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Diagnostic value of apparent diffusion coefficients to differentiate benign and malignant breast lesions

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ABSTRACT

The role of magnetic resonance diffusion-weighted imaging (DWI) to differentiate between malignant and benign lesions in the breast using mean apparent diffusion coefficient (ADC) values was evaluated prospectively in this study. Fifty female patients with 61 histopathologically proven solid breast lesions underwent dynamic contrast-enhanced magnetic resonance imaging and DWI using the spin-echo echo-planar technique. ADC maps have been obtained and ADCs of the lesions were calculated without knowledge of histopathological diagnosis. Golden standard was histology to define benign and malignant lesions. Statistical analysis was used to compare ADC values in the benign and malignant group and to calculate best cut-off value for distinguishing both groups based on receiver-operator-curve characteristics (ROC). Differentiation of the benign and the malignant masses revealed that the threshold value of the ADC in maximum sensitivity and specificity was 1.22×10^{-3} mm^2/s; at this threshold sensitivity was 96.2%, its specificity was 88.5%, and its positive predictive value was 86.2%. Its negative predictive value was 96.9%, and the accuracy rate was 91.8%. ROC analysis showed an area under the curve of 0.924 ($p<0.001$). Breast MRI with DWI using ADC measurements can be useful in the differentiation of benign and malignant breast lesions.

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1. Introduction

Mammography is still the primary imaging modality today for screening and detection of breast lesions, with a sensitivity of 70-90% (Bird et al., 1992; Robertson, 1993; Goergen et al., 1997; Yankaskas et al., 2001; Kolb et al., 2002; Brem et al., 2003). Ultrasonography (US) can complement mammography if the findings are inadequate, and it can play an important role in breast imaging, especially for conditions where the parenchyma is dense or for evaluation after radiotherapy postoperatively in the presence of breast implants. However, US alone is inadequate for detection of microcalcifications in the cases of ductal carcinoma in situ (Shin et al., 2008).

Magnetic resonance imaging (MRI) is a supplementary diagnostic method, which is used in imaging breast lesions. In the breast, the sensitivity of MRI in differentiating benign and malignant lesions is 90%, and its specificity is 72% (Peters et al., 2008). Recently, with advances in ultrafast MRI techniques, new functional sequences such as diffusion-weighted imaging (DWI) offer the potential of improving the accuracy of breast MRI (Guo et al., 2002; Hatakenaka et al., 2008; Kul et al., 2011; Sonmez et al., 2011). DWI gives information of characteristics of the microscopic cellular environment including cell density, cell organization, and membrane integrity, by measuring the mobility of water molecules in vivo (Marini et al., 2007). Initially DWI has been established as a diagnostic tool in studies of the brain, but application to other areas of the body has been challenging due to technical limitations. Recently, the application of DWI has been facilitated with advances in MRI technology in the detection and characterization of lesions in other organs such as the liver, pancreas, ovaries, prostate, and breast (Le Bihan et al., 1988;

Yamashita et al., 1998; Kim et al., 1999; Moteki and Ishizaka, 2000; Hosseinzadeh and Schwarz, 2004). Preliminary data of DWI studies of the breast showed high sensitivity for detecting cancer, based on low diffusivity in carcinomas due to higher cell density (Park et al., 2007; Yoshikawa et al., 2008). Furthermore, quantitative DWI analyses have shown that the apparent diffusion coefficient (ADC) is significantly lower in many breast carcinomas compared with benign lesions, is supporting as a potential diagnostic tool (Guo et al., 2002; Kinoshita et al., 2002; Sinha et al., 2002; Wenkel et al ., 2002; Woodhams et al., 2005; Rubesova et al., 2006; Park et al., 2007; Hatakenaka et al., 2008; Peters et al., 2008; Yabuuchi et al., 2008; Yoshikawa et al., 2008; Lo et al., 2009; Partridge et al., 2010; Kul et al., 2011; Sonmez et al., 2011).

In the present study, we performed DWI of the breast with a single-shot echo-planar imaging (EPI) sequence, calculated the mean ADC values of the breast lesions, and compared the ADC values with histopathological results prospectively. The aim of this study was to evaluate the ability of ADC values to distinguish benign from malignant breast lesions.

2. Materials and methods

Patients

The protocol of our study was approved by our institutional ethics committee, and informed consent was obtained from all patients. The study included 50 women who underwent breast MRI in our hospital from March 2010 to December 2011 after a breast mass was determined by US and/or mammography. Sixty-one histopathologically proven breast lesions were detected via dynamic contrast enhancement (DCE) MRI and DWI. In the case of premenopausal women, we performed the MRI in the second week of the menstrual cycle, whereas in women undergoing postmenopausal replacement therapy, we recommended that they suspend the therapy 4-6 weeks in advance before participating in the study. Because cystic lesions are easy to characterize with conventional breast MRI and US, we excluded these lesions from our study. None of the patients had undergone chemotherapy or radiotherapy previously. Fifty cases with 61 breast lesions were included in the study. All the patients were female and aged between 20 and 79 years (mean age: 45.2 years). All the patients underwent a core needle biopsy and received definite pathological diagnosis in our hospital.

MRI acquisition

All the patients were examined using a 1.5-T MR scanner (Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany) with a maximum gradient strength of 30 mT/m and a slew rate of 125 (Txm^{-1}). A dedicated breast coil was used for radiofrequency reception of the MR signal. Each MRI examination included a fat-suppressed T2-weighted turbo spin echo (TSE) sequence (TR/TE, 9020/70 msec; field of view [FOV], 360 mm; slice thickness, 3 mm; matrix, 480×512) and a precontrast and dynamic postcontrast gradient echo 3D T1-weighted fast low-angle shot (FLASH) sequence (TR/TE, 4.4/1.6; flip angle, 12°; FOV, 320 mm; matrix, 512×512; signal average, 1; slice thickness, 1.2 mm) in the axial plane. All the scans were acquired in the axial orientation.

The contrast agent gadolinium chelate was administered using a dose of 0.1 mmol/kg/body weight. DWI was performed prior to the injection of the contrast agent using a diffusion-weighted EPI sequence with spectral spatial fat suppression and parallel imaging (TR/TE, 3000/77; matrix, 128×128; bandwidth, 1346 Hz/pixel; FOV, 350 mm; slice thickness, 5 mm; gap=0; distance factor, 30%). Diffusion gradients were applied in three orthogonal directions with b values of 50, 400, and 800 s/mm^2, and the scan time was 170 seconds.

The MRIs were evaluated separately at a workstation (Leonardo) based on the consensus of two radiologists who are experienced in breast imaging. First, in the dynamic 3D T1-weighted subtracted images, the lesion localization and its morphology and contrast enhancement kinetics were assessed, together with the T1-weighted and the T2-weighted images. The ADC measurements were performed on ADC maps. T2-weighted and subtracted MR sections covering the index lesion were used as pilot images for localizing the lesion. The region of interest (ROI) was placed manually within the solid portion of the lesion. The ROI was determined to be 10 mm^2 or greater. At least three measurements were done for each lesion, and the lowest one was accepted as the ADC value.

Statistical analysis

The obtained ADC values were compared statistically, together with the histopathological results, by means of Mann–Whitney U and student t-tests. For differentiating the malignant and benign lesions, the threshold values were obtained by means of the receiver operating characteristics (ROC) curve. The statistical significance level was accepted as $p<0.05$. All the statistical analyses were performed with the SPSS version 15.0 package (SPSS, Chicago, IL, USA).

Table 1. ADC values and histopathological diagnosis of the lesions in our study

Histopathological diagnosis	Number of lesions	Diameter (mean ± SD) (mm)	ADC value (mean ± SD) ($x10^{-3}$ mm^2/s)
Invasive ductal carcinoma	25	22.0±15.1	0.84±0.17
Mucinous carcinoma	1	41.0±0.0	1.77±0.00
Fibroadenoma	11	12.6±3.0	1.69±0.32
Mastitis	2	56.0±49.4	1.11±0.20
Fibrocystic disease	10	13.9±8.2	1.52±0.19
Benign epithelial hyperplasia	6	19.3±12.7	1.30±0.26
Fat necrosis	2	25.0±18.4	1.17±0.36
Intraductal papilloma	2	15.5±7.8	1.47±0.85
Normal breast tissue	2	12.0±5.7	1.65±0.33
Total	61	19.7±15.4	1.23±0.42

3. Results

All 50 patients registered in this study successfully underwent both DCE-MRI and DWI. Sixty-one lesions were detected on the DCE-MRI. The mean age of the patients with benign lesion was 43.9 years (range, 20-79 years) and with malignant lesion was 47.4 years (range, 32-60 years).

The histopathological analyses revealed a malignant tumor in 26 (42.6%) of the 61 lesions. There were 25 invasive ductal carcinomas, one mucinous carcinoma, and 35 benign lesions (57.4%). Among the benign lesions, there were 11 fibroadenomas, two cases of mastitis (one case of chronic infectious mastitis, one case of plasma cell mastitis), ten fibrocystic changes, six benign epithelial hyperplasias, two fat necrosis, two intraductal papillomas, and two normal breast tissues. As defined by the largest dimension on the DCE-MRI. The mean size of the benign and the malignant lesions was 17.5 mm (8-91 mm) and 22.7 (8-63 mm), respectively (Table 1).

In all 61 lesions, we have localized and measured the ADC value of the lesions. The mean ADC value of the 26 malignant lesions was $0.87\pm0.25\times10^{-3}$ mm^2/s (ranging from 0.5 to 1.8×10^{-3} mm^2/s) (Fig. 1). The mean ADC value of the 35 benign lesions was $1.50\pm0.30\times10^{-3}$ mm^2/s (ranging from 0.9 to 2.6×10^{-3} mm^2/s) (Fig. 2). The ADC values were significantly lower in the malignant compared with the benign lesions ($p<0.0001$) (Fig. 3). In four patients-two benign epithelial hyperplasias, one fat necrosis, and one case of mastitis-the DWI was false positive. The DWI was false negative in the mucinous carcinoma, and the corresponding mean ADC value was 1.77×10^{-3} mm^2/s. The ROC curves of the ADC values are shown in fig. 4. The cut-off level for the ADC derived from the ROC analysis was 1.22×10^{-3} mm^2/s. When 1.22×10^{-3} mm^2/s was set as a threshold, the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the differential diagnosis of the malignant and the benign lesions were 96.2, 88.5, 86.2, 96.9, and 91.8%, respectively.

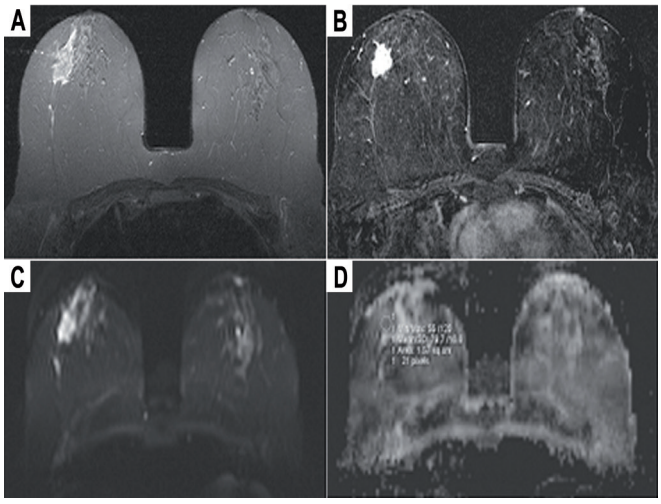

Fig. 1. Axial MR images of the breasts of a 57-year-old woman with invasive ductal carcinomaA. Axial T2-weighted fat-suppressed MR image showing a well-marginated, lobular shaped, hyperintense mass of the right breast; B. subtracted image showing strong enhancement of the mass; C. mass showing high signal intensity on DWI; D. ADC maps showing low signal intensity within the mass (the ADC value of the mass was 0.79×10^{-3} mm^2/s.)

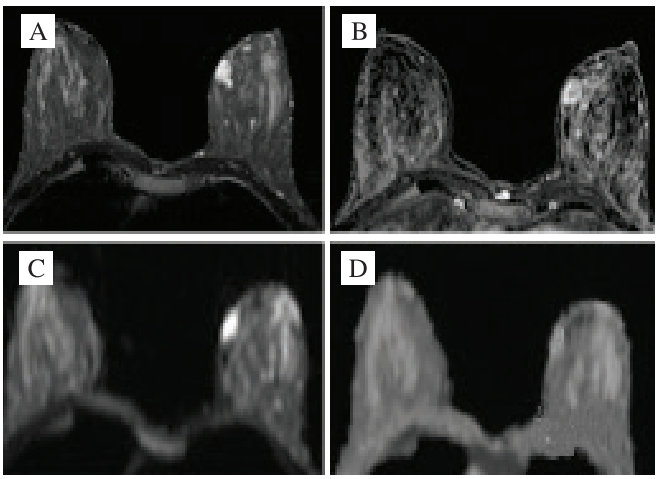

Fig. 2. Axial MR images of the breasts of a 35-year-old woman with fibroadenoma of the left breast; A. Axial T2-weighted fat-suppressed MR image showing a well-marginated, lobular shaped hyperintense mass of the left breast; B. subtracted image showing mild enhancement of the mass; C. mass of the left breast showing high signal intensity on DWI; D. ADC maps showing obviously high signal intensity within the mass (The ADC value of the mass was 2.05×10^{-3} mm^2/s).

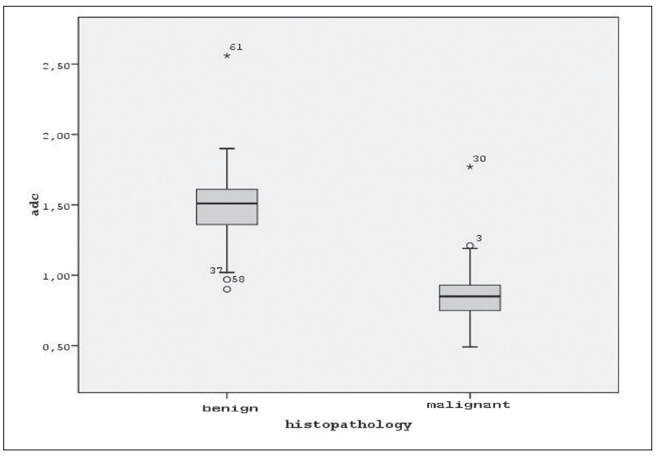

Fig. 3. Chart showing comparison between the ADC values of 35 benign and 26 malignant breast lesions The median ADCs of the benign and the malignant breast lesions were 1.51 and 0.85×10^{-3} mm^2/s, respectively.

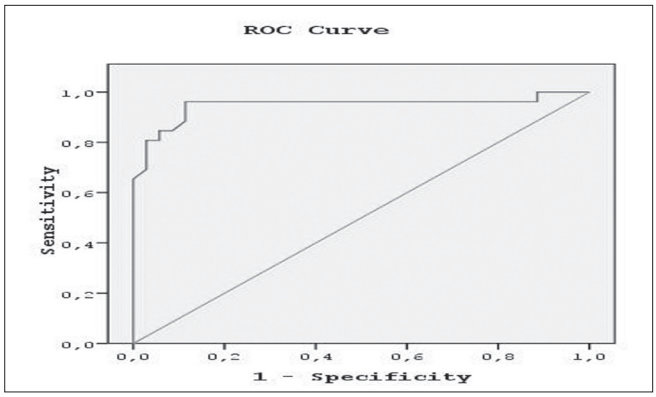

Fig. 4. Graph showing ROC curve for the ADC valuesThe area under the curve, which represents the probability that a lesion will be classified accurately as benign or malignant according to the ADC value, was 0.924. The upper left point on the curve is the cut-off value of the ADC with the highest sensitivity and specificity.

4.Discussion

Conventional breast MRI evaluation is a combined analysis of the morphology and the enhancement kinetics of the lesions. This imaging modality provides a high sensitivity for breast cancer, but the specificity is moderate (Peters et al., 2008). Similarities in morphological characteristics and kinetic features of some malignant and benign lesions cause incorrect diagnosis. We investigated the contribution of the diagnostic efficacy of the DWI, mainly on the specificity of breast MRI. DWI reflects the cellular molecular structure and early changes in water content, such as changes in the permeability of cell membranes, cell swelling, and cell lysis (Norris, 2001; Beaulieu, 2002). In addition to reports of its initial application for brain lesion evaluations, studies have been reported on the feasibility of DWI for breast MRI studies (Beaulieu, 2002). One study has investigated the differences in ADC values of normal breast parenchyma compared with those of fatty breast tissue (Englander et al., 1997). The changes of the ADC values in normal fibroglandular tissue during the menstrual cycle have been examined in other studies (Partridge et al., 2001; O'Flynn et al., 2012). A small variation of ADC during the menstrual cycle in the range of about 5.5% has been shown as normal (Partridge et al., 2001). In our study, in the case of fertile women, we conducted the imaging studies in the second week of their menstrual cycle. For the women undergoing postmenopausal replacement therapy, we have recommended to postpone the therapy 4-6 weeks to avoid any hormonal variability in the breast structure.

Several recent studies in the literature revealed the effectiveness of DWI for differentiating malignant from benign breast tumors (Guo et al., 2002; Kinoshita et al., 2002; Sinha et al., 2002; Wenkel et al., 2002; Woodhams et al., 2005; Rubesova et al., 2006; Marini et al., 2007; Park et al., 2007; Hatakenaka et al., 2008; Yoshikawa et al., 2008; Yabuuchi et al., 2008; Lo et al., 2009 Partridge et al., 2010; Kul et al., 2011; Sonmez et al., 2011) and showed a good correlation between ADC values and lesion cellularity (Guo et al., 2002; Yoshikawa et al., 2008). Guo et al. (2002) assessed the b value as 0 and 1000 s/mm^2. In their study, the average ADC value of 31 malignant lesions was $0.97\pm0.20\times10^{-3}$ mm^2/s, and the average ADC value of 24 benign lesions was $1.57\pm0.23\times10^{-3}$ mm^2/s. They also reported that the malignant and the benign lesions were diagnosed with 93% sensitivity, 88% specificity, and 91% accuracy when the threshold value was 1.30×10^{-3} mm^2/s (Guo et al., 2002). In another study of 52 patients and 27 malignant and 33 benign lesions, Luo et al. (2007) reported that the b value was 0 and 1000 s/mm^2, the average ADC value of the malignant lesions was $0.87\pm0.23\times10^{-3}$ mm^2/s, and the average ADC value of the benign lesions was $1.59\pm0.26\times10^{-3}$ mm^2/s. The sensitivity, specificity, and accuracy were 88.9%, 87.9%, and 83.3%, respectively, with a threshold value of 1.22×10^{-3} mm^2/s between the malignant and the benign lesions.The data obtained in the studies of Guo et al. (2002) and Luo et al. (2007) with the application of the same b values are similar to ours. In our study, malignant lesions had significantly lower ADC values than benign lesions. The median ADC of the malignant and the benign lesions was $0.87\pm0.25\times10^{-3}$ mm^2/s and $1.50\pm0.30\times10^{-3}$ mm^2/s, respectively. We obtained a threshold value near 1.22×10^{-3} mm^2/s that differentiated the benign and the malignant breast lesions, a sensitivity of almost 96.2%, and a specificity of 88.5%.

Although the characterization of breast lesions with the ADC values has not been standardized in previous studies regarding the clinical application of DWI to the breast, reported mean ADC values of benign lesions is ranging from 1.35×10^{-3} to 1.66×10^{-3} mm^2/s, and mean ADC values of malignant lesions and normal tissue are ranging from 0.95×10^{-3} to 1.02×10^{-3}mm^2/s and 1.51×10^{-3} to 1.90×10^{-3} mm^2/s (Iacconi, 2010). As another example, a cut-off of 1.23×10^{-3} mm^2/s has been suggested to distinguish malignant and benign breast lesions (Tsushima et al., 2009). Marini et al. (2007) reported 80% sensitivity and 81% specificity with a cut-off of 1.1×10^{-3} mm^2/s in the identification of breast cancer. The median ADC value of malignant lesions in our series was 0.87×10^{-3} mm^2/s and was similar with literature. It has been demonstrated that the differences in the ADC value between malignant and benign lesions are independent of size, appearance in MRI, and the field strength of magnet (Yabuuchi et al., 2008; Partridge et al., 2010). The only exception is Mucinous carcinomas, that showed the highest mean ADC value (1.77×10^{-3} mm^2/s), when comparing with both malignant lesions and benign lesions. In this special type of breast cancer, the presence of both low cellularity and mucin-rich compartments has been proposed to be responsible for this higher ADC value (Woodhams et al., 2009). The single mucinous carcinoma identified in our study had a higher mean ADC than the other types of breast cancers, even some of the benign lesions. This is consistent with the results of previous studies (Woodhams et al., 2009; Kul et al., 2011). Altough, the reason is not clear in the literature, there are other studies that showed similar low ADC values in fat necrosis as presented in our study (Kul et al., 2011; Fornasa et al., 2011).

DWI appears to be a very promising tool for further characterization of breast lesions and provides a real quantitative functional parameter, it does not require contrast agent administration, has both a short acquisition and post processing time which is less than five min. Even unenhanced MRI has encouraging sensitivity and specificity in the identification of nonpalpable breast cancer, according to preliminary data from two single-center prospective studies (Baltzer et al., 2010; Yabuuchi et al., 2010). Furthermore, DWI has been represented as a promising biomarker of tumor response in patients undergoing primary or neoadjuvant anticancer therapy. In this setting, both baseline ADC values and changes during treatment have been associated with a tumor response (Hamstra et al., 2007; Woodhams et al., 2010; Park et al., 2010). Martincich et al. (2012) found that the ADC obtained by breast DWI varied significantly according to the biological features of the tumor.

Despite its high sensitivity and specificity in the diagnosis of breast cancer, DWI has some limitations of the ability to detect small lesions, such as fairly low geometric resolution caused by susceptibility differences, large field of view requirement, and limited matrix size. In addition, areas of signal loss created by fat suppression, especially with fatty breast tissue, make it difficult to localize small lesions on ADC maps (Le Bihan et al., 1988). Synchronization and registration of the ADC maps with contrast-enhanced images and diffusion-weighted images can be helpful for optimal lesion localization and ROI placement on ADC maps. However, it should not be forgotten that detection and localization of small lesions on ADC maps could be difficult and lead to

misinterpretations, as in the case of morphological and kinetic analysis of small lesions on contrast-enhanced images. In our study, we applied DWI to the lesions, which were initially detected on contrast-enhanced T1-weighted images. Thus DWI was not used with the intention to detect breast lesions, but as an adjunct to CE-MRI. Benign breast lesions were especially difficult to localize on ADC maps because of poor contrast with surrounding glandular tissue. We consider that differential diagnosis based solely on ADC is not sufficiently accurate because of some overlaps in ADC between benign and malignant lesions. Other MR findings such as morphology and kinetic patterns should also be taken into account.

In conclusion, our study showed that the calculation of ADC values is a sensitive and specific adjunctive tool that can help to differentiate benign and malignant breast lesions. It may improve the overall specificity of MRI for characterizing breast lesions. With the addition of dynamic contrast-enhanced and diffusion-weighted MR images to conventional breast imaging, it might be possible to avoid unnecessary surgeries or biopsy for benign lesions on breast MRI. In addition, DWI was able to obtain images with a 3-min scan time. For these reasons, we propose to add the DWI sequence to the MRI protocol to study breast lesions.

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