Treatment Response Monitoring in Breast Cancer Patients undergoing Neoadjuvant Chemotherapy and Association of Total Choline with Receptor Status: A Feasibility Study using Serial 3D High-Speed MR Spectroscopic Imaging and Dynamic Contrast Enhanced MR Imaging at 3 Tesla

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INTRODUCTION Measuring tCho in breast cancer using single voxel MR spectroscopy (MRS) was reported to improve lesion characterization, thus improving the limited specificity of dynamic contrast enhanced (DCE) MRI[1]. Studies using single voxel MRS[2] and MR spectroscopic imaging (MRSI)[3] suggest that the change in tCho concentration between baseline and as early as 24 hours after the first dose of neoadjuvant chemotherapy can serve as an indicator for predicting clinical response to neoadjuvant chemotherapy in locally advanced breast cancer. However, the association of total Choline levels with receptor status reported in recent studies has been variable[4-6]. In this study we describe quantitative serial 3D mapping of tCho in patients with biopsy confirmed breast cancer using high-speed Proton-Echo-Planar-Spectroscopic-Imaging (PEPSI)[7] at 3 Tesla to monitor changes in total Choline during neoadjuvant therapy in comparison with dynamic contrast enhanced (DCE) MRI. A secondary goal was to investigate association of total Choline with receptor status.

METHOD Thirteen patients (age range: 28 – 77 years) with biopsy-confirmed, infiltrating ductal carcinoma (IDC) were studied with DCE-MRI and 3D MRSI using a 3T MR scanner (Siemens Trio, Erlangen, Germany) equipped with 8- and 16-channel breast array (Hologic Inc., Bedford, MA). Informed consent was obtained. Nine patients were scanned before initiation of neoadjuvant therapy and five of these patients were followed during neoadjuvant therapy. Four patients entered the study after initiation of neoadjuvant therapy and 2 of these patients were followed during neoadjuvant therapy. 3D MRSI data of an entire oblique slab on the lesion side was performed using PRESS volume prelocalized 3D PEPSI with MEGA lipid suppression using TR/TE=2000ms/135ms, matrix size up to 32×16×8, voxel size=1cc, and total acquisition time of 10 minutes (including a water reference scan acquired with TR/TE: 2000ms/30ms). The PRESS volume selection was tailored to encompass the entire lesion and adjacent glandular tissue. TE-averaging (8 steps centered around TE: 135 ms, ΔTE: 2.5 ms) was employed to minimize possible gradient sideband artifacts. Complete outer volume suppression using 8 slices was applied around the PRESS volume selection. Localized spectra were reconstructed on the scanner using a 3D Hanning filter and weighted combination of coil data. Spectral quantification was performed using LCModel-based spectral fitting in reference to tissue water as described in our recent study[7]. A customized basis set was developed that contains Cho, GPC and PCho, 10 empirically modeled Lorentzian singlet peaks representing broad and irregular line shapes of residual lipid signals within the 2.0 - 2.9 ppm range, and soft constraints for modeling lipid and macromolecule resonances using default settings in LCModel. Total Choline (Cho+GPC+PCho) was mapped using Cramer Rao Lower Bound thresholds of 50 % and line width threshold of 0.2 ppm. The molal concentration of tCho was calculated by compensating for T_1-related signal saturation and for T_2-related signal relaxation using relaxation times reported in previous studies[7]. The tCho volume (# of voxels with above threshold tCho * voxel volume) was computed. Tumor volume in DCE-MRI was measured using semi-automated tissue segmentation on an Aegis workstation (Hologic Inc., Bedford, MA) based on pixel-wise time course analysis of contrast enhancement.

RESULTS Total Cho maps showed localized enhancement in the center of focal lesions (Fig. 1a,b) and spatially distributed enhancement in multi-focal disease (Fig.1c). Triple negative tumors compared to non-triple negative tumors were associated with higher tCho concentration, larger spatial extent of tCho, larger tumor volume measured by DCE-MRI (Table 1) and higher tumor grade. Total Cho was not detected in triple positive tumors. Interindividual differences were noted: In patients 3, 7 and 9 the decrease in concentration and/or volume of total Choline at the second time point was associated with an increased tumor volume in DCE-MRI. In patient 10, tCho became undetectable at the 3rd time point while tumor volume in DCE-MRI remained unchanged.

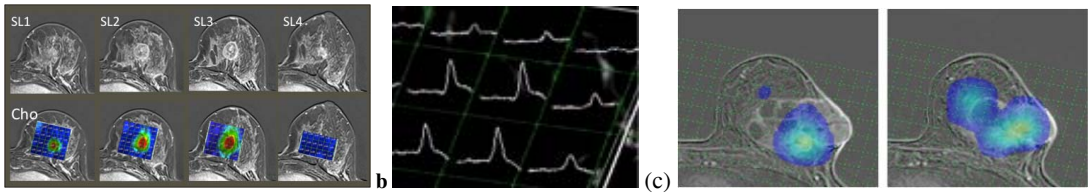

Figure 1: (a) 3D tCho mapping in a patient with IDC grade 3 (b) Spectral array from slice 3 showing tCho within the tumor (displayed spectral range: 3.0-3.5 ppm). (c) Two slices in multi-focal IDC grade 3 with spatially heterogenous tCho distribution.

						Max tCho [mM]/mean tCho [mM]/tCho volume [mL]/DCE-MRI tumor volume [cc] vs. treatment					
Patient	Age	Tumor Grade	Tumor Stage	ER & PR Status	HER-2 status	Treatment duration at scan 1	Before	1-7 days	8-21 days	3-12 weeks	> 3 months
1	55	3	T2N0M0	ER -/PR -	NEG	0	1.2/1.2/1.0/1.0				
2	35	3	T2N1Mo	ER -/PR -	NEG	0	5.3/2.1/34.0/8.5				
3	52	3	T3N1M0	ER -/PR -	NEG	0	3.3/1.6/76.0/33.5	4.2/1.9/27.0/44.1			
4	45	1	T2N0M0	ER +/PR +	NEG	0	0.5/0.5/1.0/8.2				
5	57	2	T4bN3cM0	ER -/PR -	POS	6 m					0.7/0.7/1.0/0.7
6	28	3	T3N1M0	ER -/PR +	POS	4 d		2.4/0.8/23.0/59.4	3.9/1.5/21.0/-	1.2/0.8/2/0/7.0	
7	54	3	T3N1M0	ER +/PR -	NEG	21 d			2.4/1.0/7.0/10.4	1.6/0.9/4.0/10.6	0.0/0.0/0.0/1.3
8	60	3	T3N1M0	ER +/PR+	NEG	0	TF/TF/TF/13.7	1.6/0.9/14.0/7.5			
9	50	3	T2N0M0	ER +/PR -	POS	0	0.7/0.6/2.0/6.0	0.3/0.3/7.0/9.0			0.0/0.0/0.0/0.0
10	49	3	T2N0M0	ER-/PR+	NEG	0	0.4/0.3/4.0/10.8	0.8/0.4/7.0/9.0	0.0/0.0/0.0/10.4		
11	60	2	T1cN0M0	ER +/PR +	POS	0	0.0/0.0/0.0/0.4				
12	50	2	T4dN3M0	ER +/PR +	POS	1 y					0.0/0.0/0.0/0.0
13	64	3	T2N0M0	ER +/PR +	POS	0	0.0/0.0/0.0/11.6	0.0/0.0/0.0/-			

Table 1: Tumor status, 3D tCho measurements and DCE-MRI scans in 13 patients. T/F: Technical failure

DISCUSSION AND CONCLUSION This study demonstrates that in selected patients serial quantitative 3D mapping of tCho can detect early responses to neoadjuvant chemotherapy when DCE-MRI is still unspecific. In our preliminary study, concentration and spatial extent of tCho was associated with receptor status and tumor grade, indicating an association between the high rate of cell proliferation and receptor status. This is consistent with one of the recent studies[5] but at variance with another recent study[6]. Given this heterogeneity across studies, a larger scale study is required to further examine the association of tCho with receptor status. Using 3D MRSI is also advantageous for assessing spatial heterogeneity of tCho and receptor status in in multi-focal and multi-centric disease. Regional differences in treatment response and association of changes in spatial extent of tCho with regional changes in DCE-MRI are currently under investigation. Characterization of in-vitro biomarkers in tissue samples after surgery to validate in vivo findings is planned. The long-term goals are to utilize 3D high-speed MRSI as an early predictor of treatment failure in women undergoing neoadjuvant therapy (i.e. chemotherapy, endocrine therapy or biologic therapy) for breast cancer and to develop an improved screening protocol for high-risk patients.

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