Published in final edited form as:

Breast Cancer Res Treat. 2009 November ; 118(1): 67–80. doi:10.1007/s10549-009-0369-2.

Differentiation of benign and malignant breast lesions by mechanical imaging

Vladimir Egorov¹, Thomas Kearney², Stanley B. Pollak³, Chand Rohatgi⁴, Noun Sarvazyan¹, Suren Airapetian¹, Stephanie Browning⁵, and Armen Sarvazyan¹

Vladimir Egorov: vegorov@artannlabs.com; Thomas Kearney: ; Stanley B. Pollak: ; Chand Rohatgi: ; Noun Sarvazyan: ; Suren Airapetian: ; Stephanie Browning: ; Armen Sarvazyan:

¹ Artann Laboratories, 1459 Lower Ferry Rd, Trenton, NJ 08618, USA

² The Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA

³ Mercy Medical Center, Rockville Centre, New York, NY 11510, USA

⁴ The Breast Care Center & General Surgery Practice, Easton, PA 18045, USA

⁵ New Jersey Institute of Technology, University Heights, Newark, NJ 07102, USA

Abstract

Mechanical imaging yields tissue elasticity map and provides quantitative characterization of a detected pathology. The changes in the surface stress patterns as a function of applied load provide information about the elastic composition and geometry of the underlying tissue structures. The objective of this study is the clinical evaluation of breast mechanical imager for breast lesion characterization and differentiation between benign and malignant lesions. The breast mechanical imager includes a probe with pressure sensor array, an electronic unit providing data acquisition from the pressure sensors and communication with a touch-screen laptop computer. We have developed an examination procedure and algorithms to provide assessment of breast lesion features such as hardness related parameters, mobility, and shape. A statistical Bayesian classifier was constructed to distinguish between benign and malignant lesions by utilizing all the listed features as the input. Clinical results for 179 cases, collected at four different clinical sites, have demonstrated that the breast mechanical imager provides a reliable image formation of breast tissue abnormalities and calculation of lesion features. Malignant breast lesions (histologically confirmed) demonstrated increased hardness and strain hardening as well as decreased mobility and longer boundary length in comparison with benign lesions. Statistical analysis of differentiation capability for 147 benign and 32 malignant lesions revealed an average sensitivity of 91.4% and specificity of 86.8% with a standard deviation of $\pm 6.1\%$. The area under the receiver operating characteristic curve characterizing benign and malignant lesion discrimination is 86.1% with the confidence interval ranging from 80.3 to 90.9%, with a significance level of $P = 0.0001$ (area = 50%). The multisite clinical study demonstrated the capability of mechanical imaging for characterization and differentiation of benign and malignant breast lesions. We hypothesize that the breast mechanical imager has the potential to be used as a cost effective device for cancer diagnostics that could reduce the benign biopsy rate, serve as an adjunct to mammography and to be utilized as a screening device for breast cancer detection.

Keywords

Breast cancer; Diagnostic elastography; Tissue differentiation; Malignancy detection

Introduction

The current methods of breast pathology assessment include Clinical Breast Examination (CBE), Mammography, Ultrasound, Magnetic Resonance Imaging (MRI), and biopsy. Positron emission mammography and sestamibi scans are also used occasionally. A recent large-scale clinical study (42,760 patients in USA and Canada) on the diagnostic performance of mammography for breast-cancer screening revealed that the diagnostic accuracy of digital and film mammography is 78 and 74%, respectively [1]. A European randomized mammography screening trial (23,929 patients in Norway) demonstrated a sensitivity of 77.4% and specificity of 96.5% for full-field digital mammography while a screen-film mammography yielded a 61.5% sensitivity and 97.9% specificity. Notably, the median size of detected invasive cancers was about 13.5 mm [2]. Despite the recommendation for an annual mammogram, only 58.3% of women 40 years or older in the United States had a mammogram in 2004 [3].

Ultrasound is being increasingly used as a complementary method for the assessment of mammographically or clinically detected breast masses for supplemental information on dense tissue [4]. However, there is limited data supporting the use of ultrasound in breast cancer screening as an adjunct to mammography [5]. The conventional ultrasound is more often used to determine whether an area of concern on the mammogram or clinical exam is cystic or solid. The majority of cystic masses are benign while solid masses need further evaluation [6]. Many indications for clinical breast MRI are recognized. These include resolving mammography findings, staging of breast cancer when multiple or bilateral disease is suspected, and detecting the occult primary breast cancer presenting with malignant axillary lymphadenopathy [7,8].

The CBE is applied to detect abnormalities or to evaluate a patient's report of symptoms or findings of palpable breast cancers at an earlier stage of progression [9]. The American Cancer Society guidelines suggest an annual CBE for age 40 and older for early detection of breast cancer in asymptomatic women [3]. The CBE identifies some cancers missed by mammography [10,11] and provides an important screening tool among women for whom mammography is not advised or for those that do not receive high-quality screening mammography. Nevertheless, CBE performance and reporting approaches are known to be inconsistent. Health care providers report a lack of confidence in their CBE skills and would welcome training and practical recommendations for optimizing performance and reporting [12]. Data for the six studies examined by Barton and colleagues resulted in an overall estimate of 54.1% for CBE sensitivity and 94.0% for CBE specificity [13]. These findings are comparable to the published values of CBE sensitivity (58.8%) and specificity (93.4%) observed in the US national screening program of 752,081 CBE reports [14].

Therefore, a method that mimics CBE but with enhanced sensitivity and specificity might consequently lead to a greater screening yield. Such method for detection and visualizing breast abnormalities and assessing their mechanical properties with sensitivity exceeding that of manual palpation was developed. The method, called Mechanical Imaging, is based on reconstructing the internal structure of soft tissues using the data obtained by a pressure sensor array pressed against the examined site [15]. The changes in the surface stress patterns as a function of displacement, applied load, and time provide information about elastic composition and geometry of the underlying tissue structures.

We have demonstrated earlier that the Breast Mechanical Imager (BMI), a compact device comprised of a hand-held probe equipped with a pressure sensor array, allows calculation of size, shape, consistency/hardness, and mobility of detected lesions [16]. The BMI prototype has also been validated in laboratory experiments on tissue models and tested in a clinical

environment [17]. The objective of this study is the clinical evaluation of the BMI for breast pathology characterization and differentiation between benign and malignant breast lesions.

Materials and methods

Study design and protocol

The primary objective of the clinical study was to assess the BMI's capability in lesion characterization. The examination was performed specifically for the concerned breast areas with the suspected lesions. Lesion features were calculated from the recorded BMI examination data and were used for lesion characterization. Additional diagnostic information provided by other diagnostic modalities was collected and used for the analysis of the potential of differentiation of benign and malignant lesion by BMI. Thus, the primary objective of lesion characterization has been extended to a more practical question of benign and malignant lesion discrimination. Evaluation of the classification accuracy of the BMI has been done in a non-blinded data analysis.

The clinical protocol was approved by the Institutional Review Boards at each of the clinical sites. The study was done in compliance with the Health Insurance Portability and Accountability Act. The clinical study has been conducted through a non-randomized multi-center trial in the four investigational sites: New Jersey (The Cancer Institute of New Jersey, New Brunswick), New York (Mercy Medical Center, Rockville Centre), Pennsylvania (The Breast Care Center & General Surgery Practice, Easton), and Florida (Breast Health Institute, Maitland). The exams were performed by BMI trained breast surgeons enrolled as co-investigators in the study.

Study inclusion criteria were:

- a. women (over the age of 21) with a breast mass identified by mammography, ultrasound, and/or CBE,
- b. women (over the age of 21) referred to a breast surgeon for evaluation of a particular area of concern identified either by the woman herself or her primary physician,
- c. patients with a clinical record containing CBE, US, and mammography reports with clear localization of lesion of interest.
- d. patients with a clinical record containing a pathology report with the results from a fine needle biopsy, core needle biopsy, or excisional biopsy for the identified lesion with an exception in cases where the ultrasound and mammography reports both clearly stated that the lesion is benign, predominantly a cyst, and biopsy is not required.

Study exclusion criteria were:

- a. patients with skin infection or inflammation in the breast,
- b. patients with prior breast cancer surgery or radiation,
- c. patients with scleroderma or other connective tissue disorders,
- d. patients with epidermal cysts,
- e. patients that had a biopsy recommendation, but for various reasons a pathology report was unavailable,
- f. immoderate deviation from the recommended BMI examination procedure such as losing the lesion image or keeping lesion image at the edge of pressure array during

the scan, poor pressure patterns due to insufficient level of applied force (well below the recommended level).

- g. the BMI examination was performed after biopsy.

A hard copy of lesion related clinical data with the results of clinical diagnostics for all enrolled patients was submitted for data review and analysis. Classification of each scanned lesion as benign or malignant was determined by the result of the pathology report or, as in the case of a cyst or other benign findings that did not recommend biopsy testing, from the results of the mammogram and ultrasound.

BMI system

The BMI is comprised of a probe, an electronic unit, and a touch screen laptop [17]. A pressure sensor array positioned on the probe head is designed to acquire pressure patterns between the probe surface and the exterior skin layer of the breast during contact. The sensory array size is 40 mm by 30 mm and is comprised of 192 pressure sensors. Special software was developed for processing of the data collected from the probe sensors and the calculation of certain lesion features as described below in this paper.

BMI examination procedure

Prior to the biopsy, a BMI examination was conducted on the area of clinical concern. At first, the breast surgeon (oncologist) would perform a standard CBE to determine the location of the concern. Some of the patients had non palpable lesions and the lesion was observed by ultrasound prior to biopsy. With the knowledge of this location, the patient was placed in a similar position to that of a standard CBE with her breast in the supine position on an examination table. The examiner placed a disposable sheath over the sensor head of the BMI and then applied a water soluble lubricating lotion to the sensor head or applied directly to the area of concern. Once ready, the local scan of the lesion by the BMI was done in either one of two different variations: by applying up and down probe compressions over the lesion or circular probe motions around the lesion. During the examination, the acquired pressure response patterns from the probe sensors, being processed in real time, provided visualization of the current pressure pattern and a composition of the accumulated lesion image as described earlier [17]. The examination was recorded and stored by the BMI system in a digital format file, which was analyzed later in a research laboratory environment to calculate lesion features and verify the constructed multi-parameter classifier. The duration of a typical lesion scan was approximately 1–2 min. In addition to the real time lesion image, the examiner was able to observe signals indicating excessive probe tilt, the total number of collected pressure frames and their distribution versus applied force and the level of the force applied to the probe. The acquired level of applied force was used as a guide in maintaining the recommended operational range from 7 to 18N.

Study population

The BMI clinical data set presented in this paper was collected and recorded during the period of July 2005 to November 2007. Initially, after giving written informed consent, 219 women were enrolled in the study at four different clinical sites. However, due to various clinical and procedural factors, a total of 40 patients were found to be ineligible and were excluded from the data analysis. Among them, 13 patients that were recommended for biopsy did not have the biopsy for various reasons (such as: they did not return for the appointment, their insurance changed, they moved or switched to another physician); 9 patients had the biopsy done before the BMI examination; we were unable to determine from the record the location of the lesion for 3 patients; and 2 patients had an epidermal cyst. An additional 13 patients were excluded due to the specific limitations implied by the examination procedure requirements, such as

poor distribution of recorded pressure patterns versus applied force (7 patients), lesion image was imaged on the perimeter of the pressure sensor array (3 patients), pressure sensors were zeroed on an incorrect level (2 patients), and applied force level to the BMI probe was beyond the operational range (1 patient). We observed some excessive tilt of the probe head during the lesion examinations, however, we did not exclude these cases from further consideration and analysis. Summary of the patient enrollment and exclusion for all four sites is shown in Table 1.

Table 2 displays the lesion diagnosed pathology distribution among the analyzed patients. Collectively there are 179 patients included in the data analysis of the clinical study as stated in Table 1. There are 19 patients from the first clinical site, 19 patients from the second site, 37 patients from the third site, and finally 104 patients from the fourth site. The median patient age was 43 years, from 21 to 92 years, with 36 and 52 years as the low and upper quartiles, respectively.

Overall, 147 and 32 cases were classified as benign and malignant, respectively. In 150 cases we had the pathology reports (fine needle biopsy, core biopsy or excisional biopsy) and in 29 cases we had ultrasound and mammography examination results that clearly stated that the lesion is benign, mostly diagnosed as cysts (19 cases), with no biopsy recommended. This diagnostic clinical information was used as the 'gold standard' for BMI data analysis. The benign classified lesions were divided into 11 subclasses [18] and malignant classified lesions were divided into 5 subclasses [19] as shown in Table 2.

Lesion features calculation

A detailed description of the lesion feature calculations has been given in an earlier publication [17]. Here, we will briefly outline the algorithms used for evaluation of features proposed for differentiating benign and malignant cases. Three features are related to tissue hardness and two other features are parameters characterizing lesion mobility and shape. Patient age was used as an additional input parameter for the classifier since the breast cancer risk is increased with age [20].

The input data to compose a 3D image of the breast lesion is comprised of a continuous sequence of 2D filtered images. The 3D image reconstruction starts with the formation of an initial 3D structure by stacking the series of 2D structure images along the vertical Z-coordinate (transverse plane) during the first tissue compression. Further, every 2D imprint is integrated by a parallel translation inside the 3D structure image, where x,y coordinates (coronal plane) are determined by a matching algorithm [17]. The Z-coordinate (layer number) is calculated according to:

$$Z = A \times \sum_{i=0}^{i=k} \sum_{j=0}^{j=l} S_{i,j} - B \quad (1)$$

where $A = 1.04 \times 10^{-5}$ and $B = -5$ are empirical constants, k and l are quantities of horizontal and vertical pixels inside the pressure response frame with the analyzed lesion pattern, and $S_{i,j}$ is the current pressure signal of i,j -pixels expressed in P_a . Consequently, the final 3D image is composed of 2D images $P(x,y,Z)$, which are the layers inside the 3D image, and we can calculate the maximum pressure value $M(Z)$ for each Z-layer:

$$M(Z) = \max \{P(x, y, Z)\} \quad (2)$$

where x, y are coordinates in the plane parallel to a breast surface. Further, we approximate the experimental value of $M(Z)$ by the second order polynomial:

$$P_a(Z) = F1 \times Z^2 + F2 \times Z + C \quad (3)$$

Lesion hardness related features are $F1$, $F2$ and $P_a(Z_m)$. The $F1$ -parameter characterizes nonlinearity of loading curve and is defined as strain hardening of the lesion. The parameter $F2$ characterizes the average slope of a stress-strain loading curve and the parameter $P_a(Z_m)$ is the maximum pressure value for the Z_m -layer, where the total force applied to the probe is 12N.

The mobility of the lesion Mb_{aver} is evaluated as an averaged value of $Mb(t)$ through the examination time t for all pressure patterns containing the lesion image:

$$Mb(t) = \left(1 - \frac{\sum_{x=0}^{x=l} \sum_{y=0}^{y=k} Ph(x,y,Z,Th) \times Sh(x,y,t)}{\sum_{x=0}^{x=l} \sum_{y=0}^{y=l} Ph(x,y,Z,Th)} \right) \times 100\% \quad (4)$$

$$Sh(x,y,t) = \begin{cases} 1, & S(x,y,t) \geq Th \\ 0, & S(x,y,t) < Th \end{cases} \quad (5)$$

where Ph is the accumulated 3-D binary lesion image, Th is the threshold of binarization, $Sh(x,y,t)$ is a binary image of a momentary lesion image to be placed in comparison with the Z -layer, $S(x,y,t)$ is the momentary pressure response of sensor with x, y -coordinates at time t . Prior to Eqs. 4 and 5, the image $Sh(x,y,t)$ is matched with the accumulated image $P_z(x,y)$ as detailed in a prior publication [17]. The Mb_{aver} value, expressed in percentage, characterizes the capability of the lesion to change its form and position under applied mechanical indentation by the probe's curved surface. The shape of the lesion is characterized by the ratio of the lesion boundary length to the perimeter of a circle with the same area as that of the lesion visible projection. The age of enrolled patients was the sixth parameter used in data analysis.

Statistical analysis

A statistical assessment of the diagnostic significance of each feature was completed with the aid of the statistical toolbox in MATLAB 6.1 (MathWorks, Natick, MA) and MedCalc 9.2 (MedCalc Software, Mariakerke, Belgium). For visual evaluation of the analyzed clinical data distributions within the benign and malignant patient samples, we used boxplots for data representation of each analyzed feature and their combination. In descriptive statistics, the boxplot is a convenient and widely accepted way of graphically depicting groups of numerical data or data samples [21]. Boxplots are able to visually show distinctions of data samples without making any assumptions about the underlying statistical distribution. The spacings between the different parts of the box help to compare variance. The boxplot also identifies skewness (asymmetry) and outliers. We have used a notched boxplot [22] showing a confidence interval for the median value. The intersection or divergence of confidence intervals for two patient samples is a visual analog of the paired t -test.

A correlation coefficient calculated by the standard procedure implemented in MATLAB software [23] was applied to analyze the strength and direction of the linear relationship between each of the six calculated features. We calculated Pearson product-moment correlation coefficients, which are obtained by dividing the covariance of the two variables by the product of their standard deviations.

To compare diagnostic performance of a test for the features characterizing the lesion and to evaluate feature combined effectiveness, we used the receiver operating characteristic (ROC) curve analysis [24]. The area under the curve (AUC) is determined from plotting sensitivity versus 1-specificity of a test as the threshold varies over its entire range. Conceptually, AUC is interpreted as the probability that the test will produce a value for a randomly chosen diseased subject that is greater than the value for a randomly chosen healthy subject [25]. Each data point on the plot represents a particular setting of the threshold. An area of 1 indicates a perfect prediction; an area of 0.5 is a chance result.

Statistical classifier

To differentiate benign from a malignant breast lesions, we employed a naïve Bayesian classifier [26,27]. Large-scale comparison of this Bayesian classifier with state-of-the-art algorithms for decision tree induction and instance-based learning on standard benchmark datasets found that the simple Bayesian classifier was superior to each of the other learning schemes, even on datasets with substantial feature dependencies [28]. A naïve Bayesian classifier is a probabilistic classifier based on applying Bayes' theorem with strong independence (naïve) assumptions. The goal of the Bayesian classification for our situation is to calculate the probability P of lesion being benign C_b or malignant C_m for a given set of lesion features F . Formal presentation of the probability will look as $P(C_i|F_j)$, where i is the lesion number and j is the lesion feature number. If one the values of $P(C_b|F_j)$ or $P(C_m|F_j)$ was greater than the other, then the classification of the lesion would be that of the greater value. The Bayes' theorem facilitates the computation of the $P(C_i|F_j)$ probability:

$$P(C_i|F_j) = \frac{P(F_j|C_i) \times P(C_i)}{P(F_j)} \quad (6)$$

where $P(C_i)$ is the prior probability of C_i and $P(F_j)$ is the prior probability of F_j , which acts as a normalized constant often referred to as evidence. To calculate the conditional probability $P(F_j|C_i)$ requires that we estimate the joint probability distribution, in all 6-dimensions for the six features, for the point for each of the classes. Under the independence (naïve) assumption, the covariance matrix has only diagonal members. Hence, the conditional probability $P(F_j|C_i)$ might be calculated as:

$$P(F_j|C_i) = \prod_{a=1}^6 P(F_j^a|C_i) \quad (7)$$

where F_j^a is the value of F_j in the a -th dimension. For numeric data we assume that each dimension is normally distributed. Thus, we have to estimate the variance σ_i^a and mean μ_i^a for each class C_i separately, directly from data. Once these values are computed for benign and malignant patient samples, we calculate:

$$P(F_j^a|C_i) = N(F_j^a|\sigma_i^a, \mu_i^a) = \exp\left(-\frac{(F_j^a - \mu_i^a)^2}{2(\sigma_i^a)^2}\right) / \sqrt{2\pi\sigma_i^a} \quad (8)$$

The value of the prior probability $P(C_i)$ is defined by the ratio of the sample size to the total number of patients. The evidence value was calculated according to:

$$P(F_j) = \sum_{a=1}^6 (P(F_j^a|C_b) \times P(C_b) + P(F_j^a|C_m) \times P(C_m)) \quad (9)$$

The difference between $P(C_b|F_j)$ and $P(C_m|F_j)$ was used as a threshold parameter for the construction of the ROC curve for a set of specified features.

Results

The comparative benign-malignant paired boxplots for the lesion strain hardening ($F1$), loading curve average slope ($F2$), maximum pressure peak for the fixed total force applied to the probe ($F3$), lesion shape ($F4$), lesion mobility ($F5$), and patient age ($F6$) are shown in Fig. 1. The central horizontal line inside each boxplot corresponds to the median value of the sample distribution, as the confidence interval for the median is depicted by a notched beam range on each boxplot. Lower and upper horizontal lines of the box correspond to the first (25%) quartile and the third (75%) quartile, respectively. Small circles beyond the horizontal bars illustrate the outlier data, which begins at the value of the interquartile range multiplied by 1.5 and extends beyond. Nine breast lesions (7 benign and 2 malignant) out of 179 were not palpated in the area of concern during the corresponding CBE, yet were discovered by the mammography examination.

The area under the ROC curve (AUC) characterizing the discrimination of benign and malignant lesions was calculated separately for each clinical site for each feature of the set $F1-F6$ as displayed in Fig. 2. This plot demonstrates the variability of diagnostic effectiveness of the analyzed features from site to site. We found that the average AUC value and standard deviation for feature $F1 = 68.5.1 \pm 12.6\%$, $F2 = 76.6 \pm 8.1\%$, $F3 = 79.3 \pm 4.1\%$, $F4 = 63.8 \pm 8.3\%$, $F5 = 80.2 \pm 11.2\%$, and $F6 = 77.4 \pm 6.9\%$.

Pair correlation coefficients for features $F1-F6$ used in benign and malignant lesion differentiation are shown in Table 3. The correlation indicates 1 in the case of perfect linear relationship, -1 for a decreasing linear relationship, and another value in between 1 and -1 signifying the degree of linear dependence between the variables. The closer the coefficient is to either -1 or 1 , the stronger the correlation between the features. If the features are independent then the correlation is 0 , though the converse is not true since the correlation coefficient detects only linear dependencies between two variables. This table has diagonal symmetry, which is expressed by 1 , given that each data set perfectly correlates to itself.

ROC curves constructed for each of the BMI parameters $F1-F5$ are shown in Fig. 3. Features $F3$ and $F5$ appeared to have the highest diagnostic information value with AUC of 79.4% with the 95% confidence interval (CI) from 72.7 to 85.1% . The least efficient single feature $F4$ has AUC of 60.9% with the 95% CI from 53.4 to 68.1% . The right bottom panel in Fig. 3 presents ROC curve for performance of discrimination between benign and malignant lesions for the Bayesian classifier output when the complete set of parameters $F1-F6$ for all 179 patients was used as input data of the classifier. The AUC is equal in this case to 86.1% with the 95% CI

from 80.3 to 90.9% while a significance level $P = 0.0001$ for the area of 50%; sensitivity is equal to 87.5% with the 95% CI from 71.0 to $96.4 \pm 12\%$ (95% CI) and specificity 84.4% with the 95% CI from 77.5 to 89.8%. It is important to emphasize that clinical data from all four sites have been combined together. In addition, distributions for the lesion features calculated according to Eq. 8 are different from that for the data shown in Fig. 4 where all distributions have been calculated separately for each clinical site. Figure 3 includes the calculated 95% CI lines above and below the ROC curve.

Figure 4 presents the calculated sensitivity, specificity, and AUC for the output of the Bayesian classifier applied for differentiation of benign from malignant lesions for each clinical site. All $F1-F6$ features have been used as input parameters in this analysis as described in the method section. We found the sensitivity to range from 85.7 to 100%, specificity from 78.7 to 100%, and AUC from 83.4 to 100%.

Figure 5 demonstrates the sensitivity, specificity, and AUC values calculated as average values and as combined for the 179 patients. The left bar (averaged results) represents the clinical data from all four sites analyzed separately by the Bayesian classifier as shown in Fig. 3, thus the resulting data for sensitivity, specificity and AUC have been averaged. The right bar (combined data) presents clinical data from all sites used as an input data set for the Bayesian differentiation of benign from malignant lesions. All $F1-F6$ features have been used as input parameters in this analysis as described in the method section. The average sensitivity is $91.4 \pm 6.1\%$ ($\pm$ standard deviation), average specificity is $86.8 \pm 9.2\%$, and AUC is $90.7 \pm 7.6\%$.

Discussion

As shown in Table 1, 219 patients were enrolled in the study at four clinical sites. A total of 40 patients were found not eligible and their data were excluded from the analysis. That constituted 18.3% exclusion with the largest exclusion due to the procedure deviations (13 patients or 5.9% of the total enrollment) and patients not returning for scheduled biopsy (13 patients or 5.9% of the total enrollment). The remaining 14 patients or 6.4% were excluded due to not meeting the protocol requirements. Sites 1 and 2 were only able to enroll a limited number of patients for the given period, 25 and 21 respectively, which cannot be considered reliable statistical samples. Nevertheless, the data combination from all four clinical sites (179 patients) represents a meaningful statistical population. The exclusion of 18.3% of enrolled patients cannot provide any bias because these 40 patients represent a statistically independent sub-population and related data were not analyzed due to the absence of pathology diagnosis.

It is important to emphasize that the BMI provided detection and image composition for all 179 subjects, including 9 with non palpable lesions. This observation supports an earlier conclusion that computerized palpation is more sensitive than a human finger [29–31].

Table 2 presents the breast pathology distribution among 179 cases. The benign group is subdivided into 11 categories, which were not uniform among the all clinical sites. In total, the largest benign categories were fibroadenoma (37 patients or 25.2%), cyst (26 patients or 17.7%), and fibrocystic changes (17 patients or 11.6%). More uniformity was found in the malignancy cases from each site with invasive ductal carcinoma diagnosed in 80% of site 1, 57.1% of site 2, 80% of site 3, and 70% of site 4. Invasive ductal carcinoma was diagnosed in 23 out of 32 malignant cases or 71.9%, which bears close to the screening results received for 1 million women—58.9% of invasive ductal carcinoma or 3215 cases from 5458 total detected malignant cases [32]. The breast pathology distribution observed in this study is in agreement with the data received from large scale screening and research trials [1,2,4,18,19].

Features $F1$ through $F3$ are related to the lesion hardness characterization. The increased hardness of a tissue correlates with the presence of cancer in the tissue as confirmed by various

elasticity imaging techniques [33]. Measurements of excised breast specimens exhibited that normal breast tissue has a modulus that was noticeably lower than the modulus of the breast cancer tissue. Tumors or a tissue blocked from receiving blood nutrients are stiffer than normal tissue. Benign and cancerous tumors were also shown to have distinguishing elastic properties [34–36].

Both Fig. 1 and 2 demonstrate the limited discrimination capability of the selected features being analyzed individually due to possible influence by numerous factors, such as breast lesion location, its depth, breast size, and deviation in the examination technique. The averaged values of AUC for features $F1$ – $F5$ calculated for four clinical sites vary from 64.3 to 80.0%. We can conclude that the confidence intervals of benign and malignant patient samples for features $F2$ (loading curve slope), $F3$ (maximum lesion signal for the fixed force applied to the probe), and $F5$ (lesion mobility) are not overlapped and in agreement with the relatively increased value AUC of 76.6, 79.3, and 80.2%, respectively. However, a relatively decreased AUC of 68.5 and 63.8% is seen for features $F1$ (strain hardening) and $F4$ (lesion shape) and their confidence intervals for benign and malignant boxplots have certain intersections.

Two features, strain hardening and lesion mobility, revealed standard deviations of 12.6 and 11.2% and ranged from 60.7 to 87.1% and from 73.8.1 to 91.9%, respectively. The relatively high variance of strain hardening $F1$ might be explained by sensitivity to deviations in the examination procedure and the significant range of tissue deformation (up to 30%) under the probe manipulation. The lesion mobility variance might also be explained by operator specific deviations in examination procedure. We believe that more detailed instructions and extended training of the operators, as well as real time feedback signaling on deviations in the examination technique, will increase the accuracy and robustness of the procedure.

The correlation coefficients calculated for features $F1$ – $F5$ demonstrate a low linear correlation (<0.35), except for the $F2$ – $F3$ pair of 0.68 (see Table 2). We anticipated that these two features would correlate at a more notable level due to the larger value of $F2$, which would definitely cause an increase in the value of $F3$. The decrease in the $F2$ – $F3$ correlation is observed in the beginning of the loading curve, which is plotted as the pressure maximum signal from the lesion versus the total applied force to the probe. We set the range for the initial part of the loading curve as 0–5N of the total force. Initially, the loading curve exhibits substantial nonlinearity that is not taken into account in the $F2$ calculation, but is incorporated into the $F3$ feature. Furthermore, with the addition of feature $F3$ into input parametric set of the Bayesian classifier, the lesion diagnostic accuracy and the confidence interval of AUC appeared to be better.

The $F4$ value characterizing the lesion shape for malignant lesions decreases relative to the benign lesions as it follows from Fig. 1. This reflects the fact that the shape of a harder core of a malignant lesion is closer to spherical than a benign lesion. The lesion mobility $F5$ for malignant lesions is decreased relative to the benign lesions (Fig. 1). As we mentioned in the method section, this parameter integrates not only lesion mobility, but also its deformability during the probe pressing against the lesion. Intuitively, this result might be anticipated since the malignant lesion must be more conservative and stable in these terms. It seems reasonable that $F5$ has mild correlation coefficients of -0.32 and -0.33 with $F2$ and $F3$.

Aside from the gender, age is the most important factor affecting breast cancer risk [20]. The patient age $F6$ demonstrated a clear divergence between the benign and malignant patients (see Fig. 1). The correlation coefficients of the patient age with features $F1$ – $F5$ ranged from 0.16 to 0.14. This result confirms the weak correlation of patient age with other features, a fact which enhances its significance and usefulness as an additional independent coordinate in a

multidimensional space for classification. Therefore, we have decided to incorporate this feature into the benign-malignant classifier.

A combined multi-parameter assessment composed of relatively low correlated parameters increases the discriminating power of BMI binary lesion classification. It might be seen in Fig. 3 where we represented ROC curves for BMI parameters *F1* through *F5* and ROC curve for the Bayesian classifier output (right bottom). Averaged value of AUC for parameters *F1* through *F5* is 73.5%. Combining these five BMI parameters by means of the Bayesian classifier the diagnostic accuracy is increased in averaged by 11.3%, from 72.3 to 83.6%. Additional increase by 2.5% was provided by taking into account patient age *F6* as the input parameter for the classifier. The feature combination decreases the confidence interval for diagnostic accuracy relative parameter *F1* through *F5* alone as it might be concluded from Fig. 3. On average, the confidence interval is narrowing from 13.3% for single feature to 10.6% which is also beneficial effect of features combination.

Figure 4 demonstrates the differentiation capability for benign and malignant lesions with the use of the Bayesian classifier in the case when the data have been analyzed separately for each clinical site. The variability of diagnostic accuracy from clinical site to site might be explained by deviations in the nature of patient groups enrolled at the sites, especially among the patients with benign findings.

The diagnostic accuracy calculated as average values for the four clinical sites exceeds the diagnostic accuracy calculated for the combined 179 patients, as it clearly seen in Fig. 5. This difference is 3.9% for sensitivity, 2.4% for specificity, and 4.5% for AUC. That means that the Bayesian classifier can discriminate more accurately among data sets in which the data is separated into groups (clinical sites) than those in which all patient data are combined together.

It is well recognized in the literature that the tissue elastic properties provide means for not only characterizing tissue but differentiating normal and diseased conditions. This conclusion is based on a wealth of data obtained in the studies on excised breast specimens [34,35] and clinical studies conducted by numerous researchers worldwide [37–47]. We summarized in Table 4 recently published clinical results directly related to the breast benign–malignant lesion differentiation by elasticity imaging. These data clearly demonstrate the significant diagnostic potential of elasticity imaging. The BMI data with a sensitivity of 91.4% and specificity of 86.8% is close to the results shown in Table 4. Notably, this accuracy level (AUC 91.4%) was reached using the more cost effective approach of Mechanical Imaging, rather than other elastography techniques [48]. Based on these findings, we hypothesize that the BMI has a potential to be used as a cost effective device for cancer detection as a diagnostic modality. We further hypothesize that the BMI can be used not only for binary classification but for calculating the probability distribution for multiple possible outcomes subdividing various benign and malignant classes, to distinguish between fibroadenoma, cyst, fibrosis, ductal, lobular carcinoma and other conditions.

Screening mammography is generally the recommended tool for breast cancer detection and is recognized throughout the world. The mammography results are used as the basis in making a decision about performing a biopsy at suspicious breast sites. In the United States alone, more than 1 million breast biopsies are performed annually and approximately 80% of these findings are benign [49,50].

We simulated how the use of the BMI after standard screening procedures (mammography alone or combination of mammography and conventional ultrasound) could reduce the benign biopsy rate. Figure 6 shows the results of this simulation. Applying the BMI cancer sensitivity and specificity calculated for the combined data including 179 patients (147 benign, 32 malignant) to the patient sample referred for the biopsy (20% of which will be malignant and

80% benign), we built the dependence of the benign biopsy reduction (%) versus the percentage of missed cancers as shown in Fig. 6. These results indicate that a 23% reduction of the benign biopsy is possible without any missed cancer cases and a 50% reduction of the benign biopsy with 4.6% missed cancer cases. Category 3 BIR-ADS results in a 6 months follow up rather than a biopsy. About 1% of those are cancers. Anything over 1% is probably too high. Clearly, the decrease of the benign biopsy rate is accompanied by an increased proportion of missed cancers. This could be further mitigated by the recommended 3 or 6 months clinical follow up for all patients that were originally recommended for a biopsy but then diagnosed by the BMI as benign.

Conclusions

The multisite clinical study proved the capability of mechanical imaging for real time characterization and differentiation of benign and malignant breast lesions. The BMI has the potential to be used as a cost effective device for cancer diagnostics, and it could effectively reduce the benign biopsy rate. The BMI has the potential to be positioned as an adjunct to mammography and utilized as a screening device for breast cancer detection.

Acknowledgments

The authors would like to thank Ralph Tullo, MD, Breast Health Institute of Maitland, Florida, for his assistance in the clinical study. They also appreciate the engineering support of Milind Patel for the Breast Mechanical Imager. This work was supported by National Institute of Health under research grant CA091392 "Imaging Network for Breast Cancer Mass Screening".

References

1. Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. *N Engl J Med* 2005;353:1773–1783.10.1056/NEJMoa052911 [PubMed: 16169887]
2. Skaane P, Hofvind S, Skjennald A. Randomized trial of screen-film versus full-field digital mammography with soft-copy reading in population-based screening program: follow-up and final results of Oslo II study. *Radiology* 2007;244:708–717.10.1148/radiol.2443061478 [PubMed: 17709826]
3. American Cancer Society: breast cancer facts & Figs. American Cancer Society; Atlanta: 2007–2008.
4. Altmann A, Hellerhoff K, Heywang-Köbrunner SH. Screening in women with increased breast cancer risk. *Breast Care* 2006;1:22–25.10.1159/000091116
5. Berg WA, Blume JD, Cormack JB, et al. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. *JAMA* 2008;299:2151–2163.10.1001/jama.299.18.2151 [PubMed: 18477782]
6. Ely S, Vioral AN. Breast cancer overview. *Plast Surg Nurs* 2007;27:128–133. [PubMed: 17901821]
7. Adhani AR, Ah-See ML, Makris A. MRI in the detection and management of breast cancer. *Expert Rev Anticancer Ther* 2005;239–252. [PubMed: 15877522]
8. Vandermeer FQ, Bluemke DA. Breast MRI: state of the art. *Cancer Invest* 2007;25:384–392.10.1080/07357900701360013 [PubMed: 17882648]
9. McDonald S, Saslow D, Alciati MN. Performance and reporting of clinical breast examination: a review of the literature. *CA Cancer J Clin* 2004;54:345–361.10.3322/canjclin.54.6.345 [PubMed: 15537577]
10. Oestreicher N, White E, Lehman CD, et al. Predictors of sensitivity of clinical breast examination (CBE). *Breast Cancer Res Treat* 2002;76:73–81.10.1023/A:1020280623807 [PubMed: 12408378]
11. Bancej C, Decker K, Chiarelli A, et al. Contribution of clinical breast examination to mammography screening in the early detection of breast cancer. *J Med Screen* 2003;10:16–21.10.1258/096914103321610761 [PubMed: 12790311]

12. Saslow D, Hannan J, Osuch J, et al. Clinical breast examination: practical recommendations for optimizing performance and reporting. *CA Cancer J Clin* 2004;54:327–344.10.3322/canjclin.54.6.327 [PubMed: 15537576]
13. Barton MB, Harris R, Fletcher SW. Does this patient have breast cancer? The screening clinical breast examination: should it be done? How? *JAMA* 1999;282:1270–1280.10.1001/jama.282. 13.1270 [PubMed: 10517431]
14. Bobo JK, Lee NC, Thames SF. Findings from 752, 081 clinical breast examinations reported to a national screening program from 1995 through 1998. *J Natl Cancer Inst* 2000;92:971–976.10.1093/jnci/92.12.971 [PubMed: 10861308]
15. Sarvazyan A. Mechanical imaging: a new technology for medical diagnostics. *Int J Med Inform* 1998;49:195–216.10.1016/S1386-5056(98)00040-9 [PubMed: 9741894]
16. Egorov, V.; Sarvazyan, A. Breast tissue characterization by means of surface stress patterns analysis. Abstracts of 32nd International Symposium on Ultrasonic Imaging and Tissue Characterization; Arlington. 2007. p. 45
17. Egorov V, Sarvazyan AP. Mechanical imaging of the breast. *IEEE Trans Med Imaging* 2008;28(9): 1275–1287.10.1109/TMI.2008.922192 [PubMed: 18753043]
18. Schnitt, ST.; Connolly, JL. Pathology breast disorders. In: Harris, JR.; Lippman, ME.; Morrow, M.; Osborne, CK., editors. *Diseases of the breast*. Wolters Kluwer Company; Philadelphia: 2004. p. 77-99.
19. Schnitt, ST.; Guidi, AJ. Pathology of invasive breast cancer. In: Harris, JR.; Lippman, ME.; Morrow, M.; Osborne, CK., editors. *Diseases of the breast*. Wolters Kluwer Company; Philadelphia: 2004. p. 541-584.
20. American Cancer Society Cancer Facts & Figures. American Cancer Society; Atlanta: 2007.
21. Tukey, JW. Exploratory data analysis. Addison-Wesley Publishing; Princeton: 1977.
22. McGill R, Tukey JW, Larsen WA. Variations of box plots. *Am Stat* 1978;32:12–16.10.2307/2683468
23. Gayen AK. The frequency distribution of the product moment correlation coefficient in random samples of any size draw from non-normal universes. *Biometrika* 1951;38:219–247. [PubMed: 14848124]
24. Lasko TA, Bhagwat JG, Zou KH, Ohno-Machado L. The use of receiver operating characteristic curves in biomedical informatics. *J Biomed Inform* 2005;38:404–415.10.1016/j.jbi. 2005.02.008 [PubMed: 16198999]
25. Swets JA. Measuring the accuracy of diagnostic systems. *Science* 1988;240:1285–1293.10.1126/science.3287615 [PubMed: 3287615]
26. Rish, I. An empirical study of the naive Bayes classifier. 2001 [Accessed 23 Sep 2008]. IBM Research Report RC 22230, Available online: <http://www.cc.gatech.edu/~isbell/reading/papers/Rish.pdf>
27. Kotsiantis S, Pintelas P. Logitboost of simple Bayesian classifier. *Computational intelligence in data mining. Spec Issue Informatica J* 2005;29(1):53–59.
28. Domingos P, Pazzani M. On the optimality of the simple Bayesian classifier under zero-one loss. *Mach Learn* 1997;29:103–130.10.1023/A:1007413511361
29. Sarvazyan, AP. Computerized palpation is more sensitive than human finger. *Proceeding of 12th Int Symposium on Biomedical Measurements and Instrumentation; Dubrovnik-Croatia*. 1998. p. 523-524.
30. Weiss RE, Hartanto V, Perrotti M, et al. In vitro trial of the pilot prototype of the prostate mechanical imaging system. *Urology* 2001;58(6):1059–1063.10.1016/S0090-4295(01)01407-8 [PubMed: 11744495]
31. Kearney TJ, Airapetian S, Sarvazyan AP. Tactile breast imaging to increase the sensitivity of breast examination. *J Clin Oncol* 2004;22S:103.
32. Gathani T, Bull D, Green J, Reeves G, Beral V. the Million Women Study Collaborators . Breast cancer histological classification: agreement between the Office for National Statistics and the National Health Service Breast Screening Programme. *Breast Cancer Res* 2005;7:R1090–R1096.10.1186/bcr 1352 [PubMed: 16457689]
33. Sarvazyan, AP. Elastic properties of soft tissues. In: Levy, M.; Bass, H.; Stern, R., editors. *Handbook of elastic properties of solids, liquids and gases*. Vol. 3. Academic Press; New York: 2001. p. 107-127. (Chap 5)

34. Skovoroda AR, Klishko AN, Gusakyan DA, et al. Quantitative analysis of the mechanical characteristics of pathologically changed soft biological tissues. *Biophysics* 1995;40:1359–1364.
35. Krouskop TA, Wheeler TM, Kallel F, Garra BS, Hall T. Elastic moduli of breast and prostate tissues under compression. *Ultrason Imaging* 1998;20:260–274. [PubMed: 10197347]
36. Wellman, P.; Howe, RH.; Dalton, E.; Kern, KA. Breast tissue stiffness in compression is correlated to histological diagnosis. Harvard Biorobotics Laboratory; 1999. p. 1-15. Technical Report
37. Itoh A, Ueno E, Tohno E, et al. Breast disease: clinical application of US elastography for diagnosis. *Radiology* 2006;9:341–350.10.1148/radiol.2391041676 [PubMed: 16484352]
38. Zhang XF, Liu XM, Bao XF, et al. Application of real-time tissue elastography in diagnosis of breast cancer. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2006;35:444–447. (Article in Chinese). [PubMed: 16924712]
39. Thomas A, Fischer T, Frey H, Ohlinger R, Grunwald S, Blohmer JU, et al. Real-time elastography —an advanced method of ultrasound: first results in 108 patients with breast lesions. *Ultrasound Obstet Gynecol* 2006;28:335–340.10.1002/uog.2823 [PubMed: 16909438]
40. Sinkus, R.; Siegmann, K.; Tanter, M.; Xydeas, T.; Fink, M. MR–elastography is capable of increasing the specificity of MR–mammography—influence of rheology on the diagnostic gain. *Proceedings of the 5th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity; Snowbird.* 2006. p. 111
41. Regner DM, Hesley GK, Hangiandreou NJ, et al. Breast lesions: evaluation with US strain imaging —clinical experience of multiple observers. *Radiology* 2006;238:425–437.10.1148/radiol.2381041336 [PubMed: 16436810]
42. Barr, RG.; Grajo, JR. Initial results of real-time elasticity imaging in the evaluation of breast lesions. *Proceedings of the 6th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity; Santa Fe.* 2007. p. 94
43. Garra, BS.; Mobbs, LM.; Chant, CM.; Ophir, J. Clinical breast elastography: blinded reader performance and strategies for improving reader performance. *Proceedings of the 5th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity; Snowbird.* 2006. p. 60
44. Burnside ES, Hall TJ, Sommer AM, et al. Differentiating benign from malignant solid breast masses with US strain imaging. *Radiology* 2007;245:401–410.10.1148/radiol.2452061805 [PubMed: 17940302]
45. Svensson, WE.; Zaman, N.; Barrett, NK., et al. Breast elasticity imaging aids patient management in the one stop breast clinic. *Proceedings of the 6th International Conference on the Ultrasonic Measurement and Imaging of Tissue Elasticity; Santa Fe.* 2007. p. 128
46. Kaufman CS, Jacobson L, Bachman B, Kaufman L. Digital documentation of the physical examination: moving the clinical breast exam to the electronic medical record. *Am J Surg* 2006;192:444–449.10.1016/j.amjsurg.2006.06.006 [PubMed: 16978946]
47. Tanter M, Bercoff J, Athanasiou A, et al. Quantitative assessment of breast lesion viscoelasticity: initial clinical results using supersonic shear imaging. *Ultrasound Med Biol* 2008;34(9):1373–1386.10.1016/j.ultrasmedbio.2008.02.002 [PubMed: 18395961]
48. Sarvazyan A, Egorov V, Son JS, Kaufman CS. Cost-effective screening for breast cancer worldwide: current state and future directions. *Breast Cancer Basic Clin Res* 2008;1:91–99.
49. Liang W, Lawrence W, Burnett CB, et al. Acceptability of diagnostic tests for breast cancer. *Breast Cancer Res Treat* 2003;79:199–206.10.1023/A:1023914612152 [PubMed: 12825854]
50. Gur D, Wallace LP, Klym AH, et al. Trends in recall, biopsy, and positive biopsy rates for screening mammography in an academic practice. *Radiology* 2005;235:396–401.10.1148/radiol.2352040422 [PubMed: 15770039]

Fig. 1. Benign-malignant paired boxplots for features *F1* through *F6*. *F1*, strain hardening; *F2*, loading curve slope; *F3*, max pressure signal; *F4*, lesion shape; *F5*, lesion mobility; and *F6*, patient age

Fig. 2. Performance of discrimination between benign and malignant lesions separately for the four clinical sites in consideration of features *F1* through *F6*. *F1*—strain hardening, *F2*—loading curve slope, *F3*—max pressure signal, *F4*—lesion shape, *F5*—lesion mobility, and *F6*—patient age

Fig. 3.

ROC curves for performance of discrimination between benign and malignant lesions for BMI parameters *F1* through *F5* calculated for 179 patients and for the Bayesian classifier output (*right bottom*). Calculated parameters *F1–F6* for all 179 patients were used as input data of the classifier

Fig. 4. Performance of differentiation between benign and malignant lesions with the use of Bayesian classifier evaluated for the four clinical sites separately

Fig. 5.
Performance of differentiation between benign and malignant lesions with the use of the Bayesian classifier

Fig. 6.
A projected benign biopsy reduction due to the use of BMI as a trade off with percentage of missed breast cancers

Table 1

Patient enrollment and exclusion

Relevant data	Clinical location				Total for all sites (%)
	Site 1	Site 2	Site 3	Site 4	
Enrolled patients	25	21	42	133	219 100
Excluded patients from data analysis	6	2	3	29	40 18.3
Patients included into data analysis	19	19	37	104	179 81.9
<i>Reasons of exclusion patients from data analysis</i>					
Critical deviations in examination procedure (see text)	1	2	1	9	13 5.9
Biopsy was recommended but not done	4	0	2	7	13 5.9
BMI examination was done after biopsy	0	0	0	9	9 4.1
No clear relation what lesion what examined	1	0	0	2	3 1.4
Lesion was diagnosed as epidermal cyst	0	0	0	2	2 0.9

Table 2

Pathology distribution according to clinical data for analyzed lesion

Clinical pathology diagnosis (see text)	Clinical location				Total for all sites
	Site 1	Site 2	Site 3	Site 4	
Benign					
Fibroadenoma	6	6	4	21	37
Cyst	0	1	18	7	26
Fibrocystic changes	1	0	0	16	17
Stromal fibrosis	2	0	1	13	16
Fibroadipose or adipose tissue/fragments/cells	0	0	0	8	8
Fibrostatic changes	3	2	1	3	9
Sclerosing adenosis, nodular adenosis	0	1	0	3	4
Fat necrosis, fat lobules	1	0	0	3	4
Sclerotic tissue	0	0	0	3	3
Intraductal papillomas	0	0	1	2	3
Others	1	2	2	15	19
Total benign	14	12	27	94	147
Malignant					
Invasive ductal carcinoma	4	4	8	7	23
Ductal carcinoma in situ	0	2	2	2	6
Invasive lobular carcinoma	0	0	0	1	1
Medullary carcinoma	1	0	0	0	1
Papillary carcinoma	0	1	0	0	1
Total malignant	5	7	10	10	32
Total benign and malignant	19	19	37	104	179
Gold standard for lesion diagnosis					
Biopsy pathology report	18	19	20	93	150
US + mammography reports	1	0	17	11	29

Table 3
Correlation coefficients for features $F1$ – $F6$ used in the benign and malignant lesion differentiation

Lesion features	$F1$	$F2$	$F3$	$F4$	$F5$	$F6$
$F1$	1	0.10	0.04	0.00	−0.12	0.14
$F2$	0.10	1	0.68	−0.31	−0.32	0.06
$F3$	0.04	0.68	1	−0.33	−0.33	0.13
$F4$	0.00	−0.31	−0.33	1	0.17	0.06
$F5$	−0.12	−0.32	−0.33	0.21	1	−0.16
$F6$	0.14	0.06	0.13	0.06	−0.16	1

Table 4
Recent clinical data on benign-malignant breast lesion differentiation by elasticity imaging

No.	Method	Number of analyzed lesions	Sensitivity (%)	Specificity (%)	Citation
1	USE*	52 malignant 59 benign	86.5	89.8	Itoh et al. [37]
2	USE	135 total	100.0	95.0	Zhang et al. [38]
3	USE	49 malignant 59 benign	82.0	87.0	Thomas et al. [39]
4	MRE*	38 malignant 30 benign	95.0	80.0	Sinkus et al. [40]
5	USE	88 total	96.0	61.0	Renger et al. [41]
6	USE	43 malignant 150 benign	100.0	96.0	Barr [42]
7	USE	115 total	90.0	–	Garra et al. [43]
8	USE	50 malignant 48 benign	99.3	25.7	Burnside et al. [44]
9	USE	237 malignant 584 benign	97.5	48.0	Svensson et al. [45]
10	PI*	34 malignant 76 benign	94.4	–	Kaufman et al. [46]
11	SSI*	4 malignant 11 benign	100	100	Tanter et al. [47]

USE* ultrasound elastography, MRE* magnetic resonance elastography, PI* palpation imaging, SSI* supersonic shear imaging