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 MRI at 3 Tesla

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. Studies using single voxel MRS2 and MR spectroscopic imaging (MRSI) 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 variable3. 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)4 at 3 Tesla to monitor changes in total Choline during neoadjuvant therapy in comparison with dynamic contrast enhanced (DCE) MRI.

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 protocolized 3D PEPSI with MEGA lipid suppression using TR/TE=2000ms/135ms, matrix size up to 32x16x88, 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 with a minimum of 6 mm of the normal appearing tissue. TE-averaging (8 steps centered around TE: 135 ms, ΔTE: 2.5 ms) was employed to minimize possible gradient artifact. 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 LCMR-based spectral fitting in reference to tissue water as described in our recent study. A customized basis set was derived 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 LCMR. Total Choline (Cho+GPC+PCho) was mapped using Cramer Rao Lower Bound thresholds of 50% and line width constraints for modeling lipids.

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. Intergroup differences were noted: In patients 3, 7 and 9 the decrease in concentration and/or volume of tCho became undetectable at the 3rd time point while tumor volume in DCE-MRI remained unchanged.

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 studies3 but at variance with another recent study4. This heterogeneity across studies, a larger scale study is required to further examine the association of receptor status with using 3D MRSI is also advantageous for assessing spatial heterogeneity of tCho and receptor status 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 chemotherapy. As the sensitivity of tumor detection of MRSI is challenged by the detection of normal breast tissue, we propose to use MRSI for breast cancer and to develop an improved screening protocol for high-risk patients.


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