Choline as a biomarker a better predictor of early response of breast cancer than tumor volume? Sequential study of the therapeutic response of locally advanced breast cancer patients undergoing neo-adjuvant chemotherapy (NACT)

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Objectives: To determine whether early changes in tCho and tumor volume can be used to predict the response of locally advanced breast cancer (LABC) patients undergoing neoadjuvant chemotherapy (NACT).

Introduction: Neo-adjuvant chemotherapy (NACT) is used with the aim of downsizing the tumor size, enabling breast conservation and reducing the distant metastasis in LABC patients (1-3). However, due to severe toxicity of chemotherapy drugs, early prediction of therapeutic response is essential to avoid exposure of non-responders to serious toxicity of NACT. Physical examination along with various imaging modalities like mammography, ultra-sonography, and MRI rely on the anatomical changes that have limitations like overestimation. The ability to identify non-responders early would be valuable because it would enable treatment to be tailored according to individual needs that would be more efficacious. Further, an early assessment of therapeutic response is essential in treatment planning and management. MRI is increasingly being used to monitor LABC undergoing NACT. However, changes in lesion size by dynamic contrast enhanced MRI are not detected until several weeks following chemotherapy (3). Recently, in-vivo ^{1}H MRS has been shown to be helpful in the diagnosis and treatment of breast cancer patients based on total choline-containing compounds (tCho). In this study we aim to determine: (a) the systematic changes of tCho and the tumor volume in LABC patients by sequential monitoring using in-vivo proton ^{1}MRS, and (b) to determine the clinical utility of these parameters in the early assessment of tumor response.

Materials and Methodology: Thirty LABC patients (44.4 ± 7.5 yrs, range 32 – 58 yrs) who elected to receive NACT 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 phased array breast matrix coil at 1.5 T (AVANTO, Siemens). Following the scout image, T1 and T2 weighted images were obtained in saggital plane. Thereafter, fat suppressed images in axial and coronal planes were acquired to identify the full extent of the tumor. Contrast enhanced MR 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. An additional spectrum of the same voxel without water and lipid suppression obtained for the concentration calculation using the water signal as internal reference. Pre-therapy (Tp0) spectrum was obtained from all 30 patients. Of these, 27 were monitored sequentially one week after I NACT (Tp1), 13 patients after II NACT (Tp2) and 29 patients after NACT (Tp3). The tCho concentration was calculated using the equation reported by Baik et al for 1.5 T (4), while volume was measured from MR images using perimeter method (5). RECIST criteria (6) was used to categorize patients into responders or non-responders. Responders were defined as subjects with ≥ 50% one-dimensional tumor size reduction after III cycle compared with the baseline while non-responders are with <50% of an increase in tumor size or no change. In case of tCho, responders and non-responders were categorized based on clinical response. Clinical response was evaluated by measuring the tumor volume. Statistical analyses were carried out in STATA using Generalized estimating equation (GEE). A p value of < 0.05 was considered significant in pre, I, II, III and NACT in case responders.

Table-1: Results of GEE [mean and standard error (SE)] for the changes in tCho concentration and tumor volume over the time for groups responders and non-responders.

	Responder		Non-responder	
	tCho (mmol/kg)	Volume (cm^3)	tCho (mmol/kg)	Volume (cm^3)
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Pretherapy (TP0)	5.1 (0.48) *, n=21	64.3 (13.3),n=20	2.7 (0.46),n=9	62.7 (11.2),n=10
I NACT (TP1)	2.6 (0.51) *,n=18	56.9 (13.4),n=19	3.1 (0.49), n=9	64.8 (11.4),n=8
II NACT (TP2)	1.6 (0.73) *,n=8	38.9 (14.6) *,n=7	1.9 (0.55),n=5	61.9 (11.9),n=5
III NACT (TP3)	0.43 (0.49) *,n=17	22.6 (13.3) *,n=17	2.7 (0.47),n=10	61.3 (11.2),n=10
*P<0.01 , in pre-therapy, I, II and III NACT in responders.				

Results: The MR spectral parameters obtained prior to therapy and after III NACT of a responder and non-responder is shown in Figure-1. Out of 30 patients, 21 were clinical responders and 9 were clinical non-responders. In responders, the mean concentration of tCho before therapy was 5.1 (0.48) which reduced significantly to 2.6 (0.51) after I NACT and to 1.6 (0.73) after II NACT and 0.43 (0.49) mmol/kg III after NACT (see Table-1). Whereas, in non-responders no significant difference was observed in tCho concentration following NACT. Tumor volume showed significant decrease only after II NACT in clinical responders whereas in non-responders no significant difference was observed. A cut- value off 0.88 for tCho (sensitivity 90% and specificity 85%, AUC=0.92) was obtained in order to differentiate the responders from non- responders after III NACT.

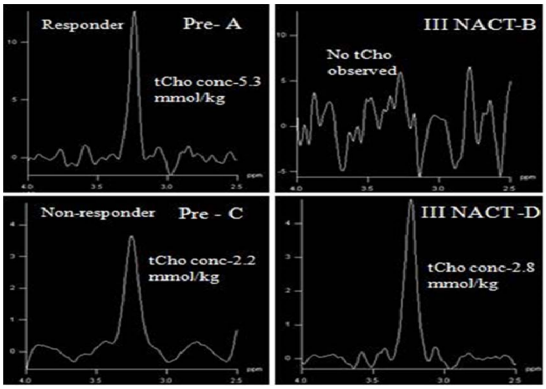

Fig-1 - The MR spectral patterns obtained prior to therapy and after III NACT of a responder and non-responder patient.

Discussion: In this study, we determined the absolute concentration of Cho containing compounds by sequential monitoring of LABC patients during various stages of NACT using in-vivo MRS. 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. While tumor volume showed significant decrease only after II NACT in clinical responders. The early reduction of tCho level can be interpreted as reflecting the inhibition of cellular proliferation and the cytotoxic effect of chemotherapy (7). The percentage reduction in tCho and tumor volume after I and III NACT were 39% and 6.5% and 86% and 58%, respectively in responders. In non-responders there was an increase of tCho by 52% and reduction of tumor volume by 7% after I NACT. After III NACT an increase of tCho by 8.5% and reduction of tumor volume by 33% was observed. Our data demonstrated that the metabolic changes occur earlier than the morphological changes after I NACT. Meisamy et al (8) and Baik et al (7) also showed similar changes in tCho concentration and tumor size. In conclusion, our results showed that the determination of absolute concentration of tCho before therapy and at various stages of NACT show promise for early detection of tumor response to therapy. Further, our data showed that choline biomarker is a better predictor of early response of breast cancer than tumor volume.

References: (1) Sachelarie et al. Oncologist. 2006; 11: 574-89; (2) Bonadonna et al. J Natl Cancer Inst. 1990; 82: 1539-45; (3) Rieber et al. Eur Radiol. 2002; 12: 1711-19; (4) Baik et al. Magn Reson Mater Phy 2006; 19: 96-104; (5) Sharma et al. NMR Biomed. 2009;22: 104-13; (6) Therasse et al. J Natl Cancer Inst. 2000; 92: 205-16; (7) Baik et al. Ann Oncol. 2008; 19: 1022-24; (8) Meisamy et al. Radiology 2004; 233: 424-31.