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TITLE: Novel Diffusion-Weighted MRI for High-Grade Prostate Cancer Detection

PRINCIPAL INVESTIGATOR: Michael Abern, MD

CONTRACTING ORGANIZATION: University of Illinois at Chicago
Chicago, IL 60612

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University of Illinois at Chicago, Department of Urology, 820 S Wood St. CSN 515 M/C 955. Chicago, IL. 60612.

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14. ABSTRACT

Our initial findings illustrate the potential of the stretched exponential model parameters to better characterize high-grade prostate cancer.Additional work is underway to establish the correspondence between the DDC and a-maps with histological sections of the entire prostate gland. Given the technical difficulty with comparison of radical prostatectomy histology with imaging, we have also introduced a method to evaluate the accuracy of our novel diffusion imaging with biopsy histology. Development of a non-invasive quantitative imaging biomarker for high grade PCa will be useful for improving biopsy yield and grade accuracy, accurately identifying men appropriate for surveillance versus curative therapy, and reduce biopsies needed.

15. SUBJECT
FROC, Prostate Cancer, MRI, Diffusion

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INTRODUCTION:

Accurate detection of aggressive prostate cancer (PCa) using existing clinical prediction tools is a challenge. Prostate MRI is promising technology for PCa detection and characterization. However, its accuracy has been sub-optimal especially in the setting of benign prostate inflammation or hyperplasia. We have developed a more sophisticated computational model of diffusion weighted MRI (FROC-DWI) that produces quantitative information regarding tissue architecture in-vivo. We hypothesize that the use of FROC-DWI in men with clinical suspicion for PCa will differentiate high grade PCa from indolent PCa and benign prostate pathology and therefore improve biopsy detection of aggressive PCa.

KEYWORDS:

FROC, Prostate Cancer, MRI, Diffusion

ACCOMPLISHMENTS:

What were the major goals of the project?

The major goal of the project is to generate a quantitative diffusion weighted MRI signature that differentiates high grade prostate cancer (PCa) from low grade PCa and benign prostate tissues. The quantitative parameters of the signature will be compared with histologic tissue architecture (Gleason score) using RP specimens from our biorepository archive. The diffusion parameters will be correlated with stromal and epithelial architecture of areas of benign and malignant prostate tissue and a predictive model will be created to differentiate Gleason pattern 4 or higher PCa from other tissue types.

Aim 1: Generate a quantitative diffusion weighted MRI signature that differentiates high grade PCa from low grade PCa and benign prostate tissues

Aim 2: Validate the MRI signature in a prospective patient cohort undergoing RP

Aim 3: Validate the MRI signature in a patient cohort undergoing MRI guided prostate needle biopsy.

What was accomplished under these goals?

Aim 1 accomplishments to date:

Year 1:

- IRB approval has been acquired for this aim

- The histology samples have been requested from the UIC biorepository for and digitized
- All MR images have been collected and prepared for image processing and analysis
- MR images have been de-identified and prepared in MatLab for quantitative analysis by the bioengineering co-investigators
- The histology specimens have all been retrieved and digitized so the grades of cancers can be outlined by the pathology co-investigators
- The UIC IRB has approved the continuing review of the protocol on 3/29/16
- 3 cases have had digital pathology annotation and MR image computation.
- Quality control testing of the MR imaging files has been completed.
- An abstract was presented to the IMPaCT conference for August 4-5 2016
- An abstract was presented to the ISMRM Workshop for September 11-16 2016

Year 2:

- The MatLab code for the production of alpha and DDC MRI maps was de-bugged, corrected, and finalized
- The MatLab code for co-registration of digital radical prostatectomy histology to T2 weighted MRI images of alpha and DDC maps to T2 weighted MRI was completed and tested
- 8 retrospective cases were analysed
- A new cohort of retrospective cases were added to the study to improve the sample size for model development : 30 patients that had pre-biopsy mpMRI and MRI targeted biopsies. This was approved in an IRB amendment.
- All MRI images for the added cohort have been collected and re-analysed
- Currently added cohort images are undergoing alpha and DDC map processing
- All biopsy pathologic data have been collected for the added cohort
- 2 abstracts were submitted to ISMRM 2018 conference – 1 for the initial results of the DDC/alpha map comparison to prostatectomy histology and 1 for the image co-registration methodology
- 1 abstract was submitted to the AUA 2018 conference with prelimary diagnostic accuracy thresholds for DDC and alpha parameters

Year 3:

- The method for the co-registration of digital radical prostatectomy histology to T2 weighted MRI images of alpha and DDC maps to T2 weighted MRI was completed

- A new cohort of retrospective cases were added to the study to improve the sample size for model development : 30 patients that had pre-biopsy mpMRI and MRI targeted biopsies.
- The analysis of the biopsy cohort was completed. The findings have been submitted as an abstract for the SUO 2018 conference.
- 2 abstracts were presented at ISMRM 2018 conference – 1 for the initial results of the DDC/alpha map comparison to prostatectomy histology and 1 for the image co-registration methodology
- 1 abstract was presented at the EUS section of the AUA 2018 conference testing the association between image co-registration accuracy using standard diffusion weighted MRI parameters. This work has been submitted to the Journal of Magnetic Resonance Imaging (pending).

Aim 2 accomplishments:

Year 1:

- The prospective experimental imaging protocol has been designed and approved by the collaborating radiology and bioengineering collaborators.
- The prospective prostatectomy sectioning protocol has been developed and approved by the IRB.
- The IRB protocol has been completed for Aims 2 and 3. Based on IRB and cancer center review, it was recommended to separate these into two separate protocols as the patients in aim 3 will be randomized. The IRB for aim 2 is completed and approved.
- The first subject enrollment under the prospective prostatectomy section (whole mount) has been scheduled for 10/14/16

Year 2:

- 5 subjects have been enrolled in the study
- Imaging and histologic digital processing is in progress
- The IRB continuing review was approved

Year 3:

- All data analysis has been completed. This has been combined with the data from Aim 1. A manuscript is under development. The planned journal is Journal of Magnetic Resonance Imaging. Please see the following data tables and figures:

Histology to image registration tables and figures: The following tables and figures quantify and validate the accuracy of our method developed to register the MR images to the processed prostatectomy histopathology.

Table 1
Patient Characteristics

Patient Number	Age	Biopsy GS	Pre-operative PSA	Radical Prostatectomy GS	Pathology Stage
1	67	4+3=7	75	4+3=7	pT3aN0
2	47	4+4=8	13.98	5+4=9	pT3aN0
3	53	3+4=7	8.2	3+3=6	pT2cNX
4	64	3+4=7	6.1	3+4=7	pT3aN0
5	58	3+4=7	174	3+4=7	pT3bN0
6	61	3+3=6	9.5	4+3=7	pT2cpNX

GS, Gleason Score; PSA, prostate specific antigen

Table 2
Control Point Optimization

Number of Control Points	Mean (SD) 1mm Contour Overlap	Mean (SD) DSC
4 control pts	0.83 (0.03)	0.95 (0.01)
8 control pts	0.92 (0.03)	0.95 (0.008)
12 control pts	0.91 (0.03)	0.95 (0.007)
16 control pts	0.89 (0.08)	0.94 (0.02)

DSC, Dice similarity coefficient

Table 3
Registration Accuracy

Patient Number	Number of Slices	Mean 1 mm Contour Overlap	Mean 5 mm Contour Overlap	Mean DSC
1	9	0.88	1.00	0.9498
2	10	0.69	1.00	0.9415
3	10	0.79	1.00	0.9440
4	9	0.73	1.00	0.9471
5	10	0.79	1.00	0.9454
6	8	0.82	1.00	0.9456
Total	56	0.78	1.00	0.9455

DSC, Dice similarity coefficient

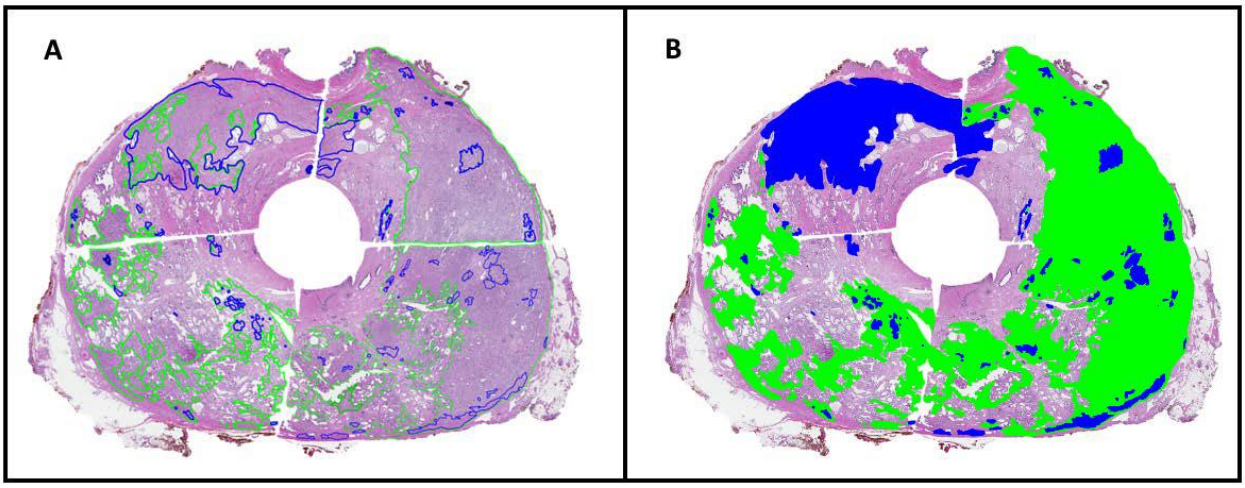

Figure 1: Reconstructed annotated axial pseudo whole mount slice **A.** before annotation filling and **B.** after annotation filling. Gleason score 3 colored green, 4 colored blue, 5 colored red (not shown).

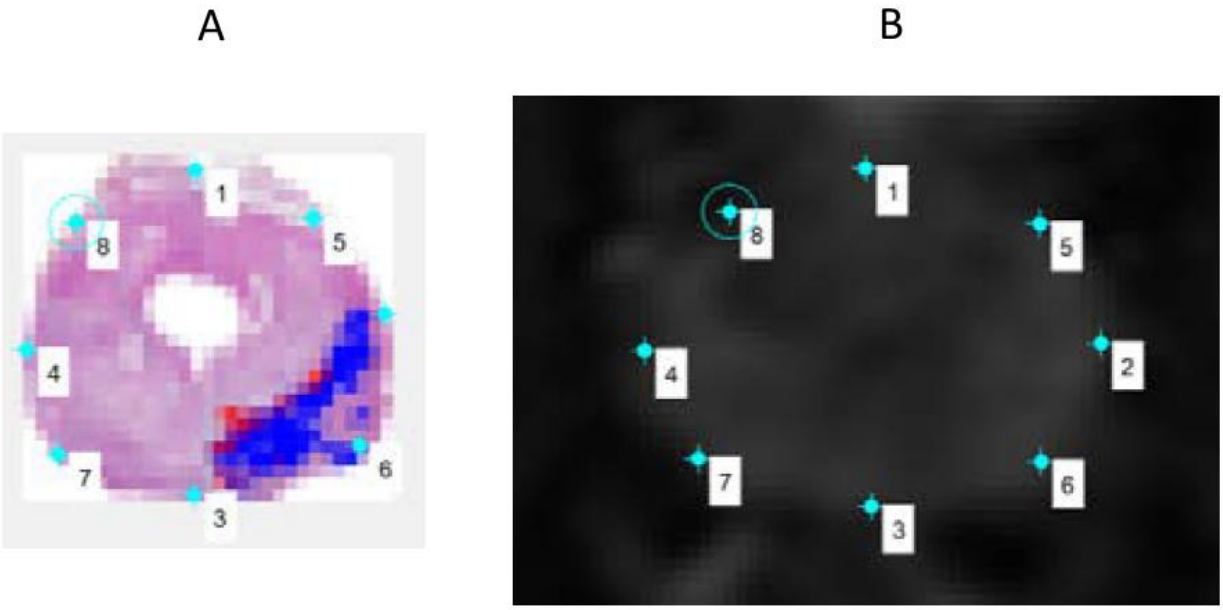

Figure 2: Control point mediated registration between the **A.** pseudo whole mount and **B.** diffusion weighted image (zoomed in). Control points are teal and numbered (1-8).

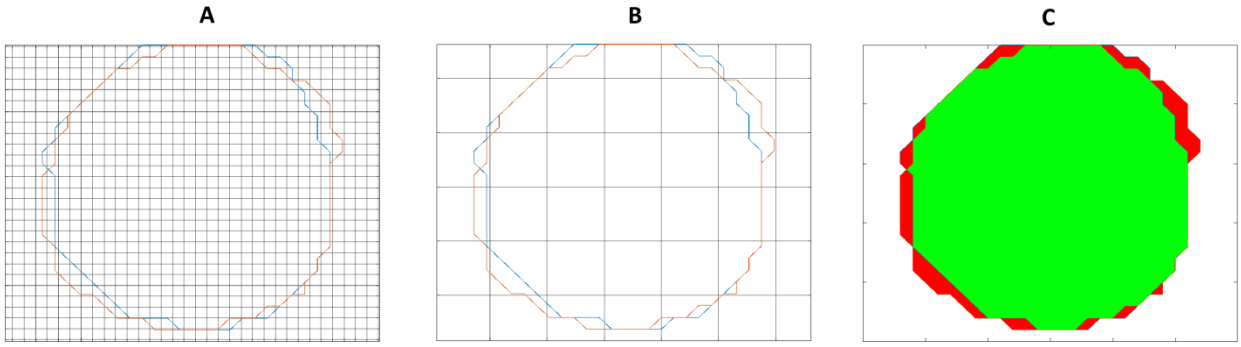

Figure 3: Quantitative registration accuracy methods. Contour overlap at **A.** 1 mm and **B.** 5 mm threshold resolution. **C.** Basis for spatial overlap index, the Dice similarity coefficient (DSC). Green indicates area overlap; red indicates non-overlapping areas.

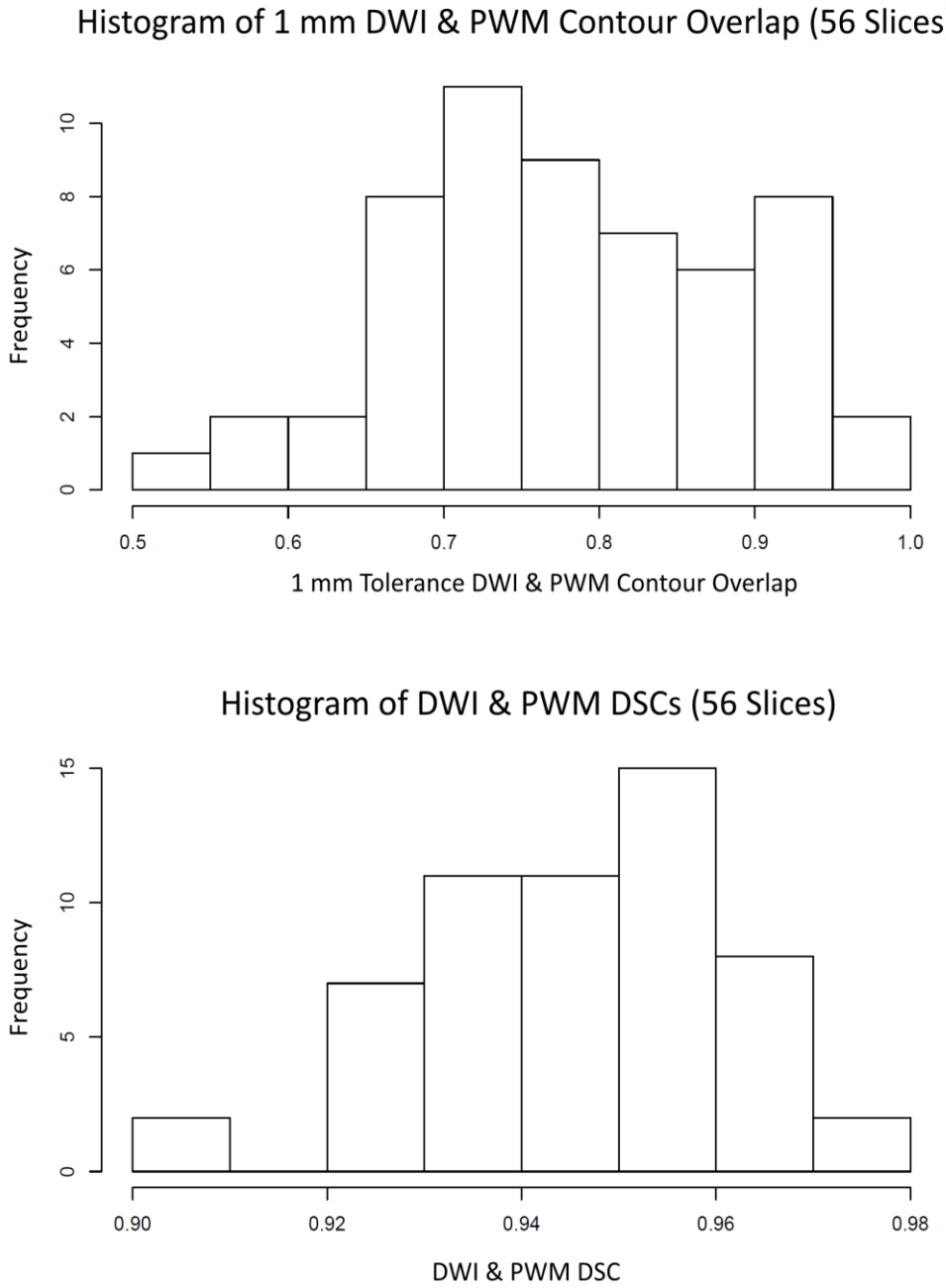

Figure 4: Histograms of quantitative registration accuracy methods: 1 mm contour overlap (**top**) and dice similarity coefficient (**bottom**). DWI, diffusion weighted image; PWM, pseudo whole mount; DSC, Dice similarity coefficient.

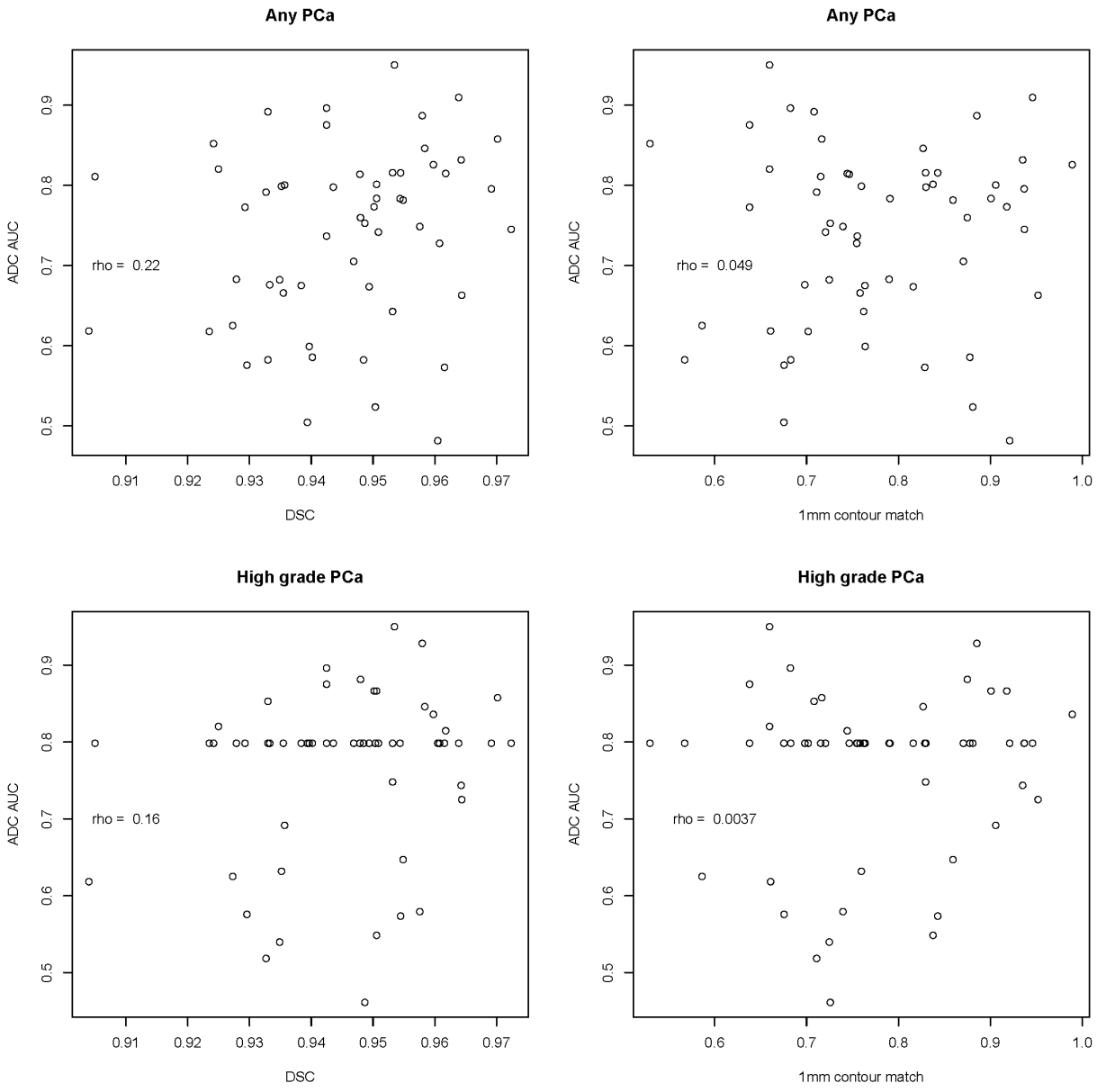

Figure 5: Scatterplots between image registration accuracy (Dice Similarity Coefficient (DSC) and 1 mm threshold contour match percentage) and ADC area under the curve (AUC) for any prostate cancer (PCa) (Gleason Score ≥ 3) and for high grade PCa (Gleason Score ≥ 4). Spearman's coefficients are listed and nonsignificant.

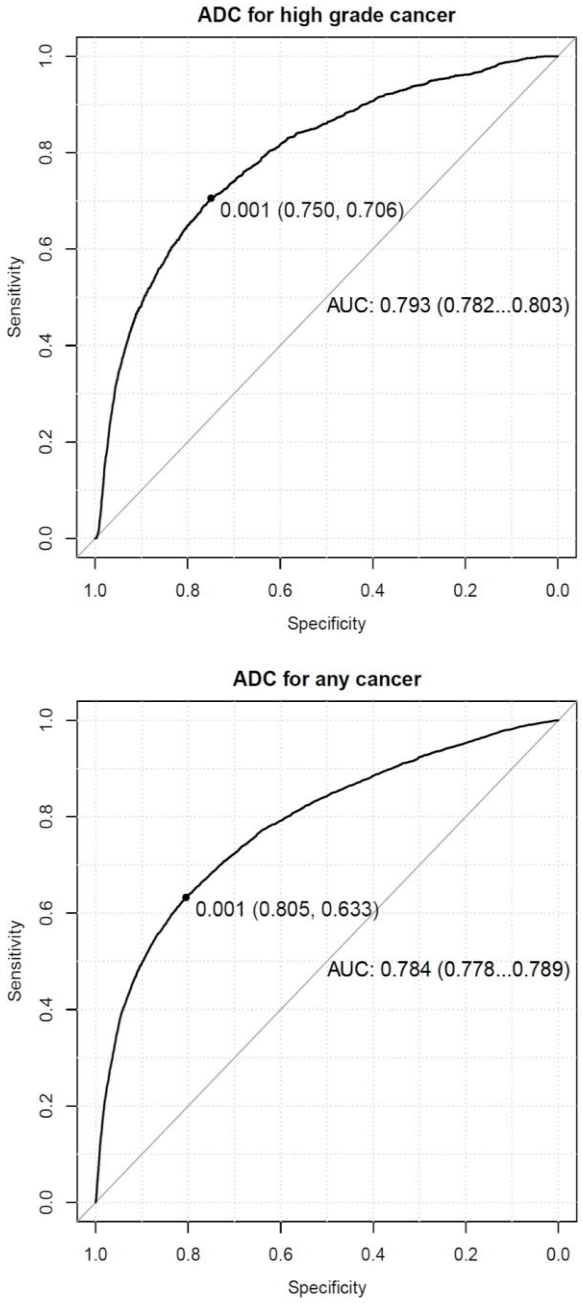

Figure 6: Receiver operator characteristic (ROC) curve comparing apparent diffusion coefficient (ADC) values and high grade cancer (Gleason score ≥ 4), **top**. ROC curve comparing ADC values and any cancer (Gleason score ≥ 3), **bottom**. Youden's Index optimal cutoff point reported on the curves (sensitivity, specificity). Area under the curve (AUC) reported with 95% confidence interval.

Novel diffusion model data: The following figure shows the accuracy and thresholds determined from the radical prostatectomy cohort for the stretched exponential diffusion model compared to the gold standard Gleason score histology:

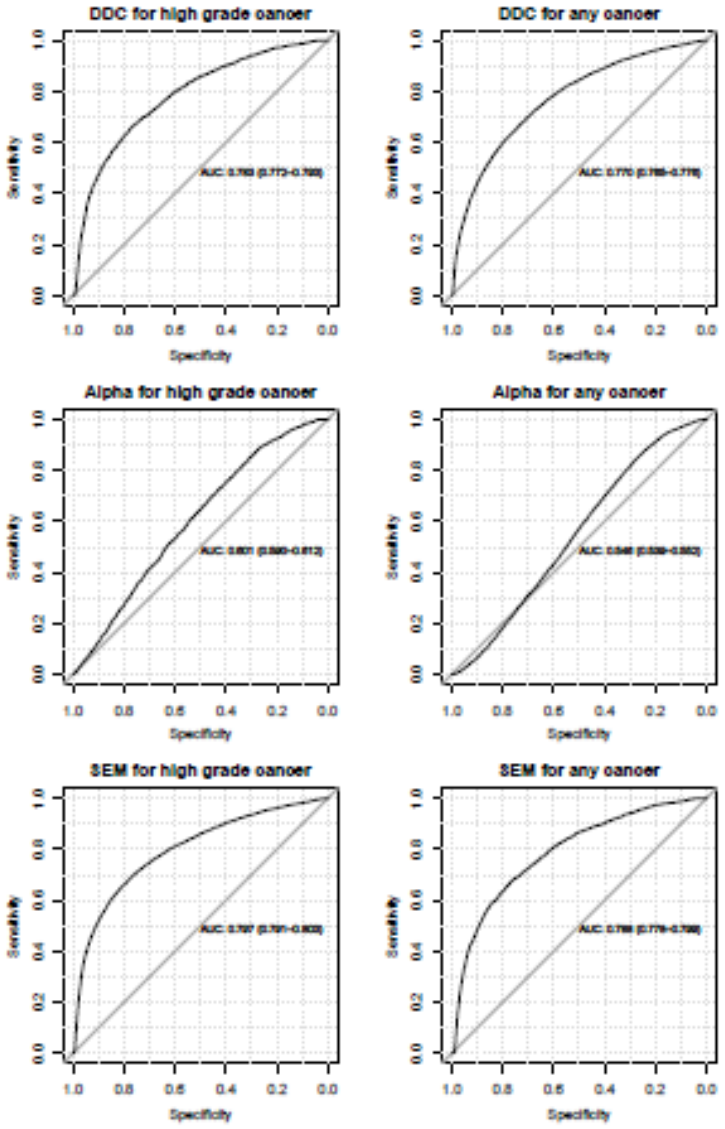

Figure 1: ROC curves for the DDC, alpha, and combined stretched exponential model (SEM) for any cancer and high grade cancer from the radical prostatectomy cohort

Novel diffusion model data: The following tables and figures show the accuracy and thresholds determined from the biopsy validation cohort for the stretched exponential diffusion model compared to the gold standard Gleason score histology:

High-Grade	*Cutoff*	*Sensitivity*	*Specificity*	*Accuracy*
ADC (mm²/s)	0.0010	0.9167	0.7037	0.7692
α	0.7959	0.6667	0.7037	0.6923
D_K (mm²/s)	0.0014	0.9167	0.7778	0.8205
K	0.8637	0.7037	0.75	0.7179
Any-Grade	***Cutoff***	***Sensitivity***	***Specificity***	***Accuracy***
ADC (mm²/s)	0.00095	0.8462	0.7692	0.7948
α	0.7959	0.6923	0.7308	0.7179
D_K (mm²/s)	0.0014	0.9231	0.8077	0.8461
K	0.8637	0.7308	0.7692	0.7435

TABLE 1. Cutoff, sensitivity, specificity and diagnostic accuracy at the Youden's Index points using ADC, α, D_K, K for differentiating benign from high or any grade prostate cancer.

High-Grade	*AUC*	*95% CI of AUC[a]*	*SE[b]*
ADC (mm²/s)	0.8025	[0.636, 0.968]	0.08486
α	0.6698	[0.473, 0.865]	0.10003
ADC & α	0.8210	[0.661, 0.988]	0.08165
D_K (mm²/s)	0.7809	[0.608, 0.953]	0.08822
K	0.7222	[0.555, 0.889]	0.08511
D_K & K	0.7716	[0.596, 0.947]	0.08954

TABLE 2. AUC values of the ROC analyses with their 95% confidence intervals and standard errors at the Youden's Index points using ADC, α, D_K, K, and a combination of *ADC* and α and a combination of D_K and K, for differentiating no-cancer from high-grade prostate cancer.

Any-Grade	***Threshold***	***Sensitivity***	***Specificity***
ADC (mm²/s)	0.001	0.9231	0.7308
α	0.8401	0.8462	0.1154
D_K (mm²/s)	0.0014	0.9231	0.8077
K	1.0723	0.9615	0.3077
High-Grade	***Threshold***	***Sensitivity***	***Specificity***
ADC (mm²/s)	0.001	0.9167	0.7037
α	0.8425	0.9167	0.1111
D_K (mm²/s)	0.0014	0.9167	0.7778
K	1.0723	0.9259	0.25

TABLE 3. Parameter thresholds at ~90% Sensitivity using ADC, α, D_K, K for differentiating benign from any or high-grade prostate cancer.

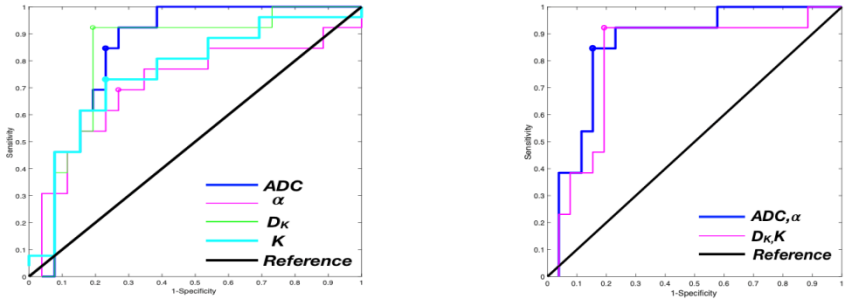

Figure 1: ROC for imaging parameters, and combined models to discriminate benign from any grade cancer

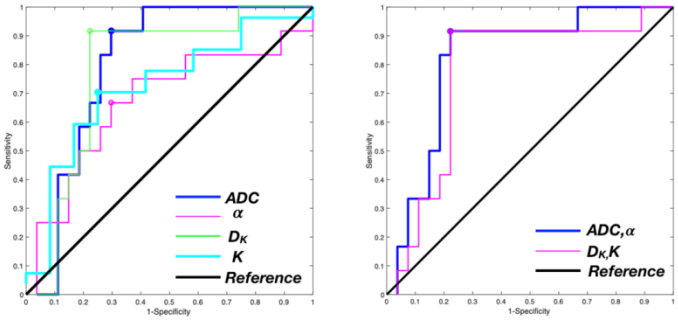

Figure 2: ROC for imaging parameters, and combined models to discriminate benign from high grade cancer

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

Dr. Abern, the PI, proposed a training plan as part of this grant. He has completed several of the objectives.

- Dr. Abern was awarded the UIC School of Public Health Clinical Research Methods certificate.
- Dr. Abern completed HPA 472 (Clinical Research Methods 1), HPA 473 (Clinical Research Methods 2), HPA 479 (Evaluation of Clinical Interventions), with a grade of A. He completed BHIS 509 (Informatics for the Clinical Investigator) with a grade of B. He completed HPA 464 (Sociocultural Dimensions of Health Disparities) with a grade of A.
- Dr. Gann has been teaching his course, Molecular Epidemiology and Biomarker Development (EPID512) , in a one-on-one fashion during weekly meetings
- He has attended the biweekly Works-in-Progress Seminar that includes participation from the Mentor's lab (Dr. Gann) as well as several other senior faculty members (including Dr. Gail Prins, Dr. Larissa Nonn) focusing on PCa.
- He attended the 2016 DOD IMPACT conference, which allowed for discussions and collaboration with several other DOD funded investigators.
- He attended the Prostate Cancer Foundation annual conference October 27-29, 2016.
- He was accepted for the EAU/AUA Exchange program for 2018 during which preliminary results from the studies supported by this grant were presented at 3 European academic medical centers (see below).

How were the results disseminated to communities of interest?

For this reporting period two abstracts were presented at the International Society of Magnetic Resonance Meeting in Paris, France and one presented at the Engineering in Urology Session of the American Urological Society 2018 conference in San Francisco, CA. These are pending acceptance and are attached to this report.

A meeting abstract has been submitted to the Society of Urologic Oncology 2018 conference in Phoenix, AZ. This is pending acceptance.

Dr. Abern made 3 oral presentations of results of this project as part of the European Urologic Association/ American Urologic Association Exchange Scholar Program. These were given in Royal Hallamshire Hospital in

Sheffield, United Kingdom, San Raffaele Hospital in Milan, Italy, and Radboud University in Nijmegen, Netherlands.

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

The following were proposed in the 2017 annual report. Please find the status of the proposed goals to date:

Aim 1:

- Complete the statistical analysis of the retrospective biopsy cohort - COMPLETED
- Submit the analysis of the retrospective biopsy cohort to a scientific meeting for presentation - COMPLETED
- Prepare the model development data (combined biopsy and prostatectomy data) for publication – COMPLETED/REVISING

Aim 2:

- Enroll 10 additional patients for the prospective cohort (validation) - COMPLETED
- Complete the imaging processing for the model validation cohort - COMPLETED
- Complete the statistical analysis of the model validation cohort - COMPLETED
- Prepare the data for publication in a peer-reviewed journal – IN PROGRESS

Aim 3:

- Determine the final imaging thresholds from Aims 1 and 2 - COMPLETED
- Design the prospective biopsy protocol using the thresholds – COMPLETED
- Obtain IRB approval for Aim 3 – IN PROGRESS
- Begin patient enrollment for Aim 3 – IN PROGRESS

Goals for the final reporting period:

- Publication of the co-registration/ radical prostatectomy model development manuscript (revise based on feedback from the Journal of Magnetic Resonance Imaging review process)

- Publication of the biopsy cohort validation dataset (target is Journal of Magnetic Resonance Imaging)
- Accrual of prospective biopsy cohort.

IMPACT:

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

The preliminary data from this project will be used to develop a prostate cancer detection specific MRI protocol.

What was the impact on other disciplines?

The development of a whole mount prostatectomy grossing protocol will be beneficial for the Research Histology and Tissue Imaging Core at UIC.

The development of a methodology of digital prostate cancer annotation and mapping will provide a valuable resource for future projects.

The development of a new imaging co-registration method will be of interest to the scientific imaging community at large

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS:

Changes in approach and reasons for change

As anticipated in the prior reporting period : Brandon Caldwell, the primary research assistant, transitioned off the project as he started medical school at Northwestern University. Significant time was needed to find his replacement, Meltem Uyanik MS, a PhD student in the Bioengineering Department at UIC. She was hired as a 50% research assistant. This has delayed the initiation of Aim 3 accrual.

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

Aim 3 accrual has been delayed due to staff turnover and therefore delay in completing the validation analysis needed to determine the quantitative thresholds. The resolution plan is to prioritize the regulatory approval for this portion of the project and delay the efforts to publish the current data.

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

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.

PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Nothing to report.

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

Nothing to report.

Other publications, conference papers, and presentations.

1. Michael Abern MD, Brandon Caldwell BS, Virgilia Macias MD, Winnie Mar MD, Karen Xie MD, Andre Kajdacsy-Balla PhD/MD, Richard Magin PhD, Joe Zhou PhD, Peter Gann ScD/MD; *High Grade Prostate Cancer Characterization Using Fractional Order Calculus Diffusion Weighted MRI*; 2016; Abstract and poster for PCRP IMPaCT Conference; Presented 10/2016; Yes (federally supported)
2. Meltem Uyanik MS, Michael Abern MD, Brandon Caldwell BS, Muge Karaman PhD, Winnie Mar MD, Joe Zhou PhD, Richard L. Magin PhD; *Prostate Cancer Classification Using a Stretched Exponential Model of Diffusion*; 2016; Abstract and poster for ISMRM Workshop; Presented 9/2016; No
3. Brandon Caldwell BS , Meltem Uyanik MS, Michael Abern MD, Virgilia Macias MD, Cristian Luciano PhD, Richard L. Magin PhD; *A methodology for Registering Prostate Histology and Radiologic Imaging to Validate*

Prostate Cancer Detection in 2D; 2017; Abstract for ISMRM Congress; Presented 6/2018; No

4. Brandon Caldwell BS , Meltem Uyanik MS, Virgilia Macias MD, Winnie Mar MD, Richard L. Magin PhD, Michael Abern MD; *Fractional order calculus model of magnetic resonance diffusion weighted imaging for high grade prostate cancer detection*; 2017; Abstract for AUA Congress; Presented 5/2018; No
5. Meltem Uyanik MS, Michael Abern MD, Brandon Caldwell BS, Muge Karaman PhD, Winnie Mar MD, Virgilia Macias MD, Xiaohong Joe Zhou PhD, Richard L. Magin PhD; *Prostate Cancer Classification Using Stretched Exponential Model Parameters of Diffusion Signal Decay*; 2017; Abstract for ISMRM Congress; Presented 6/2018; No
6. Rolf Reiter MD, Meltem Uyanik MS, Hari Vigneswaran MD, Brandon Caldwell MS, Winnie Mar MD, Karen Xie DO, Bernd Hamm MD, Dieter Klatt PhD, Richard L. Magin PhD, Michael Abern MD. DIAGNOSTIC PERFORMANCE OF PROSTATE CANCER ASSESSMENT USING THE STRETCHED-EXPONENTIAL MODEL DIFFUSION-WEIGHTED MR IMAGING; 2018; Abstract for SUO Conference; Submitted; No

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Michael Abern, MD
Project Role: PI
Researcher Identifier: mabern
Nearest person month worked: 12 x 0.4 = 4.8
Contribution to Project: Dr. Abern has acted as the project lead

Name: Peter Gann, MD
Project Role: Co-mentor
Researcher Identifier: pgann
Nearest person month worked: 12 x 0.1 = 1.2
Contribution to Project: Dr. Gann has contributed as mentor for the histologic analytic aspects of the project, and has conducted bi-weekly meetings with the PI

Name: Andre Balla, MD/PhD
Project Role: Pathology consultant
Researcher Identifier: aballa
Nearest person month worked: 12 x 0.05 = 0.6
Contribution to Project: Dr. Balla has consulted regarding the tissue preparation of the prostatectomy specimens for Aim 2

Name: Virgilia Macias, MD
Project Role: Pathology consultant
Researcher Identifier: vmacias
Nearest person month worked: 12 x 0.05 = 0.6
Contribution to Project: Dr. Macias has assisted in screening the retrospective pathology samples for adequacy for analysis

Name: Xiaohong "Joe" Zhou, PhD
Project Role: Co-mentor
Researcher Identifier: xjzhou
Nearest person month worked: 12 x 0.05 = 0.6
Contribution to Project: Dr. Zhou has contributed by holding bi-weekly meetings with the PI and consulting regarding the MR processing for aim 1, and for the scan protocol for aim 2

Name: Brandon Caldwell
Project Role: Study Coordinator
Nearest person month worked: 9 x 0.50 = 4.5
Contribution to Project: Mr. Caldwell has contributed to the study via IRB management and submissions, Cancer Center compliance and research design.

Name: Richard Magin, PhD
Project Role: Mathematical image analysis team
Researcher Identifier: rmagin
Nearest person month worked: 12 x 0.05 = 0.6
Contribution to Project: Dr. Magin has contributed as the designer of the FROC model and supervisor of the MR image processing

Name: Meltem Uyanik, MS
Project Role: Mathematical image analysis team
Nearest person month worked: 3 x 0.5 = 1.5

Contribution to Project: Ms. Uyanik has performed the MR image processing

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

Nothing to report.

What other organizations were involved as partners?

Nothing to report.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

Nothing to report.

QUAD CHARTS:

Nothing to report.

APPENDICES:

Please see the attached submitted meeting abstracts.