

# Pixel-Wise Multi-Parametric Assessment of Prostate Cancer from Co-registered regions of Pathologically defined Disease.

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**TARGET AUDIENCE:** Clinical scientists studying Prostate Cancer (PCa).

**PURPOSE:** PCa is the second most common cancer in men<sup>1</sup>. An assessment of tumor aggressiveness is essential to make treatment choices between radical prostatectomy and active surveillance. Multiparametric MRI (mpMRI) is currently one of the most promising tools for PCa detection and staging with the potential to further impacting disease management by characterizing disease aggressiveness and extent. Although individual MRI acquisitions have been shown to detect PCa and/or have strong correlation with PCa grade, the question whether mpMRI as a whole can predict PCa grade requires further investigation. The process of assessing mpMRI's ability to predict what is currently only obtained through post prostatectomy pathology (PPP), involves correlating mpMRI obtained in-vivo with post-surgical specimens. This correlation often times involves summarizing parameters from manually drawn regions of interest (ROIs) on the MRI corresponding to identified areas of disease on pathology. This process introduces a two potential biases: **1)** there is a user bias from the manual drawing of ROIs and **2)** performing analysis on summary statistics from ROIs across the mpMRI greatly simplifies what can often be a complex process where MRI derived biomarkers of disease are not always coincident. To address these issues, this study will **1)** use ROIs co-registered from pathology for identifying the regions of disease on MRI and **2)** perform pixel-wise univariate and multivariate analysis to address the relative significance of individual parameters for detecting PCa and assessing grade.

**METHODS:** Forty six patients with biopsy-proven PCa were imaged on a 3T Siemens scanner under an institutionally approved protocol. A surface array combined with an endorectal coil was used for imaging. **Quantitative MRI (qMR)** datasets included T2SEMC, T2TSE, T1DESPOT, ADC and DCE pharmacokinetic maps (Ktrans, Ve, Kep and AUGC). **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. Digital slides (quarters) were then assembled into a prostate pseudo whole mount (PWM) using our in-house prostate stitching software. Normal regions were annotated on PWMs by an experienced prostate MR researcher. **Image Registration:** PWM slides were registered to the corresponding in-vivo T2-weighted (T2w) MR images using a local affine transformation using our in-house registration tools<sup>2</sup> which have been demonstrated to have a registration accuracy of  $1.54 \pm 0.64$ mm. Registered MR tumor regions were obtained as shown in figure 1. **Image Analysis:** qMR data were resampled to the anatomic T2w images (i.e. the highest resolution dataset). Registered cancer and non-cancer regions were transferred from the T2w image to all qMR datasets and assigned the mean tumor grade of the registered tumor region. Small adjustments were made to the registered regions to account for prostate motion or distortion between the various MR datasets. qMR values for normal and cancerous peripheral zone for each registered region on a slice were calculated for each patient. Regions with high signal intensity on T1-weighted images, indicative of post biopsy changes, were not included. Image and statistical analyses were done in Matlab and R package respectively. Zero voxels from failed DCE fits were not included in the analysis. AUC (area under ROC curve) and ROC(0.1) (the sensitivity corresponding to a specificity of 90%) were calculated to determine the contribution each parameter would have individually and combined to detect PCa.

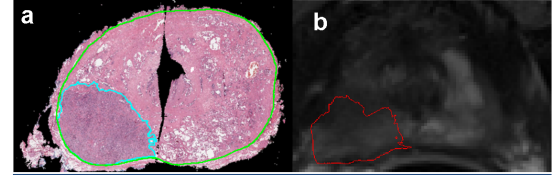
**RESULTS:** 34 cancer regions and 24 non-cancer regions were reviewed from 46 PCa patients. The number of regions and pixels processed are shown in Table 1. ADC was the best performing mpMRI parameter for PCa detection as shown in Table 2. Logistic regression based multivariate analysis showed that mpMRI parameters ADC, Ktrans, Ve and AUGC ( $p = 0.00156, 0.0094, 0.0193$  and  $0.0003$  respectively) were significantly correlated with PZ cancer grade. ROI based multivariate analysis did not result in similar significant correlation results of mpMRI datasets with grade. ADC was the only mpMRI parameter that showed significant correlation with grade in both ROI and pixel based univariate analyses. Lack of similar results in univariate analysis showed that correlation between mpMRI parameter and grade is not significant until a multivariate analysis is performed. Table 3 shows the mpMRI datasets that are significantly associated with PCa detection based ROI and pixel based univariate (U) and multivariate (M) analysis.

**DISCUSSION:** Our study shows the combined power of the mpMRI parameters in the detection of PCa and their association with grade. These results are highly unique and relevant as **1)** ROI definitions were dictated by registered pathology regions and not manual interpretations of pathologically identified disease and **2)** pixel-wise analysis was performed as opposed to the use of summary statistics from within the ROIs. Performing a pixel-wise analysis allows the apparent non-coincidence of some of the qMR parameters to be investigated. We propose this approach is a more appropriate way to apply predictive models moving forward. The results of this analysis will be used as a starting point to develop a mpMRI predictive model for detection and grading starting with ADC as the best single parameter. The multivariate results suggest a more accurate model will be possible by combining data that remains statistically significant after controlling for all other qMR parameters. Limitations of our study include the inability to reliably and automatically register between MRI datasets and the exclusion of central gland tumors. **CONCLUSION:** This study shows for the first time, that co-registered regions of cancer from pathology can be used to assess pixel-wise dependencies of qMR parameters. Several parameters show significance in a multivariate analysis demonstrating the promise of mpMRI to improve detection and grading over individual qMR parameters.

**REFERENCES:** [1] Ferlay J et al. GLOBOCAN 2008 v1.2, IARC CancerBase No. 10. [2] Kalavagunta, C et al. Proc. 20 Ann Meet ISMRM 2012: 2997.

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**Figure 1.** (a) PWM with annotated tumor region. (b) in-vivo T2w MRI with registered region overlay.



	Cancer	Non-Cancer
# Pixels $\times 10^3$	153	58
# ROIs	34	24

	AUC(95%CI)	ROC(0.1)
Pixel-wise	0.911(0.860,0.949)	0.795
ROI	0.934(0.858,0.987)	0.853

	ROI	Pixel
T2SEMC	U	U,M
T2TSE	U	U
ADC	U,M	U,M
Ktrans	U	U,M
Kep	U,M	U
AUGC	U,M	U,M