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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 98 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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Table of Contents

	<u>Page</u>
1. Introduction.....	4
2. Keywords.....	4
3. Accomplishments.....	4-7
4. Impact.....	6
5. Changes/Problems.....	7
6. Products, Inventions, Patent Applications, and/or Licenses.....	7
7. Participants & Other Collaborating Organizations.....	7
8. Special Reporting Requirements.....	8
9. Appendices.....	8

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 98 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 continuing approval. Milestones achieved in period of review, including optimized imaging and further refinements in image post-processing for quantitative evaluation, local IRB continuing approval, and HRPO continuing approval.

Major Task 2: Data collection: Imaging and pathology specimens, Aim 1. Successful patient recruitment and WB-RSI-RSI scans in 98 patients to date. Recruitment continues to be ongoing. Quantification of total tumor burden: ongoing work nearing actualization in parallel with refinements in post-processing of imaging data above. 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. Currently 10 participants have undergone serial follow-up imaging exams (7 patients with 2 scans and 3 patients with 3 scans).

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 111 scans completed in 98 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.

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 documents for successful continuing re-approval
- further optimized the whole body RSI MRI imaging post-processing routine, which is now beginning to yield quantitative metrics of tumor activity
- continuously and successfully recruited subjects
- successfully scanned 98 subjects

Among the 98 subjects scanned to date, approximately half of the subjects have RSI-MRI findings suspicious for metastatic disease while the other subjects have negative RSI-MRI scans. We have laboriously and meticulously segmented all discernible lesions that are suspicious for sites of metastatic disease. These segmented lesion regions of interest feed the post-processing pipeline for our ability to distinguish true positive sites of metastatic disease from other non-cancerous abnormalities.

We have successfully recruited a key post-doctoral fellow with a background in quantitative MRI who is working on refining the post-processing algorithms for quantitative analysis of the RSI data under the direct instruction and supervision by Dr. Dale. This post-doctoral fellow, Dr. Christopher Conlin, is making continuous improvements in quantitative analysis of complex MRI data, which is expected to yield powerful predictive insights into the course of disease progression when combined with in ongoing tertiary analysis.

Key Accomplishments/Main Conclusions:

Working together as a multi-disciplinary team inclusive of imaging scientists, clinical translational radiologists, clinical translational urologists, clinical translational medical and radiation 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:

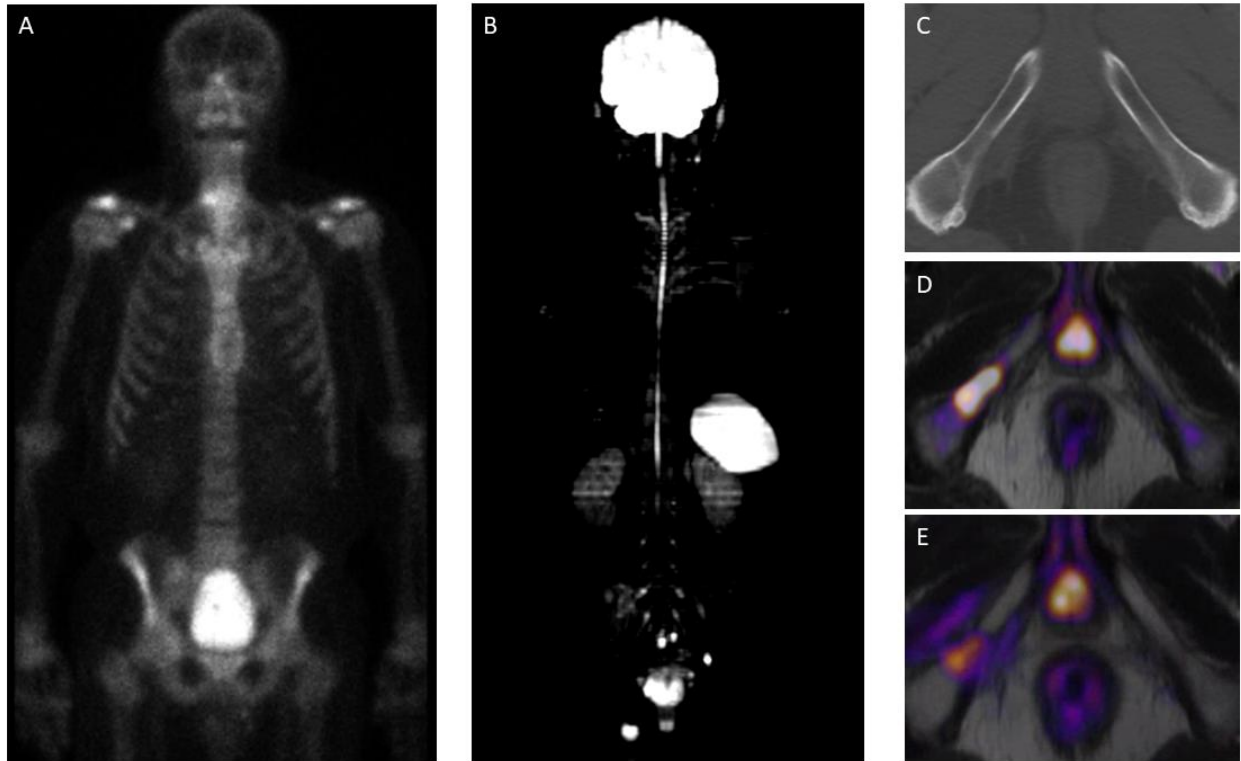


Figure 1: Patient with new diagnosis of high-risk prostate cancer. Panels A-D are at the time of initial diagnosis prior to therapy. Panel E is following systemic androgen deprivation therapy and targeted therapy to the pelvic osseous lesion. A) Nuclear medicine Tc99m-MDP bone scan shows no evidence of osseous metastatic disease. B) Whole Body RSI-MRI in coronal reformatted projection shows abnormal signal in the prostate gland, right osseous pelvis and pelvic lymph nodes. Note normal background signal in the brain, spinal cord, nerves, spleen and to a lesser extent kidneys and penile bulb. C) Axial image from a CT exam at that time showed no convincing evidence of the right pelvic osseous metastasis. D) RSI-MRI axial image displayed in color heat map fused to anatomic MRI image shows very high focal signal in the right osseous pelvic lesion, which prompted targeted bone biopsy that proved this to be a site of metastatic disease. Note background penile bulb normal signal. E) Following a course of androgen deprivation therapy and targeted radiotherapy, the signal in the right pelvic osseous lesion decreased considerably, compatible with partial favorable interval treatment change.

Opportunities for training and professional development:

Training Activities:

Image data analysis – postdocs Dr. Christopher Conlin and Dr. Rodriguez (and former postdoc Dr. 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. Dr Hahn attended a clinical trials methodology 1-week intensive course organized by the RSNA.

Professional Development:

International Society of Magnetic Resonance in Man Research Conference: Drs Dale and Rodriguez-Soto attended the ISMRM conference in 2019 which is the premier international research event for MRI researchers. Dr Hahn attended the RSNA and SAR annual conferences where whole body MRI approaches for oncology were presented.

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. Multiple papers on RSI have been accepted by the ISMRM for the 2020 conference.

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: Christopher Conlin, PhD, image processing, data analysis

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

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

Clinical Research Coordinator: Karen Cuervo, coordinate with patients, coordinate consenting of patients, coordinate scheduling of research MRI exams

8

Change in support: nothing to report

Other organizations: nothing to report

SPECIAL REPORTING REQUIREMENTS: nothing to report

APPENDICES: nothing to report