Management of Non-Mass Enhancement at Breast Magnetic Resonance in Screening Settings Referred for Magnetic Resonance-Guided Biopsy

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ABSTRACT

RATIONALE AND OBJECTIVES: According to the Breast Imaging and Reporting Data System (BI-RADS), one of the main limitations of MRI is diagnosing the non-mass enhancement (NME). The NME lesion is challenging since it is unique to the MRI lexicon. This study aims to report our experience with NME lesions diagnosed by MRI referred for MRI-guided biopsies and discuss the management and follow-up of these lesions.

MATERIALS AND METHODS: We retrospectively evaluated all MRI-guide breast biopsies. We included all patients referred for NME breast MRI-guided biopsy in screening settings. All patients had a negative second-look mammography or ultrasonography. We correlated the distribution and internal enhancement pattern (IEP) of the NME lesions with histology. Invasive ductal carcinomas (IDC) of no special type and ductal carcinoma in situ (DCIS) were considered malignant lesions.

RESULTS: From January-2018 to July-2021, we included 96 women with a total of 96 lesions in the study. There were 90 benign and 6 malignant lesions with DCIS prevalence (5/6 cancers). The most frequent benign lesion type was fibrocystic changes. There were no NME lesions with diffuse or multiple area distribution features referred to MRI-guided biopsy. The positive-predictive values (PPV) were respectively 0.0%, 2.5%, 9.0%, and 11.0% for linear, focal, regional, and segmental distribution describers, and 0.0, 3.0%, 7.9%, and 50% for homogenous, heterogeneous, clumped, and clustered-ring enhancement patterns.

CONCLUSION: We observe the high potential risk for malignancy in the clustered-ring enhancement followed by the clumped pattern. Segmental distribution presented the highest predictive-positive values.

KEYWORDS: Magnetic resonance, non-mass enhancement, positive predictive value, biopsy, breast

Introduction

Breast magnetic resonance (MRI) scan indications are increasing for diagnosis and screening in clinical practice. The main indications are staging of known cancer, screening for breast cancer in women at increased risk, and evaluation of response to neoadjuvant chemotherapy. Other indications for breast MRI are diagnosing carcinoma of unknown primary origin and problem-solving due to high negative predictive value. Uncertain benign findings at mammography or ultrasonography that cannot be sampled for biopsy could have a complementary evaluation by MRI.[1-5]

Despite high sensitivity for detecting lesions, one limitation of MRI is low specificity, as established and discussed in the literature. MRI evaluates morphology by high-resolution sequences and functionality by dynamic sequences. Some benign and malignant lesions could have the same expression in the images; since benign lesions are more common than malignant, we expect more false-positive results than true-positive ones.[3] Another factor influencing imaging interpretation is the background enhancement pattern (BEP). An asymmetrical BEP could result in a false-positive result in an asymptomatic patient.[6]

The increasing number of false-positive results is related to the broad availability and reduced cost of MRI scans and implementation of FAST screening protocol.[7,8] Some lesions newly diagnosed by MRI could be found in second-look mammography or ultrasonography and have ductal carcinoma in situ (DCIS) as the prevalent lesion at pathology.[9]

Although breast MRI safety has been exhaustively discussed and validated in the literature, some concerns regarding gadolinium brain retention and systemic nephrogenic fibrosis persist.[10,11] There are also some individual restrictions to performing an MRI scan with contrast because of reported allergies, renal failure, and MRI-unsafe implants.[12]

Most of the published articles discuss the benefits of the MRI scan.[13] However, few studies reported the MRI harms and how we can manage and reduce the false-positive results.[14-16] According to the Breast Imaging and Reporting Data System

DISTRIBUTION

1. LINEAR

2. FOCAL

3. REGIONAL

4. SEGMENTAL

5. MULTIPLE REGIONS

6. DIFFUSE

INTERNAL ENHANCEMENT PATTERN

1. HOMOGENEOUS
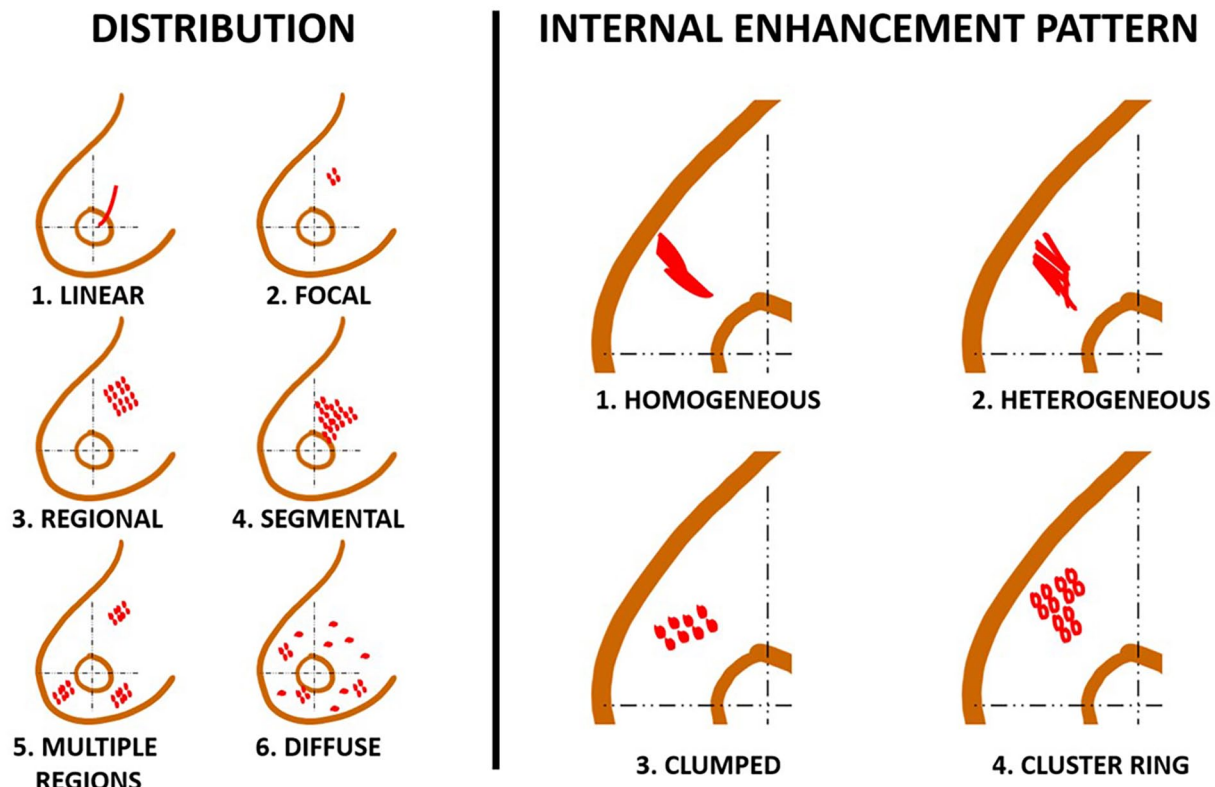
2. HETEROGENEOUS

3. CLUMPED

4. CLUSTER RING

Figure 1. Examples of the BI-RADS classification of non-mass enhancement lesions by distribution and internal enhancement pattern.

(BI-RADS) fifth edition lexicon, one of the main limitations of MRI lies in diagnosing the NME.[17] The NME lesion is challenging since it is unique for the MRI lexicon, and its management and follow-up lack standardization. (Figure 1)[18,19]

This study aims to report our experience with NME lesions diagnosed by screening MRI referred for MRI-guided biopsies and discuss the management and follow-up of these lesions.

Material and Methods

We retrospectively evaluated all MRI-guided breast biopsies from January-2018 to July-2021 in a single institution dedicated to women's health care. We included patients referred for NME MRI-guided breast biopsy in screening settings without correlation to second-look mammography or ultrasonography. Following the screening criteria, we excluded patients with masses, lesions, clinical complaints, or a previous breast cancer diagnosis within the last 5 years. We only included in the study incidental findings of NME lesions in asymptomatic patients referred for screening MRI.

Our institutional board waived the ethical committee approval. All patients signed an informed consent term for data availability for scientific purposes.

Not all patients referred for MRI biopsy in our institution had had their previous screening breast MRI performed in our practice. As the BI-RADS descriptors are subjective and have the issue of the interobserver agreement, we decided to re-evaluate these lesions. Two radiologists re-evaluated the previous exams with suspicious findings and classified the

lesions according to the latest BI-RADS lexicon. The NME lesions were classified according to distribution and IEP. (Figure 1)[17] According to the lexicon, NME consists of lesions that are neither a mass nor a focus. NME extends over small or large regions, and the enhancement pattern is discrete from the normal surrounding glandular tissue. NME can be described according to distribution (focal, linear, segmental, regional, multiple regions, and diffuse) and internal enhancement patterns (homogeneous, heterogeneous, clumped, and clustered ring).[17]

We performed a second-look ultrasound to find the NME lesion. We opted to perform the biopsy guided by ultrasound if the lesion was found.

We excluded from the study lesions other than NME, like masses and architectural distortions, and NME in diagnostic MRI.

Patients eligible for percutaneous biopsy were positioned in the MRI scan in the prone position, using a dedicated 8-channel breast coil. After breast compression, we performed a pre-contrast sequence, followed by a 4 minute dynamic series with fat suppression. The automatic subtraction reconstruction was calculated from the acquired dynamic series in the sagittal plane. All studies were performed on a 1.5 T MR scanner (Spree; Siemens. Malvern, PA). MRI-guided core needle biopsies were obtained using a 10-gauge vacuum-assisted needle (Vacora, Bard Biopsy Systems; Temple, AZ, USA). Multihance (0.1 mmol/kg, Bracco Diagnositics Inc., Monroe Township, NJ) was the IV contrast. A marker was
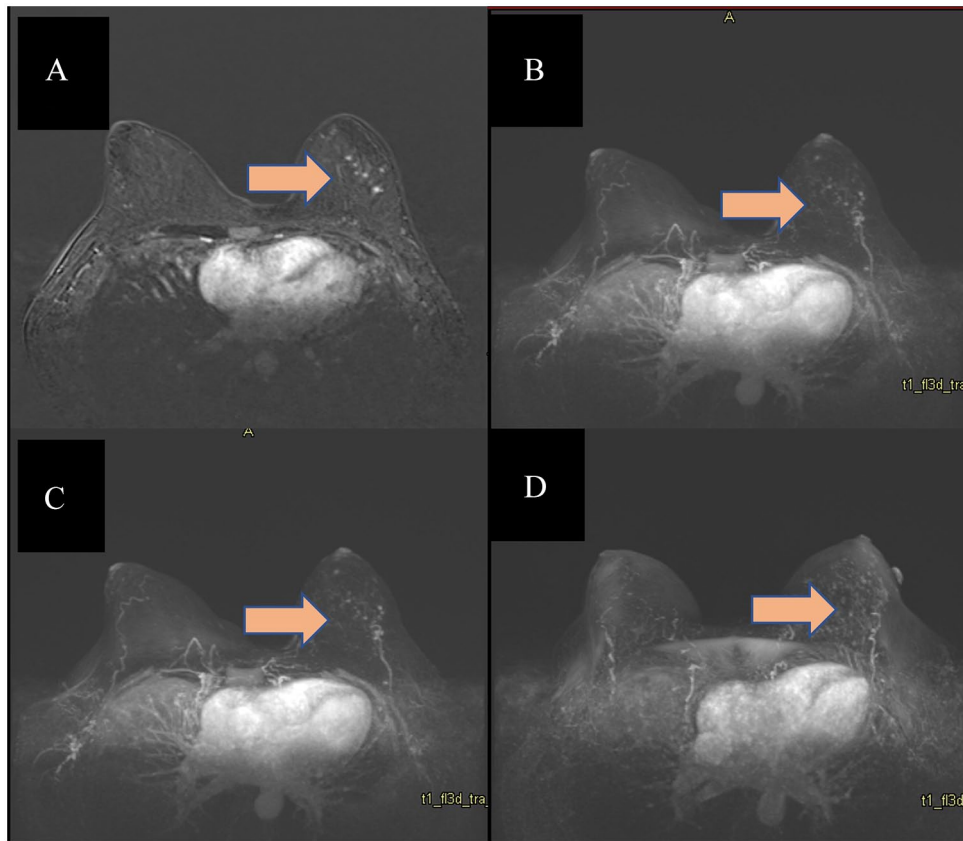
Figure 2. Figure (A, B, C, D). Screening MRI in a 56 year-old wonan. The pre biopsy MRI images, post contrast (A) and MIP reconstruction (B) shows a regional and clustered NME (orange arrow). The 6 month follow-up (C and D) shows an atenuation of the MRI findings. The biopsy was not performed.

placed at the time of biopsy for each procedure, and post-biopsy mammograms were performed.

Previously reported NME lesions, with negative findings at the biopsy scan, were followed-up after six months of the exam. These findings were considered a physiological enhancement. (Figure 2)

The radiologists correlated the imaging and pathological reports when the pathological results were available. If there was agreement, we generated a final report. We indicated further lesion evaluation when there was disagreement, indicating a surgical biopsy.

All patients with negative biopsy were scheduled for a short-time follow-up breast MRI in the following six months to evaluate the lesion stability.

We correlated the distribution and IEP of the NME lesions with histology. Invasive ductal carcinomas (IDC) of no special type and DCIS were considered malignant lesions. We also performed the same test assessing pathological lesions of uncertain malignant potential (category 3) as positive findings for comparison purposes. (Figure 3)

For the correlation between the distribution and internal enhancement pattern descriptors with the benign and malignant lesions, we used the chi-squared test (Medcalc, Acacialaan, Ostend, Belgium) software for statistical analysis, adopting a significance level for $P < 0.05$.

Results

From January-2018 to July-2021, we evaluated 122 lesions referred for MRI-guided biopsy to diagnose the NME lesions. All patients were asymptomatic, with a previous negative second-look mammography or ultrasonography.

We included 96 patients with 96 lesions in the study. The median age of the patients was 49.3 years, and the average lesion size was 2.4 cm. (Figure 2) There were six malignant lesions, with DCIS prevalence (5/ 6)). The most frequent benign lesion was fibrocystic changes (36/ 90). The lesions of uncertain malignant potential, category 3, included papillary lesion, atypical ductal hyperplasia, and radial scar, with 29 lesions (29/ 90). There were no NME lesions with the diffuse or multiple areas distributions features referred to MRI-guided biopsy. (Table 1)

When evaluating the correlation to NME exclusively with malignant histology, clustered ring pattern was the only describer associated with breast cancer with a significant p level. The result was confirmed when we associated the lesions of category 3. (Table 2)

The predictive-positive values for the distribution describer were respectively 0.0, 2.5%, 9.0%, and 11.0% for linear, focal, regional, and segmental, and for enhancement pattern respectively 0.0, 3.0%, 7.9%, and 50% for homogenous, heterogeneous, clumped, and clustered-ring.
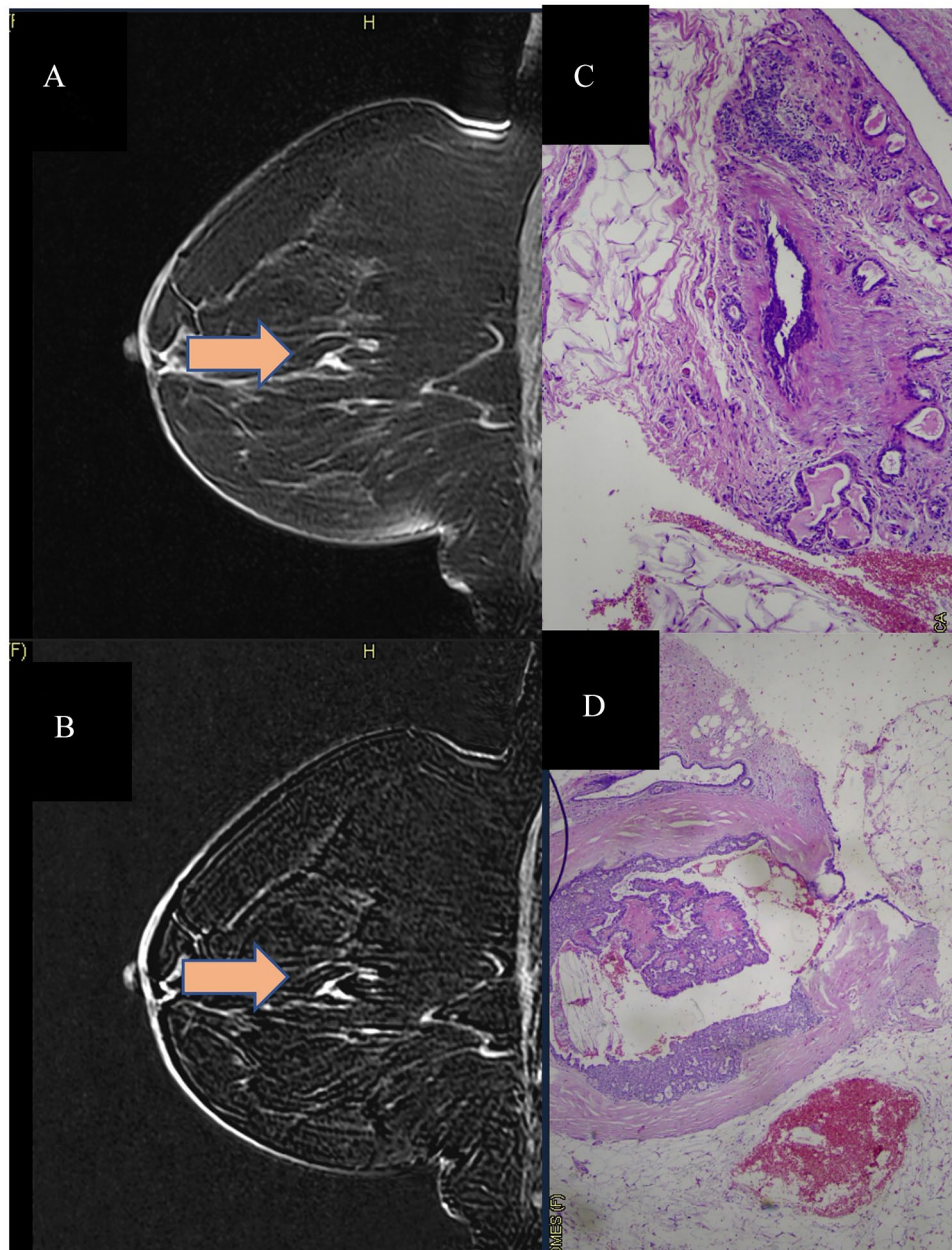
Figure 3. Figure (A, B, C, D). Screening MRI in a 45 year-old wonan. The MRI images, post contarst (A) and subtraction (B) shows a linear and heterogeneous NME (orange arrow). The histology of the biopsy was a pappillary lesion, category 3 (C and D).

Of the 20 lesions with negative findings at the MRI-guided biopsy scan, 13 patients performed follow-up scans confirming the false-positive results in the previous scan. We considered these NME lesions as physiological changes.

Of the 29 lesions of uncertain malignant potential (category 3), 12 have surgical excision biopsies with the same MRI-guided biopsy results. The other 17 were followed up by imaging as the histological results were in accordance with the images' features.

The DCI lesion that appears as NME was a heterogeneous focal enhancement in the central localization of the left breast. The lesion occurred at the surgical site of a luminal A carcinoma diagnosed and adequately treated for eight years.

Discussion

Since breast MRI has been widely used in clinical practice for diagnostic and screening purposes, we observe a rise in lesions exclusively seen at MRI scans. Despite the high sensitivity of MRI to detect breast cancer, false-positive results are the main weakness of the method. Usually, the suspected lesions described in MRI have biopsy indications, and sometimes the diagnostic procedures are not trivial. Breast MRI-guided biopsy is expensive, has the limitation of contrast usage, and has toleration concerns for claustrophobic patients. Although the biopsy is simple to perform, the number of steps to get the specimens is time-consuming as it is not a real-time procedure.[20-23]

Table 1. Characteristics of non-mass enhancement lesions referred for MRI-guided biopsy.

	N	%	AGE	SIZE	DISTRIBUTION				INTERNAL ENHANCEMENT PATTERN			
					LINEAR	FOCAL	REGIONAL	SEGMENTAL	HOMOGENEOUS	HETEROGENEOUS	CLUMPED	CLUSTERED RING
ALL	96	100	49.3	2.45	8	38	17	33	21	33	38	4
DCI	1	1.0	38	0.9	-	1	-	-	-	1	-	-
DCIS	5	5.2	51.0	3.94	-	-	2	3	0	0	3	2
FIBROCYSTIC	36	37.5	51.72	2.59	2	14	6	14	10	6	20	-
FIBROADENOSE	17	17.7	42.75	1,93	2	9	-	6	-	13	4	-
RADIAL SCAR	11	11.5	58	1,75	-	6	-	5	3	3	3	2
ADH	10	10.4	55.5	2.27	-	4	2	4	3	2	5	-
PAPPYLARRY	8	8.3	50.2	2.36	2	3	3	-	2	4	2	-
PASH	4	4.2	34.5	2.85	-	1	2	1	-	3	1	-
OTHERS	4	4.2	44.5	2.05	2	-	2	-	3	1	-	-

Table 2. Correlation of non-mass enhancement lesions to malignancy and to suspicious lesions.

|	MALIGNANT LESIONS					MALIGNANT LESIONS + CATEGORY 3			
	CHI-SQUARED	DF	SIGNIFICANCE LEVEL	CONTINGENCY COEFICIENT	PPV (%)	CHI-SQUARED	DF	SIGNIFICANCE LEVEL	CONTINGENCY COEFICIENT
Linear	0.498	1	0.480	072	–	0.009	1	0.9251	0.010
Focal	1.507	1	0.219	0.124	2.5	0.201	1	0.6542	0.046
Regional	0.685	1	0.407	0.084	9.0	0.000	1	0.9889	0.001
Segmental	1.061	1	0.3030	0.105	11.8	0.196	1	0.6576	0.045
Homogeneous	1.77	1	0.183	0.135	–	0.031	1	0.8608	0.018
Heterogeneous	0.880	1	0.348	0.095	3.0	0.814	1	0.3670	0.092
Clumped	0.287	1	0.591	0.055	7.9	0.136	1	0.7125	0.038
Clustered-ring	13.49	1	**0.0002**	0.351	50.0	7.199	1	**0.0073**	0.264
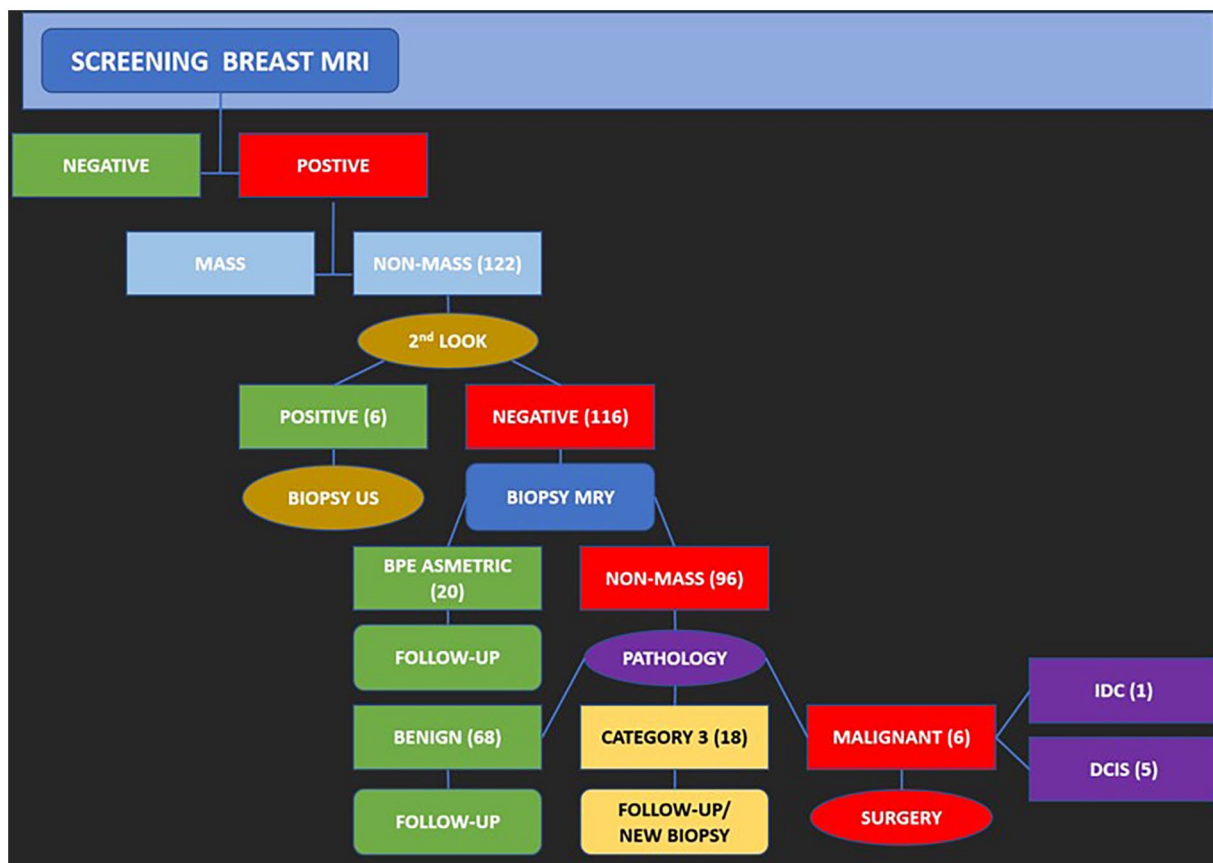
Figure 4. Flow-chart of the study design to evaluate non-mass enhancement in screening breast Magnetic Resonance.

The best alternative for MRI-guided biopsy is when the lesion is present in a second-look evaluation by ultrasound scan or mammography. When there is an unequivocal equivalence of the findings, performing the percutaneous biopsy guided by the preferred modality is safe. (Figure 3) The MRI-guided biopsy is the only alternative for percutaneous biopsy when there is no correspondence. An option in these cases when we cannot complete the biopsy is a short-time follow-up (6 months).

The MRI's unique findings are related to NME, a lesion that resembles calcifications in mammography. The most common tumors diagnosed as NME are DCIS, low-grade DCI, and lesions with an uncertain malignancy potential (category 3).[23] In contrast, the benign lesions usually related to this finding are fibrocystic changes and fibroadenosis. These lesions commonly pertain to low-aggressiveness tumors, the same observed in mammographic calcifications. The low-grade lesions have a higher duplication time and less potential for distant metastasis. For example, 50% of DCIS evolve to DCI, and a low-grade carcinoma has a median duplication time of 241 days, compared with 103 days for triple-negative cancer.[18,24]

Our study evaluated only NME lesions exclusively diagnosed at MRI in patients without clinical complaints from the MRI screening settings. We believe that understanding the relevance of the NME finding is imperative to manage this diagnosis. The primary malignant histology finding in our study was DCIS. At the same time, the invasive cancer lesion was a recurrence of a luminal-A carcinoma in the surgery site eight years after the treatment. This indolent characteristic of the NME concedes a secure 6-month follow-up for non-biopsied lesions. (Figure 4)

Based on our findings, we introduced in our clinical practice a subclassification of the BI-RADS category 4 for NME in screening settings.[17] We classify NME with clustered-ring enhancement patterns and segmental distribution as BI-RADS 4b. We base this subclassification on the BI-RADS recommendation for calcifications, where PPV ranges > 10% to =< 50. All 4b lesions are referred for percutaneous biopsy even when the second-look evaluation was negative. (Figures 5, 6, 7 and 8)

On the other hand, lesions classified with the other descriptors were classified as BI-RADS 4a and referred for a second-look evaluation by ultrasound scan and mammography. We suggest a 6-month follow-up as an alternative for the biopsy if the second look was negative. When the lesion is stable at follow-up, we recommend additional follow-ups of another 6 months and 1 year. We perform a new second-look evaluation and biopsy when the lesion progresses, regardless of the second-look result. (Figure 3)

Linear, multiple areas and diffuse distribution with homogeneous internal enhancement pattern and negative second-look evaluation are classified as BI-RADS 3 since we did not find any malignancy or lesions with uncertain malignancy
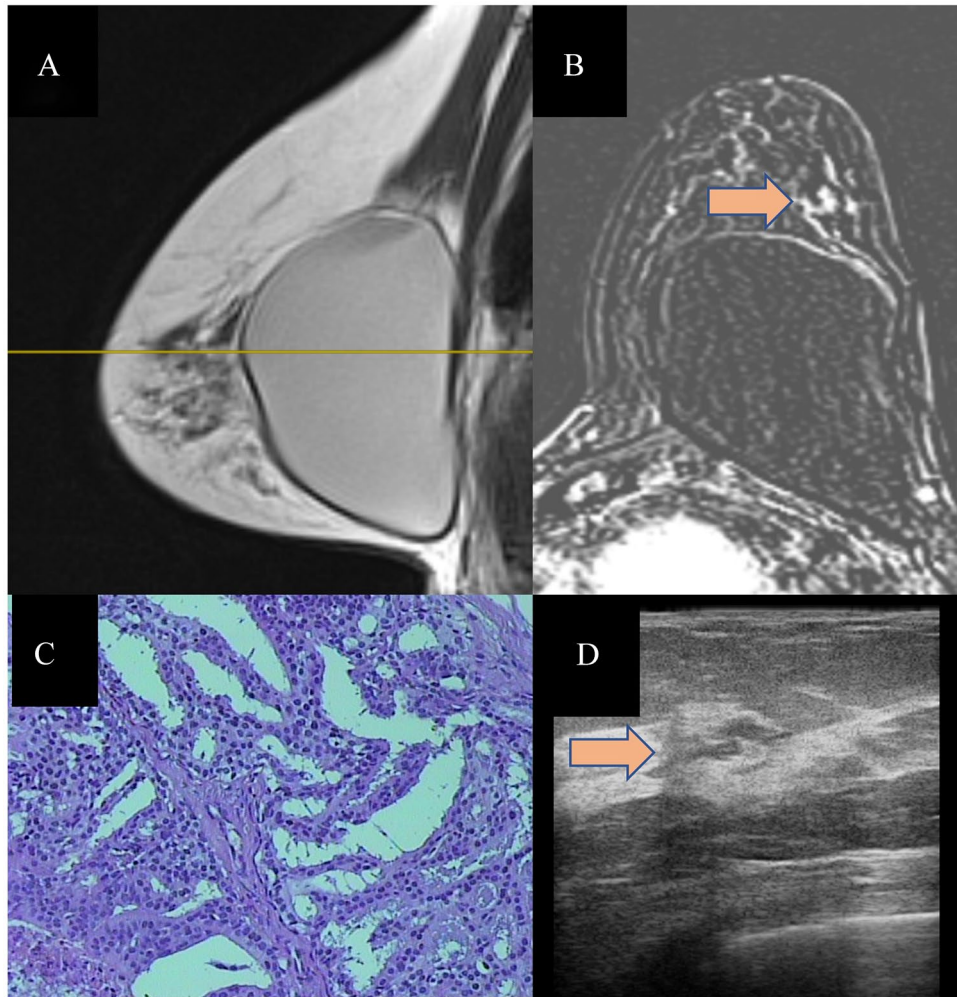
Figure 5. Figure (A, B, C, D). Screening MRI in a 45 year-old wonan with breast implants. The MRI images, PD- proton density (A) and post-contrast (B) shows a focal and heterogeneous NME (orange arrow). The histology of the biopsy was an invasive ductal carcinoma (C). The biopsy was performed guided by a second-look ultrasound (D).
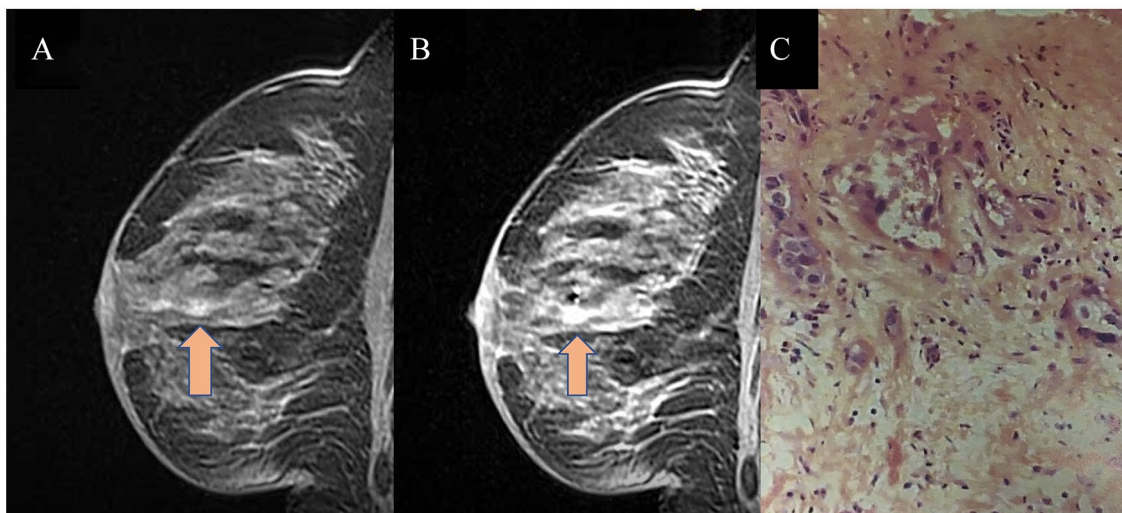

Figure 6. Figure (A, B, C). Screening MRI in a 56 year-old wonan with history of breast cancer in the right breast for 8 years. The MRI images, pre-biopsy (A) and post-biopsy (B) shows a focal and heterogeneous NME (orange arrow). Figure B shows the biopsy marker at the site of biopsy. The histology of the biopsy was an invasive ductal carcinoma (C).
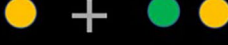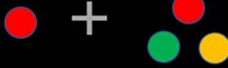
Figure 7. Proposal for final classifications of non-mass enhancement lesions as primary finding in screening breast Magnetic Resonance imaging.
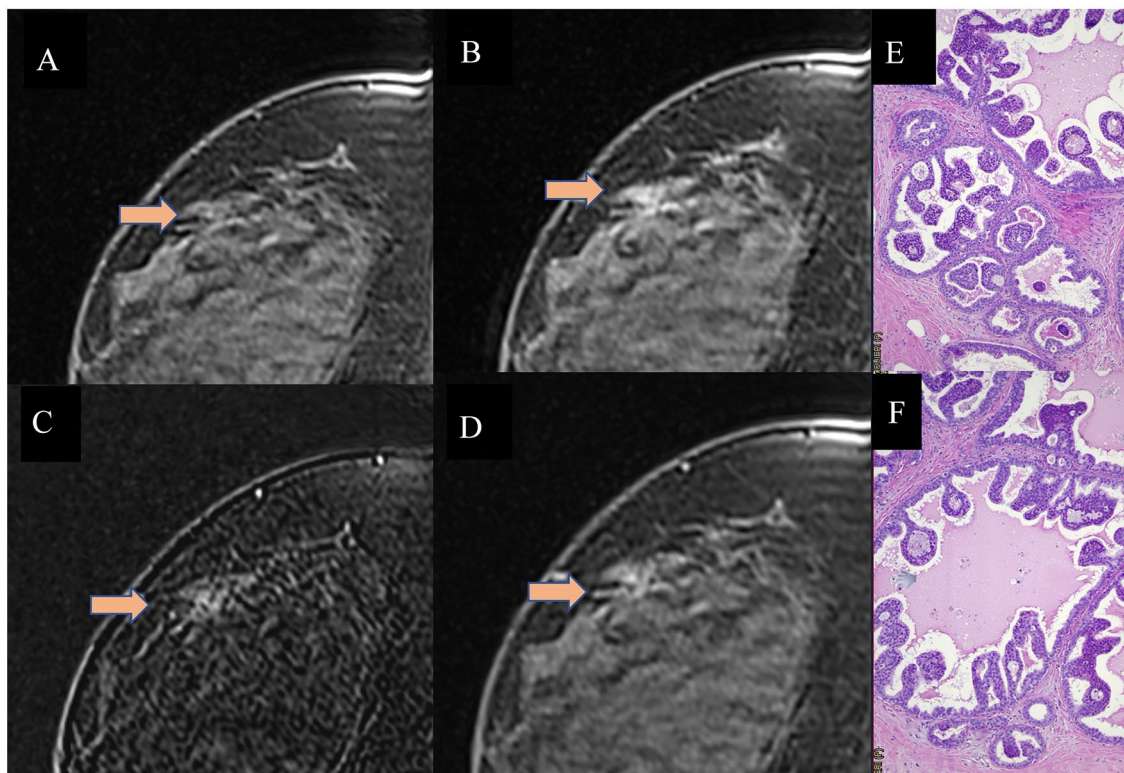

Figure 8. Figure (A, B, C, D, E, F). Screening MRI in a 43-year-old woman. The MRI images, pre-contrast (A), post-contrast (B), subtraction (C) and post-biopsy (D) shows a segmental and clustered rind NME in the upper quadrant. Figure D shows the biopsy marker at the biopsy site. The histology of the biopsy was a ductal carcinoma in-situ (E and F).

potential. We believe the introduction of this protocol should reduce the number of biopsies in false-positive MRI results.

When we analyzed the NME distribution and enhancement pattern, we observed an association with malignancy only in the clustered-ring descriptor. We expected this finding since the most suspicious feature of NME is the clustered-ring pattern, in analogy to fine-linear branching calcifications in mammography. Although malignancy was prevalent in segmental distribution, with the highest PPV value for the distribution descriptor, the association with malignancy was not statistically significant. (Figure 6)

The study has some limitations. First is the retrospective nature of the study. Another limitation is the small number of malignancies; however, since we only evaluated asymptomatic patients in screening breast MRI settings with negative ultrasound and mammography, malignancy is exceptional.

The NME lesions were incidental findings in screening MRI, and most were related to benignity. As a private practice, we did not have access to the follow-up data of all patients. We also excluded patients when the NME features were described as associated findings, which explains the PPV difference from other studies that included NME as primary and associated findings.[25-27]

Our results show the features of the breast NME lesions in asymptomatic patients referred for screening MRI. We observed the high potential risk for malignancy in the clustered-ring enhancement, followed by the clumped pattern. Regarding the distribution, segmental presented the highest PPVs.

Author Contributions

Eduardo de Faria Castro Fleury: Conceptualization, Methodology, Data curation, Writing- Original draft preparation. Caio Castro: Visualization, Investigation. Mario Sergio Campos do Amaral: Supervision, Validation. Decio Roveda Junior: Reviewing and Editing,

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REFERENCES

1. Schrager S, Lyon SM, Poore SO. Breast implants: common questions and answers. *Am Fam Physician*. 2021;104:500-508.
2. Gunduru M, Grigorian C. *Breast Magnetic Resonance Imaging*. Treasure Island, FL: Statpearls Publishing; 2021.
3. Scaranelo AM. What's hot in breast MRI [published online ahead of print August 12, 2021]. *Can Assoc Radiol J*. doi:10.1177/08465371211030944.
4. Mann RM, Cho N, Moy L. Breast MRI: state of the art. *Radiology*. 2019;292:520-536.
5. Bitencourt AGV, Chojniak R. Indications for breast magnetic resonance imaging in Brazil: past, present, and future. *Radiol Bras*. 2021;54:206.
6. Xu C, Yu J, Wu F, et al. High-background parenchymal enhancement in the contralateral breast is an imaging biomarker for favorable prognosis in patients with triple-negative breast cancer treated with chemotherapy. *Am J Transl Res*. 2021;13:4422-4436.
7. Tollens F, Baltzer PAT, Dietzel M, et al. Cost-effectiveness of MR-mammography in breast cancer screening of women with extremely dense breasts after two rounds of screening. *Front Oncol*. 2021;11:724543.
8. Partovi S, Sin D, Lu Z, et al. Fast MRI breast cancer screening—Ready for prime time. *Clin Imaging*. 2020;60:160-168.
9. Hellerhoff K, Dietrich H, Schinner R, et al. Assessment of MRI-detected breast lesions: a benign correlate on second-look ultrasound can safely exclude malignancy. *Breast Care (Basel)*. 2021;16:435-443.
10. Bruno D, Vealé BL. Effects of gadolinium depositions in vivo. *Radiol Technol*. 2021;93:46-54.
11. Fatima A, Ahmad MW, Al Saidi AKA, Choudhury A, Chang Y, Lee GH. Recent advances in gadolinium based contrast agents for bioimaging applications. *Nanomaterials (Basel)*. 2021;11:2449.
12. Ghadimi M, Sapra A. *Magnetic Resonance Imaging Contraindications*. Treasure Island, FL: StatPearls Publishing; 2021. https://www.ncbi.nlm.nih.gov/books/NBK551669/
13. Kuhl CK, Baltzer P. You get what you pay for: breast MRI screening of women with dense breasts is cost-effective. *J Natl Cancer Inst*. 2021;113:1439-1441. doi:10.1093/jnci/djab120.
14. Rahbar H, Tjoe JA. Breast MRI in the setting of DCIS: quality trials are still needed to determine its value. *Eur Radiol*. 2021;31:5877-5879.
15. Onega T, Zhu W, Kerlikowske K, et al. Preoperative MRI in breast cancer: effect of breast density on biopsy rate and yield [published online ahead of print October 22, 2021]. *Breast Cancer Res Treat*. doi:10.1007/s10549-021-06418-x.
16. Khan SA, Hernandez-Villafuerte KV, Muchadeyi MT, Schlander M. Cost-effectiveness of risk-based breast cancer screening: a systematic review [published online ahead of print April 12, 2021]. *Int J Cancer*. doi:10.1002/ijc.33593.
17. American College of Radiology. *ACR BI-RADS Atlas: Breast Imaging Reporting and Data System*. Reston, VA; American College of Radiology; 2013.
18. Kim Y, Jung HK, Park AY, Ko KH, Jang H. Diagnostic value of mammography for accompanying non-mass enhancement on preoperative breast MRI [published online ahead of print July 14, 2021]. *Acta Radiol*. doi:10.1177/02841851211030771.
19. Zhou J, Liu YL, Zhang Y, et al. BI-RADS reading of non-mass lesions on DCE-MRI and differential diagnosis performed by radiomics and deep learning. *Front Oncol*. 2021;11:728224.
20. Imbriaco M. Reducing false-positive screening MRI rates in women with extremely dense breasts. *Radiology*. 2021;301:293-294.
21. Bakker MF, de Lange SV, Pijnappel RM, et al. Supplemental MRI screening for women with extremely dense breast tissue. *N Engl J Med*. 2019;381:2091-2102. doi:10.1056/NEJMoa1903986.
22. Geuzinge HA, Bakker MF, Heijnsdijk EAM, et al. Cost-effectiveness of magnetic resonance imaging screening for women with extremely dense breast tissue. *J Natl Cancer Inst*. 2021;113:1476-1483.
23. Gity M, Arabkheradmand A, Taheri E, Shakiba M. Diagnostic investigation of breast magnetic resonance imaging in malignant and benign mass lesions. *Arch Med Sci*. 2018;14:1061-1069.
24. Ryu EB, Chang JM, Seo M, Kim SA, Lim JH, Moon WK. Tumour volume doubling time of molecular breast cancer subtypes assessed by serial breast ultrasound. *Eur Radiol*. 2014;24:2227-2235.
25. Chen ST, Covelli J, Okamoto S, Daniel BL, DeMartini WB, Ikeda DM. Clumped vs non-clumped internal enhancement patterns in linear non-mass enhancement on breast MRI. *Br J Radiol*. 2021;94:20201166.
26. Aydin H. The MRI characteristics of non-mass enhancement lesions of the breast: associations with malignancy. *Br J Radiol*. 2019;92:20180464.
27. Lunkiewicz M, Forte S, Freiwald B, Singer G, Leo C, Kubik-Huch RA. Interobserver variability and likelihood of malignancy for fifth edition BI-RADS MRI descriptors in non-mass breast lesions. *Eur Radiol*. 2020;30:77-86.