Recommendations for MRS measurement methods and endpoints for use in multicenter trials of anti-cancer therapeutics

General

- ^{1}H MRS has reached a sufficient level of maturity to be ready for multi-center, multi-vendor clinical trials in brain, prostate and breast cancer

- ^{1}H MRS trials can be performed at 1.5T or 3T, but the move toward 3T is encouraged where available.

- Qualifying technically for site entry into trial should be based upon meeting quality assurance specifications (eg, SNR) and successful acquisition of data from at least 2 volunteers.

- Post-processing and analysis software is a critical issue that will be application dependent. Centralized processing and database management are recommended for initial clinical trials.

- There is a need for ^{1}H MRS of metastatic disease. Further technical developments and pilot studies are necessary and should be performed at individual sites at this time.

- Further development and validation of ^{13}C and ^{31}P MRS methods are encouraged, but should continue at individual investigator sites at this time.

Specific Applications

Breast

- Single-voxel spectroscopy using PRESS, STEAM, or LASER, with TE-averaging to minimize sidebands

- Quality assurance test to be run each day of study.
    - Use the following breast phantom: a 750 ml bottle containing shortening (Crisco), with a centrally-located sphere (diameter ~2 cm) containing 1 mM choline in normal saline, at a constant room temperature.
    - Acquire a localized spectrum of the choline solution using a 1 mL voxel and the same set of acquisition parameters that are used for measuring choline in vivo (eg, identical TR, TE, NEX, and TE-averaging).
    - Achieve choline SNR > 3. (SNR ≡ choline peak area divided by rms noise).
    - Achieve lipid and sideband intensity (as measured anywhere beyond ±1 ppm from the water peak) not exceeding 33% of the measured choline intensity

- Voxel placement
    - Voxel selection should be based on lesion architecture and kinetics of DCE-MRI, in accordance with DCE-MRI panel recommendations

- o Operator should prescribe a voxel to fit just inside the lesion borders. Voxels should be planned to maximize coverage of the lesion while minimizing inclusion of adipose tissue.

- Data Collection

  - o Acquire choline data with TE-averaging (NEX ≥ 128).

  - o Measure the T_2-corrected water reference signal from the voxel by acquiring unsuppressed water spectra using at least 4 different TE values, TR ≥ 6 s, and NEX ≥ 1.

  - o Acquire scout image immediately before and after MRS data acquisition to verify that the subject has not moved.

  - o When possible, acquire diffusion-weighted images (with at least 3 different b-values) to estimate necrotic fraction.

- Spectral fitting and choline quantitation

  - o Use a fitting algorithm that performs robustly in the presence of intense lipids signals, such as the TDFD method of Slotboom et al, which performs fitting in the time-domain and minimizes fit residuals in the frequency domain (± 0.2 ppm about the choline peak). Use a method, such as the Cramer-Rao minimum variance bound, to estimate error and minimum detectable level (MDL).To quantify the choline in the voxel, use the T_2-corrected water signal from the voxel as an internal reference, using a method such as that proposed by Bolan et al.

Prostate

- Goal: To establish a consensus prostate MRI/MRSI acquisition and analysis protocol in order to enhance translational research through the development of multi-site, multi-platform validation trials and shared databases. The following recommendations were developed with input from those using GE, Siemens and Philips prostate MRSI protocols.

- MRI Positioning, Coils, and Acquisitions

  - o Patients should be scanned in the supine position using body coil excitation and pelvic phased array coil in combination with an endorectal coil for signal reception. Currently, studies are performed on 1.5 T clinical MR scanners, however, 3T MRSI techniques are under development and may provide significant benefits for prostate MRI/MRSI studies.

  - o Axial T1-weighted images from the aortic bifurcation to the symphysis pubis. TR/TE = 600-700/-12 msec. Slice thickness 4-6 mm. Interslice gap 0-1 mm. Matrix 256 x 192. Number of excitations = 1. Field of view = 20-32 cm.

  - o Contiguous, thin-section high-resolution axial and coronal T2-weighted images of the prostate and seminal vesicles. TR/TE = 4000-6000/90-120 msec. Echo train

length = 8 to 16. (RARE, FSE, TSE). Slice thickness 3 mm. Matrix 256 x 192. Frequency direction anteroposterior. Number of excitations = 3-4.

- o Thin-section high-resolution sagittal T2-weighted images can improve the placement of outer voxel saturation pulses for the MRSI acquisition, but usually do not add much to the clinical interpretation of the anatomic images.

- MRSI Acquisitions

  - o High spatial resolution 3D MRSI is necessary for the spectroscopic investigation of the prostate due to its complex zonal anatomy, the often small multi-focal nature of prostate cancer and the inability of anatomic imaging to accurately localize regions of interest within the prostate.

  - o The proposed 3D MRSI methods are based on techniques that have been developed for prostate and used for multi-site trials of prostate MRI/MRSI including ACRIN 6659 (GE platform), and the Siemens sponsored clinical trial.

  - o Sequence: PRESS-CSI with optimized pulses having sharp transition bands for improved volume selection and high spectral bandwidths (reduced chemical shift artifacts).

  - o MRSI volume is selected from the T2-weighted images (most often in the axial plane) with the goal of maximizing coverage of the prostate, while minimizing inclusion of periprostatic fat and the air-tissue interface of the rectum.

  - o To further improve spectral localization and reduce contamination from surrounding tissues, graphically placed high-bandwidth outer voxel suppression pulses should be utilized to shape the rectangular PRESS selected volume to match the shape of the prostate. The graphic outer voxel suppression pulses should be placed using high resolution images in multiple planes and caution must be taken to avoid suppressing spectra within the prostate.If a susceptibly matched fluid is used for inflatable Endorectal coil or a solid endorectal coil is used, problems with magnetic are dramatically reduced and volume selection becomes easier.

  - o Magnetic field homogeneity should be optimized over the selected volume until a water linewidth of <14 Hz is attained for acceptable quality proton spectra.

  - o 3D MRSI spectral resolution needs to be small enough to place spectroscopic voxels totally within the zones of the prostate and within regions of prostate cancer in order to minimize partial volume effects. Nominal resolution should be ≤ 0.3 cc ($\approx$ 7mm on a side).

  - o TE needs to be optimized for both citrate and spermine J-modulation and be sufficiently short to avoid severe signal-to-noise losses due to T2 relaxation. Optimum TE requires a compromise between the saturation of metabolite resonances, particularly those with longer T1's like choline and the MRSI

acquisition time which should be ≤ 20 min. Typical MRSI parameters: TR = 1 s; TE = 130 ms; NEX = 1; phase encoding steps = 16 x 8 x 8; FOV = 110 x 55 x 55 mm^3; scan time = 17 min.

- Quality Assurance to be run each day of study

  - Two types of phantoms have been used. One is just the brain MRS phantom supplied by the vendor and standard brain MRS QA procedures are run but with a standard 3inch surface coil. The phantom with prostate metabolites consists of 10mM creatine, 4mM choline, 33mM citrate and 12.5mM lactate.

- Prostate MRI and MRSI Data Analysis

  - Interpretation of MR images is improved by correcting for the reception profile of the endorectal and pelvic phased-array coils.

  - It is necessary to correct for constant and spatially dependent frequency and phase shifts as well as baseline variations due to broad resonances or residual water. Frequency and phase corrections may be achieved using a water reference or by using the spectra themselves to estimate correction parameters. Peak areas may be estimated by integration between a range of different frequencies or by fitting baseline subtracted data as a sum of components with particular line-shapes. Whichever fitting algorithm is used, the number of spectra involved makes it critical that the procedure is fully automated, as well as robust to low signal to noise and missing peaks.

  - Requires alignment of the spectral data with the MR images and the archiving of spectral data with the corresponding images in a standardized (DICOM) format.

  - It is also critical to have software that provides estimates of the frequency, line-widths, peak heights, and areas of the metabolite peaks and the spectral noise. S/N of 5/1 defined as a significant peak.

Brain

Two possibilities should be considered for the MRS part of the protocol. The first is more universally available and makes use of single voxel short echo MRS in an attempt to characterize different types of lesions. The second makes use of multi-voxel 3-D MRSI and is intended to define the spatial extent of the lesion for treatment planning and characterization of lesion heterogeneity, and to follow response to therapy. Based upon ongoing studies it is anticipated that perfusion weighted and diffusion weighted MRI should also be added to the protocol in order to investigate whether the combination of these technologies provides an improved characterization of brain mass lesions. Although adequate data can be obtained at 1.5T, preliminary results at 3T show that it can provide significantly improved MRSI, PW-MRI and DW-MRI. Hence the higher field strength should be used whenever possible. Automatic

shimming should be used, with higher order shims where they are available. Another clear improvement is from using an 8 channel as opposed to a volume head coil. This complicates the data analysis and requires the acquisition of coil calibration images but should also be considered whenever possible. Quality assurance for MRS data should be performed using a commercially available phantom containing brain metabolites. The protocols should include the following:

Anatomic imaging

- Scout

- axial FLAIR, typical parameters TR/TE/TI = 10000/122/2200, with 1mmin plane resolution, 3mm slice thickness

- 3-D axial T1- weighted gradient echo images, typical parameters TR/TE/Flip = 27/6/40, with 1mm in plane resolution.1.5mmslice thickness

- Post-Gd T1- weighted gradient echo images as above

Dynamic Contrast Perfusion-MRI

- Dynamic gradient echo single shot echo planar images acquired during the bolus of a Gadolinium contrast agent, 0.1mm/Kg, injection speed 5ml/s. Typical acquisition parameters TR/TE/Flip = 1250/54/35, 60-80slices, 3-6mm thick, 26cm FOV, 128x128 matrix.

DW-MRI

- Diffusion weighted spin echo single shot echo planar images, 3-4mm slice thickness, TR/TE = 5000/84, 6 gradient directions, 36x21cm FOV, 256x128 matrix, b = 1000 s/mm2

Single voxel MRS

- PRESS or STEAM volume selection with TR=2500ms, short TE (30-40ms), one voxel from the lesion and one voxel from contra-lateral normal appearing white matter, voxel size 4-8cc

3-D MRSI

- PRESS volume selection with out of voxel suppression and 3-D phase encoding to cover both the lesion, surrounding tissue and as much of the contra-lateral normal appearing brain as possible, typical parameters TR/TE=1000-1100/144, matrix 12x12x8, nominal spatial resolution 1cc

Data Analysis

- Anatomic MR images should be analyzed to estimate the volumes of the T2-hyperintensity (T2L), the volume of the contrast-enhancing lesion on T1-weighted images (CEL) and the volume of necrosis.

- PW images should be processed to estimate maps of the relative cerebral blood volume, time to peak and percentage recovery.

- DW images should be processed to estimate maps of apparent diffusion coefficient (ADC) and fractional anisotropy (ANI).

- Single voxel MRS data should be analyzed using a spectral fitting algrothm such as LC Model or the TDFD method to obtain estimates of metabolite intensities.

- Multi-voxel MRS data should be reconstructed to provide a 3-D array of spectra, centered on the selected volume. Quantification of individual spectra requires frequency, phase and baseline correction algorithms.

- For cases where the PW or DW images are distorted relative to the anatomic images they should be aligned using non-rigid registration algorithms

- For evaluation of serial MR examinations, the anatomic images should be aligned using commercially available registration algorithms and the geometric transformations applied to the images and MRSI data

- Quantitative parameters should be extracted from the parametric maps obtained from the PW and DW images to represent values in normal appearing white matter, the T2L and CEL

- For the single voxel MRS data, pattern recognition techniques should be applied to classify the spectra according to their metabolite levels.

- For MRSI data quantitative parameters should be extracted to define the extent of the metabolic abnormality, maximum choline, maximum Choline/NAA, maximum Choline/Creatine, maximum lactate and lipid intensities and the temporal changes in these parameters. Values should be normalized relative to contra-lateral normal appearing white matter.

Future

- Uniform spectral processing and analysis on the vendors' scanners will be preferred.
- Multicenter trials of ^{13}C and ^{31}P MRS are expected in the future after remaining technical issues are solved.