Relationship between MR visible metabolites, MR imaging parameters and quantitative histopathology in prostate cancer

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Introduction: Metabolic and morphologic changes due to prostate cancer (PCa) lead to changes in MR imaging (MRI) and MR spectroscopic (MRS) parameters. These cancer related changes may be caused by both increased cellularity and reduced luminal space. Attempts have been made to elucidate the relationship between MR visible metabolites and MR imaging parameters such as apparent diffusion coefficient (ADC) [1]. However, due to low spectral resolution *in vivo*, correlation between MRI parameters and individual metabolites (choline-containing compounds and citrate) has not yet been investigated. The objective of this study was to assess the relationship between MRI parameters (T2 intensity and ADC) measured on patients *in vivo,* individual metabolites measured on prostatectomy tissue *ex vivo* and quantitative histopathological features (percentage nuclei and luminal space).

Methods: Fresh frozen tissue samples (n=53 from 15 patients) were extracted from transversal prostate slices and linked to *in vivo* MR parameters as previously described [2,3]. A cryosection was taken from one end of each sample and stained with Hematoxylin, Erythrosine and Saffron (HES). These HES stained slides were digitized with 4× magnification and color-based segmentation (Positive Pixel Count algorithm in ImageScope v.11, Aperio Technologies) was used to identify luminal space and nuclei as described by Langer et al [4]. High resolution magic angle spinning ^{1}H MR spectra were obtained using a 14.1T spectrometer (Bruker Biospin) and post-processed as previously described [5]. Quantification of metabolites was performed by LC Model. T2 weighted images and ADC maps from preoperative MR examinations (3T, Siemens Trio) were used to calculate minimum T2 intensity and maximum ADC in regions of interest corresponding to tissue resection areas (Fig. 1a-c). Spearman's rank correlation (ρ) was calculated between *in vivo* MR parameters, *ex vivo* metabolite concentrations and morphological features. One sample was removed due to poor HES slide quality.

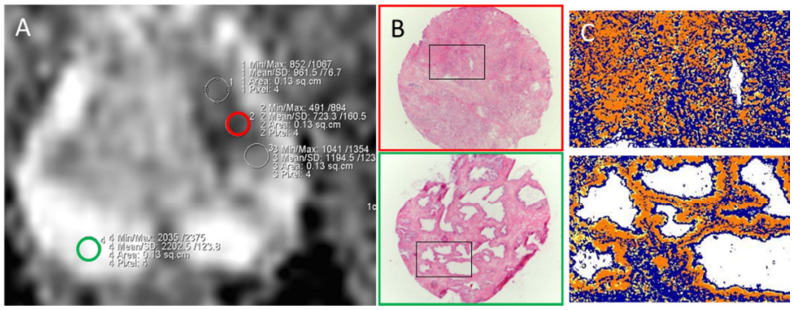

Figure 1: (A) ADC map with ROIs from cancer (red outline) and normal peripheral zone (green outline) areas corresponding to extracted tissue samples. (B) HES stained slides (4×objective) of cryosections with Gleason 5+4 (red) and non-cancer (green) tissue. (C)Close-up view of corresponding color-based segmentation (blue color corresponds to stroma, orange correspond to cytoplasm and nuclei).

Table 1: Spearmans ρ between examined parameters

	Choline	Citrate	Lumen#	Nuclei#
ADC	-0.46*	0.38*	0.54*	-0.36*
T2	-0.11	0.28*	0.49*	-0.06
Lumen#	-0.35*	0.37*	-	-0.27
Nuclei#	0.38*	0	-	-

Note: Choline is the sum of all choline containing compounds (free choline, glyserophosphocoline and phosphocoline). T2= minimum T2 in ROI, ADC = maximum ADC in ROI. #relative areas (%). *Significant at the 0.05 level.

Results and discussion: There is a positive correlation between total choline and the amount of nuclei ($\rho=0.38$, $p<0.01$) and between citrate and the amount of lumen ($\rho=0.37$, $p<0.01$) (Table 1). The latter may indicate that the reduction of citrate seen in cancer is partly due to morphological changes. ADC is positively correlated to lumen and negatively correlated to amount of nuclei ($\rho = 0.54$ and -0.36 respectively, $p<0.01$), confirming dependency to both cellularity and free diffusion in regions of luminal space. T2 was also positively correlated to amount of lumen ($\rho=0.49$, $p<0.01$), consistent with T2 being sensitive to extracellular water. However, no significant correlation between T2 and amount of nuclei was observed ($\rho=-0.06$, $p=0.68$).

Conclusion: This study shows that tumor microstructures observed by quantitative histopathology are linked to MR characteristics in prostate cancer.

References: 1.Kobus.Radiology,2012; 2.Selnaes.NMR Biomed,2012; 3.Bertilsson.Prostate,2011; 4.Langer.Radiology,2010; 5.Giskeodegard.PLoSOne,2013.