Investigation of Prostate Cancer Metabolomics with Prostate Biopsy Cores

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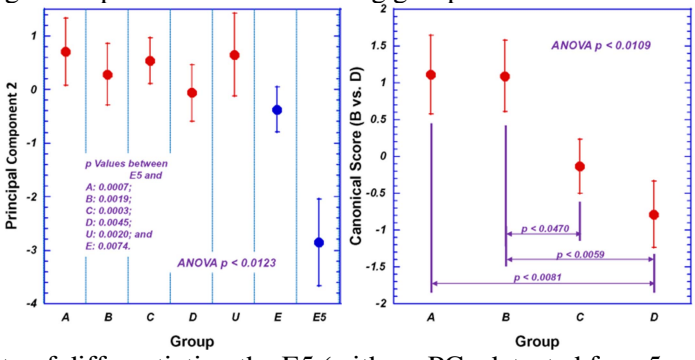
Target Audience. Prostate cancer (PCa) is the most frequently diagnosed malignancy in men worldwide, and the second leading cause of cancer death for men in the United States. Developing new PCa metabolomic biomarkers capable of predicting tumor stage, location, and potential of recurrence can drastically improve PCa treatments and patient prognostications, particularly when such markers present themselves with the potential to be implemented in vivo for non-invasive evaluations of PCa patients.

Purpose. Results from our studies of intact prostate tissue samples from PCa patients suggested the existence of metabolic or metabolomic fields, i.e. PCa metabolic information are observed to delocalize from PCa glands and into the surrounding structures that are histologically-benign (Hb). These field effects likely create PCa "metabolomic lesions" that are larger than the histology lesions. Through these metabolomic fields, metabolomic profiles measured from Hb only samples from PCa patients correlated with patient clinical and pathological status, and were able to predict PCa aggressive potential. Here, we evaluate these 'field effects' using prostate biopsy samples from patients suspected of harboring PCa.

Methods. One prostate biopsy core from each patient undergoing trans-rectal ultrasound (TRUS) guided biopsy for suspicion of PCa or for active surveillance was used for the study. Until now, 138 patients have been recruited in the study. High-resolution magic angle spinning MR spectroscopy was carried out on a Bruker AVANCE spectrometer operating at 600 MHz (14.1T). A 4mm zirconia rotor was used with Kel-F inserts to create a 10µl sample space for the biopsy core, and D2O was added for field locking. Spectra were recorded at 4ºC with the spectrometer frequency set on the water resonance. Spectra were measured with a rotor-synchronized Min (A,B) protocol with spinning at 600 and 700Hz (±1.0Hz), and analyzed using an in-house developed MatLab based program. 75 spectral regions were identified and used in principal component analysis (PCA) and canonical analysis (CanCor). *Histopathology*. After spectroscopy, biopsy cores were analyzed with traditional histopathology and recorded in the patient records. The volume percentages of histological features were quantified by a pathologist. Based on the complete pathology report for each patient, including results of multiple repeated biopsies when applicable, we categorized patients in the following groups.

Group	Diagnosis	Case #
A	Cancer in the analyzed core	*15*
B	Cancer in same quadrant as the analyzed core	*18*
C	Cancer in adjacent quadrant from the analyzed core	*32*
D	Cancer in far quadrant the analyzed core	*21*
E	No PCa detected Histologically Benign (<5-year)	*33*
E5	Histologically Benign, no PCa after >5-year	*9*
U	PCa Diagnosis but location unknown	*10*
	Total	**138**



Results. Metabolic and metabolomic results indicate the ability of differentiating the E5 (with no PCa detected for >5-year follow-up after MRS analysis of biopsy core) patient group from other groups. In addition to a number of individual metabolic peaks, such as creatine (3.026ppm), PCA results (left Figure) clearly distinguish E5 group as demonstrated by PC2. Furthermore, CanCor results (right Figure) obtained by using groups B and D as the training cohort, and groups A and C as the testing cohort, clearly present the diffusiveness of PCa metabolomic field from PCa foci (A and B) to their surrounding histologically-benign structures (C and D).

Discussion and Conclusions. Data from this study can illustrate the power of metabolomic profiles in identifying patient PCa statuses, such as the E5 group, at the time of biopsy. More importantly, our data suggest that patient PCa characteristics can be obtained from histologically benign tissue, through the presence of PCa metabolomic fields. Therefore, studies of PCa metabolomics and metabolomic fields, and the development of metabolite and metabolomic thresholds to assist diagnosis and prognosis, can provide biological information that may be able to further sub-categorize specific patient populations according to tumor-biochemical potentials both ex vivo with biopsy specimens and in vivo through metabolomic imaging, and contribute to the design of personalized treatment plans.