

Staging, Diagnosis & Detection, State of Art Imaging, Methodology, and Etc.

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More than many cancers, prostate cancer requires accurate imaging information to select the most appropriate treatment for individual patients and for assessing response to therapy. This is due to the pathologic and biologic complexity of the human prostate and prostate cancer. This complexity results in questions of whether and how to treat individual prostate cancer patients. Additionally, this complexity demands state-of-the-art high spatial resolution multiparametric MR imaging and spectroscopy techniques to accurately assess disease status in individual patients. Commercial combined 1.5T MRI/MRSI exams are currently available and a growing amount of published data has demonstrated that the metabolic biomarkers, choline, citrate and polyamines, provided by 3-D proton magnetic resonance spectroscopic imaging (¹H MRSI) combined with the anatomical information provided by magnetic resonance imaging (MRI) can significantly improve the detection and characterization of prostate cancer in individual patients at diagnosis (1, 2). Prior to therapy, prostate cancer can be identified based on reduced T₂ signal intensity on MRI, increased choline and decreased citrate and polyamines on MRSI. After therapy, T₂ signal intensity becomes less useful since there is a homogenous reduction in T₂ signal intensity in both benign and malignant tissues, and there is time dependent loss of prostate metabolites. Two metabolic biomarkers of effective (metabolic atrophy) and ineffective therapy (3 or more voxels of elevated choline to creatine) have also been identified and are being validated with 10 year clinical outcomes (1, 2).

While the current commercially available 1.5T MRI/¹H MRSI exam has shown promise for improving the detection and characterization of prostate cancer in individual patients, there is general clinical consensus that there is a need for more sensitive and specific imaging, particularly for small volume, low grade (< 0.5 cc, ≤ 3+3) early stage cancer. Recent studies have shown that accuracy of MRI/MRSI can be improved by using higher magnetic field strengths (3T) scanners, and through the addition of other functional MR techniques, namely diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI (3). At 3T, the spatial resolution of MRSI can be increased ≈ 2 fold (0.16 cc, ≈ 5 mm on a side) in the same acquisition time, and this will be clearly needed for the improved imaging of men with early stage disease prior to therapy and small amounts of residual disease after therapy. Imaging at 3T can also improve DWI and DCE imaging that can provide additional quantitative functional measures of the prostate at a higher spatial resolution than MRSI. Studies have demonstrated that DCE MRI can discriminate prostate cancer from surrounding healthy prostate tissues based on a higher and faster rate of contrast enhancement both prior to and after therapy (3). Unlike other tumors that demonstrate increased average water diffusivity (<D>) compared to surrounding benign tissues, prostate cancers demonstrate lower <D> values. After therapy there is an increase <D> in both benign and malignant tissues but in preliminary studies <D> remains lower in residual cancer as compared surrounding benign tissues (3).

An extraordinary new technique utilizing hyperpolarized ¹³C labeled metabolic substrates has the potential to revolutionize the way we use MR imaging in the clinical management of prostate cancer patients (4). Dynamic Nuclear Polarization (DNP) techniques provide an unprecedented increase in signal-to-noise, allowing high spatial and temporal resolution imaging of [1-¹³C] pyruvate and its metabolites, yielding both high contrast-to-noise and the ability to probe specific enzymatic processes. Hyperpolarized [1-¹³C] pyruvate studies in a transgenic mouse model (TRAMP) have demonstrated the ability to detect primary and metastatic prostate cancer and pathologically grade the tumors based on the hyperpolarized lactate, alanine, and total hyperpolarized carbon (THC) (5). We have also recently demonstrated that high baseline levels of hyperpolarized lactate and THC predicted poor response to hormone therapy as measured by survival. Additionally, early post-therapy (3 days) reductions in lactate and lactate/pyruvate ratio predicted improved survival after hormone therapy. Based on encouraging pre-clinical and human safety studies, the first DNP polarizer for human studies has been installed at UCSF by GE Healthcare, and a phase I clinical trial of [1-¹³C] pyruvate in patients with clinically localized prostate cancer is currently being designed.

References:(1) Kurhanewicz J, et al. *J Magn Reson Imaging* 2002; 16:451-463. (2) Kurhanewicz J, et al. *Magn Reson Imaging Clin N Am* 2008; 16:697-710. (3) Kurhanewicz J, et al. *Curr Opin Urol* 2008; 18:71-77. (4) Kurhanewicz J, et al. *J Nucl Med* 2008; 49:341-344. (5) Albers MJ, et al. *Cancer Res* 2008; 68:8607-8615.