Distinction of Invasive Lobular Carcinoma, Invasive Ductal Carcinoma, and Healthy Breast Tissue In Vivo With L-COSY at 3T

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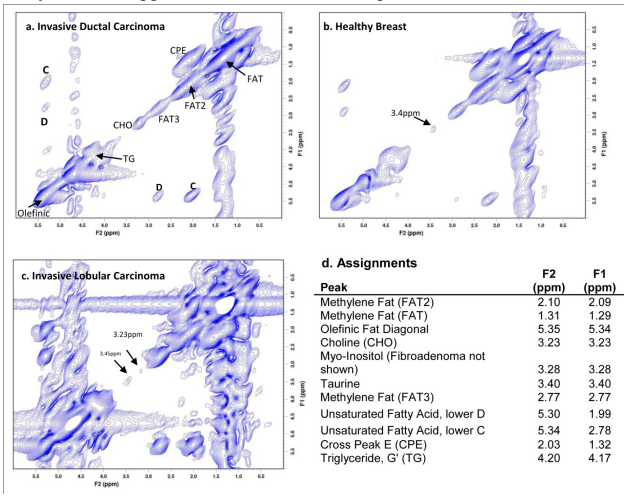
Introduction: The presence of a choline resonance at 3.23ppm has been shown by several groups to be a diagnostic marker for breast cancer in vivo. For review see[1]. A second resonance at 3.28ppm is recorded in some healthy volunteers and lactating mothers. However in some cases both these resonances can be overshadowed in 1D MRS by intense lipid resonances. Thomas, et al has suggested that the lipid itself may be diagnostic based on L-COSY methods[2]. We extend this work to study invasive lobular and ductal cancers.

Objective: To use in vivo L-COSY to study the alterations in lipid chemistry associated with breast cancer. Determine if the lipid moieties provide additional diagnostic information to that of the choline resonance at 3.23ppm for invasive cancer and to compare ductal and lobular cancer.

Patients and volunteers: Six women with histopathologically confirmed invasive breast cancer were recruited for this study. Four patients were determined, by post operative pathology, to have ductal carcinoma and two with lobular carcinoma. Four data sets were additionally acquired, from healthy age matched controls. The study had IRB approval and was HIPA compliant.



d. Assignments

Peak	F2 (ppm)	F1 (ppm)
Methylene Fat (FAT2)	2.10	2.09
Methylene Fat (FAT)	1.31	1.29
Olefinic Fat Diagonal	5.35	5.34
Choline (CHO)	3.23	3.23
Myo-Inositol (Fibroadenoma not shown)	3.28	3.28
Taurine	3.40	3.40
Methylene Fat (FAT3)	2.77	2.77
Unsaturated Fatty Acid, lower D	5.30	1.99
Unsaturated Fatty Acid, lower C	5.34	2.78
Cross Peak E (CPE)	2.03	1.32
Triglyceride, G' (TG)	4.20	4.17

Figure 1. Representative *in vivo* L-COSY from (*a*) invasive ductal carcinoma, (*b*) healthy breast, and (*c*) invasive lobular carcinoma. (*d*)Table of assigned peaks.

Data Acquisition: L-COSY was acquired on a 3T MR scanner (TIM Trio, Siemens, Germany) using a 16 channel breast coil (RAPID MR Intl, Ohio). The region of interest (mean size 3.3 cm^3) was chosen following the contrast enhanced T1 weighted imaging to identify the lesion in patients and was placed in healthy glandular tissue for the controls. Localized shimming was performed by automatic adjustment of zero- and first-order shim gradients using the automatic B0-field mapping technique (Siemens AG, Erlangen, Germany) followed by manual adjustment of zero-order shim gradients to achieve width of water at half-maximum of better than, or equal to 30Hz. Following frequency adjustment water-selective suppression was optimized using the WET-technique. The L-COSY sequence employed used three shaped and spatially selective RF pulses using TE (initial) of 30ms, TR of 1.25 sec, 8 averages per increment, spectral width in F2 was 2000 Hz, t1 increment size of 0.8 ms, indirect spectral width used was 1250 Hz and the number of increments was 64. The "WET" water suppression was applied before the acquisition sequence. Scan time was 11 minutes.

Data Processing: Raw L-COSY data were transferred to Matlab (Mathworks, Natick MA), for signal combination from multiple elements followed by row concatenation into a 2D matrix and reformatting. FELIX 2007 (FELIX NMR, San Diego CA), was used for spectral processing and analysis. The 2D time-domain data consisted of 64 FIDs with an FID length of 1024 points. Datasets were zero-filled from 512 to 2048 points in the direct dimension (F1) and from 64 to 512 points in F2. A skewed sinebell-squared window function with skew parameter of 0.3, size of 512 points, and phase of 0 degrees was applied to F1. A sinebell-squared window function with a size of 64 points and phase of 0 degrees was applied to F2. A macro was written to measure the volume of the crosspeaks and diagonal peaks referenced to the creatine volume on the diagonal.

Results and Discussion: L-COSY acquired from a healthy volunteer is compared with that recorded from an invasive ductal and invasive lobular carcinoma in Figure 1. The assignments are listed in Figure1d. The peak volume ratios of Cho/FAT3 are shown in Figure 2A and of FAT/FAT3 ratio in Figure 2B. These results suggest the use of simple algorithm to distinguish between invasive ductal carcinoma, invasive lobular carcinoma, and healthy breast tissue in vivo using the L-COSY method. If a choline resonance is recorded at diagonal position 3.23 ppm with a Cho/FAT3 peak volume ratio greater than ~0.60, then this is an invasive ductal carcinoma. If, upon inspection, the latter scenario is found not to be the case, then the FAT/FAT3 peak volume ratio may be measured. If it is below ~150, then the voxel likely contains invasive lobular carcinoma. If the FAT/FAT3 peak volume ratio is above ~150 then the voxel likely contains healthy glandular breast tissue.

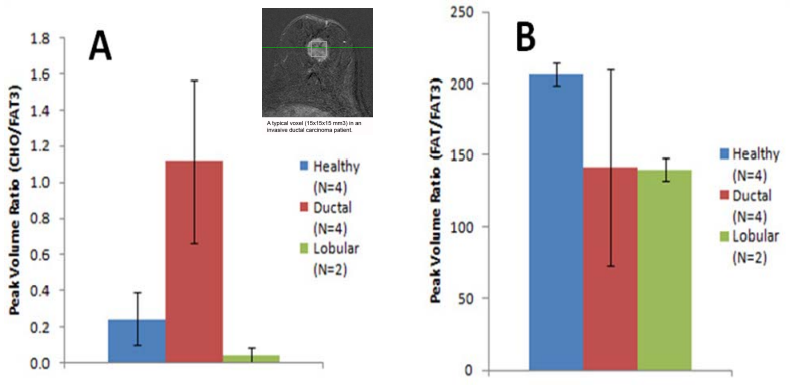


Figure 2A.Choline peak volume relative to the FAT3 peak volume for healthy breast *(blue)*, invasive ductal carcinoma *(red)*, and invasive lobular carcinoma *(green)*. Error bars indicate 95% confidence intervals. **Figure 2B.** FAT peak volume relative to the FAT3 peak volume for healthy breast *(blue)*, invasive ductal carcinoma *(red)*, and invasive lobular carcinoma *(green)*. Error bars indicate 95% confidence intervals. Inset shows a typical 15x15x15 mm^3 placed in an invasive ductal carcinoma.

Conclusion: 2D COSY can measure differences in the MR visible lipid associated with invasive breast cancer and based on preliminary data appears to assist in the distinction between invasive ductal and invasive lobular cancer. Pattern recognition methods now need to be developed to automate this diagnostic procedure.

(1) Mountford, C. et al *NMR Biomed* **2009**, *22*, 54-64.
(2)Lipnick, S. et al *NMR Biomed* **2010**, *23*, 922-930.