Histologic Basis of MRI in prostate peripheral zone: determination of the relationships between sub-cellular components and ADC, T2, Ktrans and ve

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Introduction MRI plays a vital role during prostate cancer (PCa) staging and, increasingly, in characterization of tumor location and extent. Tumor detection with MRI may be affected by heterogeneity in both normal and malignant prostate tissue [1]. Thus, understanding the relationships between MRI and tissue composition in prostate may provide insight into optimizing PCa detection with MRI, and potential sources of false positives or negatives. Early prostate MRI studies related T2-weighted signal intensity with tissue optical density [1] or dominant tissue type [2]. Image segmentation to extract sub-cellular components (*e.g.* nuclei) from hematoxylin and eosin (H&E) stained sections facilitates further study of the relationships between MRI and histology. Quantitative MRI parameters, such as apparent diffusion coefficient (ADC) and T2, have been correlated to the percentage area of nuclei (%nuc) [3]; however, their relationships with other sub-cellular components are currently unexplored. Dynamic contrast-enhanced (DCE) MRI parameters have been correlated to vascular endothelial growth factor (VEGF) expression [4], which occurs in the cytoplasm of glandular epithelium [5]. While this suggests that DCE parameters may be related to tissue composition, this has yet to be studied. In this study we have investigated the relationship between ADC, T2, and DCE parameters K^{trans} (volume transfer constant) and v_e (extravascular extracellular volume fraction) versus the underlying tissue composition, using an objective technique to divide peripheral zone (PZ) tissue in whole mount histology and MRI.

Purpose To determine histologic correlates of ADC, T2 and DCE-MRI in prostate PZ.

Materials and Methods Twenty men with known PCa had endorectal MRI on a 1.5T GE Excite HD platform prior to prostatectomy; informed consent was obtained prior to enrollment in this research ethics board approved study. T2-weighted fast-spin echo (FSE) images were acquired, followed by diffusion-weighted imaging (TR/TE = 4000/77ms, 128x256 matrix, 10 NEX, FOV = 14cm, b = 0,600s/mm^2), multi-echo FSE imaging (TR = 2000ms, 10 echo times (9.0-90.0ms), 256x128 matrix, 1 NEX, FOV = 20cm), and DCE-MRI (TR/TE = 4.3/1.9ms, 256x128 matrix, 0.5 NEX, FOV = 20cm, $\alpha = 20^o$, 10s temporal resolution, 50 phases). All MRI datasets were obtained at identical slice locations with 3mm slice thickness and no intersection gap. ADC and T2 maps were generated, and a Tofts model [6] with assumed arterial input function [7] was used to calculate K^{trans} and v_e maps. H&E stained whole mount sections were prepared to match *in vivo* MRI [8] and scanned at histologic resolution (20x) using ScanScope XT (Aperio). Histology and MRI slice locations were matched according to internal features. A representative slice from each patient containing both tumor and normal PZ, with corresponding MRI maps, was used for further analysis. The prostate was divided radially into octants in the MRI maps and digitized H&E slides, and PZ tissue outlined in each of the four posterior segments. Sub-cellular components (nuclei (nuc), epithelial cytoplasm (cyt), stroma, and luminal spaces (lum)) were segmented using Positive Pixel Count in ImageScope; a center-hue and window was defined, and pixels marked according to hue and intensity. A pathologist verified the segmentation accuracy. Percentage area of each component (*e.g.* %cyt) and median values for each MRI parameter were determined for each PZ-segment. The slope (m) of each parameter:component set was determined and tested for significance, using linear mixed effects models to account for multiple contributions from each patient.

Results and Discussion Eighty segments from twenty patients were analyzed. A sample H&E section, Positive Pixel Count mark-up image, and corresponding MRI maps, are shown in Fig 1. Median parameter values versus %area for one parameter:component set are shown in Fig 2. Regression results are summarized in Table 1. ADC and T2 had significantly negative slopes (m<0) and K^{trans} a significantly positive slope (m>0) versus %nuc. Only ADC was significantly related to %cyt (m<0) or %lum (m>0); however, T2 and K^{trans} exhibited trends versus %cyt (m<0, m>0, respectively), and T2 approached significance versus %lum (m>0). There were no significant relationships for v_e, or for %stroma. The directions of the slopes for ADC and T2 were in agreement, and opposite to that of K^{trans}. Increases in cellular content, such as %nuc, were related to a decrease in ADC and T2. ADC had a greater number of significant relationships, potentially due to higher sensitivity and/or lower uncertainty in the measurement. The slope between K^{trans} and %cyt did not achieve significance; however, a trend was observed, and a significant relationship between K^{trans} and %nuc was also present, indicating that DCE-MRI is related to the underlying individual histological components of the tissue and not just the vasculature. The ability to detect PCa relies on the inherent properties of the underlying tissues; an understanding of the relationships between quantitative MRI and cellular components in PZ, such as those determined in this study, may assist in image interpretation.

Conclusions The proportion of individual histological components significantly affects quantitative MRI (ADC, T2, DCE-parameters) in prostate PZ.

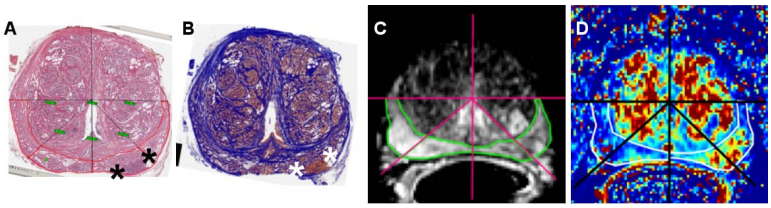

Figure 1. Representative histological sections (**A**,**B**) and MRI maps (**C**,**D**). Histology and MRI maps were initially bisected R/L and anterior/posterior, then the posterior sections divided to yield four segments. PZ within each section was delineated. Image segmentation of the digitized H&E section (**A**) with a central hue/window of 0.7/0.35 yields the mark-up image in **B**, where blue represents stromal components, and orange represents cytoplasm and nuclei. An increase in these sub-cellular components in a region of tumor ('*****' in **A** and **B**), corresponds to a decrease in ADC (**C**) and increase in K^{trans} (**D**).

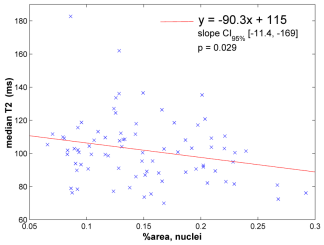

Figure 2. Median T2 values for each PZ-segment versus corresponding %area of nuclei. T2 decreases as the percentage area of nuclei increases; the slope of this relationship is statistically significant (p=0.029).

Table 1: Slope: parameter versus %area sub-cellular component ± standard error (p-value) (p<0.05 in bold)

	%nuc	%cyt	%stroma	%lum
ADC (10^{-3} mm^2/s)	**-1.46±0.39 (0.0004)**	**-0.75±0.31 (0.018)**	0.23±0.15 (0.124)	**0.73±0.30 (0.019)**
T2 (ms)	**-90.3±40.3 (0.029)**	-56.2±31.2 (0.076)	13.9±15.2 (0.36)	52.3±30.1 (0.088)
K^{trans} (min^{-1})	**0.96±0.36 (0.01)**	0.59±0.33 (0.079)	-0.07±0.14 (0.61)	-0.29±0.28 (0.29)
v_e (no units)	0.21±0.16 (0.18)	0.22±0.14 (0.118)	-0.02±0.06 (0.78)	0.05±0.12 (0.70)

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