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TITLE: Noninvasive Risk Stratification of Prostate Cancer Patients Using Radiomic Features Derived from Magnetic Resonance Fingerprinting (MRF) and MRI

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14. ABSTRACT
This project is aimed at non-invasive risk stratification of prostate cancer patients achieved through development of computer assisted tools using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Fingerprinting (MRF). During the current reporting period, we build upon earlier reported work and have established associations between MR parameters including T1, T2 MRF, T2w and ADC measurements, tissue compartment ratios derived from whole mount pathology within prostate cancer, prostatitis and normal prostate. We have also showed differential correlations between MRF measurements and tissue compartments within prostate cancer and prostatitis, both within central and transition zone. In addition, we have also developed novel radiomic methods for risk stratification of prostate cancer using MRI including peri-tumoral radiomics, delta radiomics and deep learning based features which have resulted in 4 journal publications.

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1. INTRODUCTION:

This project is aimed at non-invasive risk stratification of prostate cancer patients achieved through development of computer assisted tools using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Fingerprinting (MRF). Research involved in this project involves co-registration of ex vivo digitized prostate specimens with MRI and MRF maps to enable accurate transfer of pathologic delineations from histology on to MRF and MRI and provide accurate ground truth labels. This will be followed by identification of computer derived radiomic features from these regions of interest (ROIs) on MRF and MRI that separate cancer lesions into various risk categories. These features will be used to design predictive machine learning models for risk stratification.

2. KEYWORDS:

Prostate cancer, magnetic resonance imaging, magnetic resonance fingerprinting, machine learning, computer aided diagnosis, risk stratification.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Task	**Months**	**% Completion**
Specific Aim 1: To accurately delineate cancer and benign lesions on imaging.		**In Progress**
Major Task : Co-register whole mount digitized histopathology images with MRF and MRI *(N = 40)*		
Subtask 1: *Identify the ROIs corresponding to cancerous and benign lesions on pathology. Begin with an initial subset of N = 40 studies.*	1-6	90%
Subtask 2: *Methods for automatic segmentation of prostate on MRF and MRI*	6-12	90%
Subtask 3: *Methods for co-registering MRF and MRI*	12-18	100%
Subtask 4: *Co-register histology, MRF, MRI.*	12-18	100%
Milestone(s) Achieved: Present research on registration of digitized ex vivo prostate histology with MRF and MRI at AUA 2019	18	*Conference: ISMRM 2019*
Specific Aim 2: Identify a set of MRF and MRI derived radiomic features that stratify cancerous lesions into high, intermediate, low risk categories,		**In Progress**
Major Task : Design and discover radiomic features from MRF, MRI that differentiate various cancer grades and benign lesions *(N = 90)*		

Task	Months	% Completion
Subtask 1: *Establish morphologic basis for MRF and mpMRI signatures based on co-registration and design radiomic features. Acquire additional datasets and implement methods designed in Specific Aim 1.*	18-28	100%
Subtask 2: *Extract radiomic features from MRF and mpMRI from the ROIs*	28-30	50%
Subtask 2: *Develop a machine learning classifier using the extracted features*	28-30	10%
Milestone(s) Achieved: Present research on radiomic features derived from MRF and MRI that distinguish benign and cancerous lesions at RSNA 2019, ASCO 2020	30	*Conferences: ISMRM 2020, AUA 2020, SPIE 2020* *Journal Publications: (Eur.Rad.(2), Cancers(1), Lancet EBiomedicine(1))*
Specific Aim 3: Validate the signatures identified in Aim 2 using an independent validation dataset.		**TBC**
Subtask 1: *Extract specific radiomic features from MRF and MRI, identified in Aim 2 from the independent validation set (N = 90 training, N = 40 validation).*	30-34	
Subtask 2: *Validate these features using the machine learning classifier developed in Aim 2*	34-36	
Milestone(s) Achieved: Present research on a computerized decision support system to distinguish various grades of cancer and benign lesions using radiomic features derived from MRF and MRI at RSNA 2020, AUA 2020	36	
**TBC: To Be Completed*		

What was accomplished under these goals?

1) ***Major Activities*:**

During this reporting period, we used the developed co-registration pipeline developed during the earlier period to transfer the cancerous and prostatitis regions of interest from whole mount pathology on to imaging. We also obtained HRPO approval for our IRB and were therefore able to leverage acquired data into the designed pipeline. In addition, we computed correlations between the tissue compartment ratios derived from whole mount pathology and MR measurement (including MRF and MRI) that established the histo-morphometric basis of imaging measurements. This forms a major portion of the Specific Aim 2.

In addition, we also developed novel radiomic features such as peri-tumoral radiomics, delta radiomic features and deep learning features using MRI to develop risk stratification methods. These

radiomics and machine learning methods will be optimized for the MRF data which form the basis of Specific Aims 2 and 3.

2) ***Specific Objectives*:**

A. Establish histo-morphometric basis of MRF measurements

Summary: This is the objective under Specific Aim 2.1 to establish a histo-morphometric understanding of MRF measurements. Correlation of histopathology and MR imaging is vital for gaining deeper insights into the characterization of prostate cancer on imaging. Previous studies have explored correlations between prostate multi-parametric MRI (mpMRI) and digitized histopathology. Being able to differentiate non-cancers from cancers may significantly improve characterization of prostate cancer on imaging. While a few previous studies have shown that mpMRI could potentially help in differentiating prostatitis and prostate cancer, overlapping characteristics still exist on imaging. Quantitative MRF can potentially help in addressing these challenges as evidenced in recently published works. However, there is a need to evaluate the interpretability of these findings, specifically with respect to corresponding histopathologic characteristics. Establishing a histo-morphometric basis of MRF measurements for prostate cancer diagnosis would improve clinical adoption of MRF and also potentially improve MRF acquisition. The specific objective here was to establish the histo-morphometric basis for MRF-based T1 and T2 relaxometry measurements that have previously been shown to be strongly associated with prostate cancer.

Dataset: The HRPO approval obtained from the DoD for this proposal on 01/02/2020 allowed us to use the dataset for further analysis. To establish the histo-morphometric basis, N=14 prostate cancer patients who underwent T1, T2 MRF and mpMRI followed by radical prostatectomy were chosen.

Methods: The co-registration pipeline described in the previous report was used to transfer the regions of interest (ROI's) from whole mount pathology to MRI and MRF. These ROIs consisted of prostate cancer (PCa), prostatitis and normal peripheral zone (NPZ). The distribution of imaging variables (T1, T2 MRF, ADC, T2w MRI) and TCRs within the ROIs follow a continuous distribution. Therefore, to estimate the linear relationship between MR measurements and TCRs, Pearson's correlation coefficient (R) was computed. On the other hand, the International Society of Urologic Pathology Prognostic Groups (IPG) is an ordinal variable and therefore, the Spearman's rank correlation (ρ) was used compute the monotonic relationship between IPG and each of the imaging variables, TCRs. The differences between mean MRI, MRF measurements, tissue compartments across IPGs, prostatitis and NPZ ROIs was examined using one-way analysis of variance (ANOVA) test followed by multiple pair-wise comparisons using Tukey honest significant differences (HSD) post-hoc test. Simple pair-wise comparisons were performed using the Wilcoxon rank-sum test with $p < 0.05$ considered to be statistically significant. This is a non-parametric test that assesses whether the distributions between two separate groups are statistically significant. Statistical analyses were performed in MATLAB (v.2018a, MathWorks Inc.) and R. The ROIs obtained on MRI via mapping were eroded by 3 voxels (= 1.8 mm.) on MRI, and 2 voxels (= 2mm.) on MRF, to discard any noise arising from artifacts at the boundary of ROIs.

Mean T1, T2 MRF and ADC were all statistically significant univariate predictors of PCa (N = 33 lesions) compared to NPZ (N = 24 ROIs). A multi-variable logistic regression model with T1, T2 MRF and ADC together resulted in AUC = 0.997 in distinguishing PCa and NPZ. These observations are in line with previously published study by Yu et. al., who reported AUC = 0.99 in distinguishing PCa from NPZ with N = 109 lesions using T1, T2 MRF and ADC together.

3) **Significant Results**:

a) *Correlations between MRF and tissue compartments within prostate cancer and prostatitis ROIs*: Significant correlations between TCRs and MRF measurements on imaging were observed (Figure 3). T1 MRF was positively correlated with stroma for PCa (R = 0.35) and negatively correlated for prostatitis (R

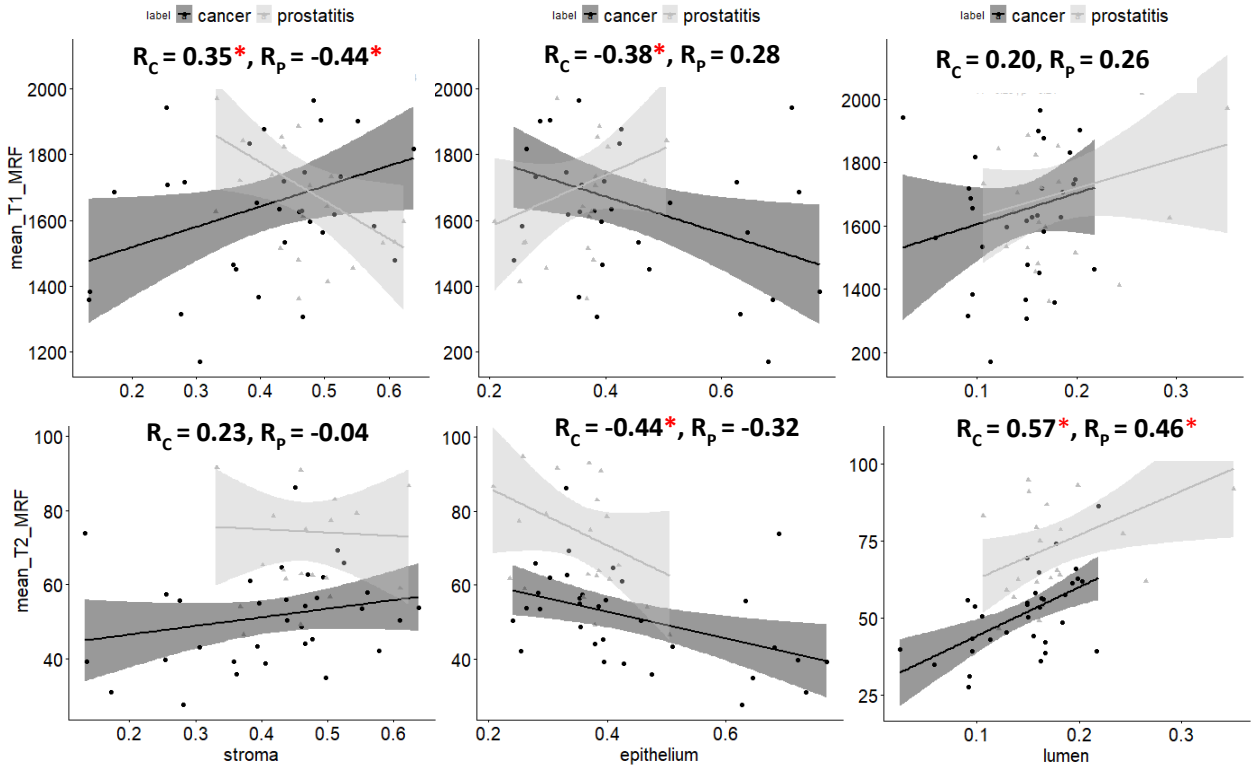

Figure 1: Scatter plots of mean T1, T2 MRF with respect to tissue compartment ratios (TCRs) of stroma, epithelium and lumen within prostate cancer and prostatitis regions of interest. An asterisk is indicated next to correlation coefficient (*R*) to suggest statistical significance.

= -0.44). T1 MRF was negatively correlated with epithelium for PCa (R = -0.38) while no significant correlations were observed in prostatitis and with lumen TCRs. There was a negative correlation of T2 MRF measurements with density of epithelium (R = -0.44) and positive correlation with lumen (R = 0.57) for prostate cancer. While T2 MRF was also positively correlated with lumen for prostatitis (R = 0.46), no significant association was observed with epithelium in this case. ADC measurements were negatively correlated to epithelial TCR and positively correlated to TCRs stroma and lumen within the cancerous ROIs. However, no significant associations were observed for prostatitis (provided in supplemental section).

Correlations between T1 MRF and stromal ratio were found to be in opposite directions for prostate cancer and prostatitis (Figure 1). Significant differences ($p < 0.01$) were observed in T2 MRF and ADC measurements between prostate cancer and prostatitis in both the peripheral zone (PZ) and the transition zone (TZ) (Figure 2). T1 MRF measurements showed significant differences between these two categories in the TZ.

b) *Differences in MRF – tissue compartment associations in peripheral and transition zone prostate cancer lesions*: When controlled for their location in specific zones, stronger correlations between T2 MRF, ADC and TCRs was observed within the PZ PCa lesions while T1 MRF showed higher correlations with

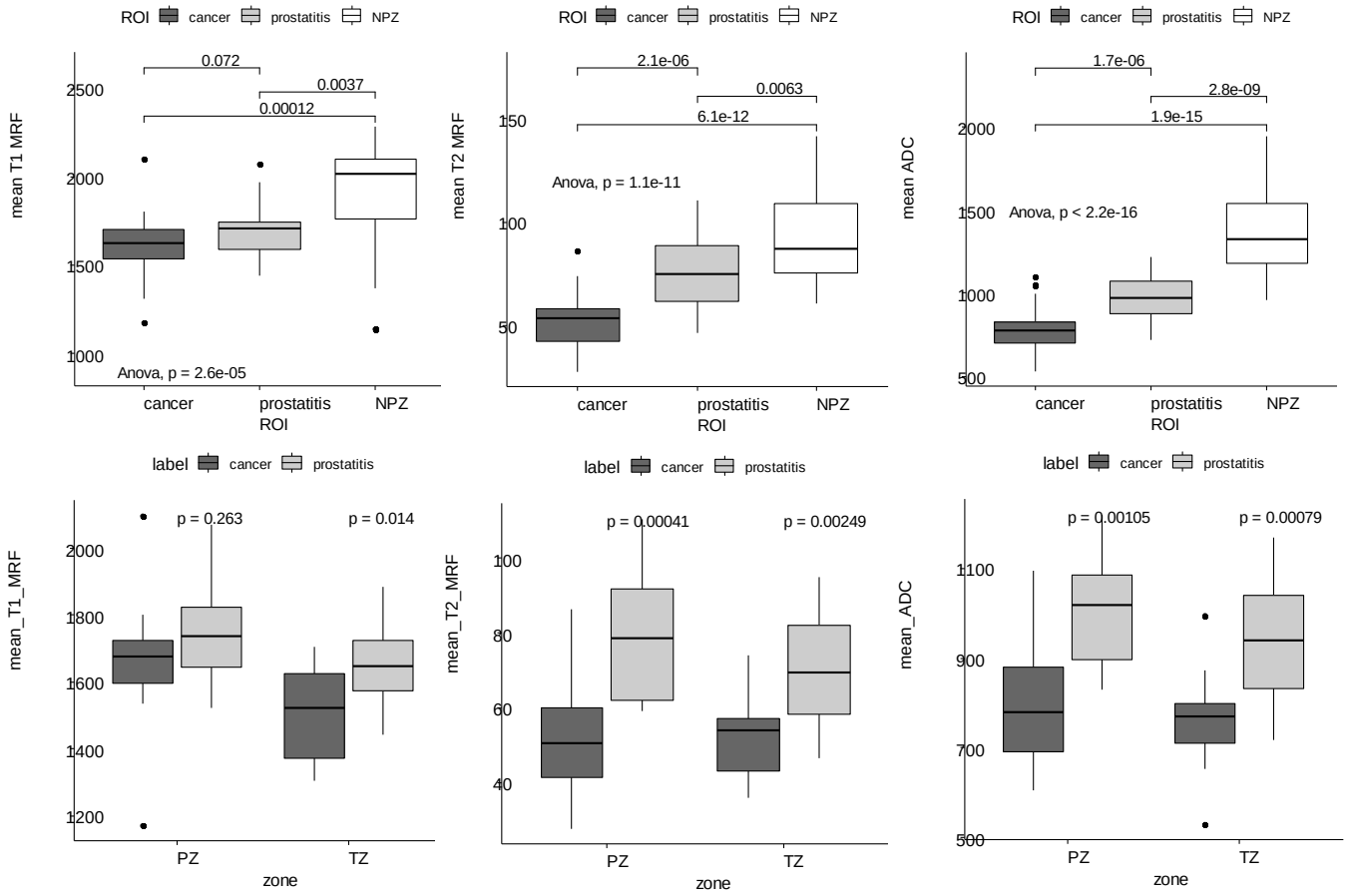

Figure 2: Top row: Box plots illustrating statistically significant differences between prostate cancer prostatitis and normal peripheral zone (NPZ) in terms of mean T1, T2 MRF and ADC values, pair-wise along with ANOVA. Bottom row: Differences between prostate cancer and prostatitis in terms of mean T1, T2 MRF and ADC. T2 MRF and ADC show significant differences across peripheral (PZ) and transition zone (TZ) while T1 MRF is significantly different in the TZ, between prostate cancer and prostatitis.

epithelium and stromal ratio within the TZ lesions. ADC was found to be strongly correlated to the lumen ration within TZ PCa lesions. These results are summarized in Table 1. With respect to prostatitis, significant correlations between TCRs and T1, T2 MRF were observed in the TZ while no significant correlations were observed in the PZ.

Table 1: Correlation coefficients between quantitative MR and tissue compartments of prostate cancer lesions and prostatitis within peripheral and transition zone

		Peripheral Zone (n_{PCa} = 19, n_P = 9)			Transition Zone (n_{PCa} = 14, n_P = 14)		
		%epithelium	%stroma	%lumen	%epithelium	%stroma	%lumen
Prostate Cancer	T1 MRF	-0.36	0.17	0.3	-0.56*	0.46*	0.42
	T2 MRF	-0.72*	0.52*	0.76*	0.1	-0.1	0.1
	ADC	-0.6*	0.63*	0.23	-0.28	-0.1	0.87*
Prostatitis	T1 MRF	0.3	-0.46	0.36	0.64*	-0.44	-0.5*
	T2 MRF	0.12	-0.45	0.54	-0.6*	0.56*	0.2
	ADC	0.05	0.08	-0.17	-0.4	0.19	0.5

*** Indicates statistical significance ($p < 0.05$); PCa: Prostate Cancer; P: Prostatitis**

4) **Key Findings:**

Within PCa ROIs, we observed that T2 MRF measurements decreased with rise in epithelium and decline of lumen. T2 values are affected by free water and fluid in the extracellular space which is significantly reduced in PCa due to a high epithelial content and poorly formed glands. T1 MRF measurements decreased with rise in epithelium and reduction of stroma compared to healthy prostate tissue as illustrated in Figure 3. The breakdown of glandular spaces that contain fluid results in shorter T1 and this was also observed in a study by Busch et.al. [31] which looked at T1 relaxation in ex vivo prostate tissue. For prostatitis, T2 MRF measurements reduced with decrease in lumen TCRs, similar to what was observed for PCa. However, on histopathology, while prostatitis is characterized by intraluminal neutrophils and glandular atrophy PCa shows decreased luminal volume. We also observed that lower stromal TCR was associated with higher T1 MRF. In our segmentation approach, lymphocytes were not categorized separately and regions with a high concentration of infiltrating lymphocytes were segmented as epithelium. Therefore, a lower stromal content could imply a higher concentration of lymphocytes, or inflammatory cells, along with extracellular fluid in the in vivo tissue. Taken together, this would result in a higher T1 signal. However, further studies on a larger dataset are needed to gain additional insights.

Significant differences between prostatitis and PCa have been observed in our study with respect to ADC and T2 MRF. When individual prostate zones were considered, ADC and T2 MRF measurements were significantly different both in the peripheral (PZ) and transition zone (TZ), while T1 MRF was significantly different in the TZ. These results are in agreement with some of the recent studies by Panda et. al. which demonstrated that T1, T2 MRF and ADC were significantly different between prostatitis and PCa. Results using quantitative MRF measurements and ADC tend to indicate that they could potentially be capturing morphologic differences between prostate cancer and prostatitis. Validation on a larger cohort of patient studies will be conducted in the future to establish these findings. When controlling for the spatial location of the disease, we observed correlations between T1 MRF and TCRs were stronger and significant in the TZ (both PCa and prostatitis) while those between T2 MRF and TCRs were stronger in the PZ. A number of earlier studies including the Prostate Imaging Reporting and Data System version 2 (PIRADS v2) guidelines, and radiomic signatures derived from MRI indicated that PZ and TZ tumors tend to have different characteristics and this observation also held with respect to MRF measurements.

While we definitely need more patients to generalize these findings, this study presented an important insight in establishing the histo-morphometric basis of prostate MRF which was recently published in *European Radiology*[1] in September 2020.

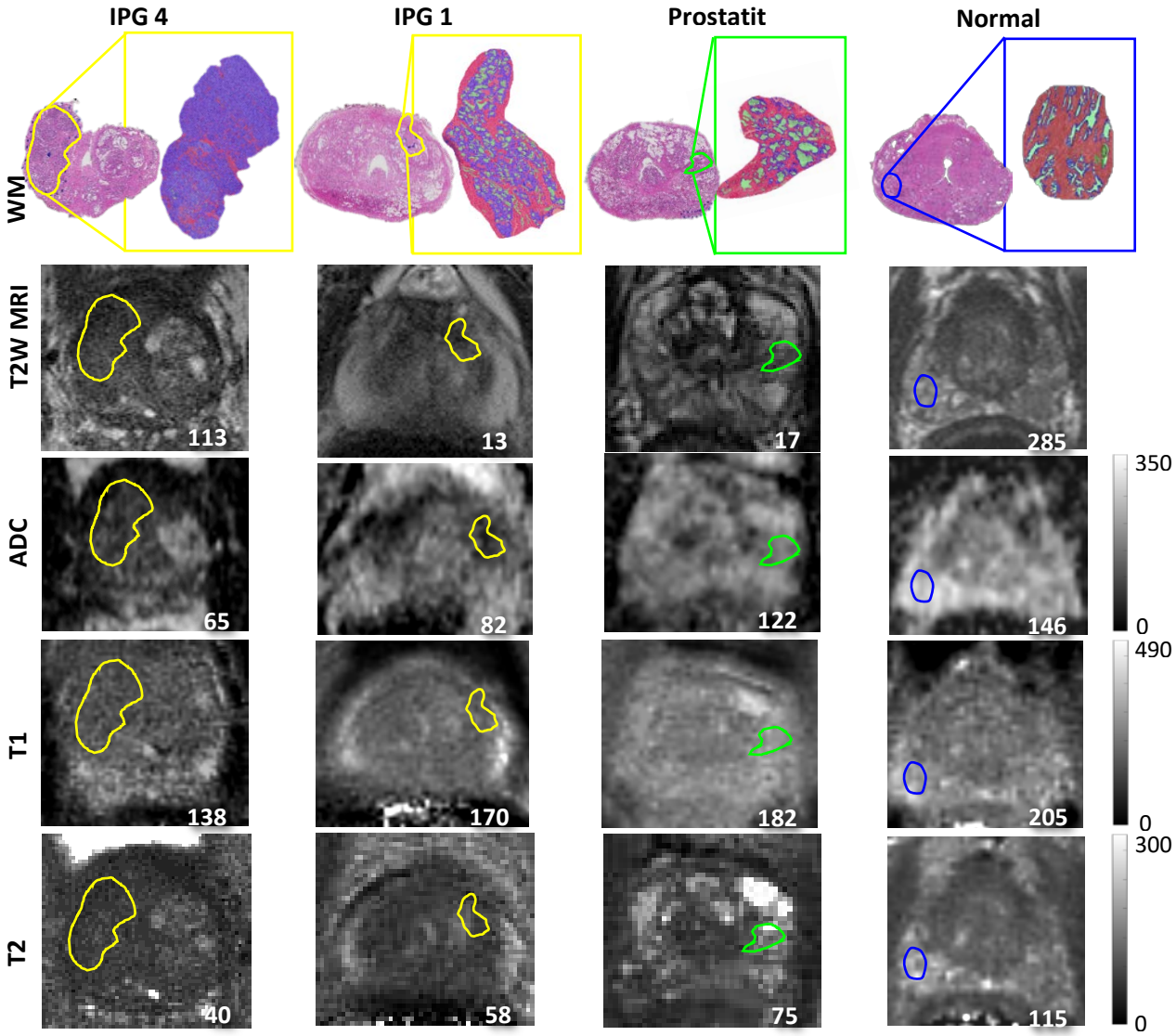

Figure 3: Row 1: Tissue compartment segmentations on clinically significant (IPG >1), insignificant (IPG = 1), prostatitis and normal peripheral zone ROIs (purple epithelium, pink stroma and green lumen). Row 2,3: T2WI and ADC containing mapped ROIs from pathology. Row 4,5: T1, T2 MRF maps showing ROI mapped from T2WI. Mean values within the ROIs are provided in the lower right corner for each image.

5) **Other achievements:**

i) Test-retest repeatability of a deep learning architecture in detecting and segmenting clinically significant prostate cancer on apparent diffusion coefficient (ADC) maps

This project is aimed at designing optimal deep learning method for risk stratification of prostate cancer using MRI which will be further optimized and leveraged in Specific Aim 2.2-3 and Specific Aim 3. The goal of this project was to evaluate short-term test-retest repeatability of a deep learning architecture (U-Net) in slice-, lesion-level detection and segmentation of clinically significant prostate cancer (csPCa: Gleason Grade Group>1) using diffusion weighted imaging fitted with monoexponential function, ADC_m. 112 patients with prostate cancer (PCa) underwent 2 prostate MRI examinations on the same day. PCa areas were annotated using whole mount prostatectomy sections. Two U-Net based convolutional neural networks were trained on three different ADC_m b-value settings for a) slice- b) lesion-level detection and c) segmentation of csPCa. Short-term test-retest repeatability was estimated using intra-class correlation coefficient (ICC(3,1)), proportionate agreement and dice similarity coefficient (DSC). A 3-fold cross-

validation was performed on training set (N=78 patients) and evaluated for performance and repeatability on testing data (N=34 patients).

For the three ADC_m b-value settings, repeatability of mean ADC_m of csPCa lesions was ICC(3,1)=0.86-0.98. Two CNNs with U-Net based architecture demonstrated ICC(3,1) in the range of 0.80-0.83, agreement of 66-72% and DSC of 0.68-0.72 for slice-, lesion-level detection, and segmentation of csPCa. Bland-Altman plots suggest that there is no systematic bias in agreement between inter-scan ground-truth segmentation repeatability and segmentation repeatability of the networks. For the three ADC_m b-value settings, two CNNs with U-Net based architecture were repeatable for the problem of detection of csPCa at the slice-level. The results are summarized in Figure 4. The network repeatability in segmenting csPCa lesions is affected by inter-scan variability and ground-truth segmentation repeatability and may thus improve with better inter-scan reproducibility. This was published in *European Radiology*[2] in July 2020.

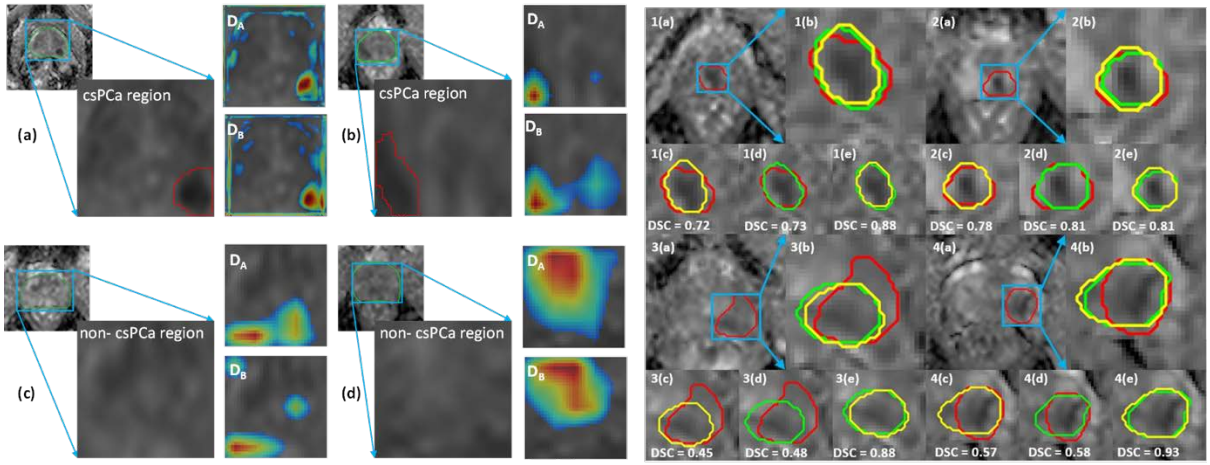

Figure 4: LEFT: Activation maps of deep learning classifiers on (a, b) clinically significant prostate cancer (csPCa: Gleason grade group (GGG) > 1) regions of ADCm maps and (c, d) noncsPCa (GGG = 1/benign) regions. The activation map shows that networks look at a darker ADCm region for csPCa regions compared with non-csPCa regions where the network looks at a brighter area. RIGHT: Clinically significant prostate cancer (csPCa) lesion segmentation maps on ADCm of deep learning networks. a Full field of view of ADC. b Overlaid ground truth delineation (GT) and segmentation maps. c), d) and e) Dice similarity coefficient (DSC) between the two networks outputs (yellow and green) and the ground truth (red).

ii) A deep learning network along with PIRADS can distinguish clinically significant and insignificant prostate cancer on bi-parametric MRI: A multi-center study

This project is aimed at risk stratification of prostate cancer using deep learning methodologies developed with prostate MRI that will be leveraged in Specific Aims 2 and 3. Bi-parametric MRI (bpMRI: T2W MRI and Apparent Diffusion Coefficient maps (ADC) derived from diffusion weighted imaging) is increasingly being used to characterize prostate cancer (PCa). However, inter- and intra- reader variability hinders interpretation of MRI. Recent works have shown that deep learning networks may aid in PCa characterization. In this study, we present a deep multi-instance learning (De-MIL) convolutional neural network (CNN) to distinguish clinically significant PCa (sPCa: GGG> 1) and insignificant PCa (iPCa: GGG=1) on bpMRI. A retrospective cohort of 359 patients with 492 lesions with data from three sites (site 1:224, 2:147, 3:121 lesions respectively) who underwent 3T bpMRI before prostatectomy or at the time of clinical suspicion was used. Three radiologists from each site annotated cancer regions by looking at prostatectomy sections and/or biopsy reports. Lesions were divided into training set (N = 105), validation set (N = 50) from one institute, and test set (N = 337) from all institutes. De-MIL (Figure 1a) was trained with T2W, ADC and their corresponding lesion segmentation masks. De-MIL aggregates the representation of patches across a lesion into a pooled representation using multiple instance learning. A logistic regression classifier was trained on combination of De-MIL predictions and Prostate Imaging Reporting and Data System (PI-RADS v2.0/2.1) score to obtain final classification result. The gleason grade grouping (GGG)

of lesions were 1: 158, 2: 171, 3: 78, 4: 22, 5: 63, respectively. Models based on PI-RADS and De-MIL alone resulted in AUC (GGG1 vs >1) of 0.75 and 0.76 respectively, while model trained on combination of De-MIL and PIRADS (M_C), yielded AUC of 0.79 (Figure 1b) with significant improvement (t-test, p=0.033, p=0.013 respectively). PI-RADS with cutoff > 3 resulted in sensitivity of 0.85 and specificity of 0.39, while cutoff of 0.5 on M_C improved the specificity to 0.64 with a drop in sensitivity to 0.76. De-MIL activation maps in (Figure 1c) show that classifications were derived based on cancerous regions. A combination of De-MIL and PI-RADS can improve the classification performance in distinguishing sPCa and iPCa compared with PI-RADS alone. This is currently under review at *Lancet Digital Health*.

iii) Combination of Peri-Tumoral and Intra-Tumoral Radiomic Features on Bi-Parametric MRI Accurately Stratifies Prostate Cancer Risk: A Multi-Site Study

This project aims at discovering novel peri-tumoral radiomics for prostate cancer risk stratification which will be leveraged in Specific Aim 2. Prostate cancer (PCa) influences its surrounding habitat, which tends to manifest as different phenotypic appearances on magnetic resonance imaging (MRI). This region surrounding the PCa lesion, or the peri-tumoral region, may encode useful information that can complement intra-tumoral information to enable better risk stratification. The objective of this project was to evaluate the role of peri-tumoral radiomic features on bi-parametric MRI (T2-weighted and Diffusion-weighted) to distinguish PCa risk categories as defined by D'Amico Risk Classification System. We studied a retrospective, HIPAA-compliant, 4-institution cohort of 231 PCa patients (n = 301 lesions) who underwent 3T multi-parametric MRI prior to biopsy. PCa regions of interest (ROIs) were delineated on MRI by experienced radiologists following which peri-tumoral ROIs were defined. Radiomic features were extracted within the intra- and peri-tumoral ROIs. Radiomic features differentiating low-risk from: (1) high-risk (L-vs.-H), and (2) (intermediate- and high-risk (L-vs.-I + H)) lesions were identified. The peri-tumoral radiomics are illustrated in Figure 5. Using a multi-institutional training cohort of 151 lesions (D1, N = 116 patients), machine learning classifiers were trained using peri- and intra-tumoral features individually and in combination. The remaining 150 lesions (D2, N = 115 patients) were used for independent hold-out validation and were evaluated using Receiver Operating Characteristic (ROC) analysis and compared with PI-RADS v2 scores. Validation on D2 using peri-tumoral radiomics alone resulted in areas under the ROC curve (AUCs) of 0.84 and 0.73 for the L-vs.-H and L-vs.-I + H classifications, respectively. The best combination of intra- and peri-tumoral features resulted in AUCs of 0.87 and 0.75 for the L-vs.-H and L-vs.-I + H classifications, respectively. This combination improved the risk stratification results by 3–6% compared to intra-tumoral features alone. Our radiomics-based model resulted in a 53% accuracy in differentiating L-vs.-H compared to PI-RADS v2 (48%), on the validation set. Our findings suggest that peri-tumoral radiomic features derived from prostate bi-parametric MRI add independent predictive value

to intra-tumoral radiomic features for PCa risk assessment. This was recently published in *Cancers*[3] in August 2020.

iv) A Novel Imaging based Nomogram for predicting post-surgical biochemical recurrence free survival and adverse pathology of prostate cancer from pre-operative bi-parametric MRI: a multi-site study

This project involved developing a nomogram to predict disease recurrence following radical prostatectomy of prostate cancer (PCa) patients using pre-treatment MRI. Biochemical recurrence (BCR) and adverse pathology (AP) (defined as pathologic stage T3-4) identified after radical prostatectomy (RP) are associated with increased risk of metastasis and prostate specific mortality. Decipher, a molecular test, illustrates significant association with risk of recurrence and metastasis post-RP, independent of clinicopathologic parameter based tool, e.g. Prostate Cancer Risk Assessment (CAPRA) score. Radiomic features characterizing lesion texture on pre-operative prostate bi-parametric magnetic resonance imaging (bpMRI) could provide a non-invasive way of determining PCa prognosis. The aim of this project was to evaluate an

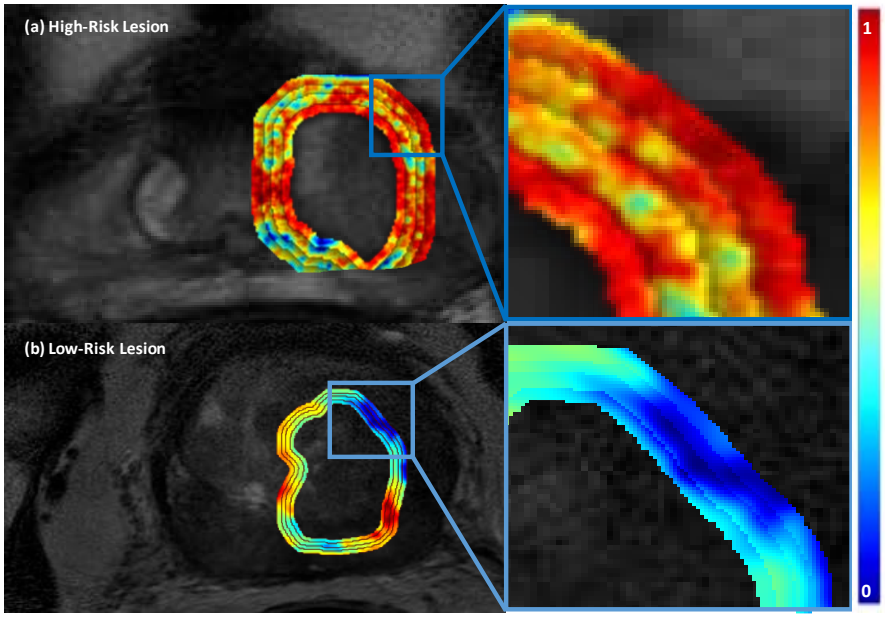

Figure 5 T2W MRI of a high risk and a low risk lesions (**left**) with their corresponding CoLlAGe entropy heat maps overlaid on the peri-tumoral (0–12 mm) regions (**right,** inset).

integrated radiomic-clinicopathologic nomogram (RadClip) that predicts post-surgical BCR free survival (bRFS) and AP, and; (2) to compare RadClip performance against CAPRA and Decipher. A retrospective study of 199 PCa patients from four institutions who underwent pre-operative 3 Tesla bpMRI followed by RP, between 2009 and 2017 with a median 35-month follow-up was performed. One cohort of patients was selected as a training set (D1, N = 71) and the rest were assigned as a test set (D2, N = 128). The patients in D1 were used to generate a bpMRI radiomic risk score (RadS) to estimate bRFS. A novel nomogram, RadClip, integrated RadS, pre-operative prostate specific antigen (PSA) and biopsy International Society of Urological Pathology (ISUP) grade to further improve bRFS prediction performance. RadClip was validated on patients in D2 and compared against the Decipher, CAPRA, and CAPRA-S score for bRFS and AP prediction. Cox proportional hazard (CPH) regression, Kaplan-Meier Survival analysis, concordance index (C-index), area under receiver operating characteristic curve (AUC), and decision curve analysis were employed to evaluate RadS, RadClip, Decipher, CAPRA, and CAPRA-S score in predicting bRFS and AP. Multivariable CPH regression was performed to establish the independence ($p<0.05$) of RadS in conjunction with other clinicopathologic variables. RadS was found to be prognostic of bRFS on D2 (univariable, C-index 0.66, 95% CI 0.54-0.79, $p < .05$, N = 128) and independent of other pre-operative clinicopathologic parameters (multivariable, $p < .05$, N = 128). RadClip demonstrated significant

association with bRFS (C-index 0.76, 95% CI 0.65-0.86, p < .05, N = 106), outperformed pre-operative CAPRA score (C-index 0.68, 95% CI 0.57-0.8, p < .05, N =106) and Decipher risk score (C-index 0.51, 95% CI 0.33-0.69, p > .05, N=106) and achieved similar performance as post-surgical CAPRA-S score (C-index 0.74, 95% CI 0.63-0.84, p < .05). RadClip was also significantly associated with AP and resulted in a higher AUC (0.74, 95% CI 0.65-0.83) compared to Decipher (AUC 0.67, 95% CI 0.57-0.77) and CAPRA score (AUC 0.69, 95% CI 0.59-0.79). RadClip, an imaging-based prognostic nomogram on a limited test set was found to have a higher performance in predicting risk of bRFS and AP compared to the Decipher and CAPRA scores. The overall pipeline is summarized in Figure 6 and this was published in *Lancet EBiomedicine*[4] in November 2020.

What opportunities for training and professional development has the project provided?

1) Interactions with my mentor and co-mentor at a higher level of project direction, collaboration has made me more independent, thoughtful in terms of designing experimental strategies, plan for future grant opportunities, publish in higher impact journals and address peer-review concerns.
2) This project thus far has enabled a deeper understanding of the histo-morphometric basis of T1, T2 MRF measurements that will result in designing optimal protocols of MRF acquisition. The ownership of this research project has made me more independent, collaborative and learn better communication skills to a wide variety of audience.
3) I have presented the work resulting out of this project at several conferences including ISMRM 2020, AUA 2020, SPIE 2020 which have provided a wide out-reach and discussion.

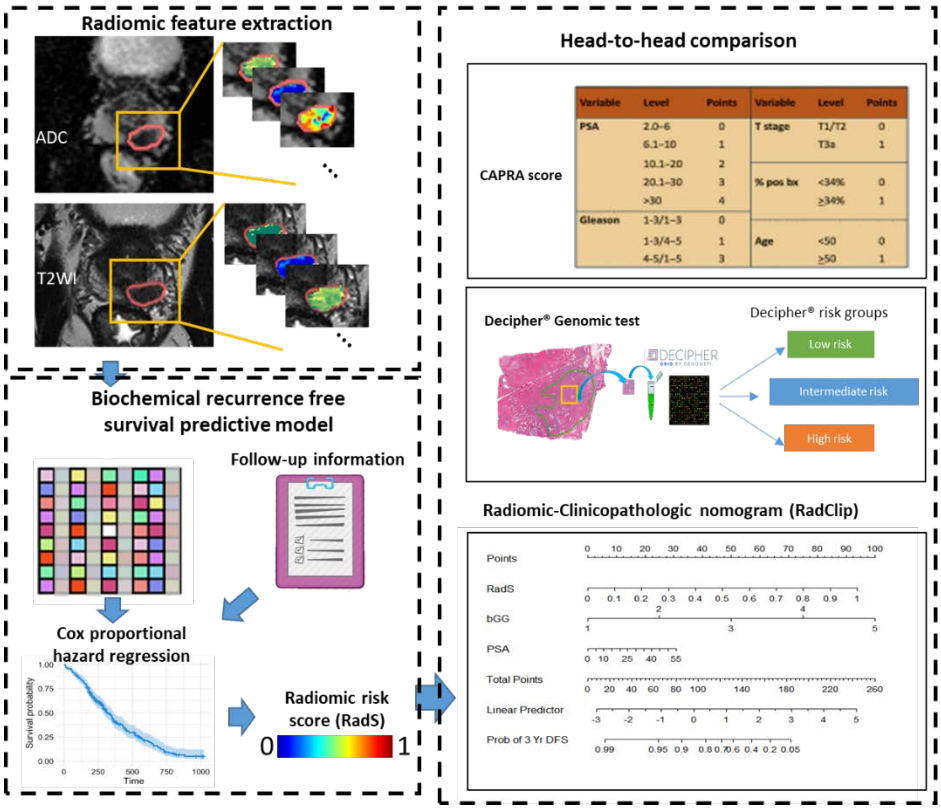

Figure 6. Overall workflow and pipeline associating radiomic risk score with biochemical recurrence free survival and decipher risk categories. T2WI = T2 weighted magnetic resonance imaging; ADC = apparent diffusion coefficient.

How were the results disseminated to communities of interest?

The major dissemination has been through presentation at conferences, especially ISMRM 2020 which had a special focus on MR Fingerprinting research. In addition, I presented my research at an internal talk to the Imaging Group at Case Comprehensive Cancer Center which is one of the 51 NCI designated comprehensive cancer centers in the United States.

What do you plan to do during the next reporting period to accomplish the goals?

In this reporting period, we accomplished most activities and goals outlined in Specific Aim1, and Specific Aim 2.1. During the next reporting period, the focus will be on completing the goals outlined in Specific Aims 2.2-2.3, and Specific Aim 3. Details are provided below:

1) Specific Aim 2.2 will focus on identifying signatures on MR Fingerprinting (MRF) that are differentially expressed between cancer of different grades as well as benign regions. This will involve extracting radiomic features from MRF maps to characterize the underlying heterogeneity and optimize differences between different regions of interest. We will acquire remainder of MRI and MRF maps from N=90 patients from our collaborating institution.
2) Specific Aim 2.3 will focus on designing optimal machine learning classifiers in conjunction with radiomic features identified in Specific Aim 2.2. The result will be the generation of a radiomic risk score that provides a degree of cancer aggressiveness.
3) The goal of Specific Aim 3 would be to evaluate the radiomics based machine learning classifier on an independent hold-out dataset of N=40 patient studies.

These results will be formally compiled as a manuscript and submitted for peer-review at high impact radiology journals (such as Radiology, JMRI, European Radiology, Investigative Radiology).

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

The results thus far have established the pathologic basis of signatures within prostate cancer, benign prostatitis, and normal prostate on MR Fingerprinting maps. This will greatly benefit in optimizing future MRF acquisition while providing a scientific basis for the reason why MRF signatures have been excellent at distinguishing prostate cancer and the normal prostate.

On completion of this project, the radiomic risk score obtained from prostate MRF and MRI sequences will enable development of a robust, non-invasive risk stratification methodology for prostate cancer. This will fill out the current void that has continued use of invasive prostate biopsies to determine the aggressiveness of prostate cancer.

What was the impact on other disciplines?
Nothing to report.

What was the impact on technology transfer?
Nothing to report.

What was the impact on society beyond science and technology?

The results from this project will result in the development of a non-invasive, imaging-based risk score that will inform clinicians of the disease aggressiveness without the need of invasive biopsies. This will have a significant impact on society in the following areas:

1) Make patients more amenable to prostate cancer screening and avoid the stigma associated with prostate biopsies. This can result in reducing over-treatment and over-diagnosis.
2) African American men are more at risk of developing prostate cancer and mortality associated with prostate cancer. One of the reasons for this again is the presence of rectal exam and biopsies that are associated with taboo and stigma within the community. A robust and accurate imaging-based risk score can help potentially reduce the disparity and outcome in African American men.

5. CHANGES/PROBLEMS: *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Changes in approach and reasons for change
Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them

We anticipate potential delay in data acquisition of patients in the validation set due to unforeseen circumstances that have arisen due to the COVID-19 pandemic. This can push back analysis and validation of the results in Specific Aim-3. We will be trying our best to include as many patients as possible to reach the proposed number of patients of N=130. In the worst-case scenario when we may not be able to recruit as many, we will work with a relatively smaller number of patients.

Another possible delay is radiologists time in acquiring delineations on prostate MRI and MRF due to the COVID-19 pandemic. We have adopted a remote working environment for this but not all collaborating radiologists are able to immediately adopt due to bandwidth and resolution constraints. We hope to be able to resume our pace for obtaining radiologist delineation with precautions in place and vaccination efforts beginning.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report.

Significant changes in use or care of human subjects
Nothing to report.

Significant changes in use or care of vertebrate animals
Nothing to report.

Significant changes in use of biohazards and/or select agents
Nothing to report.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

Journal publications.

1. **Shiradkar R**, Panda A, Leo P, Janowczyk A, Farre X, Janaki N, Li L, Pahwa S, Mahran A, Buzzy C, Fu P, Elliott R, MacLennan G, Ponsky L, Gulani V, Madabhushi A. T1 and T2 MR fingerprinting measurements of prostate cancer and prostatitis correlate with deep learning-derived estimates of epithelium, lumen, and stromal composition on corresponding whole mount histopathology. *Eur Radiol*. 2020 Sep 2; doi:10.1007/s00330-020-07214-9 PMID: 32876839 *(published*; *acknowledgement of federal support-yes)*

2. Hiremath A, **Shiradkar R**, Merisaari H, Prasanna P, Ettala O, Taimen P, Aronen HJ, Boström PJ, Jambor I, Madabhushi A. Test-retest repeatability of a deep learning architecture in detecting and segmenting clinically significant prostate cancer on apparent diffusion coefficient (ADC) maps. *Eur Radiol*. 2020 Jul 23; doi:10.1007/s00330-020-07065-4 PMID: 32700021*(published*; *acknowledgement of federal support-yes)*

3. Algohary A, **Shiradkar R**, Pahwa S, Purysko A, Verma S, Moses D, Shnier R, Haynes A-M, Delprado W, Thompson J, Tirumani S, Mahran A, Rastinehad AR, Ponsky L, Stricker PD, Madabhushi A. Combination of Peri-Tumoral and Intra-Tumoral Radiomic Features on Bi-Parametric MRI Accurately Stratifies Prostate Cancer Risk: A Multi-Site Study. *Cancers (Basel)*. 2020 Aug 6;**12**(8). doi:10.3390/cancers12082200 PMID: 32781640 PMCID: PMC7465024*(published*; *acknowledgement of federal support-yes)*

4. Li L, **Shiradkar R**, Leo P, Algohary A, Fu P, Tirumani SH, Mahran A, Buzzy C, Obmann VC, Mansoori B, El-Fahmawi A, Shahait M, Tewari A, Magi-Galluzzi C, Lee D, Lal P, Ponsky L, Klein E, Purysko AS, Madabhushi A. A novel imaging based Nomogram for predicting post-surgical biochemical recurrence and adverse pathology of prostate cancer from pre-operative bi-parametric MRI. *EBioMedicine*. 2021 Jan;**63**:103163. doi:10.1016/j.ebiom.2020.103163 *(published*; *acknowledgement of federal support-yes)*

5. Amogh Hiremath, **Rakesh Shiradkar**, Amr Mahran, Art Rastinehad, Ashutosh Tewari, Sree Harsha Tirumani, Andrei Purysko, Lee Ponsky, Anant Madabhushi, "An integrated deep learning, PI-RADS and clinical nomogram for identifying clinically significant prostate cancer on bi-parametric MRI: A multi-center study", *Lancet Digital Health (under review*; *acknowledgement of federal support-yes)*

Books or other non-periodical, one-time publications.

Nothing to report

Other publications, conference papers and presentations.

1) Hiremath, A., Shiradkar, R., Merisaari., H, Prasanna, P., Ettala, O., Taimen, P., Aronen, H., Boström, P.J., Jambor, I. and Madabhushi, A., "Test-retest repeatability of convolutional neural networks in detecting prostate cancer regions on diffusion weighted imaging in 112 patients", 28th Annual Meeting of the International Society for Magnetic Resonance in Medicine (ISMRM), 2020. (*acknowledgement of federal support-yes)*

2) *Shiradkar, R., Mahran, A., Zuo, R., Li, L., Conroy, B., Ponsky, L., Tirumani, S.H. and Madabhushi, A., "Delta Radiomic Features from serial bi-parametric MRI are associated with biopsy upgrading of prostate cancer patients on Active Surveillance", 28th Annual Meeting of the International Society for Magnetic Resonance in Medicine (ISMRM), 2020. (*acknowledgement of federal support-yes)*

3) Shiradkar, R., Mahran, A., Sharma, S., Conroy, B., Tirumani, S.H., Ponsky, L., and Madabhushi A., "Radiomic features of prostate cancer patients (Gleason Grade Group = 2) show differences between African American and Caucasian populations on bi-parametric MRI: Preliminary Findings", Annual Meeting of the American Urological Association (AUA), 2020. (*acknowledgement of federal support-yes)*

4) Rakesh Shiradkar, Ruyuan Zuo, Amr Mahran, Lee Ponsky, Sree Harsha Tirumani, Anant Madabhushi, "Radiomic features derived from periprostatic fat on pre-surgical T2w MRI predict extraprostatic extension of prostate cancer identified on post-surgical pathology: Preliminary Results", SPIE Medical Imaging 2020 (*acknowledgement of federal support-yes)*

5) Amogh Hiremath, Rakesh Shiradkar, Harri Merisaari, Nathaniel Braman, Prateek Prasanna, Otto Ettala, Pekka Taimen, Hannu J. Aronen, Peter J. Bostrom, Ivan Jambor, Andrei Purysko, and Anant Madabhushi, "A combination of intra- and peri-tumoral deep features from prostate bi-parametric MRI can distinguish clinically significant and insignificant prostate cancer", SPIE Medical Imaging 2020 (*acknowledgement of federal support-yes)*

- **Website(s) or other Internet site(s)**
  Nothing to report

- **Technologies or techniques**
  Nothing to report

- **Inventions, patent applications, and/or licenses**

1) A Madabhushi, L Li, A Purysko, R Shiradkar, "Radiomic features of prostate bi-parametric magnetic resonance imaging (bpmri) associate with decipher score". US Patent App. 16/395,922, 2020 (filed)
2) A Madabhushi, A Algohary, R Shiradkar, "Predicting prostate cancer risk of progression with multiparametric magnetic resonance imaging using machine learning and peritumoral radiomics". US Patent App. 16/395,904, 2020 (filed)

- **Other Products**

  Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

1) Rakesh Shiradkar (PI) – no change
2) Lin Li (graduate student) – no change
3) Anant Madabhushi (mentor) – no change
4) Vikas Gulani (co-mentor) – no change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

1) **Rakesh Shiradkar (PI)**

Ongoing Research Support

W81XWH-18-1-0524 Shiradkar (PI) 10/01/2018 – 09/30/2021
DOD PC170688
Title: Noninvasive Risk Stratification of Prostate Cancer Patients Using Radiomic Features Derived from Magnetic Resonance Fingerprinting (MRF) and MRI
Objectives: The goal of this project is to study various computational imaging or radiomic tools in the context of prostate MR Fingerprinting (MRF) and MRI to obtain attributes that capture subtle sub-visual differences between benign and cancerous tumors and also of the different grades of cancer. The attributes will then be used in the training of robust machine learning and deep learning models that could be used in clinical settings. This will enable development of computational imaging based methods to determine the risk or aggressiveness of disease of a prostate cancer patient. The current standard of care uses core needle biopsies and blood tests which are both painful and inaccurate. Leveraging radiomics and machine learning methods using MRF and MRI can definitely advance management and care of prostate cancer patients.

Overlap: None

Annual Pilot Grant 2020, Shiradkar (PI) 05/01/2020 – 04/31/2021
CTSC Cleveland, UL1TR002548
Title: Development of a Prostate Cancer Risk Stratification Nomogram Integrating Clinical Variables and MRI derived Radiomic Signatures for Patients on Active Surveillance.
Objectives: Current standard of care for prostate cancer patients on active surveillance (AS) or watchful waiting involves repeat biopsies which are stressful, invasive and cause immense discomfort. In this proposal, we aim develop a machine learning based non-invasive prostate cancer risk stratification nomogram to identify which patients are at higher risk of progression from those at low risk on AS by leveraging computer derived imaging signatures from MRI and routinely acquired clinical variables.

Overlap: None

Completed Research Support

None

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

References:

1. Shiradkar R, Panda A, Leo P, Janowczyk A, Farre X, Janaki N, Li L, Pahwa S, Mahran A, Buzzy C, Fu P, Elliott R, MacLennan G, Ponsky L, Gulani V, Madabhushi A. T1 and T2 MR fingerprinting measurements of prostate cancer and prostatitis correlate with deep learning-derived estimates of epithelium, lumen, and stromal composition on corresponding whole mount histopathology. *Eur Radiol*. 2020 Sep 2; doi:10.1007/s00330-020-07214-9 PMID: 32876839

2. Hiremath A, Shiradkar R, Merisaari H, Prasanna P, Ettala O, Taimen P, Aronen HJ, Boström PJ, Jambor I, Madabhushi A. Test-retest repeatability of a deep learning architecture in detecting and segmenting clinically significant prostate cancer on apparent diffusion coefficient (ADC) maps. *Eur Radiol*. 2020 Jul 23; doi:10.1007/s00330-020-07065-4 PMID: 32700021

3. Algohary A, Shiradkar R, Pahwa S, Purysko A, Verma S, Moses D, Shnier R, Haynes A-M, Delprado W, Thompson J, Tirumani S, Mahran A, Rastinehad AR, Ponsky L, Stricker PD, Madabhushi A. Combination of Peri-Tumoral and Intra-Tumoral Radiomic Features on Bi-Parametric MRI Accurately Stratifies Prostate Cancer Risk: A Multi-Site Study. *Cancers (Basel)*. 2020 Aug 6;**12**(8). doi:10.3390/cancers12082200 PMID: 32781640 PMCID: PMC7465024

4. Li L, Shiradkar R, Leo P, Algohary A, Fu P, Tirumani SH, Mahran A, Buzzy C, Obmann VC, Mansoori B, El-Fahmawi A, Shahait M, Tewari A, Magi-Galluzzi C, Lee D, Lal P, Ponsky L, Klein E, Purysko AS, Madabhushi A. A novel imaging based Nomogram for predicting post-surgical biochemical recurrence and adverse pathology of prostate cancer from pre-operative bi-parametric MRI. *EBioMedicine*. 2021 Jan;**63**:103163. doi:10.1016/j.ebiom.2020.103163

Copies of journal articles resulting from research in this grant are provided.