Evaluation of prostate cancer metabolomic field effects using prostate needle biopsies

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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. Currently, most PCa cases are detected by the annual serum prostate specific antigen (PSA) screening test. With the confirmation of elevated PSA levels in patients, biopsies are taken from the prostate and evaluated with histopathology. However, as radiological imaging is currently unable to detect suspicious areas for targeted biopsy in general, theses randomly conducted biopsies often result in false negatives for early-stage PCa patients as the method is ineffective in detecting small, heterogeneously distributed lesions. If metabolomic profiles from these benign biopsies could reveal the cancer status of the rest of the prostate, the number of prostate cancers missed would be greatly reduced.

Purpose: Results from our previous studies of intact 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 benign tissue according to histology. These field effects likely create PCa "metabolomic lesions" that are larger than the histology lesions. We designed the current study to test the metabolomic field hypothesis by evaluating prostate biopsy cores for patients possibly harboring PCa.

Table 1.

Group	Location of PCa Glands	Number of Patients	Age (years)	Number of prostatectomies	Stage pT2	Stage pT3
A	analyzed PCa core	14	M: 64.1 SD: 5.8	6	2	4
B	PCa in same quadrant	13	M: 65.9 SD: 7.4	3	3	0
C	PCa adjacent quadrant	26	M: 65.2 SD: 8.3	6	4	2
D	PCa in far quadrant	15	M: 64.5 SD: 6.2	4	2	2
E	PCa status unknown	43	M: 64.5 SD: 8.0	0	0	0

Methods: From patients undergoing trans-rectal ultrasound (TRUS) guided biopsy for suspicion of PCa or for active surveillance, we collected an additional prostate needle biopsy, with the location recorded, for MR analysis. Detailed patient information is listed in **Table 1**. *MR Spectroscopy.* MR experiments were carried out on a Bruker AVANCE spectrometer operating at 600 MHz (14.1T) and pre-cooled to 4°C. 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 2H field locking. Spectra were acquired using slow spinning rates of 600 and 700Hz and post-spectral edited with Min(A, B) scheme. Spectroscopic data were processed using an in-house MatLab based program. Following the MRS analysis, the analyzed biopsy core from each patient was evaluated by histopathology and included in the final pathology report along with the other biopsy cores from the same patient.

Results: Among the 111 measured biopsy cores, to evaluate the spatial distribution of the hypothesized PCa metabolomic fields, we identified the following five groups of patients, as also shown in Table 1. A) The measured biopsy cores contained PCa glands (n=14). For the cases where the measured cores were histologically benign, we divided them into: B) PCa glands were detected from the same quadrant by another biopsy core (n=13), C) PCa glands were seen in the adjacent quadrants (n=26), and D) PCa glands were located in the further away quadrants (n=15). Additionally, Group E includes patients for whom the analyzed core was benign as well as all additional biopsies, or when the location of the analyzed core was unknown; the spectra from these cores were not included in the preliminary analysis. Our results show that while some spectral regions or metabolomic profiles represented by principal components do not show statistically significant differences among these groups, a number of other spectral regions and profiles do display significant differences (after Bonferroni corrections) among groups, as shown for taurine, alanine, PC1 and PC4 (Figure 1).

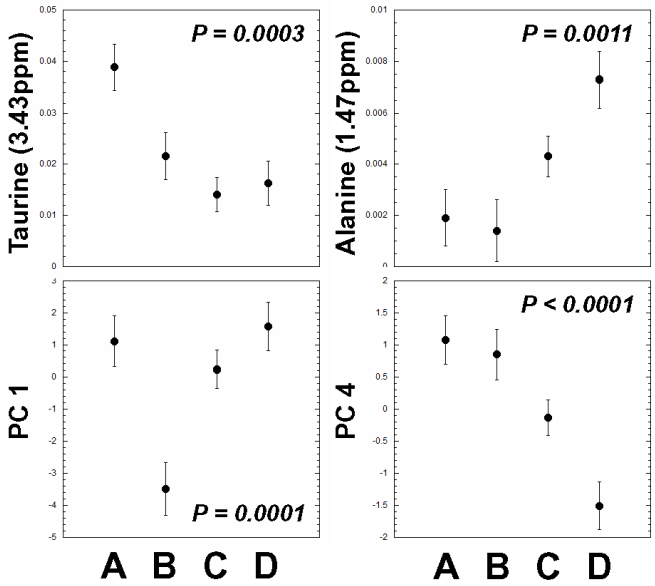

Figure 1. Spatial distributions of PCa metabolites and metabolomic profiles (p-values are calculated from ANOVA. See text for the identifications of the four patient groups).

Discussion and Conclusions: Our results presented here demonstrate the existence of PCa metabolomic fields. However the spatial distributions of these fields may be more complicated depending on the each metabolite of interest. While more systematically designed studies are necessary to fully evaluate and understand the extent of the fields, the existence of these fields, nevertheless, presents an immediate clinical implication: with the enlarged PCa "metabolomic lesions", the implementation of PCa metabolomic imaging may realize the widely searched goal of targeted PCa biopsy to overcome the current histology error seen in the PCa clinic.