^{1}H MRSI for *in vivo* lactate detection in prostate cancer

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Introduction: *In vivo* ^{1}H MRSI of the prostate focuses on the metabolites in the frequency range between 2.4 and 3.3 ppm; these are choline, creatine, citrate and polyamines (mainly spermine). Generally, frequency-selective refocusing pulses are applied that suppress lipid and water signals at both sides of this frequency range. This prevents detection of other metabolites like lactate (1.3 and 4.1 ppm), which could be of interest for prostate cancer (PCa) evaluation. Lactate is a reporter of the Warburg effect and/or hypoxic conditions in tumors. Previously a semi-LASER sequence without frequency-selective lipid suppression pulses was presented, enabling lactate assessment (1). In this study, the semi-LASER sequence was used to evaluate the presence of lactate in patients with highly aggressive PCa, and minimal detectable lactate levels were determined by adding artificial lactate signals to *in vivo* spectra.

Methods: On a Siemens Trio 3T system, 17 patients with high grade PCa were measured. High grade PCa was defined as either a Gleason score of 7 or higher or a PSA level higher than 20 ng/ml. The local ethical committee waived informed consent for a short prolongation of a clinical MRI exam. An endorectal coil was combined with a body-array matrix for signal reception. High resolution T2w images in three directions and diffusion weighted images were acquired as part of the clinical exam. The semi-LASER sequence was implemented with an echo time of 144 ms to obtain an inverted lactate signal due to J-coupling. The timing of the four adiabatic pulses was adjusted to obtain an in-phase maximized line-shape for citrate (1) (Figure 1). The volume of interest of the MRSI grid was placed completely inside the prostate to minimize lipid contamination. Large voxels with an effective voxel volume of 1.5 cm[3] were chosen. Around the prostate spatial saturation slabs were placed to saturate periprostatic lipid signals. In previous phantom work was demonstrated that lactate could be detected with the sequence (1).

All tumor-containing voxels were selected by a spectroscopist, blinded for the spectra, guided by the clinical reading of a radiologist, based on T2w images and diffusion weighted images. To analyze the spectra a LCModel basisset was developed for the fitting of choline, creatine, spermine, citrate and lactate. The fitting was done without zero-order phase restrictions and a first-order phase of 0. LCModel provides the Cramer-Rao lower bound (CRLB) for all fits and fits with a CRLB smaller than 20 were accepted. LCModel provides the option of fitting several lipid signals. This was used to determine whether a spectrum was contaminated with lipids. Spectra were analyzed for lactate if the SNR was sufficient (SNR $\geq$4), the line-width was appropriate for small molecule metabolites (FWHM $\leq$0.1 ppm) and no lipids were fitted by the software. The hypothetical minimal lactate concentration was determined in the patients without a detectable lactate signal with the use of creatine as an internal reference. A simulated lactate signal was added to all spectra in a dataset. As the zero-order phase varies over the spectra, the simulated lactate signal of each spectrum was added with the phase determined by LCModel on the original dataset. This way, lactate is added in each spectrum with the correct phase for that spectrum. For all tumor voxels with a CRLB of the lactate fit smaller than 20, the lactate concentration was determined as described in (2). Relaxation times of 1550 ms (T1, (3)) and 225 ms, (shortest T2 found in literature (4)) were assumed for lactate (values obtained in brain measurements on 1.5T). T1 and T2 of creatine (as measured in the prostate at 1.5T) were assumed to be of 864 and 209 ms, respectively (5). A creatine concentration of 4.4 mM (*in vivo* MR measurement in the prostate) was used as the standard for all voxels (5). The amplitude of the simulated lactate signal was iteratively lowered by 10% until in none of the tumor voxels lactate was detectable. The lowest minimal detectable concentration was determined for all tumor voxels in each patient.

Figure 1. semi-LASER sequence with the timings of the adiabatic refocussing pulses (AFP) leading to an inverted lactate signal and in-phase maximized citrate shape.

Figure 2. In vivo spectrum of one voxel in which the lactate fit was acceptable (CRLB ≤ 20)
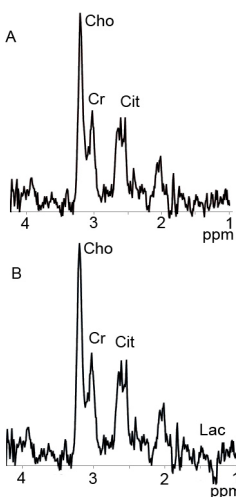

Figure 3. A The original spectrum. B The same spectrum as in A, but with lactate added at the detection limit, leading to a minimal detectable concentration of 2.0 mM.
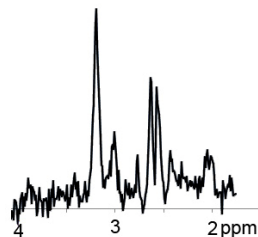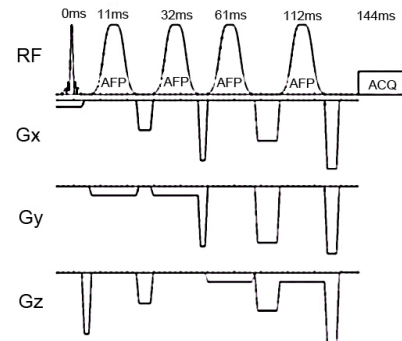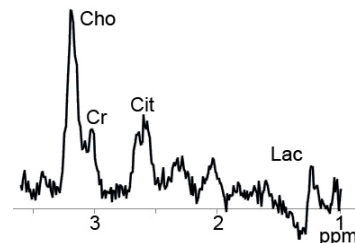

Figure 4. Spectrum of a patient in which the creatine peak seems lower than in figure 3 and 4 in relation to the other metabolites.

Results: The 17 patients had an average PSA level of 20 ng/ml and the following Gleason scores on biopsy: 6 (n=1), 7 (n=4), 8 (n=4), 9 (n=7) and 10 (n=1). In the semi-LASER MRSI data of 13 patients, tumor voxels could be selected that had no or limited fat contamination and could be used to determine the presence of lactate. Only in one voxel of one patient a lactate fit with a CRLB smaller than 20 was observed. However, the baseline in the 1.3 ppm range was not flat so whether truly lactate was detected remains questionable (Figure 2). Excluding that patient, in 10 other patients the minimum detectable lactate level could be determined and was 3.0 mM on average (range 2.0 - 5.7 mM). In Figure 3 the original spectrum and spectrum with lactate added at the detection limit is shown for one voxel of the data set of one of the patients.

Discussion and conclusion: While in mice lactate was associated with prostate cancer progression (6), in this study in none of the patients lactate was detected convincingly. Also in HRMAS data of human prostate biopsies, an increase of lactate in malignant compared to benign samples was seen (7). Lactate levels in *ex vivo* samples should be assessed with caution, as anaerobic energy metabolism of substrates could quickly produce lactate. The lack of lactate detection in the tumors could mean that either the lactate is rapidly cleared from the prostate, since this is a well perfused organ, or that prostate tumors do not produce lactate above our detection limit. From the determined minimal detectable lactate concentrations, we can estimate lactate levels to stay below 3.0 mM. It should be noted that for the calculation a constant Cr concentration is assumed. Visual inspection of the spectra showed in several patients small creatine signals (An example is given in Figure 4). This will result in a higher minimal detectable lactate concentration. In this study the use of ^{1}H MRSI for the detection of lactate in patients with highly aggressive prostate cancer was evaluated, and we had to conclude that – if present – lactate levels stay below the detection limit of 3 mM in aggressive prostate cancer.

References: [1] Kobus, ISMRM 19, 3057 (2011) [2] Bolan, MRM (2003) [3] Frahm, MRM (1989) [4] Sappey-Marinier MRM (1992) [5] Heerschap, MRM (1997) [6] Albers, Cancer Res (2008) [7] Asten, Magn Reson Mater Phy (2008).