Simple magnetic resonance imaging criteria can differentiate ductal carcinomas *in situ* from invasive carcinomas

Critérios simples de imagem por ressonância mangética podem diferenciar carcinomas ductais in situ de carcinomas invasivos

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ABSTRACT

Objective: To investigate if apparent diffusion coefficient (ADC) values can discriminate ductal carcinomas *in situ* (DCIS) from invasive carcinomas and to test the incremental gain of a model combining these measurements to dynamic contrast-enhanced (DCE) main pattern (mass *versus* non-mass). **Methods:** Forty-four lesions (12 DCIS and 32 invasive cancers) were reviewed by two examiners, their ADCs were averaged, and they were classified according to enhancement patterns. A logistic regression model with ADC values and enhancement patterns was devised. Receiver operating characteristic (ROC) curves were used to compare the discriminative performance of isolated ADCs to the regression model by their areas under the curve (AUCs). **Results:** ADC values were significantly different between lesion types (p=0.034), with mean of 1.23×10^{-3} mm^2/s for DCIS and 1.05×10^{-3} mm^2/s for invasive cancers. The model grouping enhancement patterns and ADC values had better performance (AUC=0.80) than isolated ADCs (AUC=0.71), though the difference was not statistically significant (p=0.105). **Conclusion:** ADC measurements of pre-invasive breast lesions are substantially different from those of invasive cancers. When ADC measurements are associated with main enhancement patterns, the performance of the technique is increased.

RESUMO

Objetivo: *Investigar se valores de coeficiente de difusão aparente (ADC) podem discriminar carcinomas ductais in situ (CDIS) de carcinomas invasivos e testar o ganho incremental de modelo combinando tais medidas ao padrão principal de realce (nódulo versus realce não nodular) do estudo contrastado dinâmico (ECD).* ***Métodos:*** *Quarenta e quatro lesões (12 CDIS e 32 cânceres invasivos) foram revisadas por dois examinadores, seus ADCs médios calculados e elas foram classificadas de acordo com padrões de realce. Um modelo de regressão logística com valores de ADC e padrões de realce foi delineado. Curvas receiver operating characteristic (ROC) foram utilizadas para comparar a performance discriminativa dos ADCs isolados ao modelo de regressão através de suas áreas sob a curva (AUCs).* ***Resultados:*** *Os valores de ADC foram significantemente diferentes entre tipos de lesão (p=0,034), com média de $1,23 \times 10^{-3}$ mm^2/s para CDIS e $1,05 \times 10^{-3}$ mm^2/s para cânceres invasivos.*

O modelo agrupando padrões de realce e valores de ADC teve melhor performance (AUC=0,80) do que ADCs isolados (AUC=0,71), ainda que a diferença não tenha sido estatisticamente significante (p=0,105). **Conclusão:** *Medidas de ADC de lesões mamárias pré-invasivas são substancialmente diferentes daquelas de cânceres invasivos. Quando medidas de ADC são associadas aos principais padrões de realce, a performance da técnica é aumentada.*

Introduction

Ductal carcinomas *in situ* (DCIS) have imaging characteristics that consistently differentiate them from invasive breast cancers[1,2]. Although microcalcifications demonstrated by mammography are considered their most typical finding[3,4], ultrasound and, particularly, magnetic resonance imaging (MRI) have been shown to play an important role in their identification[2,5,6]. In fact, recent data have demonstrated that MRI has the highest sensitivity in detecting this type of lesion (around 92%), with acceptable specificity and greater overall accuracy for higher-grade lesions than mammography[1,6].

Traditional MRI criteria based on dynamic contrast-enhanced (DCE) imaging might be coupled with newer techniques — diffusion-weighted imaging (DWI), diffusion-tensor imaging (DTI), proton spectroscopy etc. — to better explore the histologic intricacies of breast neoplasms[7-9]. Among these techniques, DWI is probably the most widespread, due to its availability, relatively fast acquisition and ease of interpretation[10]. It reflects the microstructural properties of *in vivo* tissue, such as cell density, nucleus-to-cytoplasm ratio and membrane integrity[11,12]. When apparent diffusion coefficients (ADCs) are derived, a valuable quantitative parameter is obtained. There is evidence that these measurements are even correlated to biologic minutiae like the histologic grades of DCIS[13]. As a logical consequence, it could potentially discriminate pre-invasive from invasive carcinomas, leading to relevant therapeutic management implications[14].

In this study, we intend to investigate (a) if ADC measurements of DCIS are significantly different from those of invasive breast carcinomas, and (b) what would be the incremental gain of a predictive model that incorporates ADC values and simple DCE-MRI criteria.

Methods

This study is derived from a larger project started by the collaboration of a private reference center in Women's Care and an academic institution. The independent review board of the latter approved it and Informed Consent was waived due to the anonymization protocol and retrospective nature.

Patients and lesions

The original imaging databank was composed of 158 anonymized studies performed between November 2009 and December 2013, in which 199 lesions considered suspicious (BI-RADS® 4) were found. This patient collective was already used for other purposes[15]. For the present study, we have excluded non-malignant lesions, those smaller than 0.5 cm (foci) or without available histopathologic confirmation, and studies without DWI acquisition or with imaging artifacts considered, by any of the reviewers, as prominent enough to interfere with their diagnostic performance. As a consequence, 78 lesions were excluded for lack of documented pathology, 59 findings were non-malignant, 16 were dropped because of image artifacts (magnetic field inhomogeneity and patient movement) and 2 lesions were too small to be adequately evaluated by DWI, resulting in 44 available lesions in 40 patients.

Imaging technique

All the examinations were performed on a single 1.5 T MR unit (Signa Excite HDxT, GE Healthcare, Waukesha, Wiscosin), with patients in the prone position using an eight-channel dedicated breast coil. Sagittal T1 and fat-saturated T2-weighted images were followed by DCE imaging (VIBRANT, GE Healthcare; TR/TE, 5,5/2,7; flip angle, 15°; bandwidth, 50.0; number of excitations, 1; matrix size, 320 X 192; field of view, 200 X 200 mm; slice thickness, 3 mm; intersection gap, 0 mm; reduction factor, 2), with 1 prior and 5 post-contrast serial acquisitions. We injected 0.1 mmol/kg of gadoterate meglumin (Dotarem, Guerbet) in *bolus*, followed by 20 mL saline flush. DWI sequence is always the last to be acquired and we employ gradients in six directions with b=0 and 750 sec/mm^2 (TR/TE, 11.7/96; number of excitations, 8; matrix size, 256 x 224; field of view, 340x340 mm; slice thickness, 3.5 mm; intersection gap, 0.5 mm), using array spatial sensitivity parallel imaging (ASSET, GE Healthcare). Detailed protocol has been published elsewhere[15].

Image analysis

Two experienced radiologists (each with a minimum of 1,000 breast MRI readings), blinded to any patient data and pathologic outcome, independently analyzed and described the lesions according to BI-RADS® directives and worst-curve delayed enhancement kinetics (*i.e.* late progressive enhancement was classified

as Type 1 curve, plateau enhancement was described as Type 2, and washout pattern was described as Type 3). They also measured ADC values, which were later arithmetically averaged. Any divergences were settled by consensus review. These evaluations took place in an offline workstation (Advantage, version 4.4, GE Heatlhcare) with full post-processing capabilities, equipped with the FuncTool software package (GE Healthcare).

Pathologic analysis

All the available pathologic outcomes were obtained from a restricted version of our electronic records, which was linked to the anonymized image databank by our information technology team. The private institution's pathologists in charge of analyzing the biologic material are all subspecialized in breast diseases and classified them according to standard criteria. One of the authors of this study is a member of the Pathology Department of the clinic and reviewed the reports for inconsistencies. Therefore, all the outcomes classified as DCIS or invasive carcinomas, of any subtype, were selected from the main cohort of participants. Cases of mixed pathologic findings, such as DCIS with unambiguous invasive component, were grouped according to the most aggressive feature.

The majority of the biologic specimens were obtained by surgical excisions. We also included more limited tissue sampling methods that provided sufficient material for histopathologic analysis. Therefore, core biopsies using 14-gauge needles and spring-loaded device (Magnum-Bard), as well as vaccum-assisted biopsies employing 9-gauge needles and the automatic tissue extraction and collection system (ATEC, Suros Surgical Systems), were deemed acceptable. We routinely guide biopsy procedures by mammography or ultrasound after thorough site-correlation with MRI findings. This is done due to practical and monetary reasons. Whenever there is doubt about the proper location of the abnormality, we recommend MRI-guided localization or vaccum-assisted biopsy, as our center has the means for such procedures.

Statistical analysis

We have studied, as dependent variables, age of patients, lesion size, frequency of each outcome, main enhancement patterns (mass *versus* non-mass) and averaged ADC measurements. Non-parametric tests were applied and consisted of Wilcoxon Sum-Rank test and Pearson's χ^2 test for frequencies (or Fisher's exact test when less than five outcomes were available). We also designed a simple unsaturated logistic regression model with forceful insertion of ADC measurements and main enhancement types as predictor variables, examining its goodness of fit by Hosmer-Lemeshow test. Receiver operating characteristic (ROC) curves, with their respective areas under the curve (AUC), were calculated and compared. The level of significance considered for all the tests was 5% (p<0.05).

Results

The 40 patients studied had median age of 54 years (interquartile range — IQR=43–62 years) and presented 44 malignant lesions ranging from 0.6 to 10.0 cm, median of 2.2 cm (IQR=1.5–4.7 cm), with no significant difference between DCIS and invasive cancers concerning these two parameters (p=0.906 and p=0.187, respectively). We observed 12 (27.3%) cases of DCIS and 32 (72.7%) invasive carcinomas, which comprised 22 (68.8%) invasive ductal carcinomas, 6 (18.8%) invasive lobular cancers, 2 (6.3%) mucinous carcinomas and 2 (6.3%) neuroendocrine tumors (these percentages might not add to 100% due to rounding). Thirty-two surgical procedures provided most of the diagnoses (9 DCIS and 23 invasive carcinomas); the remaining outcomes were delivered by 11 core-biopsies (2 DCIS and 9 invasive carcinomas) and 1 vacuum-assisted biopsy (DCIS) guided by mammography.

Eleven out of 12 *in situ* carcinomas displayed non-mass enhancement (NME) pattern (91.7%), while 18 out of 32 invasive cancers (56.3%) presented as masses (p=0.006). ADC values were also significantly different between histologic types (p=0.034), with mean of 1.23×10^{-3} mm²/s (standard deviation — SD=0.23) for DCIS and 1.05×10^{-3} mm²/s (SD=0.32) for invasive carcinomas; their medians and IQRs are presented in a boxplot graph (Figure 1). An ADC cutoff level correspondent to the mean displayed by invasive cancers would provide an overall sensitivity of 59.4% and specificity of 83.3%, correctly classifying 65.9% of the lesions (Table 1).

The pre-invasive or invasive nature of cancers was not distinctively associated to any particular kinetic enhancement curve in the sample (Table 1). It is worth noting, though, that only 1 DCIS (8.3%) displayed washout (Type 3) curve. In addition to that, Types 2 and 3 curves, when considered together,
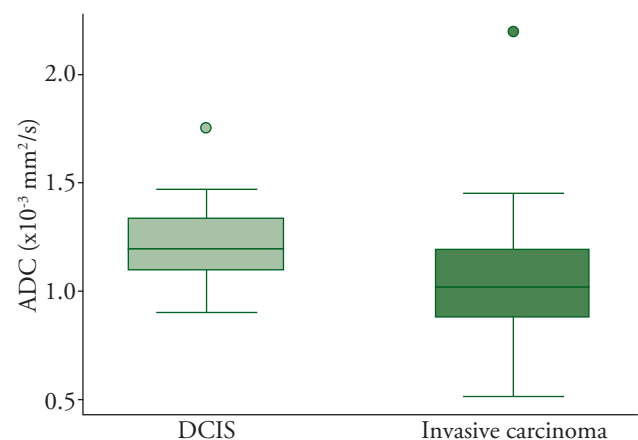
ADC: apparent diffusion coefficient; DCIS: ductal carcinomas *in situ*
Figure 1. Boxplot graph displays different medians, with interquartile ranges for ductal carcinomas *in situ* and invasive carcinomas: 1.19 (IQR 1.10–1.34) and 1.02 (IQR 0.88–1.19). The outlier observed in the invasive cancers' group (dark green circle) corresponds to a mucinous carcinoma

were significantly more prevalent (p=0.038) in invasive cancers, as 26 out of 32 (81.3%) showed these types of enhancement (Figures 2 and 3).

ADC measurements alone demonstrated acceptable performance in differentiating DCIS from invasive cancers (AUC=0.71). The regression model containing these values and main enhancement patterns (mass *versus* non-mass) was well fitting (p=0.707) and showed improved discrimination of lesions (AUC=0.80), although not reaching the statistical significance level (p=0.105) (Figure 4).

Table 1. Imaging characteristics of ductal carcinomas *in situ* and invasive carcinomas (n=44)

	DCIS (n=12)	Invasive carcinoma (n=32)	p-value*
	n (%)**	n (%)**	
Enhancement pattern			0.006
Mass	1 (8.3)	18 (56.3)	
Non-mass	11 (91.7)	14 (43.8)	
Kinetic curve			0.082
Type 1	6 (50.0)	6 (18.8)	
Type 2	5 (41.7)	15 (46.9)	
Type 3	1 (8.3)	11 (34.4)	
ADC cutoff (x 10^{-3} mm²/s)			0.017
>1.05	10 (83.3)	13 (40.6)	
≤1.05	2 (16.7)	19 (59.4)	

*p-values calculated using Fisher's exact test; **percentages might not add to 100% due to rounding; ADC: apparent diffusion coefficient; DCIS: ductal carcinomas *in situ*
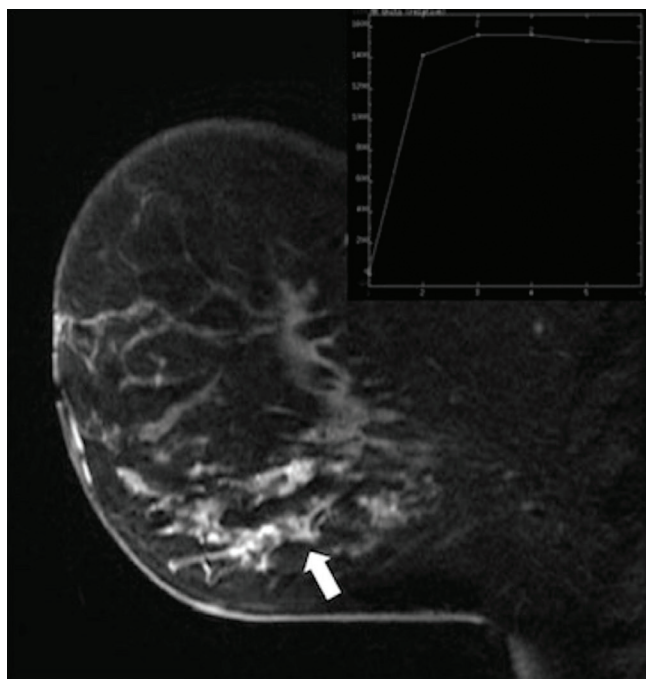

Figure 3. Axial fat-saturated post-contrast T1-weighted image with kinetic enhancement curve (detail). Irregular and heterogeneous mass is observed in the upper outer quadrant of the left breast, with rapid initial enhancement and late washout pattern (Type 3 curve). It was diagnosed as invasive ductal carcinoma by core-needle biopsy

Figure 2. Sagittal fat-saturated post-contrast T1-weighted image with kinetic enhancement curve (detail). There is non-mass clumped enhancement in the lower quadrants of the left breast (arrow), with rapid initial enhancement and late phase plateau tendency (Type 2 curve). The lesion was proven to be high-grade ductal carcinoma *in situ* with necrosis, after surgical excision
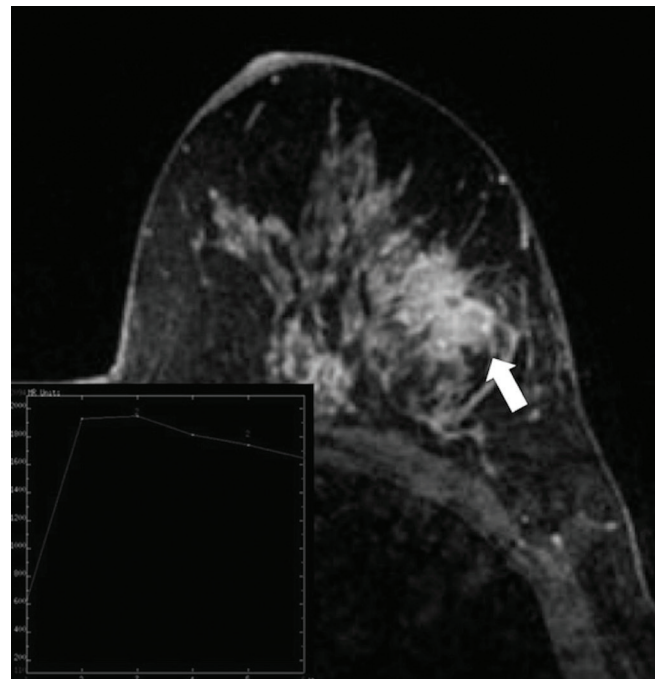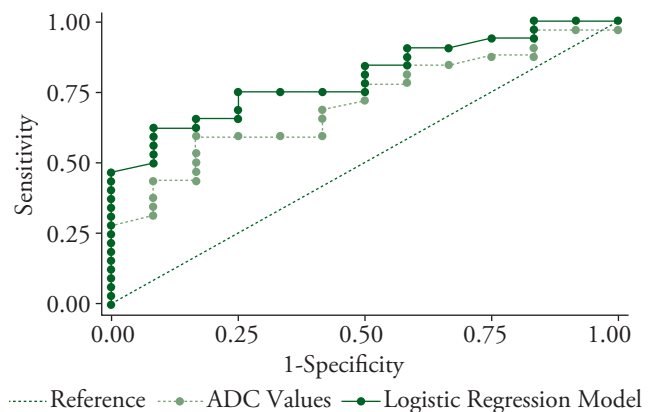

ADC: apparent diffusion coefficient

Figure 4. Receiver operating characteristic curves for apparent diffusion coefficient values (green dashed line) and logistic regression model with ADC values and main enhancement patterns (green solid line). Area under the curve with 95% confidence interval (95%CI) for ADC values alone was 0.71 (95%CI 0.55−0.87) and 0.80 (95%CI 0.67−0.93) for the regression model. This difference was not significant (p=0.105)

Discussion

In this study, we investigated if invasive breast carcinomas could be satisfactorily differentiated from DCIS by ADC measurements alone and if there would be substantial incremental gain of a predictive model associating these measurements to DCE-MRI criteria. Our results show that it is indeed possible to separate these two types of lesions by DWI standards and that combining them to basic enhancement patterns (mass *versus* non-mass) has the potential to improve diagnostic proficiency.

Initially, we detected that invasive cancers presented significantly lower ADC values when compared to those of DCIS, as illustrated by a 0.18 x 10^{-3} mm^2/s difference of means. The ADC mean of invasive lesions would permit correct classification of approximately 66% of the findings, with good specificity, even when considered in isolation as a cutoff parameter. Consequently, it would lead to an acceptable diagnostic performance attested by the ROC curve assessment. Secondly, we found that most of the invasive carcinomas appeared as masses, while all but one of the DCIS showed NME pattern. When these enhancement characteristics were modeled together with ADC measurements, the diagnostic discrimination improved by almost 10%, as demonstrated by the ROC curves.

Evidence that pre-invasive carcinomas present with particular DCE-MRI imaging features has been already demonstrated in the scientific literature[1,2,16]. These lesions are commonly associated to NME pattern and frequently display less suspicious kinetic enhancement characteristics[17,18], which is in agreement to our own results. When microinvasion or frank invasion ensues, the imaging findings tend to become more typically suspicious[19]. Therefore, masses are more common among invasive neoplasms, especially when portraying spiculated margin, strong initial enhancement followed by washout (Type 3 curve), or other suspicious descriptors, as we have shown in concordance to others[20].

The interest in DWI as a diagnostic and predictive surrogate biomarker for breast malignancy has increased in parallel to improvements in MRI technique[21-23]. In their preliminary results, Iima et al.[23] have shown a strong negative correlation between ADC measurements and DCIS grade, with high specificity in discriminating low-grade lesions, in a series of 25 patients. Bickel et al.[22] have broadened the subject to explore the accuracy of ADC values in differentiating DCIS from invasive disease at 3.0 T imaging. They have studied a similar ADC threshold to ours (1.10x10^{-3} mm^2/s), but obtained greater accuracy (AUC=0.895), with sensitivity of 78.06% and specificity of 90.5%. Our results are more in keeping with those attained by Mori et al.[14], who investigated if DWI could be used to distinguish pure DCIS from DCIS with occult invasive component. Their diagnostic performance, as assessed by ROC curves, was exactly the same as ours (AUC=0.71) for the minimum ADC values. In general, we observed mean ADC values for DCIS and invasive carcinomas that are very close to those reported in the literature[17,22], even when considering technical differences (*e.g.* different *b* values, higher field units, diverse protocols etc.).

We tried to compose a realistic logistic regression model to discriminate DCIS from invasive breast cancers based on only two MRI parameters: main enhancement patterns (mass *versus* non-mass) and ADC averaged measurements. In opting for this simplistic methodology, we expected to increase external generalizability, which is probably the greatest strength of this study. As a consequence, our approach is supposed to be feasible in routine clinical practice without cumbersome adaptations.

This study has some intrinsic limitations. The small sample size might prevent extrapolation of our conclusions to larger populations with varied breast anomalies. In addition to that, we have studied only lesions considered suspicious (BI-RADS® 4), which also restrains the application of our results to patients harboring this particular type of finding. DWI is prone to an increased number of imaging artifacts, which could have impaired adequate ADC measurements. We have also adopted a *b* value that is not so frequently found in the literature and performed DWI after contrast injection, which could introduce issues caused by microperfusion of contrast media[24,25] — though we do not expect DWI particularities to substantially interfere with the presented results[26,27]. Pathologic classification of lesions was grounded on the most aggressive abnormality. Thus, DCIS mixed with invasive carcinomas would be arbitrarily grouped as the latter, hindering more detailed analysis. This is also true to the different histologic DCIS grades, as they are out of the scope of this study.

Conclusion

The ADC measurements of pre-invasive breast lesions are substantially different from those found in invasive tumors, which further iterates that DWI is a valuable diagnostic and problem-solving technique. When associated with simple DCE-MRI criteria, such as main enhancement patterns (mass *versus* non-mass), the diagnostic performance of the method is bound to increase.

References

1. Greenwood HI, Heller SL, Kim S, Sigmund EE, Shaylor SD, Moy L. Ductal carcinoma in situ of the breasts: review of MR imaging features. Radiographics. 2013;33(6):1569-88.

2. Lehman CD. Magnetic resonance imaging in the evaluation of ductal carcinoma in situ. J Natl Cancer Inst Monogr. 2010;2010(41):150-1.

3. Barreau B, de Mascarel I, Feuga C, MacGrogan G, Dilhuydy M-H, Picot V, et al. Mammography of ductal carcinoma in situ of the breast: review of 909 cases with radiographic-pathologic correlations. Eur J Radiol. 2005;54(1):55-61.

4. Hofvind S, Iversen BF, Eriksen L, Styr BM, Kjellevold K, Kurz KD. Mammographic morphology and distribution of calcifications in ductal carcinoma in situ diagnosed in organized screening. Acta Radiol. 2011;52(5):481-7.

5. Kim WH, Chang JM, Moon WK, Cho N, Yi A, Koo HR, et al. Intraductal mass on breast ultrasound: final outcomes and predictors of malignancy. Am J Roentgenol. 2013;200(4):932-7.

6. Kuhl CK, Schrading S, Bieling HB, Wardelmann E, Leutner CC, Koenig R, et al. MRI for diagnosis of pure ductal carcinoma in situ: a prospective observational study. Lancet. 2007;370(9586):485-92.

7. Domingues NA, Domingues RC, Mirian L. The use of diffusion-weighted magnetic resonance imaging in the differentiation between benign and malignant breast lesions. Radiol Bras. 2009;42(5):283-8.

8. Baltzer PAT, Schäfer A, Dietzel M, Grässel D, Gajda M, Camara O, et al. Diffusion tensor magnetic resonance imaging of the breast: a pilot study. Eur Radiol. 2011;21(1):1-10.

9. Bolan PJ. Magnetic resonance spectroscopy of the breast: current status. Magn Reson Imaging Clin N Am. 2013;21(3):625-39.

10. Partridge SC, DeMartini WB, Kurland BF, Eby PR, White SW, Lehman CD. Quantitative diffusion-weighted imaging as an adjunct to conventional breast MRI for improved positive predictive value. AJR Am J Roentgenol. 2009;193(6):1716-22.

11. Chenevert TL, Sundgren PC, Ross BD. Diffusion imaging: insight to cell status and cytoarchitecture. Neuroimaging Clin N Am. 2006;16(4):619-32.

12. De Figueiredo EHMSG, Borgonovi AFNG, Doring TM. Basic concepts of MR imaging, diffusion MR imaging, and diffusion tensor imaging. Magn Reson Imaging Clin N Am. 2011;19(1):1-22.

13. Rahbar H, Partridge SC, Demartini WB, Gutierrez RL, Allison KH, Peacock S, et al. In vivo assessment of ductal carcinoma in situ grade: a model incorporating dynamic contrast-enhanced and diffusion-weighted breast MR imaging parameters. Radiology. 2012;263(2):374-82.

14. Mori N, Ota H, Mugikura S, Takasawa C, Tominaga J, Ishida T, et al. Detection of invasive components in cases of breast ductal carcinoma in situ on biopsy by using apparent diffusion coefficient MR parameters. Eur Radiol. 2013;23(10):2705-12.

15. Maltez de Almeida JR, Gomes AB, Barros TP, Fahel PE, de Seixas Rocha M. Subcategorization of suspicious breast lesions (BI-RADS Category 4) according to MRI criteria: role of dynamic contrast-enhanced and diffusion-weighted imaging. AJR Am J Roentgenol. 2015;205(1):222-31.

16. Newstead GM. MR imaging of ductal carcinoma in situ. Magn Reson Imaging Clin N Am. 2010;18(2):225-40.

17. Cheng L, Bai Y, Zhang J, Liu M, Li X, Zhang A, et al. Optimization of apparent diffusion coefficient measured by diffusion-weighted MRI for diagnosis of breast lesions presenting as mass and non-mass-like enhancement. Tumour Biol. 2013;34(3):1537-45.

18. Imamura T, Isomoto I, Sueyoshi E, Yano H, Uga T, Abe K, et al. Diagnostic performance of ADC for non-mass-like breast lesions on MR imaging. Magn Reson Med Sci. 2010;9(4):217-25.

19. Hahn SY, Han B-K, Ko EY, Shin JH, Hwang J-Y, Nam M. MR features to suggest microinvasive ductal carcinoma of the breast: can it be differentiated from pure DCIS? Acta Radiol. 2013;54(7):742-8.

20. Goto M, Yuen S, Akazawa K, Nishida K, Konishi E, Kajihara M, et al. The role of breast MR imaging in pre-operative determination of invasive disease for ductal carcinoma in situ diagnosed by needle biopsy. Eur Radiol. 2012;22(6):1255-64.

21. Rahbar H, Partridge SC, Eby PR, Demartini WB, Gutierrez RL, Peacock S, et al. Characterization of ductal carcinoma in situ on diffusion weighted breast MRI. Eur Radiol. 2011;21(9):2011-9.

22. Bickel H, Pinker-Domenig K, Bogner W, Spick C, Bagó-Horváth Z, Weber M, et al. Quantitative apparent diffusion coefficient as a noninvasive imaging biomarker for the differentiation of invasive breast cancer and ductal carcinoma in situ. Invest Radiol. 2015;50(2):95-100.

23. Iima M, Le Bihan D, Okumura R, Okada T, Fujimoto K, Kanao S, et al. Apparent diffusion coefficient as an MR imaging biomarker of low-risk ductal carcinoma in situ: a pilot study. Radiology. 2011;260(2):364-72.

24. Yuen S, Yamada K, Goto M, Nishida K, Takahata A, Nishimura T. Microperfusion-induced elevation of ADC is suppressed after contrast in breast carcinoma. J Magn Reson Imaging. 2009;29(5):1080-4.

25. Nilsen LB, Fangberget A, Geier O, Seierstad T. Quantitative analysis of diffusion-weighted magnetic resonance imaging in malignant breast lesions using different b value combinations. Eur Radiol. 2013;23(4):1027-33.

26. Chen G, Jespersen SN, Pedersen M, Pang Q, Horsman MR, Stødkilde-Jørgensen H. Intravenous administration of Gd-DTPA prior to DWI does not affect the apparent diffusion constant. Magn Reson Imaging. 2005;23(5):685-9.

27. Pereira FPA, Martins G, Figueiredo E, Domingues MNA, Domingues RC, da Fonseca LMB, et al. Assessment of breast lesions with diffusion-weighted MRI: comparing the use of different b values. AJR Am J Roentgenol. 2009;193(4):1030-5.