Diffusion-Weighted Imaging in Breast MRI* – An Easy Way to Improve Specificity

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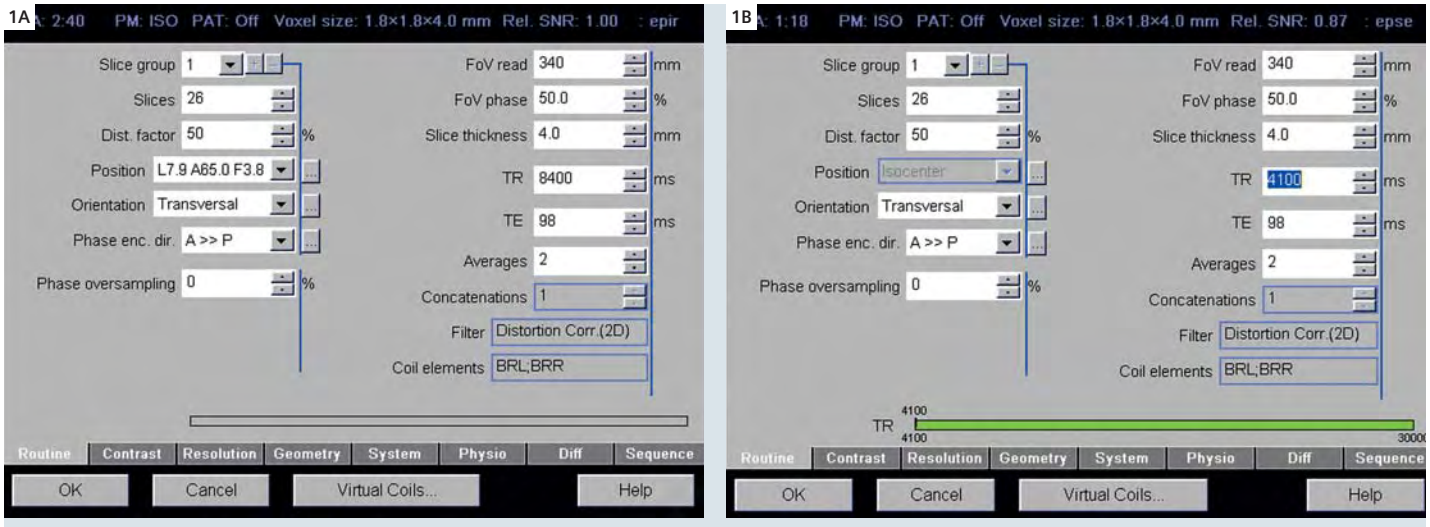
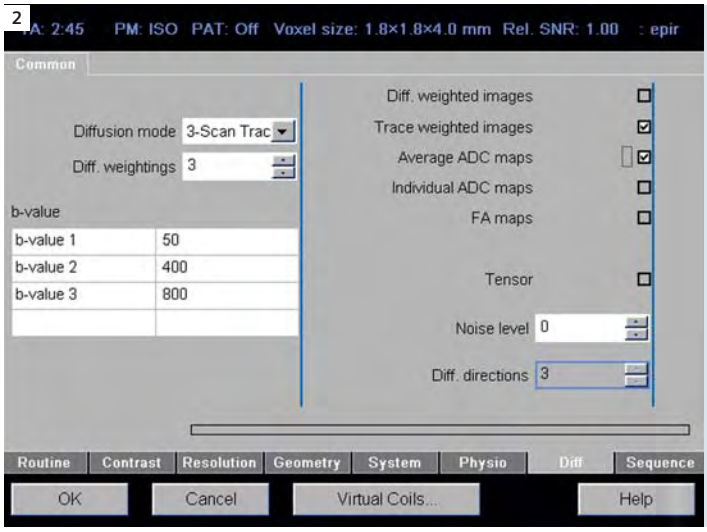
Introduction

Classic breast magnetic resonance imaging (MRI) is based on the enhancement pattern of lesions in dynamic breast MRI, and morphologic changes [1–3]. With these two criteria breast MRI has a sensitivity of about 85–99% in detecting malignant breast lesions [1–10]. However, there is an overlap of these criteria with benign lesions which leads to a reported specificity of about 40 to 80% [1, 10, 11]. There is an increasing number of congress abstracts and published studies that the specificity of breast MRI could be increased using diffusion-weighted (DW) sequences [12–16]. DW MRI is based on the principle that random motion of molecules during the interval of excitation and signal measurement reduces the amplitude of the resulting signal. The application of appropriate pulse sequences (using, for example, bipolar gradient pulses in one or several directions) allows the measurement of the signal cancellation due to diffusion in the given direction. While normal tissue exhibits gross signal loss, areas with restricted motion of molecules like densely packed tumor cells show less signal loss and become bright in diffusion-weighted images. The value of the diffusion of water in tissue is called the apparent diffusion coefficient (ADC). Based on the diffusion-weighted images an ADC map can be calculated which shows the ADC value of each voxel in every slice. Restricted water movement in tumors with high cellularity leads to smaller ADC values [13]. In some organs, especially the brain, the direction of the diffusion contains important information which can be used, for example, for tracking of fibers by diffusion tensor imaging in many directions. However, in tumor clusters the diffusion is vastly restricted in every direction and therefore it is sufficient to measure DWI of the breast in just one orientation. In most applications the diffusion gradients are integrated in echo planar imaging (EPI) sequences which exhibit high signal intensity in areas with restricted diffusion as well as in fatty tissue. Furthermore, the fat signal is displaced in the direction of the chemical shift as compared to the water signal. This makes fat saturation techniques necessary to identify



1 Sequence card of the diffusion-weighted EPI STIR **(A)** and the diffusionweighted EPI fs sequence **(B)**.



2 Parameters in the diffusion card.

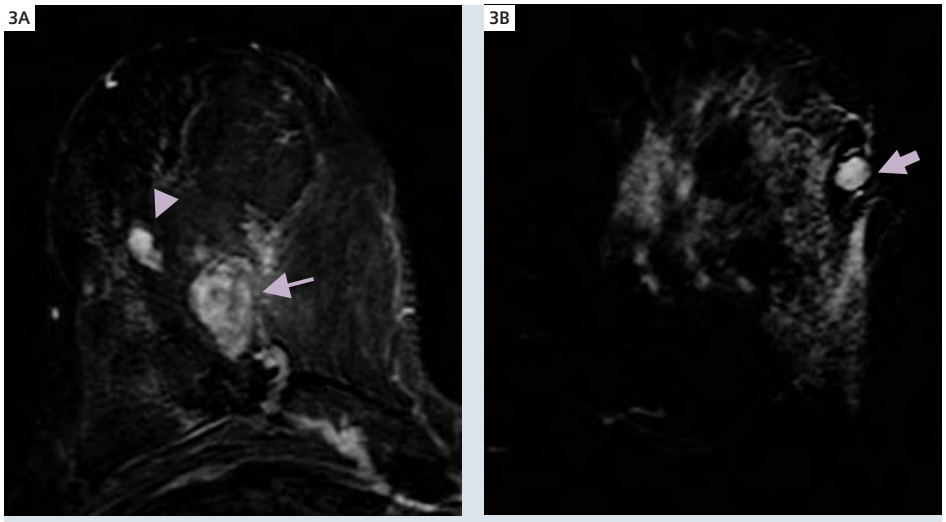
the lesions in the diffusion-weighted images. There are two main possibilities for fat saturation: spectral fat saturation (fs) and a 180° pre-pulse with a short inversion time (STIR or TIRM).
In *syngo* MR B13 both methods can be applied. In our setup we acquire the DW images in axial slice orientation using echo planar imaging pulse sequences incorporating diffusion gradients. TR/TE/TI for the inversion recovery diffusion-weighted EPI (DW EPI STIR) are 8400/98/180 ms (Fig. 1A). The fat saturated diffusion weighted EPI (DW EPI fs) pulse sequence is scanned with a TR = 4100 ms and a TE = 98 msec (Fig.1B). Both sequences are acquired with a FoV of 340 x 170 mm, matrix: 192 x 96 and a slice thickness of 4 mm. We apply the DW sequences prior to the dynamic scan as the T1 relaxation due to the contrast agent will cause changes to the inversion of the tissue and thus can have a strong impact. All DW measurements were acquired with two averages of 26 slices and b-values of 50, 400 and 800 using 3-scan trace calculation, i.e. the sum of the diagonal elements D_{xx}, D_{yy} and D_{zz} of the diffusion tensor is calculated for each slice position and b-value (Fig. 2). With the MAGNETOM Avanto scanner the DW EPI STIR takes 2:40 minutes while DW EPI fs is performed in 1:18 minute. ADC maps are calculated automatically on the basis of the b50, b400 and b800 images using the scanner software. As mentioned above we suppose that a diffusion gradient in just one direction would also lead to sufficient results.

Image interpretation

Image interpretation starts like conventional breast MRI. If a lesion is visualized in the dynamic scan (Fig. 3) it has to be identified in the corresponding slice of the diffusion weighted images. As a second step, a region-of-interest (ROI) is drawn in the centre of the lesion on the b-800 DWI and copied to the ADC map (Fig. 4). The scanner software provides the mean value within the ROI which equals the ADC value (multiplied by 10^{-3} mm²/s). If the lesion is not visible in the b-800 images, the location of the lesion can be identified in the b-400 or b-50 image. Where the lesion is not visible in the b-50, b-400 or the b-800 image the ADC value cannot be evaluated. Lesions smaller than 5 mm and lesions with central necrosis and an enhancing rim smaller than 5 mm are often hard to delineate in the DWI or lead to wrong ADC values. So we do not recommend evaluating such lesions with DWI.

Results of DWI of the breast

In a pilot study with 56 patients and 69 histologically proven lesions > 5 mm only 5/69 lesions could not be evaluated with DW-MRI [17]. Three of these five lesions were not visible in the DWI sequences and therefore could not be matched with the ADC map. Histology of these lesions were one septated invasive lobular carcinoma with two tumor portions of 9 and 6 mm, one recurrent invasive ductal carcinoma with a maximum diameter of 10 mm in the MRI and one tubulolobular invasive carcinoma with 7 mm. In two patients the DWI images were not evaluable due to patient movement. ADC values were finally measured in 51 women (age 50



3 Your diagnosis? Subtraced image of the dynamic contrast enhanced sequence: **(A)** 45- year-old woman with a palpable mass and two suspicious lesions with blurred borders. The bigger one with inhomogeneous contrast enhancement (small arrow) and a smaller non-palpable lesion with nearly homogenous enhancement. **(B)** 41-year-old woman with a suspicious lesion in mammography and a sharp lined lesion in the outer-upper quadrant (big arrow).

Table 1: Histology of 69 lesions with DW sequences

Histology, N = 69	IDC	ILC	DCIS	Rare	FA	FD	BP	total
Evaluated	39	6	1	3	8	6	1	64
Not evaluated	2	2	0	1	0	0	0	5

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, DCIS: ductal carcinoma in situ, Rare: rare malignant tumors (medullary, tubular carcinoma, carcinosarcoma, angiosarcoma), FA: fibroadenoma, FD: fibrocystic disease, BP: benign phylloides tumor.

Table 2: Apparent diffusion coefficient (ADC) values (10^{-3} mm²/s) of all evaluated lesions (b = benign, m = malignant) in both MR diffusion weighted sequences

			ADC values (10^{-3} mm²/s)							
	n		Mean ± SD		Maximum		Minimum		95% CI	
	b	m	b	m	b	m	b	m	b	m
DW EPI STIR	15	45	1.92 ± 0.53	0.91 ± 0.24	3.20	1.43	1.10	0.35	1.62-2.22	0.83-0.98
DW EPI fs	15	49	1.76 ± 0.42	0.90 ± 0.18	2.58	1.19	1.21	0.34	1.53-2.00	0.85-0.96

SD: Standard deviation, EPI STIR: echo planar imaging with short time inversion recovery, EPI fs: echo planar imaging with spectral fat saturation.

years ± 15 years) with 64 focal mass lesions (15 benign, 49 malignant).
The mean longest diameter of the evaluated lesions was 17 ± 10 mm (benign 17 ± 10 mm, malignant lesions 17 ± 10 mm). The size of the ROI for the ADC value calculation was 24 ± 11 mm² (benign 27 ± 13 mm², malignant lesions 23 ± 10 mm²). There was no statistical difference of the size of the lesions or the ROI between benign or malignant masses. In the DW EPI STIR sequence the ADC values of 4 lesions could not be evaluated correctly due to patient movement between the b-50 and the b-800 sequence. So the ADC values of 60 lesions in the DW EPI STIR sequence and 64 lesions in the DW EPI fs sequence were evaluated (table 2). Lesion delineation was significantly better in the EPI fs sequence than in the EPI STIR sequence.
The mean ADC values were 1.92 ± 0.53 and 1.76 ± 0.42 x 10^{-3} mm²/s in benign lesions (DW EPI STIR and, DW EPI fs), and 0.91 ± 0.24 and 0.90 ± 0.18 x 10^{-3} mm²/s in malignant lesions, respectively. There was a highly significant difference in ADC values between benign and malignant lesions in both DW sequences. In the DW EPI STIR sequence the range of the ADC values of benign lesions was 1.10 – 3.20 x 10^{-3} mm²/s (95% CI: 1.62 – 2.22 x 10^{-3} mm²/s) and in malignant lesions 0.35 – 1.43 x 10^{-3} mm²/s (95% CI: 0.83 – 0.98 x 10^{-3} mm²/s, table 2). Assuming a threshold of 1.26 x 10-3 mm²/s for the DW EPI STIR sequence, 1/15 benign lesion and 1/45 malignant lesion would be misdiagnosed. In the DW EPI fs sequence the range of ADC values of benign lesions was 1.21 – 2.58 x 10^{-3} mm²/s (95% CI: 1.53 – 2.00 x 10^{-3} mm²/s) and of malignant lesions 0.34 –1.19 x 10^{-3} mm²/s (95% CI: 0.85 – 0.96 x 10^{-3} mm²/s) . There was no overlap in the ADC values of benign and malignant lesions in the DW EPI fs sequence.

Discussion

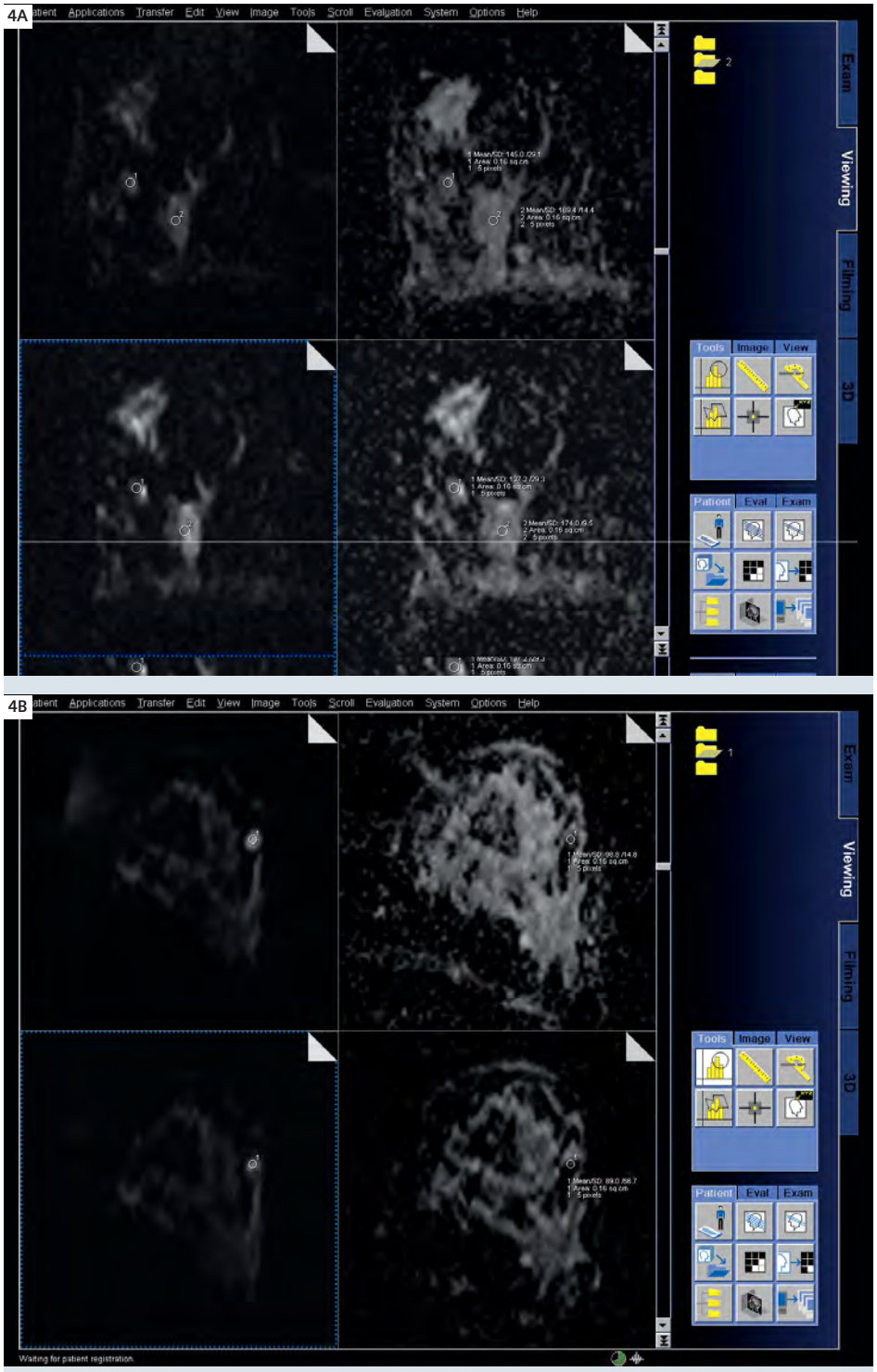
Detection of breast lesions has become more sensitive in mammography, ultrasound and MRI due to technical developments in the last years. Digital mammography seems to be more sensitive for breast lesion detection in dense breasts [18]. Higher spatial resolution leads to higher detection rates in ultrasound [19] and MRI.
However, the characterization of the detected lesions can be difficult. Up to now breast MRI is analyzed according to morphologic criteria, the enhancement kinetics and the T2 characteristic of breast lesions. However, all these criteria show an overlap between benign and malignant lesions [2, 4, 20-22]. In this situation an additional feature to characterize suspicious lesions would be helpful in order to decrease the number of invasive breast procedures. Prior studies with breast MRI and DWI have already addressed this question and show promising results [13-15]. In our study we compared two different DW sequences, an EPI STIR sequence and an EPI sequence with spectral fat saturation. Both DW sequences revealed a significant difference between ADC values of malignant and benign breast lesions. Comparing both sequences there was no overlap between the ADC values of benign and malignant breast lesions in the DW

sequence with spectral fat saturation. Assuming a threshold of 1.26 x 10^{-3} mm^2/s, 2/60 lesions (1 benign and 1 malignant) would have been misclassified in the DW EPI STIR sequence.

In our opinion placement of the ROI is the crucial point in analyzing DWI. In most prior studies the ROI was placed with direct reference to the subtracted images of the dynamic contrast enhanced sequence. However, the spatial localization of a lesion in the dynamic contrast enhanced sequence is not necessarily the same as in the DW images due to distortion of echo planar images or patient movement between the DW sequence and the dynamic contrast enhanced sequence. Especially in small lesions this may lead to inadequate placement of the ROI. To overcome this problem the easiest and possibly more exact method to evaluate the ADC value is to localize the lesion in the contrast enhanced sequence, match it with the corresponding lesion in the DWI, select a ROI in the DWI and copy this ROI to the ADC map (Fig. 4). Using this method, lesion delineation in the DW sequence plays an important role for ADC measurement. In terms of lesion delineation the EPI fs sequence was significantly better than the EPI STIR sequence. This can be explained with the reduced signal-to-noise ratio (SNR) with inversion recovery as opposed to fat saturation.

Lesion delineation may also have an impact on the ADC map. Calculating the ADC map is a voxel per voxel analysis in the b-50, b-400 and b-800 DWI. A good delineation of the lesion in all three DW measurements should result in a sharp edged and homogenous ADC map of this lesion and vice versa. In our study the better lesion delineation in the DW EPI fs sequence corresponded with a significant lower standard deviation within the ROI in the ADC measurements.

There are some limitations of DW MRI of the breast. Patient movement between the acquisitions of the three DW sequences leads to wrong ADC values. In our study four lesions scanned with the EPI STIR



4 DWI (b=800, left side) of the corresponding lesions in figure 3 and the calculated ADC-maps (right side). Upper row: DW EPI fs, lower row DW EPI STIR. A region of interest was drawn in the centre of the lesions and copied in the ADC-map. **(A)** The ADC value of the bigger lesion reveals 1,7 x 10^{-3} mm^2/s and the EPI fs and EPI STIR sequence. The ADC value of the smaller lesion is 1.5 x 10^{-3} mm^2/s (EPI fs) and 1.4 x 10^{-3} mm^2/s (EPI STIR). Histology of both lesions was a fibroadenoma. **(B)** The ADC value of the solitary lesion is 1.0 and 0.9 x 10^{-3} mm^2/s (DW EPI fs and DW EPI STIR) Histology of the lesion was an invasive ductal carcinoma.

sequence were excluded from the evaluation due to patient movement. The reason for this may be the longer acquisition time of the EPI STIR sequence compared to the EPI fs sequence (2 min 40 s vs. 1 min 18 s) which makes patient movement more likely. But even under optimal circumstances DWI can fail to categorize breast lesions. Some lesions cannot be visualized in the DWI and therefore the exact localization of the ROI in the ADC map cannot be determined. In our study 3/69 lesions were not visualized in DWI and could not be evaluated. This ratio would be higher if lesions smaller than 5 mm had been analyzed. However, according to Liberman et al. there is a low likelihood of cancer in lesions smaller than 5 mm [23]. Malignant lesions with central necrosis often show high ADC values in the area of necrosis [24, 25] and the rim of the lesion may be too thin for correct ROI placement. Non focal mass lesions as often seen in DCIS may not be categorized correctly with DWI even with a small ROI due to diffuse tumor spread and partial volume effects [15]. Carcinoma with very high signal intensities in T2-weighted images – like mucinous tumors – could result in misleading ADC values due to different tumor cell packing compared to classic intraductal breast cancer [26]. Despite these limitations DWI of the breast provides additional information to characterize focal breast lesions in a fast and easy way and will hopefully help to reduce invasive procedures.

*Some of the concepts and information presented in this paper are based on research and are not commercially available in the U.S.

Conclusion

DW MRI of the breast with EPI fs and EPI STIR sequences has a high potential to differentiate between benign and malignant breast lesions. Due to significantly better lesion delineation, better selectivity and shorter acquisition time the DW EPI fs sequence is superior.

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References

1 Macura KJ, Ouwerkerk R, Jacobs MA, et al. Patterns of enhancement on breast MR images: interpretation and imaging pitfalls. Radiographics 2006; 26:1719-1734; quiz 1719.

2 Schnall MD, Blume J, Bluemke DA, et al. Diagnostic architectural and dynamic features at breast MR imaging: multicenter study. Radiology 2006; 238:42-53.

3 Szabo BK, Aspelin P, Wiberg MK, et al. Dynamic MR imaging of the breast. Analysis of kinetic and morphologic diagnostic criteria. Acta Radiol 2003; 44:379-386.

4 Bluemke DA, Gatsonis CA, Chen MH, et al. Magnetic resonance imaging of the breast prior to biopsy. Jama 2004; 292:2735-2742.

5 Wiener JI, Schilling KJ, Adami C, et al. Assessment of suspected breast cancer by MRI: a prospective clinical trial using a combined kinetic and morphologic analysis. AJR Am J Roentgenol 2005; 184:878-886.

6 Bedrosian I, Mick R, Orel SG, et al. Changes in the surgical management of patients with breast carcinoma based on preoperative magnetic resonance imaging. Cancer 2003; 98:468-473.

7 Heywang-Kobrunner SH, Bick U, Bradley WG, Jr., et al. International investigation of breast MRI: results of a multicentre study (11 sites) concerning diagnostic parameters for contrast-enhanced MRI based on 519 histopathologically correlated lesions. Eur Radiol 2001; 11:531-546.

8 Kaiser WA. [Magnetic resonance tomography of the breast. The results of 253 examinations]. Dtsch Med Wochenschr 1989; 114:1351-1357.

9 Kinkel K, Helbich TH, Esserman LJ, et al. Dynamic high-spatial-resolution MR imaging of suspicious breast lesions: diagnostic criteria and interobserver variability. AJR Am J Roentgenol 2000; 175:35-43.

10 Kuhl CK, Mielcareck P, Klaschik S, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? Radiology 1999; 211:101-110.

11 Fischer U, Kopka L and Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. Radiology 1999; 213:881-888.

12. Sinha S, Lucas-Quesada FA, Sinha U, et al. In vivo diffusion-weighted MRI of the breast: potential for lesion characterization. J Magn Reson Imaging 2002; 15:693-704.

13 Guo Y, Cai YQ, Cai ZL, et al. Differentiation of clinically benign and malignant breast lesions using diffusion-weighted imaging. J Magn Reson Imaging 2002; 16:172-178.

14 Rubesova E, Grell AS, De Maertelaer V, et al. Quantitative diffusion imaging in breast cancer: a clinical prospective study. J Magn Reson Imaging 2006; 24:319-324.

15 Woodhams R, Matsunaga K, Iwabuchi K, et al. Diffusion-weighted imaging of malignant breast tumors: the usefulness of apparent diffusion coefficient (ADC) value and ADC map for the detection of malignant breast tumors and evaluation of cancer extension. J Comput Assist Tomogr 2005; 29:644-649.

16 Kuroki Y, Nasu K, Kuroki S, et al. Diffusion-weighted imaging of breast cancer with the sensitivity encoding technique: analysis of the apparent diffusion coefficient value. Magn Reson Med Sci 2004; 3:79-85.

17 Wenkel E, Geppert C, Schulz-Wendtland R, et al. Diffusion weighted imaging in breast MRI comparison of two different pulse sequences. Acad Radiol 2007; 14:1077-1083.

18 Pisano ED, Gatsonis C, Hendrick E, et al. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med 2005; 353:1773-1783.

19 Schulz-Wendtland R, Bock K, Aichinger U, et al. [Ultrasound examination of the breast with 7.5 MHz and 13 MHz-transducers: scope for improving diagnostic accuracy in complementary breast diagnostics?]. Ultraschall Med 2005; 26:209-215.

20 Bartella L, Liberman L, Morris EA, et al. Nonpalpable mammographically occult invasive breast cancers detected by MRI. AJR Am J Roentgenol 2006; 186:865-870.

21 Kuhl CK, Klaschik S, Mielcarek P, et al. Do T2 weighted pulse sequences help with the differential diagnosis of enhancing lesions in dynamic breast MRI? J Magn Reson Imaging 1999; 9:187-196.

22 Nunes LW, Schnall MD and Orel SG. Update of breast MR imaging architectural interpretation model. Radiology 2001; 219:484-494.

23 Liberman L, Mason G, Morris EA, et al. Does size matter? Positive predictive value of MRI-detected breast lesions as a function of lesion size. AJR Am J Roentgenol 2006; 186:426-430.

24 Chang SC, Lai PH, Chen WL, et al. Diffusion-weighted MRI features of brain abscess and cystic or necrotic brain tumors: comparison with conventional MRI. Clin Imaging 2002; 26:227-236.

25 Dorenbeck U, Butz B, Schlaier J, et al. Diffusion-weighted echo-planar MRI of the brain with calculated ADCs: a useful tool in the differential diagnosis of tumor necrosis from abscess? J Neuroimaging 2003; 13:330-338.

26 Kawashima M, Tamaki Y, Nonaka T, et al. MR imaging of mucinous carcinoma of the breast. AJR Am J Roentgenol 2002; 179:179-183.