^{1}H MR Spectroscopy of high grade prostate cancer

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Introduction:

^{1}H MRSI is a promising technique for *in vivo* assessment of prostate cancer aggressiveness, which is of clinical importance for treatment management. For prostate MRSI usually a PRESS sequence is used combined with frequency-selective refocusing pulses and gradient crushers to suppress lipid and water signals. In the remaining frequency range, the metabolites choline (Cho), creatine (Cr), citrate (Cit) and spermine (Spm) can be studied. In prostate cancer, an increase in choline and a decrease in citrate is observed. Earlier studies have shown a correlation between the Gleason score (GS) – the histopathological measure of aggressiveness - and the Cho+Cr/Cit ratio [1,2] and the Cho/Cr ratio [2]. Previously, ^{1}H MRSI of the prostate using a semi-LASER sequence, optimized for the coupled spin systems of lactate and citrate, was presented and enabled detection of metabolites in a wider frequency range due to the absence of frequency selective pulses for water and lipid suppression [3]. In this study we explore the use of PRESS and semi-LASER based MRSI for high grade prostate cancer.

Methods:

17 patients with high grade prostate cancer (GS on biopsy > 7 or PSA >20 ng/ml) were measured on a Siemens Trio 3T system. Informed consent for a short prolongation of a routine clinical protocol was waived by the local ethical committee. For signal reception an endorectal coil in combination with a body-array coil was used. As part of the clinical protocol, high resolution T2w images, diffusion weighted images and PRESS-based MRSI were acquired. For the PRESS-based MRSI TE=145 ms and TR=750ms was used. The effective voxel volume varied between patients from 0.36 to 1.0 cm^3, depending on the prostate size. The timing of the semi-LASER sequence (four adiabatic refocusing pulses) was implemented with an echo time of 144ms to obtain an inverted lactate signal due to J-coupling and an in-phase maximized line-shape for the citrate strongly coupled spin system. The T2w images were used to place the volume of interest of the 3D MRSI grid completely inside the prostate to minimize lipid contamination. The effective voxel volume was 1.5 cm^3. Spatial suppression slabs were placed around the prostate to suppress periprostatic lipid signals.

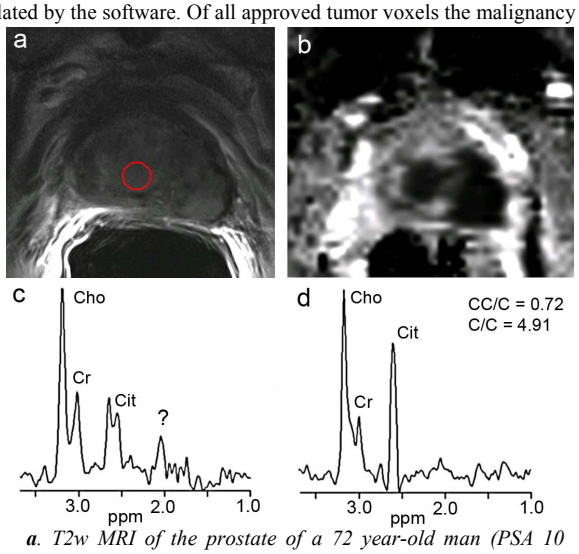
A spectroscopist, blinded for the spectra, selected all tumor-containing voxels in the PRESS and semi-LASER datasets based on the clinical reading of a radiologist, T2w images and diffusion weighted images. Metabolite Report (Siemens) was used to fit the PRESS spectra as described in [4]. The quality of the fits and spectra were visually inspected and of the approved voxels the intensity Cho+Cr/Cit and Cho/Cr ratios were calculated by the software. Of all approved tumor voxels the malignancy rating of the standardized threshold approach was determined. The standardized threshold approach bases an initial malignancy rating on the Cho+Cr/Cit ratio of the spectrum and adjusts this for deviating Cho/Cr ratios [2].

Visual inspection of the semi-LASER spectra revealed in many spectra an unassigned singlet at 2.05 ppm. To analyze the semi-LASER spectra, a LCModel basisset was developed for the fitting of Cho, Cr, Cit, Spm, lactate and the unassigned resonance. In the spectra with sufficient SNR (SNR ≥4) and a proper linewidth (FWHM ≤ 0.1 ppm), the unassigned resonance was analyzed. An accepted fit is defined as a Cramer Rao Lower Bound (CRLB) smaller than 20. To eliminate the influence of the coil profile on the analysis, the ratio of the unassigned resonance to Cr was determined, as were the Cho/Cr and Cit/Cr ratios. The correlations between the unassigned component over Cr ratio and the Cho/Cr and Cit/Cr ratio were determined.

Results:

The 17 patients had a mean PSA level of 20 ng/ml and the following GS on biopsy: GS 6 (n=1), GS 7 (n=4), GS 8 (n=4), GS 9 (n=7) and GS 10 (n=1). In 16 patients the metabolite ratios measured with the PRESS sequence could be determined. For each patient, the tumor voxel with the highest Cho+Cr/Cit and Cho/Cr ratio was determined. Of all patients the mean maximum Cho+Cr/Cit was 12.4 (range 1.6 - 105.3) and the mean maximum Cho/Cr ratio was 12.3 (range 3.7 - 34.3). The maximum malignancy rating of the standardized threshold approach was determined for each patient, and all patients had the maximum malignancy rating of 5.

Of the 17 patients measured with the semi-LASER sequence, one had no tumor voxels with sufficient SNR and two patients had no voxels with an accepted creatine fit. In 10 of the remaining patients (226 tumor voxels in total) the unassigned singlet was fitted with a CRLB < 20. No significant correlation was found between the unassigned resonance over Cr ratio and the Cho/Cr or Cit/Cr ratio. The mean ratio of the component over Cr was 0.7 (range 0.3 - 1.3).



***a**. T2w MRI of the prostate of a 72 year-old man (PSA 10 ng/ml, GS 4+5). The red circle indicates the location of the spectra in c. and d. **b**. Apparent diffusion coefficient map. **c**. Spectrum acquired with the semi-LASER sequence (1.5cm^3). **d.** spectrum acquired with PRESS (0.64cm^3). Notice the difference in spectral shape of Cit in c. and d.*

Discussion and conclusion :

A previous study reported a mean Cho+Cr/Cit ratio of 0.22 in healthy peripheral zone and 1.3 in tumor tissue at 3T with the PRESS-based sequence [4]. In the present study only patients with highly aggressive prostate cancer were included and the maximum Cho+Cr/Cit ratio in all patients was higher than 1.6 (mean 12.4). This demonstrates that either prostate metabolism was extremely disturbed or morphologic changes led to an absence of citrate-containing luminal space. To estimate malignancy with the standardized threshold approach a Cho/Cr ratio of 2.3 was used to increase the malignancy rating [2]. Here, the maximum Cho/Cr ratios was higher than 3.7 in all patients, which further demonstrates the aberrant metabolism of these tumors.

The absence of frequency-selective refocusing pulses for lipid suppression in the semi-LASER sequence enables studying metabolites in a wider frequency range. This enabled the detection of an unassigned metabolite at 2.05 ppm. In the nineties, before the implementation of frequency-selective lipid suppression, a broad peak was detected around 2 ppm *in vivo* at 1.5T. The authors assigned this peak to glutamate, glutamine and polyamines [5]. Also in HRMAS studies a broad resonance around this chemical shift is visible [6,7] and was assigned to polyamines [7]. We modeled one of the polyamines in our LCModel basisset, that is spermine, which has resonances at 3.14, 2.1 and 1.8 ppm. However, the 2.05 resonance was not assigned to the spermine resonance in the LCModel analysis. Furthermore, in the spectra no peak was visible at the 1.8 resonance of spermine, which should have the same intensity as the 2.1 ppm resonance. Simulations with Bruker Topspin showed that glutamate (2.03-2.12 ppm) and glutamine (2.12 ppm) are disperse at the used TE and could not have led to a clear singlet. The singlet was also seen in healthy voxels, but not analyzed yet. Because of its presence close to 2.1 ppm and persistence at longer TE this peak most likely represents an acetyl group.

To conclude, MRSI without lipid suppression is feasible and at longer echo time reveals an additional resonance of which the origin still has to be established. Prostate cancer aggressiveness leads to very abnormal spectra as demonstrated in this group of patients with highly aggressive prostate cancer.

References: [1] Zakian, Radiology (2005) [2] Kobus, Eur Urol (2011) [3] Kobus, ISMRM 19, 3057 (2011) [4] Scheenen, Radiology (2007) [5] Kurhanewicz, Urology (1995) [6] Swanson, MRM (2003) [7] Asten, Magn Reson Mater Phy (2008). **Acknowledgement:** Dutch Cancer Society: KUN 2007/3971, ERC Grant agreement n° [243115], Elisabeth Weiland, Siemens Healthcare, Erlangen for supplying and supporting Metabolite Report