Strain Elastography for Prediction of Breast Cancer Tumor Grades

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Objectives—The purpose of this study was to determine whether the elasticity imaging/B-mode ratio on strain elastography can predict breast cancer tumor grades.

Methods—A retrospective review of patients with breast lesions who underwent strain elastography and had a diagnosis of breast cancer by image-guided or surgical biopsy was performed. The axis of the maximum elastographic dimension was compared to the B-mode dimension to form an elasticity imaging/B-mode ratio. Lesions were categorized according to their pathologic type, including atypical ductal hyperplasia (ADH), mucinous or colloid cancer, ductal carcinoma in situ (DCIS), grade I invasive ductal carcinoma (IDC), grade II IDC, grade III IDC, invasive lobular carcinoma (ILC), and lymphoma. The mean elasticity imaging/B-mode ratio of each tumor type was calculated. The elasticity imaging/B-mode ratio of the tumor was compared to the tumor type by Kruskal-Wallis and Tukey-Kramer tests (lymphoma and ADH excluded because of small numbers).

Results—Tumor grades included lymphoma (n = 3), ADH (n = 2), mucinous cancer (n = 11), DCIS (n = 19), IDC (grades I–III; n = 200), and ILC (n = 31). The mean elasticity imaging/B-mode ratio varied with increasing tumor grade. Tumor grades could not have been selected at random from one population ($P < .0001$, χ^2 test). Invasive lobular carcinoma and grade III IDC were statistically different from mucinous or colloid cancer, DCIS, and grade I and II IDC.

Conclusions—The elasticity imaging/B-mode ratio on strain elastography is related to the tumor grade.

Key Words—breast; breast cancer; breast ultrasound; elastography; strain; tumor grade

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Abbreviations

ADH, atypical ductal hyperplasia; BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma

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Despite major medical and socioeconomic advances in breast cancer screening over the past 3 decades, breast cancer continues to be the most commonly detected cancer and the second leading cause of cancer mortality in women across the United States.[1] A 1999 consensus statement by the College of American Pathologists discussed several factors that determine the prognosis in breast cancer, some of which include tumor size, nodal status, histologic type, histologic grade, and hormone receptor status.[2] Although several variables exist for different patients, the breast cancer prognosis is intimately associated with the balance between the tumor grade and host defense.[3] Mammography is the primary screening examination for detection of breast cancer. Currently, the most used and readily available adjunct to mammography in the diag-

nostic workup of a breast mass is sonography, which has long been used as an adjunct to mammography in the evaluation of suspicious breast lesions.[4] It is also frequently used to guide fine-needle aspiration and core biopsies of breast masses.[5] Over the last 2 decades, a new sonographic technique, elastography, has been developed. This technique determines lesion stiffness, which was previously not available in the standard sonographic lexicon.[6–12] Studies have shown that elastography of the breast has potential to differentiate benign and malignant breast lesions with high sensitivity and specificity.[13–18] In a recent multicenter trial of 635 patients, we reported sensitivity of 99% and specificity of 87% in differentiating benign from malignant breast lesions via strain elastography.[19]

Breast tumor grading requires histologic evaluation of a tissue sample obtained by image-guided biopsy or surgical excision. Breast malignancies are graded according to the Scarff-Bloom-Richardson grading system. This grading system relies on the frequency of cell mitosis (rate of cell division), tubule formation (percentage of tumor-containing tubular structures), and nuclear pleomorphism.[20] The grades are listed in Table 1. The importance of the tumor grade cannot be understated, as it has been found to directly correlate with the degree of axillary lymph node involvement.[21] Moreover, several studies have shown that histologic grade is a critical factor in the overall patient prognosis.[22–24]

In our previous studies,[15,19] it was noted that the ratio of the tumor length on elastography to the length of the lesion on B-mode imaging (the elasticity imaging/B-mode ratio) was larger for higher-grade tumors. The purpose of this study was to determine whether the elasticity imaging/B-mode ratio correlates with breast cancer tumor grades.

Table 1. Number and Mean Elasticity Imaging/B-Mode Ratio by Tumor Grade

Tumor Grade	n	Mean
Lymphoma	3	0.8
ADH	2	1.0
Mucinous	11	1.2
DCIS	19	1.2
IDC I	43	1.4
IDC II	97	1.5
IDC III	60	1.7
ILC	31	1.8

Materials and Methods

Study Procedures

In this retrospective study approved by our Institutional Review Board, the reports of patients referred for diagnostic sonography because of a palpable abnormality, mammographic abnormality, magnetic resonance imaging abnormality, or sonographic abnormality from January 1, 2007, to June 30, 2012, were reviewed. Patients who received a strain elastogram as part of their sonographic evaluation and had a biopsy-proven malignancy were included. Strain elastography was performed on an Acuson S2000 system (Siemens Medical Solutions, Mountain View, CA) with a 14-MHz linear probe or an iU22 system (Philips Healthcare, Bothell, WA) with a 12-MHz linear probe. Strain elastographic examinations were performed by either a radiologist (R.G.B.) with 10 years of experience in strain elastography or 1 of 2 sonographers with 2 years of experience in strain elastography. Images were reviewed by the radiologist (R.G.B.). Precompression was minimized with the use of a method previously described.[25] The displacement needed for obtaining elastograms was provided by the patient's breathing or cardiac rebound. If required, minimal manual compression/decompression was used to obtain the elastogram. Images were displayed side by side during a real-time sonographic examination. Elasticity imaging/B-mode ratios were obtained by dividing the axis of the maximum dimension of the lesion on the elastogram by the axis of the maximum dimension on the B-mode image. Three measurements were obtained from each lesion, and the largest elasticity imaging/B-mode ratio used. The highest ratio was selected to reflect the area of the highest grade in the tumor. Figure 1 shows the method used for calculation of the elasticity imaging/B-mode ratio. A copy or shadow function was used to ensure that measurements were taken in the same location of the lesion. The greatest axis of maximum dimension of the lesion was measured on the B-mode image.

For image-guided biopsies, a 12-gauge core needle (C. R. Bard, Inc, Covington, GA; or Hologic, Inc, Indianapolis, IN) was used. Pathologic reports were reviewed for the histologic diagnosis and grade. In patients who underwent a surgical biopsy, the pathologic report was reviewed. In patients undergoing both image-guided and surgical biopsies, the surgical pathologic tumor type and grade were used.

Statistical Analysis

Pathologic tumor types were grouped according to lesion aggressiveness. Invasive ductal carcinomas (IDCs) were graded according to the Scarff-Bloom-Richardson grading

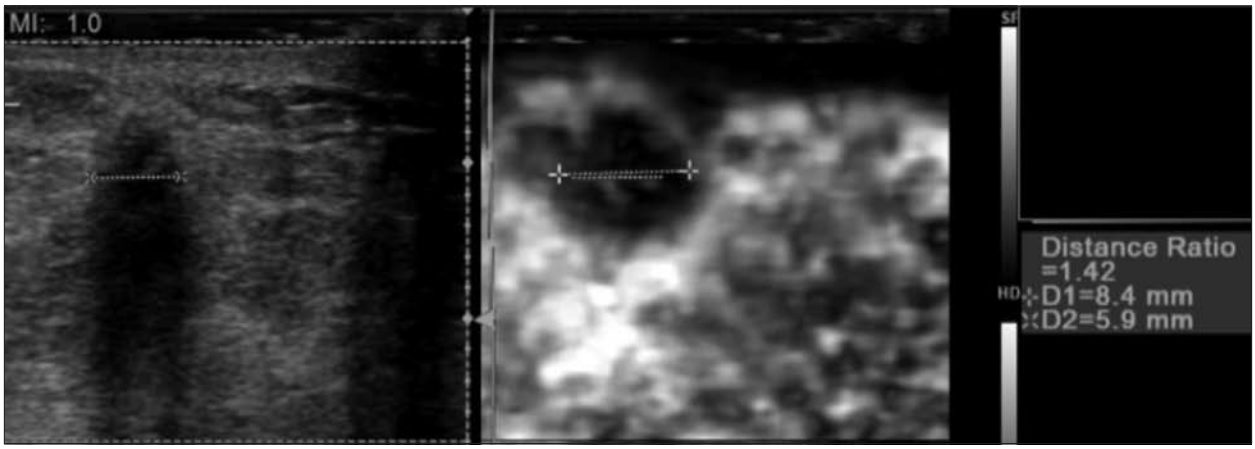


Figure 1. Breast Imaging Reporting and Data System category 4C lesion in a 68-year-old woman presenting with abnormal mammographic findings. We display the B-mode image on the left and the elastogram on the right. The length measurement of the lesion on the B-mode image (line between calipers) is duplicated on the elastogram with a copy or shadow function. The elasticity imaging/B-mode ratio is calculated and displayed on the right.

system. The groups were as follows: atypical ductal hyperplasia (ADH), mucinous or colloid cancer, ductal carcinoma in situ (DCIS), grade I IDC (Scarff-Bloom-Richardson grades 3–5), grade II IDC (Scarff-Bloom-Richardson grades 6 and 7), grade III IDC (Scarff-Bloom-Richardson grades 8 and 9), invasive lobular carcinoma (ILC), and lymphoma. The mean elasticity imaging/B-mode ratio was calculated for each tumor type.

Since the elasticity imaging/B-mode ratio data set was not normally distributed, for statistical analysis, the Kruskal-Wallis test was used to determine whether any group had elasticity imaging/B-mode values that were statistically significantly different from those of any other group. A Kruskal-Wallis test is a nonparametric statistical measure for determining whether data originate from the same distribution. It is the nonparametric equivalent to a 1-way analysis of variance test. Subsequently, if statistical significance was found, the Tukey-Kramer minimum significant difference test was used to determine which groups were significantly different from each other. Box plots of elasticity imaging/B-mode ratios by pathologic grade with quantiles were created. Because of the small numbers of lymphoma and ADH, they were not included in the analysis.

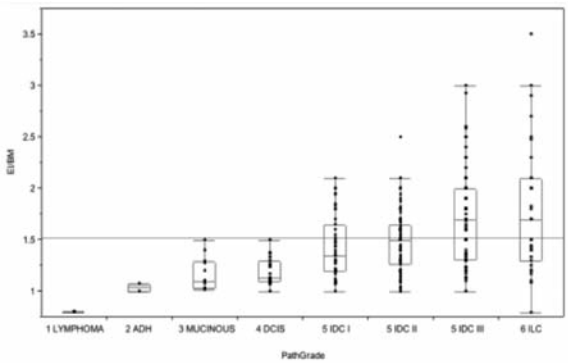
Results

There were 266 biopsy-proven malignancies from 238 patients between the ages of 36 and 95 years (mean ± SD, 63.9 ± 13.2 years). Tumor sizes ranged from 2 to 66 mm (mean, 14.8 ± 9.4 mm).

Pathologic grades included lymphoma (n = 3), ADH (n = 2), mucinous cancers (n = 11), DCIS (n = 19), IDC (grades I–III; n = 200), and ILC (n = 31). The overall elasticity imaging/B-mode ratios varied from 0.8 to 3.5. Ratios varied depending on the aggressiveness of the tumor (Table 1 and Figure 2). The Kruskal-Wallis analysis demonstrated statistical significance between the pathologic grades (lymphoma and ADH excluded because of small sample sizes) included in the study ($\chi^2 = 48.352$; $df = 7$; $P < .0001$).

To determine whether any pathologic groups were statistically significant from one another, we used the Tukey-Kramer method, which is often used in conjunction with analysis of variance to find means that are statistically significant from one another. The analysis of the

Figure 2. Quantiles (10%, 25%, 50%, 75%, and 90%) of the elasticity imaging/B-mode ratio (EI/BM) by pathologic grade.



various pathologic grades by the Tukey-Kramer test showed that ILC and grade III IDC were statistically different from mucinous cancer, DCIS, and grade I and II IDC at a 0.05 level. Table 2 shows a comparison of all pairs using the Tukey-Kramer method, with positive values showing pairs that were significantly different.

Discussion

In terms of the American College of Radiology's Breast Imaging Reporting and Data System (BI-RADS) lexicon for sonography, certain descriptors inherently portend a more aggressive nature of a breast mass. For example, masses that show an irregular shape, angular or spiculated margins, an antiparallel orientation, and posterior shadowing with or without an echogenic halo have classically been assigned suspicious BI-RADS categories 4A–4C and 5. A study by Blaichman et al[26] investigated the ability to predict the IDC grade based on these descriptors. They found that the IDC grade was slightly to moderately predicted by the margin, lesion boundary, and acoustic features. Somewhat surprisingly, grade III IDCs were more likely to show microlobulated margins and posterior acoustic enhancement compared to lower-grade IDCs. Another study by Evans et al[27] measured the relationships of high mean stiffness using shear wave elastography. They demonstrated that a high histologic grade, a large size, the tumor type, and lymphovascular invasion all had a statistically significant positive association with high mean stiffness.

The breast is unique in that it is the only organ in which the tumor size differs between the B-mode image and the elastogram. Benign masses appear smaller on breast strain elastography, whereas malignant masses appear larger. All other organs, including the prostate, thyroid, and kidneys, show elasticity imaging/B-mode ratios of 1, regardless of whether the lesion is benign or malignant.[28] This unique feature allows for a highly significant and specific prediction of breast lesion benignity or malignancy with potential for even more diagnostic characterization. Our study demonstrates a trend that higher-grade breast cancers have larger elasticity imaging/B-mode ratios than lower-grade tumors. Statistical analysis proved with high confidence that the various pathologic groups investigated could not have been selected at random from one population. Moreover, our analysis showed that grade III IDC and ILC generated the highest elasticity imaging/B-mode ratios and were statistically significantly different from mucinous cancer, DCIS, and lower-grade IDC (grades I and II).

The ability to predict the breast cancer grade by sonoelastography may have several potential applications in clinical practice. One realistic and practical application would be the implementation of elastographic properties in real-time sonographic examinations to contribute to the interpretation of BI-RADS classifications. In particular, elasticity imaging/B-mode ratios obtained at the time of a sonographic examination could help focus the interpreting breast radiologist on differentiating BI-RADS category 4 lesions. Consideration of elasticity imaging/B-mode ratios along with the other classic descriptors such as mass shape, margin, and orientation could help distinguish BI-RADS 4A–4C lesions. For example, higher-grade IDCs with relatively less conspicuous characteristics like microlobulated margins and posterior acoustic enhancement, such as the grade III IDCs observed by Blaichman et al,[26] may become more suspicious to the radiologist given relatively higher elasticity imaging/B-mode ratios. Suspicion of a higher grade due to increased elasticity imaging/B-mode ratios, despite a relatively small mass size and inconspicuous margins, could lead the radiologist to search more vigilantly for satellite lesions or axillary adenopathy, which would subsequently affect staging and clinical management. Increased suspicion on the part of the breast imager would be valuable information to provide to the interpreting pathologist, as differentiation between certain grades of breast cancer can be histologically difficult and can vary among pathologists.[29–31]

Table 2. Comparison of All Pairs Using the Tukey-Kramer Method

	ILC	IDC III	IDC II	IDC I	DCIS	Mucinous
ILC	–0.30	–0.20	0.07[a]	0.09[a]	0.26[a]	0.20[a]
IDC III	–0.20	–0.22	0.06[a]	0.07[a]	0.24[a]	0.17[a]
IDC II	0.07[a]	0.06[a]	–0.17	–0.16	–0.005	–0.07
IDC I	0.09[a]	0.07[a]	–0.16	–0.25	–0.09	–0.15
DCIS	0.26[a]	0.24[a]	–0.005	–0.90	–0.38	–0.44
Mucinous	0.20[a]	0.17[a]	–0.07	–0.15	–0.44	–0.50

[a]Pairs that were significantly different; ILC and IDC III were statistically different from IDC II, IDC I, DCIS, and mucinous cancer.

There are several acknowledged factors that limited this study. First, this study was retrospective and performed at a single outpatient imaging center. Although we have previously shown the ability to reproduce our sensitivity and specificity figures for differentiation of benign and malignant breast lesions in a multicenter trial,[26] we have not investigated the correlation with tumor grades on a larger scale. Second, elasticity imaging/B-mode ratio measurements were made by a single observer, which could inherently have introduced an observer bias. Moreover, we presume that ILC acts in a more aggressive manner than IDC, which may not always be the case. The fact that our data demonstrate a consistent trend of ILC to have higher elasticity imaging/B-mode ratios with a statistically significant difference from other pathologic types, similar to grade III IDC, is a potential source of further investigation. Another limitation was the small number of cases for some tumor types (lymphoma and ADH).

In conclusion, our study suggests that the elasticity imaging/B-mode ratio is related to breast tumor grades. This observation could add to the potential of breast elastography as a future component of the standard breast imaging algorithm. Additional studies correlating the same pathologic and elastographic findings are needed to fully understand what is actually being measured in both strain and shear wave elastography.

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