Detection and grading of prostate cancer using model-based spectral fitting

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TARGET AUDIENCE: Researchers and clinicians interested in methods for identifying clinically significant prostate cancer.

PURPOSE: While multi-parametric MRI (mpMRI) of the prostate has been shown to be a valuable tool for non-invasively localizing and staging prostate cancer (PCa), its success at assessing disease aggressiveness has been limited. One potentially powerful tool in the mpMRI arsenal is spectroscopy. Three dimensional spectroscopic imaging (3DSI) is actively being pursued at many centers as a means to further detect and identify clinically significant disease. It has been previously shown that quantification of prostate 3DSI data can be improved through model-based fitting using LCModel[1] to fit and quantify overlapping resonances in the prostate ^{1}H spectrum at 3 Tesla[2-5]. Herein, we further investigate the promise of this quantification strategy to yield sensitive biomarkers for detecting disease and assessing aggressiveness (i.e. grade).

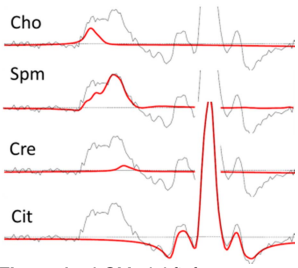

Figure 1: LCModel fit from a non-cancer voxel. (Nominal voxel volume 180 μL)

METHODS: Acquisition Details: From a cohort of 53 subjects who received an mpMRI study for whom complete MRI and fully digitized pathology data existed, 22 patients were identified with lesion larger than 0.5 cm^3 and included in this study. Anatomic scout T2 weighted (T2w) turbo spin echo (TSE) images were acquired for spectroscopy planning. Studies used a surface array combined with a perfluorocarbon-filled endorectal coil (ERC) for signal reception. A product PRESS-SI sequence was used for localization with sequence timing following that detailed by Scheenen et al.[6].

LCModel Fitting: The metabolites of interest in the prostate consist of the choline-containing compounds (glycerophosphocholine (GPC), phosphocholine (PCho) and choline (Cho)), spermine (Spm), which represents the polyamine signal, creatine (Cre) and citrate (Cit). The basis functions used for LCModel fitting were generated by solving the Liouville equation while also accounting for the RF pulses and timing details of the field-dependent acquisition sequence for all metabolites except spermine. For spermine, a basis function was directly measured experimentally. The choline-containing compounds were grouped together as total choline (tCho) in the analysis. An example of a non-cancer spectrum fitted with the basis set is shown in Figure 1.

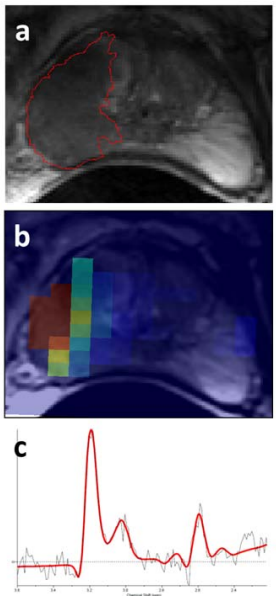

Figure 2: (a) Registered region of cancer from pathology on the T2w anatomic scan. (b) tCho/Cit metabolite map overlayed on same T2w image. (c) Spectrum with maximum tCho/Cit used for analysis.

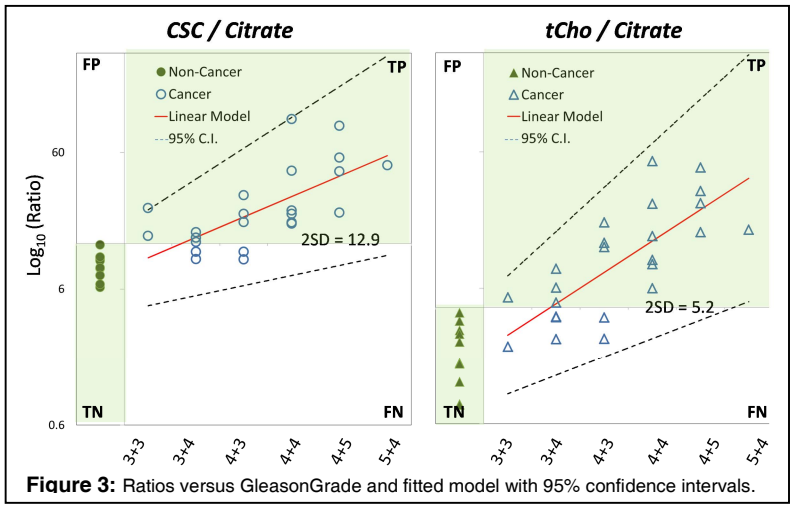

Figure 3: Ratios versus GleasonGrade and fitted model with 95% confidence intervals.

Voxel Selection: All spectra from the 3DSI data sets were fit and loaded into a software program for voxel selection providing overlayed spectroscopic and T2w images (Figure 2b). Cancer voxels were selected from within areas of graded cancer as identified by histopathologic regions co-registered to the T2w anatomic images[7], Figure 2a. Non-cancer voxels were selected preferentially from individuals with low volume disease and with the criteria that the voxel have a physical distance of ≥ 9 mm (i.e. 3 slices) from any region of cancer within the prostate, as facilitated by the volumetric assembly of the pathology data. Spectra were required to have an SNR > 8, limited baseline artifacts and lipid contamination for inclusion in the analysis.

Analysis Methods: In this study, two biomarkers were compared from the model fitted data: **1)** the standard ratio of tCho+Spm+Cre to citrate (CSC/Cit) and **2)** total choline to citrate (tCho/Cit). For cancer regions the voxel with the maximum ratio was used in the analysis for a given region of PCa. For non-cancer regions, the average ratio was taken from several voxels if possible. The average ratio plus 2 standard deviations of the non-cancer regions was used for the threshold of detection [8]. To assess correlation of ratios with grade, linear regression was applied to a log-linear model of the ratios to determine significance and 95% confidence intervals. Cramer-Rao Lower Bounds (CRLB) were used to assess fitting accuracy.

RESULTS / DISCUSSION: The relative performance of the CSC/Cit versus tCho/Cit for detection and grading are summarized in Figure 3. For the chosen detection threshold of 2SD above the non-cancer mean, CSC/Cit had a sensitivity of 87% while tCho/Cit a sensitivity of 81%. However, increasing the threshold to 3SD resulted in the same sensitivity of 67%. A highly significant correlation between grade and ratios was found with both ratios with p-values of 0.0005 and < 0.0001 for CSC/Cit and tCho/Cit, respectively. This is in contrast to other studies which did not find a correlation with grade [5]. This finding may be attributable to improved pathology correlation, better patient selection resulting in decreased partial volume effects, and Gleason scoring consistency. While both ratios appear to perform similarly in terms of detection and grading, the tCho/Cit has tighter confidence interval and increased dynamic range compared to CSC/Cit. One confounding factor is that the tCho/Cit ratio has increased dependence on an accurate fit of both the choline and Spm resonances. The CRLB of cancer spectra evaluated in this study varied with grade, where Spm decreased 6-fold faster than tCho increased. Improving the CRLB and reducing the correlation of peaks would therefore have a potentially large impact on improving accuracy of this ratio. With increased field strength (3T→7T) it has been demonstrated that the fitting accuracy of tCho and Spm was improved, with CRLB decreasing by 50% and the correlation between the two resonances decreasing from 0.55 to 0.12. These advantages may yield further improvement of tCho/Cit in both detection and grading relative to CSC/Cit when going to even higher field.

CONCLUSION: Model-based fitting of prostate spectra can produce more selective metabolite ratios than conventional peak integration. The model-based ratio tCho/Cit was found to have a strong correlation with cancer aggressiveness (grade), comparable with the standard approach of CSC/Cit ratio, but with the advantage of greater potential selectivity at higher fields.

REFERENCES: [1] Provencher, (1993) Magn Reson Med 30, 672., [2] Metzger, et al. (2007) ISMRM 15, 802., [3] Metzger, et al. (2007) ISMRM 15, 3668., [4] McLean, et al. (2011) Magn Reson Med 65, 914, [5] Garcia-Martinet al. (2011) Magn Reson Med 65, 329., [6] Scheenen et al. (2005) Magn Reson Med 53, 1268., [7] Kalavagunta et al. (2012) Proc Intl Soc Mag Reson Med 20, 2997., [8] Jung et al. (2004) Radiology 233, 701., [9] Henry et al. (2006) Magn Reson Med 55, 250., [10] Swanson et al. (2003) Magn Reson Med 50, 944.

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