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TITLE: Whole-Body RSI-MRI as an Indicator for Radiation Therapy Response of Metastatic Prostate Cancer

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14. ABSTRACT Prostate cancer is the second leading cause of cancer death in men. New treatment paradigms are entirely dependent on a) accurate diagnosis of sites of metastatic disease, and b) the ability to accurately characterize response to treatments. We aim to determine if Restriction Spectrum Imaging (RSI) can improve detection of metastatic disease as well as monitor the effects of therapy targeted to metastatic sites. This is an IRB-approved longitudinal prospective cohort study of men with known metastatic prostate cancer and men who are at high risk of metastatic disease. To date, we have surmounted numerous regulatory hurdles (e.g. IRB approval) and technical challenges (e.g. optimization of the RSI-MRI protocol for whole body imaging). We have successfully recruited multiple patients leading to whole body RSI-MRI scans in 38 men to date. Greater than half of the men who participated were shown to have metastatic disease, several of whom were not known to have metastatic disease prior to RSI-MRI. Accurate depiction of sites of metastases is expected to aid in treatment of patients.					
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INTRODUCTION:

Prostate cancer is the second leading cause of cancer death in men. New treatment paradigms such as focal radiation therapy in the setting of oligometastatic disease and next generation anti-androgen, biologic, and chemotherapeutic agents are entirely dependent on a) accurate diagnosis of sites of metastatic disease, and b) the ability to accurately characterize response to treatments. We aim to determine if Restriction Spectrum Imaging (RSI), an advanced diffusion weighted imaging (DWI) magnetic resonance imaging (MRI) method, can improve detection of metastatic disease as well as monitor the effects of therapy targeted to metastatic sites. This is an IRB-approved longitudinal prospective cohort study of men with known metastatic prostate cancer and men with known prostate cancer who are at high risk of metastatic disease. To date, we have surmounted numerous regulatory hurdles (e.g. IRB approval) and technical challenges (e.g. optimization of the RSI-MRI protocol for whole body imaging). We have successfully recruited multiple patients leading to whole body RSI-MRI scans in 35 men to date. Greater than half of the men who participated were shown to have metastatic disease, several of whom were not known to have metastatic disease prior to RSI-MRI when evaluated on standard of care imaging (typically CT and bone scan). Accurate depiction of sites of metastases is expected to aid in optimizing treatment of patients and may also inform prognosis.

KEYWORDS:

MRI

Prostate cancer

Metastasis

Treatment response

ACCOMPLISHMENTS:

Major Goals:

Specific Aim 1, Goals for period of review:

Major Task 1: Optimize RSI pulse sequences and post-processing techniques for whole body imaging using volunteers. Obtain IRB approval. Milestones achieved in period of review, including optimized imaging and processing, local IRB approval, and HRPO approval.

Major Task 2: Data collection: Imaging and pathology specimens, Aim 1. Successful patient recruitment and WB-RSI-RSI scans in 35 patients to date. Recruitment is ongoing. Quantification of total tumor burden: ongoing work. Pathology specimens: incomplete due to few biopsies to date, ongoing work.

Specific Aim 2, Goals for period of review:

Major Task 3: data collection is continuously ongoing

Major Task 4: not applicable to this period of review

Accomplishments under major goals:

We have identified and surmounted IRB related issues that led to a pause in recruitment of some subjects, specifically those with prior surgical implants. This has now been resolved.

We have increased our sample population dramatically, now with 37 scans completed in 35 patients. Within this population there are patients at the beginning of their prostate cancer journey at high risk of developing metastatic disease, though without evidence of metastatic disease on conventional imaging. Some of these patients also are without evidence of metastatic disease on RSI-MRI. However, we have identified patients without evidence of metastatic disease on conventional imaging who do have evidence of metastatic disease on RSI-MRI, especially among very recent study participants.

Other patients within our cohort have a more heterogeneous prior history, such as mCRPC patients who have undergone various therapies over their years with prostate cancer. This heterogeneous population has proven difficult to analyze due to the complexity of prior treatments though we do believe that our method is able to highlight sites of active disease among other sites that have been more completely treated.

We have made substantial progress toward the above goal in the review period. Specifically, we have:

- prepared necessary IRB amendments
- successfully received approval of IRB amendments and overall IRB renewal
- further optimized the whole body RSI MRI protocol
- successfully recruited subjects
- successfully scanned 35 subjects

Among the 35 subjects scanned to date, 19 subjects have RSI-MRI findings suspicious for metastatic disease while the other 16 subjects had negative RSI-MRI scans. Of the 19 subjects with findings of metastatic disease on RSI-MRI, 14 had known metastatic disease as shown on preceding conventional imaging. All known sites of metastatic disease from prior conventional imaging were able to be demonstrated on RSI-MRI. **The remaining 5 patients with metastatic disease had sites of disease that were not depicted on the preceding conventional imaging.**

Key Accomplishments/Main Conclusions:

Working together as a multi-disciplinary team inclusive of imaging scientists, clinical translational radiologists, clinical translational urologists, clinical translational medical oncologists, clinical research coordinators, and clinical trials regulatory specialists we have successfully expanded our patient subject population and now have a meaningful number of cases to analyze in aggregate. Ongoing analysis will hopefully allow for generalizable quantitative insights to inform metastatic disease diagnosis, treatment planning, prognosis, and post treatment evaluation.

Illustrative Example:

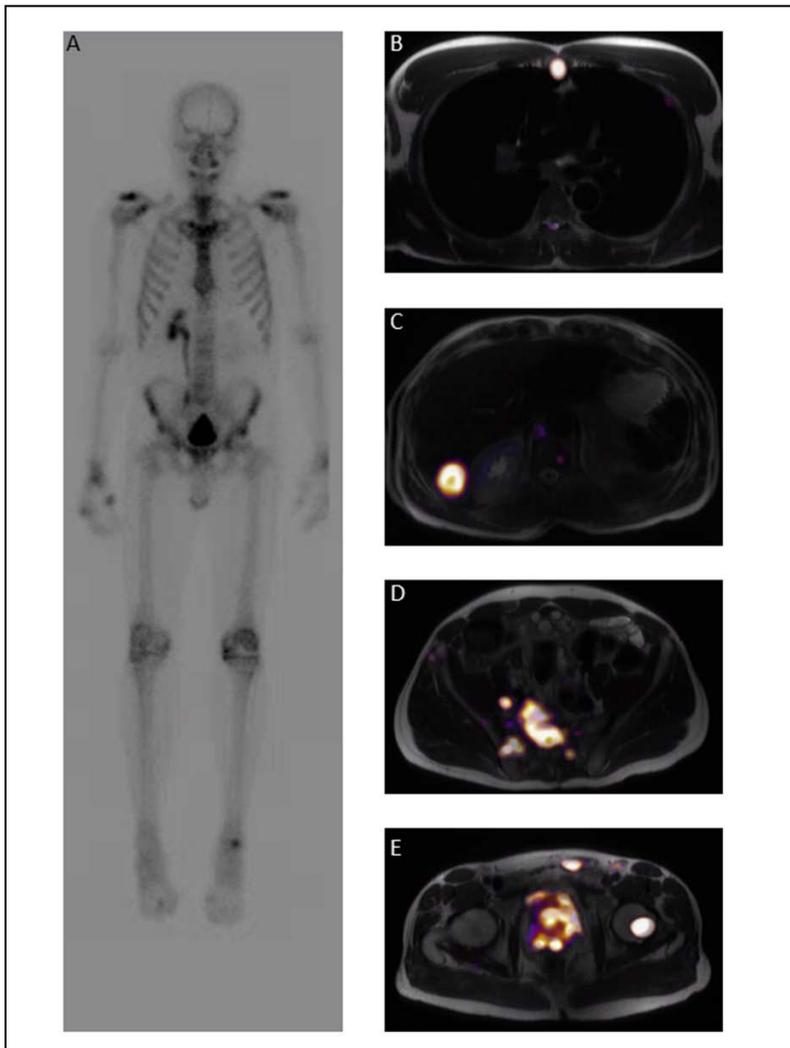


Figure 1: Patient with new diagnosis of high risk prostate cancer. Pre-therapy scans shown. A) Nuclear medicine Tc99m-MDP bone scan shows no evidence of osseous metastatic disease. A CT exam at that time demonstrated one suspicious lymph node abutting the right ureter causing hydronephrosis. B-E) RSI-MRI at selected axial slices shows sternal metastasis (B), hepatic metastasis (C), multiple lymph nodal and osseous pelvis metastases (D,E). **NOT FOR DISTRIBUTION.**

Opportunities for training and professional development:

Training Activities:

Image data analysis – postdocs Dr. Rodriguez and Zavala-Bojorquez have spent innumerable hours with mentor Professor Dale learning how to analyze imaging data, both in group sessions and one-on-one sessions.

Clinical study design: Dr Hahn has benefitted greatly from direct one-on-one mentoring sessions as well as working group meetings with Drs Parsons and McKay who are experts in clinical study design and results analysis.

Professional Development:

International Society of Magnetic Resonance in Man Research Conference: Drs Dale, Hahn, and Rodriguez-Soto attended the ISMRM conference in 2018 which is the premier international research event for MRI researchers.

Results dissemination: Preliminary results have been disseminated to target audiences via research seminars/conferences both at a sister institution (University of California San Francisco) as well as to leaders in the field from multiple institutions at the Prostate Cancer Foundation's Prostate Cancer Academy.

Plan for accomplishing goals in next reporting period: Recruitment of new patients will continue. Follow up scans of patients with metastatic disease who have undergone therapy since their first scan will be performed to evaluate treatment response. Overall cohort data analysis will be continuous.

IMPACT:

Impact on the development of the principal disciplines of the project: possible impact on diagnostic radiology is profound as if RSI-MRI is proven to be more efficacious than standard of care imaging it could conceivably replace standard of care imaging for the assessment of metastatic disease in prostate cancer patients.

Impact on other disciplines: Potential impact on related clinical fields including medical oncology, radiation oncology, and urologic surgical oncology is also profound as elucidation of sites of metastatic disease will change treatment paradigms for patients with prostate cancer.

Impact on technology transfer: nothing to report

Impact on society beyond science and technology: As described in the accomplishments section, we have already seen that RSI-MRI can find metastatic lesions that are not depicted on standard of care imaging assessment. This has the potential to change clinical practice as depiction of sites of metastatic disease informs treatment for metastatic cancer patients.

CHANGES/PROBLEMS:

Changes in approach: nothing to report

Actual or anticipated problems: Several requirements of our local institutional IRB as well as for DoD regulatory officers in the Human Research Protection (HRPO) were presented to us during this period of review. We worked closely with our local regulatory officers as well as the HRPO regulatory officers to successfully provide now accepted solutions in the form of IRB amendments. As the IRB meets only once per month, the need to amend the IRB documents over a course of a few cycles led to delay in commencement of the study, though now all approvals are in place and patient subject recruitment has accelerated.

Expenditure changes: nothing to report

Human and other subject changes: nothing to report

PRODUCTS:

Research presentations:

Dale and Hahn, invited research presentations at University of California San Francisco

Hahn, invited research presentation at the Prostate Cancer Foundation Prostate Cancer Academy Meeting

Webites: nothing to report

Technologies or techniques: nothing to report

Inventions, patents, licenses: nothing to report

Other products: nothing to report

PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS:

Individuals:

PI: Anders Dale, PhD, Overall project oversight, image review, data analysis

Co-I: Michael Hahn, MD PhD, radiologist, image review, overall project coordination, data analysis

Co-I: Rana McKay, MD, GU medical oncologist, patient recruitment, study design, data analysis

Co-I: John Kellogg Parsons, MD, GU surgical oncologist, patient recruitment, study design, data analysis

Co-I: Donna Hansel, MD, PhD, study design, pathologic analysis

Co-I: Tyler Seibert, MD PhD, GU radiation oncologist, patient recruitment, study design, data analysis

Co-I: Farshad Moradi, MD PhD, nuclear medicine physician, image review

Post-doc: Ana Rodriguez-Soto, PhD, image processing, data analysis

Post-doc: Jorge Zavala-Bojorquez, PhD, image processing, data analysis

Clinical Research Coordinator: Tyler Brocklehurst, coordinate with patients, coordinate consenting of patients, coordinate scheduling of research MRI exams

Change in support: nothing to report

Other organizations: nothing to report

SPECIAL REPORTING REQUIREMENTS: nothing to report

APPENDICES: nothing to report