Comparative Study by Analytical Multidisciplinary Methods and Oxidative Stress in Breast Cancer Diagnosis

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To evaluate the diagnostic performance of mammography, elastography and breast magnetic resonance imaging (MRI), as tools for breast cancer diagnosis, against pathological diagnosis as the gold standard. Other risk factors such as obesity and oxidative stress are also disccused. In this comparison study, a total of 169 female patients (mean age 51 years, range 35-77 years) were enrolled between January 2016 and June 2017. After the physical examination of the breasts, patients were further randomized into three groups to mammography, elastography, or breast MRI. Only women with detected lesions classified into breast imaging and reporting data system (BI-RADS) category or Tsukuba elasticity score from 2 to 5 were included. Histopathology was used as the gold standard for diagnosis. The diagnostic performance of each modality was calculated. Of a total of 50 pathologically confirmed cancers, 25 were detected by mammography, 11 by elastography, and 14 by breast MRI, which resulted in sensitivities of 84% (PPV = 78%), 75% (PPV = 64%) and 86% (PPV = 75%), respectively. Mammography, elastography, and breast MRI led to 6, 5, and 4 false positive findings, which resulted in specificities of 86% (NPV = 90%), 87% (NPV = 92%) and 89% (NPV = 94%), respectively. The area under the curve (AUC) values for the mammography, elastography and breast MRI were 0.849 (95% CI, 0.758-0.939), 0.809 (95% CI, 0.670-0.948) and 0.876 (95% CI, 0.769-0.983). The DOR values were 32 (95% CI, 8-125), 20 (95% CI, 4-99) and 51 (95% CI, 8-315). The breast MRI proved a slight advantage over mammography as a diagnostic tool in breast cancer diagnosis.

Keyword: breast elastography; breast MRI; diagnostic performance

Breast cancer constitutes an important medical, social and economic problem being the most common type of cancer in women worldwide. Although symptoms bring patients to medical attention, many of them are non-specific, and unable to discriminate between breast cancer (BC) and other breast diseases. There are several risk factors for breast cancer including femily history, genetics, chest radiotherapy, certain benign breast lesions and many others; among them an important role plays overweight and obesity, which has been associated with an increased risk of postmenopausal and premenopausal breast cancer [1-3].

In addition, oxidative stress, which is considered the imbalance between antioxidants and pro-oxidants [4], could exert some clear effects on the breast cancer pathology, as stated in very recent papers in this area of research [5-8], as well as in most of the current disorders, including the metabolic diseases [9]. Most of the mechanism suggested could be represented by fibroblasts activation to become myofibroblasts [5], some related BRCA1 gene connections to the redox homeostasis [6], various modulatory effects [7] combined with different genotypes I specific populations [8].

Moreover, imaging plays a central role in diagnosis, staging and guiding the treatment in BC. Mammography is the primary imaging modality for breast cancer screening, detection, and diagnosis. It is noninvasive, widely available, relatively inexpensive, and has a reasonable sensitivity (72–88%) that increases with age [10-14]. Although mammography continues to be the method of choice for screening and diagnosis, efforts have been made to improve the accuracy of breast cancer diagnosis using other imaging modalities. The use of multimodality imaging in depicting the primary tumor, lymph node involvement and metastasis would be helpful to early identification, appropriate staging and accurate outcome of patients [15-17].

Elastography-based imaging techniques have received substantial attention in recent years for non-invasive assessment of tissue stiffness and hardness [18]. Combined conventional breast ultrasound (US) and elastography provide supplementary information for characterization of lesions found on mammography or palpable masses with a negative mammogram [19-21]. However, lesions characteristics and high variability in appearance are often difficult to differentiate between benign or malignant.

Magnetic resonance imaging (MRI) and dynamic contrast-enhanced breast MRI (DCE-MRI) has emerged as a valuable tool during the past decade in the detection of primary breast cancer [22]. Breast MRI shows great promise for detecting mammographically occult breast cancers and for defining the extent of malignant disease. MRI has exceptional sensitivity for the detection of breast cancer and can depict cancers that are entirely occult on conventional imaging [23]. Still, the value of this technique

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is limited by the low specificity with a moderate amount of false-positive results, availableness, cost, as well as different acquisition protocols and of lack of large-scale routine diagnostics [24].

The aim of the current study was to evaluate the diagnostic performance of three imaging techniques for the prediction of lesion malignancy: screen-film mammography, breast ultrasound in conjunction with elastography and dynamic contrast-enhanced breast MRI. We hypothesized that identifying the most appropriate method for predicting malignancy may help clinicians to establish the earliest possible delivery of effective interventions.

Experimental part

Materials and methods

Inclusion Criteria

This is study aims to evaluate the efficacy of mammography, breast US combined with elastography and breast MRI, in the differential diagnosis of benign and malignant breast tumors. The study protocol was approved by the institution's Ethics Review Board, and all patients signed a written informed consent before enrollment, according to the rules of the Helsinki Declaration, and some published models and guidelines [25 - 27]. The study subjects were selected from patients who were referred to our department due to specific diagnostic requests. Women with suspected primary breast cancer based on signs and symptoms were eligible.

All patients underwent a physical examination. Patients were further randomized into three groups, according to a simple randomization scheme, to bilateral mammography, breast ultrasound/elastography or DCE-MRI.

Study population**.** A total of 169 patients were enrolled between January 2016 and June 2017. Only women with detected lesions classified into breast imaging and reporting data system (BI-RADS) category or Tsukuba elasticity score from 2 to 5 were further included. Exclusion criteria comprised of masses known to be malignant, severe medical conditions, pregnancy and lactation and contraindications to breast MRI. Women under 40 years of age were referred only to elastography and MRI. The characteristics of the study subjects are listed in table 1.

Gold standard test. The reference standard in this study was the histological evaluation of the breast biopsy. A biopsy was performed if either the mammogram, the elastography, or the MRI examination was considered to be suspicious.

Imaging and Interpretation

Mammography**.** All mammographic examinations were performed in accordance with ACR standards, by using a Senographe DMR (GE Healthcare, Milwaukee, Wisconsin, USA) unit along with a screen-film technique (Kodak Min-RS Film; Carestream Health Medical Imaging, Rochester, NY). A standard bilateral 2D mammogram with medio-lateral-oblique and cranio-caudal views was obtained. Additional views and spot compression were performed where appropriate. All lesions were described by using the terminology of the fifth edition of the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) lexicon, and a final BI-RADS category was assigned according to the mammography, even US was performed (fig. 1).

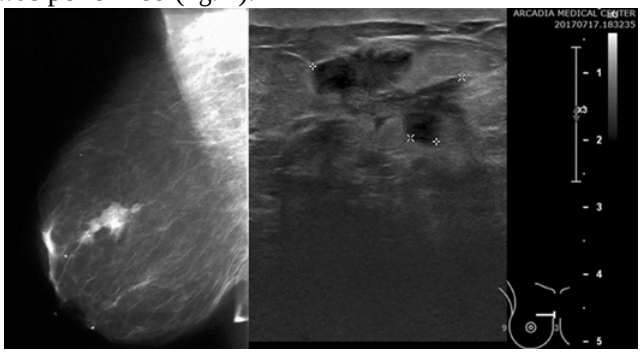

Fig. 1. Screen film mammography, right mediolateral oblique (RMLO) view and right breast ultrasound, BI-RADS 4

Ultrasound**.** An ACUSON S2000 ultrasound machine (Siemens Medical Solutions, Inc., Mountain View, CA, USA) with elastography module and a linear transducer (5.5–18 MHz) was used for all patients. A standard protocol which involves bilateral breast examination was applied to all patients. After the optimum B mode image was obtained, strain elastography was performed with the transducer placed perpendicularly on the skin.The elastograms were displayed side by side with the conventional B-mode images. Each lesion was assessed based on shape, margins, internal echotexture, long-axis orientation, and acoustic transmission followed by classification according to the BI-RADS category (fig. 2).

The elastographic data sets were evaluated qualitatively using the 5-point Tsukuba classification proposed by Itoh et al. . A Tsukuba elasticity score (TS) of 4 or 5 was considered to indicate malignancy.

MRI. MR examinations were performed on a 1.5 T MR unit (Achieva, Philips Medical Systems, Best, Netherlands) using a dedicated breast phased array coil. The protocol included 2 mm thick contiguous sections, field of view (FOV) 18 cm, matrix 256 x192, axial T1, T2 weighted sequences with and without fat suppression, T1 3D fat suppression fast spin echo (FSE) before and every minute after gadolinium injection (Gadovist, Bayer Schering

Imaging	MG and US	Elastography	MRI
Subjects included (n)	67	50	52
Age at study entry, years			
Average	51	44	46
Range	35 - 77	18-77	21-72
Age group at imaging examinations			
< 40 years	6	19	22
40 – 77 years	61	31	30
Age at menarche, mean (SD), years	13.5±1.2	13.1±1.1	13.1±1.1
Menopausal status			
Premenopausal	30	35	32
Postmenopausal	37	15	20
Familial history of breast or ovary cancer			
Present	6	2	1
Absent	43	28	47
Unknown	18	20	2

Table 1
CHARACTERISTICS OF THE STUDY SUBJECTS

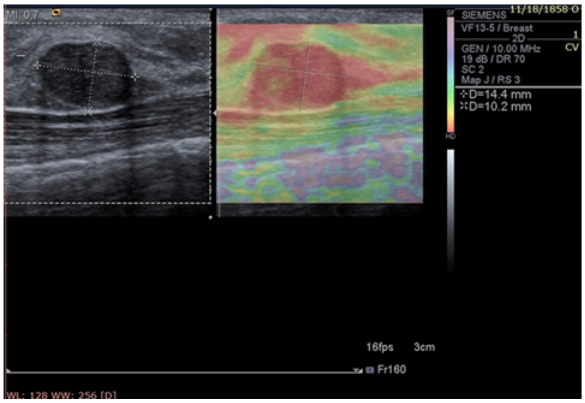

Fig 2. BI-RADS (US) 3 lesion with a suspicious elastogram, TES 4. The lesion was revealed to be malignant (true positive case).

Pharma, Germany, 0.2 mmol/kg, injection rate 2 mL/s), for 5 min, repetition time (TR) to echo time (TE), TR/TE 11.0/4.2, FOV 18 cm, matrix 256 x 192, 2 mm contiguous sections.

Criteria for distinguishing between benign and malignant contrast-enhancing lesions were based on lesion morphology and the time course of signal intensity changes. Lesions detected with MR imaging were classified according to the BIRADS–MRI lexicon descriptors, including morphologic and kinetic features (fig. 3).

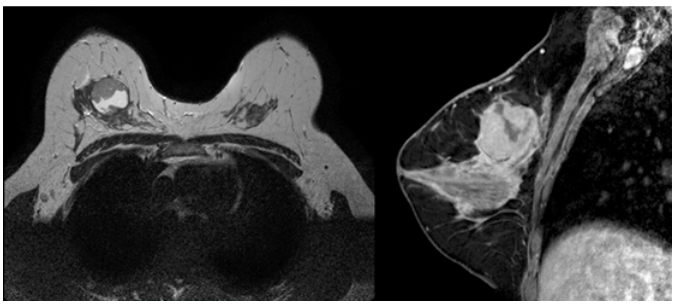

Fig. 3. T2-weighted (T2W) T2w turbo-spin-echo (TSE) and bilateral imaging in the sagittal plane using sensitivity encoding (SENSE) of the right breast (BLISS)

Mammograms, elastographic and breast MRI studies were assessed independently by different radiologists. Three breast radiologists were involved, each of whom had more than 10 years of experience in interpreting breast studies.

Statistical analysis

All statistical tests were performed with MedCalc for Windows (MedCalc Software, Mariakerke, Belgium). The continuous data were expressed as mean ± standard deviation. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV), for each imaging modality, were assessed. A true positive (TP) was defined if the biopsy confirmed breast cancer and as false positive (FP) if no breast cancer was found. A false negative (FN) was defined if a breast cancer was diagnosed and as true negative (TN) if it was not. At imaging, BI-RADS categories 1 to 3 were considered negative imaging findings and BI-RADS categories 4 and 5 were considered positive findings. For computing purposes, the test results were dichotomized as either positive (>3, malignant) or negative (≤ 3, benign). As a general estimation of the discriminative power of diagnostic imaging procedures diagnostic odds ratio (DOR) were calculated for each modality [28]. A receiver operating characteristics (ROC) curve was generated for each diagnostic method and accuracy was measured by the area under the ROC curve (AUC). Nominal data, such as sensitivity and specificity, are presented using percentages.

Results and discussions

Breast biopsy. A total of 169 breast lesions (mean size 14.1 ± 10.9 mm; range 5–87 mm) were biopsied, of which 45 (27 %) lesions were malignant, and 124 (73 %) were benign. At pathology, lesions were grouped into malignant (in situ and invasive), and benign lesions (fibroadenoma, fibrocystic changes, cysts and all other histopathologic findings). A diagnosis of invasive or intraductal breast cancer was considered disease positive. The histopathological results after biopsy are summarized in table 2.

Suspicious findings. A total of 107 suspicious findings (BIRADS category or TS scores of 4 and 5) were detected, with at least one of the three modalities in 169 patients. The suspicion findings by each imaging method, are summarized in table 3.

Film-screen mammography. At mammography, 21 (84%) of the total 25 cancers were detected. A total of 21 breasts were classified as BI-RADS 5, and 5 as BI-RADS 4.

Elastography. Ultrasound elastography identified a total of 9 (82%) malignant lesions of the total 11 cancers. Classification of the elastography scores was as follows: TS 5 in 4 cases and TS 4 in 10 cases. The TS scores were significantly higher ($P<0.05$) in malignant proved tumors (4.44 ±0.53), as compared with benign lesions (2.2±1.0).

MRI. With MRI, 12 lesions (86%) were detected to have malignant histology of the total 14 cancers. BI-RADS category 5 was noted in 15 of the 53 patients and category 4 in one case.

Comparison of Imaging Modalities. Mammography, elastography, and MRI led to 6, 5, and two false-positive findings, which resulted in false-positive rates of 14%, 13%, and 11%, and respectively in false-negative rates of 16%, 25%, and 14%. The sensitivities and specificities, the negative predictive value (NPV) and positive predictive value (PPV), as well as likelihood ratios and diagnostic odds ratios (DOR) for all three modalities are listed in table 4.

Histologic Finding	MG	US and Elastography	MRI
Malignant (n, % of total biopsies)	**25 (14.79)**	**11 (6.5)**	**14 (8.28)**
Invasive breast carcinoma	12	6	8
Ductal carcinoma in situ	3	1	4
Benign (n, % of total biopsies)	**42 (24.85)**	**39 (23.07)**	**38 (22.48)**
Fibroadenoma	16	12	20
Fibrocystic changes	12	4	13
Cyst	5	10	2
Others	9	13	3

Table 2
NUMBER OF SURGICAL BIOPSIES WITH HISTOPATHOLOGIC DIAGNOSIS

Modality	Total	BI-RADS Category		
		5	4	3 - 2
Mammography	67	21	5	41
< 40 years	12	4	0	8
40 – 77 years	55	15	5	35
US Elastography	50	9	6	35
< 40 years	18	0	2	16
40 – 77 years	32	8	4	20
MRI	52	15	1	36
< 40 years	18	3	0	15
40 – 77 years	34	8	1	25

Table 3
OVERVIEW OF IMAGING RESULTS

Table 4
PERFORMANCE CHARACTERISTICS OF IMAGING MODALITIES IN THE DIAGNOSIS OF BREAST CANCER

Modality	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Mammography	84* (64-95)	86* (71-95)	78 (62-88)	90 (78-96)	5.9 (2.8-12.6)	0.2 (0.1-0.5)	32 (8-125)
Elastography	75* (43-95)	87* (72-96)	64 (43-81)	92 (80-97)	5.7 (2.4-13.7)	0.3 (0.1-0.8)	20 (4-99)
MRI	86* (57-98)	89* (75-97)	75 (54-89)	94 (82-98)	8.1 (3.1-21.1)	0.2 (0.1-0.6)	51 (8-315)

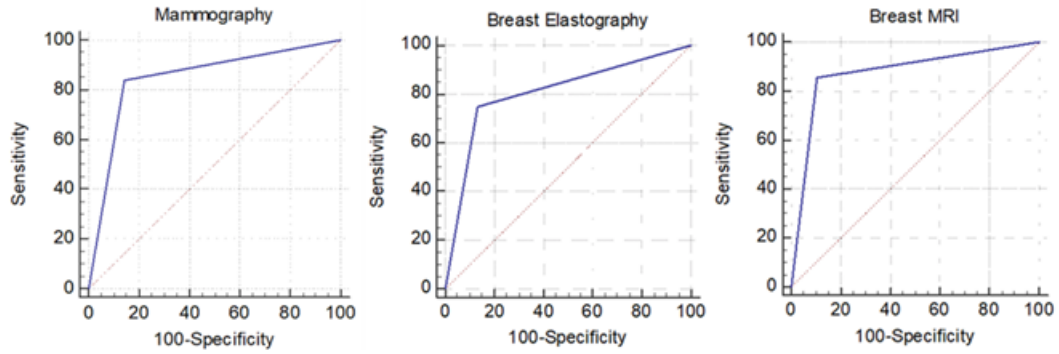

Fig. 4. ROC curves for mammography, breast elastography and breast MRI

In this study, the comparison of diagnostic accuracies between the diagnostic methods involved, showed that breast MRI was the most accurate method for the detection of breast cancer, followed by mammography and elastography (fig. 4).

Overall, we found that breast MRI proved superior (AUC 0.876, 95% CI: 0.769-0.983) in the detection of breast cancers compared with mammography (AUC 0.849, 95% CI: 0.758-0.939) and elastography (AUC 0.809, 95% CI: 0.670-0.948). In our study, the sensitivity and specificity of breast DCE-MRI (86%, respectively 89%) are in agreement with previous reports [29-33]. MRI had a negative predictive value of 94%, with 2 of 36 women with a negative MRI having breast cancer diagnosed by biopsy. However, other studies reported a higher specificity of breast MRI for detecting malignancies, but this could be partly explained due to differences in imaging protocols [34, 35], study populations, as well as substantial overlaping between benign and malignant features in contrast enhancement curves [36]. The physiological changes associated with a woman's age, menopausal status, and phase in the menstrual cycle which may have influenced the degree of background enhancement, that may lead to a false-positive findings [37-40].

Our results suggest that similar levels of performance was achieved by mammography to determine whether a given lesion is malignant or not. Comparison of area under the ROC curves revealed a small nonsignificant negative difference of -0.027 ($p = 0.7$) between mammography and breast MRI. This is in agreement with findings of Sardanelli et al., which reported a detection sensitivity of 75% for mammography and 80% for MRI ($p > 0.05$), in breasts with a fatty pattern. Similar results were reported by Kacl et al. [41] in 50 patients which found that mammography and brest MRI yielded a sensitivity and specificity of 82 and 64%, and 92 and 76%, respectively,

but statistically not significant ($p > 0.05$) with areas under the ROC curves of 0.807 for mammography and 0.906 for MR imaging [42].

US elastography was the least performant of the three diagnostic methods. The volume of the breast lesion might contributed in differentiating benign and malignant lesions based on TS scores. We found that patients with malignant lesions have the average lesion size slightly increased (malignant vs benign, 15.6 mm vs 12.6 mm) but, not statistically significant ($p = 0.052$). This finding is consistent with other studies using elastography to characterize breast lesions as malignant or benign [43].

There are several factors in our study that that could potentially affect the results. First, only patients with detected lesions were included, so the positive predictive value of mammography was relatively high (78%) compared with other reported values in the literature of 15% to 30% [44]. Second, when analyzing B-mode and elstography images placed side by side, some degree of bias may have influenced the assignement of the elastography scores. Third, we have to be aware of the wide variation of the MRI equipment and substantial differences in reliability between MRI system vendors across the different centres.

Conclusions

Our results show that breast MRI has a slight advantage over mammography as a diagnostic tool in breast cancer, so is a better imaging diagnostic approach, but in countries with limited health care resources we must choose wise the most efficient technique.

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