

Diffusion Weighted Imaging with Background Body Signal Suppression/ T₂ Image Fusion in Magnetic Resonance Mammography for Breast Cancer Diagnosis

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Rezumat

Fuziunea dintre imagistica prin difuzie cu supresia semnalului de fond și T₂ în mamografia prin rezonanță magnetică pentru diagnosticul cancerului mamar

Introducere: Mamografia prin rezonanță magnetică cu contrast dinamic (DCE-MRM) este considerată cea mai sensibilă examinare în diagnosticul cancerului mamar (CM), dar cu specificitate variabilă. Scopul studiului nostru a fost de a evalua eficiența clinică a unei tehnici MRM noi - fuziunile între imagistica prin difuzie cu supresia semnalului de fond și T₂ (DWIBS/T₂) în diagnosticul CM, în comparație cu DCE-MRM.

Material și Metodă: Am analizat retrospectiv 50 de examinări DCE-MRM consecutive cu secvență DWIBS din arhiva Spitalului Lyon Sud, (perioada: 02.2010-02.2011), însumând 64 leziuni mamare. Fuziunile au fost create în programul Osirix folosind imaginile DWIBS ($b=1000 \text{ s/mm}^2$) și corespondentul lor în T₂. Interpretarea a fost făcută folosind un sistem BI-RADS adaptat, având examenul histopatologic, respectiv

evoluția pe minim 6 luni ca și gold standard.

Rezultate: Din cele 64 de leziuni mamare examinate, 35 (54.7%) au fost clasificate maligne prin DCE-MRM respectiv 24 (37.5%) prin fuziunile DWIBS/T₂. Astfel, fuziunea DWIBS/T₂ a prezentat o sensibilitate de 62.5% (95% CI:35.4-84.8) și o specificitate de 70.8% (95%CI:55.9-83.3), în timp ce DCE-MRM a prezentat o sensibilitate mai mare: 87.5% (95%CI: 61.6-98.4), dar o specificitate mai mică: 56.2% (95%CI:41.1-70.5).

Concluzii: Fuziunile DWIBS/T₂ reprezintă o tehnică MRM inovatoare, cu o specificitate superioară față de DCE-MRM, demonstrând un mare potențial de îmbunătățire al eficienței MRM clasice.

Cuvinte cheie: rezonanță magnetică mamară, DWIBS, T₂, fuziune, cancer mamar

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Abstract

Introduction: Dynamic Contrast-Enhanced Magnetic Resonance Mammography (DCE-MRM) represents the most sensitive examination for breast cancer (BC) diagnosis. However literature data reports very inhomogeneous specificity. The aim of our study was to evaluate the clinical efficiency of a new MRM technique – diffusion weighted imaging with background body signal suppression/T₂ image fusion in BC diagnosis, compared to DCE-MRM.

Methods: We retrospectively analyzed 50 consecutive DCE-

MRM examinations with DWIBS sequence from the archives of the Department of Radiology, Lyon Sud Hospital, (02.2010-02.2011), summing up to 64 breast lesions. Fusions were created using the Osirix software from the DWIBS images ($b=1000 \text{ s/mm}^2$) and their T_2 correspondents. Interpretation was performed using an adapted BI-RADS system. The final histopathological examination or a minimum 6-months follow-up served as gold standard.

Results: Out of the 64 examined breast lesions, 35(54.7%) were classified as malignant by DCE-MRM and 24(37.5%) cases by DWIBS/ T_2 , respectively. Thus the DWIBS/ T_2 fusion had a Sensitivity of 62.5%(95%CI:35.4-84.8) and a Specificity of 70.8%(95%CI:55.9-83.3) while DCE-MRM had a higher Sensitivity: 87.5%(95%CI:61.6-98.4) but a lower Specificity: 56.2%(95%CI:41.1-70.5).

Conclusion: DWIBS/ T_2 fusion is an innovative MRM technique, with a specificity superior to DCE-MRM, showing a large potential for improving the clinical efficiency of classical MRM.

Key words: magnetic resonance mammography, DWIBS, T_2 , fusion, breast cancer

Introduction

Dynamic Contrast-Enhanced Magnetic Resonance Mammography (DCE-MRM) is the actual state-of-the-art in breast imaging diagnosis, with sensitivity rates as high as 89-100%, but with a an inhomogeneous specificity ranging from 65% to 93% (1-5). DCE - MRM is also characterized by a high negative predictive value. This aspect is particularly important in patients with prior mammary surgery, as a precise diagnosis of tumor-free status is necessary for performing precocious or delayed breast reconstruction surgery (6,7). Indicated in breast cancer screening (for high-risk patients), staging (for newly diagnosed cancers) and follow-up, DCE-MRM is often associated with new diagnostic sequences, aimed to improve specificity. This results in a more accurate diagnosis and staging with important consequences in surgical planning, thus avoiding unnecessary or excessive surgical procedures (8,9).

One of these sequences is Diffusion Weighted Imaging with Background body signal Suppression (DWIBS). It was introduced by Takahara et al in 2004 and it is based on tissue water diffusion (Diffusion Weighted Imaging - DWI) which becomes altered in tumors with high cellularity (10,11). Thus, DWIBS is an improved DWI technique, offering heavy diffusion weighting (with b values up to 1500 s/mm^2), enhanced STIR (Short TI Inversion Recovery) fat suppression and the possibility of free-breathing. This results in reduced scan times, less DWI-specific (like magnetic susceptibility) and movement artefacts with subsequent good quality examinations (10,11). All in all, DWIBS offers a better sensitivity and specificity for breast cancer diagnosis, but the lack of clear anatomical information makes the mapping of the lesion challenging (12,13).

Similarly to PET/CT imaging, lesion mapping and conspicuity could be improved in Magnetic Resonance Imaging (MRI) by digitally overlapping functional (DWIBS) and anatomical (T_2) images, resulting in a DWIBS/ T_2 image fusion (14).

However, literature data on DWIBS/ T_2 image fusions is scarce. Moreover, the existing published studies have evaluated only small groups of patients on various pathologies, but none on breast imaging diagnosis using MRM (15,16).

The aim of our study was to evaluate the diagnostic efficiency (in terms of sensitivity, specificity, negative and positive likelihood ratios) of DWIBS/ T_2 image fusion compared to standard DCE-MRM in a retrospective cohort study. The reference examination (gold standard) in our study was the final pathological diagnosis of the corresponding breast lesions. When the pathological examination was not available, the final diagnosis was set based on the patient disease status after a minimum 6-months of follow-up. To the best of our knowledge, this is the first large patient-group study on the clinical efficiency of the DWIBS/ T_2 image fusion in breast imaging.

Material and Methods

Selection protocol

We retrospectively reviewed the MRI database from the Department of Radiology, Lyon Sud Hospital, France. All MRMs performed from February 2010 to February 2011 (300 consecutive examinations) and their corresponding histopathological reports were assessed for consistency to the study protocol.

All patients with good quality examinations and a complete scan protocol, including DWIBS were included in our study. DWIBS images were considered adequate only if they were artefact-free and taken at a b value of 1000 s/mm^2 . All study examinations had to contain at least one target lesion that had either a biopsy/surgery or a minimum 6 months follow-up. Patients with normal examinations (BI-RADS 1) were excluded.

Invasive gestures on the breast before MRI examination can be responsible for hematomas, edema and scarring, conditions that could influence the interpretation (13,17). In order to clearly assess the DWIBS/ T_2 image fusion we excluded all patients with any type of invasive gestures, as well as radiation and chemotherapy performed 6 months before MRM.

Patients with multiple examinations were identified and only one examination per patient was selected, mainly the most recent one. Patients with examinations bearing important artifacts or technical errors were also excluded.

Our final study group consisted in 50 women with an average age of 51.8 ± 14.4 years, summing up to 64 examined lesions.

MRM scan procedure

All MRM examinations were performed on a Philips Achieva

1.5 T MRI scanner (Philips Healthcare, Eindhoven, The Netherlands) with the patient in prone position, using a SENSitivity Encoding (SENSE) breast coil with 7 elements.

The clinical MRM protocol included the following sequences: T2-weighted Turbo Spin Echo (TSE), T1-weighted Dynamic Contrast-Enhanced (DCE), T1 contrast-enhanced High Resolution Isotropic Volume Examination (THRIVE) and DWIBS. All acquisitions were performed in the axial plane.

The DCE acquisitions were performed using a T1-weighted Fast Field Echo (FFE) sequence with SENSE: FOV 300 mm, TR/TE: 9.3/ 4.6, flip angle 200, turbo factor 1, EPI factor 1, NSA 2, with 2 mm slices, 1 mm gaps and a scan matrix of 258/448. The dynamic scan was done in 6 consecutive acquisitions (1 unenhanced and 5 enhanced) centered at 90, 180, 270, 360 and 450 seconds. The operator performed digital subtraction on the 4th series (270s) using the first pre-contrast phase as mask. Contrast was injected with a power injector in a dose of 0.2 ml/Kg (Dotarem 0.5 mmol/ml, Guerbet, France) with a bolus of 3 ml/second, followed by a 20 ml saline flush.

DWIBS was performed after DCE administration at 3 b values ($b=0$, $b=500$ and $b=1000$ s/mm²) using the SENSE technique: FOV 340 mm, TR 8403 ms, TE 0.0(69) ms, TI 180 ms. Turbo and EPI factors were both 47, NSA 5, in 5 mm slices with 0.5 mm gaps and a matrix of 160/240 (136/240).

After having defined the study group, the DWIBS/T2 fusions were created off-line using the OsirixR Medical Imaging Software, by overlaying the signal from the $b=1000$ s/mm² DWIBS images onto the T2-weighted ones. Although the software automatically adjusted the fusions for differences in slice level and FOV, the radiologist also performed some fine adjustments where the automatic process was incomplete

MRM interpretation

All MRM examinations (including fusions) were analyzed

off-line using a DICOM viewer (K-PACS, IMAGE Information Systems, Ltd). Interpretation was performed in a blinded manner, the radiologist having access only to the DWIBS/T2 fusion images. He was aware of the target lesion, but had no information on other sequences, pathological diagnosis or follow-up results. Prior to interpretation, the rest of the study team had identified the target-lesions on DCE-T1, DWIBS and subsequently on DWIBS/T2 fusions, using the MRM reports.

DWIBS/T2 fusions were interpreted using both original sequences' characteristics. Thus T2 images offered important morphological information (like lesion size, shape, contours, etc), while DWIBS contributed with signal intensity. By replacing contrast information (enhancement, dynamic enhancement curve) with DWIBS signal intensity, a new custom version of the BI-RADS MRI lexicon was created (18). As quantitative DWIBS interpretation through the Apparent Diffusion Coefficient (ADC) was not possible, DWIBS signal was interpreted in a qualitative manner and lesions were considered either benign (low intensity lesions) or malignant (high intensity lesions). Our interpretation protocol is depicted in *Table 1*.

The original DCE-MRM interpretations were performed by senior radiologists from the Department of Radiology, Lyon Sud Hospital specialized in breast imaging, using the special BI-RADS MRI lexicon. Each examination was classified according to the BI-RADS scale from 1 to 6 (18). We considered the original interpretation as adequate and included its results in the study database. For cases that had incomplete or insufficient data, our team performed a re-interpretation in consensus.

Statistical analyses

Data analysis was performed using the EpiInfo v 3.5.3 (Centers for Disease Control and Prevention, Atlanta, USA) and the GraphPad InStat (GraphPad Software, Inc. California, USA) software. After dichotomization of the initial BI-RADS

Lesion type	Benign	Malignant
Focus	A lesion smaller than 5 mm with moderate DWIBS signal	N/A
Mass		
- shape	Lobulated, round or oval	Irregular
- contour	Smooth	Irregular, Spiculated
- signal	Low/Moderate	High signal
Non-mass like lesions	N/A	Focal area, linear, ductal or segmental signal
Associated signs	Simple cysts	Nipple retraction/invasion Spontaneous ductal high intensity signal Skin thickening (local/diffuse) Skin invasion Edema Lymphadenopathy Pectoralis muscle invasion Chest wall invasion Hematoma/Blood Abnormal signal void

Table 1. *The DWIBS/T2 image fusion interpretation protocol*

Legend: The DWIBS/T2 image fusions interpretation protocol was obtained from the 2003 BI-RADS lexicon for MRM; it was adapted for the absence of DCE-T1, which was replaced by DWIBS

classification on DCE-MRM in benign (1,2,3) and malignant (4,5,6) lesions, contingency tables were created and clinical efficiency indicators (sensitivity, specificity, positive and negative likelihood ratios) were calculated both for the DWIBS/T₂ fusion and DCE-MRM, referring to the gold standard. In order to have an analytical comparison of the two diagnostic methods, we created special contingency tables according to the method described by Hawass N.E. (19). Row-column associations within the contingency tables were analyzed using nonparametric significance tests (Fisher Exact Test). The statistical significance was defined as a p-value <0.05 for a 95% confidence interval.

Ethical issues

Our study used images that were already available in the hospital archives at the time of the study, without implying any actual patients. Furthermore, no gestures or interventions were performed on patients. The identity of the patients and all their medical data was strictly confidential and was included in a secure database used only by the study team.

Results

Our study included a total of 64 breast lesions with an average size of 14.9 ± 11.3 mm. The majority were masses (n=50, 78%), followed by foci (n=7, 10.9%) and non-mass lesions (n=7, 10.9%). BI-RADS 4 (suspicious abnormality, biopsy should be considered) represented the majority of lesions (n=22, 34.4%) on DCE-MRM, followed by BI-RADS 3 (probably benign finding—short-interval follow-up suggested) (n=20, 31.3%) and BI-RADS 5 (highly suggestive of malignancy) (n=14, 21.9%). After BI-RADS dichotomization at BI-RADS 4, 35 lesions (54.7%) were classified as malignant on DCE-MRM interpre-

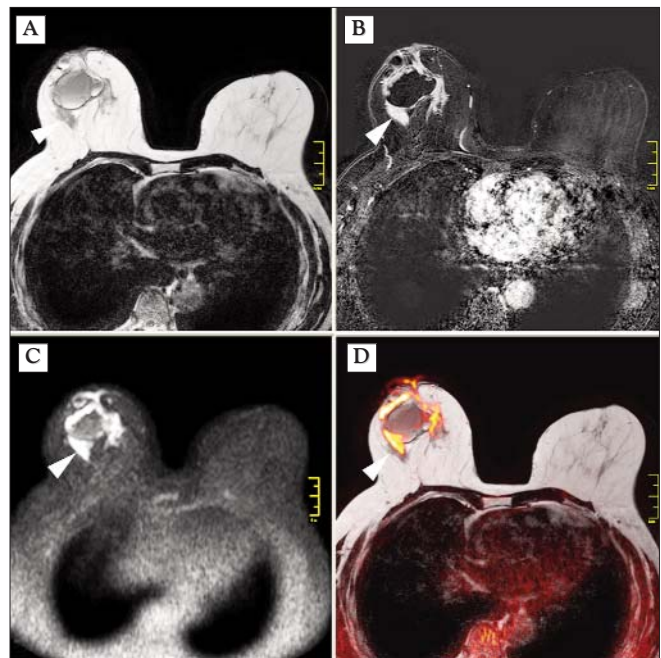


Figure 1. A 78-year old female patient presented with a palpable mass in her right breast in the external quadrants. The MRM showed an irregular thick-walled complex cystic mass with a partially hematic content (A) that exhibited strong enhancement (B). Both DWIBS (C) and the DWIBS/T₂ fusion (D) clearly depicted the extent of the tumor. Mastectomy and right lymph node dissection was performed and the histopathological result was poorly differentiated invasive ductal carcinoma

tation, while 24 lesions were found malignant (37.5%) on DWIBS/T₂ fusion. Detailed data on lesions' characteristics, BI-RADS and DWIBS/T₂ classifications are depicted in Table 2, Fig. 1.

Table 2. Descriptive data concerning patient demographics, lesions' characteristics and classifications according to size, type, BI-RADS category and DWBS/T₂ image fusion interpretation

Characteristic	Mean value \pm SD or N(%)
Age	51.8 \pm 14.4
Lesion size (A total of 64 lesions)	14.9 \pm 11.3
Lesion classification according to size category	
Lesion equal to or larger than 1 cm	28(43.8%)
Lesion larger than 1 cm but smaller than 2 cm	21(32.8%)
Lesion larger than 2 cm	15(23.4%)
Lesion classification according to type	
Focus lesion	7(10.9%)
Mass lesion	50(78.1%)
Non-mass lesion	7(10.9%)
Lesion classification according to the BI-RADS category	
BI-RADS 2	8(12.5%)
BI-RADS 3	20(31.3%)
BI-RADS 4	22(34.4%)
BI-RADS 5	14(21.9%)
Lesion classification after BI-RADS dichotomization	
Malignant lesions	35(54.7%)
Benign lesions	29(45.3%)
Lesion classification after DWIBS/T ₂ fusion interpretation	
Malignant lesions	24(37.5%)
Benign lesions	40 (62.5%)

Table 3. Classification of the lesions according to gold standard

Characteristic	N(%)
<i>Lesion classification according to histopathological diagnosis</i>	
Invasive ductal carcinoma	7(13.5%)
In situ ductal carcinoma	3(5.8%)
Atypical ductal hyperplasia	2(3.8%)
Ductal and lobular carcinoma in situ	1(1.9%)
Invasive lobular carcinoma	3(5.8%)
Mucinous carcinoma	1(1.9%)
Fibroadenoma	14(26.9%)
Fibrocystic change	12(23.1%)
Adenosis	4(7.7%)
Radial scar	1(1.9%)
Fibrosis	1(1.9%)
Others	3(5.8%)
<i>Lesion classification according to the gold standard*</i>	
Benign lesions	48(75%)
Malignant lesions	16(25%)

*The gold standard was represented by a diagnostic strategy, comprising the histopathological diagnosis of target lesions or, in its absence, the patient's disease status after a minimum 6 months follow-up

Pathological examination was available for 52 lesions and follow-up information was used for the remaining 12. All these 12 patients had a disease-free status after a minimum 6 months follow-up, thus they were classified as benign. The most frequent benign lesions were fibroadenomas (n=14, 26.9%) and fibrocystic change (n=12, 23.1%). For the malignant ones, invasive ductal carcinoma was found in 7 cases (13.5%), while invasive lobular carcinoma was found in 3 (5.8%). Information concerning the pathological categories and case classification is depicted in Table 3, Fig. 2.

For the DWIBS/T₂ fusion, contingency table analysis revealed a sensitivity of 62.5% (95% CI:35.4-84.8) and a specificity of 70.8% (95% CI:55.9-83.3) with p=0.03, suggesting that the DWIBS/T₂ fusion was rather more specific than sensitive. The positive likelihood ratio was 2.14, resulting post-examination odds that was more than 2 times higher than the initial one for a "malignant" case on the DWIBS/T₂ fusion. The corresponding negative likelihood ratio was 0.53 showing that for a lesion classified as "benign" by the DWIBS/T₂ fusion, the post-examination odds for breast cancer drop to almost half of the initial ones.

In the case of DCE-MRM there was a sensitivity of 87.5% (95% CI:61.6-98.4) and a specificity of 56.2% (95% CI: 41.1-70.5) with p=0.003, suggesting a more sensitive than specific test. The positive likelihood ratio was 1,99, showing an almost two-fold increase in odds for breast cancer being present in a patient having a "malignant" DCE-MRM examination. The corresponding negative likelihood ratio was 0.22, resulting in a decrease in odds of little more than a quarter for the presence of breast cancer in a "benign" DCE-MRM patient.

The direct analytical comparison of the DWIBS/T₂ fusion and DCE-MRM revealed differences in terms of sensitivity and specificity, although it did not reach statistical significance.

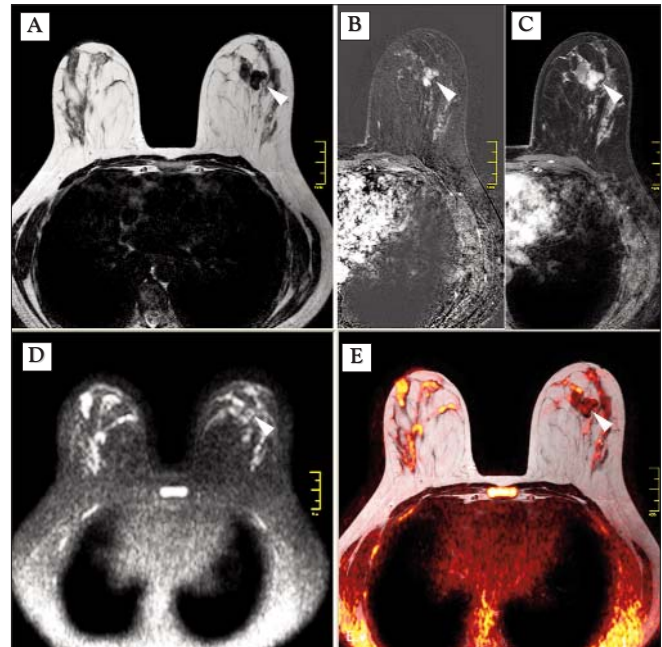


Figure 2. A 46-year old patient with a history of benign breast nodules was admitted for a recent, blackish nipple discharge. The DCE-MRM exam revealed a suspicious lesion in her left breast: a 12/20 mm, solid lobulated mass showing low T₂ signal (A), with strong precocious and late enhancement seen on digital subtraction - (B) and late THRIVE - (C), respectively. Adjacent to the mass, a second dense fluid-filled lesion was noted (low T₂ signal - A), showing only a discrete late enhancement (B, C), suggestive for a ductal ectasia. These lesions were visible on the DWIBS (D) and the DWIBS/T₂ fusion (E); they showed low signal intensity and benign morphological characteristics. The biopsy of the lobulated lesion revealed a sclerosing adenosis

Discussion

In this broad, retrospective cohort study we analyzed a new, revolutionary, anatomical and functional method (DWIBS/T₂ fusion) created by the association of DWIBS to a morphological sequence (T₂). The images obtained thru DWIBS/T₂ fusions provided an insight both in the lesion's diffusion status (a reflection of tumor cellularity, histologic composition, extracellular space – thru DWIBS) and its morphological features (size, borders, shape, contour – thru T₂). This resulted in better lesion conspicuity and localization.

On the other hand, the DCE T₁-weighted scan performed in standard DCE-MRM offered information on the lesion's microvascular network based on the intravascular presence of Gadolinium. The presence and speed of enhancement (thus the necessity for a dynamic scan) indicated that there was a rich vascular supply and fast enhancement meant that the lesion could be considered malignant. According to the BI-RADS lexicon, the final diagnosis could be set only after analyzing the morphological features of the lesion on the anatomical sequences (like T₁). T₂ images are mostly preferred in fusions as they are more sensitive to the presence of inflammation and edema which are depicted in shades of white, more visible than their black equivalents in T₁.

DWIBS/T₂ images were interpreted using a custom protocol based on the original BI-RADS lexicon and assessment categories, replacing contrast enhancement information with functional DWIBS signal intensity. Its clinical performance was assessed by the means of a complex gold standard, a diagnostic strategy, comprising the histopathological diagnosis of the target lesions or, in its absence, the patient's disease status after a minimum 6 months follow-up.

Using our custom interpretation protocol, the DWIBS/T₂ fusion revealed to be a more specific than sensitive: 70.8% (95%CI:55.9-83.3) compared to 62.5% (95%CI:35.4-84.8). By contrast, DCE-MRI proved more sensitive (87.5%; 95%CI:61.6-98.4) but less specific (56.2%; 95%CI:41.1-70.5). In terms of positive likelihood ratios, the DWIBS/T₂ fusion showed an odds increase almost similar to the one of DCE-MRM (2.14 and 1.99, respectively) for a positive result. The negative likelihood ratios revealed a more substantial decrease in the post-test odds for the DWIBS/T₂ fusion than for DCE-MRM in the case of a negative result (0.53 and 0.22, respectively).

Stadlbauer et al. reported good sensitivity and specificity values for DWIBS alone when compared to conventional DWI, but not to DCE-MRM. They performed a full quantitative and qualitative interpretation of DWIBS and found it superior to conventional DWI (13).

To our knowledge, no prior studies using DWIBS/T₂ image fusions in MRM exist in the literature. However, DWIBS/T₂ fusions have been reported related to other pathologies. For example, Nishie et al. has found an important gain in specificity by using DWI/T₂ fusions, compared to standard T₂ and DWI taken alone when evaluating local recurrent pelvic malignancies (15). Similarly, Fischer et al. has reported an improved efficiency of DWI and T₂ when

interpreted side-by-side, as compared to separate interpretation in whole body MRI for detecting malignant tumors (16).

The association between DWI and an anatomical sequence (without fusion) has already been described in the literature, mainly in studies evaluating new, contrast-free MRM examination techniques. Thus, the study performed by Baltzer et al. tested the association of DWI and T₂ without fusion in MRM (unenhanced MRM) for differentiating benign and malignant mass lesions. The authors reported a similar efficiency for the association DWI - T₂ to that of DCE-MRM, but with reduced lesion visibility due to poor spatial resolution (17).

Conclusion

The DWIBS/T₂ image fusion is a new and innovative imaging technique with an improved specificity when compared to DCE-MRM. Created on an user-friendly imaging software, the DWIBS/T₂ image fusion is an accessible and highly reproducible method of enhancing DWIBS by associating anatomical information from T₂. Its use as a complement to DCE-MRM can offer the specificity needed to improve breast cancer detection rates on MRM and subsequently advance towards a new non-contrast MRM examination. However, further studies on larger number of cases are needed.

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Abbreviations

BC – Breast Cancer; DCE-MRM – Dynamic Contrast-Enhanced Magnetic Resonance Mammography; DCE – Dynamic Contrast Enhanced; DICOM – Digital Imaging and Communications in Medicine; DWI – Diffusion Weighted Imaging; DWIBS – Diffusion Weighted Imaging with Background body Signal Suppression; EPI – Echo Planar Imaging; FFE – Fast Field Echo; FOV – Field of View; MRM – Magnetic Resonance Mammography; NSA – Number of Signal Averages; PET/CT – Positron Emission Tomography/Computer Tomography; SENSE – Sensitivity Encoding technique; THRIVE – T₁ contrast-enhanced High Resolution Isotropic Volume Examination; TE – Echo Time; TI – Inversion Time; TR – Repetition Time; TSE – Turbo Spin Echo.

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