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Diagnostic value of dynamic and morphologic breast MRI analysis in the diagnosis of breast cancer

Małgorzata Stusińska^{1ABCEFG}, Jadwiga Szabo-Moskal^{1ABDEG},
Barbara Bobek-Billewicz^{2ACDEF}

¹ Department of Diagnostic Imaging and Interventional Radiology, Oncology Center in Bydgoszcz, Bydgoszcz, Poland

² Department of Radiology and Diagnostic Imaging, Oncology Center in Gliwice, Gliwice, Poland

Author's address: Małgorzata Stusińska, Department of Diagnostic Imaging and Interventional Radiology, Oncology Center in Bydgoszcz, I. Romanowskiej 2 Str., 85-796 Bydgoszcz, Poland, e-mail: gosia_stusinska@wp.pl

Background:

Mammography is the most widely used method of breast imaging. However, its low sensitivity poses a problem. Breast MRI is one of so the called "complementary" breast imaging methods. The purpose of this study was to improve the specificity of breast MRI by combining 2 methods: dynamic and morphologic analysis of enhancing lesions.

Material/Methods:

222 women aged 19–76 years, who underwent breast MRI examination between November 2002 and April 2004 at the Radiology Department of Oncology Center in Bydgoszcz, were included in this study.

Results:

The pathological examination revealed cancer in 55 women (25%). No cancer was found in 167 women (75%), 56 of which were verified pathologically, 111 by cytology and/or during follow-up (at least 24 months). Results of breast MRI were positive in 80 women (36%), in 54 of which cancer was found during pathological examination, 26 breast MRI results were false positive. Sensitivity and specificity of breast MRI for dynamic analysis were 87% and 72%, respectively; in case of morphologic analysis 98% and 74%, respectively. The combined dynamic and morphologic analysis achieved high (84%) specificity without loss of sensitivity (98%). The difference in specificity between the evaluated methods was statistically significant ($p < 0.05$).

Conclusions:

The combined dynamic and morphologic breast MRI analysis is a useful method for the diagnosis of breast cancer.

MeSH Keywords:

Breast Neoplasms – diagnosis • Sensitivity • Specificity • Magnetic Resonance Imaging

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Background

Mammography is a widely used breast imaging method. It is simple, inexpensive and widely available. Unfortunately, mammography does not detect all breast lesions [1–3]. As a consequence, other methods of breast imaging have been developed. They include ultrasound, scintigraphy ^{99m}Tc-MIBI, PET, breast magnetic resonance imaging, electrical impedance imaging, elastography, thermography, CTLM – 3-dimensional computed tomography laser mammography. Among complementary methods, ultrasound has the most extensive clinical use in the basic version as well as the optional Doppler or contrast agent.

Breast Magnetic Resonance Imaging (breast MRI) is a relatively new method. It quickly gained interest due to its very high sensitivity. However, it was soon revealed that its specificity is not satisfactory [4–6]. The issue mostly concerns the false positive results. Such results not only raise unnecessary "oncologic anxiety" in the women tested, but also triggers unjustified, costly and complicated diagnostic procedures. Combining 2 methods of MRI assessment (evaluation of morphologic characteristics of lesions displaying contrast enhancement and evaluation of the dynamics of enhancement) made possible with modern MRI scanners, creates an opportunity to improve specificity of the test.

Table 1. Combinations of signal intensity in pathological lesions. Native T1, T2 and T2 fat suppressed images.

T1WI signal before CM	T2WI signal	T2WI signal with fat suppression	Interpretation of the type of lesion	
			Benign lesions	Suspicious/malignant lesions
Low	High	High	Benign, with high water content	Mucinous carcinoma
Low	Very low	Intermediate	Fibrotic lesions	(–)
High	High	Low	Benign, with high fat content	(–)
Low or intermediate	Low or intermediate	Intermediate or high	(–)	Suspicious lesion

The purpose of this study was to evaluate the growth rate of signal intensity after administration of contrast medium and the evaluation of morphologic features of focal lesions shown on breast MRI. It also included both separate and combined assessment of sensitivity and specificity of the diagnostic methods in comparison with histopathological verification of breast lesions in the women studied.

Material and Methods

The study group consisted of 222 women aged 19–76 years (mean age 50 years) who underwent breast MRI in the period from November 2002 to April 2004 at the Center of Oncology in Bydgoszcz.

Image acquisition

Tests were performed using Siemens Magnetom Symphony, with a 1.5T high-field. Patients were examined in prone position, using a dedicated coil which allowed simultaneous examination of both breasts. In order to reduce the risk of false positive symptoms associated with hormone influence on breast tissue, the study was performed between the 7th and 14th day of the menstrual cycle [7].

MR images were obtained as follows: T2-weighted cross-sectional (TSE, TR 5130 ms, TE 97 ms, FA 150°, thickness 3.5 mm, with no space between the layers, FOV 320×320 mm, 512×384 matrix, number of repetitions: 2, acquisition time 4'39"), T2-weighted fat suppressed cross sections (TSE, TR 9020 ms, TE 70 ms, FA150°, thickness 4 mm, spacing between the layers 20%, FOV 320×320 mm, 512×256 matrix, number of repetitions: 1, data acquisition time 5'8"), T1-dependent in frontal sections (3D GRE, TR 11 ms, TE 4.76 ms, FA25°, thickness 2 mm, with no space between the layers, number of layers: 64, FOV 340×170 mm, 512×215 matrix, voxel size 0.8×0.7×2 mm, number of repetitions: 1, acquisition time 1'20").

T1-weighted images were performed before and five times after the administration of contrast agent without interruptions between successive acquisitions. Contrast agent (gadolinium compound) was administered at a dose of 0.2 mmol/kg body weight at a rate of 2.5 ml/s into a vein in the antecubital fossa using an automatic syringe. Following the administration of the entire volume of contrast medium, 20 ml of 0.9% NaCl was administered at a rate of 2.5 ml/sec.

Evaluation of MR images

Areas displaying higher signal intensity in comparison to the surrounding breast parenchyma shown on T1-weighted images made after the administration of contrast medium. Subtraction images were performed for the purpose of easier detection of the lesions. Equivalents of contrast-enhancing lesions as well as other areas displaying abnormal signal were sought after on T1-dependent images prior to the administration of contrast, T2-weighted images and T2 images with fat suppression. The most common and significant changes in the variance of signal combinations are shown in Table 1.

Analysis of contrast enhancement

Region of interest (ROI) was selected within the area showing abnormal contrast enhancement following the administration of contrast agent. In order to obtain correct measurements, ROI was placed in an area where the degree of amplification appeared to be the highest. The size of ROI was at least 1–3 pixels [4]. Relative contrast enhancement was determined automatically using SIEMENS software. The result was presented as a relative, percentage increase in signal intensity (SI) with respect to the value from before the administration of contrast agent in the form of SI plotted per unit time. The analysis of contrast enhancement curve considered 2 elements [4,5]: the rate of growth of signal intensity in the first phase of the study and the course of the curve at a later stage. Four levels of enhancement (Figure 1) and 3 types of curve in the late phase of the study were identified (Figure 2).

Based on the character of contrast enhancement, benign changes included lesions that did not display contrast enhancement or have shown minimal, moderate or intermediate contrast enhancement and a constant growth or weak enhancement and plateau on the graph. Malignant changes included those showing wash-out or displaying an intermediate or high degree of amplification and plateau on the graph or exhibited a high degree of amplification in the first phase.

Analysis of morphologic features

Analysis of morphologic characteristics of lesions showing contrast enhancement was based on the definitions of symptoms shown in breast MRI (Table 2, Figures 3–7) [8].

Figure 1. Early enhancement ratios: a) no enhancement or minimal enhancement (close to the enhancement of healthy breast parenchyma, equal to about 40%), b) weak enhancement (40–60%), c) moderate enhancement (60–100%), d) strong enhancement (over 100%).

Figure 2. Late enhancement curves: a) persistent upslope: increase of signal intensity by over 10% measured 2 min. after reaching peak enhancement or after change of the curve; b) plateau: change of signal intensity $\pm 10\%$ after peak enhancement; c) wash-out: decrease of signal intensity by over 10% after peak enhancement.

Table 2. Morphologic features of contrast-enhancing foci.

Type	Analyzed parameter	Detailed characteristic of analyzed parameter		
		Benign lesions	Malignant lesions	Intermediate lesions
Focus	Focus of enhancement up to 5 mm, too small for morphologic MRI analysis			
Mass – 3-dimensional spatial lesion	Shape	Regular – round, oval, layered	Irregular	
	Outline	Sharp	Blurred, frequently spiculated	
	Enhancement distribution within the mass	Uniform distribution and specific types of heterogeneous enhancement	Uneven distribution Rim enhancement with strengthening in the center of the lesion	
Non-mass-like enhancement	Distribution of areas of enhancement within the breast*	Uniform distribution of areas of enhancement in the entire breast	Segmental distribution	Focal area of enhancement
			Ductal enhancement, finely granular enhancement	Regional distribution Linear enhancement

* Segmental distribution of areas – “mimics” lobules; ductal enhancement – finely granular areas of enhancement arranged in a manner similar to milk ducts, regional distribution of enhancement areas – does not “mimic” lobules or ducts.

Outlines of the lesions were evaluated on subtraction images from the second acquisition following the administration of contrast agent. In terms of contrast enhancement consistency, specific types of benign lesions were identified: rim changes without enhancement in the center around the lesion with the characteristics of a cyst or high fat content before the administration of a contrast agent, and heterogeneous enhancement with areas of no contrast enhancement. The final designation of a lesion as benign was made once all the characteristics of a benign lesion had been met. Lesion was regarded as malignant if any morphologic

feature typical of malignancy was present, including indirect findings (Table 2).

Combined analysis of morphologic features and contrast enhancement

In cases where the morphologic characteristics and the nature of the graph suggested a benign course, the lesion was interpreted as benign and vice versa, when the morphologic characteristics and the nature of the graph suggested malignant nature of the lesion, it was defined as malignant. In cases of discrepancy between the

Figure 3. Rim enhancement (arrows) around cysts (A) and malignancies (B).

Figure 4. Localized heterogeneous enhancement with non-enhancing septae (Fibroadenoma).

Figure 5. Multiple, scattered enhancing foci (high content of glandular tissue, normal) – reconstruction of MIP subtraction images.

morphologic features and the character of the graph, the lesion was regarded as malignant. Exceptions to this rule included the following scenarios:

a. lesions characteristic of a mass showing nonuniform contrast enhancement distribution typical of benign lesions; in these cases, lesion was regarded as benign

regardless of the degree and the character of contrast enhancement;

b. amorphous areas of contrast enhancement displaying intermediate morphologic characteristics, with high, low or weak degree of contrast enhancement and continuous SI growth curve, were regarded as benign.

Figure 6. Segmental enhancement, sagittal plane (DCIS/I).

In case of contrast enhancing lesions visible on breast MRI with their equivalents not visible in previous imaging studies, an attempt was made to locate the pathological lesions on an ultrasound. The search for pathological lesions was limited to an area suggested by an MRI. Mammography images were also re-examined. If suspicious lesion was located, further diagnostic procedures were performed under the guidance of an ultrasound or mammography [9]. In cases where no pathological lesions were found on ultrasound or mammography, close observation and follow-up breast MRI in 3 months was recommended. In the event of recurrence of an abnormal contrast enhancement in the same location, open surgical biopsy and histopathological evaluation was recommended. If the lesion did not reappear on a follow-up breast MRI, the initial image was regarded as an incidental contrast enhancing lesion [10,11].

Statistical analysis

For statistical purposes, the following rules were assumed: a positive test (MRI evaluation) result was one showing

features of malignancy, a negative test (MRI evaluation) result was that in which no evidence of cancer was found. Patients were considered sick when histopathological examination confirmed the presence of breast cancer. Patients were considered healthy if histopathological examination or biopsy samples were negative or no signs of malignancy were observed in clinical examination or imaging studies during the 24 month follow-up.

We compared the sensitivity and specificity of breast MRI in the detection of cancerous lesions of the breast using a separate and a combined analysis of signal intensity growth following the administration of contrast agent and morphologic characteristics of focal lesions observed on an MRI of the breast. Positive predictive value (PPV) and negative predictive value (NPV) was calculated for individual characteristics which were taken into account in the assessment of morphologic values.

Statistical analysis was performed using Statistica 6.0 software by StatSoft Inc.. Statistical significance of variance was performed using Wilcoxon rank-sum test for dependent samples. Probability threshold was selected as $p < 0.05$.

Results

Based on histopathological examination, breast cancer was diagnosed in 55 out of a total of 222 women studied (25%). A positive MRI result was achieved in 80 women (36%). The diagnosis of breast cancer was confirmed in 54 cases, in 26 cases the diagnosis was a false positive. A negative result on an MRI was reported in 142 out of 222 women. The diagnosis was confirmed in 141 cases. Only in one case, a negative MRI result was found to be DCIS on histopathological evaluation. The parameters of a diagnostic value of an MRI in the diagnosis of breast cancer are shown in Table 3.

Figure 7. Ductal enhancement (benign lesion) – reconstruction of 3D MIP subtraction images.

Table 3. Sensitivity and specificity of dynamic, morphologic and combined methods of evaluation.

	Dynamic	Morphology	Dynamic + morphology
Sensitivity	87%	98%	98%
Specificity	74%*	76%*	84%

* p<0.05.

Table 4. The number of kinetic characteristics. Dark cells represent malignancy.

		Shape of enhancement curve		
		Constant growth	Plateau	Wash-out
Degree of enhancement	Minimal	13	–	–
	Low	57	4	–
	Moderate	6	3	2
	High	–	34	52

Table 5. Number of cases with morphologic features of contrast-enhancing lesions.

Type of enhancement (n)	Analyzed parameter	Detailed characteristics (n)	Final histopathological result in terms of the characteristic		PPV	NPV
			Benign lesions	Malignant lesions		
Mass (124)	Shape	Regular (74/124)	95%	5%	—	95%
		Irregular (50/124)	26%	74%	74%	—
	Outline	Sharp (78/124)	97%	3%	—	97%
		Blurred (46/124)	15%	85%	85%	—
	Distribution of enhancement within the mass	Uniform (49/124)	98%	2%	—	99%
		Nonuniform (31/124)	7%	93%	93%	—
		Rim with central enhancement (17/124)	35%	65%	—	100%
		Rim around a lesion with features of a cyst (2/124)	100%	0%	—	100%
		Rim around a lesion with high fat content (3/124)	100%	0%	—	100%
		Partitions without enhancement (22/124)	100%	0%	—	100%
Amorphous area of enhancement (47)	Distribution of areas of enhancement within the mammary gland	Uniform (19/47)	100%	0%	—	100%
		Segmental (11/47)	36%	64%	64%	—
		Ductal (5/47)	20%	80%	—	80%
		Regional (5/47)	80%	20%	—	80%
		Linear (3/47)	67%	33%	—	67%
No enhancing lesions (51)			98%	2%	—	—

Based on the analysis of dynamic parameters, a positive result of breast MRI was observed in 91 women (41%), negative MRI result was found in 80 women (36%) – Table 4. In

51 cases (23%), no contrast enhancing lesions were found, which resulted their integration into the group of negative results (degree of contrast enhancement = 0).

Based on the analysis of morphologic features of lesions showing contrast enhancement, a positive MRI result was observed in 94 women (42%) and a negative in 77 cases (35%). The results of histopathological verification of the various types of lesions are shown in Table 5.

The results suggest an increased predictive value of morphologic evaluation of an MRI than the dynamic evaluation of this diagnostic test (Table 3). MRI evaluation solely on the basis of the dynamics and character of contrast enhancement failed to recognize 7 out of 55 (13%) cases of breast cancer. Histologically, they were DCIS (1 case), DCIS/I (2), DCI (2), Paget's disease of the breast (1) and undetermined type (1). In contrast, 6 of them were diagnosed using morphologic criteria. A total of 82 benign lesions with contrast enhancement were found in the study group. These were: fibroadenoma (19), mild dysplasia (31), papilloma and papillomatosis (4), fat necrosis (9), sclerosing adenosis (6), radial scar (2) and inflammatory lesions (11). In the dynamic assessment, a positive MRI was observed in 37 cases and in morphologic assessment in 34 of these lesions. An overall assessment had helped reduce the number of false positive results to 19.

Regardless of contrast enhancement lesions, study group revealed 85 changes visible before the administration of a contrast agent but showed no contrast enhancement. These changes were classified as benign. In a follow-up observation (at least 24 months) none of them developed cancer.

Discussion

Early detection of cancerous lesions is undoubtedly the biggest challenge of diagnostic imaging of breast disease. Mammogram is among the most widely used imaging methods. Unfortunately, its sensitivity in breast cancer detection (particularly in cases of dense breast tissue) is not satisfactory [1,3,12]. Additionally, mammography is associated with exposure to harmful x-rays and for that reason cannot be repeated frequently [13-15]. Ultrasound examination serves as a complementary diagnostic method [16-18]. Magnetic resonance imaging of the breast is highly sensitive, but the differentiation of benign and malignant lesions proves a challenge. Lack of high specificity, results in a large number of false positives, which is a significant disadvantage of this method [4,5,19]. This study attempted to improve the specificity of breast MRI by combining 2 methods of evaluation: analysis of the dynamics and characteristics of contrast enhancement and the evaluation of morphologic characteristics of contrast enhancing lesions.

According to the presented analysis, MRI evaluation utilizing only one of the presented methods does not provide satisfactory outcomes. Similar is the experience of other authors [5,20-26]. However, the combination of morphology and the dynamics of contrast enhancement required the images to be obtained with high spatial resolution during short acquisition time, to allow for simultaneous evaluation of morphology and contrast enhancement dynamics. Ever since it became technically possible, subsequent studies had achieved sensitivity of 93-97% and specificity of 74-96% [23-25]. Had this study of breast MRI assessment been based solely on the analysis of dynamic parameters of

malignant lesions, the number of undetected cases would have been equal to 13%, which would be similar to the result reported by Teifke et al. [26]. Additional evaluation of morphologic characteristics helped avoid false negative diagnosis in 6 out of 7 cases and reduce the percentage of false negative diagnoses to 2%.

Many researchers have attempted to explain the reasons for the lack of contrast enhancement or low degree of contrast enhancement of proliferative malignant lesions in breast MRI. Teifke et al. [26] evaluated 464 breast MRI examinations, 354 of which were malignant. Forty-one of 354 (12%) cancerous lesions did not show any contrast enhancement in breast MRI. The authors provide several possible causes for the false-negative diagnoses. They include: technical errors (location of the lesion outside of the study area, presence of motion artifacts, incorrect administration of contrast agent), an inability to distinguish cancerous lesions from the strongly enhancing surrounding tissues, small (<5 mm) size of invasive tumor in cases of early cancers and small size of preinvasive cancer. Orell et al. [26] and Gilles et al. [24] suggest other possible causes besides small tumor size, the most important of which is poor vascularization of the tumor.

In the study group, one cancerous lesion (ductal carcinoma preinvasive) not shown on an MRI of the breast, was diagnosed on mammography due to presence of suspicious microcalcifications. Other researchers report similar experiences. Authors of many publications, Orel et al. [27], Teifke et al. [26] and Liberman et al. [28], agree that the sensitivity of breast MRI in the presence of preinvasive cancer is lower than in case of invasive lesions, and equals about 70-88%. Therefore, in cases where mammography revealed clusters of suspicious microcalcifications, the exclusion of cancer based on the absence of abnormally contrast enhancing lesions on breast MRI is not possible.

Most authors agree that a strong increase in signal intensity during the initial phase and a washout effect in a later phase of dynamic study is typical of malignancy [4,5,19,29]. In the analyzed material, some pathological changes demonstrating dynamic characteristics of malignant lesions (high degree of contrast enhancement and/or wash-out or plateau on the graph), proved to be benign. Most of them were fibroadenomas and mild dysplasia. This was also observed by other authors [30-32]. The degree of enhancement in fibroadenomas may vary and depends on the relative proportions of fibrous and cellular elements within them [33].

Final interpretation of the lesions displaying intermediate morphologic characteristics on an MRI is debatable. Such contrast enhancing lesions were observed by Brown et al. in 29% of patients (most frequently in young women with dense breast tissue); breast cancer was detected in only 1 case [10]. In his publication, Kuhl [6] called the lesion "UBO" (unidentified breast object), and points out that distinguishing them from malignant lesions is challenging due to suspicious morphologic features and frequent high degree of contrast enhancement. The author recommends observation rather than histopathological verification of UBO (especially if no equivalents are present in other imaging studies) and provided that they do not present with a

wash-out on a graph. It is believed that the wash-out effect is associated with increased permeability of the vessel walls, which in turn, correlates with (characteristic feature of malignancy) strong expression of VEGF. The degree of contrast enhancement corresponds to the number of blood vessels as a unit of volume, which increases in both malignant and benign proliferative changes [11,34,35].

In the analyzed material, consistent and positive characteristics in terms of dynamic and morphologic assessment were found in 67 cases. We believe that in cases of such high (71%) probability of cancer, where the morphologic and dynamic features point to the malignant nature of a lesion visualized on breast MRI, steps should be taken to remove it surgically. Such lesions should be categorized as BI-RADS 5. In turn, consistent and negative characteristics of dynamic and morphologic evaluation were observed in 53 cases. In no case was malignant proliferative change found in histopathological and/or follow-up examination. Consequently, such lesions should be categorized as BI-RADS 2.

Among the 51 cases negative for contrast enhanced lesions, 98% were free of malignant proliferative process in histopathological evaluation or long-term observation. One case of false-negative MRI finding, demands a very careful exclusion of malignant proliferative process in the absence of contrast enhancing lesions on breast MRI and the presence of suspicious clusters of microcalcifications on mammography. Considering our own experience and the support of available literature [11,36,37], we believe that in cases where contrast enhancement is not found on breast MRI, description of the examination should state that in such case mammography results should be considered more

reliable. Therefore, if an MRI shows no focal lesions, such result will be categorized as BI-RADS 1. On the other hand, if breast MRI does reveal focal lesions with no contrast enhancement, the result will be categorized as BI-RADS 2. However, in the presence of suspicious microcalcifications on mammography, breast MRI description must always contain appropriate commentary.

In case of discrepancy between morphologic and dynamic assessment, the final interpretation should be based on the evaluation of morphologic characteristics with high PPV or very high (>99%) NPV. Lesions displaying morphologic features with NPV <99% should be categorized according to the contrast enhancement curve.

The use of a little known diagnostic method, based on the experience gained in a relatively short period of time, certainly requires a critical approach. Therefore, at our facility, the interpretation of breast MRI results is always based on available clinical data, the results of other imaging studies, in consultation with a clinician who manages the patient. The development of patient management recommendations should be guided by a principle that the patient should have the opportunity to benefit the most with the least adverse effects.

Conclusions

Breast MRI is a sensitive method for the diagnosis of breast malignancy. The combination of morphologic evaluation with a dynamic assessment of contrast enhancement significantly improves the specificity of breast MRI without losing its sensitivity.

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