Clinical potential of absolute concentration of total choline in breast cancer patients using in-vivo proton MR spectroscopy: Assessment of early therapeutic response following neo-adjuvant chemotherapy.

R. G. Sah[1], U. Sharma[1], R. Parshad[2], and N. R. Jagannathan[1]

[1]Department of NMR and MRI Facility, All India Institute of Medcial Sciences, New Delhi, Delhi, India, [2]Department of Sugical Disciplines, All India Institute of Medcial Sciences, New Delhi, Delhi, India

Objective: To evaluate the clinical potential of total choline (tCho) concentration quantitatively using in-vivo proton MRS in predicting the tumor response of locally advanced breast cancer (LABC) patients undergoing neo-adjuvant chemotherapy (NACT).

Introduction: Neo-adjuvant chemotherapy (NACT) offers the advantages like downsizing the tumor, enabling breast conservation surgery and reducing the distant metastases in patients with inoperable locally advanced breast cancer (LABC). However considering the severe toxicity of chemotherapy drugs, early identification of non-responders is essential. Physical examination together with various imaging modalities like mammography, ultra-sonography, and MRI rely on the anatomical changes that occur later and also have limitations like overestimation of the extent of the residual tumor. A technique that provides an early assessment of therapeutic response is essential in treatment planning and management of breast cancer. Proton MRS has documented differences in water-fat ratio and levels of choline containing compounds in benign, malignant and normal breast tissues (1-3). Treatment induced changes in the levels of water-fat ratio and choline have been used to monitor the tumor response (4,5). The present study was designed to determine the potential clinical utility of absolute concentration of tCho resonance in the assessment of tumor response in LABC patients during the various stages of NACT.

Material and Methods: A total of seventeen patients with LABC (age 44.4 ± 7.5 yrs, range 32 – 58 yrs) who elected to receive NACT with cyotologically proven malignant lesions were studied. Written informed consent was obtained and Institutional ethical committee approved the study. Clinical evaluation and TNM classification was carried out prior to MR. 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 (MAGNETOM Avanto, Siemens Healthcare Sector, Germany). Following the scout image, 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. MRI with contrast was carried out using a fat-saturated 3D FLASH-whenever indicated for proper identification of the tumor. The in-vivo proton MRS with water+lipid suppression was carried out using a single-voxel PRESS pulse sequence. The acquisition parameters used were: TR = 1500 ms, TE=100 ms and averages=128. A spectrum of water (without water and lipid suppression) was also obtained from internal water signal from the same voxel that served as internal reference. Pre-therapy (Tp0) spectrum was obtained from all 17 patients. Of these, 15 were monitored sequentially one week after I NACT (Tp1) and one week after III NACT (Tp3). After II NACT (Tp2) only 6 patients could be monitored due to non-cooperation of patients. The concentration of tCho was determined using the formula given by Baik et al (6). Clinical response was evaluated by measuring the tumor volume and diameter. One way ANOVA was used to compare the tCho concentration among Pre, I, II and III NACT. All statistical analyses were carried out using statistical software SPSS 11.5.

Result: The pooled analysis of the data showed that pre-therapy mean concentration of tCho was 3.8 ± 2.3 mmol/kg that decreased to 2.7 ± 1.6 after I NACT and to 1.6 ± 2.2 mmol/kg after III NACT. A retrospective comparison of tCho concentration after classifying the patients as responders and non-responders (based on clinical response) was carried out. Of 17 patients, 11 were responders and 6 were non-responders. The MR spectral patterns obtained prior to therapy and after III NACT of a responder is shown in Figure 1 (note Y-scale being different in Fig. 1A and 1B). In responders, the mean concentration of tCho before therapy was 4.8 ± 2.4 mmol/kg which showed statistically significant reduction after I NACT (see Table 1). Further reduction was observed following II and III NACT (see Table 1). In non-responders, the mean tCho concentration before therapy was 2.1 ± 0.9 mmol/kg that remained same after III NACT (2.1± 2.6 mmol/kg).

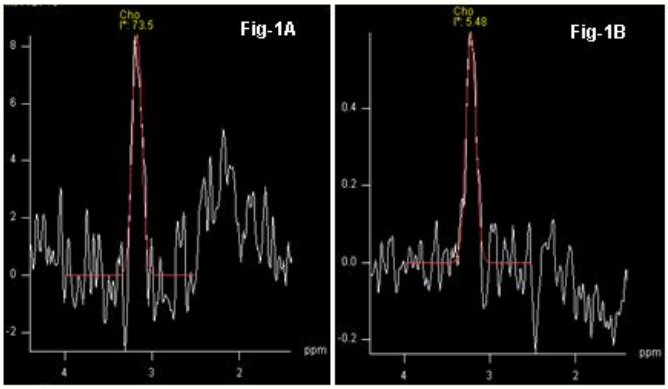

Table-1	Pre-therapy mmol/kg	I NACT mmol/kg	II NACT mmol/kg	III NACT mmol/kg
Reponder*	4.8±2.4* (n=11)	2.6±1.6* (n = 10)	1.7±0.9* (n = 4)	0.4±0.1* (n = 9)
Non-Responder	2.1±0.9 (n = 6)	2.8±1.7 (n = 6)	1.0±0.7 (n = 2)	2.1±2.6 (n = 6)
*P<0.05 , in pre-therapy, I, II, III NACT in responders				

Discussion: Despite several advantages of NACT, toxicity of chemotherapy drugs is a serious concern and requires close monitoring of the response of patients to NACT. Nearly 30-40% of patients does not respond to chemotherapeutic drugs or show partial response. Early prediction of treatment response may avoid the exposure of these patients to serious side effects of NACT. We have earlier documented the tumor response in LABC patients undergoing NACT using single-voxel ^{1}H-MRS using presence or absence of tCho (2) and reduction of water-to-fat ratio (3). In this study, we determined the absolute concentration of Cho containing compounds in monitoring the response of LABC patients during various stages of NACT. The pre-therapy concentration of tCho showed significant reduction as early as after I NACT in responders compared to non-responders. Further reduction was observed after II and III NACT. Meisamy et al (7) showed changes in tCho concentration after 24 hrs of the first dose of primary systemic therapy. Roebuck et al (1) reported the tCho concentration in the range of 0.7-2.1 mM using external referencing method. Baik et al (6) reported choline concentration at in the range of 0.76 – 21.2 mmol/kg in malignant lesions at 1.5 T using water peak as an internal reference. The use of internal reference method overcomes some of the limitations of the external reference method like the need for correction for partial volume effect and separate calibration experiments. In conclusion, our data on the determination of absolute concentration of tCho before therapy and at various stages of NACT showed promise for early detection of tumor response to therapy. However, more number of patients needs to be studied to obtain a cut-off value of tCho concentration to differentiate responders from non-responders.

References: [1] Roebuck JR et al. Radiology 1998; 209: 269-275. [2]. Jagannathan NR et al. *NMR Biomed.* 1998;11: 414-422. [3]. Jagannathan NR et al. *Br. J. Cancer* 2001; 84: 1016-1022. [4]. Meisamy S et al. *Radiology* 2004; 233: 424-431. [5]. Kumar M et al. *J. Magn. Reson. Imaging* 2006; 24: 325-332. [6] Baik HM *et al. Magn Reson Mater Phy* 2006; 19: 96-104. [7] Meisamy S *et al. Radiology* 2005; 465-475.

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