness range) and the parts were ordered from hard to soft. The top 33% of the possible hardness values were defined as constituting the hard component (indicated with a pink arrow in Fig. 1). The PHC (ie, the portion above the upper 33% criterion) within each lesion was determined with embedded software. PHC values were then determined by tracing each lesion and designating this upper 33% hardness region as Z1 (shown in “b” of Figs. 2–4). The results are displayed in the upper left corner of each panel (indicated with white arrows in Fig. 1). A total of 91 frames of video (5 seconds) were saved when each patient was examined; 5 measurements were performed for each lesion. At the conclusion of each imaging day, 5 frames were selected for measurement with a digital randomization table. The highest and lowest measurements were excluded and the median value of the remaining 3 measures was recorded for each lesion. PHC analysis is, in principle, based on the notion that malignant tumors tend to be harder than benign ones, and as such, the expectation that an optimal diagnostic PHC cut-off for malignancy (which may be higher or lower than the 33% criterion used in this analysis) can be developed to provide additional information based on noninvasive data.

2.3. Pathology examination

Each biological specimen collected during surgery, or collected with a Mammotome system, was formalin-fixed and embedded in paraffin. Analysis of each specimen was performed by the Pathology Department at our institution. A final diagnosis was made by a specialized breast pathologist with 20 years of experience. The pathologist was also blinded to the results of both conventional and elastographic ultrasound. A diagnosis was made according to classification criteria established by the National Cancer Institute.

2.4. Statistical analysis

Data are presented as the mean ± standard deviation or the number of cases and percentage of the total. Differences among SR and PHC values determined for the benign and malignant breast lesions were assessed with Student t test. Receiver operating characteristic (ROC) curves were used to describe and compare the diagnostic performances of the SR and PHC methods. To optimize SR and PHC for differentiation between benign and malignant masses, the best cut-off points were
obtained by calculating the Youden index, then applying a z-test to compare the area under the curve (AUC). The quality of each diagnostic parameter was evaluated based on sensitivity, specificity, accuracy, and predictive values (both positive and negative). The sensitivity, specificity, and accuracy values were subsequently compared with the McNemar test. The extent to which the predictive accuracy of SR and PHC depends on the maximum diameter and maximum depth of a lesion was also investigated with bivariate correlation analysis. Statistical analyses were performed with SPSS version v20.0 software (International Business Machines, Armonk, NY) and $P$-values less than .05 were considered significant.

3. Results
3.1. Pathological diagnoses
Pathological diagnoses for the 500 lesions examined are summarized in Table 1. There were 245 (49%) malignant lesions and 255 (51%) benign lesions. The mean maximum depths of the malignant and benign lesions were 2.14 ± 0.54 cm and 1.64 ± 0.45 cm, respectively ($P < .001$). The mean maximum diameters of the malignant and benign lesions were 1.66 ± 0.59 cm and 1.22 ± 0.52 cm, respectively ($P < .001$). The most common malignant tumor was invasive ductal carcinoma ($n = 214$) and the most common benign tumor was fibroadenoma ($n = 116$) (Table 1).
There were 95 lesions that were excluded from analysis based on unsatisfactory elastograms. The mean maximum diameter and maximum depth for these lesions (2.99 ± 1.06 cm and 3.21 ± 0.38 cm, respectively) differed significantly from those of the lesions that were included for analysis (1.44 ± 0.60 cm and 1.89 ± 0.56 cm, respectively) (P < .001).

3.2. Diagnostic performance of SR and PHC

When only elastography data were used, there was no significant difference between the AUC values for SR (0.864) and PHC (0.821) (z-test, P = 1.90, z = 1.64). The ROC curves obtained are presented in Figure 5. Threshold, Youden index, and 95% confidence interval values for SR and PHC were 2.69, 0.62, and 0.83 to 0.90, and 82.45, 0.60, and 0.78 to 0.86, respectively.

The mean SR values for the malignant and benign lesions were 4.61 ± 1.75 (range, 0.71–10.90) and 2.34 ± 1.80 (range, 0.74–20.50), respectively. The difference between these SRs was significant (P < .001) (Fig. 6). Meanwhile, the mean PHC values for the malignant and benign lesions were 90.46 ± 13.29 (range, 13.14–100) and 62.03 ± 25.61 (range, 1.51–100), respectively. The difference between these values was also significant (P < .001) (Fig. 7).
The SR and PHC values for the malignant invasive ductal carcinoma lesions (n=214) were 4.67±1.75 and 91.18±11.73, respectively, compared with 2.16±2.14 and 53.93±25.14 for the benign fibroadenomas and 2.54±1.37 and 71.70±23.37 for the benign fibrocystic mastopathy lesions.

### 3.3. Comparison of the diagnostic performance of CU, SR +CU, and PHC+ CU

The Breast Imaging-Reporting and Data System of the American College of Radiology ultrasound criteria\(^{13}\) were used to evaluate each nodule from CU mode grayscale and Doppler scans. Cut-off values were determined from SR and PHC ROC curves in conjunction with Youden index value calculations.

When SR and PHC were each combined with CU (eg, SR + CU and PHC + CU), the original categories assigned to the lesions were upgraded (or downgraded) (except categories 3 and 2, which remained the same) if the SR was ≥2.69 (or <2.69) and the PHC was ≥82.45 (or <82.45). ROC curve analysis yielded AUC values of 0.956, 0.960, and 0.956 for CU, SR + CU, and PHC + CU, respectively (Tables 2 and 3, Fig. 8). No significant differences were observed among the 3 methods.

When the cut-off points for the 3 methods were compared, the cut-off point used for 4a and 4b categorization was found to improve accuracy and specificity compared with the cut-off point...
used for 3 and 4a categorization. In contrast, sensitivity did not change significantly. These results are consistent with the findings reported by Hao et al.[14] Consequently, for further comparison between the methods, a cut-off value between 4a and 4b was established.

Accuracy, sensitivity, and specificity were compared for the 3 methods. SR+CU exhibited greater accuracy than PHC+CU, followed by CU. There were no differences in sensitivity and specificity between SR+CU and PHC+CU, while CU exhibited lower sensitivity, yet greater specificity, than SR+CU and SR+PHC (Table 3).

A bivariate correlation analysis showed no correlation between the diagnostic accuracy of maximum diameter and maximum depth parameters. Chi-square tests revealed no significant differences when the maximum diameter and maximum depth values were divided into 4 groups (group I: ≤0.99 cm; group II: 1–1.99 cm; group III: 2–2.99 cm; and group IV: ≥3 cm).

4. Discussion

Previous studies have provided evidence of the benefits of sonoelastography as an adjunct procedure to breast ultrasound.[15,16] One of the main methods for evaluating lesion elasticity involves the use of a scoring system with a pseudo-colored map representing the varying stiffness values of a focal tissue. However, this approach is subject to observer-based
variations\textsuperscript{,11} which can result in interobserver variance in scoring of the same lesion\textsuperscript{,13} Another widely used method is determination of SR. However, in this approach, selection of reference tissue type, position, and area\textsuperscript{17–19} can differ among individuals responsible for the selection criteria. Therefore, here, we measured PHCs and SRs for lesions and then used ROC curve analysis to compare the diagnostic performance of the PHC and SR methods. When only elastography data were used, diagnostic performance did not differ significantly between SR (AUC = 0.821) and PHC (AUC = 0.864). Moreover, when CU was used in combination with elastography data, no significant differences in AUC, sensitivity, or specificity values were observed between SR and PHC. Thus, PHC analysis was reliable for diagnosis of breast cancer and comparable to SR analysis.

When SR and PHC were combined with CU, the number of category 4a lesions decreased (Table 2). Fewer lesions being suspected to be malignant suggests a lessened biopsy risk for benign breast lesions. Thus, measurement of PHC represents a potential new analysis tool for lesion hardness with a similar diagnostic performance as SR. In previous studies, SR values were calculated by using the same layer of glandular tissue, the same layer of adipose tissue, or more commonly, superficial adipose tissue\textsuperscript{7,9,17–19} An advantage of the PHC method is that it does not require selection of a reference tissue.

There are additional advantages provided by the PHC method owing to it being independent of surrounding tissues. First, as described above, PHC does not require the selection of a reference

| Table 1 |
| --- |
| **Histology diagnoses of the 500 lesions examined.** |
| **Benign lesions** (n = 255) | **Malignant lesions** (n = 245) |
| Lesion | n | Lesion | n |
| Fibroadenoma | 116 | Invasive ductal carcinoma | 214 |
| Fibrocystic mastopathy | 67 | Invasive lobular carcinoma | 3 |
| Cyst | 20 | Mixed carcinoma | 3 |
| Hyperplasia | 15 | Ductal carcinoma in situ | 16 |
| Papilloma | 12 | Mucinous carcinoma | 3 |
| Chronic inflammation | 19 | Papillary carcinoma | 3 |
| Fat necrosis | 5 | Malignant phyllodes tumor | 1 |
| Benign phyllodes tumor | 1 | Metastatic tumor | 2 |


diagram
normal tissue. Additionally, only 1 region of interest needs to be drawn. These considerations reduce selection bias, potential variation in selection of a reference normal tissue, and the time needed to obtain measurements. Second, cystic lesions do not need to be excluded from PHC measurements. In the present study, all cystic lesions were diagnosed with great accuracy by PHC. In contrast, cystic lesions cannot be included in calculations of SR because they appear as blue, green, red artifacts. Generally, a diagnosis of cystic lesions by CU is relatively easy. However, when lipid cysts are hypoechoic and not echoless, a diagnosis is not straightforward. An example of this issue is shown in Figure 4(b). In the present study, there were 20 cystic lesions with a mean PHC value of 49.66 ± 14.19 (range, 24.49–80.19). All of these cysts could be diagnosed correctly with 82.45% as the threshold value.

In some studies, a combination of elastography with CU improved differentiation between benign and malignant breast masses. However, this result was not observed in the present study. ROC curve analyses showed that the diagnostic efficiencies of CU, SR+CU, and PHC+CU were not significant, yet the accuracy of each was significant according to the McNemar test.

There are several possible reasons for this result. One is a statistics-based consideration. In the McNemar test, when a large number of samples are analyzed, a small difference is often not practically significant. Second, the method of combining 2 different kinds of methods, such as CU and elastography, is a key consideration. Third, during clinical examinations, radiologists use CU to characterize the anatomy of lesions and their surrounding tissues, and these observations are the basis for a diagnosis. If lesion hardness was the only criterion for differentiating benign from malignant lesions, greater divergence among lesions may be observed. Fourth, with the technological improvements of the past 30 years, conventional ultrasonography has made a qualitative leap forward, including markedly improved resolution as well as improved diagnostic accuracy. The efficacy of CU has been demonstrated to be excellent. Fifth, it should be noted that there remains substantial room for improving elastography technology. Finally, it should be noted that our center is a tertiary specialized center with a high frequency of malignant cases and very experienced radiologists. Hence, less experienced radiologists could obtain different results. When we analyzed the correlation between maximum depth and gray maximum diameter with diagnostic accuracy, no obvious correlation was observed. Based on our preference to preserve the quality of the images examined, lesions with a size

| Parameter | CU  | SR+CU | PHC+CU |
|-----------|-----|-------|--------|
| Category  | 2   | 106 (21.2%) | 94 (18.8%) | 98 (19.6%) |
|           | 3   | 81 (16.2%)  | 76 (15.2%) | 71 (14.2%)  |
|           | 4a  | 67 (13.4%)  | 44 (8.6%)  | 41 (8.2%)   |
|           | 4b  | 36 (7.2%)   | 49 (9.8%)  | 51 (10.2%)  |
|           | 4c  | 62 (12.4%)  | 39 (7.8%)  | 42 (8.4%)   |
|           | 5   | 148 (29.6%) | 198 (39.6%)| 197 (39.4%) |
| AUC       | 0.956 | 0.960 | 0.956 |
| Sensitivity (%) | 88.57 | 96.73 | 97.55 |
| Specificity (%) | 88.63 | 84.31 | 83.39 |
| Accuracy (%) | 88.60 | 90.40 | 90.20 |
| PPV (%)   | 88.21 | 85.56 | 84.45 |
| NPV (%)   | 88.98 | 96.41 | 97.36 |

The cut-off value was between 4a and 4b.

AUC=area under ROC curve, CU=conventional ultrasound, PHC+CU=combination of PHC with conventional ultrasound, SR+CU=combination of SR with conventional ultrasound.
and depth < 1 cm or > 3 cm were rarely included. Moreover, in the groups with lesions with a size and depth < 1 cm, there was no significant difference between the diagnosis of benign and malignant lesions among the 3 methods. A possible reason for this result is that the small size of these lesions could have precluded the observation of imaging signs; meanwhile, the measurement error of elastic imaging is also large. Generally, lesions with a maximum diameter and depth > 3 cm exhibit obvious CU characteristics, making it easy to make a correct diagnosis without elastography. Therefore, a correlation between lesion size and diagnostic accuracy was not observed in the present study, consistent with the results of Carlsen et al.[21]

5. Limitations of the present study

There were several limitations associated with this study. First, since the patients included in this study were recruited from a single tertiary specialized center, they were more likely to have advanced stage malignancies than individuals in the general population, which may have introduced sampling bias. Therefore, additional multicenter studies are needed to validate the usefulness of the PHC method. Second, although quantitative elastography, including shear wave and acoustic radiation force impulse elastography, are available in clinics, semiquantitative quasistatic ultrasound elastography was applied in this study for economic reasons. Thus, additional studies of a larger number of patients, and studies that apply more meticulous techniques, such as shear wave elastography, are needed to confirm the present results. Third, due to image quality control, a few lesions that were larger and at greater depths were excluded. However, for these excluded lesions, their CU features were generally much more obvious and diagnosis by CU was not difficult.

6. Conclusions

The results of the present study demonstrate that PHC analysis is comparable to SR calculation in providing a differential diagnosis of breast lesions. ROC analyses outcomes did not differ significantly among the CU, SR+CU, and PHC+CU methods.

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