# $^{31}$P MR spectroscopic imaging of patients with prostate cancer at 7T

Miriam W. Lagemaat[1], Eline K. Vos[1], Marnix C. Maas[1], Thiele Kobus[1], Andreas K. Bitz[2,3], Mark J. van Uden[1], Stephan Orzada[2,3], Arend Heerschap[1], and Tom W.J. Scheenen[1,2]

*[1]Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands, [2]Erwin L. Hahn Institute for Magnetic Resonance Imaging, Essen, Germany, [3]Diagnostic and Interventional Radiology, University Hospital Essen, Essen, Germany*

**Introduction –** Prostate cancer studied by in vivo $^{1}$H MRS usually expresses decreased citrate and elevated total choline (tCho) levels compared to normal prostate tissue. Several high resolution (HR) $^{31}$P NMR and $^{1}$H HR-MAS studies have demonstrated that the elevation of the tCho peak in cancer is the result of significant increases in several choline- and ethanolamine-containing metabolites[1–3]. Early in vivo $^{31}$P MRS studies at 1.5-2T showed differences between normal and diseased prostates, but did not resolve individual phosphomonoesters (PME) or phosphodiesters (PDE)[4,5]. The individual levels of the PMEs phosphocholine (PC) and phosphoethanolamine (PE) and of the PDEs glycerophosphocholine (GPC) and glycerophosphoetanolamine (GPE) have been linked in vitro to tumor aggressiveness[2,3], so it is of major interest to study these compounds with in vivo $^{31}$P MRSI at ultra-high field strength, where the spatial resolution may become clinically relevant. Recently, it was shown feasible and safe to perform 3D $^{31}$P MRSI of the prostate at 7T, resulting in well-resolved $^{31}$P spectra of the human prostate[6], with resonances from phospholipid and energy-related metabolites. In this study, we investigated the potential of $^{31}$P MRSI to detect prostate cancer in vivo at 7T.

**Methods –** Data of 12 patients with or suspected of having prostate cancer (age: 65.5±5.0y, median PSA=6.5) were acquired on a 7T whole body MR system (Magnetom, Siemens, Erlangen). A $^{31}$P $T_X/R_X$ endorectal coil tuned to 120.3 MHz was used in combination with a $^{1}$H multi-$T_X/R_X$ 8-channel body array coil. 3D phasemapping and $B_1^+$-phase shimming were used to optimize the $B_0$ homogeneity and maximize $^{1}$H phase coherence in the prostate, respectively. Transversal $T_2$-weighted TSE images (TR=3s, TE=71ms) were recorded to provide an anatomical background for $^{31}$P MRSI. In 9:51 minutes (TR=1.5s) pulse acquire 3D $^{31}$P MRSI with adiabatic 45° RF pulses was recorded (FOV=120x120x120cm$^3$, matrix 10x10x10). In 9 patients, NOE enhanced spectra were obtained, by saturating the proton spins of water during the 1.5s TR (except during 204ms signal acquisition)[7]. All measurements were performed within SAR safety limits. Based on histopathological information and/or the radiological report of the 3T clinical prostate exam of each patient, a radiologist and a spectroscopist selected spectroscopy voxels in consensus. Voxels were selected representing mainly tumor tissue (n=16, Gleason score (GS) 3+3 (n=9), 3+4 (n=2), 4+5 (n=2), cancer suspicious region on 3T (n=3)), mainly normal peripheral zone (PZ) (n=11) and mainly normal transition zone (TZ) (n=18), see fig. 1. A maximum of 5 non-neighbouring voxels were selected per patient. Metabolite Report (Siemens Healthcare) was used for complex fitting including baseline of the $^{31}$P spectra of the selected voxels. The spectroscopist visually inspected the original spectra and the fits and discarded non-reliable spectra and metabolite fits. Non NOE enhanced metabolite amplitudes were corrected for by NOE factors determined in a separate study, before calculating metabolite ratios. T-tests were performed to determine possible differences in ratios between tumor, PZ and TZ.

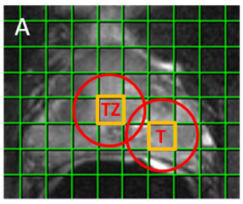


*Figure 1 A: Example of voxel selection. One voxel was placed at the cancer lesion (T, GS 3+3), one in unaffected TZ. The red circles show the true voxel size.*

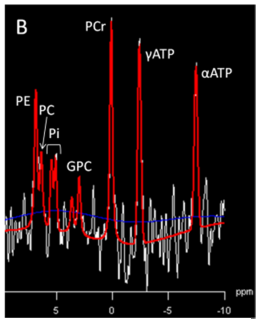


*Fig 1 B: spectrum and fit of voxel T.*

**Results –** Metabolite ratios found in tumor, PZ and TZ are presented in Table 1. PE/γATP and PE/tPLM (total of PE, PC, GPE and GPC) were significantly lower in tumor compared to normal TZ (p=0.03 and p<0.01, respectively) and to PZ and TZ together (p=0.02 and p<0.01, respectively). The inorganic phosphate (Pi) to γATP ratio was significantly lower in tumor compared to normal PZ (p=0.03). However, the ratio data generally showed considerable overlap between tumor and normal prostate tissue. GPE and GPC were observed in only a small number of the spectra, however the detection rate in tumor voxels was higher than in normal voxels (table 2).

| | PC/PE | PE/yATP | PC/yATP | PE/GPE | PC/GPC | PE/tPLM | Pi (1, high pH) | Pi (2, low pH) |
|---|---|---|---|---|---|---|---|---|
| tumor | 0.67 ± 0.23 (14) | 1.05 ± 0.28 (13) | 0.66 ± 0.19 (14) | 5.17 ± 3.7 (5) | 1.60 ± 0.70 (6) | 0.52 ± 0.09 (14) | 0.39 ± 0.12 (11) | 0.40 ± 0.10 (9) |
| normal PZ | 0.63 ± 0.19 (8) | 1.28 ± 0.25 (9) | 0.77 ± 0.13 (9) | 4.74 (1) | 1.98 ± 1.16 (4) | 0.63 ± 0.16 (9) | 0.54 ± 0.17 (8)* | 0.39 ± 0.13 (8) |
| normal TZ | 0.51 ± 0.22 (14) | 1.34 ± 0.37 (15)* | 0.65 ± 0.23 (15) | 1.49 (1) | 1.89 ± 0.81 (2) | 0.65 ± 0.11 (14)# | 0.41 ± 0.13 (8) | 0.42 ± 0.15 (9) |

*Table 1: Metabolite ratios in tumor, PZ and TZ; mean ± std (# of voxels). * Significant difference (p=0.03) with tumor. # Significant difference (p<0.01) with tumor.*

**Discussion** – Despite the small number of patients with high grade prostate tumors included in this study and the large real voxel size of $^{31}$P MRSI (5.1cc), we found some significant differences in $^{31}$P ratios between cancer and normal prostate tissue. A lower PE/tPLM value in tumor with respect to normal tissue as observed in this study was also reported in HR $^{31}$P NMR[3,8]. Quantitative $^{1}$H HR-MAS studies showed that this decrease is mainly caused by increases in PC, GPE and GPC rather than a decrease in PE[1,2], possibly corresponding to our increased detection of PDE in tumors. We cannot confirm a significant increase in PC/PE in tumor, reported in in vitro studies. Moreover, PC/PE observed here differs largely from in vitro results, where PE was far more abundant (10-100x) than PC[1,2], suggesting metabolite content changes during extraction and in vitro measurements.

| | GPE | GPC |
|---|---|---|
| detection % in tumor | 33 | 40 |
| detection % in PZ and TZ | 7 | 21 |

*Table 2: Detection rate of GPE and GPC in prostate $^{31}$P spectra. Other metabolites were detected in nearly all tumor and normal spectra.*

In many $^{31}$P studies of prostate, phosphocreatine (PCr) has been used as reference compound. This was not possible in the current study, since voxel bleed induced contamination of smooth muscle PCr signals in the spectra, resulting in local differences of PCr through the prostate (high laterally, low in the center). Instead, γATP was chosen as reference compound, which showed limited difference between prostate and muscle. In the light of the quantitative $^{1}$H HR-MAS results, the decrease in the PE/ γATP ratio in tumor with respect to TZ tissue observed in vivo might reflect an increase of γATP in tumor. The coil sensitivity profile prevented assessment of individual metabolite amplitudes however. Intensity corrections of the coil profile should be considered. Moreover, local variations of $^{31}$P metabolites within the healthy prostate should be taken into account. We observed higher PC levels in the prostatic base near the seminal vesicles than in the mid-prostate and apex, likely due to high PC in seminal fluid.

In many in vivo 7T $^{31}$P prostate spectra, two peaks were present in the pH-dependent chemical shift range of inorganic phosphate (Pi). These peaks may reflect Pi in two compartments with different pH (e.g. stromal, epithelial cells versus luminal space). The decrease in Pi1/γATP in tumor compared to normal PZ probably reflects changes in metabolism which cannot be reliably studied in vitro due to accumulation of Pi caused by degradation of other metabolites after extraction.

The partial volume effects resulting from the large voxel sizes in this study obscured precise assessment of the metabolites in the tissues of interest, which probably caused the large spread of the data. It was shown before that prostatic HR-MAS samples containing <20% tumor tissue did not have significant differences in choline-containing metabolites compared to normal tissue, in contrast to samples containing >20% tumor tissue[9]. This emphasizes the need to increase spatial resolution in $^{31}$P MRSI. New rigid coil concepts may provide enough SNR to accomplish this.

**Conclusion –** In vivo $^{31}$P MRSI at 7T showed significant differences in $^{31}$P metabolite ratios between prostate cancer and normal prostate tissue. The performance of $^{31}$P MRSI to detect prostate cancer may improve further by increases in spatial resolution.

**References –** [1] Swanson et al, MRM 60:33-40(2008), [2] Keshari et al, NMRbiomed 24 :691-699(2011), [3] Komoroski et al, MRM 65 :911-913(2011), [4] Narayan et al, J.Urol. 146:66-74(1991), [5] Hering et al, Urol.Res. 19:349-52(1991), [6] Kobus et al, MRM 2012 Feb 14 (Epub ahead of print), [7] Lagemaat et al, ISMRM 2012 (1728), [8] Cornel et al, J.Urol. 150:20-30(1993), [9] Swanson et al, MRM 50:944-954(2003) **Acknowledgement -** ERC Grant agreement n° [243115]