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FULL PAPER

Additional diagnostic value of MRI in patients with suspicious breast lesions based on ultrasound

O SARICA, MD and F ULUC, MD

Department of Radiology, Taksim Gaziosmanpasa Research and Training Hospital, Istanbul, Turkey

Address correspondence to: Dr Ozgur Sarica

E-mail: sozgur@yahoo.com

Objective: Biopsy has long been the standard approach in Breast Imaging Reporting and Data System® (BI-RADS) 4 or BI-RADS 5 (American College of Radiology, Reston, VA) lesions despite a wide variation in reported incidence of malignancy in BI-RADS 4 lesions. This study examined the diagnostic value of breast MRI as well as its ability to decrease unnecessary biopsies in patients with solid breast lesions who had an indication for biopsy.

Methods: In this retrospective study, 277 breast lesions with a documented histological diagnosis as established by ultrasound-guided biopsy were included. All patients were female, and biopsy was performed owing to a BI-RADS score of 4 or 5 on ultrasonography. In addition, all patients had undergone MRI before biopsy. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MRI in predicting malignancy were calculated.

Results: When all lesions were analysed, sensitivity, specificity, NPV and PPV of MRI in detecting malignancy were 94.2%, 56.1%, 90.7% and 68.1%, respectively. When only ultrasonographic BI-RADS 4 lesions are considered, the corresponding figures were as follows: 90.9%, 56.7%, 93.8% and 46.4%, respectively. False-negative rate of MRI for the latter group of lesions was 2.6%. 42% of unnecessary biopsies were avoided in sonographic BI-RADS 4 lesions.

Conclusion: Despite promising results obtained in this study, dynamic MRI currently does not seem to be effective in ruling out the need for biopsy in the assessment of sonographic BI-RADS 4 lesions. However, advanced MRI techniques may assist in improving possible benefits of MRI in this patient group.

According to data from the American Cancer Society, Atlanta, GA, benign lesions account for nearly 80% of all breast biopsies performed. Although mammography is effective in detecting occult breast cancer, it is also associated with false-positive findings, resulting in the detection of different types of benign tissue in approximately 71–75% of the cases undergoing biopsy owing to suspicious mammography.¹ This usually prompts the clinicians to use ultrasound or MRI to obtain additional information on the character of the lesions. However, this approach has resulted in higher cancer detection yields in females who are at increased risk of breast cancer at the expense of increased false-positivity rates.^{2,3}

Although it may be appropriate to monitor Breast Imaging Reporting and Data System® (BI-RADS) 3 (American College of Radiology, Reston, VA) (probably benign) lesions radiologically owing to their low cancer risk (0.3–1.7%),^{4–8} biopsy has long been the standard approach in BI-RADS 4 or BI-RADS 5 lesions. The reported risk of malignancy for BI-RADS 5 lesions is >95%, while a wide variation in reported incidence of malignancy is noted in BI-RADS 4

lesions (from 2% to 95%). Biopsy is recommended for any lesion with an estimated risk of malignancy exceeding 2% based on imaging findings. Therefore, most of the solid lesions visualized through imaging modalities are candidates for biopsy. In recent years, a good deal of research has been devoted to the combined use of different imaging modalities in order to decrease false-positive biopsies and to improve the well-known low specificity of radiological imaging techniques in general and ultrasound in particular. In this regard, breast MRI has been shown to provide a high negative predictive value (NPV) that may help safely exclude a diagnosis of malignancy.^{9–12}

In this study, the diagnostic value of breast MRI as well as its ability to decrease unnecessary biopsies has been examined in a group of patients with solid breast lesions who had an indication for biopsy based on ultrasound results.

METHODS AND MATERIALS

Patients

We performed a retrospective review of 1266 consecutive breast MRI examinations acquired in 1148 females at

Taksim Gaziosmanpasa Research and Training Hospital, Istanbul, Turkey from April 2009 through November 2012. Many females who underwent breast MRI for the clinical indication of high-risk screening had multiple examinations over the course of the study period. According to the standards of our clinical routine practice, the indications for breast MRI were unclear findings on mammography, ultrasound or clinical examination and pre-operatively staged lesions. In this study, a total of 339 histopathologically proven lesions of 307 patients were analysed.

Exclusion criteria were as follows: less than 24 months of follow-up after a diagnosis of benign lesion was made with percutaneous biopsy; non-mass-like contrast enhancement in MRI; ongoing hormone replacement therapy; surgery, Tru-Cut® (Angiotech, Vancouver, BC) biopsy or chemotherapy prior to MRI examination.

Owing to potential disruption of internal signal characteristics of the lesions (especially T_2 signal), we planned MRI prior to biopsy for all cases in our radiology department. Therefore, two benign (sonographically BI-RADS 4) cases excluded from our study because biopsy was performed in the surgical department prior to MRI.

The remaining cases that met the criteria were 277 breast lesions with a documented histological diagnosis as established by ultrasound-guided biopsy. These were included in the study.

All patients were female, and ultrasound-guided biopsy was performed owing to a BI-RADS score of 4 or 5. Lumpectomy, mastectomy or core biopsy samples were histologically examined at the Department of Pathology, Taksim Research and Training Hospital (Istanbul, Turkey). In our study, all the ultrasound and MRI images through picture archiving and communication system were analysed by two separate radiologists retrospectively. Both radiologists were not aware of the radiological reports at the time of submission and the histopathological results. For all the mass MRI and ultrasound, the BI-RADS scores were recorded separately. In cases of discrepancy between the two observers, BI-RADS scores were decided according to both observers' consensus.

Additional lesions not biopsied and detected only by MR were assessed on the basis of histological examination of post-operative specimens or MR follow-up. The results of these latter assessments have also been reported.

Imaging protocol

A pre-defined technical protocol of MRI was used in all cases. MRI was performed using a 1.5-T magnet (MAGNETOM® Avanto; Siemens Medical Solutions, Erlangen, Germany) with a dedicated bilateral breast surface coil in the prone position. The imaging protocol and parameters consisted the following: axial T_1 weighted image [repetition time (TR)/echo time (TE), 450/11 ms] and non-fat-suppressed T_2 weighted turbo spin-echo image (3740/122 ms) of both breasts obtained with 3-mm cross sections. Next, T_1 weighted dynamic images were acquired using a three-dimensional fast low-angle shot pulse sequence (3D

FLASH) without fat suppression through both breasts (TR/TE, 5.19/2.38 ms; flip angle, 10°). T_2 weighted short-tau inversion recovery sequences were obtained in the coronal plane (TR/TE, 5900/78 ms; inversion time (IR), 130 ms; cross sections, 4.5 mm; field of view, 40 × 40 cm).

Non-fat-suppressed T_2 weighted turbo spin-echo images, with a total of 30–35 sections and a full 512 × 512 imaging matrix were also obtained. The contrast-enhanced dynamic series consisted 60 sections, each T_2 weighted image with 3-mm slice thickness compensated with 2 dynamic images with a slice thickness of 1.5-mm without gap. Contrast-enhanced dynamic series were exactly matched with the T_2 weighted images to allow an accurate comparison of signal intensity.

Six series of T_1 weighted 3D FLASH sequences were acquired in both breasts on the axial plane: one series before and five series after the administration of contrast material (with 20-s intervals).

Diagnostic assessments

Sensitivity, specificity, positive predictive value (PPV) and NPV were calculated for all breast lesions ($n = 277$) and for the subgroup of lesions with a sonographic BI-RADS score of 4 ($n = 189$). Lesions with a MRI BI-RADS score of 4 or 5 were considered malignant.

Statistical analyses

Statistical analyses were performed using the Number Cruncher Statistical System 2007, Power Analysis and Sample Size 2008 statistical software (Kaysville, UT). For the assessment of study data, descriptive statistical methods (mean, standard deviation, median, frequency and percentage) and diagnostic surveillance tests (specificity, sensitivity, PPV and NPV) were used.

RESULTS

The mean age was 48 years. The lesion diameter was <10 mm in 51 cases (18.41%), whereas it was between 10 and 20 mm in 114 lesions (41.16%) and >20 mm in 98 (35.38%). In a total of 14 cases (5.05%) with no contrast enhancement and ill-defined lesion margins, dimensions of the lesion could not be estimated by MRI.

Histological findings obtained from the samples revealed that there were 138 malignant and 139 benign lesions. In the 138 malignant lesions, the average lesion diameter was 19.6 mm, with 90 (65.2%) and 48 (34.8%) of these having a diameter <20 mm and >20 mm, respectively. Histologically, invasive ductal carcinoma was the most common malignancy ($n = 105$), followed by lobular carcinoma ($n = 11$), intracystic–intraductal papillary carcinoma ($n = 5$), invasive papillary carcinoma ($n = 5$), mucinous carcinoma ($n = 3$), pure high-grade *in situ* ductal carcinoma (IDC) ($n = 2$), medullary carcinoma ($n = 2$) and one case each of pure low-grade IDC, pure intermediate-grade IDC, tubular carcinoma, *in situ* lobular carcinoma and unspecified adenocarcinoma. The benign lesions diagnosed were as follows: fibroadenoma–fibroadenomatoid hyperplasia, fibrocystic changes, intraductal papilloma–papillomatosis, stromal fibrosis, sclerosing adenosis, abscess and granulomatous mastitis.

In our study, 24.55% (68/277) of the masses were categorized as probably benign with MRI (BI-RADS 3). Cancer yield was calculated as 5.88% (4/68) in our probably benign evaluated masses.

The diagnostic value of MRI in lesions considered as malignant according to a MRI BI-RADS score of 4 or 5 are summarized in Table 1. Histologically confirmed malignancy rates in ultrasound BI-RADS Score 4 lesions and subcategories are shown in Table 2.

Of the 189 lesions with an ultrasound BI-RADS score of 4, 79 (41.80%) had benign MRI findings. However, histology showed malignancy in five (2.65%) of these lesions (*i.e.* false-negative MRI). The distributions of lesions downgraded by MRI are shown in Table 3.

2 of 88 cases were interpreted as BI-RADS 5 with ultrasound evaluated as pathologically benign. Both false-positive cases were evaluated also as false-positive with MRI. There was no case that was characterized as BI-RADS category 5 with ultrasonography and downgraded by MR.

Of the 277 patients with MRI assessment, eight cancer cases (2.89%) were evaluated as false negative.

There were also a total of 110 additional lesions with contrast enhancement, of which 100 had available data for assessment. Of these lesions, 40 could be imaged by only MRI (40/277, 14.44%). Among these, a biopsy was offered in 27 (27/40, 67.50%) based on a MRI BI-RADS score >4 , establishing a diagnosis of malignancy in 16 (16/27, 59.26%).

DISCUSSION

Discrete mass lesions of the breast are among the most common abnormalities detected by screening mammography or ultrasound examination.¹³ The use of breast MRI as an adjunct to physical examination and mammographic screening dates back to nearly 15 years ago as an attempt to improve the sensitivity and specificity of mammography. In two previous studies examining the diagnostic value of MR in mammographic BI-RADS 3 breast lesions, a reduction in the number of invasive procedures has been proposed, with the NPV of MRI approaching almost 100%.^{9,14} In both of these reports, non-calcified mass lesions and asymmetric densities comprised the majority of the lesions detected.

BI-RADS score 4, which points to the presence of suspicious abnormality, can be further subdivided into 4a, 4b and 4c categories to reflect the radiologist's level of suspicion for malignancy in the following manner: category 4a, low suspicion (3–8%); category 4b, intermediate suspicion (9–49%); and

category 4c, moderate suspicion (50–94%).¹⁵ In our series, the rates of malignancy for BI-RADS 4 subcategories paralleled the reported data.

In our patient group, although 42% of the unnecessary biopsies could be prevented by the use of MRI in sonographic BI-RADS 4 lesions, this was also associated with a false-negative detection rate of 2.6%. This figure should be viewed in the context of the fact that, to our knowledge, our study is the first of its kind to examine the diagnostic value of MRI specifically in ultrasonographic BI-RADS 4 lesions.

According to Kuhl,¹⁶ the evidence for the efficacy of breast MRI in helping solve mammographic interpretation problems is relatively weak, since studies such as the multicentre trial conducted by Bluemke et al¹⁷ do not seem to provide adequate NPVs to exclude malignancy in the presence of suspicious lesions detected by conventional imaging modalities. In that study, the diagnostic accuracy of MRI was examined in 821 patients with suspicious (BI-RADS 4 or 5) mammographic findings (85%) or suspicious clinical findings with a negative or benign conventional work-up (15%) prior to biopsy.¹⁷ MRI had a NPV of 85%, with a missed diagnosis of malignancy in 48 of 329 (14.6%) negative MRI examinations. However, it should be pointed out that this widely referenced multicentre study was performed in 14 hospitals from 1998 to 2001, whereby the MRI equipment used for study purposes could possibly be considered relatively outdated compared with current imaging systems. Furthermore, microcalcifications of the breast were also included in the study by Bluemke et al,¹⁷ which are known to affect NPV negatively.

Elastography has been found to reduce benign biopsies when used as a complementary tool to conventional ultrasound, and reports suggest that 46.0–85.7% of benign biopsies can be reduced using this approach.^{18–20} When elastography was used to downgrade BI-RADS category 4a lesions, the malignancy rate increased from 7% to 9% with ultrasound BI-RADS assessment alone to 17–18% with ultrasound BI-RADS plus elastography.^{15,21}

In this study, the estimated risk of malignancy in ultrasound 4a lesions was 8.5% (11/130); however, this rate was increased to 10.9% (6/55) when both ultrasound and MRI findings were positive. This increase in the estimated risk is lower than that of studies using elastography.

In the landmark 1995 study by Stavros et al²² involving 750 lesions, strict criteria for the greyscale ultrasound diagnosis of benignity were applied, resulting in the impressive sensitivity and NPV rates of 98.4% and 99.5% for malignancy, respectively.

Table 1. Diagnostic value of MR Breast Imaging Reporting and Data System® (BI-RADS) Grade 4–5 in identifying malignancy

Patient groups	Sensitivity	Specificity	NPV	PPV
All patients, ultrasound BI-RADS 4–5 ($n = 277$)	94.2	56.1	90.7	68.1
Ultrasound BI-RADS 4 only ($n = 189$)	90.9	56.7	93.8	46.3

NPV, negative predictive value; PPV, positive predictive value.

Table 2. Histologically confirmed malignancy rates among ultrasonographic Breast Imaging Reporting and Data System® (BI-RADS) 4 lesions and its subcategories

BI-RADS classification	Patient number, <i>n</i>	Histologically confirmed malignancy, <i>n</i> (%)
BI-RADS 4	189	55 (29.1)
BI-RADS 4a	130	11 (8.5)
BI-RADS 4b	20	10 (50.0)
BI-RADS 4c	39	34 (87.2)

However, the high sensitivity resulting from the use of these strict criteria was achieved at the expense of a poor PPV of 38%. In a study assessing the role of elasticity only, despite lower sensitivity and NPV values for elasticity (95% and 88%, respectively) than those in the study by Stavros et al,²² PPV was superior (84%).²³ The sensitivity (90.91%) and NPV (93.83%) were also lower in our study than those of Stavros et al,²² whereas the NPV was superior compared with elasticity studies, approaching that reported in the study by Stavros et al.²² Among BI-RADS 4 lesions undergoing ultrasound-assisted biopsy based on the ultrasound criteria proposed by Stavros et al, MRI showed a lower PPV than that of elastography studies, but it was superior to that reported by Stavros et al.

In our study, the NPV of 90.7% in BI-RADS 4–5 lesions was associated with a missed diagnosis in 8 out of 86 (9.3%) negative MRI examinations. Although we achieved better results than the study by Bluemke et al, the strict criteria proposed by Stavros have not been met. When these strict criteria are taken into consideration, our sensitivity and NPV rates appear to be inadequate, and PPV appears to be lower than those reported in elastography studies.

The well-known shortcomings of percutaneous image-guided core biopsy are limitations in the assessment of calcifications and histological underestimation. However, percutaneous biopsy is less invasive than surgery, does not deform the breast, causes minimal to no scarring on subsequent mammograms, allows the determination of multifocal carcinoma and can be performed easily.²⁴ The main advantage of percutaneous image-guided

biopsy is the ability to prevent surgery if imaging findings are concordant with benign histopathological results. One of the most common reasons for false-negative diagnosis is lack of imaging follow-up after a benign biopsy result. In clinical follow-up studies, after stereotactic 14-gauge automated core biopsy, the frequency of missed carcinoma averaged 2.8% (range, 0.3–8.2%).^{25,26} 2.6% false-negative rate that we have reached with MRI evaluation is observed in the range of missed cancer by biopsy. However, assuming the prevalence of breast cancer is 20% of biopsy specimens (BI-RADS 4), the calculated false-negative rate is <1%. Assuming a breast cancer prevalence of 70–80% (BI-RADS 5), the false-negative rate would be 6%.²⁷ Low false-negative rate may be related to just the BI-RADS 4 lesion group that was included in our study. Newer technologies should be assessed with respect to their accuracy, safety and cost-effectiveness. Considering the high cost of MRI examination, it is hard to propose MRI examination in all BI-RADS 4 cases. Our results suggest that it is still early to propose MRI as a safe alternative to biopsy in patients with a biopsy indicated based on ultrasound results. However, high NPV is a promising observation despite inclusion of high-risk BI-RADS 4–5 patients in our study.

In previous publications when only BI-RADS 3 lesions were considered, NPV of mammographic⁸ and sonographic²⁸ follow-up were 100% and 99%, respectively. In our study, the NPV of MRI was 93.83%. According to our findings, MRI does not seem to take the place of ultrasound follow-up.

In our study, 24.5% of the masses were categorized as MRI BI-RADS 3 with 5.88% cancer yield ratio. The probably benign (MRI BI-RADS 3) assessment has been applied to 17–24% of patients in previous studies with a wide range of cancer yields (0.6–10.0%).^{29–31} The wide range of cancer yield in cases that are categorized as MR BI-RADS 3 is >2–3% of the threshold value for those categorized as BI-RADS 3 in the literature. Similar to the literature, we have seen in our study that the cancer yield ratio in the group considered as BI-RADS 3 on MRI was higher than expected. Therefore, we think follow-up is necessary for this group. Eby et al³¹ reported that MR BI-RADS 3 evaluation may be a reliable alternative biopsy. In terms of timeliness evaluation, eliminating delay in diagnosis and anxiety of the patient are advantages of biopsy when compared with follow-up imaging. In our daily radiological practice despite

Table 3. Distribution of lesions downgraded by the use of MRI

Ultrasound BI-RADS class (<i>n</i>)	Downgraded with MR to BI-RADS 1, 2, 3 (<i>n</i>)	Histologically benign (<i>n</i>)	Histologically malignant (<i>n</i>)
4a (130)		119	11
	75	70	5
4b (20)		10	10
	3	3	0
4c (39)		5	34
	1	1	0

BI-RADS, Breast Imaging Reporting and Data System®.

benign concordant biopsy results, ultrasound follow-up is necessarily performed for each case. Therefore, according to our opinion, a negative MRI assessment and ultrasound follow-up may be offered to a restricted group of cases, BI-RADS 4 patients who decline the biopsy, clinically low risk cases, instead of biopsy and ultrasound follow-up.

Incidental detection of benign lesions is common during MRI examination of the breast leading to additional biopsy and follow-up, which may also increase patient anxiety and costs. In our study, the percentage of additional lesions detected only by MRI was 14%, and 41% of these lesions were benign. In previous studies, a benign diagnosis was made in 55–70% of lesions that underwent MRI-guided biopsy.^{32–34} On the other hand, lesions evaluated in this study represent a high-risk group for malignancy, which may explain the low rate of biopsies with negative findings.

Our results seem to suggest a high efficacy of MRI in detecting the malignancy in the overall lesion group (ultrasound BI-RADS score 4 or 5) and in BI-RADS 4 lesions only. When only BI-RADS 4 lesions are taken into consideration, the decrease observed in sensitivity (from 94.20% to 90.91%) and PPV (from 68.06% to 46.30%) may be explained on the basis of the exclusion of lesions with a high risk of malignancy, most of which have a BI-RADS score of 5. The NPV was slightly higher when only BI-RADS 4 lesions were considered. This result is an expected one as the probability of encountering true cases of malignancy is less in BI-RADS 4 cases than in BI-RADS 5 cases.

A major drawback of our study was the inclusion of lesions with lowest interobserver agreement (*i.e.* BI-RADS 4 lesions), as

previously suggested.^{35,36} Despite this, the rates of malignancy in each diagnostic subcategory were in line with previous reports. Another possible limitation is the inclusion of lesions requiring biopsy according to ultrasound results (BI-RADS 4–5 lesions), hindering comparisons with some previous studies. Such comparisons are complicated by the different proportions of benign and malignant lesions in different populations, since a large proportion of cancers increases the pre-test probability and promotes a high PPV, whereas a large proportion of benign cases promotes a high NPV. Also, relatively shorter follow-up period (2 years), retrospective design and exclusion of non-mass-like lesions from the study should be mentioned as limitations. During the study period, MR-guided biopsy was not available in our radiology clinic. In our study more non-mass-like lesions were detected with MRI than with ultrasound. Also, there was an obvious difference between the extent of non-mass-like lesions determined by MRI and those by ultrasound. Radiopathological correlation could not be made with certainty because of the reasons stated above and non-mass-like lesions removed from our study.

In conclusion, dynamic MRI does not seem to be effective in ruling out the need for biopsy in the assessment of sonographic BI-RADS 4 lesions owing to its low sensitivity (90.91%) and NPV (93.67%) in light of the criteria proposed by Stavros et al.²² However, a 41% reduction in the number of biopsies could be achieved, resulting in a missed diagnosis rate of only 2.6%. Inclusion of additional morphological criteria that are not included in the BI-RADS classification and the use of 3-T MRI devices as well as diffusion MR and MR spectroscopy in further studies may assist in improving possible benefits of MRI in this patient group.

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