Ductal carcinoma *in situ* of the breast: Evaluation of main presentations on magnetic resonance imaging compared with findings on mammogram and histology

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Summary

Objective: The purpose of this study was to evaluate the various morphologies and kinetic characteristics of the ductal carcinoma *in situ* (DCIS) on breast magnetic resonance imaging (MRI) exam, to establish which are the most prevalent and to determine the effectiveness of the method in the detection of DCIS.
Method: A prospective observational study, starting in May 2014. We evaluated 25 consecutive patients with suspicious or highly suspicious microcalcifications on mammography screening, BI-RADS categories 4 and 5, who underwent breast MRI and then surgery with proven diagnosis of pure DCIS. Surgery was considered the gold standard for correlation between histologic findings and radiological findings obtained on MRI.
Results: The most frequent morphological characteristic of DCIS on MRI was non-mass-like enhancement (NMLE), p<0.001, observed in 22/25 (88%) patients (95CI 72.5-100). Of these, segmental distribution was the most prevalent, represented by 9/22 (40.91%) cases (95CI 17.4-64.4), p=0.306, and a clumped internal enhancement pattern was most commonly characterized in DCIS, observed in 13/22 (50.09%) cases.
Conclusion: DCIS has a wide variety of imaging features on MRI and being able to recognize these lesions is crucial. Its most common morphological presentation is non-mass-like enhancement, while segmental distribution and a clumped internal enhancement pattern are the most common presentations. Faced with the combined analysis of these findings, percutaneous core needle biopsy (core biopsy) or vacuum-assisted biopsy (VAB) should be encouraged.

Keywords: breast neoplasms, non-infiltrating intraductal carcinoma, mammography, magnetic resonance imaging, large-core needle biopsy.

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Introduction

Ductal carcinoma *in situ* (DCIS) is a type of non-invasive breast malignancy. The pathological findings are characterized by proliferation of malignant epithelial cells in the terminal ductal lobular unit, with no evidence of invasion through the basement membrane. They may affect more than one breast lobule, or occur bilaterally; and if detected before invasion, the chances of cure reach approximately 100%.[1,2]

Some authors consider DCIS a precursor of invasive carcinoma. The clinical manifestation of DCIS is quite variable, so that those of low nuclear grade may remain

silent for a long time or never leave the duct, while those of highest degree exhibit high growth rates, high mitotic indices, and in 30-50% of times progress to high-grade carcinoma.[3]

Its main presentation is grouped microcalcifications, seen on mammography, which helped to establish this imaging exam as a screening method for breast cancer.[4]

After the introduction of mammographic screening, the incidence of DCIS has increased from 2 to 20% of all diagnosed cases,[5,6] contributing to the reduction of the mortality rate for breast cancer.[6-8] However, not all DCIS calcify, and mammographic sensitivity ranges from 27 to 80%.[5,9,10]

The limitations of mammography have raised interest in the use of other imaging methods for the detection of DCIS. Magnetic resonance imaging (MRI) has a sensitivity in the diagnosis of carcinoma of 86-96%[11,12] and some series of studies have shown sensitivity for DCIS detection using this method ranging from 20 to 95%.[13-27]

Due to the wide variation observed in sensitivity rates, demonstrating the most common presentations of this condition in Brazilian patients derived from a screening program in a Teaching Hospital is justified.

The hypothesis is that as MRI allows to evaluate the functional part of the lesions by injecting the paramagnetic contrast, and as DCIS progresses with increased permeability of the basement membrane and protease in its pathophysiology,[28] the vast majority of DCIS detected using this method features non-nodular enhancement, and about 90% of the cases are characterized by microcalcifications on mammography.[29]

Our study aims to evaluate the various morphologies and kinetic characteristics of DCIS on breast MRI, establish which are the most prevalent, and determine the effectiveness of the method in detecting DCIS.

Method

Sample

Prospective observational study approved by the Institutional Ethics and Research Committee and held by the Diagnostic Imaging Service of Santa Casa de Misericórdia de São Paulo. 110 consecutive patients were evaluated over a period of 24 months starting in May 2014. The participants presented suspicious or highly suspicious microcalcifications on mammographic screening, classified as BI-RADS category 4 and 5. They underwent breast percutaneous thick needle (core) or vacuum assisted (mammotomy) biopsy for laboratory diagnosis, and underwent breast MRI prior to biopsy.

Six cases that did not undergo biopsy due to follow-up loss were excluded. Other two were deleted because they performed MRI only after biopsy, contrary to the methodology of the study, and also three cases were eliminated for lack of access to their surgical results.

99 cases remained and underwent breast biopsy. Of these, 56 had histological results consistent with benign lesions. The other 43 were treated with surgery, as they either demonstrated increased risk for malignancy, i.e. atypical ductal hyperplasia (ADH), or were cases positive for malignancy.

In all cases, microcalcifications were observed on radiographs of post-biopsy fragments, ensuring that the target of diagnostic investigation was reached.

Cases negative for malignancy were monitored during visits for examinations over a period of 2 years, as recommended by the BI-RADS lexicon. They were considered true negatives in the presence of lesion stability. During this period, there were no cases with increased number of calcifications and in need of new breast biopsy.

Cases that met all inclusion criteria, which had mammographic changes of microcalcifications classified as BI-RADS categories 4 and 5, who underwent breast MRI and subsequent biopsy, and with histological results of DCIS obtained after surgery, were the basis of our study.

Therefore, surgery was considered the gold standard for correlation between histologic findings and radiological findings obtained using MRI.

The mean interval between mammograms and breast MRI was 21 days (range 3-60 days).

Mammography technique

The mammograms were performed in full-field digital mammography (DR) Selenia/Lorad (Hologic, Bedford, U.S.) model, with standard mediolateral-oblique and craniocaudal views bilaterally and digital zooming of areas of microcalcifications.

Breast MRI technique

MRI examinations of breasts were performed with the patient in prone position, using equipment with 1.5 Tesla and a 4-channel dedicated breast coil (MRI Philips Anchieva, Eindhoven, Netherlands). The examination consists of protocol sequences for conventional MRI breast, including acquisition of dynamic sequences with image subtraction, and 3D reconstruction.

The images include axial T1-weighted fat-suppressed sequences with image gradient reversal (STIR), followed by T2 SPAIR and T2 STIR, sagittal right and left T2-weighted sequences without fat suppression, axial dynam-

ic study divided into five phases with image acquisition every 60 seconds after administration of the paramagnetic agent. Gadolinium was used as contrast (Gadovist®) at a dose of 0.1 mL/kg (Bayer Schering Pharma AG, Berlin, Germany), administered intravenously, often as "bolus" and either followed by saline injection or not. Lastly, subtraction of post and pre-contrast series is performed.

Interpretation of mammograms and breast MRIs

The mammograms and breast MRI were interpreted by two radiologists specialized in breast imaging with at least 10 years of experience. Image interpretation was carried out by correlating clinical data and other imaging studies, including mammography and ultrasound, when available, as recommended by the BI-RADS lexicon.

The images of the scans were acquired from the communication system (PACS, Agfa HealthCare, Mortsel, Belgium) and analyzed on high resolution monitors with 5 megapixels for mammograms and 3 megapixel monitors for breast MRI (BARCO NV, Kortrijk, Belgium) with software that allows manual windowing and optimization of image parameters.

The tests were analyzed and classified according to the fifth edition of BI-RADS (0 – need evaluation of additional tests; 1 – negative radiographic findings; 2 – benign findings; 3 – probably benign findings, recommending reassessment at 6 months; 4 – suspicious findings; 5 – highly suspicious findings, recommending histological correlation; 6 – proven positive radiographic findings for breast cancer).

Lesions referred for biopsy in this study included suspicious and highly suspicious microcalcifications (BI-RADS 4 and 5), regardless of the findings featured in breast MRI.

Biopsy methods

Biopsies of microcalcifications were guided by stereotaxy done on a dedicated table with a high-resolution digital camera (Lorad Multicare Platinum, Hologic, Bedford, U.S.). The success of the procedure was measured by the presence of microcalcifications in radiographs of the fragments, ensuring that the target was correctly achieved.

The protocol used in the service restricts the use of needles for vacuum-assisted biopsy (mammotomy) for cases of microcalcifications with area smaller than 1 cm, due to its limited availability and high financial cost. 9-gauge needles (Suros System, Hologic, Bedford, U.S.) were used, and 11 fragments were collected. Cases involving microcalcifications greater than one centimeter in length underwent core biopsy by using 12-gauge needles (SACN, Biopsy Needle, Medical Device Technologies) coupled to an automated biopsy gun (Magnum, BARD, Covington, U.S.) with advancement of 2.2 cm.

Analysis of the findings on breast MRI

The breast MRI studies were interpreted by the two radiologists specialized in breast imaging. For each case, the presence or absence of findings on breast MRI related to the topography of microcalcifications found on mammography was reported. All lesions with enhancement after contrast administration were classified as nodules or non-nodular enhancements, or both, and their morphological and kinetic characteristics were described according to BI-RADS lexicon. Nodules were reported according to shape (oval, round or irregular), margin (limited, irregular or spiculated) and internal enhancement patterns (homogeneous, heterogeneous or peripheral enhancement), while non-nodular enhancements were classified according to distribution (diffuse, regional, segmental, linear, focal) and internal enhancement patterns (homogeneous, heterogeneous or clumped enhancement). The lesions were measured on film images using software and digital calipers.

The findings of breast MRI were correlated with the histological result obtained from surgery to ensure that there was no diagnostic underestimation of biopsies and this was the gold standard for analyzing the variety of DCIS presentations to the method.

Statistical analysis

The strength of association between the variables studied and DCIS presentations on MRI were evaluated using Fisher's exact test, Pearson's chi-square test, and intervals with 95% confidence (95CI).

A p-value below 0.05 was considered statistically significant.

Results

Of the 43 cases treated with surgery, five were ADH, 13 were invasive ductal carcinoma (IDC), and 25 DCIS, which constituted the study population. This group of patients presented age range 33-84 years (mean 56.6 years, median 55 years).

The lesions were present in MRI according to the final histological results obtained after surgery in 24/25 (96%) of pure DCIS cases (95CI 86.6-100) and 13/13 (100%) of IDC. In one case DCIS showed no enhancement patterns on MRI (method's false negative). There was, however, statistically significant difference between the detection of DCIS and IDC on MRI ($p>0.001$).

Furthermore, there was no statistically significant difference among the patterns of morphological characteristics of DCIS characterized on MRI, manifesting most often as non-nodular enhancements (p<0.001), observed in 22/25 (88%) cases (95CI 72.5-100) (Figures 1 and 2). Less commonly characterized by nodules in 2/25 (8%) of the cases and in 1/25 (4%) of the cases, there were no findings on MRI (Table 1).

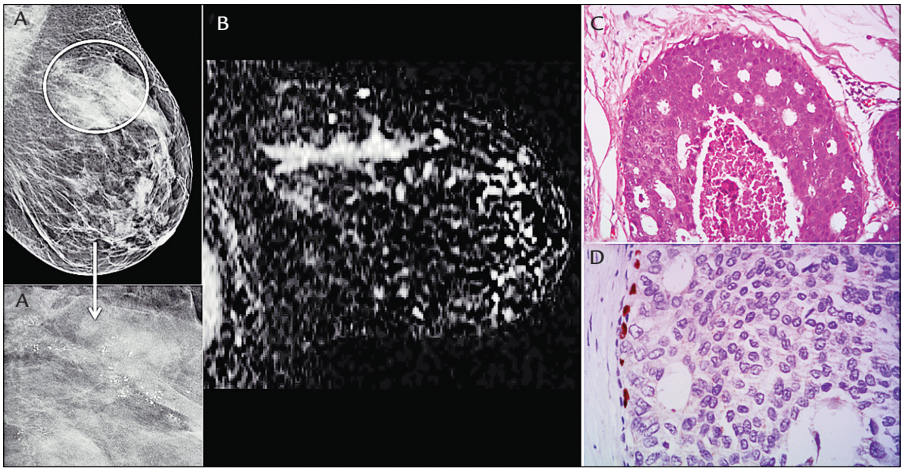

FIGURE 1 64 year-old woman with DCIS. A: Mammography shows pleomorphic microcalcifications grouped at the junction of the upper quadrants (JUQ) in the left breast. B: MRI – T1 axial post-contrast sequence with image subtraction reveals non-nodular linear enhancement on the microcalcifications' topography (arrow). C: Histopathological confirmation of moderate grade DCIS after surgery.

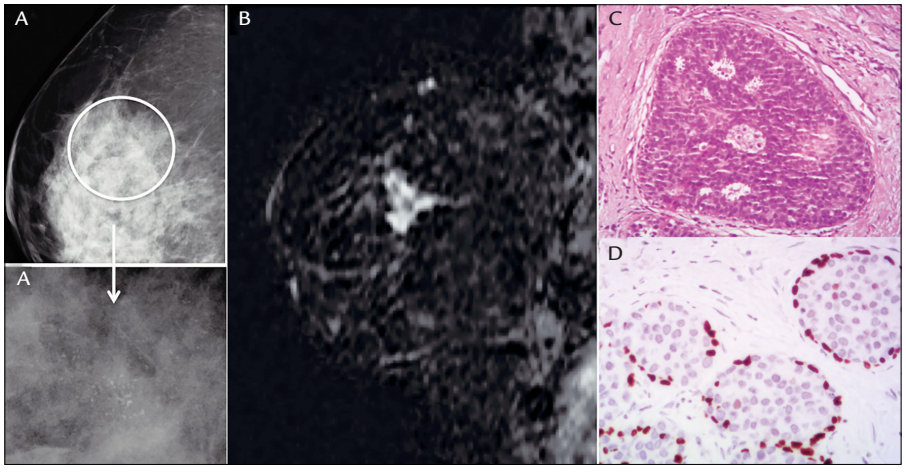

FIGURE 2 53 year-old woman with DCIS. A: Zoomed mammogram shows amorphous and clustered microcalcifications in retroareolar region of the right breast. B: MRI – T1 axial post-contrast sequence with image subtraction reveals non-nodular segmental enhancement on the microcalcifications' topography (arrow). C: Histopathological confirmation of high grade DCIS after surgery.

TABLE 1 Correlation between histopathological diagnosis of DCIS obtained from surgery and radiological findings on breast MRI.

Radiological finding on MRI	Histological diagnosis of DCIS from surgery
Nodule	2 (8%)
Non-nodular enhancement	22 (88%)
Focal	0
None	1 (4%)
Total of cases	**25**

MRI: magnetic resonance imaging; DCIS: ductal carcinoma *in situ*.

Table 2 summarizes the patterns of distribution and internal enhancement of non-nodular enhancements on MRI, with histological result of DCIS obtained by surgery. Segmental distribution was the most prevalent among pure DCIS, representing 40.91% of lesions (95CI 17.4-64.4), p=0.306. Clumped internal enhancement was the most frequently observed in DCIS. This finding was related to DCIS in 13/22 (50.09%) of the cases, followed by heterogeneous enhancement in 8/22 (36.36%) of the cases.

TABLE 2 Patterns of distribution and internal enhancement of non-nodular enhancements on MRI and histopathological results of DCIS obtained from surgery.

Non-nodular enhancements on MRI	Histological results of DCIS from surgery
Distribution	
Segmental	9 (40.91%)
Linear	5 (22.73%)
Focal	8 (36.36%)
Regional	0
Diffuse	0
Internal enhancement pattern	
Heterogeneous	8 (36.36%)
Homogeneous	1 (4.55%)
Clumped	13 (59.09%)
Total of cases	**22**

MRI: magnetic resonance imaging; DCIS: ductal carcinoma *in situ*.

Of the 25 cases of DCIS, 15 had a high nuclear grade; nine had intermediate grade; and only one did not appear on MRI and presented nuclear grade 1. There was one statistically significant difference between the detection of DCIS of high and intermediate nuclear grade compared with low-grade (p<0.005).

Discussion

Although the detection of DCIS has increased significantly with the spread of mammographic screening programs, some authors believe that having a more accurate assessment of the extent of disease is essential to the success of conservative surgery. Patients with positive margins after surgery, as well as patients with other synchronous foci of DCIS have an increased risk of local disease recurrence and it can occur in 50% of cases in the form of invading carcinoma, with 20% of these cases progressing to distant metastases in 10 years.[30]

In order to improve the diagnostic accuracy of DCIS, MRI can be used as a tool and recent studies demonstrate that MRI sensitivity is greater than that of mammography (92 *vs.* 56% respectively),[27,31] reinforcing the importance of being able to identify the different forms of the disease by method.

The purpose of this study was to characterize the radiological findings of MRI that are more associated with DCIS based on the fifth edition of BI-RADS lexicon for MRI. The lexicon provides names and definition for each imaging finding and improves standardization in MRI reports, facilitating the comparison of studies based on similar terminology.

According to scientific research, the most common manifestation of DCIS on MRI is non-nodular enhancement (60-81% of cases), while it is less commonly characterized as nodular (14-41% of cases) or focal (1-12% of cases).[26,32,33] In our study, 22 of the 25 cases of pure DCIS (88%) were non-nodular enhancements and two cases were nodules (8%). Focal enhancements were not found on MRI in the topography of suspicious microcalcifications detected on mammogram; therefore, there was no association between this morphological pattern and DCIS. These results diverge slightly from those expected in the literature, probably due to the small sampling.

Among the non-nodular enhancements, segmental distribution was the most frequent finding associated with DCIS (Table 2), in line with international articles[26,32,33] Secondly, focal distribution was observed, with 36.36% of cases, close to the upper limit expected from the literature. Interestingly, linear distribution was close to that expected according to the studies by Jansen et al.[32] (24%) and higher than expected by Rosen et al.[26] (6%) and Chan et al.[33] (7%). This result can be attributed to the fact that our study does not employ the term ductal distribution, which is no longer used in the latest edition of BI-RADS, incorporating this pattern to linear distribution. Table 3 correlated the results of our study with those expected in the literature.

TABLE 3 Comparison of distribution patterns of non-nodular enhancements on MRI in cases positive for DCIS in the study and the expected results according to the literature.

Distribution of non--nodular enhancements	Present study	Literature review[26,32,33]
Segmental	40.91%	14 – 77%
Linear	22.73%	6 – 24%
Focal	36.36%	16 – 33%

Among the non-nodular enhancements obtained in the study, with histological results of DCIS obtained from

surgery, the clumped internal enhancement pattern was present in 50.09% of the cases. This result is in accordance with the literature (41-64%),[26,32,33] where it is also the most observed finding.

In our study, 24/25 (96%) of the cases of DCIS presented intermediate or high nuclear grade, and only one (4%) showed low nuclear grade and was not diagnosed by the method (false negative). There was a significant association between intermediate or high nuclear grade and detection on MRI compared to low grade (p<0.005). These results were not observed by Menell et al.,[10] but reproduce the results obtained by Kuhl et al.[27] The data suggest that MRI might predict the aggressiveness of DCIS when characterized by the method, and a clinically inert DCIS when there are no radiological findings.

As limitations, MRI was assessed only in patients with mammographic changes BI-RADS categories 4 or 5, composed of suspicious or highly suspicious microcalcifications and the valorization of MRI findings may have been influenced by the presence of microcalcifications in the same topography.

Conclusion

DCIS has a wide variety of imaging features on MRI and being able to recognize these lesions is crucial. Our study showed that MRI can detect the presence of DCIS in 96% of the cases. Its most common morphological presentation is non-mass-like enhancement, while segmental distribution and a clumped internal enhancement pattern are the most common presentations. Faced with the combined analysis of these findings, percutaneous core needle biopsy (core biopsy) or vacuum-assisted biopsy (VAB) should be encouraged.

Resumo

Carcinoma ductal *in situ* mamário: avaliação das principais apresentações à ressonância magnética em correlação com os achados da mamografia e histologia

Objetivo: avaliar as várias morfologias e características cinéticas do carcinoma ductal *in situ* (CDIS) ao exame de ressonância magnética (RM) de mama, estabelecer as mais prevalentes e determinar a eficácia do método na detecção do CDIS.

Método: estudo prospectivo e observacional, com início em 2011 e duração de 24 meses. Foram avaliadas 25 pacientes consecutivas que apresentaram microcalcificações suspeitas ou altamente suspeitas ao exame mamográfico de rastreamento, categorias 4 e 5 de BI-RADS, que realizaram RM mamária e, posteriormente, foram submetidas à cirurgia com resultado comprovado de CDIS puro. A cirurgia foi considerada padrão-ouro para correlação entre os resultados histológicos e os achados radiológicos obtidos à RM.

Resultados: a característica morfológica do CDIS mais frequente à RM foi o realce não nodular (p<0,001), observada em 22/25 (88%) casos (IC 95% 72,5-100). Dentre estes, a distribuição segmentar foi a mais prevalente, representada por 9/22 (40,91%) casos (IC 95% 17,4-64,4), p=0,306, e o realce interno tipo *clumped* foi o padrão mais frequentemente caracterizado no CDIS, observado em 13/22 (50,09%) casos.

Conclusão: o CDIS tem uma grande variedade de características imaginológicas à RM e é fundamental reconhecê-las. A apresentação morfológica mais comum é o realce não nodular, sendo a distribuição segmentar e o padrão interno de realce tipo *clumped* as apresentações mais frequentes. Diante da análise combinada desses achados, a biópsia percutânea por agulha grossa (*core biopsy*) ou assistida a vácuo (mamotomia) deve ser encorajada.

Palavras-chave: neoplasias da mama, carcinoma intraductal não infiltrante, mamografia, imagem por ressonância magnética, biópsia com agulha de grande calibre.

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