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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. To date, 40 subjects have been enrolled and 32 subjects have completed MRI and PET imaging with subsequent biopsy procedure. An interim analysis has shown that a total of 66 subjects are needed to fully investigate the goals of this research. Accordingly, we have initiated an addendum to the research protocol to extend the recruitment goal to 66 subjects (in 4 years). We are now able to perform targeted prostate biopsies with high precision. The interim analysis from 32 subjects as shown that targeted biopsies increased the number of significant prostate cancer lesions found at biopsy (targeted biopsy: n=12; standard biopsy: n = 5). At the same time, the rate of low grade prostate cancer decreased dramatically (targeted biopsy: n=1; standard biopsy: n = 9). These preliminary data show that targeted biopsies increase the chance to identify significant disease requiring fewer biopsy cores, and decreasing the chance to find (indolent) low grade cancer. The second aim (to assess the value of parametric imaging to identify significant prostate cancer) is currently being evaluated. Target metabolite analyses are underway from tissue materials obtained thus far (as well for Aim 3).					
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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)

Completed task. 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 2 cases in sufficient radiochemical yield.

The navigated endorectal transducer with software update for the GE E9 ultrasound system was obtained. A 3T endorectal coil was obtained.

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

Completed task. 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)

Completed task. 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)

Completed task. 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.

Currently, target metabolite analyses are being performed on acquired frozen prostate biopsy core tissues.

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).

Recruitment has improved significantly 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. Until now, 40 subjects have been enrolled and 32 subjects have received PET and MR imaging followed by prostate biopsy.

The initial recruitment goal was 40 subjects in 4 years. However, statistical sample size calculations performed at $n=20$ determined that 66 subjects would be needed to maintain the statistical power (84%) to assess the study goals (see Task 9 below). We have taken steps to achieve the new recruitment goal ($n=66$) as described below.

Task 6: Return visits (months 16 to 44)

Thus far, two subjects returned for a second (repeat) imaging session and biopsy procedure. We assume that the rate of repeat biopsies will slightly increase in upcoming months.

Definitive treatments: Four subjects received prostatectomy (2 on the outside) and 3 patients went on to receive radiation treatment. One subject is undergoing palliative systemic treatment due to identified distant metastatic disease. Two additional subjects are scheduled to receive prostatectomy (within the next 6 weeks) at our institution following identification of high grade disease within this trial.

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

18F-choline PET/CT and multi-sequence MR imaging are 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. A first batch of tissues is currently being analyzed.

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

The recruitment goal was 40 subjects in 4 years. Due to a lower than expected rate of significant prostate cancer in biopsy materials, and due to fewer subjects returning for repeat biopsies, an interim statistical analysis was performed to evaluate the statistical power of the study. Based on initial estimations, 20 patients were needed to have at least one biopsy core with significant disease. We simulated power for this sample size assuming an average of three tumor-positive biopsy cores per patient per year, and that

5% of surveillance patients will have at least one biopsy (average of 2) with significant disease at some point in the study. In our simulation studies, we varied the standard deviation of the random intercept and assumed 12 non-guided biopsy specimens per subject and biopsy, and an average of two image-guided biopsy specimens. We also assumed an odds ratio of 1.5. That is, the odds of detecting significant disease using image-guided biopsy is 1.5 times the odds of standard biopsy. (Note that we will retrospectively determine, via imaging, whether the standard biopsy locations have significant disease). It was determined that 66 subjects would be needed to maintain the statistical power (84%) to assess the study goals.

Currently, the IRB is reviewing an addendum to the application to allow for 66 subjects and approval is expected in November 2014.

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

Our initial data are being presented at the EANM meeting in October 2014.

A first journal manuscript is in preparation (likely submission by the end of the year 2014).

(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
- Targeted biopsies improved detection rate for significant prostate cancer (Gleason grade 3+4 or higher) while at the same time requiring less biopsy cores
- Neither choline PET nor multi-sequence MRI allow visualization of low grade (indolent) prostate cancer (Gleason 3+3)

(5) **REPORTABLE OUTCOMES**

- Planned presentation at the 2015 American Urological Association (AUA) meeting
- Planned publication regarding the “Feasibility and initial results of PET/MRI fusion imaging for targeted prostate biopsies”.

(6) **CONCLUSION**

Early study results (after 32 evaluable subjects) indicate that the combination of 18F-choline PET/CT and multi-sequence MRI identifies more significant (Gleason 3+4 and higher) prostate cancer than standard prostate biopsies while requiring less tissue cores. At the same time, less low grade cancers (Gleason 3+3) were detected.

Together, these initial data suggest that

- a) image-guided prostate cancer biopsies improve the detection of significant disease,
- b) lower the risks of biopsy procedures by significantly reducing the number of biopsy cores, and

c) reduce the chance to identify low grade (indolent) prostate cancer.

Together, these data indicate that image-guided prostate biopsies may be the future modality of choice for patients undergoing surveillance for rising tumor markers (PSA) and low-grade prostate cancer.

(7) REFERENCES

N/A

(8) APPENDICES

N/A

(9) SUPPORTING DATA

As follows

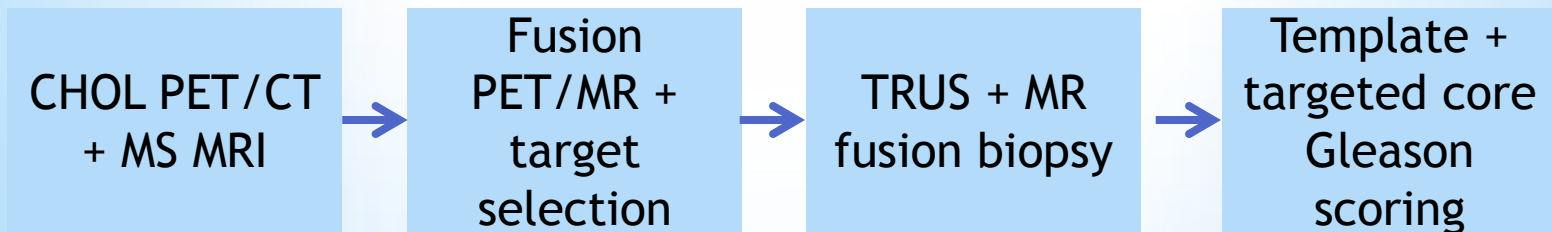
Background

- Considerable uncertainty in management of primary prostate cancer
- Many cases initially present with indolent low risk disease
- Clinical, financial and ethical dilemma of **overtreatment**
- Active surveillance (AS) is recommended

- Standard method of diagnosis is **template prostate biopsy**
- Considerable rate of sampling errors with significant underestimation (~42%) or overestimation (~15%) of true Gleason score
- Recommendation **saturation biopsy** improves detection, higher risk
- Result is **poor acceptance of AS protocols**, limiting effectiveness

Methods

- ^{18}F -choline PET/CT (~220 MBq IV)
- Multi-sequence 3T MR (incl. T2,DWI,CE dyn. MRI)
- Spatial registration (fusion PET/MR), mutual image information
- Target selection (based on visual interpretation)
- Prostate biopsy procedure (< 4 weeks after PET/MR)
 - standard 12-core template + targeted biopsies
- Fusion of real-time TRUS + MR with embedded targets
- Histological evaluation of cores (Gleason score)



Patient Characteristics

- 40 subjects enrolled (64 y, range 56 - 77 y);
32 completely valuated (reported here)
- New enrollment goal = 66
- Suspected (n=23) or known (n=12) prostate cancer (PCa)
- PSA median 8.6 (range 3.6 - 153)
- **Prior biopsy** procedure:
 - Time interval: 22 (range 6 - 96) weeks prior
 - Histological result (19 negative, 10 Gleason 3+3, 2 Gleason 3+4)

Prior biopsy procedures	N
None	4
One	14
Two	9
Three	3
4 to 6	4

Methods of Evaluation

- **Prediction** of presence of significant PCA by imaging (MRI and PET) prior to biopsy determined as low, intermediate, or high (scores 1-3)
- **Assessment of quality of registration** between real-time TRUS vs. MRI
- Assessment of **targeting accuracy**
 - visual evaluation of each biopsy
 - scores: on target (3), questionable (2), miss (1)
 - % involvement of positive biopsy cores
- **Standard of reference**
 - biopsy core with highest Gleason score (n=32)
 - final pathology from prostatectomy specimen (n=3)

Interim Results:

Template vs. Targeted Biopsy

Targeted biopsies detected significantly more Gleason \geq 3+4 disease compared to template biopsy ($p < 0.01$) Wilcoxon

Patient-based data (n = 32)

Highest Gleason score	Template biopsy	Targeted biopsy
Gleason \geq 3+4	4	9 (p < 0.01)
Gleason = 3+3	9	1 (p < 0.001)
No Prostate cancer (PCa)	19	22

Interim Results:

Template vs. Targeted Biopsy

Targeted biopsies detected more Gleason $\geq 3+4$ compared to template biopsy requiring less biopsy cores

Sector / target based data

	Template biopsy (sectors no.= 384)		Targeted biopsy (target no. = 62)	
Highest Gleason score	N	% core involved	N	% core involved
Gleason $\geq 3+4$	5	33 (range 5-85)	12 (p <0.01)	76 (range 40-100)
Gleason = 3+3	9	13 (range 5-25)	1 (p <0.001)	5
No prostate cancer	371		49	

Interim Results: Biopsy-Core-Based

Visual judgment of individual targeting
(only positive for Gleason $\geq 3+4$)

Visual judgment	N = 65	Probability
Targeting excellent (score 3)	41	0.85
Targeting questionable (score 2)	20	0.55
Target missed (score 1)	4	0.22

Odds to identify significant PCa did not increase
with overall quality of registration (US to MRI)



Mental registration is effective

Conclusions (Interim Analysis)

- After learning curve, PET/MR guided prostate biopsies are feasible
- Neither choline PET nor multi-sequence MRI allow visualization of low grade prostate cancer (Gleason 3+3)
- Targeted biopsies **improved detection rate for Gleason 7+** and **requires less biopsy cores**
- Promising tool to improve diagnosis particularly for anterior tumors
- Combination of choline PET with MRI may further improve detection rate in larger series
- Imaging **may limit the need for repeated prostate biopsy** in surveillance population