

Non mass-like enhancement categories detected by breast MRI and histological findings

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Abstract. – OBJECTIVE: To correlate the different non masslike enhancement categories detected by Magnetic Resonance Imaging (MRI) and the corresponding histological findings.

PATIENTS AND METHODS: Two experienced radiologists reviewed the MRI examinations of 94 patients presenting non mass-like enhancements who had performed histological evaluation. According to the BI-RADS (Breast Imaging Reporting and Data System) lexicon, non masslike enhancements were classified as focal, linear, segmental, regional, ductal and diffuse enhancements. We focused on segmental, regional and ductal patterns.

RESULTS: Among the 94 patients, 52.1% showed a regional pattern, 27.7% a segmental pattern and 20.2% a ductal pattern of enhancement. Of the 49 patients showing a regional pattern, the histological diagnosis was ductal invasive carcinoma (DIC) in 28 cases, ductal carcinoma in situ (DCIS) in 4 cases, lobular invasive carcinoma (LIC) in 3 cases and a benign disease in 9 cases. Of the 26 patients showing a segmental pattern, the histological outcome was DIC in 10 cases, DCIS in 7 cases and a benign disease in 5 cases. Among the 19 patients showing a ductal pattern, the result was DIC in 4 cases, DCIS in 4 cases and a benign disease in 7 cases. In most cases DIC presented as a regional pattern, while DCIS showed a segmental pattern in 26.9%, a ductal pattern in 21.1% and a regional pattern in 8.2% of cases.

CONCLUSIONS: Our findings about ductal and segmental enhancements agree with the literature. We found a high rate of DIC presenting as a regional enhancement, instead; thus, we recommend a more detailed diagnosis, especially when an homogeneous/heterogeneous and clumped internal enhancement pattern is present.

Key-Words:

Magnetic resonance imaging, Non mass-like enhancements, Breast.

Introduction

Over the past 30 years, we have attended a gradual and substantial improvement of the Magnetic Resonance (MR) technique. According to the EUSOMA guidelines, breast dynamic contrast enhanced magnetic resonance represents an important diagnostic tool for local staging before surgical treatment, for monitoring the response to medical and/or surgical treatment, for surveillance of high-risk women, for studying breast already treated for carcinoma¹. According to recent studies², MRI demonstrates a specificity of about 72%, and a sensitivity of about 90%.

Nevertheless, other studies investigating sensitivity and specificity in relation to specific histological categories have put in evidence for ductal carcinoma *in situ* (DCIS) a sensitivity variable between 77 % and 96%³⁻⁵.

According to the “MR Breast Imaging Reporting and Data System (BI-RADS)” lexicon of the American College of Radiology, published in July 2003 and recently updated in 2010, the “first step” in assessing the lesion morphology consists in classifying the type of enhancement as mass, non mass or focus⁶. In particular the following definitions are specified: I) Mass, spaceoccupying lesion which may distort or displace the normal surrounding breast parenchyma; masses can be characterized by round, oval, lobular, or irregular shape; II) Non-mass, enhancement of an area that is not a mass, that may extend over small or large regions, and whose internal enhancement characteristics can be distinguished from the normal surrounding breast parenchyma; III) Focus, enhancement less than 5 mm in size with no definable shape.

Non mass-like enhancements (NME) include the following patterns: regional, segmental, ductal and linear.

Regional enhancement covers more than 25% of a breast quadrant; segmental enhancement follows

the distribution of one or more ducts and their branches, thus, giving it a roughly pyramidal shape, with the apex pointing toward the nipple and the base toward the chest wall; ductal enhancement presents shape and positioning similar to a duct, pointing toward the nipple; finally, linear enhancement is enhancement forming a line, not necessarily with the orientation of a duct and it usually corresponds to a vascular enhancement^{6,7} (Figure 1).

The “second step” consists in describing the lesion morphologic and dynamic characteristics: shape, localization, margins and internal enhancement pattern. Finally, the BI-RADS lexicon recommends the lesion kinetic assessment; two parameters have to be considered: the early and the delayed phase of enhancement, and the resulting kinetic curve.

The early phase constitutes the first two minutes after contrast, when contrast is generally washing into the lesion. The curve during this period demonstrates the rate of uptake of contrast by the lesion, which is described in the lexicon as slow, medium or rapid. Most invasive malignant lesions generally show rapid, intense uptake of contrast and will have reached their peak enhancement by the end of this phase. The remainder of this curve is considered the delayed phase; according to BI-RADS lexicon, the curve can be described in three ways, based on the shape: persistent, plateau, and wash-out⁶.

It is well known that the diagnostic value of the kinetic curve is moderate, because the high preva-

lence of DCIS may lead to a benign curve^{8,9}. For this reason we didn't focus on the correlation between the curve morphology and the lesion histology.

Although the prevalence in the general population of mass enhancements is significantly higher than that of non masslike enhancements with 76% versus 13%¹⁰ we focused on the second category of enhancement for some reasons.

First of all, 57% of non-palpable invasive cancers may show non masslike enhancements¹¹; additionally, non masslike enhancements may represent malignant lesions, which are usually intraductal processes^{7,12}, as well as a diffuse benign disease (fibrocystic mastopathy), an inflammatory disease, or diffuse parenchymal breast enhancement⁷.

In this perspective, the aim of our study was to assess the existence of a significant statistical relationship between the enhancement morphology and the histological result; we also studied the correlation between the enhancement morphology and the presence/absence of menopause.

Patients and methods

Patients

This study was performed after approval of the protocol from our Institutional Review Board and behind subscription of a radiological consensus by all the patients.

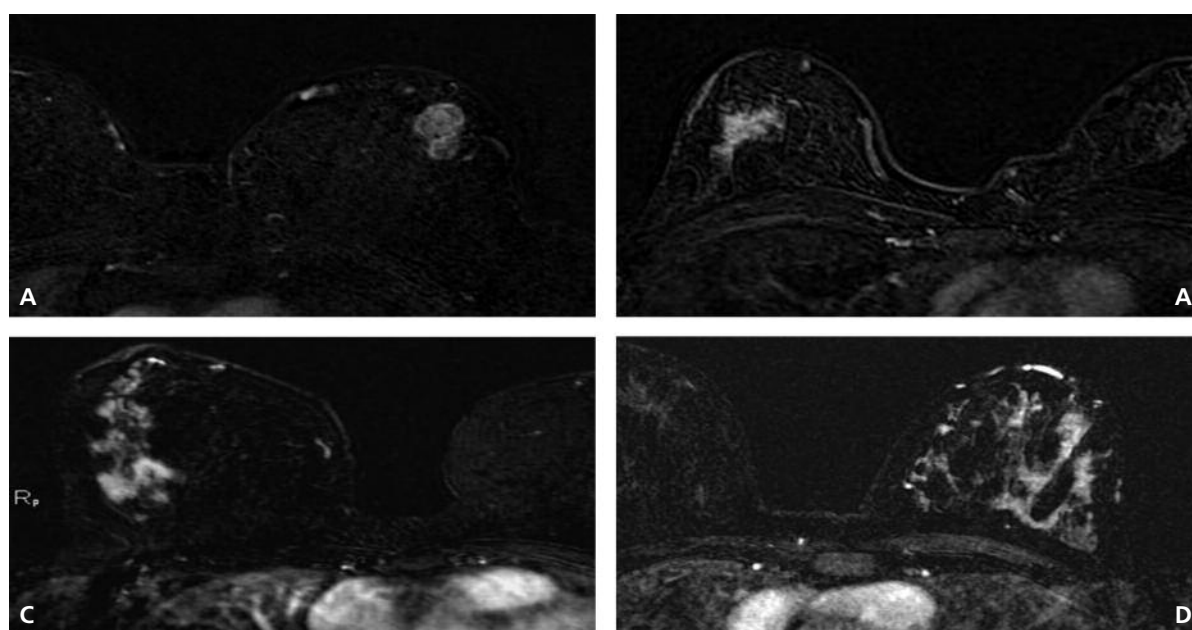


Figure 1. Different types of enhancement on post-contrast sequences of breast MRI. In the current order we can see a mass (A), regional (B), segmental (C) and another regional pattern of enhancement (D).

Two radiologists (one having a 4-year experience and another having a 15-year experience in breast imaging) have retrospectively viewed the MRI performed in our Institute from January 2007 to October 2010.

Ninety-four (94) patients, aged 27-81 years old (median age 45), presenting non mass-like enhancements, were included in our study; all the patients had performed MRI according to the following indications:

1. Local staging before surgical treatment
2. Evaluation of the effect of neo-adjuvant chemotherapy
3. Breast already treated for carcinoma (in order to differentiate between local recurrence or residual tumour and surgical scar)
4. Surveillance of high risk women
5. Patients with nipple discharge
6. Carcinoma of unknown primary (CUP) syndrome¹.

All the lesions analyzed had undergone biopsy; otherwise, lesions without histological result were excluded.

MRI

MRI was performed with a 1.5 T magnet (Avanto, Siemens Medical System, Erlangen, Germany) with patients in prone position using a dedicated breast array coil. Standard MR protocol consisted on: T2-w SHORT-TAU Inversion Recovery (STIR) SEQUENCE on the transverse plane (TR 5320/TE 58 ms; FOV read 300; FOV phase 100; thickness 3.5 mm); T1-w 3D Fast Lowangle Shot (FLASH) Sequence non Fat Saturation (TR 7.73/TE 4.76 ms; FOV read 320; FOV phase 100; thickness 1 mm) on the axial plane and dynamic study with 3D gradient recalled echo (GRE) fat saturation on the transverse plane (TR 5.16/TE 2.38 ms; FOV read 330; FOV phase 100; thickness 1.55 mm) acquiring one scan before and four scans after the intravenous injection of 0.1 mmol of gadolinium diethylene triaminopentaacetic acid (Gd-DTPA) per kilogram of body weight at a rate of 2.0 ml/s followed by 15 ml of saline solution.

Image analysis

Image post-processing included subtraction of pre-contrast sequences from post-contrast ones and maximum intensity projections (MIP). Moreover, time-intensity curves were created by regions of interest (ROI) placed over the more enhancing areas during the early minutes of acquisition after contrast injection. The increased enhancement areas were classified as mass or non

masslike enhancements; we included in the study only non mass-like enhancements and interpreted them according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon¹³.

Areas of non mass-like enhancement were classified into the following categories: focal, linear, regional, segmental, ductal, diffuse.

In this study we focused on regional, segmental and ductal enhancements because, at the moment, the other enhancement patterns have not a significant pathologic correlation. In particular, few studies have been carried out on focal enhancements, which are perhaps the least well understood among NMLE, while linear and diffuse enhancements have a very low positive predictive value for malignancy⁷ because they usually reflect parenchymal enhancements⁶.

Moreover, NMLE can be described by the internal features of enhancement⁶. We analyzed the internal enhancement patterns of regional enhancements. First of all, they can be homogeneous or heterogeneous; in addition, they can present three more specific patterns: clumped, stippled/punctuate and reticular/dendritic. The clumped pattern is also named "cobblestone pattern" because it consists on a closed group of rounded enhancement areas. It is highly suspicious for malignancy (PPV 88% according to Tozaki and Fokuda¹⁴). The stippled pattern consists on multiple tiny dots of enhancement throughout a large area. Finally, the reticular pattern is perhaps the least well understood and used. That is why in this study we focused only on clumped, stippled and homogeneous/heterogeneous internal enhancement patterns.

Histopathological analysis

Histological diagnosis were established on the base of percutaneous biopsy or surgical excision. Pathological diagnosis of core biopsies and surgical excisions were formulated by expert pathologists, including the histological type (according to the World Health Organization classification) and tumor grade (G1, G2, G3, according to the Elston-Ellis Easton System)¹⁵.

Statistical analysis

Statistical analyses were performed by SPSS (version 13.0; SPSS Inc, Chicago, IL, USA). Data are expressed either as frequencies and proportion. Differences between groups were tested for significance using chi-square test for qualitative variables. *p* values < 0.05 were considered statistically significant.

Table I. Relationship between enhancement pattern and histological diagnosis (seven categories).

	Histological diagnosis							Total (# cases)
	DIC	DCIS	LIC	Benign Disease	Papillary Carcinoma	Atypical Hyperplasia	Tubular Carcinoma	
Enhancement pattern	(%)	(%)	(%)	(%)	(%)	(%)	(%)	
– Regional	57.1	8.2	6.1	18.4	0.0	6.1	4.1	49
– Segmental	38.5	26.9	3.8	19.2	11.3	0.0	0.0	26
– Ductal	21.1	21.1	10.5	36.8	5.3	5.3	0.0	19
Total	44.7	16.0	6.4	22.3	4.3	4.3	2.1	94

Results

Ninety-four (94) patients responded to the inclusion criteria, showing non mass-like enhancements on the dynamic acquisition. Seven (7) histological categories were identified: 1st ductal invasive carcinoma (DIC); 2nd ductal carcinoma *in situ* (DCIS); 3rd lobular invasive carcinoma (LIC); 4th papillary carcinoma; 5th atypical hyperplasia; 6th tubular carcinoma; 7th benign disease (Table I).

Among the 94 patients, 49 (52.1%) showed a regional pattern, 26 (27.7%) a segmental pattern and 19 (20.2%) a ductal pattern of enhancement.

Among the 49 patients showing a regional pattern of enhancement, the histological analysis demonstrated DIC in 28 cases (57.1%), DCIS in 4 cases (8.2%), LIC in 3 cases (6.1%), and a benign disease in 9 cases (18.4%) (Figure 2).

Among the 26 patients showing a segmental pattern of enhancement, the histological analysis demonstrated DIC in 10 cases (38.5%), DCIS in 7 cases (26.9%), LIC in 1 case (3.8%) and a benign disease in 5 cases (19.2%) (Figure 3).

Finally, among the 19 patients showing a ductal pattern of enhancement, the histological analysis demonstrated DIC in 4 cases (21.1%), DCIS in 4 cases (21.1%), LIC in 2 cases (10.5%) and a benign disease in 7 cases (36.8%) (Figure 4) (Table I).

From Table I we can argue that the 57.1% of DIC shows a regional pattern of enhancement by MRI, while only the 8.2% of DCIS shows a regional pattern of enhancement. Interestingly, in our sample DCIS showed a segmental pattern of enhancement in 26.9% of cases, a ductal pattern of enhancement in 21.1% of cases and a regional pattern of enhancement only in 8.2% of cases (4 patients).

6 among the 73 patients affected by cancer had the histological finding of LIC and 3 of them presented a regional pattern, 1 of them a segmental pattern and 2 of them a ductal pattern of enhancement on MRI.

Moreover, 4 among the 73 neoplastic lesions were diagnosed as papillary carcinoma, which presented in 3 cases as a segmental pattern and in 1 case as a ductal pattern of enhancement. Furthermore, from the analysis of Table I we can ar-

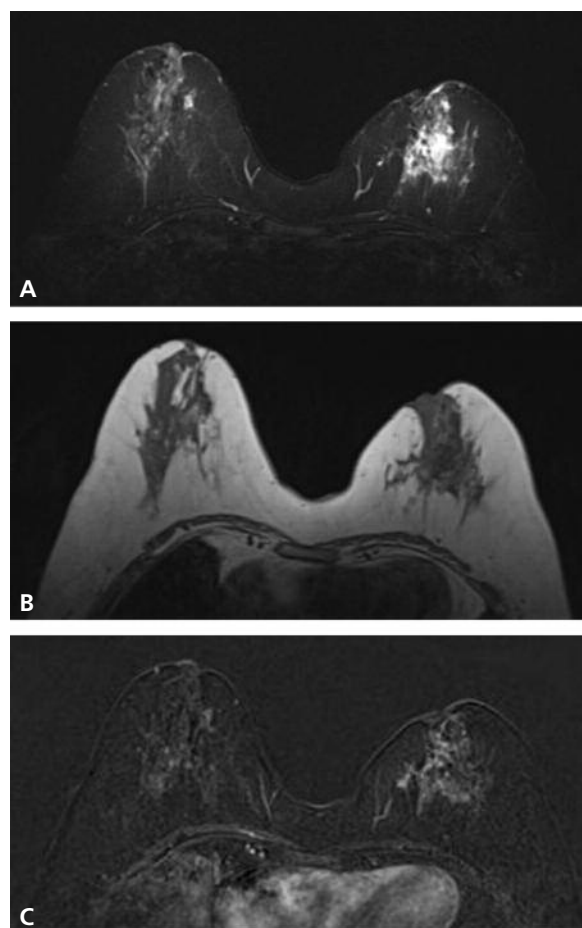


Figure 2. A large lesion located in the subareolar region presenting as an area of structural asymmetry with heterogeneously hyperintense signal intensity on T2 W sequence (A) and hypointense on T1W sequence (B), with regional morphology in post-contrastographic images (C). The surgical excision demonstrated the presence of invasive lobular carcinoma (ILC).

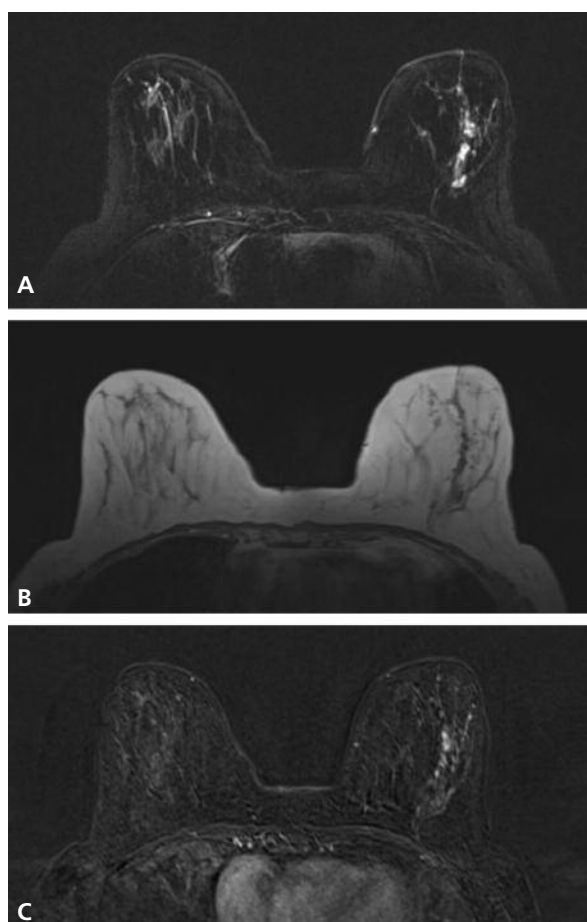


Figure 3. Pre-contrast sequences show an area of structural asymmetry with inhomogeneous hyperintensity on T2 weighted images **(A)** and hypointense on T1 weighted images **(B)**. After contrast agent injection the lesion showed an enhancement with segmental morphology pointing toward the nipple **(c)**. The histologic result was ductal invasive carcinoma (DIC).

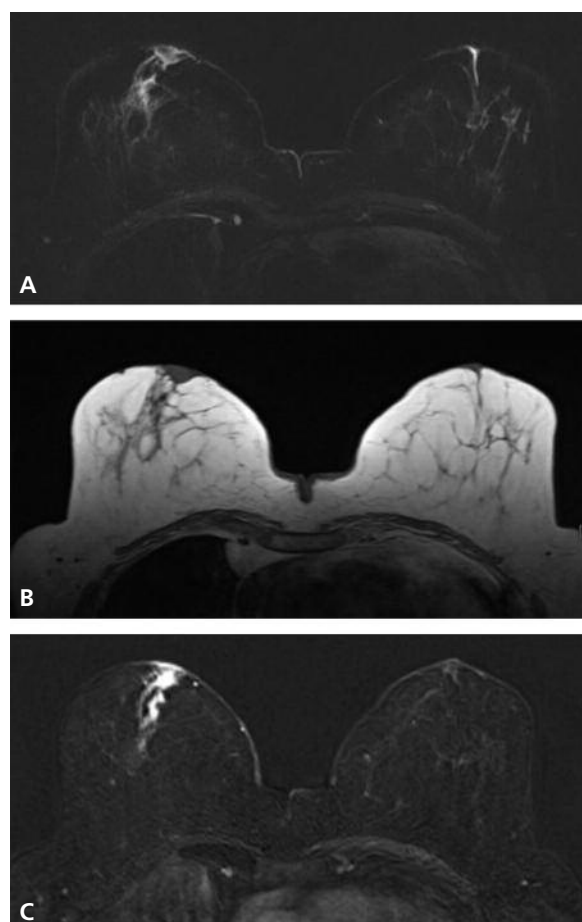


Figure 4. Axial pre-contrast images show an area of structural asymmetry in the para-areolar region, mildly hyperintense on T2 weighted images **(A)** and hypointense on T1 weighted images **(B)**. Post-contrastographic images show an enhancement with ductal morphology **(C)**. The histological outcome which was DCIS.

gue that the benign disease was well represented in percentage as segmental, regional and ductal pattern of enhancement; however, the highest percentage of the benign disease showed a ductal pattern of enhancement, presented by 7 of 19 patients (36.8%).

As it's showed in Table II, we afterwards reduced the initial 7 histological categories into 4 classes (1st DIC; 2nd DCIS; 3rd benign disease; 4th other histological diagnosis, including LIC, papillary carcinoma, tubular carcinoma and atypical hyperplasia, because of the low frequency of these categories in our sample of patients). From the data analysis we found that 28 (57.1 %) of the 42 patients diagnosed with DIC, showed a regional pattern of enhancement on MRI; that 7 (26.9 %) of the 15 patients diagnosed with DCIS

showed a segmental pattern of enhancement; finally, that 7 (36.8 %) of the 21 patients diagnosed with a benign disease showed a ductal pattern of enhancement.

In Table II we carried out a statistical analysis of the correlation between the different histological classes and the presence/absence of menopause (respectively 57 menopausal patients versus 37 nonmenopausal patients); we found similar percentages of DIC in the two categories (menopausal and non-menopausal patients) ($p < 0.05$); however, on the other hand we observed a highest percentage of DCIS in the menopausal group (22.8 % versus 5.4 %). Finally, as expected, we observed that benign disease was more frequent in non-menopausal patients (35.1 % versus 14%).

Table II. Relationship between enhancement pattern and histological diagnosis (four categories).

	Histological diagnosis				Total (# cases)
	DIC	DCIS	Benign Disease	Other	
Enhancement pattern	(%)	(%)	(%)	(%)	
-Regional	57.1	8.2	18.4	16.3	49
-Segmental	38.5	26.9	19.2	15.4	26
-Ductal	21.1	21.1	36.8	15.4	19
Total	44.7	16.0	22.3	17.0	94

$$\chi^2_{(6df)}=11.4; p = 0.02$$

At last, according to the literature⁶, we considered the internal enhancement pattern of regional enhancements of our sample; we distinguished 4 patterns: clumped, stippled, homogeneous and heterogeneous.

Through a work of revision of the MRI examinations, we found that among the 49 patients presenting a regional pattern of enhancement 14 (28.6%) showed a clumped internal enhancement pattern, 11 (22.4%) showed a stippled internal enhancement pattern, 10 (20%) showed an homogeneous internal enhancement pattern and 14 (28.5%) showed an heterogeneous internal enhancement pattern.

We also calculated the PPV of each internal enhancement pattern; furthermore, we studied the correlation between each internal enhancement pattern and the histological outcomes. In particular, among the 14 patients presenting a clumped internal enhancement pattern the histological diagnosis was DIC in 7 cases, DCIS in 1 case, LC in 1 case, benign disease in 5 cases, for a total of 9 neoplastic lesions (PPV 69.2%). DIC represented the 70% of all cancers.

Among the 11 patients presenting a stippled internal enhancement pattern the histological di-

agnosis was DIC in 5 cases, TC in 1 case, DCIS in 1 case, and benign disease in 4 cases, for a total of 7 neoplastic lesions (PPV 63.6%). DIC represented the 71.4% of all cancers.

Among the 10 patients presenting an homogeneous internal enhancement pattern the histological diagnosis was DIC in 7 cases, TC in 1 case, DCIS in 1 case, and benign disease in 1 case, for a total of 9 neoplastic lesions (PPV 90 %). DIC represented the 77.7 % of all cancers.

Finally, among the 14 patients presenting an heterogeneous internal enhancement pattern the histological diagnosis was DIC in 10 cases, LC in 1 case, DCIS in 1 case, and benign disease in 2 cases, for a total of 12 neoplastic lesions (PPV 85.7 %). DIC represented the 76.9 % of all cancers.

In conclusion, in our sample the most represented internal enhancement patterns were the clumped and the heterogeneous ones and DIC was the most frequent histological finding.

Discussion

Our study demonstrates the existence of a statistically significant correlation between the regional enhancement pattern and the histological finding of DIC (57.1% of the lesions); on the

Table III. Menopause and Histological diagnosis (four categories).

	Histological diagnosis				Total (# cases)
	DIC	DCIS	Benign Disease	Other	
Menopause	(%)	(%)	(%)	(%)	
-Presence	45.6	22.8	14.0	17.6	57
-Absence	43.2	5.4	35.1	16.3	37
Total	44.7	16.0	22.3	17.0	94

$$\chi^2_{(3df)}=8.78; p = 0.042$$

contrary, the regional enhancement pattern shows a lower correlation with the presence of a breast benign disease (18.4% of the lesions).

The objective difficulty in classifying and analyzing non masslike enhancements detected by MRI has led to a lack of literature about this subject.

Many studies have been carried out on ductal and segmental enhancement patterns, and in particular on their correlation with DCIS^{3,12,16,17}.

According to the literature, DCIS is more strictly associated with segmental and ductal enhancement patterns, specifically with the ductal branched pattern¹⁴. However, the ductal enhancement pattern is quite infrequent, as reported by Morakkabati-Spitz et al¹⁷: among 1003 patients performing MRI they found 50 segmental or linear enhancement patterns.

Our work consisted on a retrospective analysis of all the non mass-like enhancements scored as BIRADS 3, 4 or 5 and so having a histological diagnosis; it has several bias: first of all its retrospective design, and then the smallness of our sample.

Additionally, we analyzed the internal enhancement pattern of regional enhancement because its PPV varies significantly in the literature: Schnall et al¹⁰ reported a PPV of 21%, while Morakkabati¹⁷ didn't find any malignant lesion presenting as regional enhancement. Thus, the internal features of regional enhancements may be helpful for an appropriate interpretation of the MR images. On the contrary, segmental enhancement has the highest PPV for carcinoma, according to Tozaki and Fukuda¹⁴ (PPV 100%); moreover, many reports dealing with the internal enhancement patterns of ductal and segmental enhancements have been published^{7,12,14,16}.

Among the 49 patients presenting a regional enhancement pattern, the histological diagnosis was DIC in 28 cases and benign disease in 9 cases.

Concerning the analysis of regional internal enhancement patterns, we demonstrated that the heterogeneous, the homogeneous and the clumped patterns have the highest PPV for malignancy (respectively 85.7%, 90% and 69.2%); the highest PPVs found in our sample compared to Schnall et al¹⁰ (PPV respectively 53%, 67% and 60%) can be explained considering the different study inclusion criteria.

As reported in the study by Tozaki and Fukuda¹⁴, segmental enhancement pattern has the highest PPV for malignancy, reported as about 100%. In our sample 26 patients presented a segmental enhancement pattern with a PPV of 80.7%.

The 28% of 73 neoplastic lesions showed a segmental enhancement pattern; among the 26 segmental enhancement patterns the histological finding was cancer in 21 cases (80.7%) and benign disease in 5 cases (19.3%). Our data are in contrast with those found by Morakkabati-Spitz et al¹⁷, who reported an overall PPV for segmental or linear enhancements of 34%¹⁷.

Among the 73 neoplastic lesions, in 4 cases the histological diagnosis was papillary carcinoma, an uncommon neoplasm representing about 0.5% of all invasive breast cancers diagnosed in 2009¹⁸; in 3 cases it presented as segmental enhancement pattern.

Finally, 19 patients presented a ductal enhancement pattern on MR imaging; the histological analysis demonstrated cancer in 11 cases (57%) and benign disease in 8 cases (43%). Therefore, we observed a slight prevalence of malignancy in patients presenting a ductal enhancement pattern.

According to the literature, the ductal enhancement pattern has a PPV ranging from 26 to 84%, depending on the Authors^{16,19}; we observed a PPV of 61%.

The frequency of the ductal enhancement pattern in our sample (20%) matches with the one observed by Liberman et al¹⁶.

In our study we focused only on the morphological features of non mass-like enhancements; we didn't consider the kinetic evaluation, because of the difficulty in obtaining effective kinetic curves in non mass-like enhancements, as largely reported in the literature⁷. In fact, above all DCIS and LIC present as non masslike enhancements and in both cases the carcinoma doesn't necessarily cause significant tumor angiogenesis and thus it's not expected to produce rapid enhancement or washout curves⁶. However, no significant difference in contrast uptake curves can be found to differentiate benign from malignant lesions²⁰.

Conclusions

Our findings about ductal and segmental enhancements agree with the literature. On the contrary, few studies concerning the regional enhancements have been carried out. We found a high rate of DIC presenting as regional enhancement, instead. Thus we recommend a more detailed diagnosis, especially when an homogeneous/ heterogeneous and clumped internal enhancement pattern is present.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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