Design of Quality Control Measures for a Multi-site Clinical Trial of Breast MRS - ACRIN 6657

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Introduction: The American College of Radiology Imaging Network (ACRIN) is supporting a multi-site clinical trial using single voxel spectroscopy (SVS) for characterizing breast cancer. ACRIN 6657, *Contrast-Enhanced Breast MRI and MRS for Evaluation of Patients Undergoing Neoadjuvant Treatment for Locally-Advanced Breast Cancer*, is being conducted as part of the I-SPY multi-center trial evaluating imaging and tissue-based biomarkers for assessing response to neoadjuvant chemotherapy (website reference). In an extension of the original trial aims, ACRIN 6657 is testing the utility of MRS for quantifying early response to therapy in 140 patients and will acquire quantitative estimates of the total choline concentration ([tCho]) using SVS and using water as an internal reference. A previous single-site pilot study showed that an acute decrease in [tCho], measured one day after the administration of the first dose of adriamycin/cytoxan chemotherapy, was predictive of overall clinical response (*2*). ACRIN 6657 will test this finding in the multi-site trial setting by making longitudinal measurements of [tCho] pre-treatment, shortly after the initial dose of chemotherapy, and after completion of therapy prior to definitive surgery.

Ensuring that the spectroscopic [tCho] measurements can be performed with sufficient accuracy and precision to address this clinical aim is a difficult challenge. The heterogeneity of the eleven participating sites, which will use MR scanners and breast coils from several different manufacturers and at different field strengths (1.5 and 3T), makes the task of ensuring consistency even more critical. The goal of this abstract is to describe the design of the study and its various quality control measures and present initial findings from the quality control phantom scans.

Materials and Methods: The spectroscopic acquisition and analysis generally follows Meisamy *et al.* (*2*). SVS is performed with a PRESS localization sequence, CHESS water suppression, and either TE averaging or spectral lipid suppression if needed to suppress lipid sidebands. A separate water T2 measurement is acquired from the same voxel with identical B1 and B0 adjustments to use as an internal reference and to correct for changes in water T2, which have been reported in the neoadjuvant setting (*3*). The water, lipid, and tCho resonances are individually fit in the frequency domain with Voigt lineshape models. The tCho concentration is calculated from the ratio of the tCho:water resonance amplitudes and corrected for relaxation rates and acquisition differences (gain, averages), and reported as [tCho] in units of mmol tCho per kg water (mmol/kg). Several quantitative quality metrics are extracted from the data, including the water-to-fat ratio, spectral linewidth, signal-to-noise ratio, and the Cramer-Rao estimate of the fitting standard deviation. The final spectra are reviewed by a spectroscopist along with images showing voxel placement, and qualitatively scored for presence of artifacts, patient motion, and voxel placement. Both quantitative and qualitative criteria must be met for acceptance of the MRS data. After acquisition, all raw spectroscopy data is sent to a central repository at ACRIN and then processed at a single central laboratory.

Regular quality-control scans are performed at each site using a standardized phantom to evaluate consistent MRS performance. The phantoms were produced at a central lab and distributed to all participating sites. The normal phantom, shown in Fig. 1, consists of a 2 liter leak-proof bottle containing vegetable oil and a 2" plastic sphere mounted on a post ~2" above the bottom. The sphere contains 1 mM phosphocholine, a small amount of Gd-DTPA, 10 mM deuterated TSP as a frequency reference, and 0.1% sodium azide. The control phantom is identical except it contains no phosphocholine. Prior to enrolling any subjects, each site must submit a *Entry Quality Control* (QC) data set showing acceptable MRS performance in both the normal and control phantoms for each MRI system used in the study. Throughout the trial each site must also perform a condensed *Weekly QC* scan. All QC data is sent to ACRIN and processed centrally to evaluate the consistency of each system.

The patient acquisitions are similar to the QC scans. After a complete dynamic contrast-enhanced MRI study, the operator and radiologist plan the voxel placement and perform pre-scan calibrations as needed. Then the water reference is acquired, followed by the water suppressed choline scan. After the MRS acquisition an additional 3D image is acquired to evaluate patient motion. All patients that enroll receive a MRI/MRS scan prior to therapy (MR1), an acute post-treatment scan either 1 day (20-28 hrs) or 2-4 days (48-96 hrs) after their first chemotherapy treatment (MR2), and a final scan after all chemotherapy and prior to definitive surgery (MR4). A subset of 30 patients will be recruited to undergo a second baseline scan (MR1.1) to evaluate *in vivo* reproducibility.

Results: Two of the ten sites have successfully completed their Entry QC scans and are eligible to begin scanning subjects. The trial opened for enrollment in September 2007, with four patients enrolled to date. Example spectra from the Entry QC of one site are shown in Fig 2, showing positive tCho in the normal phantom and a clean baseline in the control phantom. Acquisitions of both QC and patient data are ongoing and expected to continue throughout 2008.

Discussion: The quality control strategy for the MRS acquisitions in this trial is to set performance criteria and monitor compliance with those criteria, rather than dictate specific acquisition sequences and hardware that must be used. This enables sites to use the best scanner, pulse sequence variation, and breast coil available provided it performs acceptably. Although this leads to a variety of MRS acquisition methods, there are controls built in to the study design that correct for the primary sources of variation across sites. Table 1 shows a list of factors that can contribute to variations in [tCho] measurements and the mechanism(s) used to control or correct for these variations. The primary tactics for maintaining consistency are the use of water as an internal reference, regular quality-control scanning, centralized data analysis, and a relatively rapid acquisition-analysis-feedback cycle to alert sites with have data problems.

References: 1) http://www.acrin.org/6657_protocol.html; 2) Meisamy S, I. Radiology. 2004 Nov;233(2):424-31; 3) Manton DJ, *et al.* Br J Cancer. 2006 Feb 13;94(3):427-35. **Acknowledgements:** The American College of Radiology Imaging Network and its supporting grants U01 CA079778 and U01 CA080098, the Breast Cancer Research Foundation, NCI SPORE grant CA58207, CALGB CA31964, NCICB, and R01 CA120509.

Table 1 – Methods for addressing different sources of variation in [tCho] measurements

Potential Source of variation	Control Mechanism
Field strength	Stratified by design
Timing of post therapy scan	Stratified by design
PRESS sequence variations	Phantom performance testing (Entry QC)
Scanner instability	Weekly QC scans
Scanner & breast coil sensitivity	Water referencing
Nominal voxel size	Water referencing
Voxel placement	Training; review and feedback
B0 shim performance	Water referencing; review and feedback
B1 mis-calibration	Water referencing
Intrasubject water T2 change	Water referencing and T2 measurement
Patient motion	Imaging pre- and post-MRS
MRS Analysis	Standardized at central lab
Effects of Biopsy	Uncontrolled
Effects of Gd	Uncontrolled

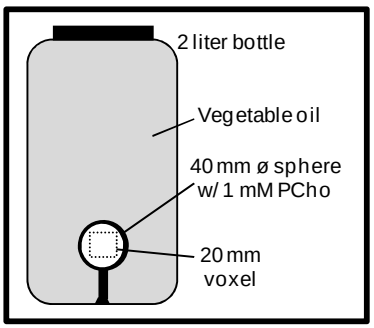

Fig. 1 – ACRIN 6657 Breast MRS phantom, emulating a focal lesion in adipose-dominant breast.

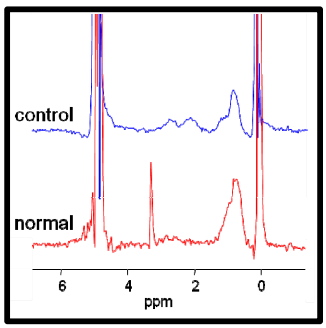

Fig. 2 – Resultant spectra from an Entry QC scan, showing a clear tCho resonance at 3.2ppm acquired in the normal phantom (red) and a smooth baseline at 3.2 ppm in the control phantom (blue).