Diffusion MR Breast Imaging: Correlation of ADC values to the Prognostic Factors

S. B. Thakur[1], D. D. Dershaw[2], D. Giri[3], J. Zheng[4], C. Moskowitz[5], J. Ferrara[2], J. A. Koutcher[1], and E. A. Morris[2]

[1]Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [2]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [3]Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [4]Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [5]Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Introduction

In recent years, diffusion imaging has demonstrated potential in discriminating malignant from benign breast tumors and in assessing progression of disease following therapy[1]. Treatment decisions and determination of prognosis have traditionally been based on pathologic parameters such as tumor size and axillary nodal status[1], tumor grade[2], and the results of tumor markers mainly ER/PR[3] and HER-2/neu[4].

In this work we present the clinical usefulness of diffusion weighted imaging (DWI) and apparent diffusion coefficients (ADCs) and correlate to traditional markers such as histology and molecular markers such as ER (estrogen receptor), PR (progesterone receptor) and HER-2 (HER-2/neu, EGFR2). Diffusion MRI examinations were performed on patients who had positive MRI findings and underwent MRI-guided interventional procedures. We have shown that ADC measurements are useful to differentiate malignant lesions from benign lesions yielding 98.4 % specificity and 90.9 % sensitivity with ADC cut-off value of 1.28×10^{-3} mm^2/s (Abstract1). Our objective was to determine if the acquisition of quantitative ADC values can be correlated to traditional and molecular prognostic factors.

Methods

The IRB approved this HIPAA-compliant study. 140 lesions from 126 patients with suspicious or biopsy-proved cancer lesions were studied between Sep'2008 and June'2009 (median age, 49 years; range, 25–84 years) who underwent 1.5-T MR imaging as part of their diagnostic MRI protocol.

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, 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=6000 ms, TE=90-100 ms, FOV=26-32 cm, slice thickness is 4 or 5 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. The gradient *b* values were 0 and 1000 sec/mm^2. With 4 to 6 averages, and the duration of the DWI examination was about 2-3 minutes. All studies were conducted with 1.5T GE Excite systems with the body coil as the transmitter and a sentinel coil or phase arrayed coil as the receiver.

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. Briefly, tumor grades combined nuclear and histological grades. In *nuclear grade 1* there was minimal pleomorphism between individual tumor cell nuclei; with moderate and marked pleomorphism in *nuclear grades 2 and 3* respectively. In *histologic grade 1*, the tumor was composed of well formed glands; in *histological grades 2 and 3* there was moderate to minimal gland formation respectively. Receptors were analyzed using immunohistochemistry employing protocols for commercially available antibodies to ER (6F11, Ventana, Tucson, AZ, USA), PR (1E2, Ventana, Tucson, AZ, USA) and HER-2 (4B5, Ventana, Tucson, AZ, USA). For ER and PR the results were reported as percent tumor cells showing nuclear staining. HER-2 results were reported using the ASCO/CAP guidelines. Accordingly tumors were HER-2 *negative* if the staining was 0 or 1+, *positive* if it was 3+ and *equivocal* with any combination with 2+ staining. All cases with equivocal results for HER-2 on immunohistochemistry were confirmed by fluorescent in situ hybridization (FISH) analysis.

The lesion pathology was determined from a histological examination performed on biopsy or needle localization samples obtained after the MR scan. ADC maps were calculated with GE's FUNCTOOL software. Regions of interest (ROIs) were manually drawn well within the enhancing lesions on diffusion images. Quantitative ADC measures were correlated to prognostic markers (Table.1). The differences between the categories of continuous variables were tested using Wilcoxon rank-sum test or Kruskal-Wallis test for more than 2 levels. Based on false positive rates and true positive rates of using all observed ADC values to detect malignancy status, the ROC curves and the corresponding AUC with 95% CI were provided. All analyses were done within SAS® 9.2 and R 2.9.2.(5)

Table 1: Median (Range) of malignant ADC measurement by clinical factors

ADC value (x 1e3 mm^2/s)				
Factor	**Positive**		**Negative**	**Wilcoxon Rank –Sum Test p-value**
ER	1.02(0.60-1.49)		0.90(0.70-1.21)	0.135
PR	1.10(0.60-1.49)		0.96(0.60-1.21)	0.092
HER2	0.96(0.70-1.49)		1.08(0.60-1.49)	0.337
	Metastasized		**Non-Metastasized**	
Tumor Size	1.79 ± 1.20		3.70 ± 2.35	<0.001
Factor	**Grade 1**	**Grade 2**	**Grade 3**	**Kruskal-Wallis Test p-Value**
Histology	0.99(0.66-1.10)	0.90(0.70-1.30)	0.98(0.60-1.49)	0.912
Nuclear	1.07(0.85-1.30)	1.02(0.60-1.49)	0.96(0.60-1.49)	0.421

Results and Discussions: ADC parametric map and matching T1-post contrast MR image (Fig.1a &b) for a woman with invasive ductal carcinoma with ER+ lesion. By drawing a region of interest (red circles on image) on hypointensity (mixed green and blue) lesion, we calculated the diffusion coefficient to be 0.00090±0.00022 mm^2/s (Mean±SD). SD represents the standard deviation. Fig. 2a & 2b show the ADC map (mixed yellow and green) and the corresponding T1-post contrast MRI of invasive lobular carcinoma with ER- lesion. ADC coefficient was calculated as 0.00096±0.0002 mm^2/s. The pathology results showed that 77 of the 140 lesions were malignant. Malignant lesions were further classified groups specified by molecular prognostic markers such as ER+ (n=57), ER- (n=12), PR+ (n=51)/PR-(n=18), HER2+(n=51)/HER2-(n=17), nuclear and histology grades 1 to 3. Among malignant lesions, 8 lesions did not have information about ER/PR information and 9 lesions did not have HER-2 information and were excluded from the analysis. Malignant lesions were also classified according to traditional prognostic markers such as nuclear grade and histology grade. There are 26 patients with positive lymph nodes and 45 with benign lymph nodes. Table 1 lists the average mean and standard deviations of diffusion coefficients calculated from malignant lesions correlating to various clinical factors and the box plot showing difference between these groups (Fig.3). The average mean and range of diffusion coefficients calculated for group of ER+ and ER- lesions are not statistically different (p=0.135). These results are consistent with reported values in the literature (6). ADC value is slightly high in PR + lesions compared to PR – lesions with no statistical significance (p=0.092). ADC coefficients are statistically not significant in distinguishing HER2+/ HER2- lesions. Although ADC values are not significantly different between patients with and without positive lymph nodes, the size of tumor does make a difference in measuring metastatic status (Fig. 4). As seen from Fig.4, tumor size is significantly higher in patients with positive lymph nodes compared to patients with only benign lymph nodes. Areas under the ROC curves were 0.78. **Conclusion:** Mean tumor size is significantly higher in patients with positive lymph nodes in comparison to benign lymph nodes. Although ADC values represent a valuable biomarker for detecting malignant lesions, the ADC measurement cannot be a prognostic indicator for patients with breast cancer. Increased sample size of ER-, PR-, or HER2- population may help in obtaining better correlations with prognostic factors.

References: 1) Kuroki, Y et al., Breast Cancer 15, 212 (2008). 2)Say CC et al., Cancer 34:468 (1974),3) Elston CW et al., Histopathology 19:403(1991).4) Donegan WL.,Cancer 70:1755(1992),5) DiGiovanna MP., PPO Updates 13,1(1991), 6) Hilden J. et al., Stat. in Med.15,969(1996), 7) Kim SH *et al.,JMRI* **30**, 615 (2009).