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TITLE: Parametric PET/MR Fusion Imaging to Differentiate Aggressive from Indolent Primary Prostate Cancer with Application for Image-Guided Prostate Cancer Biopsies

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14. ABSTRACT The study investigates whether fusion PET/MRI imaging with 18F-choline PET/CT and diffusion-weighted MRI can be successfully applied to target prostate cancer using image-guided prostate biopsies. The study further aims to establish whether fusion PET/MRI-derived parametric imaging parameters identify significant prostate cancer better than standard prostate biopsies. In order to achieve these objectives, prostate cancer patients will undergo PET and MR imaging, followed by standard prostate biopsy with additional targeted prostate biopsies. Biopsy samples will undergo histological evaluation and target metabolite analysis to evaluate underlying metabolic changes observed with prostate cancer progression. Depending on the pathology result of biopsies, some subjects will undergo prostatectomy involving additional MRI of the prostate specimen and registration of imaging to whole mount pathology. We obtained IRB approval prior to the start of the project. During the first year of the 4 year study, we established and optimized various aspects of the study procedures. The 18F-choline radiotracer synthesis was established, we obtained a 3T endorectal coil, tested and optimized immunohistochemistry of prostatectomy specimen, modified existing mass spectrometry methods for choline pathway metabolite analyses, implemented multi-modality image fusion to generate PET/MR fusion images for targeted prostate biopsies using mutual information software and performed such targeted biopsies. PET/MRI volumes were loaded into the GE Logic E9 ultrasound system and a rigid fusion with real-time ultrasound was obtained. The procedural steps for the prostate biopsy were optimized to allow for sufficient registration with real-time ultrasound. To date, 11 subjects have been enrolled (recruitment goal is 40 subjects in 4 years). The first goal of the study, to perform targeted prostate biopsies with high precision, has been achieved. The second aim, to assess whether parametric imaging parameters identifies significant prostate cancer better than standard prostate biopsies cannot be answered at this early stage of the project. An interim data analysis is planned for the end of year 2 of the program.					
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(2) INTRODUCTION

The study investigates whether fusion PET/MRI imaging with 18F-choline PET/CT and diffusion-weighted MRI can be successfully applied to target prostate cancer using image-guided prostate biopsies. The study further aims to establish whether fusion PET/MRI-derived parametric imaging parameters identify significant prostate cancer better than standard prostate biopsies. In order to achieve these objectives, prostate cancer patients are undergoing PET and MR imaging, followed by standard prostate biopsy with additional targeted prostate biopsies. Biopsy samples will undergo histological evaluation and target metabolite analysis to evaluate underlying metabolic changes observed with prostate cancer progression. Depending on the final pathology result of individual biopsies cores, some subjects will undergo prostatectomy involving additional MRI of the prostate specimen and registration of imaging to whole mount pathology.

(3) BODY

The following research accomplishments were made according to the statement of work:

Task 1: Administrative steps (months 0 to 4)

The 18F-choline synthesis was implemented and optimized for routine radiotracer production. RDRC committee approval as part of the IRB process was obtained. To date, 18F-choline production was successful in all but one case in sufficient radiochemical yield.

The navigated endorectal transducer with software update for the GE E9 ultrasound system was obtained. Recently, the 3T endorectal coil was made available by the vendor (Philips) and will be used for future cases.

Task 2: Prepare image registration tasks (months 0 to 4)

Program-specific in-vivo image registration sub-tasks were implemented in the registration software (MIAMI fuse). We first simulated image registration process (PET and MRI) with data from earlier studies, confirming functionality of the programming, and established necessary data connectivity between image fusion lab, PET, US, and MRI research data storage. As the US system cannot project color images, a suitable (gray-scale) method to display targets on MRI was developed and tested in humans.

Task 3: Prepare immunohistochemistry tasks (months 0 to 4)

Antibody dilutions for immunohistochemistry (IHC) were tested and optimized in spare prostate tissues and control tissues.

Task 4: Prepare target metabolite validation (months 0 to 4)

Target authentic isotope labeled metabolite standards, HPLC grade solvents, and reagents for mass spectrometry (MS) sample preparation were ordered. Then the extraction methodology and development of MS method for individual metabolites were optimized.

Task 5: Recruitment (months 4 to 24)

The study was opened for recruitment on Dec. 6, 2012. We are recruiting subjects undergoing clinically indicated prostate biopsy from two populations: a) patients undergoing surveillance for known prostate cancer, and b) patients with known or suspected prostate cancer in need for a prostate biopsy who would be eligible for prostatectomy (if indicated). The recruitment goal is 40 subjects in 4 years. Since subjects not undergoing definitive treatment are followed, a total of 71 biopsy procedures are to be performed of which 18 should be within the first year.

To date, 11 subjects have been recruited, one subject who did not tolerate MR imaging was excluded from the study (10 evaluable subjects). Recruitment was slow at the start of the trial, but has recently significantly improved. The last 7 subjects were recruited within the last 3 months. Recruitment has improved after implementing the following steps:

- We created a study protocol summary sheet which will be made available to interested referring physicians, which was approved by the IRB.
- An additional urologist seeing surveillance patients, Prof. John Wei, was included into the study team to better identify potential candidates. The required IRB amendment was approved.
- In addition, after IRB approval we obtained access to a Urology database, which contains potential candidates ahead of their scheduled yearly surveillance biopsy.
- Use of endorectal coil MRI is optional. Explanation: The endorectal MRI procedure can be unpleasant or is not possible in subjects with specific contraindications for glucagon.

These changes were communicated to the Grants Officer prior to their implementation. Since the recruitment rate (7 within 3 months) is now above the goal (18 in year 1 and 2), we anticipate to be able to recruit sufficient subjects within the first 2 years.

Task 6: Return visits (months 16 to 44)

Returning participants are expected between month 16 and 44.

Task 7: Imaging, prostate biopsies and registration tasks (months 4 to 44)

18F-choline PET/CT and multi-sequence MR imaging are now reliably available to study subjects. The image data analysis of 18F-choline PET/CT and MRI to register in vivo PET with MRI and create parametric fusion PET/MRI is implemented. PET/MRI data can be imported and registered with real-time US. Image guided (targeted) prostate biopsies are performed with sufficient registration accuracy. Mainly, once real-time US and PET/MRI target volumes are registered, it is often possible to identify corresponding lesions on US which simplifies the targeting process.

Task 8: Perform target metabolite validation (months 4 to 44)

Biopsy tissue specimens for metabolite MS analysis are being collected and stored for later MS analysis. Because the MS analysis is performed in batches, results will be available as soon as a sufficient number of samples are collected.

Task 9: Data analysis and statistical evaluation (months 12 to 48)

We anticipate a sufficient number of biopsy samples to be available for data analysis within the next 4-6 months.

Task 10: Communication of results and publications (months 12 to 48)

At this early stage of the project, project results are limited. We are, however, planning to submit a presentation for the upcoming annual meeting of the Society of Nuclear Medicine 2014 regarding the feasibility of PET/MRI fusion imaging for targeted prostate biopsies. During the year 2014, a respective publication is planned, which will however require a larger patient population.

(4) **KEY RESEARCH ACCOMPLISHMENTS**

- all preconditions for successful conduction of the trial have been met
- targeted (image-guided) prostate biopsies based on PET/MRI are feasible

(5) **REPORTABLE OUTCOMES**

- Planned presentation at the 2014 SNMMI meeting

- Planned publication regarding the “feasibility of PET/MRI fusion imaging for targeted prostate biopsies”.

(6) **CONCLUSION**

While specific results pertaining the ultimate study question (whether fusion PET/MRI-derived parametric imaging parameters identify significant prostate cancer better than standard prostate biopsies) are yet not available at this time, the study is on track.

(7) **REFERENCES**

N/A

(8) **APPENDICES**

N/A

(9) **SUPPORTING DATA**

N/A