Multi-parametric Longitudinal Study for the Evaluation of Tumor Heterogeneity in Breast Cancer Patients Using Simultaneous MRSI & DWI Techniques

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OBJECTIVE: To evaluate the potential utility of signal-to-noise ratio (SNR) of total choline (tCho) peak calculated from multi voxel MRS (MRSI) together with the apparent diffusion coefficient (ADC) values using diffusion weighted imaging (DWI) in predicting the response of tumor to neo-adjuvant chemotherapy (NACT) in locally advanced breast cancer (LABC) patients.

INTRODUCTION: Previous studies have demonstrated the utility of single-voxel MRS and diffusion weighted imaging (DWI) in monitoring treatment response to NACT in breast cancer patients (1, 2). However simultaneous MRSI and DWI may provide valuable information associated with the metabolism and water diffusion characteristics of breast tumors in response to therapy. MRSI provides evidence of metabolic changes in regions of cancer and can be used for discriminating the viable and necrotic portions of tumor (3) as well as at the margin of tumor (4). The utility of DWI in differentiating viable from necrotic domains inside a tumor using ADC values has already been documented by us earlier (5). ADC within tumor tissue and the peri-tumor area provides quantitative information on tumor cellularity and characterization of tumor-related edema that is not readily discernible on conventional MRI (6). The aim of the present study was to measure the ChoSNR and ADC in viable solid tumor, necrotic domains and at the tumor margin in LABC patients (both prior to and after III NACT) and to understand its potential utility in predicting tumor heterogeneity and tumor response which may help in surgical planning.

PATIENTS AND METHODS: Eleven LABC patients (age 43 ± 8 yrs) with cytologically proven malignancy were investigated at 1.5 T (Avanto, Siemens) using a dedicated bilateral breast coil with the body coil as transmitter. Institutional ethical committee approved the study and written informed consent was obtained. Following MR image acquisition (T1 and T2 weighted), 2D MRSI was carried out using PRESS sequence. The acquisition parameters for MRSI were: TR = 2000 ms, TE = 135 ms, number of scans = 4, FOV = 80 × 80 mm with scan resolution of 16 × 16 (acquisition time 9 mins). DWI was carried out in axial plane with the following parameters: b = 0, 500, and 1000 mm^2/s; TR = 5000 ms; TE = 87 ms; FOV = 250-350 mm; NSA = 1; EPI factor = 128 and acquisition matrix = 128 × 128; and slice thickness = 5 mm without any inter-slice gap with a total acquisition time = 42 s. Both DWI and MRSI were carried out at the same sitting in all patients sequentially at two time points: prior to and after III NACT. ChoSNR was calculated using the formula: SNR = [amplitude of Cho resonance / RMS amplitude of noise] and ADC was calculated by drawing small circular ROIs of 5 pixels in respective voxels.

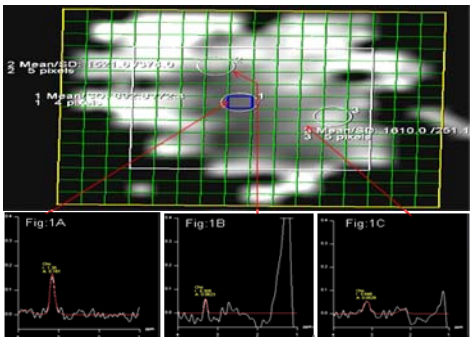

Figure 1: MRSI spectrum from a breast cancer patients showing tCho peak at (A) solid tumor, (B) tumor margin and, (C) intra-tumoral necrotic voxels with the respective ADC values obtained.

RESULTS: The MRSI spectra overlapped with ADC map of a patient suffering from LABC is shown in Fig 1. The ChoSNR and ADC of 11 patients were analyzed from different voxels after classifying them as responders (R) and non-responders (NR) using clinical evaluation at the end of III NACT. In 6 responders the pre-therapy ChoSNR was 8.80 ± 1.79 for solid tumor: 4.31 ± 1.64 at the margin of tumor and 1.60 ± 0.44 at the necrotic area. A value of SNR of ≥ 2 was considered consistent with malignancy (7). In 2/6 responders, no choline was observed after III NACT while in remaining four patients, the ChoSNR reduced to 2.55 ± 0.87 for solid tumor and 2.47 ± 1.13 at the margin. ADC of the solid tumor showed a significant increase after therapy in responders (1.18 ± 0.04 × 10^{-3} mm^2/s) compared to the pre-therapy value of 0.91 ± 0.05 × 10^{-3} mm^2/s. Although ChoSNR decreased significantly at tumor margin after NACT, no such change was evident in necrotic areas in responders. ADC showed no significant change at both the margin and the necrotic areas of tumor in responders. In non-responders there was no significant change in ChoSNR and ADC following NACT in any of the tumor regions. On further analysis, a positive Pearson correlation was obtained between changes in ChoSNR (pre-therapy vs. post-therapy) and changes in ADC for all three regions of the tumor (solid tumor, necrotic domain and tumor margin) in both responders and non-responders (see table).

Table: Mean ± SD for ADC & ChoSNR in different tumor regions

		Pre-therapy		Post-therapy (after III NACT)	
		ADC x 10^{-3} mm^2/s	Cho SNR	ADC x 10^{-3} mm^2/s	Cho SNR
Responders (n=6)	Solid tumor (T)	0.91±0.05	8.80±1.79	1.18±0.04*	2.55±0.87*
	Margin (M)	1.21±0.15	4.31±1.64	1.11±0.12	2.47±1.13*
	Necrosis (Nec)	1.5±0.37	1.60±0.44	1.81±0.35	1.93±0.52
	r=0.88 (ΔSNR_T & ΔADC_T); r=0.84 (ΔSNR_M & ΔADC_M); r=0.79 (ΔSNR_{nec} & ΔADC_{nec})				
Non-responders (n=5)	Solid tumor	1.01±0.13	7.18±3.16	1.1±0.13	6.7±3.46
	Margin	1.18±0.08	4.40±1.77	1.28±0.19	3.82±1.84
	Necrosis	1.42±0.26	1.62±0.53	1.58±0.54	1.57±0.77
	r=0.91 (ΔSNR_T & ΔADC_T); r=0.92 (ΔSNR_M & ΔADC_M); r=0.97 (ΔSNR_{nec} & ΔADC_{nec})				
Here r= correlation coefficient and * denotes p < 0.05					

DISCUSSION: In the present study we investigated the heterogeneous nature of breast tumors following NACT using MRSI and DWI from different regions of the tumor (viable solid area, necrotic domain and margin) and assessed the correlation between the changes in ChoSNR and ADC. Our data indicated a positive correlation between the change in SNR and ADC change at different regions (solid tumor, necrotic domain and tumor margin) in both responders and non-responders. The ChoSNR decreased significantly after therapy with simultaneous increase in ADC in solid tumor areas in responders. This shows that as a result of chemotherapy, the decrease in cellular density in tumors leads to decreased ChoSNR and increased ADC. On the contrary, at the tumor margin an intermediate value for choline SNR was observed between necrosis and viable tumor area, reflecting the proliferation activity of cancerous cells at the margins of the tumor. Whereas, at the necrotic regions no significant difference was observed in the ChoSNR and the ADC value after therapy as cells in this region are dead and are not affected by the drug (8). Moreover, in non-responders neither the ChoSNR nor the ADC showed any significant change following NACT in any of the tumor regions which shows the lack of drug effect in this group of patients. Thus monitoring the viability of cancer cells at different regions of a tumor using MRSI and DWI simultaneously, gives an insight into the spatial variations of the tumor as a result of drug administration. Breast tumors are heterogenous and consist of variation in viable and necrotic regions which is furthermore affected by drugs. Therefore, combined use of MRSI and DWI techniques might be useful method to map tumor areas for both treatment and surgical planning in breast cancer patients.

REFERENCES: (1) Bathen TF et al. **MAGMA** 2011; 24: 347-57 (2) Sharma U et al. **NMR Biomed** 2009; 22: 104-113 (3) Kurhanewicz J et al. **Neoplasia** 2006; 2: 166-189 (4) Bulakbasi N. **Spectroscopy** 2004;18:143-153 (5) Yuan Z et al**. Oncol Lett**. 2014; 8: 831-836 (6) Yamasaki F. et al. **Radiology** 2005; 235: 985-991 (7) Bartella L et al**. Radiology** 2007; 245: 80-7 (8) Fukumura D et al. **J Cell Biochem** 2007; 101: 937-949.