Development of Quantitative Multi-Parametric MRI Models for Prostate Cancer Assessment using Registered Correlative Pathology

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TARGET AUDIENCE: Genitourinary Radiologists; Urologists; Researchers involved in predictive modeling using correlative pathology.

PURPOSE: Multi-parametric magnetic resonance imaging (mpMRI) continues to evolve as an increasingly valuable tool in the diagnosis and management of prostate cancer. While there has been much effort to improve and standardize radiological reporting of mpMRI, it is well documented that detection performance is directly related to the experience level of the radiologist[1]. Predictive models, which can be trained to identify disease from the mpMRI data, are an alternative or adjunct to direct radiologic interpretation [2-4]. Constructing such models requires the use of correlative pathology which, depending on how the data is used, could have a large impact on model relevance and performance. In this work, a method for mapping regions of cancer identified and graded on assembled pathology sections is used to develop the needed ground truth for building voxel-wise mpMRI models for cancer detection.

METHODS: *Developing the Data:* Patients with biopsy proven prostate cancer received an mpMRI study prior to definitive therapy. Imaging was performed at 3T with an endorectal coil. The acquired data included anatomic and functional imaging which allowed for the calculation of quantitative maps including apparent T2 (T2), apparent diffusion coefficient (ADC), and pharmacokinetic parameters K^{Trans}, k_{ep} and AUGC. For surgical patients, resected prostates underwent tissue sectioning, digitization, and annotation (i.e. marking of cancer extent and grade) by following a study specific protocol developed to improve the correspondence between the pathology and in vivo MRI slice planes[5]. The digitized and annotated pathology specimens were then assembled into pseudo-whole mount (PWM) slices (Fig. 1a) and volumetrically reassembled. PWM slices from the center of each lesion were deformably registered using LATIS to the corresponding in vivo MRI slice (Fig. 1b)[5]. The mapped areas of disease, along with information from the manual segmentation of the prostate capsule and zonal anatomy, provided the data necessary to explore predictive models for PCa detection. Through this process, MRI voxels were labeled as cancer or non-cancer from registered pathology and labeled as peripheral zone (PZ) or central gland (CG) based on manual segmentation of the anatomic MRI (Fig. 1c).

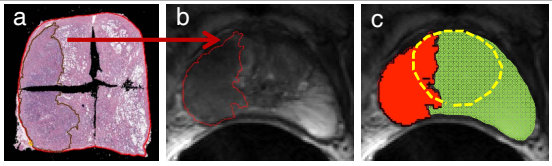

Fig. 1: Annotated regions of cancer from pathology (a) are mapped to the in vivo MRI data (b). Further segmentation of the capsule, central gland and peripheral zone allow various models to be considered using all voxels from the MRI slice.

Table 1: PZ-Model: AUC and S90 for combinations of MRI parameters versus ADC. Best model is highlighted in gray.

Parameters	AUC	p-value	S90	p-value
ADC (single param.)	0.82	--	0.60	--
ADC + AUGC	0.83	0.17	0.62	0.42
Above + KEP	0.83	0.03	0.63	0.12
Above + T2	0.85	<0.01	0.65	0.04
Above + KTRANS	0.84	<0.01	0.64	0.03

Table 2: WG-Model: AUC and S90 for combinations of MRI parameters versus ADC. Best model is highlighted in gray.

Parameters	AUC	p-value	S90	p-value
ADC (single param.)	0.74	--	0.34	--
ADC + KEP	0.72	0.89	0.25	0.92
Above + AUGC	0.78	0.16	0.44	0.21
Above + KTRANS	0.77	0.07	0.43	0.16
Above + T2	0.77	0.10	0.41	0.18

Predictive Modeling: Predictive modeling was performed using LASSO in RStudio[6] with performance assessed through a leave-one-out cross validation. A total of 36 patient datasets were included in this study from which 43 unique lesions were obtained. From the 5 quantitative MRI parameters considered in this study, models consisting of the most significant 2, 3, 4 and 5 parameters were developed and compared against the best performing single MRI parameter. Two distinct data pools were investigated for model development. The first model focused on cancer detection in the PZ alone (PZ-Model). The second model focused on cancer detection over the whole gland (WG-Model). The multi-parametric models were compared against the best single parameter results using area under the ROC curve (AUC) and the sensitivity at a specificity of 90% (S90). The significance of the improvement for the mpMRI model as compared to the best single MRI parameter was assessed in terms of its p-value. Composite biomarker score (CBS) maps are created as a linear combination of the quantitative mpMRI parameters using the LASSO regression coefficients.

RESULTS: For all 5 quantitative imaging parameters investigated in this study, the difference in medians between cancer and non-cancer were statistically significant, $p<0.05$. For both the PZ-Model (Table 1) and the WG-Model (Table 2), ADC was the best performing single parameter. As the number of terms increased beyond 2, both models outperformed ADC alone in terms of both AUC and S90, however only the PZ mpMRI model showed statistical significance with the inclusion of the 4th and 5th parameters (i.e. K^{Trans} and T2). A CBS map is shown along with the cutoff used to identify voxels identified as cancer with 90% specificity (Fig. 2)

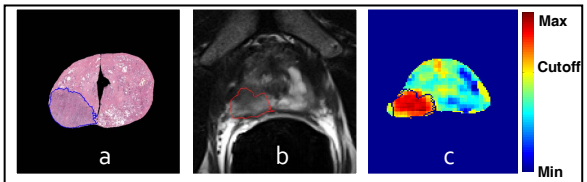

Fig. 2: (a) Annotated Pathology, (b) mapped area of cancer on T2w image (c) CBS map.

DISCUSSION: The classifiers presented here are one of a myriad that can be generated using the available data. While the four-parameter PZ-Model showed significant improvement over ADC alone, the WG-Model is an interesting option as it could be applied to the whole prostate without the need for segmentation. For the CBS maps, a cutoff with a defined sensitivity and specificity, optimized for the application of interest (i.e. guiding biopsy, targeting focal therapy) could be used to detect disease and define its extent. As a continuous variable, CBS could be used as a quantitative means to monitor patients on active surveillance or post therapy. One caveat to the use of these models clinically is the need for more effective methods to register the MRI datasets comprising the mpMRI study.

CONCLUSION: A process is presented for generating critical correlative pathology for developing predictive models from voxel-wise mpMRI data based on mapping regions of disease from assembles pathology to in vivo MRI. The models generated from this novel data show improved performance over single quantitative MRI parameters for detection. The generation of composite biomarker maps has the potential to improve the use of mpMRI in the management of prostate cancer.

REFERENCES: [1]Mullerad et al. Radiology 232, 140 (2004). [2]Litjens et al. IEEE Trans Med Imaging 33, 1083 (2014). [3]Morton et al. Radiology 239, 375-383 (2006). [4]Stember et al. JMRI 40, 301 (2014). [5]Kalavagunta, et al. JMRI (2014). [6]R Foundation for Statistical Computing, Vienna, Austria, 2013.

ACKNOWLEDGEMENTS: Funding Provided by NCI R01 CA131013, NCI R01 CA131013-S1, NCI R01 CA155268 and NIH P41 EB015894.