Introduction – Prostate cancer studied by in vivo $^3$P MRS usually expresses decreased citrate and elevated total choline (tCho) levels compared to normal prostate tissue. Several high resolution (HR) $^3$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. $^3$P MRS studies at 1.5-2T showed differences between normal and diseased prostates, but did not resolve individual phosphomonoesters (PME) or phosphodiesters (PDE). The individual levels of the PMEs phosphocholine (PC) and phosphoethanolamine (PE) and of the PDEs glycerophosphocholine (GPC) and glycerophosphoethanolamine (GPE) have been linked in vitro to tumor aggressiveness, so it is of major interest to study these compounds with in vivo $^3$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 $^3$P MRSI of the prostate at 7T, resulting in well-resolved $^3$P spectra of the human prostate, with resonances from phospholipid and energy-related metabolites. In this study, we investigated the potential of $^3$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 (Magneton, Siemens, Erlangen). A $^3$P Tx/Rx endorectal coil tuned to 120.3 MHz was used in combination with a $^1$H multi-Tx/Rx 8-channel body array coil. 3D phasemapping and B1+ -phase shimming were used to optimize the B1 homogeneity and maximize $^3$P coherence in the prostate, respectively. Transversal T2-weighted TSE images (TR=3s, TE=71ms) were recorded to provide an anatomical background for $^3$P MRSI. In 9:51 minutes (TR=1.5s) pulse acquisition 3D $^3$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).

Results – Metabolite ratios found in tumor, PZ and TZ are presented in Table 1. PE/ATP and PE/PLM (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/ATP PC/ATP PC/GPC PE/PLM Pi (1, high pH) Pi (2, low pH)
tumor 0.67 ± 0.23 (14) 1.05 ± 0.28 (13) 0.66 ± 0.19 (14) 3.17 ± 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 ± 0.10 (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 0.31 ± 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)

Discussion – Despite the small number of patients with high grade prostate tumors included in this study and the large real voxel size of $^3$P MRSI (5.1cc), we found some significant differences in $^3$P ratios between cancer and normal prostate tissue. A lower PE/PLM value in tumor with respect to normal tissue as observed in this study was also reported in HR $^3$P NMR studies. Quantitative HR-MAS studies (Siemens) showed that this decrease is mainly caused by increases in PC, GPE and other phosphomonoesters while the phosphodiester peaks showed limited difference between tumor and normal prostate tissue. However, a decrease in PE/PC2, possibly corresponding to our increased detection of PDE in tumors. We cannot confirm an increased increase in PC/PE in tumor, reported in vitro studies. Moreover, PC/PE observed here differs largely from in vitro results, where PE was far more abundant (100x) than PC12, suggesting metabolite content changes during extraction and in vitro measurements. In many $^3$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, limited variations of $^3$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 vivo $^3$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 Pi/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 effect resulting from the large voxel size and 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. This emphasizes the need to increase spatial resolution in $^3$P MRSI. New rigid coil concepts may provide enough SNR to accomplish this.

Conclusion – In vivo $^3$P MRSI at 7T showed significant differences in $^3$P metabolite ratios between prostate cancer and normal prostate tissue. The performance of $^3$P MRSI to detect prostate cancer may improve further by increasing spatial resolution.