Retrospective Analysis of Prostate Cancer Recurrence Potential with Tissue Metabolomic Profiles

A. Maxeiner[1,2], C. B. Adkins[2], W. S. McDougal[3], C. L. Wu[2,3], and L. L. Cheng[2,4]

[1]Radiology and Urology, Charité Universitätsmedizin Berlin, Germany, [2]Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [3]Urology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States, [4]Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy of male adults. It is the second leading cause of cancer death in men resulting from metastatic disease presented as "cancer biochemical recurrence" (BCR) and defined by an increase in serum prostate specific antigen (PSA) level after prostatectomy. About 20–40% of PCa patients experience BCR within 5 years of surgery. Early indication of BCR potential and aggressive therapies may improve the survival rates among these patients. Unfortunately, at present, no effective clinical protocol exists for the evaluation of BCR potentials either before or after radical prostatectomy. In this study, we retrospectively evaluated the value of intact tissue metabolomic profiles for the prediction of BCR. These evaluations were carried out with BCR cases and their matched patient groups to test the utility of tissue metabolomic profiles obtained from tissue magnetic resonance spectroscopy.

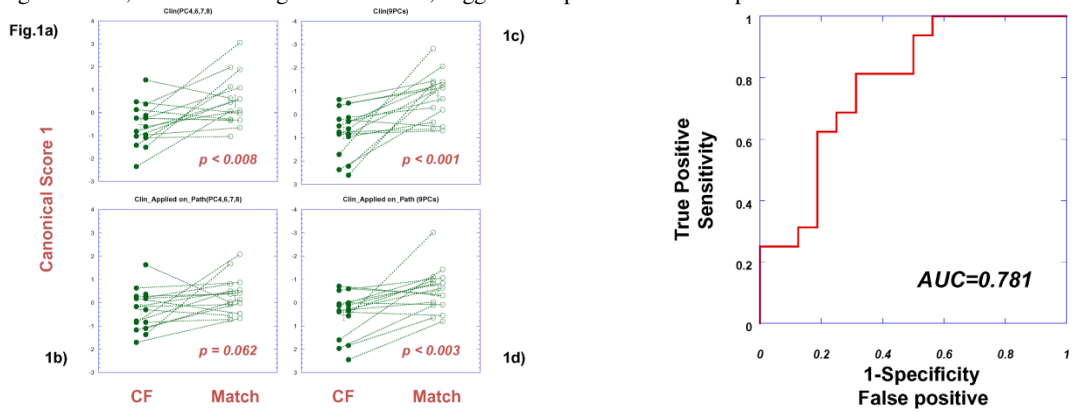
Methods

From 183 prostatectomy cases we have measured with intact tissue MR spectroscopy since 2002, we identified 16 cases with which patients have experienced BCR, defined as an increase of the serum PSA level to >0.2 ng/ml, and confirmed by a second elevation at least 15 days after surgery. For these 16 BCR cases, we randomly selected 32 age-, Gleason-score-, and observation-period-matched cases without BCR from the entire analyzed patient pool. These 32 cases formed two control groups that pair with the 16 BCR cases according to clinical or pathological stages. Clinical stages included C1 and 2, while pathological stages varied from T2N0 to T3aN1. Samples from these 48 cases were measured with high-resolution magic angle spinning (HRMAS) proton MRS followed by quantitative pathology. All spectra were processed according to the following procedure: 1-HZ apodization before Fourier transformation, baseline correction, and phase adjustment. Resonance intensities used in this study were integrals of curve fittings with Lorentzian-Gaussian line shapes. The 27 most intense resonance peaks/groups of specific metabolites from BCR and their clinical-stage-matched cases were selected and subjected to principal component analysis (PCA) and canonical analysis. The resulting metabolomic profiles were then applied and tested with the pathological-stage-matched cases. The differentiation power of these profiles between these controls and their paired BCR cases were evaluated by ANOVA and ROC curves.

Results

We observed that the first nine principal components (PC1 to PC9) represented more than 85% of the total variability of the 27 resonance values. We examined these nine PCs for their abilities to correlate with the amount of epithelium, cancer and stroma measured with quantitative pathology measured from the same specimens, and to differentiate recurrent from non-recurrent clinical-stage-matched groups. These analyses identified PCs 4, 6, 7, and 8 as having statistically significant or nearly significant values in achieving these tasks. Canonical analyses were conducted both for these identified four PCs and PCs 1 through 9.

Figure 1 summarizes the metabolomic profiles resulting from canonical analysis performed on PCs obtained with clinical-stage-matched groups, where Figures 1a and 1c are calculated from the identified four PCs and PCs 1 through 9, respectively. The existence and identification of these profiles with the abilities to differentiate BCR from their clinical-stage-matched groups (1a and 1c) as a result of discriminant analysis cannot self-prove the utility of these profiles. However, the application of these profiles to another paired group, the experimental data obtained from the matched control groups of patient pathological stages, and the observed differentiation between the recurrent group and its new paired group of pathological stage matches, as shown in Figures 1b and 1d, suggests the potential of these profiles.



Examinations of these overall loading coefficients revealed that the major contributing factors to the observed metabolomic profiles were the changes in metabolites included spermine/polyamines, glutamine, myo-inosital, phosphoryl choline, scyllo-inosital and glutamate. In summary, the overall accuracies for predicting BCR with the pathological-stage-matched groups based on metabolomic profiles established with clinical stage-matched groups according to four and nine PCs are 71.1 and 78.1%, respectively, as shown in **Figure 2**.

Conclusion

Identification of BCR potential after positive prostate cancer biopsy is critical since a radical prostatectomy is a major operation with known risks of urinary and sexual dysfunctions. While identification of non-life-threatening prostate cancer patients to enter active-surveillance instead of immediate prostatectomy is of great clinical interest, the design of the current study targets the opposite side of the spectrum of prostate cancer clinic: to isolate cases with potential post-prostatectomy BCR for aggressive therapies. Our results suggest that prostate metabolomic profiles measured with intact tissue HRMAS 1HMRS are capable of providing an additional parameter for predicting the risk of BCR that is beyond the capacity of the current predicting monograph used in clinic.