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FULL PAPER

The MRI characteristics of non-mass enhancement lesions of the breast: associations with malignancy

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Objective: The American College of Radiology updated the terms used for expressing the imaging characteristics of non-mass enhancement (NME) lesions in the fifth edition of the breast imaging-reporting data system (BI-RADS) lexicon. Both the distribution and internal enhancement descriptors were revised for NME lesions. Our aim was to determine the MRI characteristics of NME lesions and to investigate their association with malignancy.

Methods: The MRI results of 129 NME lesions were retrospectively evaluated. The medical files, biopsy results and follow-up findings of lesions were recorded. Patients who had benign biopsy and those who had stable or regressed lesions during follow-up were classified as benign. All MRI results had been obtained with a 1.5 Tesla Signa HDx MR system (GE Healthcare).

Results: Segmental and diffuse distribution along with clustered-ring internal enhancement were significantly associated with malignancy, while linear distribution and homogeneous enhancement pattern were associated

with benignancy. Additionally, the plateau type (Type II) curve was significantly more frequent in malignant lesions. There was no association between the presence of cystic structures and the benign/malignant nature of the lesion. However, multivariate logistic regression showed that only segmental distribution and diffusion restriction were associated with malignancy.

Conclusion: In the current study, segmental distribution, clustered-ring enhancement, Type II dynamic curve and the presence of diffusion restriction were found to be associated with malignancy. There is a requirement for multicenter studies which include higher numbers of patients in order to better evaluate lesions with rarer characteristics for distribution and enhancement pattern.

Advances in knowledge: Our aim in this study was to investigate the MRI characteristics of NME lesions. We have reported the MRI findings of NME lesions and have found that segmental distribution and clustered-ring enhancement patterns are significantly more frequent in malignant lesions.

INTRODUCTION

The breast imaging-reporting and data system (BI-RADS) was first published in 2003 by the American College of Radiology (ACR) with an aim to standardize the interpretation and reporting of breast imaging.¹ Apart from standardization, the BI-RADS lexicon may be used as a tool to distinguish between benign and malignant lesions and resolve uncertainties in tumor identification.^{2,3}

In MRI, areas which show enhancement without a mass in the pre-contrast sequence are defined by the term non-mass enhancement (NME).⁴ Until recently, the terms used to express the internal enhancement characteristic of an NME included reticular/dendritic, ductal and stippled enhancement, among others. However, with the fifth edition of BI-RADS, the use of these terms were discontinued and enhancement characteristics of NMEs were updated as follows: homogeneous, heterogeneous, clumped

and clustered-ring enhancement.^{4,5} While the prevalence of NME is much lower than that of mass enhancement, several studies have reported that invasive cancers may present with NME lesions on MRI.^{6,7} Additionally, the BI-RADS has been shown to be insufficient in distinguishing between benign and malignant lesions when NME lesions are concerned.^{8–11} Thus, determining the MRI characteristics of NME lesions may reveal important findings and improve the interpretation of imaging data.

Currently there are few studies on this topic and research is required to identify the MRI characteristics of and their association with malignancy in NME lesions.⁴ Our aim in this study was to investigate the MRI characteristics of NME lesions and to determine if some characteristics could be used to distinguish between benign and malignant lesions.

METHODS AND MATERIALS

A retrospective evaluation was performed of 3250 breast MRI results which were obtained at Ankara Oncology Research and Training Hospital from January 2015 to December 2017. Among these 3250 images, patients without complete medical files and imaging results were excluded. A final total of 202 images consistent with NME were evaluated for inclusion into the study. The imaging results, medical files, biopsy and/or follow-up findings of these 202 MRI results were re-evaluated by a breast radiologist with at least 5 years of experience in breast MRI imaging who was blinded to the pathology reports. The lesions were grouped according to progression during a 2-year follow-up period (stable, regression, progression). Lesions which were stable or showed regression during this period were classified as benign (BIRADS-2). Patients who had lesions without growth and were followed for at least 6 months but did not reach the 2-year follow-up duration were classified as probably benign (BIRADS-3). Biopsy was performed on lesions which demonstrated progression.

Inclusion criteria were as follows: presence of NME on breast MRI, a diagnosis of benign or malignant lesion with follow-up or biopsy, and having previous imaging results which were accessible from our database (in order to perform re-evaluation). Patients with an NME lesion suggestive of BIRADS-3 but with follow-up duration shorter than 6 months, patients who were directed for biopsy but whose biopsy results were absent from our records, those who were lost to follow-up, and patients whose images were not accessible through the PACS database were excluded from the study. According to these criteria, a final total of 129 MR images (from 127 patients) were included in the study. Three of these patients with NMEs had a prior diagnosis of BIRADS-6 cancer. Among these 127 patients, 8 patients had "MR only" lesions which were ordered due to clinical suspicion and risk groups; 10 patients had undergone MRI due to other lesions and NME was found incidentally leading to biopsy; 12 patients were defined MG BIRADS-0 and did not have lesions in ultrasonography imaging, they underwent MRI due to clinical suspicion which showed BIRADS-4 lesion and they underwent biopsy; 57 patients had been defined as BIRADS-0 prior to MRI according to ultrasonography results, after MRI, these patients also underwent biopsy due to the presence of BIRADS-4 lesions;

Table 1. Indications for breast MRI.

Screening of females at high risk of breast cancer
Pre-operative staging of newly diagnosed breast cancer (ipsilateral and contralateral)
Evaluation of the effect of neoadjuvant chemotherapy
Evaluation of females with breast implants
Occult primary breast carcinoma (search for breast cancer in patients with metastases and negative mammography and ultrasound)
Suspected local recurrence ^a
Problem solving (equivocal findings at mammography/ultrasound) ^a

Other new indications were recently proposed, such as nipple discharge and evaluation of lesions with uncertain malignant potential (so-called high-risk or B3 lesions) detected at mammography or ultrasound, and needle-biopsied under their guidance

^aWhen needle biopsy cannot be performed

taking the final total of biopsies to 87. Among these patients, 67 underwent biopsy with ultrasonography, 8 with MRI and 12 with MG guidance. Overall, the suspicion for malignancy was based on MG and ultrasonography results, clinical findings, presence of progression during follow-up, and family history in the majority of patients ($n = 79$), while it was based on MRI findings in eight patients.

Ethics approval was obtained from local ethics committee. Additional approval was obtained from the hospital board as Dr AY Ankara Oncology Research and Training Hospital institution is considered as a reference hospital for breast cancer. The study was performed according to the principles put forth by the Helsinki Declaration.

The biopsy results and MRI findings of patients, including the distribution and internal enhancement pattern of NME lesions, dynamic curve type, presence/absence of diffusion restriction and presence/absence of cystic lesions on short tau inversion recovery (STIR) were evaluated.

MRI evaluation

All MRI results were obtained with 1.5 Tesla MR (Signa HDx, 1.5T, GE Healthcare) before biopsy and treatment. All images were evaluated in the clinical routine according to the BI-RADS-MR lexicon by at least one of three radiologists with at least 5 years of experience in breast MRI evaluation. The radiologists were blinded to pathology results when re-evaluating MRI results; however, while assessing the NME characteristics, they had knowledge of MG and ultrasonography findings. These findings were used only to support NME diagnosis and spread. On a final note, the decision for pre-operative MRI was based on the European Society of Breast Imaging recommendations (Table 1).¹²

Imaging parameters were as follows: repetition time/echo time (TR/TE) = 6500/45, TI: 150 ms, field of view (FOV): 320 mm, matrix: 416 × 224, number of excitations (NEX): 1 and slice thickness [ST]: 5 mm for axial STIR sequences; TR/TE = 400/8.8, FOV: 320 mm, matrix: 448 × 224, NEX: 1 and ST: 5 mm for axial fast spin echo T_1 images; TR/TE = 4/1.5, FA: 10°, FOV: 320 mm, matrix: 350 × 350, NEX: 1 and ST: 2.8 mm for dynamic axial gradient fat suppressed T_1 images (before and after contrast injection); and TR/TE = 1000/83, FOV: 320 mm, matrix: 192 × 192, NEX: 4 and ST: 5 mm for echoplanar imaging (EPI) based diffusion-weighted imaging (DWI).

Firstly, the NME lesion was identified on axial images via background parenchymal enhancement (BPE) (obtained at 128 s after contrast injection). Later, the distribution characteristics of lesions (focal, linear, segmental, regional, multiregional, diffuse) were determined according to the following images: post-contrast axial image obtained at 128 s, maximum intensity projection (MIP) image and sagittal multiplanar reconstruction (MPR) images. Lesions which showed regional and multiregional distribution were evaluated according to their enhancement pattern. Internal enhancement patterns were classified as homogeneous, heterogeneous, clumped (cobblestone pattern)

and clustered-ring enhancement. Time-intensity curve (TIC) was classified as persistent (Type I: lesser than 50% increase of enhancement during the early phase followed by slow continuation of enhancement in the late phase), plateau (Type II: greater than 50% increase of enhancement during the early phase followed by stable enhancement or lesser than 10% change during the late phase) and washout (Type III: greater than 50% increase of enhancement during the early phase followed by greater than 10% signal reduction during the late phase).

Statistical analysis

Data were analyzed with the SPSS 20.0 computer program. The χ^2 or Fisher's exact tests were used to determine differences in MRI findings between benign and malignant lesions. The multivariate logistic regression analyses were made to find the associated factors with malignancy. A p -value lower than 0.05 was accepted to show statistical significance.

RESULTS

In the current study, 129 NME lesions from 127 patients were evaluated. The age of patients ranged from 18 to 79 with an average of 45.9 ± 11.4 years. 30 lesions were identified as malignant with diagnoses such as invasive ductal carcinoma, ductal carcinoma *in situ* and tubular carcinoma. Benign lesions were diagnosed as sclerosing adenosis, atypical ductal hyperplasia, fibroadenoma and mastitis.

We categorized 30 malignant lesions in this study. 13 patients had non-invasive malign lesion, 3 patients had invasive malign lesion and 14 patients had invasive and non-invasive components. We determined mass with NME in 2 patients, architectural distortion with NME in 3 patients and nipple retraction with NME in 1 patient among the 13 patients with non-invasive malignancy. No mass was determined in 5 of the 14 patients who had both invasive and non-invasive components of malignancy. Finally, mass lesions were observed in 3 of the patients with invasive malign lesions. In these 30 patients, largest diameter

of NMEs on MRI ranged from 10 to 92 mm (median 33, mean, 38.56 mm). 6 of these 30 patients who had local advanced breast carcinoma used neoadjuvant chemotherapy after core needle biopsy. In one patient who had non-invasive malign lesion, pathologic examination demonstrated the positive surgical margin and patient underwent reexcision surgery. Five of the patients had disseminated multiple non-invasive malign focuses in NME area. Diameter of the malign lesions in these 12 patients could not be calculated pathologically. The largest diameter of remaining 18 invasive and/or non-invasive masses on pathologic examination ranged from 2 to 75 mm (median 23, mean 30.26 mm).

When the NME distribution characteristics of the study group were evaluated, 40 (31.0%) were found to be focal, 37 (28.7%) were linear, 21 (16.3%) were regional, 17 (13.2%) were segmental, 10 (7.8%) were multiple regional and 4 (3.1%) were diffuse. 12 (40%) of the malignant lesions showed segmental distribution. The type of distribution with the highest number of malignancies was the segmental type (Figure 1a). This difference was statistically significant ($p = 0.003$). Malignancy was also significantly more frequent with diffuse distribution ($p = 0.039$) (Figure 1b) and significantly less frequent with linear distribution ($p = 0.002$). The positive predictive value (PPV) of segmental distribution was 70.5% (12/17), while the same value was 75% (3/4) for diffuse distribution.

The most frequent internal enhancement pattern in the current study was the clumped pattern ($n = 60$, 46.5%) followed by the clustered-ring ($n = 31$, 24%), heterogeneous ($n = 24$, 18.6%) and homogeneous ($n = 14$, 10.9%) patterns. Among malignant lesions, 13 (43.3%) had clustered-ring, 12 (40%) had clumped and 5 (16.7%) had heterogeneous type internal enhancement (Figure 2a-c). None of the malignant lesions had homogeneous enhancement pattern. The clustered-ring pattern was the most common pattern among malignant lesions ($p = 0.013$). The PPV of clustered-ring pattern was 41.9% (13/31).

Figure 1. A 79-year-old female with diffuse hyperemia and peau d'orange findings of the breast. Contrast-enhanced breast MRI shows clustered ring non-mass enhancement with segmental type distribution and heterogeneous contrast enhancement of skin (arrow heads). Core biopsy results showed malign epithelial lesion. (b) A 32-year-old patient with palpable mass and bloody nipple discharge. Contrast-enhanced breast MRI shows clustered ring non-mass enhancement with diffuse type distribution. Final biopsy showed ductal carcinoma *in situ* and invasive ductal carcinoma.

Figure 2. (a) A 51-year-old female with bloody nipple discharge. Contrast-enhanced breast MRI shows clustered ring non-mass enhancement and final biopsy showed high grade ductal carcinoma *in-situ*. (b). Second phase of dynamic contrast enhanced breast MRI in 53-year-old female. Axial contrast-enhanced view shows clumped non-mass enhancement with linear distribution. Biopsy showed high grade ductal carcinoma *in situ*. (c). Dynamic contrast-enhanced breast MRI in 47-year-old female. Contrast-enhanced breast MRI shows non-mass enhancement with heterogeneous internal pattern and regional distribution (arrow head). Final biopsy showed low grade ductal carcinoma *in situ*.

Table 2. The distribution of MRI findings of NME lesions according to benignancy and malignancy.

Characteristics	Benign (<i>n</i> = 99)	Malignant (<i>n</i> = 30)	<i>p</i> -value
Distribution pattern			
Focal	33 (%33.3)	7 (%23.3)	0.300
Linear	35 (%35.4)	2 (%6.7)	0.002
Regional	16 (%16.2)	5 (%16.7)	0.948
Segmental	5 (%5.1)	12 (%40.0)	0.001
Multiple regional	9 (%9.1)	1 (%3.3)	0.451
Diffuse	1 (%1.0)	3 (%10.0)	0.039
Internal enhancement pattern			
Clumped	48 (%48.5)	12 (%40)	0.414
Clustered-ring	18 (%18.2)	13 (%43.3)	0.005
Heterogeneous	19 (%19.2)	5 (%16.7)	0.756
Homogeneous	14 (%14.1)	0 (%)	0.039
Dynamic curve type			
Type 1	59 (%59.6)	8 (%26.7)	0.006
Type 2	29 (%29.3)	15 (%34.1)	
Type 3	11 (%11.1)	7 (%23.3)	
Diffusion restriction			
Present	22 (%22.2)	21 (%70.0)	0.001
Absent	77 (%77.8)	9 (%30.0)	
Cystic structures in STIR images			
Present	24 (%24.2)	5 (%16.7)	0.384
Absent	75 (%75.8)	25 (%83.3)	

NME, non-mass enhancement; STIR, short tau inversion-recovery.

In terms of dynamic curves, the most frequent was the persistent type (Type I, *n* = 67, 51.9%). 44 (34.1%) lesions showed plateau type curve (Type 2) and 18 (14%) lesions were found to have washout type curve (Type III). Among malignant lesions, 15 (50%) had Type II, 8 (26.7%) had Type I, and 7 (23.3%) had Type III curves. The Type II curve was significantly more frequent

in malignant lesions (*p* = 0.006). The PPV of Type II curve was 34.1% (15/44).

When DWI was evaluated, diffusion restriction was observed in 43 (23.3%) of the lesions. Among malignant lesions, 21 (70%) had diffusion restriction. The frequency of diffusion restriction

Table 3. Comparison of benign and malignant lesions in terms of distribution/internal enhancement combinations.

Distribution/internal enhancement	Benign (<i>n</i> = 99)	Malignant (<i>n</i> = 30)	<i>p</i> -value
Segmental/Clustered ring	5 (%5.1)	8 (%26.7)	0.001
Focal/Clustered ring	6 (%6.1)	2 (%6.7)	0.904
Diffuse/Clustered ring	1 (%1.0)	2 (%6.7)	0.135
Regional/Clumped	16 (%16.2)	5 (%16.7)	0.948
Linear/Clumped	20 (%20.2)	2 (%6.7)	0.101
Focal/Clumped	17 (%17.2)	5 (%16.7)	0.949
Multiple regional/Heterogeneous	5 (%5.1)	0 (%)	0.590
Focal/Heterogeneous	8 (%8.1)	0 (%)	0.197
Linear/Homogeneous	9 (%9.1)	0 (%)	0.116

was significantly higher in malignant lesions compared to benign lesions ($p < 0.001$). The PPV of diffusion restriction was 48.8% (21/43). The evaluation of STIR sequences showed that 29 (23.3%) cases had cystic structures. Among malignant lesions, 5 (16.7%) were found to have cystic structures. There was no association between the presence of cystic structures and malignancy ($p > 0.05$). The MRI findings of NME lesions are summarized in [Table 2](#).

Further analysis of findings showed that, in lesions which presented with both segmental distribution and clustered-ring pattern, the potential for malignancy was significantly higher ($p = 0.001$) with a PPV of 61.5% (8/13). There was no association with malignancy for other distribution/pattern combinations ($p > 0.05$). The comparison of benign and malignant lesions in terms of distribution/internal enhancement combinations are depicted in [Table 3](#).

In multivariate logistic regression, the benign/malignant nature of the NME (according to biopsy result) was defined as the dependent variable. Independent variables were defined as characteristics that showed significant associations in univariate analysis (dynamic curve type, diffusion restriction, clustered-ring pattern and segmental distribution). The results showed that segmental type and diffusion restriction parameters were associated with malignancy. Multivariate logistic regression results are shown in [Table 4](#).

DISCUSSION

In the current study, the MRI findings of NME lesions were evaluated according to the fifth edition of the BI-RADS lexicon. While segmental type was the third most frequent (13.2%) distribution type overall, it was the most frequent distribution type among malignant lesions. This difference was statistically significant ($p < 0.05$). Furthermore, the PPV of segmental distribution was high (70.5%). This finding is similar to previous studies which have reported PPV values ranging from 67 to 100%.^{13–18} When malignant and benign lesions were compared in regard to distribution and internal enhancement couples, we found that lesions with segmental distribution along with clustered-ring enhancement were significantly associated with malignancy ($p < 0.05$). This finding was also reported in a study by Asada et al.¹⁹ We also found a significant relationship between malignancy and diffuse distribution ($p < 0.05$); however, this may have been due to the low number of cases with diffuse distribution. The most frequent distribution types in our study were focal (31%) and linear (28.7%) distribution which were not associated with malignancy ($p > 0.05$). Previous studies have reported a wide range of PPV results for focal and linear distribution; however, these values were consistently lower than that of segmental distribution. Furthermore, a couple of studies have reported that association with malignancy was the lowest with linear distribution.^{19,20}

The clustered-ring internal enhancement pattern has been reported by several studies to be a reliable predictor of

Table 4. Multivariate logistic regression analysis (backward selection method) results (Step 3)

	β Coefficient	Standard error	Wald statistic	<i>p</i>	Exp(β)	95% CI for Exp(β)	
						Lower	Upper
Diffusion restriction	1.720	0.497	11.995	0.001	5.585	2.110	14.785
Segmental distribution	1.961	0.638	9.460	0.002	7.108	2.037	24.804
Constant	−2.318	0.370	39.207	0.000	0.098		

malignancy.^{18,21–23} We also found a similar relationship ($p < 0.05$). The PPV of clustered-ring enhancement was 41.9%; however, the combination of clustered-ring and segmental distribution yielded a PPV of 61.5%. In a large meta-analysis study comprised of 858 NME lesions, the sensitivity and specificity of combined diagnostic approach was found to be higher than single criterion diagnoses. In the same study, the specificity of segmental distribution and clustered ring pattern combination was reported as 67%.²⁴ Yang et al also reported a strong association between clustered-ring pattern and malignancy.¹⁷ However, the specificity and PPV values of clustered-ring pattern vary from study to study; which may be explained by various factors such as, differences in study group size, use of different BI-RADS lexicons leading to different internal enhancement classifications, and variations in evaluation.

The most frequent internal enhancement pattern in the current study was the clumped pattern. There was no association between malignancy and clumped pattern enhancement; which was also true when analysis was performed with distribution type and clumped pattern combinations. In our study, homogeneous pattern was not seen in any malignant lesions, making it the most favorable enhancement pattern. Likewise, various studies have reported a lack of association between malignancy and homogeneous pattern and very low PPV values.^{16,19,21,22,25}

The most frequent dynamic curve type among malignant lesions was Type II curve (with a PPV of 34.1%) in the current study. In a study by Yang et al, the most frequent curve type among malignant lesions was also reported as Type II curve; however, their PPV of 74.1% was significantly higher than our result.¹⁷ Bluemke et al, in their study comprised of NME and mass enhancement cases, reported that Type II and III curves may be used as indicators of malignancy.²⁶ Yang et al, in their study aimed at determining MRI findings associated with malignancy, found that malignant NME lesions rarely presented with Type III curve.¹⁷ Several other studies have also reported a lack of association between Type III curve and malignant lesions.^{27,28} Thus, Type II curve can be considered to be a better indicator of malignancy in NME lesions. However, while Type II curve was significantly more frequent in malignant lesions (50%), 29.3% of benign lesions also presented with type II curve. Thus, the use of

curve type alone for the determination of malignancy may not be feasible.

The apparent diffusion coefficient (ADC) value which is used to determine diffusion restriction is remarkable in differentiating benign and malignant lesions in mass lesions of the breast.^{29,30} However, previous studies report that the same cannot be said for NME lesions.³¹ In the current study, diffusion restriction was evaluated as a categorical variable (minimal and mild restrictions were included in the “present” group) and the presence of diffusion restriction was significantly more frequent in malignant lesions ($p < 0.05$). This may suggest that instead of using ADC values for benign/malignant differentiation, the presence or absence of diffusion restriction may provide better distinction between benign and malignant lesions. However, PPV was low (48.8%); therefore, this result should be interpreted with caution. There was no association between the presence of cystic structures in STIR images and malignancy in the current study.

A major limitation of our study is the fact that patients who underwent breast MRI at our center were those who were strongly suspected to have malignancies (referrals to our center usually consist of patients with high suspicion for malignancy due to the fact that Dr AY Ankara Oncology Research and Training Hospital is a major oncology center in the region). This may have caused unavoidable bias in patient selection. Another limitation is the retrospective nature of our study; however, the design was unavoidable due to the rarity of NME lesions.

CONCLUSION

We have reported the MRI findings of NME lesions and have found that segmental distribution and clustered-ring enhancement patterns are significantly more frequent in malignant lesions. Additionally, Type II dynamic curve and the presence of diffusion restriction were found to be associated with malignancy. We conclude that multicenter studies with higher numbers of patients are required to better understand the MRI characteristics of NME breast lesions. We also believe that establishing a protocol in the evaluation of these lesions (maybe even beyond the BI-RADS lexicon) will contribute to the interpretation of NME breast lesions.

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