Staging of Untreated Patients with Very High-risk and High-risk Prostate Carcinoma Utilizing Hybrid C11-choline PET/MR and Pelvic Multiparametric MRI for Personalized Precise Treatment: a Pilot Study

NCT03404648

05/03/2019

Staging of Untreated Patients with Very High-risk and High-risk Prostate Carcinoma Utilizing Hybrid C11-choline PET/MR and Pelvic Multiparametric MRI for Personalized Precise Treatment: a Pilot Study

PI: Ming Yang, M.D., Dept. of Radiology

Co-PI: Akira Kawashima, M.D., Ph.D., Dept. of Radiology

Regulatory Sponsor: Ming Yang, M.D.
Department of Diagnostic Radiology
Mayo Clinic in Arizona
13400 East Shea Blvd
Scottsdale AZ 85259
[redacted]
Yang.ming@mayo.edu

Study Product: C-11 choline

Protocol Number: (IRBe) 16-007897

IND Number: 134646

Initial version:	9/26/2016	Version (1.0)
Revised:	2/27/2017	Version (2.0)
Revised:	4/24/2017	Version (2.1)

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
BCR	Biochemically recurrence
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computerized Tomography
DSMB	Data and Safety Monitoring Board
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
mpMRI	Multiparemetric magnetic resonance imaging
PCa	Prostate cancer
PET/CT	Positron Emission Tomography/Computerized Tomography
PET/MR	Positron Emission Tomography/Magnetic Resonance
PHI	Protected Health Information
PI	Principal Investigator
PSA	Prostate specific antigen
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
T	Tesla

Study Summary

Title	**Staging of Untreated Patients with Very High-risk and High-risk Prostate Carcinoma Utilizing Hybrid C11-choline PET/MR and Pelvic Multiparametric MRI for Personalized Precise Treatment: a Pilot Study**
Running Title	C11-choline PETMR and pelvic mpMRI on primary prostate cancer
Protocol Number	16-007897
Phase	NA
Methodology	Prospective, pilot study
Overall Study Duration	16 weeks
Subject Participation Duration	90 minutes, single day, in the nuclear medicine suite.
Single or Multi-Site	Single
Objectives	1): Test whether a hybrid combination of focused C-11 choline PET/MR and pelvic mpMRI on a PET/MR system is feasible. 2): Determine the efficacy (added values) of a hybrid combination of molecular focused C-11 choline PET/MR and functional and anatomic pelvic mpMRI in comparison with clinical findings. 3): Determine the efficacy (added values) of a torso C-11 choline PET/MR in comparison with conventional CT and bone scan in depicting metastasis to lymph node and bone.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Clinically diagnosed high and very high risk prostate cancer. Adult patients who are able to provide informed consent.
Study Product, Dose, Route, Regimen	C-11 choline PET tracer, One dose, totally 12-14 mCi, intravenous administration while patient is lying on the table
Duration of Administration	1 study day
Reference therapy	None
Statistical Methodology	Descriptive statistics will be used, including sensitivity, specificity, and accuracy, based on histopathological correlation.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Prostate cancer is the most common solid cancer in men in the United States and the second most common cancer death in American men[1]. Early and correct diagnosis of prostate cancer together with accurate staging is vital for appropriate clinical management strategy. To date, morphological and functional pelvic mpMRI and molecular imaging C11-choline PET have been playing vital roles in standard of care of prostate cancer.

Pelvic mpMRI, typically including T1-weighted, T2-weighted, diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCEI) with or without MR spectroscopic imaging (MRSI), is an established imaging modality and has been increasingly utilized for lesion detection and characterization, monitoring for active surveillance, detection of local recurrence in suspect cases, and MR guided intervention. In a prospective study of 70 consecutive patients with histopathologic correlation, the sensitivity, specificity, false-positive and false-negative rates, and the accuracy of mpMRI for extracapsular extension and seminal vesicle invasion have been reported to be 78.2% and 80%, 80.9% and 97%, 19.1% and 3.7%, 21.7% and 20%, 80% and 95.7%, respectively[2]. However, the major limitation of pelvic mpMRI is the distant metastasis outside the field of view of prostate cancer.

Choline, a component of the phosphatidylcholines increased in prostate cancer, can be radiolabelled with either 11Carbon (C11-choline) and 18Fluoro (F11-choline). Unlike F18-fludeoxyglucose (FDG) tumoral uptake, which depends on increased cellular glycolytic pathway activity, choline uptake depends on active cell membrane synthesis, a metabolic pathway which more reliably reflects tumor metabolism in prostate cancer. C-11 choline PET has been shown to help identify sites of metastatic disease in men with biochemical recurrence after primary treatment failure. In the past decade, multiple investigations have demonstrated satisfactory sensitivity and specificity for the detection of recurrent PCa patients, and led to the FDA approval of C-11 choline production at Mayo Clinic 2012[3-5].

Additional effort has been taken to compare pelvic mpMRI and C11-choline PET in BCR PCa patients and demonstrated complimentary role of them for restaging prostatectomy patients with suspected recurrent disease. Kitajima K and colleagues compared the C11-choline PETCT with pelvic mpMRI with endorectal coil in detection of local recurrence, pelvic nodal metastasis and distant metastasis. They found that mpMRI is superior to C11-choline in detection of local recurrence; PET is superior for pelvic lymph node metastasis[6].

The newly FDA approved hybrid GE SIGNA 3T PET/MR scanner provides an opportunity to investigate the clinical value of combined C11-PET/MR and pelvic mpMRI in primary prostate cancer. It is anticipated that the improved comprehensive imaging techniques may more

accurately stage untreated patients with high risk prostate cancer as well as better characterize the intra-parenchymal tumor. Therefore, we wish to determine the feasibility and efficacy (added value) of a hybrid, combined torso and focused C-11 choline PET/MR with pelvic mpMRI in characterizing and staging very high-risk and high-risk prostate cancer patients, which could provide a more accurate tumor characterization and staging information and lead to individualized precise treatment.

1.2 Investigational Agent

The investigational agent for this study is C11-choline, a cyclotron synthesized PET tracer to be manufactured in the Mayo Clinic Arizona radiochemistry facility.

1.3 Clinical Data to Date

Since 2000, there have been several studies investigating clinical role of choline PET and PETCT in diagnosing and staging primary prostate cancer. However, there is limited sensitivity and specificity in differentiating primary prostate cancer from normal prostate tissue due to overlapping choline uptake by hyperplasic prostate tissue, high-grade intraprostatic epithelial neoplasia (HGPIN), prostatitis, BPH, even urinary excreted activity in the base of urinary bladder and urethra. In addition, there is no proven significant correlation between C11-choline uptake by localized primary prostate cancer and serum PSA level, Gleason score[7,8]. Therefore, there is clinical consensus of limited clinical value of choline PET and PETCT in characterizing primary PCa.

However, the pursuit of combined advantages of choline PET and pelvic mpMRI in PCa persists. In one recent clinical trial, it is found that fused F18-Choline PET/MR images could provide added value for MR guided transrectal prostate biopsies[9].

1.4 Dose Rationale

The dose of C-11 choline selected for use in the study patients is 12-14 mCi,(444-518 MBq) based on prior published reports [6, 10, 11]. The tracer must be given intravenously.

1.5 Risks and Benefits

C-11 choline is involved in phosphorylation process integrated into phospholipids in the cell membrane as part of phosphatidylcholine, which is vital in prostate cancer cell. The main risk involves the exposure to the radioactivity associated with the C-11 isotope incorporation. This exposure has been calculated to be much lower than the F-18 FDG. In addition, there is no radiation risk related to MR scan. For MR safety concern, each subject will undergo MR safety screening performed by PET/MR technologist prior to imaging.

2 Study Objectives

Primary Objective:

1) Test whether a hybrid combination of focused C-11 choline PET/MR and pelvic mpMRI on a PET/MR system is feasible

Secondary Objective(s):

1) Determine the efficacy (added values) of a hybrid combination of molecular focused C-11 choline PET/MR and functional and anatomic pelvic mpMRI in comparison with clinical findings.
2) Determine the efficacy (added values) of a torso C-11 choline PET/MR in comparison with conventional CT and bone scan in depicting metastasis to lymph node and bone.

3 Study Design

This study will be a prospective study to test and optimize the feasibility of hybrid 3T PET/MR scan in diagnosing and staging high and very high risk prostate cancer patients.

The FDA approved C-11 choline PET tracer at a dose of 12-14 mCi will be administered intravenously prior to fused PET/MR scan, and prior to diagnostic pelvic mpMRI scan while patient lying in the scanner.

In addition, single dose of Gadavist® (Gadobutrol, Bayer) is at no more than 0.1 mmol/kg will be administrated intravenously for pelvic mpMRI.

The whole imaging procedure will be conducted on an FDA approved GE SIGNA 3T PET/MR scanner.

The C11-choline PET/MR and pelvic mpMRI findings and results will be compared with serum PSA level, Gleason score, clinical CT and nuclear medicine whole body bone scintigraphy findings, and histopathological results obtained through standard of care management.

Our primary interest is to investigate the feasibility of hybrid C11-Cholime PET/MR fusion and pelvic mpMRI in imaging primary prostate cancer.

3.1 General Description

It is possible that improved comprehensive imaging techniques may more accurately stage untreated patients with high risk prostate cancer as well as better characterize the intra-parenchymal tumor. It is of interest to focus on potential synergy between molecular focused C-11 choline PET and functional and anatomic pelvic mpMRI. Therefore, we wish to determine the feasibility and efficacy (added value) of a hybrid, combination of torso and focused C-11 choline PET/MR with pelvic mpMRI on a clinical 3T PET/MR system in characterizing and staging very high-risk and high-risk prostate cancer patients, which could provide a more accurate tumor characterization and staging information and lead to individualized precise treatment.

3.2 Number of Subjects:

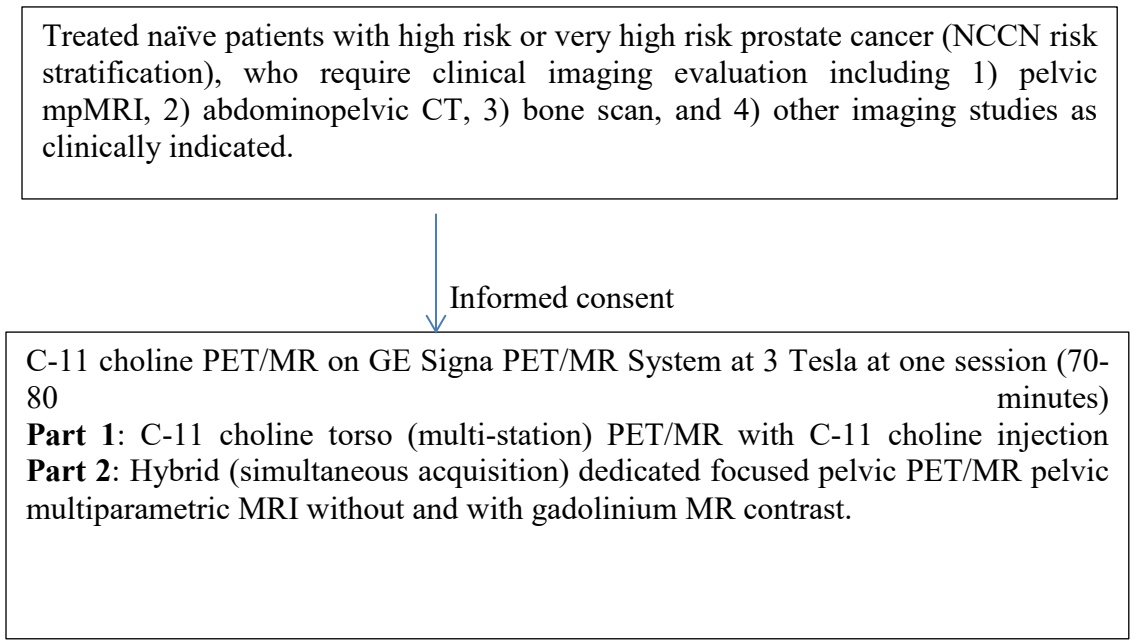
A total of twenty subjects will complete the study. Additional candidates may be screened to ensure completion of twenty subjects.

3.3 Duration of Participation

Subjects will complete one day of in-department participation. A second study day will consist of a phone call to the subject after completion of day 1.

Human subjects will be subject to Mayo Department of Radiology policies and procedures. Candidates for enrollment will be first queried by the study coordinator for possible exclusion using the departmental MRI safety guidelines for clinical MRI. The study coordinator will review the medical history and use the subject's serum creatinine level to determine his eGFR based on patient age, gender, and ethnicity. If necessary, the subject will undergo a blood test to determine an up-to-date creatinine level, performed at no expense to the subject. eGFR will be determined prior to performing any contrast-enhanced scan.

Patient flow in the nuclear suite



IMAGING TECHNIQUES

PET/MR scanner/equipment

Clinical GE SIGNA 3 Tesla PET/MR system

PET/MRI Technique (Figure 1)

1. There are two integrated components of fused PET/MR and focused Pelvic mpMRI
    a. Indications/Protocols: Primary prostate cancer.

Part	Description of imaging sequences
1	Torso (multi-station) PET/MR fusion scan with injection dose of C-11 choline
2	Hybrid focused (single-station) PET/MR and mpMRI of the pelvis (simultaneous acquisition of pelvic PET/MR and mpMRI without and with IV gadolinium contrast at the same table position)

- Parts 1 and 2 will be done at one session with the patient on the same PET/MR table.
- .
- The entire PET/MR fusion with focused pelvic mpMRI scanning time is 75-80 minutes.

Part 1: Torso PET/MR Fusion Scan with C-11 choline

- Coil: Three pieces of array coils from vertex of head to the level of upper thigh; No use of endorectal coil.
- Patient supine, head first
- Arms down for all procedures
- Metallic objects should be removed from the patient whenever possible

PET Tracer:

While patient lying on scanner table, 444-518MBq (12-14[i] mCi) C-11 choline will be injected as a bolus through a catheter inserted into a large peripheral vein.

Scan Range:

- Routinely from upper thigh to vertex of head, otherwise specified

Scan direction for PET

- Inferior to superior
- Start imaging immediately after the injection of tracer and acquire images with 2–5 minutes per bed position (totally about 5-6 bed positions). The total scanning duration is around 25-30 minutes

MR attenuation correction:

- Simultaneous PET/MR imaging with PET emission data reconstructed in 3D time-of-flight mode at multiple bed positions. During each bed position, coronal Dixon fat/water sequence, in-phase, and out-phase images will be performed for MR segmented attenuation correction.
- Diagnostic quality axial LAVA-FLEX only was obtained simultaneously with PET emission imaging acquisition at each bed position.

Part 2: Hybrid Focused PET/MR and mpMRI of the Pelvis (simultaneous acquisition of pelvic PET/MR and mpMRI without and with IV gadolinium contrast)

MR contrast agent and medicine

- For a contrast-enhanced scan the technologist will load and connect a power injector for administration of contrast material via a peripheral venous access. The contrast material and dose are both determined by the radiologist subject to departmental policy.

- Typically a single dose of Gadavist® (gadobutrol, Bayer) is used for studies of the prostate gland at our institution. The target contrast dose is no more than 0.1 mmol/kg for subjects with eGFR of higher than 30 mL/minute/1.73 m2. Those with a GFR of 30 or less will not be admissible to the study. Contrast material is administered at 3 ml/sec followed by a saline flush of 20 ml at 3 ml /sec.

- 1 mg of glucagon will be administered subcutaneously at the start of the scan as an anti-peristaltic. Glucagon will not be given if the patient has a history of DM.

The following multiparametric prostate MR protocol will be applied. Simultaneous PET emission image will also be acquired. The total mpMRI scan time is around 40-50 minutes.

- Multiparametric MRI of the pelvis technique utilizing an institutional clinical MRI protocol.

Sites	Image sequences
Pelvis	
	Axial T1-weighted LAVA-FLEX*
	Axial DWI
Prostate (high resolution with small FOV)	
	Sagittal T2 FRFSE
	Axial T2 FRFSE
	Axial FOCUS DWI
	Coronal T2 FRFSE
	Axial DCE
Pelvis	
	Post Gd ax LAVA-FLEX (water only, fat only)

* Axial T1-weighted LAVA-FLEX acquired in Part1. may be used for pre-contrast T1-weighted images.

Image review:

- PET/MR fusion study, including PET emission data, MRAC image and focused pelvis PET/MR fusion images will be sent to MIM Vista workstation for review by an independent, experienced board certified nuclear medicine radiologist without knowing clinical findings except for high risk prostate cancer.
- Focused mpMRI of pelvis images will be sent to PACS for review by an independent, experienced board certified body MR radiologist without knowing clinical findings except for high risk prostate cancer.

Evaluation of imaging findings:

Reviewers review images to evaluation imaging findings without knowing clinical findings except all subjects are recently diagnosed with very high-risk or high-risk prostate cancer. Readout workflow is illustrated in Figure 2. The scores will be recorded and stored in a secured REDCap file.

Pelvic mpMRI:

1. Lesion detection and characterization utilizing PI-RADS version 2 (15).
2. Tumor staging utilizing AJCC TNM staging system (3)
3. Detection of suspicious pelvic lymph nodes.
4. Detection of suspicious osseous lesion in the pelvis.

Torso and focused C-11 choline PET/MR:

1. Lesion detection and characterization.
2. Tumor staging
3. Detection of suspicious pelvic and extrapelvic lymph nodes.
4. Detection of suspicious osseous lesion in the pelvis and extrapelvic regions.
5. Document SUV in the region of interest (ROI) if possible.

Reference standards

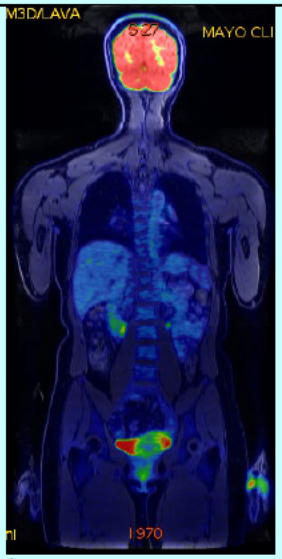
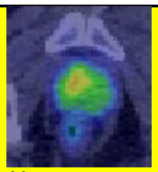
1. Histopathology results when available
2. Clinical imaging study (CT, bone scan, etc).
3. Clinical follow-up (progression or regression at follow-up routine clinical imaging after treatment).

Prostate tumor localization and characterization: Focused C-11 choline PET/MR and pelvic mpMRI findings to be correlated with clinical prostate biopsy and surgery results.

Lymph node metastases: Torso and focused C-11 choline PET/MR and pelvic mpMRI findings to be correlated with clinical CT, lymph node biopsy, and surgery results

Bone metastases: Torso and focused C-11 choline PET/MR and pelvic mpMRI findings to be correlated with whole body bone scan, F-18 NaF PET/CT (if available), CT, dedicated MRI, and biopsy results.

Figure 1. Illustration of Part 1 "Torso C-11 Choline PET/MR" and Part 2 "Hybrid Focused C-11 Choline PET/MR and Pelvic mpMRI.

Acquisition time per table bed	Part 1: Torso C-11 choline PET/MR				Part 2: Hybrid dedicated focused C-11 choline PET/MR and pelvic mpMRI		
2-5 min/bed	PET		AC	Diagnostic MR pulse sequences			
2-5 min/bed	PET		AC	Diagnostic MR pulse sequences			
2-5 min/bed	PET		AC	Diagnostic MR pulse sequences			
2-5 min/bed	PET		AC	Diagnostic MR pulse sequences			
2-5 min/bed	PET		AC	Diagnostic MR pulse sequences	**Focused C-11 choline PET/MR**		**Pelvic mpMRI** (anatomic and functional sequences) without e-coil
Time	25-30 min				45-50 min		

*

**

***

AC=attenuation correction

mpMRI = multiparametric MRI

e-coil = endorectal coil (for illustration purpose only, will not be used in current study)

* = F-18 FDG PET/MR shown for illustration purpose

** = C-11 choline PET/CT shown for illustration purpose

*** = T2W shown for illustration purpose

Figure 2. Workflow of Readout Sessions (parts 1-3)

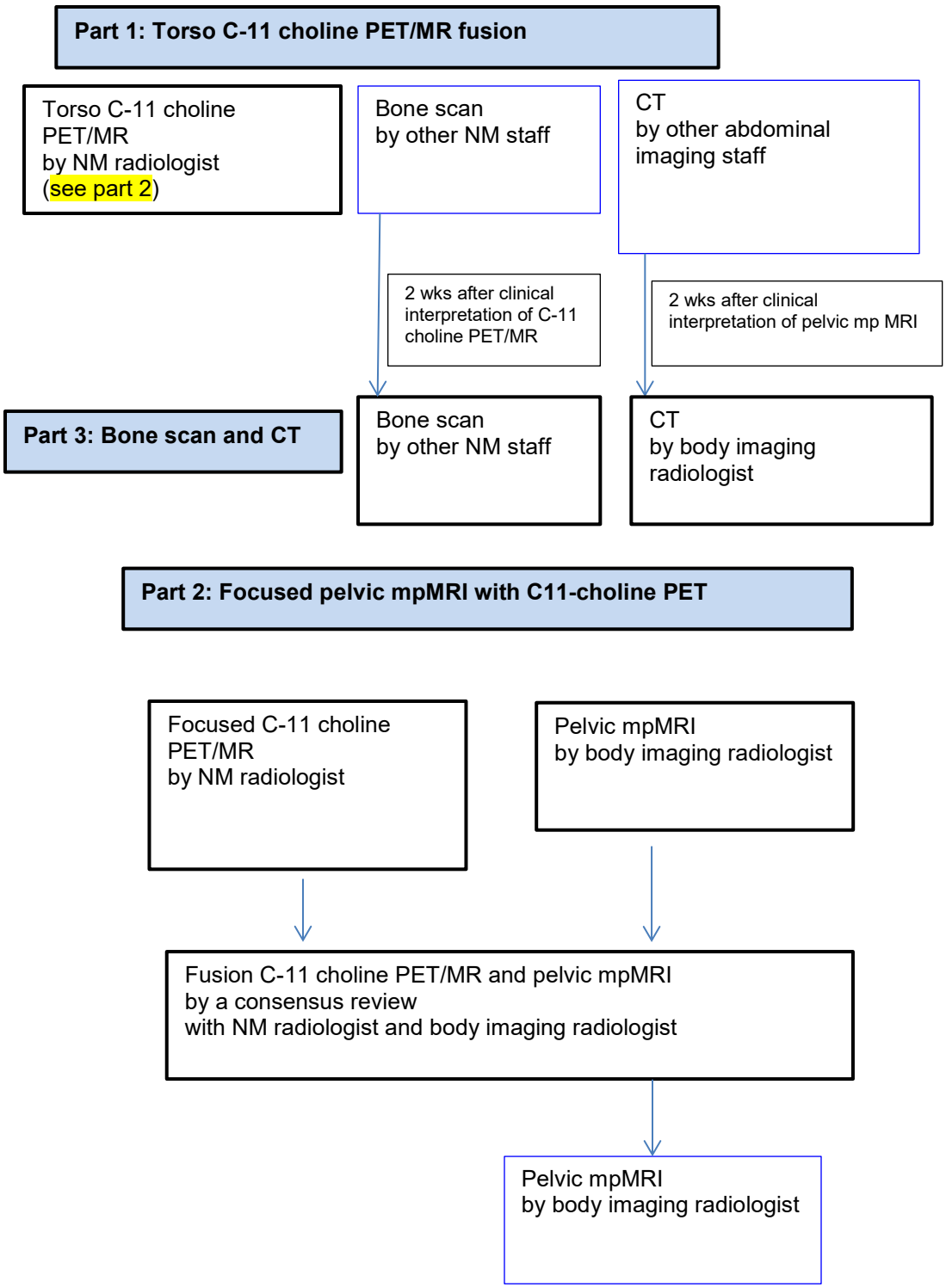


Table 1. Summary of imaging finding evaluation

		C-11 choline PET/MR (research)	Clinical imaging exams	Reference standard	Findings
Local T staging: Prostate		Focused pelvic C-11 choline PET/MR	Pelvic mpMRI	Pathology results (biopsy, surgery if available)	Localization Characterization Local tumor (T) staging
Metastasis to pelvic lymph nodes(N)					
	Pelvis	Focused C-11 choline PET/MR	Pelvic mpMRI CT	Pathology results (biopsy, surgery if available)	Localization SUV values
	Torso	Torso C-11 choline PET/MR	CT	Pathology results (biopsy, surgery if available)	Localization SUV values
Metastasis to pelvic bone (M)					
	Pelvis	Torso and focused C-11 choline PET/MR	Pelvic mpMRI CT Bone scan	Pathology results (biopsy, surgery if available)	Localization SUV values
	Extra-pelvis	Torso C-11 choline PET/MR	CT Bone scan	Pathology results (biopsy, surgery if available)	Localization SUV values
Visceral metastasis (M)					
Visceral metastasis (M)		Torso C-11 choline PET/MR	CT	Pathology results (biopsy, surgery if available)	Localization SUV values

3.4 Primary Study Endpoints

Patient: Completion of all imaging examinations with laboratory results.

Data analysis:

Objective 1: Descriptive study. With biopsy and/or surgical histopathology as gold standard, the sensitivity, specificity and accuracy of PET/MR will be calculated.

3.5 Secondary Study Endpoints

NONE

3.6 Primary Safety Endpoints

Since C-11 choline is an essential nutrient needed for physiologic process as an integrated part of cell membrane component, and the quantities actually administered are in the micromolar range, there are no expected adverse reactions due to the primary study drug. The primary safety endpoint would be documentation of either lack of reaction to C-11 choline injection or detailed description of any adverse reaction (rash, fever, hypotension, dyspnea, chest pain) and treatment measures undertaken.

3.7 Identification of Source Data

The following source data will be directly recorded on the Case Report Form (CRF):

- Vital signs
- Events
- Dosage of C-11 choline, route of administration
- Patient Reported Outcomes

The following source data will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (study source documents, EMR):

- Laboratory results can be utilized from outside facilities for this study
- Prostate biopsy reports and pathology reports can be utilized from outside facilities for this study.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Adults, age 18 and older
- Untreated male patients with high-risk and very high-risk prostate cancer, who require clinical pelvic mpMRI, CT, and bone scan as standard clinical care for diagnosis and management of prostate cancer.

4.2 Exclusion Criteria

- Patients who already received primary treatment or neo-adjuvant therapy.
- Patients who refuse undergoing routine clinical imaging (i.e., pelvic mpMRI, CT, bone scan) for staging. Reimbursement of pelvic mpMRI may be provided. CT and bone scan may be done elsewhere outside of Mayo Clinic but should be of diagnostic quality. Research C-11 choline PET/MR will not substitute pelvic mpMRI, CT, or bone scan in this study.
- Patients cannot tolerate MRI (e.g., claustrophobia, severe back pain or spasm, involuntary movement [e.g., tremor, dystonia]).
- Patients have total hip arthroplasty (THA), which can cause substantial susceptibility artifact and degrade image quality of mpMRI.
- Patients have cardiac pacemaker, cochlear implants, neurostimulator, medical device which is unsafe at 3 Tesla, or foreign metallic body in the eyes or orbit.
- Patients have contraindication to gadolinium based MR contrast agents (e.g., renal failure, severe reaction to gadolinium based MR contrast agents). eGFR should be above 30 within 30 days the time of mpMRI.

4.3 Subject Recruitment, Enrollment and Screening

Subjects who are scheduled to undergo standard care of primary prostate cancer diagnosis and staging will be identified, informed about this study and referred to our study coordinator by urologists from their clinical practice schedule. C11-choline PET/MR imaging could be performed before and/or after routine clinical imaging.

4.4 Early Withdrawal of Subject

If a subject cannot finish the PET/MR imaging due to claustrophobia, he will be withdrawn. After PET/MR imaging, if a subject declines to undergo clinical evaluation and standard care of imaging, he will be withdrawn.

We plan to recruit a replacement subject in the event that a subject withdraws early to maintain the target number of 10 subjects.

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study if consent is withdrawn, if they no longer satisfy enrollment criteria or if they are unable to continue participation due to discomfort.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

The C-11 choline PET/MR data will be retained for potential future analysis. Data collected on study subjects up to the time of withdrawal will remain as part of the study in a secured database in order for the study to maintain scientific validity.

Regardless of enrollment status, subjects will be contacted to collect Day 2 follow up information. This information will be recorded in the case report form documentation.

5 Study Drug

5.1 Description

C-11 choline is identical to endogenous choline in the human body. Choline is a central molecule in cellular metabolism via the citric acid cycle (as acetyl CoA), in cell membrane fatty acid synthesis, and in gene expression regulation through acetylation of nuclear histones.

5.2 Treatment Regimen

A total of 12-14 mCi,(444-518 MBq) doses are dispensed. The doses are described based on the amount of radioactivity since the actual quantity of choline is in the micromolar range, as is true for many radiopharmaceuticals.

5.3 Method for Assigning Subjects to Treatment Groups

All study subjects will undergo the same protocol.

5.4 Preparation and Administration of Study Drug

Choline C11 Injection is prepared on site at the Mayo Clinic PET Radiochemistry Facility in Phoenix, AZ. Cyclotron produced C11-carbon dioxide is used as a precursor to generate C11-methyl iodide followed by C11-choline. All chemistry is performed using automated radiochemical synthesizers inside lead-lined hot cells.

Following quality control testing, the drug product is packaged in a 6 mL sterile shielded syringe containing approximately 12-14 mCi. .

5.5 Subject Compliance Monitoring

C-11 choline is only administered under direct supervision of study personnel.

5.6 Prior and Concomitant Therapy

None.

5.7 Packaging

The drug product is packaged in a 6 mL sterile syringe containing approximately 12-14 mCi of radioactivity. It is placed inside a lead syringe shield and labeled with the date, batch number, radioactive assay, drug product name, and the following statement “Caution: New Drug—Limited by Federal (or United States) law to investigational use”. It is then placed inside specially designed tungsten lined pneumatic tube capsule and sent to the PET imaging suite.

5.8 Masking/Blinding of Study

The interpreters of the imaging tests will be blinded to any patient information. However, the type of tracer and imaging approach will be apparent due to inherent differences in the techniques.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The drug product will be manufactured on the same campus as the imaging suite and will be delivered via pneumatic tube.

5.9.2 Storage

Choline C 11 Injection should be stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) (see USP Controlled Room Temperature). The solution should be used within 120 minutes of the end of synthesis calibration time.

5.9.3 Dispensing of Study Drug

The dosage administered will be recorded on the CRF.

5.9.4 Return or Destruction of Study Drug

After injection of the C 11 choline the syringe will be assayed for residual radioactivity, to be used in calculation of the precise injected dose. The syringe will then disposed of in the radioactive container for 3-4 hours, about ten half-life durations of C11-Choline (C11-Choline half-life of 20 minutes).

6 Study Procedures

Patients who have completed or will complete diagnostic body CT scan and nuclear medicine bone scan as part of standard care will be recruited and consented for participation in the study

PET/MRI is preferably scheduled 6 weeks after prostate biopsy to minimize the effects of post biopsy hemorrhage.

6.1 Day 0

Informed consent discussion with subject by research coordinator. Consent form signed by subject. Medical records will be reviewed by study coordinator. Subject's eGFR will be determined. If current serum creatinine level is unavailable, labs will be obtained for review.

Subject will be reminded to drink 48 ounces of water the day prior to study procedures. On the morning of the procedure, subjects will be counseled to fast for four hours prior to the procedure and drink 24 ounces of water.

6.2 Day 1

The patient will be screened for MR safety prior to entering the scan room, which may include the use of ferromagnetic screening.

1. Vital signs (sitting blood pressure, heart rate, respiratory rate, temperature) are measured by the radiology nurse, who records the results on the source document.

2. Investigator MD or research coordinator to see patient, review vital signs and discuss study objectives, explain the imaging procedures, answer questions. MD will sign and date the source document.

3. Subject is brought to the PET/MR imaging suite. Total dose of 12-14 mCi C-11 choline is injected I.V.

4. Torso PET/MR fusion scan is completed. Imaging time 20-30 minutes.

5. Pelvic mpMRI with PET data of pelvis completed. Imaging time 40-45.

6. Following completion of imaging, subject will return to the relax room and vital signs (sitting blood pressure, heart rate, respiratory rate and temperature) will be re-checked by

the radiology nurse, with the study coordinator recording the data in the source documents.

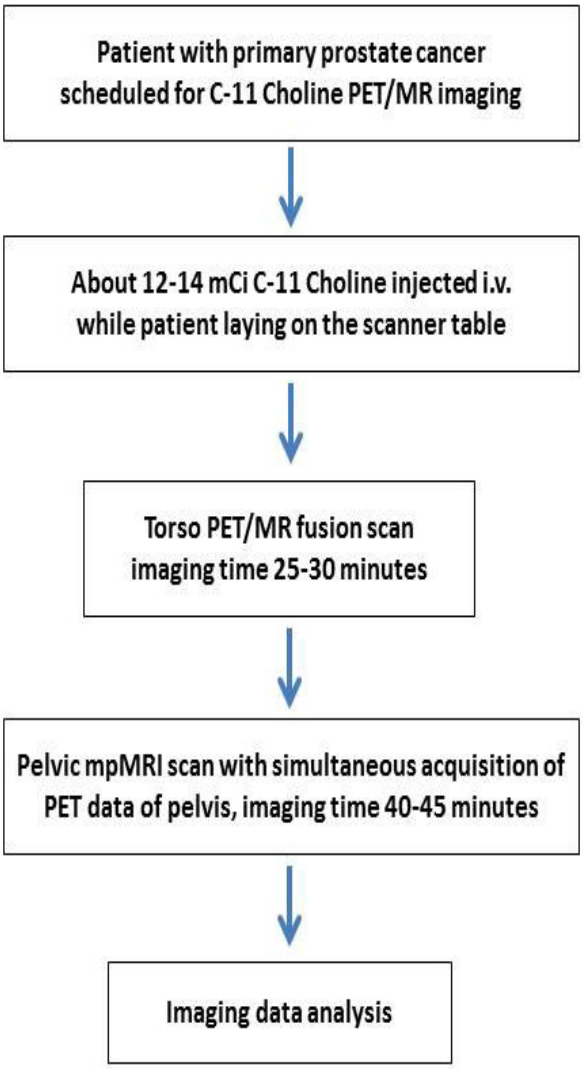
7. Subject will be discharged.

6.3 Day 2- Follow up Procedures

1. Research coordinator will call patient to ask if patient has experienced fever, shortness of breath, palpitations, headache or other symptoms. If any of the above have been experienced, investigator MD is immediately notified.

2. Investigator MD is notified of results by the research coordinator. MD will sign and date source document.

3. All pre-data analysis study data forms and consent are confirmed intact and in the study binder. Binder is kept in a secured file cabinet in the research coordinators office.


Patient with primary prostate cancer scheduled for C-11 Choline PET/MR imaging
About 12-14 mCi C-11 Choline injected i.v. while patient laying on the scanner table
Torso PET/MR fusion scan imaging time 25-30 minutes
Pelvic mpMRI scan with simultaneous acquisition of PET data of pelvis, imaging time 40-45 minutes
Imaging data analysis

6.4 Schedule of Events

Study Activity	Day 0	Day 1	Day 2 (follow up)
Informed consent	X		
Medical records review. Confirm study inclusion criteria. Data recorded on source document.	X		
Subject eGFR determined. Labs obtained if Current serum creatinine is unavailable.	X		
Vital signs prior to and following imaging sessions recorded on source document (sitting blood pressure, respiratory rate, temperature, heart rate)		X	
Torso PET/MR fusion scan		X	
Pelvic mpMRI (SOC)		X	
Adverse event evaluation. Results recorded on source document.		X	
Follow-up call to collect adverse events. Result recorded on source document.			X

7 Statistical Plan

7.1 Sample Size Determination

Our null hypothesis is the hybrid C11-choline PET/MR and pelvic multiparametric MRI will have an equal accuracy of detecting patients with malignant lymph nodes in the very high risk/high risk prostate cancer patients compared to that in the conventional CT and bone scan method. With 20 patients, a McNemar's test with a 0.05 two-sided significance level will have 82% power to reject the null hypothesis if the difference in accuracy of the two methods is 0.3 or greater and assume discordant pairs is expected to be 0.31.

7.2 Statistical Methods

Descriptive Statistics

Descriptive statistics will be used to describe the average time of the total procedure, patients' tolerance and satisfaction level about the procedure. Paired t-test will be used to compare the suspicious lymph nodes and suspicious osseous lesions in the pelvis and extrapelvic regions detected by hybrid C11-choline PET/MR and pelvic multiparametric MRI method and by conventional CT and bone scan to investigate if the new method is able to detect more lymph nodes and osseous lesions compared to the conventional method. Paired t-test will also be used to compare the average SUV of lymph nodes and osseous lesions in the pelvis and extrapelvic regions by new method with that by conventional method to investigate if the new method provided more clarity in terms detecting the lymph nodes and lesions compared to the old method. If the patients' biopsy and surgery results available, sensitivity, specificity, positive predictive value and negative predictive value of detecting malignant lymph nodes and osseous lesions by the new method and by conventional method will be estimated and compared using McNemar's test.

Handling of Missing Data

As the sample size is 20 and imaging is completed over one day, no missing imaging data is anticipated.

Multiplicity

In current project, there is one primary objective and we don't have to adjust for multiple comparison.

Interim Analysis

There will not be interim analysis for the study.

7.3 Subject Population(s) for Analysis

All-completed population: Only subjects who completed ALL study related procedures and follow-up will be included

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study treatment follow-up period is defined as the end of the day 2 follow-up phone call for the study (1 day following the last administration of study treatment). This phone call concludes the Adverse Event Reporting Period.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-

investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

Laboratory values associated with this study will be a part of the patient's clinical medical record, and clinically indicated. No follow up laboratory values will be obtained following imaging.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

The relationship of an AE to the Investigational Drug is a clinical decision by the sponsor-investigator (PI) based on all available information at the time of the completion of the CRF and is graded as follows:

1. **Not related:** a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.

2. **Unlikely:** a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. **Possible:** a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. **Probable:** a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.

5. **Definite**: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

8.3.2 Sponsor-Investigator reporting: Notifying the FDA

The sponsor-investigator will report to the FDA all unexpected, serious suspected adverse reactions according to the required IND Safety Reporting timelines, formats and requirements.

Unexpected fatal or life threatening suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 7 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Other unexpected serious suspected adverse reactions where there is evidence to suggest a causal relationship between the study drug/placebo and the adverse event, will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Any clinically important increase in the rate of serious suspected adverse reactions over those listed in the protocol or product insert will be reported as a serious suspected adverse reaction. This will be reported to the FDA on FDA Form 3500A no later than 15 calendar days after the sponsor-investigator's initial receipt of the information about the event.

Findings from other studies in human or animals that suggest a significant risk in humans exposed to the drug will be reported. This will be reported to the FDA on FDA Form 3500A, no later than 15 calendar days after the sponsor-investigators initial receipt of the information about the event.

8.4 Stopping Rules

Stopping rules not applicable as standard radiology safety procedures will be followed.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

8.5.1 Internal Data and Safety Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records

include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

Case report forms will be organized in a binder, maintained in a locked cabinet in the research coordinator's office.

Data Processing

Data will be analyzed via the statistical methods outlined in this protocol.

Data Security and Confidentiality

Patient identification codes will be used. A number will be assigned to all subjects and any published report will not identify subjects by name.

A study-specific REDCAP file will be utilized to consolidate and analyze data from the written CRFs and printed data from the EMR. The file will be a password protected within a secured folder with permissions limited to study staff. Several layers of permissions are required to access the study data. Patient-specific information will only be available on the written CRF. Only the patient number will be entered on the spreadsheet.

Data Quality Assurance

Data transcribed from the written CRFs or the EMR will be double checked by the study staff member on an ongoing basis during the study. The CRFs and EMR lab printouts will be kept in

the study binder. At the end of the study, the PI, Co-PI or a Co-investigator will again double check all data entered into the spreadsheet from the CRFs and printout EMR sheets for each subject to detect any transcription errors.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717, whichever is longer.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Principal Investigator will review study process, progress, and data security in conjunction with the research coordinator. Study progress will be reviewed on a weekly basis and documentation of this review will be recorded in the study review log, even when there are not irregularities or remedial measures which need to be taken. Study data will be reviewed throughout the study to ensure the validity of the data in addition to the protection of study subjects.

In order to assist the sponsor-investigator in complying with Food and Drug Administration regulations, the Mayo Clinic Office of Research Regulatory Support will provide assistance with clinical monitoring activities as a service for the sponsor-investigator. Clinical trial monitoring requires review of the study data generated throughout the duration of the study to ensure the validity and integrity of the data along with the protection of human research subjects.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure

the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This project will be financially supported by Department of Radiology, at Mayo Clinic in Arizona.

12.2 Subject Stipends or Payments

No stipends or payments will be provided to study subjects.

13 Publication Plan

We intend to submit the results of this pilot study for publication to nuclear medicine, molecular imaging, or oncology journals as is deemed justified by the results of the data analysis. P.I. Dr. Yang, in conjunction with Co-I Dr. Kawashima, will determine the best publication plan to pursue. Permission and agreement will be sought from each co-author attached to this project.

14 References

1. Siegel, R. L., et al. (2016). "Cancer statistics, 2016." CA Cancer J Clin 66(1): 7-30.
2. Turkbey, B., et al. (2010). "Prostate cancer: value of multiparametric MR imaging at 3 T for detection--histopathologic correlation." Radiology 255(1): 89-99.
3. Castellucci, P., et al. (2009). "Influence of trigger PSA and PSA kinetics on 11C-Choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy." J Nucl Med 50(9): 1394-1400.
4. Giovacchini, G., et al. (2010). "Predictive factors of [(11)C]choline PET/CT in patients with biochemical failure after radical prostatectomy." Eur J Nucl Med Mol Imaging 37(2): 301-309.
5. Mitchell, C. R., et al. (2013). "Operational characteristics of (11)c-choline positron emission tomography/computerized tomography for prostate cancer with biochemical recurrence after initial treatment." J Urol 189(4): 1308-1313.
6. Kitajima, K., et al. (2014). "Detection of recurrent prostate cancer after radical prostatectomy: comparison of 11C-choline PET/CT with pelvic multiparametric MR imaging with endorectal coil." J Nucl Med 55(2): 223-232.
7. Picchio M, et al. (2015). Imaging biomarkers in prostate cancer: role of PET/CT and MRI. Eur J Nucl Med Mol Imaging. 2015 Apr;42(4):644-55.
8. Reske, S. N., et al. (2006). "Imaging prostate cancer with 11C-choline PET/CT." J Nucl Med 47(8): 1249-1254.
9. Piert, M., et al. (2016). "18F-Choline PET/MRI: The Additional Value of PET for MRI-Guided Transrectal Prostate Biopsies." J Nucl Med 57(7): 1065-1070.
10. Tolvanen, T., et al. (2010). "Biodistribution and radiation dosimetry of [(11)C]choline: a comparison between rat and human data." Eur J Nucl Med Mol Imaging 37(5): 874-883.
11. Scattoni, V., et al. (2007). "Detection of lymph-node metastases with integrated [11C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: results confirmed by open pelvic-retroperitoneal lymphadenectomy." Eur Urol 52(2): 423-429.

i