Original Investigation

Microwave Breast Lesion Classification – Results from Clinical Investigation of the SAFE Microwave Breast Cancer System

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Rationale and Objectives: Microwave breast cancer imaging (MWI) is an emerging non-invasive technology used to clinically assess the internal breast tissue inhomogeneity. MWI utilizes the variance in dielectric properties of healthy and cancerous tissue to identify anomalies inside the breast and make further clinical predictions. In this study, we evaluate our SAFE MWI system in a clinical setting. Capability of SAFE to provide breast pathology is assessed.

Materials and Methods: Patients with BI-RADS category 4 or 5 who were scheduled for biopsy were included in the study. Machine learning approach, more specifically the Adaptive Boosting (AdaBoost) model, was implemented to determine if the level of difference between backscattered signals of breasts with the benign and malignant pathological outcome is significant enough for quantitative breast health classification via SAFE.

Results: A dataset of 113 (70 benign and 43 malignant) breast samples was used in the study. The proposed classification model achieved the sensitivity, specificity, and accuracy of 79%, 77%, and 78%, respectively.

Conclusion: The non-ionizing and non-invasive nature gives SAFE an opportunity to impact breast cancer screening and early detection positively. Device classified both benign and malignant lesions at a similar rate. Further clinical studies are planned to validate the findings of this study.

Key Words: breast cancer; breast lesion classification; machine learning; SAFE.

INTRODUCTION

Female breast cancer has surpassed lung cancer as the most diagnosed cancer in females, with an estimated 2.3 million new cases (11.7% of all cancer diagnoses). It is the leading cause of cancer deaths in most countries (1). Over the years, the 5-year survival rate from breast cancer has increased largely due to improvements in treatment and earlier diagnosis due to increased use of mammography screening. The 5-year relative survival approaches 100% for patients diagnosed at stage 1 but declines to 26% for those diagnosed with stage 4 breast cancer. Screening mammography has decreased breast cancer related mortality by 40% in US women from 1989 to 2016 (2). Mammography (MMG) has been an accepted and widely used clinical tool for breast cancer screening and diagnostics. Still, it is limited by several risk factors such as false negativity in dense breasts, exposure to ionizing radiation, false-positive examinations, and patient discomfort (3–9). MMG is discouraged in women under the age of 40 due to the cumulative radiation dose over the years and increased breast density in younger patients, where the sensitivity is reported to be as low as 45 % (10). Working groups now recommend additional screening in women with extremely dense breasts (11). Along with MMG, ultrasonography (US) and magnetic resonance imaging (MRI) are commonly used for breast cancer imaging. Using a hand-held probe to image an entire breast with US can be time-consuming and operator-dependent. Furthermore, US can result in an increased number of benign biopsies, leading to patient

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anxiety and higher costs (12−14). Although there is increased advocacy for breast MRI to be used in women with dense breasts for breast cancer screening, it is more widely recommended for high-risk patient groups. It is not considered a practical tool due to the per- scan time, costs, and the special facility requirements (11,15−17).

There have been efforts to develop a screening method without the shortcomings of MMG. Microwave imaging (MWI) has emerged as a promising technique in this context. The technology utilizes the difference in dielectric properties of healthy and cancerous breast tissue to detect the presence of anomalies inside the breast. It has been demonstrated that cancerous tissue is characterized by higher dielectric permittivity compared to the healthy glandular tissue (18−26). One of the most appealing features of the MWI is the non-ionizing nature of the electromagnetic waves used to penetrate the breast tissue, which allows safe and repeated examinations of all women, regardless of their age or condition (e.g., in pregnancy). This can have a major impact on the younger population, especially for women at high risk of developing breast cancer, like those with genetic mutations, where there is a necessity to start screenings at an early age.

We reported the results of our MWI-based SAFE (Scan and Find Early) device in our previous clinical study (27), which detected 63% of lesions in the study group using prior clinical information. Building on our previous research (27), the aim of this study is to engage the Adaptive Boosting approach (AdaBoost) on SAFE raw-data frequency responses for an automated classification of benign and malignant breast lesions.

MATERIALS AND METHODS

Patients

The study was approved by the Ethics committee of Marmara University School of Medicine (Protocol number: 70737436-050.06.04; Date of approval: Jun. 09, 2014). Patient participation was voluntary, and written informed consent was obtained from all participants. All protocols and procedures were in accordance with both institutional and national ethical standards in research and with the World Medical Association Declaration of Helsinki.

Between August 2019 - March 2020, consecutive patients older than 18 years with BI-RADS Category 4 or 5 lesions, who were scheduled for breast biopsy, were included in the study. The sample population consisted of the same patients previously published in another study (27). Other BI-RADS categories were not included because histopathological verification was sought as a gold standard. Lesion size and location were recorded on conventional imaging. Breast density was recorded in patients who underwent mammography or breast MRI before or after biopsy. Forty-five patients were scanned with US, 25 with MMG, and 43 with MRI. Patients with breast implants were not included in the study. The radiologist was blinded to the results of the SAFE scanning.

Patients were divided into two groups according to histopathological results, age, breast density, and breast size. Patients were classified as benign or malignant according to histopathological results. High-risk (B3) lesions (i.e. Atypical Ductal Hyperplasia, Flat Epithelial Atypia, Lobular Neoplasia, Papillary Lesions, Phyllodes Tumor, and Radial Scars) were classified into respective categories after surgery or at least one-year follow-up (28). Classification according to age was dichotomized as ages 18-39 and 40 and above. Breast density was evaluated according to BI-RADS density classification, and densities were dichotomized as non-dense (types A and B) and dense (types C and D) (29). Breast size was classified into small and large breasts according to which size adjustable matching cup was used during SAFE scanning (explained below).

Breast lesions were divided into three groups: T_1 − lesions with a size between 0 mm-20 mm, T_2 - lesions with a size between 21 mm-50 mm, and T_3 - lesions with a size above 50 mm.

Radiological equipment used on site were Mammography (Mammomat Inspiration, Siemens Healthcare, Erlangen, Germany), Ultrasound (Toshiba Aplio 400, Canon Medical Systems Corporation, Tochigi, Japan), and MRI (3 Tesla scanner, Magnetom Verio, Siemens Healthcare, Erlangen, Germany).

Scanning

Patients were scanned with SAFE on the day of the biopsy before the procedure. SAFE microwave breast imaging device (Figure 1) is a mechanically rotating bistatic system that consists of one transmitting (TX) and one receiving (RX) antenna touching a cylindrical medium intended for impedance matching. During the scanning process, patients are required to lie prone on the bed with one breast inserted into the matching medium through the bed aperture. Since breast size differs between patients, size adjustable cups are available as a part of a cylindrical medium. For each TX position, a number of 36 RX corresponding positions are available, ensuring the total number of 1296 measurements for all TX positions employed. The frequency used for scanning is between 1GHz and 8GHz, chosen to ensure a suitable balance between absorption rate and resolution.

The scanning process was led by Mitos Medical Technologies (MITOS) medical staff. SAFE acquisition time was approximately 7-10 minutes per breast. For each breast measurement, S_{21} parameters (parameters proportional to the electromagnetic field emerging after the incident wave, radiated by TX, interacts with the breast) were collected and used for classification purposes. More specifically, as S_{21} is a complex matrix, we employed the real parts of the S_{21} as features for signal classification through the Adaptive Boosting (AdaBoost) model, where the histopathological results (benign and malignant) were used to train the algorithm to identify the backscattered signals from the breast automatically via the SAFE.

Figure 1. SAFE (Scan and Find Early) Microwave Imaging Device for breast cancer early screening and diagnostic: (a) SAFE industrial design, (b) SAFE's patient scanning process.

The concept of AdaBoost is based on learning from previous mistakes, where the next classifier is fed with the misclassification error of its predecessor. These errors are used to correct the mistakes of current classifiers until the final model predicts accurate results. In other words, the method focuses on the training samples which are hard to classify (misclassified samples) by the weak classifiers (models that misclassify the mentioned samples), and use them to eventually create a strong classifier.

Probability values between 0 and 1 were used to determine if the patient is at risk of malignancy. Higher the value is, higher is the possibility that the lesion present in the patient breast is malignant. Cases where the probability values are below the value of 0.5 are characterized as low risk malignancy cases.

Statistical Analysis

As the number of data available is limited, stratified 5-fold cross-validation was employed to assess the model and test its performance. Stratified 5-fold cross validation considers splitting the dataset into 5 subsets, where training is performed on all subsets but one (n-1), which is used to test the trained model. In this method, we iterate 5 times with a different subset reserved for testing purposes each time. Two-sample t-test was conducted to evaluate if real-parts of S_{21} are suitable to be used for classifying benign and malignant signals. The null hypothesis of the test (H_0) assumes that the two categories tested have no statistically significant difference, meaning that if we want to assume that the real-parts of S_{21} are suitable for classification, an alternative hypothesis ($H\alpha$) should be accepted. We assumed that the statistical significance was achieved, and thus the null hypothesis (H_0) was rejected for the condition of p (p-value) $< \alpha$, whereas α (confidence level) equals 0.05. The outcome of the test, where the $p = 2.69 \times 10^{-18}$ satisfies the condition $p < \alpha$ and accepts the alternative hypothesis ($H\alpha$), indicates that the real-parts of S_{21} can be considered suitable for the classification of benign and malignant signals. Sensitivity, specificity, and accuracy in detecting malignancy were calculated.

Two-sample t-tests were also conducted for subgroups of interest such as: breast density, breast size, patient's age and lesion size. The outcomes of the tests, where $p = 0.025$, $p = 0.011$, $p = 0.03$ and $p = 0.022$, respectively, satisfy the condition $p < \alpha$, showing that significant difference between the real-parts of S_{21} inside subgroups exists. This indicates that the real-parts of S_{21} can also be considered suitable for the classification of benign and malignant signals in the subgroups of interest. Sensitivity, specificity and accuracy in detecting malignancy were calculated for mentioned groups.

RESULTS

One-hundred-thirteen patients were evaluated with SAFE. The mean patient age was 45 years (±14 years; Range 18-86). There were 70 benign and 43 malignant lesions (Table 1). No SAFE scan was considered inconclusive. Two patients who were scanned with SAFE did not undergo a biopsy. One case was a complicated cyst resolved completely after aspiration. There was no cytological evaluation since the aspirate was non-hemorrhagic. There was no recurrence at six months follow-up. The other patient had a diagnosis of granulomatous mastitis, for which a microbiological evaluation was requested, and thus, was not evaluated histopathologically. Both patients were evaluated as benign cases. Thirty-three patients had non-dense breasts (BI-RADS type A and B), and 35 patients had dense breasts (BI-RADS type C and D). In 45 patients, breast density was unknown because only US imaging was available. Thirty-seven patients were in the younger age group, and 76 patients were in the older age group. Lesion size ranged from 5-120 mm (±20 mm; Mean lesion size = 25 mm; Median lesion size = 20 mm).

Considering all samples involved, SAFE was not able to correctly classify 25 out of 113 breasts (False Positive: 16, False Negative: 9), thus achieving the accuracy of the test of

TABLE 1. Histopathological Results of the Lesions Included in the Study

Histopathological Results	
Subtype	Number of Cases
Fibroepithelial lesions	24
Adenosis	10
Sclerosing adenosis	1
Acute and chronic inflammatory changes	8
Chronic inflammatory changes	6
Inflammatory changes	1
Columnar cell changes	4
Fibrosis	4
Granulomatous mastitis	1
Granulomatous lymphadenitis	1
Ductal ectasia	1
Pseudo-angiomatous hyperplasia	1
Fat necrosis	2
Intraductal papilloma	4
Invasive ductal carcinoma	31
Invasive lobular carcinoma	4
Ductal carcinoma in situ	6
Papillary malignancy	1
Lymphoma	1

78%. SAFE achieved similar sensitivity and specificity, 79% and 77%, respectively. Results are presented in Figure 2.

We analyzed the effect of breast size on the classification model proposed. Figure 3 gives a representation of classification outcomes for two breast size categories, considering the pathological findings. The sensitivity, specificity, and accuracy for small breasts were 75%, 79%, and 78%, respectively, and for large breasts, 85%, 76%, and 80%, respectively.

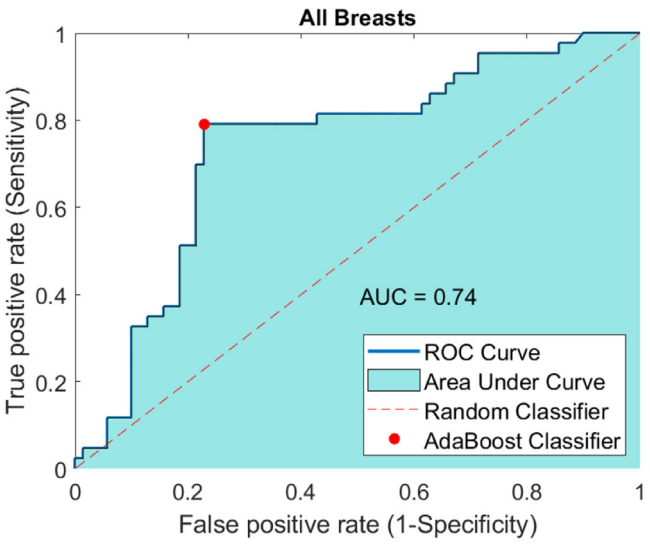

Figure 2. Classification results considering all samples involved in the study. SAFE achieved similar sensitivity and specificity of 79% and 77%, respectively. Considering all breasts involved, SAFE correctly classified 88/113 of the breasts achieving accuracy of 78%.

Density analysis showed that SAFE had an accuracy of 80% in dense breast tissue. In non-dense breast tissue, accuracy increased to 85% (Figure 4). Sensitivity and specificity for the non-dense breast category were 88% and 81%, respectively. In the dense breast category, SAFE had lower sensitivity of 73%, while specificity was higher compared to non-dense breasts with 85%.

Considering the participant's age (Figure 5), higher accuracy was noticed in the young patient group (84%). In the old patient group, 76% of the lesions were classified correctly. Sensitivity and specificity achieved for the younger population were 100% and 81%, respectively, while in the case of elderly patients, sensitivity and specificity achieved were 78% and 75%, respectively.

The effect of lesion size on diagnostic accuracy is presented in Figure 6. The number of lesions in each group was as follows: 58 lesions in the T_1 group, 40 lesions in the T_2 group, and 15 lesions in the T_3 group. The T_3 group was not analyzed due to the limited dataset. Sensitivity of the device increased according to the lesion size, having a value of 82% for lesions within the T_1 group and 87% for the lesions within the T_2 group. Specificity achieved for T_1 and T_2 lesions was similar (75% and 72%, respectively). Accuracy achieved for the T_1 group was 77%, whereas, for the T_2 group, it was 79%. The smallest lesion correctly classified was 4 mm.

DISCUSSION

This study evaluated the efficacy of SAFE microwave breast imaging device in distinguishing benign and malignant breast lesions with an overall 79% sensitivity, 77% specificity, and 78% diagnostic accuracy. In this study, a machine learning model, namely AdaBoost, was trained using the real part of the S_{21} complex matrix as a feature for the benign and malignant signal classification. SAFE exhibited similar performance in both smaller and larger breasts. It was noted that sensitivity was mostly affected by the breast size, where higher rate at 85% was achieved in larger breasts, compared with the 75% in the smaller ones. Better results in larger breasts can be explained by the electromagnetic interaction between the breasts and antennas. As the breast size gets smaller, it is possible that the direct coupling of field between antennas may increase, hence decreasing the electromagnetic wave interaction with the breasts. If the antennas are coupled to each other, it is very hard to differentiate small variations of the fields, which may influence capability of the SAFE to correctly classify malignant lesions in smaller breasts. Up to this point, various MWI clinical evaluations have been demonstrated in the literature (27,30–40). A comprehensive overview was given by (Benny et al., 2020; Kwon & Lee, 2016; O'Loughlin et al., 2018) (41–43). The vast majority of clinical trials studied MWI for lesion detection only, and most studies were performed on a limited number of patients (44).

In one of the most influential studies on the dielectric properties of breast lesions, Lazebnik et al studied 155 tissue samples extracted from cancer surgeries in vivo (25). They

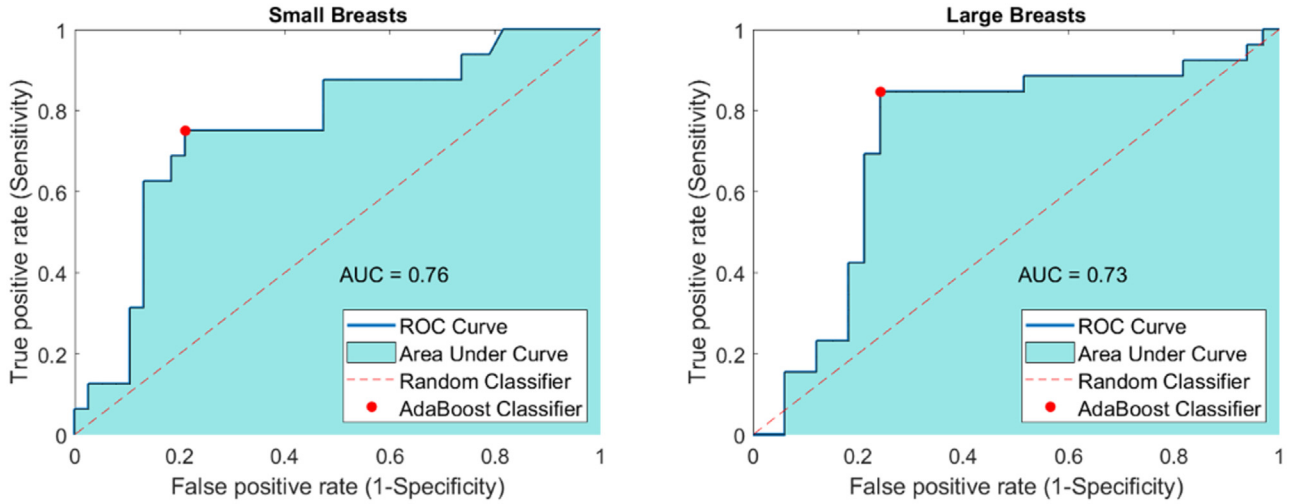

Figure 3. Breast size effect on the classification outcome. Similar accuracy was achieved for both small and large breasts (78% and 80%, respectively). Also, similar specificity was noticed in both breast categories (79% in small and 76% in large breasts), whereas sensitivity was higher in large breasts (85%) compared to smaller ones (75%).

reported that dielectric properties of benign tissues are similar to the properties of the lower-adipose-content normal breast tissues. The study also reported that difference in dielectric properties of malignant tissues and normal breast tissue can depend on the content of adipose tissue present in normal breast tissue. If the breast tissue is almost entirely adipose, reported difference in dielectric properties between malignant and healthy breast tissue was up to the 10:1, while if the breast tissue is dominantly fibroconnective\glandular difference in dielectric properties is no more than 10%.

To the best of our knowledge, the only study directly investigating breast lesion characterization using MWI was recently published by Moloney et al (45). Their final analysis included 24 patients (11 malignant, 13 benign) with bra sizes larger than 32B and cup sizes larger or equal to B. Employing a Quadratic Discriminant Analysis (QDA) classifier based on 10-fold cross validation, they were able to properly classify 88.5% of the lesions, from which 77.1% of malignant lesions were classified correctly, while the percentage of correctly classified benign lesions was 100%. Estimated overall classification loss was 11.5%. In addition, probability of malignancy was estimated based on the likelihood of each detection to be associated with malignant lesion class. Similar to our study, probability was calculated with a 50% cut-off value, where probability above 50% was used to predict malignant class, whereas probability below 50% was used for benign predictions. After radiological review, malignancy risk calculation was deemed useful in 70.6% of cases. Compared to our study, where raw-data (S_{21}) were used to classify benign from malignant lesions, this study used microwave images where classification was done based on the 3D shape (solidity) and texture-based features (correlation and busyness).

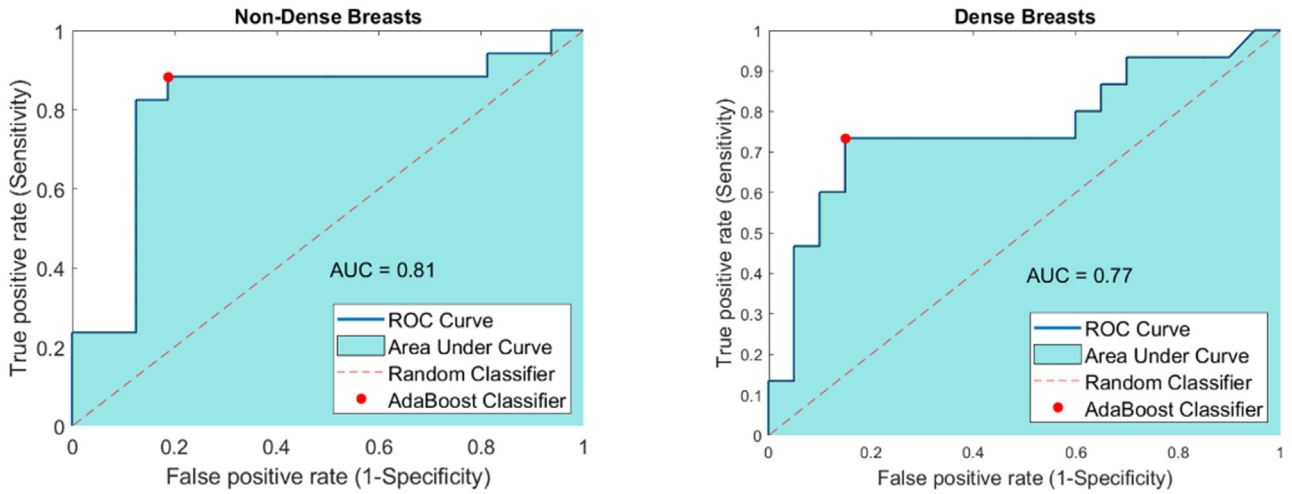

Figure 4. SAFE performance based on the breast density. SAFE performed better in non-dense breasts, achieving an accuracy of 85% compared to 80% achieved for dense breasts. Sensitivity in non-dense breast was 85%, whereas SAFE had lower sensitivity of 73% in dense breasts. Contrary, specificity of 85% was higher in dense breast category compared to the specificity of 81% in non-dense breasts.

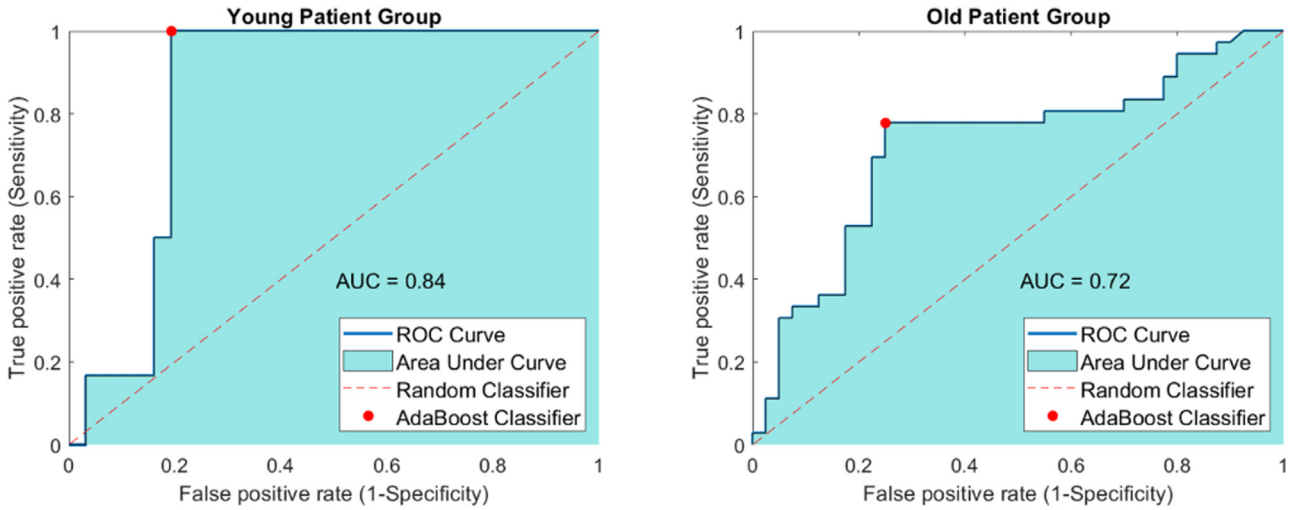

Figure 5. Representation of the SAFE performance in different age groups. SAFE showed enviable performance in younger participants, achieving an accuracy of 85%. Accuracy for older patient group was 76%. Sensitivity and specificity were also higher in younger patient group, 100% and 81%, respectively, compared to the sensitivity and specificity of 78% and 75% achieved in older patient group.

Breast density is one of the most important factors impacting the performance of mammography (4). This study showed that our MWI device is not considerably affected by breast density, achieving the accuracies of 85% and 80% for non-dense and dense breasts, respectively. On the other hand, SAFE capability to classify malignant lesions was affected by density, where in non-dense breasts device classified correctly 88% of malignant lesions, while in dense breasts 73% of malignant lesions were classified correctly. This observation remains to be tested on the larger sample size.

Ultrasound is usually the preferred modality as the first line of imaging of breast pathologies in women younger than 40 years. The benchmark PPV3 ratio of screening US, which is the ratio of true positive biopsies to the total number of recommended biopsies, provided by the American College of Radiology (ACR) is 7.4% (29). This ratio is reported to be 9-11.7% in women with an elevated breast cancer risk (46). This means that around 90% of lesions recommended for biopsy by US are expected to be benign (false positive). In the young age group, SAFE correctly classified 81% of benign lesions (false positive ratio of 19%), without any false negative misclassification of malignancies. Prospective studies with larger sample size are needed to verify the higher specificity of SAFE compared to US.

The previous version of the device was able to detect lesions as small as 6 mm (27). The current version of SAFE is able to classify both benign and malignant lesions as small as 4 mm in diameter. This early evidence suggests that SAFE could be capable of detecting and classifying lesions in their early stage of development. Sensitivity increases correlated

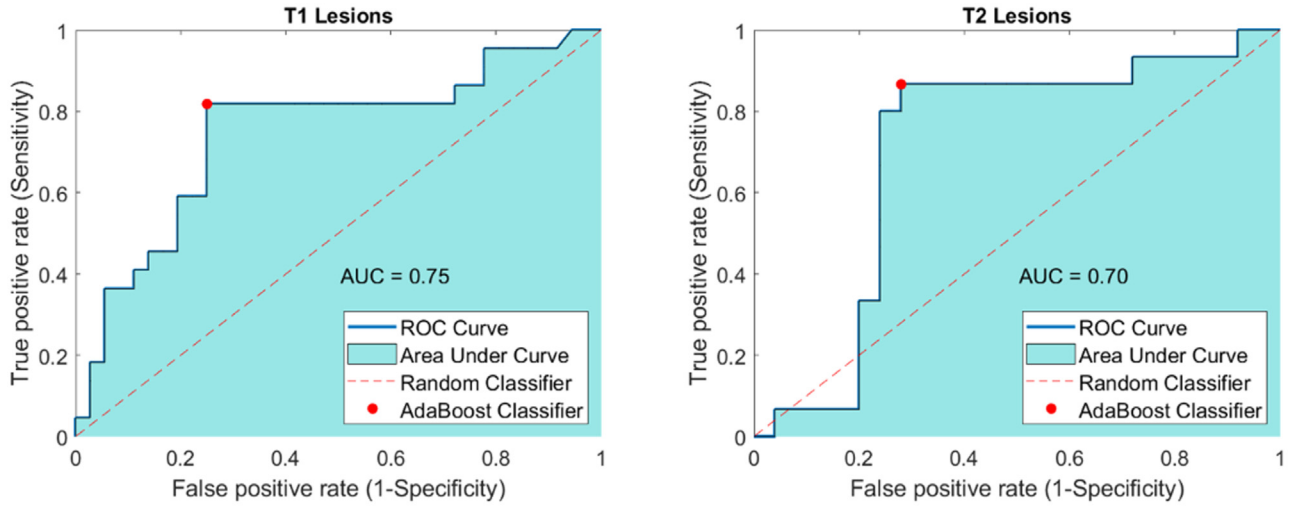

Figure 6. SAFE classification performance according to the lesion size groups. SAFE performed better when larger lesions were involved achieving an accuracy of 79% compared to the 77% achieved for the smaller ones. Sensitivity, contrary to specificity, increased with the lesion size having the scores of 82% and 87% for smaller and larger lesions, respectively.

with the lesion size, as would be expected, from 82% for the smallest lesions up to 87% for the largest ones.

The study has its limitations. Firstly, the number of participants is limited, having only 113 lesion samples included in the study. Patients included in the study were only the ones intended for biopsy. This means that we cannot be certain how the device would behave in a screening environment. The possible impact of the post-biopsy analysis is mentioned in the study by Fasoula et al. (47). In 45 patients, breast density information was not available because patients only underwent US. As the matching cups, used as a part of impedance cylinder matching, are determined based on the subjective assessment of the medical staff performing the scanning, a mismatch between the cup and breast size is possible. Additionally, lesions larger than 50 mm were not analyzed due to the limited dataset (15 lesions in total). The menstrual cycle of the patients was not considered since this information was not available. Thus, its effect on the performance of SAFE is unknown.

CONCLUSIONS

SAFE was able to correctly classify 79% of breast lesions. Breast density, breast size or lesion size can have a significant impact on the ability of SAFE to classify both benign and malignant lesions. At its current state, SAFE performs better in younger patients, a population where MMG is usually not the first line diagnostic method. Development of SAFE is ongoing, and multicenter clinical trials are planned with the support of the Scientific and Technology Research Council of Turkey (TUBITAK) in order to establish the capabilities of SAFE and its clinical and screening role.

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