ADC measurements of malignant and benign breast tumors and their correlation to prognostic markers: Preliminary 3T study

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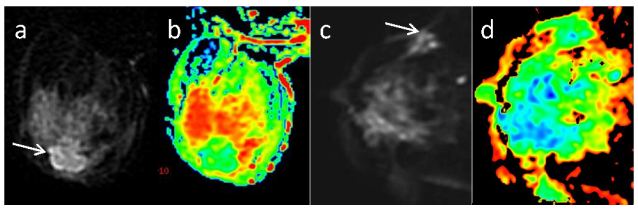
Introduction Diffusion-weighted MRI (DWI or DW-MRI) is a noninvasive technique which provides information about early changes in morphology and physiology of tissues by measuring apparent diffusion coefficient (ADC) of water molecules. In recent years, diffusion imaging has demonstrated potential in discriminating malignant from benign breast tumors (1, 2) and in assessing progression of disease following therapy (3). Treatment decisions and determination of prognosis have traditionally been based on pathologic parameters such as tumor size and axillary nodal status, tumor grade, and the results of tumor markers mainly ER/PR and HER-2/neu. In this work, we present the clinical usefulness of DWI and ADC measurements at 3T field strength and correlate them to traditional markers such as histology and molecular markers such as ER (estrogen receptor), PR (progesterone receptor) and HER-2 (HER-2/neu, EGFR2). Our objective was to determine if the acquisition of quantitative ADC values can improve the detection efficiency of breast malignancy. Histopathology examination was used as the reference standard.

Methods This HIPAA-compliant IRB-approved study included all 280 patients undergoing 3T Breast MR imaging for screening or pre-operative planning at a single institution from August and September 2010. Review of the institutional radiology database and electronic medical records identified 27 suspicious breast lesions and 31 biopsy-proven malignant lesions among 51 patients (mean=48 years; range=20-78 years). Few patients were not included due to complete radiologic response resulting in no lesion to measure or due to positive margins with no visible lesion on MRI. Of the 27 suspicious lesions, 26 underwent subsequent biopsy yielding 13 benign results, 2 high-risk lesions, and 11 malignancies. Therefore, the total number of lesions included 29 malignant lesions and 15 benign lesions. All studies were conducted with 3T GE Excite systems with the body coil as the transmitter and a phase arrayed coil as the receiver. The diagnostic breast MRI protocol includes multi-slice FSE T_2-weighted MRI with fat saturation, pre-contrast 3D SPGR T_1-weighted MRI with and without fat saturation, DWI with fat-saturation(b=1000 sec/mm^2), and DCE MRI (3D SPGR) with fat saturation. The reading of MRI was based on morphology of contrast enhanced lesion and contrast wash-out kinetics. In addition, DWI images were obtained by using single-shot spin-echo EPI sequence with a pair of gradient pulses in all three orthogonal axes. The parameters were TR=4000 ms, TE=90-100 ms, FOV=26-32 cm, slice thickness is 4 mm with 0 mm spacing and matrix size of 192x128. The orientation and location of these images were prescribed similar to the sagittal T_1- weighted images for unilateral and axial T_1-weighted images for bilateral breast cases. With 8-10 averages, and the duration of the DWI examination was about 2-3 minutes.

	Total n=44	Benign n=15	Malignant n=29
Age	48.5 ± 10.7	47.5 ± 10.8	49.4 ± 10.7
Tumor Size	2.05 ± 1.66	1.53 ± 1.14	2.48 ± 1.89
Average ADC	1.35 ± 0.47	1.77 ± 0.33	1.00 ± 0.20

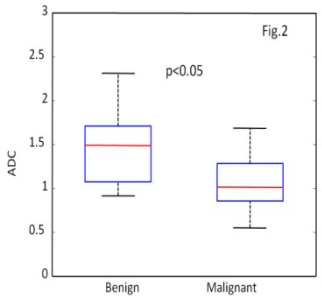
Pathological diagnosis was rendered on paraffin embedded tissue sections of tumors stained with Hematoxylin and Eosin. Histological parameters assessed include: tumor type, tumor grade, tumor size and evaluation of tumor markers viz. ER, PR and HER-2. Tumors were classified in various histological types using the WHO classification. Tumors were graded using our institution's department of pathology protocol for breast tumor grading. Surgical pathologist provided information of histological grade, ER+/ER-, PR+/PR-, HER2+/HER2-, and lymph node (LN) status (we grouped positive LN as metastasized group and benign lymph node represents non-metastasized group).

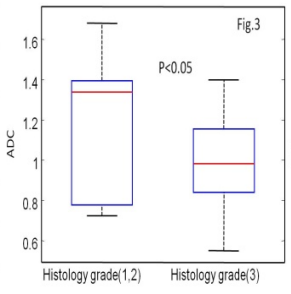
Fig.1

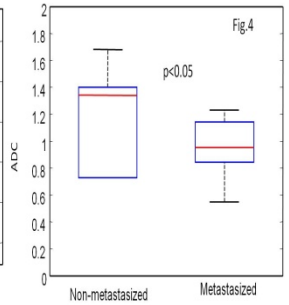


ADC maps were calculated with GE's Functool or Sentinels' Aegis software. Regions of interest (ROIs) were manually drawn well within the enhancing lesions on diffusion images. All statistical analyses were done with matlab software. All ADC values are represented in units of (x 10^{-3} mm2/s).

Results and Discussions Fig. 1a and 1b shows the DW image and ADC parametric map for a woman with invasive ductal carcinoma that was confirmed with biopsy procedure. By drawing a region of interest corresponding to enhanced lesion from DWI images, we calculated the diffusion coefficient to be (0.95±0.12) (Mean±SD). SD represents the standard deviation. Fig. 1c and 1d show the DWI and ADC color maps of benign fibroadenoma lesions. Lesions are indicated by arrows. ADC coefficients were calculated as (1.65±0.32) for fibroadenoma lesion. In these color maps, blue/red represents high ADC and green/yellow represents low ADC value. The pathology results showed that 29 of the 44 lesions were malignant and the other 19 were benign. **Table** lists the average mean and standard deviations (Mean±SD) of diffusion coefficients calculated from group of benign, malignant lesions. Fig 2 represents the box plot showing difference between these groups and the average mean and standard deviations of diffusion coefficients calculated from group of malignant and benign lesions are (1.00±0.20) x 10^{-3} mm^2/sec and (1.77±0.33) x 10^{-3} mm^2/s respectively. Areas under the ROC curves were 0.78.







Among 29 malignant lesions, 5 lesions did not have information about ER/PR/HER2 information, 8 patients did not have histology grade information, 9 patients did not have lymph node information and were excluded from the analysis. Malignant lesions were further classified groups specified by molecular prognostic markers such as ER+ (n=23), ER- (n=1), PR+ (n=22), PR-(n=2), HER2+ (n=4), HER2-(n=20) and traditional markers such as histology grades 1, 2 (n=7), histology grade 3(n=14). Due to low numbers in PR- and ER- groups, statistical analysis was not performed. Within HER2 group, ADC coefficients are statistically not significant in distinguishing HER2+/ HER2- lesions (p=0.12). Using box plot (Fig.3) of ADC values and histology grades, it is shown that histology grade 3 lesions have lower ADC values compared with the rest of group (p<0.05). These results are consistent with reported values in the literature (4).Within patient group with known LN status, 9 patients had positive LN and 11 had benign LN with box plots shown (Fig.4) and ADC values are significantly different between patients with and without positive lymph nodes (p<0.05).

Conclusion This preliminary study concludes that ADC values represent a valuable biomarker for detecting malignant lesions. This study also suggests that the ADC measurement can be a prognostic indicator for patients with breast cancer. Increased sample size of ER-, PR-, HER2+ population may help in obtaining better correlations with prognostic factors. **References 1)** Guo, Y. JMRI 16, 172(2002). 2) Woodhams, R et al., Magn Reson Med. Sci. 4, 35 (2005). 3) Kuroki, Y et al., Breast Cancer 15, 212 (2008). 4) Kim SH *et al.,JMRI* **30**, 615 (2009).