Analysis of Quantitative MRI and Pathology based on Co-registered Regions of Prostate Cancer

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INTRODUCTION: There is increasing interest in the use and development of multi-parametric MRI to detect prostate cancer (PCa) and assess aggressiveness. In order to develop multi-parametric models, in vivo MRI results are evaluated against corresponding pathology data post prostatectomy. Typically, the information used from pathology consists solely of the approximate cancer location and Gleason score. In this work we demonstrate methods which improves the information pathology imparts to MRI by co-registering pathologist annotated regions of cancer onto the corresponding MRI data. In addition to providing the location of disease, quantitative pathologic information can also be obtained which can be used to better understand the correspondence between the anatomic and molecular pathologic status of disease and the MRI parameters measured in-vivo. The proposed methods are demonstrated in this study by correlating calculated T_2 values and apparent diffusion coefficients (ADC) with pathologically derived metrics of grade and nuclear density.

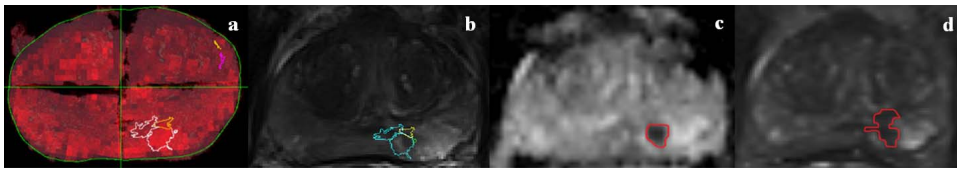

Fig. 1 (**a**) Multi grade tumor region displayed on nuclear density map on pseudo whole mount pathology section; (**b**) Registered tumor region displayed on corresponding T_2-weighted MRI; ROI drawn at hypointense region at registered tumor location on **(c)** ADC Map and (**d**) T_2 Map.

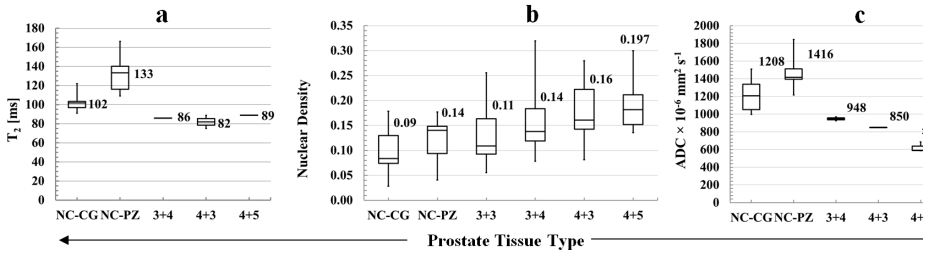

Fig. 2 (a) T_2 **(b)** Nuclear Density **(c)** ADC values for non-cancerous-central gland (NC-CG), non-cancerous-peripheral zone (NC-PZ) and peripheral zone tumors of increasing Gleason score (GS). *Data labels are the median values.*

METHODS: Patients with biopsy-proven prostate were imaged on a 3T Siemens scanner under an institutionally approved protocol. A surface array combined with an endorectal coil was used for all imaging. The endorectal coil was inflated with 60 ml of perfluorocarbon to reduce air induced susceptibility artifacts. *Quantitative MRI*: *T_2 maps* were generated from a multi-echo spin echo acquisition: 6m25s scan duration, 6000 ms TR, variable TE from 13.1 to 157.2 ms in 13.1 ms increments, 3mm slice thickness, 256×192 matrix, 19 slices, 280×280 mm^2 FOV. *ADC maps* were generated from single shot EPI diffusion weighted images; 4m35s scan duration, TR/TE 3200/88 ms, 8 averages, 3mm slice thickness, 128×128 matrix, GRAPPA 2, 19 slices, 180×180 mm^2 FOV and b-values of 50,400 and 800 s/mm^2. *Pathology Processing*: Excised prostates were formalin fixed, gross sectioned, paraffin embedded and cut at 3 µm. H&E stained slides were digitized using a whole slide scanner (ScanScope CS, Aperio, Vista, CA). Tumor regions within stained sections were annotated by an experienced pathologist. A Positive Pixel Count algorithm (v9, Aperio) was tuned (Hue value-0.77; Hue-width-0.1) to detect the fraction of pixels that exceeded pre-set weak, moderate, and strong threshold in the H&E colorimetric channel for all pixels within each tumor region. Digital slides were then assembled into a prostate pseudo whole mount (quarters that were reassembled) using our in-house prostate stitching software. Nuclear densities for annotated tumor regions and non-cancerous-central gland (NC-CG) and non-cancerous-peripheral zone (NC-PZ) regions were calculated by drawing regions of interest (ROIs) in contralateral non-cancerous (NC) regions. Fig 1a shows a pseudo whole mount slice over which nuclear density data and tumor regions have been displayed. Pseudo whole mount slides were registered to the corresponding in-vivo MR images using local affine transformation using our in-house registration software developed using Matlab and registered MR tumor regions were obtained as shown in Fig 1b. ROIs were drawn on the T_2 & ADC maps on hypointense regions coincident or at same anatomical location as the registered tumor regions as shown in figures 1c and 1d. A T_2 or ADC ROI coincident with a registered tumor region composed of many tumor grades was assigned the highest intra-tumor grade. T_2, ADC & nuclear density values for NC-CG and NC-PZ regions on a slice were calculated for each patient by drawing ROIs in cancer free contralateral regions. CG tumors, extra capsular extensions and regions with high SI on T_1-weighted images indicative of post biopsy changes were not included. ADC and T_2 image analysis was done in Matlab.

RESULTS: Tumor statistics were calculated from 8 PCa patients. The number of regions included for each quantitative metric were as follows: (*Nuclear Density*: NC regions-6, Tumors-28; *T_2*: NC regions-5, Tumors-5; *ADC*: NC regions-5, Tumors-8). The Wilcoxon signed rank test for matched pairs was used to assess statistical significant differences between tumor and NC values for each parameter. As seen in figures 2a and 2c, median tumor T_2 and ADC values were lower than NC-CG and NC-PZ ($p< 0.0625$ & $p<0.003$, respectively) while tumor nuclear densities were significantly higher (Fig 2b: CG: $p<0.003$, PZ: $p< 0.003$). Negative correlations between tumor nuclear density and tumor ADC ($r = -0.98$) and tumor ADC and tumor T_2 ($r = -0.65$) were found. The accuracy of registered tumor regions calculated by using superimposed landmarks and was found to be 2 ± 1.5 mm which provides confidence that they will be coincident with areas suspicious on T_2 and ADC maps.

DISCUSSION: In this study we demonstrate the ability to use regions of pathologist annotated cancer and derived quantitative pathologic information to correlate with quantitative MRI measures of prostate cancer. This work is different from previous studies as the co-registration employed has the potential to improve the correspondence of annotated cancer regions with regions chosen for analysis on the MRI. Compared to previous studies investigating T_2 and ADC versus nuclear density, our values for T_2 and ADC in NC-PZ and tumor are considerably lower while our nuclear density values for NC-PZ and Gleason score 4+5 are closer to those reported by Gibbs et al. [2]. The discrepancy in quantitative MRI parameters is most likely a result of differences in acquisition strategies between the two studies.

This study, as well as others, demonstrates that there are discernible pathologic features which correlate with quantitative MRI metrics of prostate cancer thus providing insight into the microstructure of the tissue. While it has been shown that Gleason score correlates positively to increased cellularity [10] and that nuclear density correlates with tumor aggressiveness [8,9], it is unknown how well these microscopic findings correlate to the macroscopic scale we currently operate in when imaging with MRI. Image registration of the ground truth histological annotated tumor regions with in-vivo MR and subsequent correlation of quantitative histopathological and pre-therapeutic MR parameters, as demonstrated in this abstract, will help address these questions.

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ACKNOWLEDGEMENTS: Funding Provided by NCI R01 CA131013, NCI R01 CA131013-S1, and BTRC P41 RR008079.