Elastography for the Characterization of Breast Lesions: Initial Clinical Experience
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Background: While breast biopsy remains the gold standard for diagnosis of suspicious lesions, a large proportion of biopsy specimens reveal a benign result. Therefore, a noninvasive and reliable method to identify low-risk lesions would be a valuable tool.

Methods: We assessed the application and diagnostic performance of elastography for the characterization of breast lesions in patients referred for biopsy. Subjects referred for ultrasound-guided biopsy of sonographically apparent breast lesions were included in this study. The Hitachi Hi-Vision 900 ultrasound was used to generate index test results for elastography scoring (ES) and for strain ratio (SR) measurement. Sensitivity, specificity, and positive and negative predictive values were determined using pathologic results from 14-gauge core needle biopsy as the reference standard.

Results: A total of 310 lesions in 288 patients were included in this series. Of these 310 lesions, 223 (72%) were benign and 87 (28%) were malignant. Sensitivity was 0.76 for ES and 0.79 for SR. Specificity was 0.81 for ES and 0.76 for SR. Positive predictive value was 0.60 for ES and 0.57 for SR. Negative predictive value was 0.90 for ES and 0.90 for SR. SR values for malignant lesions were significantly higher (median ratios 10.5 and 2.7, respectively, P < .001).

Conclusions: While the initial clinical performance of elastography imaging shows potential to reduce biopsy of low-risk lesions, a large-scale trial addressing appropriate patient selection, diagnostic parameters, and practical application of this technique is necessary prior to widespread clinical use.

Introduction
Although the total number of women referred for breast biopsy represents a small percentage of the screening population, the resources consumed for biopsy is disproportionately high.1 Ultimately, the pathologic result in up to 75% of these patients is benign.2,3 Therefore, a reliable, noninvasive method that would reduce the number of percutaneous or surgical biopsies would be valuable.5-7 Elastography is an emerging imaging technique that quantifies the "stiffness" of a breast lesion in relation to the background adipose and fibroglandular tissues. Elastography can be thought of as an imaging correlate to the use of palpation to differentiate breast lesions by physical examination.5 With palpation, malignant lesions tend to feel subjectively hard, while benign lesions are typically described as soft.8
Fig 1. — Elastography scoring system. Color elastography images are scored according to the scale described by Itoh et al.5 The higher the score, the higher the likelihood of invasive breast carcinoma. Pathology 1: Lipoma; 2: Fibroadenoma; 3: Fibroadenoma; 4: Lobular carcinoma; 5: Invasive ductal carcinoma. Note: Score 0, an elastography pattern seen with simple cysts, is not shown. Adapted from Itoh A, Ueno E, Tohno E, et al. Breast disease: clinical application of US elastography for diagnosis. Radiology. 2006;239(2):341-350. Reprinted with permission by Radiological Society of North America.
The basis of elastography imaging depends on the deformation of the target lesion compared to the background tissue. Softer tissues deform to a greater degree when compressed and therefore show higher "strain" compared to the background tissue. Conversely, hard tissues tend to deform less and show a lower degree of strain. The strain of the lesion is compared to the strain measured in the background adipose tissue. The strain differences are then utilized to generate a visual elastogram, which accentuates the relative difference in the stiffness of the target lesion compared to the background tissue. The elastogram can then be used to predict the likelihood of malignancy, based on the measured “hardness” of the targeted lesion.

Clinical Application of Elastography in Breast Imaging

Color Elastography Imaging

The breasts are both superficial and readily compressible, and most breasts contain identifiable adipose tissue that can be used as an internal control. These physical characteristics allow for the practical application of elastography, as each of these are essential in the production of a quality elastogram. Current methods allow a freehand technique to be used with commercially available breast sonography equipment. The process begins with conventional gray-scale ultrasound imaging of the target lesion. Slight manual pressure is then applied in a direction perpendicular to the skin. Differences in the echo reflection from selected lesion tissue and background tissue during compressed and noncompressed intervals are quantified and then used to produce an elastogram. Current image processing allows for the production of a color elastogram that can be used to further categorize the stiffness or strain of the target tissue. Areas of high strain, indicating easily compressed tissue such as adipose tissue, generate a red pixel on the ultrasound-viewing screen. Areas of high strain, demonstrated by tissues that tend to compress to the same degree as fibroglandular or benign tissue, generate green pixels, while areas of lower strain, indicating hard or malignant tissue, generate blue pixels. A color map is then generated and is superimposed over the gray-scale ultrasound images.

A grading scale used to categorize lesions based on the color signature generated by evaluation of target lesions has been proposed by Itoh et al. Category 0 lesions have a unique red-green-blue signature that is seen with simple cystic lesions. Category 1 lesions demonstrate a uniform pattern of high strain, marked by an evenly distributed green color throughout the lesion. Category 2 lesions show a heterogeneous but mostly green color signature, indicating a predominantly high strain pattern of the lesion. Category 3 lesions show a pattern of high peripheral strain with central low strain pattern, and they produce a small central blue area that is surrounded by a green peripheral color. Category 4 lesions produce a low strain pattern and a uniformly blue color signature confined to the visible margin of the lesion, while category 5 lesions show a similar blue signature that extends beyond the lesion into the adjacent tissues.

On subsequent histological analysis, lesions that are designated category 0, 1, or 2 are considered to have a higher likelihood of benign result. Category 3 lesions are indeterminate, while lesions graded as category 4 or 5 are more likely to be malignant. The initial study of freehand color elastography by Itoh et al used a benign to malignant cutoff of category 3 to category 4 and yielded a sensitivity of 86.5%, a specificity of 89.8%, and an accuracy rate of 88.3%. Comparable results were achieved by Tardivon et al, with a sensitivity of 78.7% and a specificity of 86.9%.

Strain Ratio Measurement

A semiquantitative method of lesion assessment, referred to as strain ratio (SR) measurement, has also been developed recently. Calculation of the SR value is based on determining the average strain measured in a lesion and comparing it to the average strain of a similar area of fatty tissue in the adjacent breast tissue. Using proprietary software, the average strain of the
lesion is determined by selecting a region of interest (ROI) encompassing the lesion. The ROI for the lesion is expressed as $ST - ave LESION$. A corresponding ROI of adjacent adipose tissue is then selected and is expressed as $ST - ave FAT$. The ratio of these two measurements is calculated according to the formula $Ratio = ST - ave FAT / ST - ave LESION$ (Fig 2). The ratio value increases as a function of the relative stiffness of the target lesion. As the SR increases, the likelihood of invasive breast cancer increases. Clinical experience with SR imaging in the assessment of breast cancer is limited, but combining this technique with color elastography may improve overall performance. Strain imaging may help to offset subjective factors in the scoring of color images, and it may show an advantage in the evaluation of lesions in dense or small breasts.

**Initial Clinical Experience**

**Methods**

A feasibility study was conducted at our institute to evaluate the utility and diagnostic performance of both color elastography scoring (ES) and SR assessment. The study population consisted of consecutive patients referred to our center for ultrasound-guided biopsy of a sonographically apparent breast lesion. Subjects were included following their consent for the index testing. Pathologic diagnosis from 14-gauge core biopsy was selected as the reference standard prior to recruitment. Pathologic analysis was completed on site by the pathology department at our center. Pathologic results considered to be malignant included invasive breast carcinoma and all carcinoma subtypes, ductal or lobular atypia, sarcoma, lymphoma, and carcinoma in situ. All other pathologic results were considered benign. All subjects were prospectively evaluated with the index tests immediately prior to ultrasound-guided core biopsy; thus, the readers were blinded to the reference standard result. Prior diagnostic imaging (e.g., mammogram and diagnostic sonogram) for each subject was available to the readers at the time of testing.

The Hitachi Hi Vision 900 Ultrasound (Hitachi Medical Systems America Inc, Twinsburg, Ohio) was used to generate ES images and SR measurements for each lesion. Elastography system operators and elastogram readers were considered newcomers to the technique, but they received training from the equipment manufacturer prior to study initiation. Lesions were assigned an ES using the five-point visual scoring system (Fig 1) proposed by Itoh et al. The lesion was considered ES test-negative if scored 0, 1, or 2; while a score of 3, 4, or 5 was considered ES test-positive. Calculation of the SR value (Fig 2) was based on the average strain measured in the lesion compared to adjacent adipose tissue in the breast. Using proprietary software, the average strain of the lesion was determined by selecting a representative ROI from the center of the lesion, and this was expressed as $ST - ave LESION$. A corresponding ROI of adjacent adipose tissue was then selected and expressed as $ST -$
The resultant SR value was expressed as a ratio according to the equation $\frac{ST - ave\ FAT}{ST - ave\ LESION} = SR$. A lesion was considered SR test-negative if the ratio was < 4.5, while a ratio of ≥ 4.5 was considered to be SR test-positive according to criteria provided by the manufacturer. Sensitivity, specificity, negative and positive predictive values, and test accuracy were calculated using core needle biopsy result as the standard. The aims of the study were to determine the feasibility of using both ES and SR scoring and to assess the performance of these techniques in the diagnosis of breast malignancy. Study design is summarized in Fig 3.

**Results**

Subjects were recruited from October 9, 2008, to July 6, 2009. A total of 316 lesions in 288 subjects were tested. Of these, 310 lesions were included in the final analysis. Two subjects were excluded because fine needle aspiration was done with a 22-gauge needle instead of the 14-gauge core biopsy. Four additional lesions were excluded from 2 subjects due to inadequate assessment of index text results.

Of 310 lesions, 223 (72%) were benign and 87 (28%) were malignant. Lesion size ranged from 3 to 42 mm (mean 11.9, median 10, SD ± 7.6). Benign lesion size ranged from 3 to 38 mm (mean 11.3, median 9, SD ± 7.2), while malignant lesion size ranged from 3 to 42 mm (mean 13.4, median 11, SD ± 8.2).

The diagnostic performance of ES and SR testing is summarized in the Table. For benign lesions, the most frequent ES was 2 (n = 130). For malignant lesions, the most frequent ES was 4 (n = 81) (Fig 4). SR values for all lesions ranged from 0.8 to 114.2 (mean 9.4, median 3.3, SD ± 15.6). SR values for benign lesions ranged from 0.8 to 114.2 (mean 5.2, median 2.7, SD ± 10.9), while SR for malignant lesions ranged from 1.0 to 107.3 (mean 20.2, median 10.5, SD ± 17.7). The malignant group demonstrated a significantly higher SR compared with the benign group (median ratios 10.5 and 2.7, respectively, $P < .001$).

**Discussion**

Breast cancer remains the most common malignancy in women worldwide. In prior studies, elastography imaging has shown potential for differentiating benign from malignant breast disease and could possibly reduce the overall number of breast biopsies. Elastography is a noninvasive technique that was readily integrated into our prebiopsy assessment of patients referred for biopsy. The secondary aim was to deter-

![Fig 4. — Elastography score (ES) distribution among 310 lesions.](image-url)
mine the overall diagnostic performance of color elastography and SR imaging. Our results show lower sensitivity, specificity, and negative and positive predictive values compared to previously published results.\textsuperscript{2,3,5,9,12} Limitations to our study include potential for selection bias since our center serves as a breast cancer referral site. Our overall malignancy/atypia rate was higher than expected in a standard screening population. Operator inexperience and interobserver variability are also likely sources of error.

In our opinion, the clinical value of elastography should depend on its capability to minimize false-negative results. Ideally, the negative predictive value (NPV) would approach 0.98. This would be equivalent to the expected NPV of a lesion graded as category 3 according to the Breast Imaging Reporting and Data System (BI-RADS). Therefore, these lesions could be followed in lieu of biopsy with equivalent safety. With our initial criteria, we achieved an NPV of 0.90 for ES and SR. Unfortunately, this is inferior to reported B-mode ultrasound NPV of 0.95 using strict criteria.\textsuperscript{13} However, a recent retrospective study of SR assessment of breast lesions suggested that a narrowed SR cutoff of 2.45 improves the specificity of the technique, thus reducing the frequency of a false-negative result.\textsuperscript{14} We observed 21 false-negative cases with ES and 18 cases with SR assessment. The most frequent pathology observed in the false-negative group was invasive ductal carcinoma. Atypia, ductal carcinoma in situ, lymphoma, and invasive lobular carcinoma occurred less frequently (Fig 5). Retrospective use of the lower cutoff value of 2.45 proposed by Thomas et al\textsuperscript{14} would improve the NPV in our study to 0.98, with non-capture of 2 cases of lymphoma (5 and 18 mm) and 1 case of atypia (23 mm). All false-negative cases showed an ES of 2. Therefore, additional narrowing of the ES to include only 0 or 1 as test-negative would increase the NPV to 1.00. Combined use of these tightened criteria would have reduced our biopsy rate by 15% (47 total biopsies avoided). A larger prospective trial with narrowed criteria could place subjects into short-term follow-up with reasonable safety and a low risk for non-capture of invasive malignancy.

References

Fig 5. — False-negative pathology. IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, ILC = invasive lobular carcinoma.