The influence of polyamines on metabolite ratios in the prostate at 7 tesla

Mariska P Luttje[1], Catalina S Arteaga de Castro[2], Peter R Luijten[1], Marco van Vulpen[1], Uulke A van der Heide[2], and Dennis WJ Klomp[1]
[1]*Imaging Division, University Medical Center Utrecht, Utrecht, Netherlands,* [2]*Department of Radiotherapy, the Netherlands Cancer Institute - Antoni van Leeuwenhoek hospital, Amsterdam, Netherlands*

Introduction: Using ^{1}H MRSI, prostate metabolites including total choline (tCho), polyamines (PA, predominantly spermine), creatine (Cr) and citrate (Cit), can be detected [1-2]. MRSI has proven to be useful for the detection and staging of prostate cancer using the tCho/Cit ratio, as choline levels increase and citrate levels decrease in aggressive prostate tumors [3-5]. However, accurate measurement of the tCho/Cit ratio is challenging, as the tCho peak is close to PA and Cr. Therefore, the sum of all compounds is usually considered ((tCho+PA+Cr)/Cit) [5-6]. This may limit the detection of prostate cancer as studies have shown a significant decrease in the concentrations of polyamines and citrate [7-8]. The increased spectral resolution offered by high magnetic field strengths e.g. 7T, makes it possible to detect the metabolites individually, particularly when using LC Model fitting. Therefore it is hypothesized that the ratio tCho/(Cit+PA+Cr) would be more sensitive than (tCho+PA+Cr/Cit) in grading prostate cancer. In this study, the newly proposed metabolite ratio is compared to the conventional ratio using ^{1}H MRSI in 15 prostate cancer patients at 7 tesla.

Materials and Methods: 7 tesla prostate MRI was performed in 15 patients with biopsy-proven prostate cancer using a two-elements 1H transmit and receive endorectal coil [9] filled with fluorinated fluid (GALDEN; Solvay Solexis, Milan, Italy). ^{1}H MRSI was acquired (nsLASER [10], TE/TR=56/2000 ms, 24x8 matrix, 5x5x5 mm3 voxel, acquisition time=7.46 min). The spectra were fitted using an LCModel based fitting algorithm [11]. A basisset was created by simulations of citrate, creatine, spermine and choline using published values of chemical shifts and scalar couplings [11] Fitting was performed using a varying phase and linewidth and a variable, but limited frequency offset(±4Hz). Each voxel was manually checked for insufficient SNR(<3), no splitting of citrate when present and the presence of strong lipid. Delineation of tumor areas was based on the clinical performed 3 tesla scan. Voxels were assigned to be either peripheral zone (PZ), central zone (CZ) or tumor when more than 80% of the voxel was placed in this region. For each voxel the metabolite ratios: (tCho+PA+Cr)/Cit and tCho/(Cit+PA+Cr) were calculated and divided by the median ratio in the PZ of the patient for normalization purposes. The Kruskal-Wallis test with Dunn post test was used to compare tumor with healthy tissue for both ratios. Furthermore ROC analyses were done (GraphPad Prism 6, San Diego, CA).

Results: In all 15 patients (Gleason 3+3 and 3+4, mean age 65 years, mean PSA level 8.5ng/mL) total choline, polyamines, creatine and citrate could be detected, Figure 1 & 2. As one patient did not have any voxel with at least 80% tumor, the patient data was removed from the analysis. For the ratio (tCho+PA+Cr)/Cit the median value of the PZ, CZ and tumor area differed significantly (P<0.0001). The median values of the tumor area vs. PZ and vs. CZ were significantly different from eacho ther (P<0.01) while the median values of the PZ and CZ were not significantly different (P>0.05), Figure 3A. Using the ratio tCho/(Cit+PA+Cr) no statistical difference was found between the regions of interest (P=0.17), Figure 3B. The metabolite ratios were further investigated by ROC analysis, Figure 4,resulting in an AUC of 0.79 for the discrimination of tumor vs. PZ and 0.70 for tumor vs. CZ using (tCho+PA+Cr)/Cit. For the ratio tCho/(Cit+PA+Cr) the AUC of tumor vs PZ was 0.60 and for tumor vs CZ 0.54. In two patients the levels of polyamines were low in both tumor and healthy regions, Figure 2.

Discussion: In the current study the discriminating power of the new metabolite ratio tCho/(Cit+PA+Cr) was less than obtained by the conventional ratio (tCho+PA+Cr)/Cit. This is in contrast to reports obtained from tissue samples where a significant decrease in the concentrations of polyamines and citrate has been shown when comparing high grade (Gleason score≥7) to low grade (Gleason score=6) tumors [7-8]. However no data was reported on the difference in polyamines between healthy and low grade tumor tissue. A previous study by Garcia-Martin et al. [12] at 3 tesla shows a significant difference between healthy PZ and tumor tissue for the ratio tCho/(Cit+PA). However in that study no significant difference in spermine (the most dominant resonance of the polyamines group) between healthy and tumor tissue was detected, therefore this difference might be based on changes in Cit levels only. In the current study data of 14 patients with a relatively low Gleason score (3+3 and 3+4) were included, which might cause an increased overlap of the ratios between healthy and tumor metabolite ratios.
A larger difference in metabolite ratios between tumor and healthy tissue might be expected for high grade prostate cancer.

Conclusion: In contrast to MRSI at lower field strength, where polyamine signals overlap with choline signals, our results at 7T demonstrate the ability to fit each of these resonances distinctively. This facilitated investigation of the role of polyamines in the results of ^{1}H MRSI in detecting prostate cancer. The conventional metabolite ratio (tCho+PA+Cr)/Cit significantly discriminates between tumor and healthy tissue areas at 7 tesla, whereas the new ratio tCho/(Cit+PA+Cr) performs less in discriminating tumor areas from healthy tissue in the prostate.

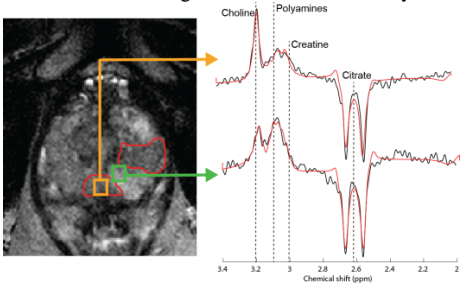

Figure 1: Spectra (black) and results of the basis set fitting (red) of patient 4. The orange box points out a tumor region, while the green box indicates healthy peripheral zone tissue. Changes in levels of choline and polyamines are clearly detectable in this patient.

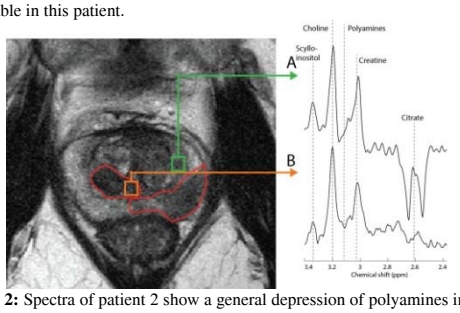

Figure 2: Spectra of patient 2 show a general depression of polyamines in the prostate. Spectrum A shows a healthy voxel on the border of the CZ and PZ. While a tumor spectrum is shown in B with low citrate and polyamines and high choline levels. In this patient the resonance of scyllo-inositol was detected as well.

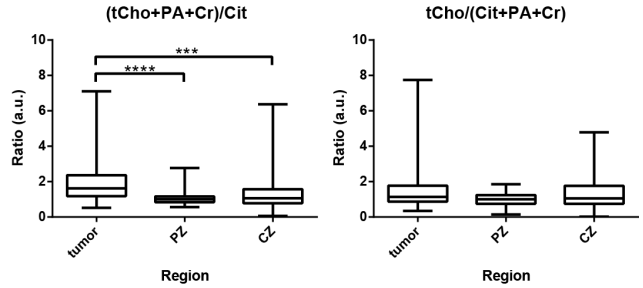

Figure 3: Boxplots of the calculated metabolite ratios. For the conventional ratio tCho+PA+Cr)/Cit statistical significant differences between the regions of interest exist.

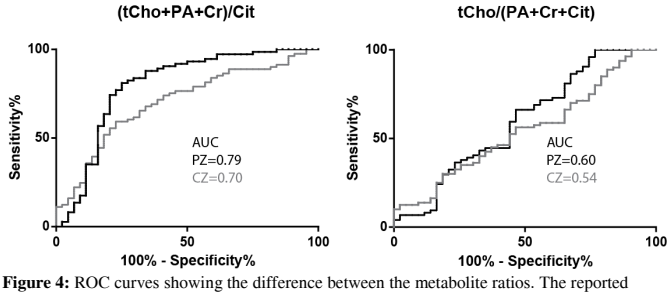

Figure 4: ROC curves showing the difference between the metabolite ratios. The reported AUC shows that the discrimination between tumor and healthy tissue is best for the conventional ratio (tCho+PA+Cr)/Cit.

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