Characterization of Prostate Cancer with HRMAS 1HMRS

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Prostate cancer is a lethal, controversial disease. Morphometry-based prostate pathology until recently has proven effective in assessing patients with symptoms. However, with improved detection modalities, it has shown inadequacy in directing treatment for those with moderately differentiated adenocarcinomas, who represent more than 70% of all newly diagnosed patients. Currently, no available technique exists that can predict the likely aggressiveness of a specific tumor. Tumor metabolism results from a cascade of genetic and molecular transformations. These transformations precede histologically observable changes in cell morphology and reflect disease-related biochemical reactivity. Thus, the quantification of alterations in prostate metabolism may permit disease classification according to precise biochemical criteria, and lead to improved diagnostic accuracy based on tumor biological behavior.

The diagnostic utility of prostate cancer metabolites measured with high-resolution magic angle spinning proton magnetic resonance spectroscopy (HRMAS 1HMRS) has been tested. A total of 199 tissue samples (10mg) from 82 prostatectomy cases have been analyzed. The newly developed HRMAS 1HMRS method can obtain accurate *ex vivo* metabolite measurements directly from unaltered biological tissue. Through the use of mechanical magic angle spinning (MAS), this method achieves spectral resolution sufficient for the identification and quantification of individual metabolites and preserves tissue pathological structures for subsequent examination by histopathology.

The results of principal component analysis (PCA) of spectroscopic (45 metabolite resonance intensities) and quantitative histopathological (volume percentages of cancer, normal epithelia, and stroma) measurements performed on the same specimens indicate that 1) PCs generated from the 45 most intensive metabolite resonances can differentiate cancer from normal epithelial and stromal cells (**Table 1**); 2) these PCs confirm the reported prostate metabolites in association with cancer (such as phosphocholine, PCh) and normal epithelium (e.g. spermine, citrate, etc.); 3) metabolites identified by the PCs can differentiate cancer versus non-cancer tissues from the same patient with statistical significance (e.g. **Figure 1** for PCh); 4) the level of cancer related PC12 measured from histopathologically defined normal tissues of Gleason score 6 and 7 tumors correlate with patient clinical status, such as Gleason scores, pathological stages (**Figure 2**), and tumor perineural invasion (**Figure 3**).

In conclusion, prostate cancer metabolite markers obtained with *ex vivo* MRS may be more sensitive than the current histopathology. These markers measured from isolated tissue samples (e.g. biopsies) may have the ability to predict tumor clinical status, such as pathological stage, currently determined only after radical prostatectomy, earlier on to allow for optimal treatment planning.

	EigenValue	%	Cum%	Epithelium (r, p)	Cancer (r, p)	Stroma (r, p)
PC2	6.33	14.07	37.22	**0.332, <.0001**	-0.017, 0.8066	**-0.262, 0.0002**
PC12	0.87	1.92	80.84	0.078, 0.2747	**-0.167, 0.0181**	**0.179, 0.0114**

Table 1. Results of PCA on intensities of 45 resonances from 199 prostate tissue specimens of 82 prostatectomies. % - each eigenvalue as a percent of the total eigenvalue; Cum% - the cumulative percent of variation represented by this and all the previous PCs. For Epithelium, Cancer and Stroma columns: numbers are correlation r and p values.
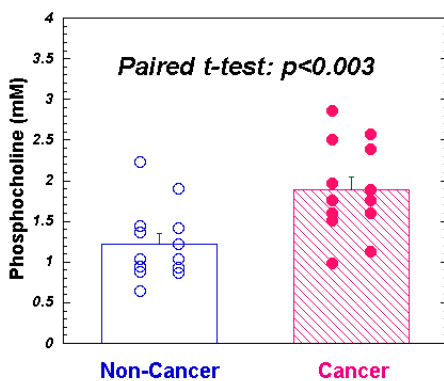

Figure 1. Metabolite concentrations of PCh suggested by PC12 as cancer correlated can differentiate cancer from non-cancer tissues; these results were obtained using paired Student's t-test for all 13 cases in which both types of tissues were available.
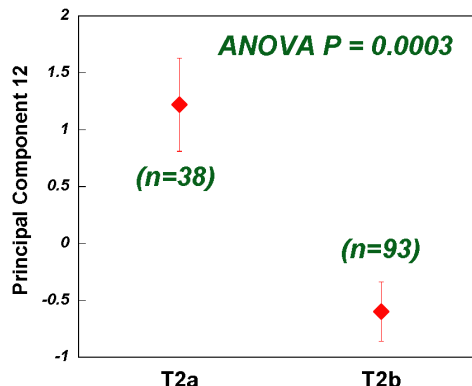

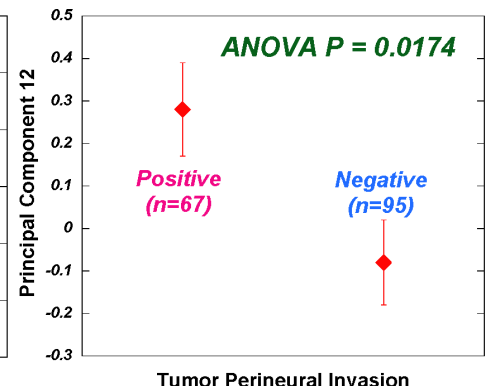**Figure 2.** PC12 can differentiate JACC (American Joint Commission on Cancer) T2a tumors from those of T2b.

Figure 3. PC12 can differentiate tumors with presence or absence of perineural invasion.