Multi-parametric approach for the assessment of tumor response to chemotherapy in locally advanced breast cancer (LABC) patients: Sequential MRI, DWI and in-vivo MRS study

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Introduction: Neoadjuvant chemotherapy (NACT) is used in the management of locally advanced breast cancer (LABC) to reduce tumor size and in the treatment of metastasis. However, the toxicity of chemotherapy drugs and variable responses of patients require periodic assessment of tumor response of patients. Early prediction of response enables the non-responders to opt for early surgery or alternative drug therapy. Tumor response is monitored primarily by measuring the tumor size after three cycle of chemotherapy. Thus, techniques that measure biochemical and physiological changes in tumor activity may show promise in early prediction of the response. In this direction, the utility of diffusion weighted imaging (DWI) and in vivo MR spectroscopy (MRS) has been explored. Recently, apparent diffusion coefficient (ADC) of tumors measured using DWI has been shown to predict the early response compared with the anatomical parameters (1). Proton magnetic resonance spectroscopy (^{1}H-MRS) studies have documented treatment induced changes in the levels of water-fat ratio and choline containing compounds (2). In the present study we carried out sequential monitoring of multi-parameters, like volume, apparent diffusion coefficient and tCho concentration in patients with locally advanced breast cancer (LABC) after I, II and III NACT and explored the potential of these parameters individually and in combination for the early prediction of tumor response.

Material and Methods: Forty one LABC patients (n=41; 42.77 ± 8.49 yrs; range 28 – 58 yrs) who elected to receive NACT with cyotologically proven infiltrating ductal carcinoma (IDC) were recruited in the study. Of these, the data of 2 patients could not be used due to motion artifacts. Written informed consent was obtained and Institutional ethical committee approved the study. Clinically the tumor size was measured using Vernier calipers. MR examinations were performed using a circularly polarized breast matrix coil with four channels at 1.5 T (Siemens, Avanto). Following the scout images, T1 and T2 weighted images were obtained in sagittal plane. Thereafter, fat suppressed images in axial and coronal planes were acquired to identify the full extent of the tumor. DCEMRI was carried out using a fat-saturated 3D FLASH, whenever indicated. In-vivo proton MRS with water+lipid suppression was carried out using a single-voxel PRESS pulse sequence with TR = 1500 ms, TE=100 ms and averages=128. A spectrum without water and lipid suppression was also obtained from internal water signal from the same voxel that served as internal reference. DWI were acquired with TR = 5000 ms; TE= 87 ms; NS = 1; EPI factor =128; acquisition matrix = 128 x 128; and slice thickness = 4 to 5 mm (without gap) and b= 0, 500 and 1000 s/mm^2. Sequential MRI, DWI and MRS were carried out at 4 time points for 39 patients. Of these, 32 patients were monitored one week after I NACT (Tp1), 18 after II NACT (Tp2) and 35 after III NACT (Tp3). Mean ADC values were calculated from the ADC map by drawing contiguous circular ROIs of 5 pixels. Tumor volume was measured from MR images using formula: volume = Slice thickness × [A1+A2...An]. Concentration of tCho was determined using the formula given by Baik et al (3). General estimated equation was used to compare the tCho concentration among Pre, I, II and III NACT. All statistical analyses were carried out using statistical software SPSS 16.0 and STATA 9.

tCho (mmol/kg), ADC (x 10^{-3} mm^2/s) and tumor volume (cm^3) in responders and non-responders

	Responders			Non-responders		
	tCho	ADC	Volume	tCho	ADC	Volume
Pre-therapy	4.8±2.9* (n=28)	1.0±0.2* (n=28)	61.0±53.0 (n=28)	3.0±1.8 (n=11)	1.2±0.2 (n=11)	112.4±72.2 (n=11)
I NACT	2.7±1.8* (n=23)	1.1±0.2* (n=23)	42.3±30.2 (n=23)	3.7±2.3 (n=9)	1.2±0.2 (n=9)	126.0±69.9 (n=9)
II NACT	1.6±1.3 * (n=12)	1.2±0.1* (n=12)	27.5±25.2* (n=12)	2.5±2.1 (n=6)	1.2±0.2 (n=3)	120.4±65.6 (n=5)
III NACT	0.5±0.7* (n=25)	1.5±0.2* (n=25)	19.8±19.4* (n=25)	3.0±2.1 (n=10)	1.3±0.3 (n=10)	78.5±47.7 (n=10)

*P<0.01, in pre-therapy, I, II and III NACT in responders.

Results: Of the 39 patients, who were monitored sequentially, 28 were clinical responders (R) and 11 were non-responders (NR). The pre-therapy tCho concentration was significantly higher in responders compared to non-responders while pre-therapy mean ADC and the mean tumor volume were significantly lower in responders compared to non-responders. Further in responders, the tCho concentration and the mean ADC showed significant changes as early as after I NACT. While the tumor volume showed significant change only after II NACT in responders (see Table). The percentage reduction in tCho concentration after I NACT was higher compared to ADC and volume in responders (see Figure 1). The sensitivity to detect responders for ADC was 80% with 100% specificity. While volume showed higher sensitivity of 88%, however, lower specificity of 80%. The sensitivity for tCho was 84 % with specificity of 80%. Combining all three parameters (tCho, ADC and volume), a sensitivity of 84% and a specificity of 100% was achieved.

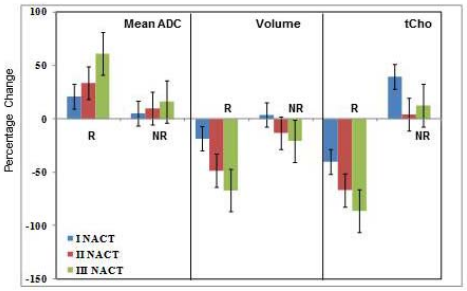

Figure 1: Percentage change in responders (R) and non-responders (NR) after I, II and III NACT in mean ADC, volume and tCho concentration.

Discussion: The retrospective analysis of MR data showed significant reduction in tCho concentration and an increase in ADC after the I NACT in responders which may be due to cell damage mediated by chemotherapy. The percentage reduction in tCho concentration after I NACT was significantly higher compared to ADC and tumor volume in responders, which demonstrated early change in the metabolic activity compared to the structural changes. Meisamy *et al* reported that NACT increases apoptosis within 24 hours after the initiation of therapy in breast cancer (4). A significant decrease in tumor volume was observed only after II NACT in responders. Interestingly, prior to therapy, we observed a significantly higher tCho concentration and lower ADC and tumor volume in responders compared to non-responders. This suggest that larger volume tumors observed in non-responders might have various nests of necrotic areas and hence lesser perfusion. Thus, the delivery of drug might not be reaching the whole tumor volume uniformly and thereby not able to destroy the tumor cells. Hence, these patients may not respond to therapy. While tumors with lower volume may have more proliferating cells that take up the chemotherapeutic drugs much faster and turn out as responders. In conclusion, our present data showed the potential of MR parameters in predicting the tumor response prior to therapy. In addition, changes in tCho concentration and ADC were found to occur as early as first cycle. Furthermore, the specificity to differentiate responders and non-responders was found higher when all the three parameters were used in combination.

References: (1) Sharma et al. *NMR Biomed*. 2009; 22: 104-13; (2) Sharma et al. *NMR Biomed.* 2011; 24: 700-711; (3) Baik et al. *Magn Reson Mater Phy* 2006; (4) Meisamy et al. *Radiology* 2004; 233: 424-31.