Clinical Efficiency of Diffusion Weighted Imaging with Background Body Signal Suppression in Magnetic Resonance Mammography — Choosing a Qualitative or a Quantitative Approach

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Objectives: Diffusion Weighted Imaging with Background Body Signal Suppression (DWIBS) is a new and promising imaging technique designed to improve diagnostic performance of Dynamic Contrast-Enhanced-Magnetic Resonance Mammography (DCE-MRM). The aim of our study was to assess the diagnostic efficiency of both qualitative and quantitative DWIBS in a retrospective cohort study.
Methods: We performed a registry-based study at the Department of Radiology, Lyon Sud Hospital. All consecutive MRM examinations from 02.2010 to 02.2011 were reviewed. DWIBS was interpreted blindly, both qualitatively (lesion characteristics and signal) and quantitatively (Apparent Diffusion Coefficient – ADC). The ADC cut-off value was determined using Receiver Operating Characteristics (ROC) curve analysis. Clinical efficiency indicators were calculated using either the pathological examination or the disease status after a minimum of 6 months follow-up as gold standard.
Results: The lot consisted of 78 women, with a mean age of 50.3±14 years and a total of 112 breast lesions. Qualitative DWIBS found 73 suspicious and 39 non-suspicious lesions, while the gold standard (pathological diagnosis/follow-up) reported 56 benign and 56 malignant ones. The sensitivity and specificity values for qualitative DWIBS were 84% and 53.37%, respectively. ROC curve analysis revealed the best performance for quantitative DWIBS at an ADC of 1.1×10^{-3} mm^2/s, resulting in a sensitivity of 71.4% and a specificity of 76.8%.
Conclusion: DWIBS is a new and improved diffusion technique with a dual and efficient interpretation system applicable in clinical settings. Moreover, its use as a complement to DCE-MRM offers large potential for improving MRM efficiency in breast cancer diagnosis.

Keywords: MRI, mammography, breast cancer

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Introduction

Standard Dynamic Contrast-Enhanced Magnetic Resonance Mammography (DCE-MRM) is considered the most sensitive method for diagnosing invasive breast cancer; the reported sensitivity is as high as 89–100% [1–5]. However, the specificity of DCE-MRM is low and heterogeneous, ranging from 65% to 93% [1–5]. In an effort to improve DCE-MRM specificity in breast cancer diagnosis, Diffusion Weighed Imaging (DWI) could represent a potential candidate [6].

DWI is a new Magnetic Resonance Imaging (MRI) sequence that analyses the diffusivity of water molecules in tissues [7]. Water diffusion restriction is found in malignant breast tumors as a direct consequence of their generally high cellularity. This is depicted as a high intensity DWI signal [7].

Image quality in MRM using DWI is an important issue, as breast tissue composition and topography makes it subject to a large array of artifacts (chemical shift, magnetic susceptibility and breathing). This results in an impaired image resolution and quality, making DWI interpretation difficult [8].

A revolutionary solution was proposed in 2004 when Takahara et al introduced a free-breathing DWI technique called DWIBS (Diffusion Weighted whole body Imaging with Background body signal Suppression) [9]. This new sequence offered the possibility of free-breathing, with an improved examination speed and an important decrease in artifacts. Besides that, DWIBS was further characterized by heavy diffusion-weighting (with b values up to 1000–1500 s/mm^2) and an efficient fat suppression (using Short TI inversion recovery – STIR), resulting in an optimum background signal suppression and improved lesion conspicuity [8–10].

DWI can be interpreted in triple fashion: qualitative, quantitative or both [11]. Qualitative DWI is performed by directly appreciating benign or malignant lesion characteristics from the DWI image (margins, shape and signal intensity) [11,12]. On the other hand, quantitative DWI diagnosis is obtained by interpreting the apparent diffusion coefficient (ADC), a parameter calculated from the signal intensity of the lesion, taken at different diffusion weightings [11,13].

Literature data concerning the use of both qualitative and quantitative DWIBS in MRM is scarce. To our knowledge, only one prior study evaluated the use of quantitative DWIBS in MRM and demonstrated better results when using DWIBS compared to classical DWI. However, the authors did not compare DWIBS to conventional DCE-MRM [8].

The aim of our study was to evaluate the diagnostic efficiency (in terms of sensitivity, specificity, positive and

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negative likelihood ratios) of both qualitative and quantitative DWIBS compared to standard DCE-MRM in a retrospective cohort study. The reference examination (gold standard) in our study was the pathological diagnosis of the corresponding breast lesions. When the pathological result was not available, the final diagnosis was set based on the patient disease status after a minimum 6-month follow-up.

Methods

Selection protocol

We retrospectively reviewed the MRI database from the Department of Radiology, Lyon Sud Hospital, France. A total of 300 consecutive MRMs performed from February 2010 to February 2011 and their corresponding pathology reports were reviewed for study protocol consistency.

A series of strict inclusion and exclusion criteria were then applied to all patients and our study group was created. It consisted of 78 patients, summing up to 112 examined lesions.

All patients with good quality exams with a full scan protocol, including DWIBS were included in our study. DWIBS images were considered adequate only if they were artifact-free and taken at a b value of 1000 s/mm^2. All study examinations had to contain at least one target lesion that was either biopsied/operated or had a follow-up of at least 6 months.

Large invasive gestures performed on the breast before MRI can be responsible for extensive hematomas and scarring and can influence interpretation. Considering this, we accepted only patients that had minimally invasive gestures (breast biopsies or FNA) performed before their first MRMs.

Patients with multiple examinations were identified and only one examination per patient was selected, mainly the one performed before extensive invasive gestures (breast surgery). A history of breast surgery (including breast implants), radiation or chemotherapy performed in the 6 months period previous to the examination was considered an exclusion criterion, as the extensive edema and scars would have resulted in a faulty interpretation. Patients with examinations bearing important artifacts or technical errors were also excluded.

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) with one unenhanced and multiple contrast-enhanced acquisitions, 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 (b0, b500 and b1000) using the SENSE technique: FOV 340 mm, TR 8403, 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).

MRM Interpretation

All MRM examinations were analyzed off-line using a DICOM viewer (K-PACS, IMAGE Information Systems, Ltd). Using the MRM reports, the study team identified the target lesions both on the DCE-T1 and DWIBS images, prior to interpretation. During interpretation the radiologist had access only to the DWIBS images and was aware of the location of the biopsied lesion, but had no information on other sequences, pathological diagnosis or follow-up results. Qualitative DWIBS interpretation was performed and lesions were classified according to signal intensity as benign (low intensity lesions) or suspicious (high intensity lesions). For each lesion the ADC was calculated using the following formula:

$$ADC = -\,{}^{1}/_{b} \ln\left({}^{S_{1000}}/_{S_0}\right)$$

where b stands for the b-value of the DWIBS sequence (i.e. b=1000s/mm^2 in our study) and S1000 and S0 are the lesion signal intensities measured on the diffusion-weighted image (b=1000 s/mm^2) and the reference one (b=0 s/mm^2), respectively. The signal intensities (mean pixel intensities) were obtained by drawing Regions of Interest (ROIs) over the lesions at their maximum intensity on the axial images. In foci, ADC calculation was not possible, as the software gave no possibility of drawing small-enough ROIs adapted to the small lesion size. The signal intensity values were influenced by surrounding tissues resulting in a faulty interpretation. As a consequence, foci were excluded from ADC analysis.

ADC calculation was performed in the Excel Software (Microsoft Office 2007, Microsoft, Redmond, USA) and all resulting values were collected in the study database along with the original interpretation, qualitative DWIBS and the pathology result.

The original DCE-MRM interpretations had been performed by senior radiologists from the Department of Radiology, Lyon Sud Hospital trained in breast imaging. This was done using the special BI-RADS MRI lexicon and each examination was classified using the BI-RADS scale [14]. 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. The pathological examination and, when not available, the disease status after a minimum 6-month follow-up was considered as the final diagnosis (for the gold standard).

Statistical Analyses

Data analysis was performed using the EpiInfo v 3.5.3 (Centers for Disease Control and Prevention, Atlanta, USA) and the IBM-SPSS V19.0 demo (SPSS Inc, an IBM company) software. After dichotomization of the initial BI-RADS classification on DCE-MRM as benign (1, 2, 3) and malignant (4, 5, 6), clinical efficiency indicators (sensitivity, specificity, positive and negative likelihood ratio) were calculated for qualitative DWIBS and DCE-MRM, both referring to the gold standard. ADC values were analyzed according to lesion type and final diagnosis using the Mann-Whitney and Kruskal-Wallis tests.

Receiver Operating Characteristic (ROC) curve analysis was used to assess the performance of ADC thresholds for differentiating benign and malignant lesion. Boxplot charts were generated for the ADC values corresponding to all pathologic conditions.

Ethical issues

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

Results

As mentioned above, our final study group consisted in 78 patients, with an average age of 50.3±14 years. There were a total of 112 examined lesions with a mean size of 19±13.6 mm, consisting mainly in masses (n=88, 78.6%).

The original DCE-MRM interpretation found a majority of BI-RADS 4 (suspicious abnormality, biopsy should be considered) lesions (n=36, 32.1%). The BI-RADS 5 (highly suggestive of malignancy) and BI-RADS 6 (known, biopsy-proven malignancy) categories followed closely with 27 (24.1%) and 25 (22.3%) cases, respectively. After BI-RADS dichotomization at a cut-off value of 4, 89 (79.5%) lesions were classified as malignant. Qualitative DWIBS found 73 (65.2%) suspicious lesions. Detailed data concerning lesion characteristics, BI-RADS and qualitative DWIBS classification are depicted in Table I.

Table I. Descriptive analysis of patient and lesions' characteristics, BI-RADS classification and qualitative DWIBS classification

Characteristic (n=78)	Mean±SD or N (%)
Patient age	50.3±14 years
Lesion size (A total of 112 lesions)	19±13.6 mm
Lesion size category	
Less than 1 cm	37 (33%)
Between 1 and 2 cm	28 (25%)
Larger than 2 cm	47 (42%)
Lesion type	
Focus	11 (9.8%)
Mass	88 (78.6%)
Non-mass	13 (11.6%)
ACR classification categories	
BI-RADS 1	0 (0%)
BI-RADS 2	11 (9.8%)
BI-RADS 3	13 (11.6%)
BI-RADS 4	36 (32.1%)
BI-RADS 5	27 (24.1%)
BI-RADS 6	25 (22.3%)
DCE-MRM lesion classification after dichotomization of the BI-RADS categories	
DCE-MRM discovered lesions classified as benign	23 (20.5%)
DCE-MRM discovered lesions classified as malignant	89 (79.5%)
DWIBS classification of discovered lesions	
Benign DWIBS lesions	39 (34.8%)
Suspicious DWIBS lesions	73 (65.2%)

The pathological examination was available for 100 le-

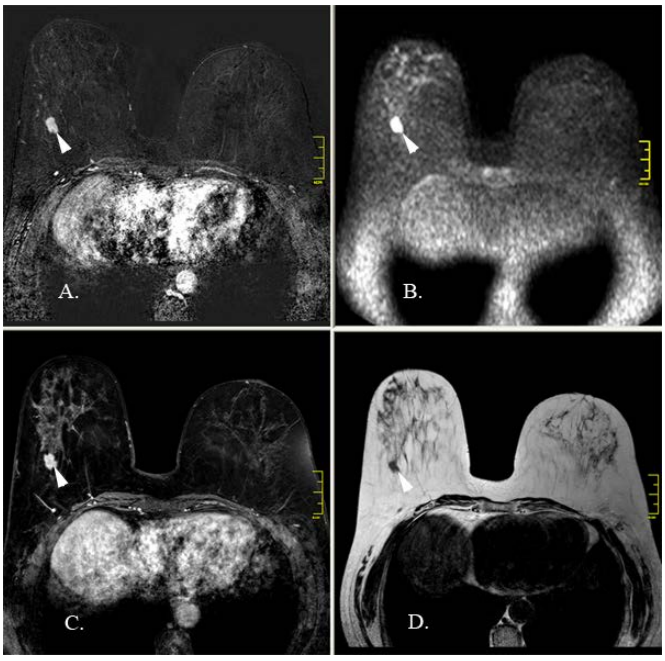

Fig. 1. A 71-year-old patient with a history of breast cancer in the left breast, presented with a palpable nodule in the right breast. MRM revealed a 13 mm mass in the lower external quadrant (arrowhead) with an irregular contour and low signal on T2-weighted images (D) and a strong mass enhancement on digital substraction (A) and THRIVE (C) images. Qualitative DWIBS (B) found this lesion suspicious based mainly on its highly intense signal. The pathological examination of the surgical specimen found a poorly-differentiated infiltrative ductal carcinoma.

Table II. Descriptive ADC analysis results according to histological classification and lesion type

Lesion type	ADC descriptive for all pathologic categories (*10^3 mm^2/s)					
	N (%)	Mean	SD	Minimum	Median	Maximum
Invasive ductal carcinoma	34	0.9	0.2	0.6	0.9	1.5
In situ ductal carcinoma	6	1.2	0.3	0.7	1.2	1.6
Atypical ductal hyperplasia	3	1.2	0.6	0.8	1.0	1.9
Ductal and lobular carcinoma in situ	1	1.1	0	1.1	1.1	1.1
Invasive lobular carcinoma	12	1.0	0.5	0.2	0.8	2.1
Mucinous carcinoma	3	1.9	0.4	1.6	1.7	2.3
Fibroadenoma	11	1.2	0.9	-1.6	1.4	1.8
Fibrocystic change	23	1.2	0.3	0.6	1.2	1.8
Adenosis	3	1.3	0.2	1.1	1.3	1.4
Radial scar	3	1.1	0.4	0.8	1.1	1.7
All benign lesions*	56	1.3	0.5	-1.6	1.3	2.2
All malignant lesions	56	1.0	0.4	0.2	0.9	2.3
Benign mass lesions	37	1.2	0.6	-1.6	1.4	2.1
Malignant mass lesions	51	1.1	0.4	0.6	0.9	2.3
Benign non-mass lesions	8	1.3	0.2	1.1	1.2	1.7
Malignant non-mass lesions	5	0.7	0.3	0.2	0.7	1.1
Malignant non-mass lesions	5	0.7	0.3	0.2	0.7	1.1

*All lesions, including the 12 follow-up ones are included resulting in a total of 112.

sions, summing up to 44 benign and 56 malignant ones. For the remaining 12 lesions, follow-up information was used. As these patients were disease-free for at least 6 months following the initial discovery, all these lesions were classified as benign.

The most frequent benign lesions were fibrocystic change (n=23, 52.2%) followed by fibroadenomas (n=11.25%). In the malignant group, the majority, 34 (60.7%), were invasive ductal carcinomas, followed by 12 (21.4%) invasive lobular carcinomas. Mucinous carcinoma appeared in 3 (5.3%) cases.

ADC values were calculated for each target lesion and all values were stratified according to and final pathological and follow-up diagnoses as seen in Table II.

In benign lesions the mean ADC value was higher than in malignant ones (1.3±0.5 mm^2/s versus 1.0±0.4 mm^2/s), $p<0.05$, with variations corresponding to different lesion types. Masses and non-mass lesions had different ADC values according to the final diagnosis. In benign lesions, non-mass lesions had a higher mean ADC (1.3±0.2 mm^2/s) than masses (1.2±0.6 mm^2/s), p=0.796.

Malignant lesions had also different ADC values according to lesion type: 1.1±0.4 mm^2/s for masses and 0.7±0.3 mm^2/s for non-mass lesions (p=0.07). According

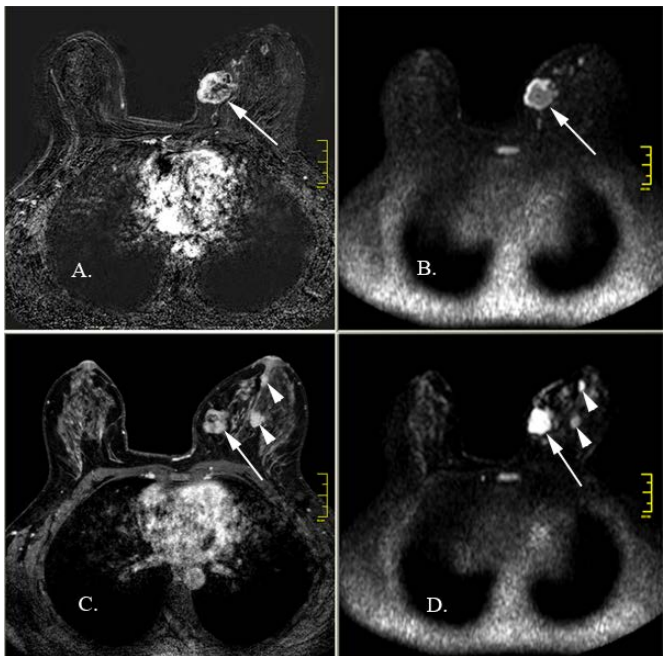

Fig. 2. A 44-years-old patient presented with a large palpable mass in the left breast localized at the union of her left internal quadrants. The ultrasound examination raised suspicion for multiple lesions. MRM found a 38 mm suspicious nodule (arrows) showing an inhomogenous rapid contrast uptake on substraction images (A). This lesion has a high signal on T2 images and a low signal on T1 ones suggestive for a fluid content. This is confirmed by DWIBS (B) that shows intense restriction on the lesion borders. Several similar nodules (arrow) were found both on THRIVE (C) and DWIBS (D). The pathological exam revealed mucinous carcinoma in all revealed nodules.

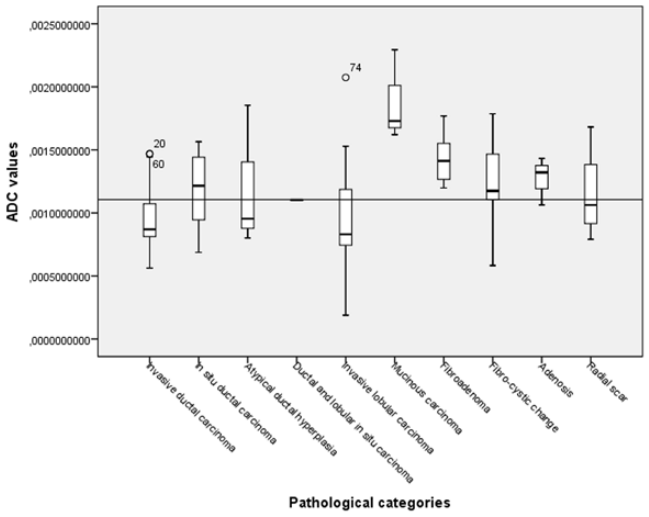

Fig. 3. All ADC values were regrouped on a box-plot chart. Based on the final benign or malignant diagnosis, a large overlap between the different pathological categories can be observed.

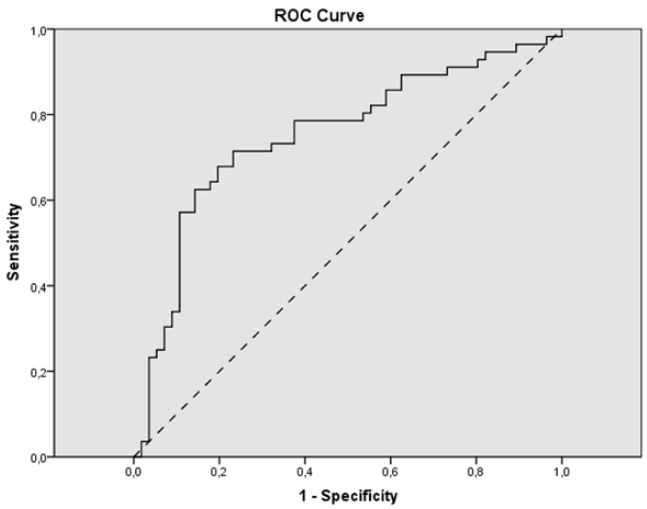

Fig. 4. ROC curve analysis was performed for the different ADC values in order to determine the adequate cut-off point for maximum diagnostic efficiency.

to histological subtypes, the highest mean value was found in adenosis (1.3±0.2 mm^2/s) while the lowest was found in invasive ductal carcinoma (0.9±0.2 mm^2/s). Mucinous carcinoma had a very high ADC value (1.9±0.4 mm^2/s), even higher than in most benign lesions.

All ADC values were joined in a boxplot chart and the corresponding value intervals were depicted. As seen in Figure 3, there is a large overlap between both benign and malignant lesions and also between different histological subtypes.

Contingency table analysis for qualitative DWIBS revealed a Sensitivity of 84% (95%CI: 71.7–92.3) and a Specificity of 53.57% (95%CI: 39.76–67.05) with $p<0.0001$. The corresponding positive and negative likelihood ratios were 1.81 and 0.52.

For DCE-MRI the analysis found a Sensitivity of 98% (93.62–99) and a Specificity of 41.07% (28.11–55.04) with $p<0.0001$. The positive likelihood ratio was 1.66 while the negative one was 0.05.

For quantitative DWIBS, an adequate ADC cut-off value was determined using Receiver Operating Characteristic (ROC) curve analysis (Figure 4). The Area Under the Curve (AUC) had a value of 0.752±0.48 (95%CI: 0.658–0.845) with the following lower and upper bounds: 0.658 and 0.845. The analysis showed that the ADC value of 1.1×10^{-3} mm^2/s offered the best performance for quantitative DWIBS, resulting in a Sensitivity of 71.4% and a Specificity of 76.8%.

Discussion

In this large-scale retrospective cohort study the diagnostic role of a new, promising MRM sequence (DWIBS) was evaluated and the results obtained using its dual interpretation method were compared to the ones of standard DCE-MRM. The gold standard (reference examination) in our study was represented by a diagnostic strategy, comprising the histopathological report of target lesions and disease status of the patient after a minimum follow-up of 6 months.

We performed both a qualitative and a quantitative interpretation (ADC) of DWIBS and assessed their efficiency separately [11,12,15]. Using the current interpretation method, qualitative DWBS had a good sensitivity 84% (95%CI: 71.7–92.3) and a medium specificity 53.57% (95%CI: 39.76–67.05). In comparison, DCE-MRI had a better sensitivity but a poorer specificity which highlights a better accuracy for qualitative DWIBS. By choosing the cut-off value of 1.1×10^{-3} mm^2/s quantitative DWIBS revealed a sensitivity of 71.4% and a specificity of 76.8%, resulting in an important gain in specificity.

We obtained a smaller mean value for ADC in malignant lesions, which is in agreement to the results of Stadlbauer et al although the absolute ADC values differ [8]. We consider that our results on DWIBS can be integrated in the general pool of ADC values for benign and malignant lesions, with the reserve that there is a different cut-off value according to each author [6,7,16,17]. Mucinous carcinoma revealed a distinct ADC pattern mainly because of its special tissue composition. The resulting ADC value was 1.9±0.4 which was higher than for most benign and malignant lesions. This is in agreement with other studies dedicated to mucinous carcinoma diagnosis using DWI [7].

Although there is a difference between the mean ADC values of different lesions, one can find a strong overlap between the confidence intervals for each pathological type. Our ADC values for the different pathologically-verified lesions included in the study were different from those of Stadlbauer et al [8]. This can be explained by the different population composition in terms of pathologies and proportions. Also, there are important differences between the two DWIBS protocols.

In our study, the case selection was made from the clinical registries using inclusion criteria that were certified in other literature studies [8,12,13,18,19]. Several authors excluded the already-biopsied BI-RADS 6 lesions because they were considered as a potential bias source [18,19]. As the Lyon Sud hospital is a major reference center for breast imaging and treatment, the majority of patients are referred from other centers and they generally had biopsies performed before the MRM examination. After an initial analysis of the registries, we considered that by rejecting them it would result in a major loss of most malignant tumors, resulting in a faulty ADC analysis. This is why we decided to include these cases in the study, but only if the biopsy was not a cause for an artifacted examination.

Our study has strengths and weaknesses. The main strength resides in its large number of patients, the uniform acquisition protocol and experts' interpretation. The main weakness comes from the comparison system between the two methods: a time tested one with a rather uniform interpretation system and a new one with interpretation styles specific to each research group. Warren et al demonstrated in their wide review on MRM technical

details, a large inhomogeneity concerning the examination protocols and reporting methods for MRM, making results comparison challenging [20]. We agree that these findings are valid also in the field of DWI in MRM.

Conclusion

DWIBS is a new and improved DWI technique that can offer a dual and efficient interpretation system applicable to the clinical settings. Due to its complex and versatile (ADC) interpretation method, DWIBS can be used as an efficient method for breast cancer diagnosis. Moreover, its use as a complement to DCE-MRM offers large potential for improving MRM diagnostic efficiency.

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Conflicts of interest statement

There are no conflicts of interest.

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