PSMA Positron Emission Tomography (PET) and Magnetic Resonance (MR) Imaging in Gynecological Cancers

UW IRB Tracking # 2017-0456

NCT03302156

Principal Investigator:

Steve Cho, MD
University of Wisconsin, School of Medicine & Public Health
Department of Radiology

Co-Principal Investigators:

Elizabeth Sadowski, MD
University of Wisconsin, School of Medicine & Public Health
Departments of Radiology, Obstetrics and Gynecology

Lisa Barroilhet, MD
University of Wisconsin, School of Medicine & Public Health
Departments of Obstetrics and Gynecology

Funding Sponsor: UWCCC Imaging and Radiation Science Pilot Award

June 8, 2020

Protocol Revision History

Version Date	Summary of Revisions Made
15 FEB 2017	Original Version
07 APR 2017	Addition of a follow-up phone call 1-3 days post PET/MR imaging exam.
10 APR 2017	Revise biodistribution and radiodosimetry procedures for aim 1
02 MAY 2017	Updated statistics
17 OCT 2017	PET/CT replacing PET/MR for dosimetry studies; correcting imaging time; revising eligibility; make glucagon optional.
25 JAN 2018	Revise exclusion criteria to allow women with a history of cancer to participate.
10 July 2018	Revise inclusion criteria to allow women with a history of gynecological cancer, hysterectomy and/or salpingo-oophorectomy to participate; addition of blood and urine samples for dosimetry subjects
05 NOV 2019	Clarifications to dosimetry cohort; edits made for consistency in ^{18}F-DCFPyL dosing. The dose should be “less than 9 mCi”
08 JUN 2020	Revised blood collection for dosimetry subjects and removed the urine collection requirement. Revisions to the consenting process during the COVID-19 pandemic.

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse event
CAEPR	Comprehensive Adverse Events and Potential Risks
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DSMB/DSMC	Data Safety Monitoring Board/Committee
FDA	Food and Drug Administration
GE	General Electric
GFR	Glomerular filtration rate
HIPAA	Health Insurance Portability and Accountability Act
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
IV	Intravenous
IND	Investigational New Drug
kg	kilogram
MBq	megabecquerel
mCi	millicurie
mGy	milligray
mL	milliliter
mmol	millimole
MR	Magnetic Resonance
OB/Gyn	Obstetrics and Gynecology
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PI	Principal Investigator
PSMA	Prostate-specific member antigen
REM	Roentgen Equivalent Mammal
RF	Radio frequency
RPF	Radiopharmaceutical Production Facility
SAE	Serious Adverse Event
UP	Unanticipated Problem
UW	University of Wisconsin
UWHC	University of Wisconsin Hospital and Clinics

STATEMENT OF COMPLIANCE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

I agree to ensure that all staff members involved in this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Steve Y. Cho, MD

Signed: _____ Date: _____

Steve Y. Cho, M.D.
Department of Radiology, Nuclear Medicine Section
University of Wisconsin School of Medicine and Public Health
University of Wisconsin Carbone Comprehensive Cancer Center

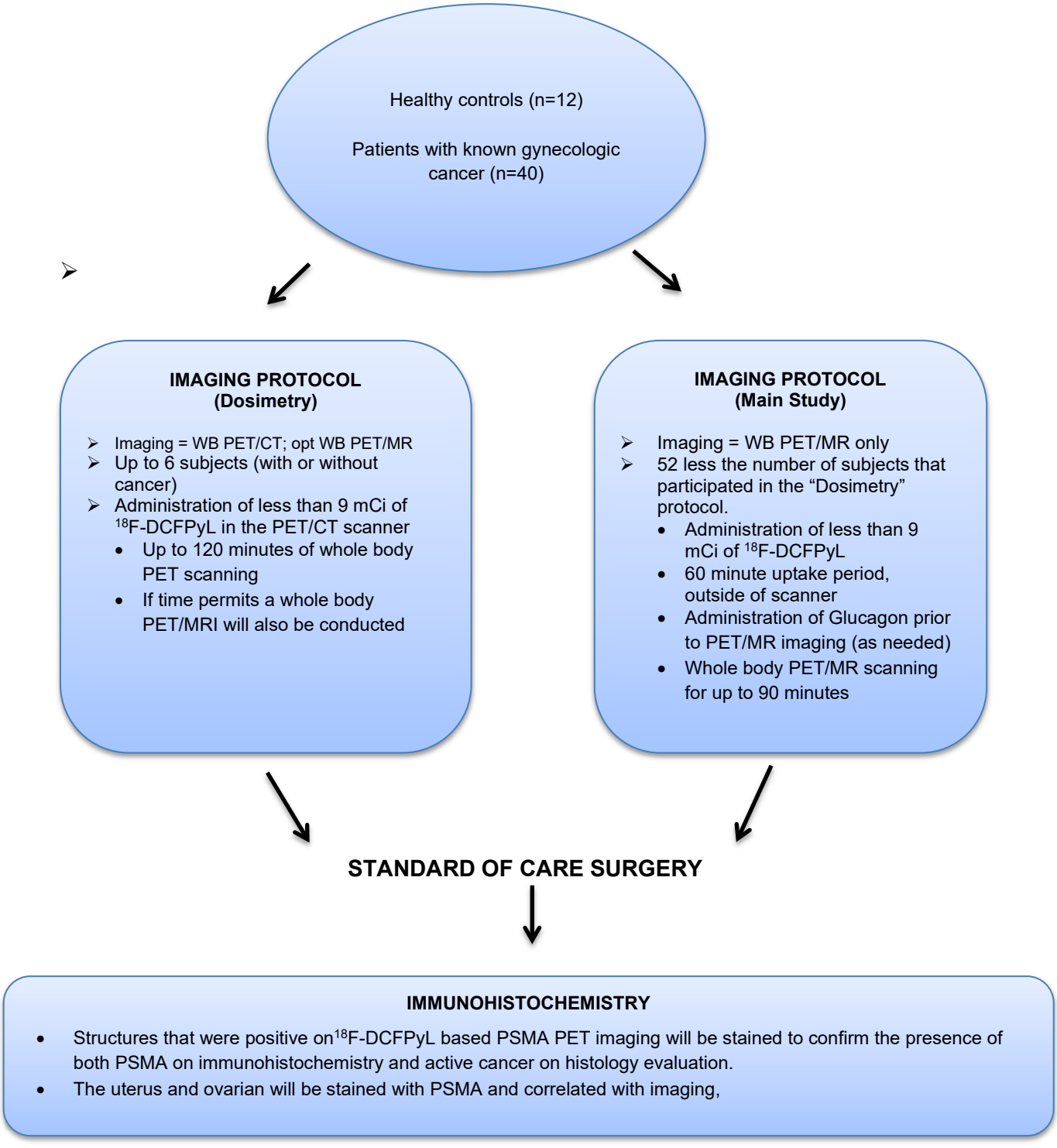
PROTOCOL SUMMARY

Title	PSMA PET and Magnetic Resonance (MR) Imaging in Gynecological Cancers
IND Sponsor-Investigator	Steve Y. Cho, MD
Co-Investigators	Elizabeth Sadowski, MD; Lisa Barroilhet, MD
Participating Site	University of Wisconsin-Madison
Patient Population	1. Adult women with known or suspected gynecological cancers who have had or are scheduled to undergo a hysterectomy and/or salpingo-oophorectomy. N=40 2. Normal controls: Women with no imaging evidence of gynecological cancer, who are undergoing hysterectomy and/or salpingo-oophorectomy. N=12 (includes up to 6 Dosimetry subjects) a. Dosimetry : Women with or without suspected gynecological cancer.
Accrual Objective	52 women
Study Design	Phase 2, single-center, open-label study
Study Duration	The estimated accrual period is over 3 years.
Primary Objective	The purpose of this research is to evaluate whether a novel imaging approach using PSMA-based ^{18}F-DCFPyL PET and MR imaging can: 1. Document the normal distribution of PSMA in the abdomen and pelvis on PET imaging. 2. Document the normal appearance of the fallopian tubes and ovaries on high resolution MR imaging 3. Accurately determine the presence or absence of cancer 4. Accurately identify the distribution of cancer
Specific Aims	1. To establish the biodistribution and radiodosimetry of PSMA-based ^{18}F-DCFPyL on PET imaging in normal female controls and in females with known or suspected cancer. 2. To determine the ability of PSMA-based ^{18}F-DCFPyL PET and MR imaging to detect cancer in women with known or suspected gynecologic malignancy and differentiating cancerous tissue from non-cancerous tissue. The performance of PSMA-based ^{18}F-DCFPyL PET imaging in the detection and localization of cancerous and non-cancerous tissue will be compared to the final surgical pathology reports and to the histological and immunostaining for PSMA positive cancerous tissue on pathology. 3. To determine the most accurate approach in assessing disease burden and location, assessment of tumor burden on both the PSMA-based ^{18}F-DCFPyL PET and MR imaging together, and then each modality separately will be performed and sensitivity, specificity, and accuracy values will be calculated.
Inclusion Criteria	• Women with no imaging evidence of cancer • Women with suspected or documented gynecological cancer and previously underwent or scheduled to undergo a hysterectomy and/or salpingo-oophorectomy • No contraindications for MR or PET imaging. • Greater than or equal to 18 years
Exclusion Criteria	• Women that are pregnant or breast feeding. • Age <18

	• Severe kidney dysfunction (GFR <30 mL/min/1.73m^2)
Treatment Description	^{18}F-DCFPyL whole body PET/CT or PET/MR scan
Study Procedures	• ^{18}F-DCFPyL whole body PET/CT imaging for dosimetry studies; PET/MR scan to achieve other aims • Review of relevant imaging and medical record information
Statistical Considerations	There are no formal hypothesis tests planned. Our primary goals are to: 1. Record the normal biodistribution and radiodosimetry of PSMA in the body 2. Record the frequency the normal fallopian tubes and ovarian are seen on high resolution MR imaging. 3. Record the distribution of PSMA in cancer tissue 4. Estimate the frequency with which PSMA PET and MR imaging and final IHC staining disagree in their classifications of presence of disease. We will classify each data point as either an agreement or disagreement between imaging findings and IHC staining. The proportion of disagreements across all time points will be estimated with an intercept-only GEE regression model that accounts for correlation among measures from the same patient. This proportion will be reported with a 95% confidence interval. The lower bound of this confidence interval will be used to help us decide whether this approach is worthy of future study. Based on this pilot study we plan to pursue further evaluation in larger more appropriately powered studies if the lower bound of the confidence interval excludes 20%, which is chosen as a guideline to determine whether the method shows promise.

SCHEMATIC OF STUDY DESIGN

Subject Populations



1.0 PROJECT SUMMARY:

The purpose of our proposal is to use PSMA PET and multi-parametric MR imaging, to detect the presence of gynecological cancer cells in the body. Imaging evaluation would include the appearance of normal ovaries/fallopian tubes, and cancerous tissue on different MR sequences and the distribution of PSMA in normal and pathological tissues on PET images. To determine the accuracy of the PSMA PET imaging localization in malignant tissues, PSMA staining of surgical pathology specimens will be used as the reference standard.

2.0 INTRODUCTION

Background:

The detection and distribution of cancer prior to definitive treatment is the standard of care currently [1]. Imaging plays a crucial role in this process of identifying possible areas of tumor prior to initiation of treatment [2]. Currently, imaging techniques used in clinical practice to visualize cancer mainly involve basic cross sectional anatomical imaging with or without intravenous contrast administration. These imaging techniques are limited by only providing "anatomical" information, and the diagnosis of cancer and normal tissue is partly determined by the location of the tissue. Imaging contrast agents can help visualize abnormalities, but currently cannot differentiate between malignant, inflammatory or fibrotic (scar) tissues. There have been major research advancements in functional imaging, which allow the physician to determine better what type of tissue is present in an anatomical location. Advanced PET and MR imaging techniques can evaluate the chemical composition and metabolic activity of different tissues [3, 4]. MR imaging can depict the composition of tissue (water, fat, blood and cellular) by imaging the molecules in the human body. PET imaging can depict whether or not tissue is metabolically active by imaging the injectable metabolic tracer which is taken up by different area or tissue types in the body. Knowing both the composition of the tissue and the metabolic fingerprint can help differentiate more accurately between non-cancerous and cancerous tissue types [5]. This in turns allows for more accurate cancer screening and pre-treatment staging, both which have been shown to improve outcomes in gynecologic cancer patients [1, 6]. ^{18}F-FDG PET imaging is widely used for cancer detection and staging, but can be limited due to nonspecific uptake at sites of inflammation. A more specific PET imaging agent for more specific tumor detection, particularly in gynecologic malignancy, would help meet an unmet clinical need.

PSMA, also known as folate hydrolase 1 andglutamate carboxypeptidasse II, is an enzyme associated with prostate cancer but has been also found to be expressed in the tumor neovasculature of many different types of non-prostate cancer tumors [7, 8]. The PSMA molecule can be bound to a PET radionuclide as an imaging agent, specifically, ^{18}F-DCFPyL, and this agent can be detected non-invasively using PET imaging. PSMA-based ^{18}F-DCFPyL PET demonstrates very high tumor-to-background ratio when studied in other tumors, including prostate tumors [9]. In prostate cancer, the agent has been shown to improve detection of prostate tumors and the amount of tumor present throughout the body (tumor burden). Similar high tumor-to-background uptake of PSMA-based PET imaging has been demonstrated targeting the tumor

neovasculature of non-prostate solid tumors (example: renal cell carcinoma and lung) with potential improved tumor specificity [10, 11]. There is growing evidence in the literature which demonstrates that correctly identifying the tumor burden allows the treating physician to tailor the treatment more specifically to the individual patient to assure all the cancer cells are treated [12]. Recently, an immunohistologic pathology study demonstrated PSMA is highly and specifically expressed in the tumor vasculature of ovarian and uterine tumor specimens [9]. This makes exploring PSMA as a potential functional imaging agent for ovarian cancer very intriguing.

MR imaging is a highly sensitive and specific imaging modality that can be used for gynecologic cancers. MR images can be obtained in conjunction with PSMA PET, adding additional anatomic and multi-parametric MRI information without the need for a second imaging appointment. Emerging data demonstrates that the inclusion of functional MR sequences, specifically diffusion weighted sequences, increases the sensitive and specificity of MR imaging in the detection of tumors, including metastatic cancer deposits [3, 5].

The overarching goals of this pilot study are to determine if imaging can depict PSMA ^{18}F-DCFPyL uptake in gynecological cancers seen on MR imaging, and to correlate both the PSMA PET and MR imaging with histological and immunologic staining of resected tumor specimens in women undergoing the standard of care surgical treatment of their gynecological cancers. If it is possible to see PSMA on acquired images, PSMA ^{18}F-DCFPyL could potentially be used for both screening and pre-treatment assessment of women with gynecologic cancers with improved sensitivity and specificity.

3.0 STUDY AIMS/STUDY OBJECTIVES

The primary outcome of this research is to evaluate whether a novel imaging approach using PSMA-based ^{18}F-DCFPyL PET and MR imaging can accurately determine the presence or absence of cancer, the accurate distribution of cancer and the normal biodistribution of PSMA in the abdomen and pelvis on PET imaging. The reference standard for the PSMA localization in cancerous tissue will be histologic and immunologic correlation on the pathologic specimens obtained at the time of standard of care surgical resection for treatment of the gynecological cancer. Specific aims for this research include the following:

1. To establish the biodistribution and radiodosimetry of PSMA-based ^{18}F-DCFPyL on PET imaging in normal female controls and in females with known or suspected cancer.

2. To determine the sensitivity, specificity, and accuracy values of PSMA-based ^{18}F-DCFPyL PET and MR imaging in the detection of cancer in women with known or suspected gynecologic malignancy and differentiating cancerous tissue from non-cancerous tissue. The performance of PSMA-based ^{18}F-DCFPyL PET imaging in the detection and localization of cancerous and non-cancerous tissue will be compared to the final surgical pathology reports and to the histological and immunostaining for PSMA positive cancerous tissue on pathology.

3. To determine the most accurate approach in assessing disease burden and location, assessment of tumor burden on both the PSMA-based ^{18}F-DCFPyL PET and MR imaging

together, and then each modality separately will be performed and sensitivity, specificity, and accuracy values will be calculated.

4.0 RESEARCH DESIGN AND METHODS:

Subject population

Fifty-two subjects will be enrolled in this research, 12 healthy controls and 40 patients with known or suspected gynecologic cancer. Up to 6 subjects will be used for the dosimetry portion. Eligibility requirements include the following:

Inclusion Criteria for healthy female controls N=12 (includes up to 6 Dosimetry subjects)

1. Women with no suspected gynecological cancer
2. No contraindications for MR or PET imaging
3. Greater than or equal to 18 years of age
4. Scheduled to undergo a hysterectomy and/or salpingo-oophorectomy

Inclusion Criteria for female controls (Dosimetry)

1. Women with or without suspected gynecological cancer
2. No contraindications for MR or PET imaging
3. Greater than or equal to 18 years of age

Inclusion Criteria for gynecologic cancer patients N=40

1. Women with known or suspected gynecological cancer
2. No contraindications for MR or PET imaging.
3. Greater than or equal to 18 years
4. Have had or are scheduled to undergo a hysterectomy and/or salpingo-oophorectomy

Exclusion Criteria

1. Women that are pregnant or breast-feeding.
2. Age <18
3. Inability to provide informed consent on their own behalf
4. Severe kidney dysfunction (GFR <30 mL/min/1.73m^2)

Subject identification and recruitment

Healthy controls will be recruited from UWHC OB/Gyn and Women's Health and PATHS clinics through referrals and from posted flyers. Healthy controls may also be recruited from the Department of Radiology Volunteer Database (2017-0004). Potential subjects will either be introduced to the research by someone involved in their care or they will be required to contact

the study team by phone or email. Those interested in participating will be scheduled for an initial visit to learn more about participation and to complete the informed consent process.

Gynecologic Oncology staff will identify cancer patients who meet the eligibility criteria and will introduce them to this research opportunity. Those interested will be referred to a study team member who will review the purpose of the research as well as details about participation.

Informed Consent and Subject Information

The consent process will occur either on a day prior to or on the day of but prior to the administration of research procedures. During the COVID-19 pandemic, consent procedures will be conducted by phone to minimize face-to-face contact subjects have with the research team. An encrypted copy of the consent form will be mailed or emailed to subjects prior to the scheduled consent phone call. A study team member will call potential subjects at the scheduled time to review the information in the consent form including study procedures, risks associated with participation, alternatives to participation and whom to contact for additional information. Any questions will be addressed during the course of the phone call and subjects will be encouraged to contact the study team with any questions or concerns they might have at any time. Upon completion of the consent process, subjects will be asked to return a copy of the signed consent form by either scanning the entire document and email back to the study team member or taking a photo of the signature page and emailing a copy to the study team member.

Once institutional requirements are met, remote consenting will continue by obtaining electronic signature using the DocuSign software platform.

Prior to the start of any research procedures and all subjects will be reminded that participation is optional and they can change their mind at any time.

5.0 STUDY PROCEDURES

Subjects will be asked to complete a single research visit that will include the administration of a PSMA PET/CT and/or PET/MR exam. Subjects participating in the PET/MR imaging studies will be screened for contraindications to MRI and MR contrast agents using the standard UWHC MR Safety screening form. A urine pregnancy test will only be done for women with childbearing capacity that are unable to verify their non-pregnancy status by self-report.

Aim 1. Biodistribution and radiodosimetry of PSMA-based ^{18}F-DCFPyL in normal female controls or cancer patients (Up to 6 subjects for non-dosimetryand 6 subjects for radiodosimetry (dosimetry)

The research visit is estimated to take 2-3 hours, which includes approximately 60-120 minutes of scanning time. Subjects will be asked to fast for 4 to 6 hours prior to the research visit and to stay well hydrated.

The remainder of the time will be preparatory for the scanning. An IV will be placed to allow injection of the PET tracerduring the exams.

Dosimetry Subjects: A less than 9 mCi dose of ^{18}F-DCFPyL radiotracer will be administered by slow IV push after subject has been positioned in the PET/CT scanner. The subject's imaging session will include multi-pass PET scans to allow for normal organ and tumor biodistribution for a total of 5 PET scans from the vertex of skull through mid-thigh. Initial low-dose CT will be followed by 4 PET scans (PET1 through PET4) lasting approximately 60 to 75 minutes (depending on the height of the patient). The subjects will be allowed to leave the table to void between the fourth and fifth (PET5) PET scans. The fifth PET/CT scan (PET5) is obtained with another low-dose CT scan to allow for CT attenuation correction followed by the PET scan starting at approximately 90 minutes after radiotracer administration to last up to approximately 30 minutes (again, depending on the height of the patient). If the PET/CT takes less than 120 minutes, the subject may undergo a PET/MR, as time allows.

Dosimetry Subjects Only - Blood Collection:

- Blood (5mL Purple top at each time point) will be collected at 3 time points, after the completion of the 2nd, 4th and 5th PET passes on the PET dosimetry PET/CT protocol. Blood will be collected for the first 3 subjects and as needed for the remaining 3 subjects.

- Blood and will be counted on a gamma counter after dilution to determine radioactivity on the same day as the scan. After radioactive decay overnight, blood will be disposed of as per routine biohazard.

Non-dosimetry subjects: An IV will be placed to allow injection of the PET tracer, MR gadolinium agent, and glucagon (if needed) during the exams. A less than 9 mCi dose of ^{18}F-DCFPyL radiotracer will be administered by slow IV push outside the scanner, after which, the subject will be required to sit quietly for 60 minutes to allow for adequate biodistribution of the tracer. The subjects will then be placed in the PET/MR scanner and will remain in the scanner for up to 90 minutes. After which, the whole body (defined in this protocol as base-of-skull to mid-thigh) PET and MR images will be obtained to include images post-intravenous gadolinium contrast. Glucagon (0.5mg-1mg, IV) may be administered by IV prior to the MR imaging if excessive bowel movement is seen on initial images. Glucagon is known to diminish bowel motion and improve MR image quality.

<u>Aims 2 & 3. Sensitivity, specificity, and accuracy values of PSMA-based ^{18}F-DCFPyL PET and MR imaging and assessment of tumor burden (40 subjects with known or suspected gynecological cancer).</u>

This research visit is estimated to take 2-3 hours. For subjects with gynecologic cancer, the subjects will be in the scanner for up to 90 minutes. The remainder of the time will be preparatory for the scanning. An IV will be placed to allow injection of the PET tracer, MR gadolinium agent, and glucagon (if needed) during the exams. Subjects will be asked to fast for 4 to 6 hours prior to the research visit and to stay well hydrated. There will be a 1-hour uptake period after IV administration of less than 9 mCi of ^{18}F-DCFPyL radiotracer by slow IV push. After which, the whole body (defined in this protocol as base-of-skull to mid-thigh) PET and MR images will be obtained to include images post-intravenous gadolinium contrast. Glucagon (0.5mg-1mg, IV) may

be administered by IV prior to the MR imaging if excessive bowel movement is seen on initial images. Glucagon is known to diminish bowel motion and improve MR image quality.

A member of the study team will follow-up with all subjects approximately 1 to 3 days, by phone, after their PET/MRI or PET/CT exam to inquire about delayed side effects. If the subject is experiencing any late occurring side effects, they will be asked to return to the research clinic for a follow-up exam.

All PET and MR hardware are FDA approved as are the PET and MR sequences to be used.

Histopathological, Immunologic Staining and Image Correlation

We will correlate the final surgical pathology report with the images to determine if all sites of disease were seen on PSMA PET and MR imaging. In addition to this, we will identify very specific sites (eg. Left obturator node; Right ovarian mass; etc) for PSMA immunologic staining pre-operatively by review of the imaging between the radiologist and the gynecologic oncology surgeon and the surgeon will make every attempt to send these PSMA specimens labeled and separate from the other specimens obtain during surgery.

The surgical pathology specimens will be processes per routine clinical protocol. The same tissue blocks used for routine pathological evaluation will be used for the immunolabeling of the PSMA in the TRIP lab. After the clinical processing is complete, the pathologist with choose the appropriate tissue block(s) for immunolabeling, which consumes only a minute amount of tissue. This process will in no way compromise patient care.

Review of Medical Records

Medical records will be reviewed to obtain medical history including physical exams, medications, laboratory tests, imaging results and any other information related to the diagnosing, treatment, or outcomes of subjects diagnosis.

Remuneration

Subjects will receive $100 as compensation for their participation in this study.

Study Withdrawal

Reasons for withdrawal or termination

Enrolled patients will be removed from the study in the following circumstances:

- The patient does not complete the imaging examinations per study protocol
- The subject withdraws consent
- Exclusion criteria are discovered after registration but prior to the research examinations
- The patient has a contrast reaction to the gadolinium based contrast agent utilized for the MRI
- The PI or co-investigators determine it is within the best interest of the subject to remove them from the research.

6.0 RISKS AND BENEFITS

PET:
Detailed organ dosimetry derived from four representative patients is included in the table below. Of note, the effective dose from ^{18}F-DCFPyL was 0.0165 mSv/MBq or 6.1 mGy (0.61 rem) for an injected dose of 370 MBq (10 mCi), or 5.49 mGy or 5.49 mSv (0.549 rem) for 333 MBq (9 mCi) which is the highest dose administered for this study.

Dosimetry:
Highest radiation dose was estimated for the kidneys (0.0945 mGy/MBq) followed by urinary bladder wall (0.0864 mGy/MBq), submandibular glands (0.0387 mGy/MBq) and liver (0.0380 mGy/MBq). The mean absorbed dose to the bone marrow was 0.01 mGy/MBq. In comparison to the published data on our first generation agent, ^{18}F-DCFBC, ^{18}F-DCFPyL shows significantly lower (under 50 %) doses in most radiosensitive organs such as the thymus, ovaries, red marrow and osteogenic cells. Less radiation dose was also measured in lower large intestinal wall, small intestine, stomach wall, lungs, muscle and skin. Radiation dose from the two radiotracers was similar (within +/-50 %) in the gallbladder wall, upper large intestinal wall, spleen, testicles, thyroid, and pancreas. Radiation dose from ^{18}F-DCFPyL was higher in the adrenals, kidneys, liver, pancreas, spleen, and bladder wall.

Organ	Absorbed Dose (mGy/MBq)
Adrenals	3.11E-02
Brain	2.19E-03
Breasts	4.57E-03
Gallbladder Wall	1.44E-02
Heart Wall	1.29E-02
Kidneys	9.45E-02
Lacrimal Glands	3.50E-02
Lens	1.25E-03
Liver	3.80E-02
LLI Wall	1.05E-02
Lungs	1.08E-02
Muscle	6.32E-03
Osteogenic Cells	9.58E-03
Urinary Bladder Wall	8.64E-02

Organ	Absorbed Dose (mGy/MBq)
Ovaries	8.89E-03
Pancreas	2.44E-02
Parotid Glands	2.68E-02
Red Marrow	1.04E-02
Skin	4.05E-03
Small Intestine	9.13E-03
Spleen	1.85E-02
Stomach Wall	1.16E-02
Submandibular Glands	3.87E-02
Testes	1.01E-02
Thymus	5.56E-03
Thyroid	8.56E-03
ULI Wall	1.67E-02
Uterus	1.15E-02

CT:
Low-dose CT imaging is used to provide attenuation correction for the PET scan and PET signal localization. The addition radiation dose associated with this imaging is approximately 1.0 rem or 10 mSv. For the dosimetry PET/CT scans, there will be two low-dose CT scans obtained for a total of approximately 2.0 rem or 20 mSy.

MR:

Because the MR scanner is comprised of a very strong magnet, the primary risk associated with MRI imaging is the risk of having ferrous metal in the body such as pins, rods, screws, pacemakers, etc.

Risks will be minimized by making subjects feel as comfortable as possible in the PET/MR scanner. They will be repositioned and provided with as much padding as needed. Subjects will be able to communicate with the imaging staff in the event they decide they cannot continue to lie still for the duration of the study, in which case the study procedure will be terminated. Potential subjects who are asked to participate in MR imaging will be screened for contraindications to MRI and gadolinium contrast.

Gadolinium based contrast agents: Gadobenate dimeglumine be administered according to a weight-based algorithm (0.1 mmol/kg), not to exceed 20 mL. The risks of administering a gadolinium-based agent are exceedingly low; common side effects may include headache, nausea, reaction at injection site, and vasodilatation (temporary widening of a blood vessel) that occurred in less than 3% of subjects. Other less-common side effects reported were bad taste in the mouth, skin rash, dizziness, or warm tingling or burning feeling on the skin.

Acute allergic reactions are extremely uncommon, far less common than occur with iodine-based contrast agents used in CT scanning. To treat unexpected contrast reactions, we maintain a fully up-to-date contrast reaction/resuscitation kit adjacent to our scanners in the UWHC Department of Radiology. The contrast reaction kit is identical to those used throughout our department to treat allergic reactions to iodinated contrast or gadolinium based contrast agents, and is fully stocked with all necessary medications to treat contrast reactions. Further, there is always an experienced radiologist who is trained in treating contrast reactions available within the UWHC during working hours, for this purpose.

There are no immediate benefits anticipated for the participants. This research has a long-term benefit of validating the feasibility of a PET/MR imaging technique with enhanced diagnostic, prognostic and treatment response monitoring capabilities. Ultimately, this trial may allow us to perform PET scans in a much shorter period of time and achieve better quantification.

Glucagon: Contraindications to glucagon include known hypersensitivity to the drug, known pheochromocytoma or insulinoma. Subjects that are diabetic will not be given this drug. The nurse administering glucagon will screen subjects for a history of diabetes prior to its administration. Glucagon is typically well tolerated and is rapidly metabolized with a half-life of approximately 8-18 minutes.

Blood Collection: The blood sample will be collected via IV. Subjects may experience some discomfort, minor bruising, bleeding, or inflammation in the area where the blood is drawn. They may also experience nausea, lightheadedness, or fainting associated with this blood draw. There is also a very small chance (less than 1%) of infection at the needle puncture site.

7.0 ADVERSE EVENTS AND SAFETY ISSUES

Definition of adverse events and potential risks: The term “adverse event” is defined in the International Conference on Harmonization Guideline for Good Clinical Practice as follows: “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not related to the medicinal (investigational) product”.

Medical conditions of a subject that exist prior to receiving the investigational imaging tracer will be recorded as medical history. After administration of the investigational imaging tracer, all new medical conditions are considered adverse events. Adverse events occurring in this trial will be recorded in data collection forms, regardless of whether or not they are thought to be associated with the investigational imaging tracer throughout the study period. However, the Investigator also will assess the possible relationship between the adverse event and the investigational imaging tracer.

For the purposes of this protocol, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding) that emerges or worsens relative to pre-imaging baseline. We anticipate minimal adverse effects or toxicity with the investigational imaging tracer ^{18}F-DCFPyL in this study.

Definition of Serious Adverse Events (SAE), SAE list: Any adverse drug experience, occurring at any dose that results in any of the following:

- Death
- Is life-threatening (an event in which the patient was at immediate risk of death; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires or prolongs inpatient hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and/or may require intervention to prevent one of the outcomes listed.

All other AEs will be treated as “non serious” and are described in the final study report. An SAE that is definitely, probably or possibly related to the investigational imaging tracer will be reported immediately (within 24 hours of its determination) by telephone or fax by the Principal Investigator.

AE Characteristics: Toxicity will be graded according to the NCI Common Toxicity Criteria (CTCAE), version 4.03 (Appendix A; which can also be accessed and downloaded via the website: http://ctep.cancer.gov/reporting/ctc.html. The Investigators will monitor the occurrence of adverse events during the course of each patient in the study. The Investigators need to assess whether there is a reasonable possibility that the study imaging agent caused or contributed to an AE using the following criteria as a guide:

- Definite: The adverse event is clearly related to the investigational agent.

- Probable: There is a clinically plausible time sequence between the onset of the AE and administration of imaging tracer. The AE is unlikely to be caused by the concurrent/underlying illness, other drugs, or procedures.

- Possible: There is a clinically plausible time sequence between the onset of the AE and administration of imaging tracer, but the AE could also be attributed to the concurrent/underlying disease, other drugs, or procedures. "Possibly" should be used when the administration of the study imaging tracer is one of several biologically plausible causes of the AE.

- Unlikely: The adverse event is doubtfully related to the investigational imaging tracer.

- Not Related: Another cause of the AE is the most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the AE and the investigational imaging tracer; and/or a causal relationship is considered biologically implausible.

If any adverse event is considered to be definitely, possibly or probably related to the investigational imaging tracer, that event will be followed until resolution or until it is deemed chronic or irreversible by the Investigator. If an event is unlikely or not related to the investigational imaging tracer, the event will not be reported.

All AE will be documented and recorded in the medical record and will include:

I. Specific reaction according to NCI Common Toxicity Criteria, version 4.0.

II. Duration of the reaction

III. Severity/grade according to NCI Common Toxicity Criteria, version 4.03. If the adverse event is not addressed by the Common Toxicity Criteria, the severity should be rated as mild (grade 1), moderate (grade 2), severe (grade 3), or life threatening (grade 4).

IV. Relation of reaction to study agent

V. Management of reaction, including any interruption or dose modification of the study drugs.

Event Severity: In addition to classifying an adverse event as serious or non-serious, the Investigator and/or designated personnel will grade the adverse event to describe The Maximum intensity of the event. Specific criteria for the intensity of adverse events are described in the Common Toxicity Criteria (CTC: National Cancer Institute). Investigators should follow these criteria for grading and reporting adverse events.

An event may be severe, but may not be serious (e.g., severe headache). The severity of an adverse event will be assessed by study personnel using their best clinical judgment and includes but is not limited to taking into account the patient's past history, the patient's chart, interviews with the patient and caregivers, and direct observation. The Investigator will also be asked to assess the possible relationship between the adverse event and the administration of the investigational imaging tracer.

Adverse Event Reporting: Per 21CFR312.32(c), all adverse events deemed both serious and unexpected associated with the use of the drug must be reported to the FDA and to all participating investigators as soon as possible and in no event later than 15 days.

The FDA will be notified of any unexpected fatal or life threatening experience associated with the drug as soon as possible but in no event later than 7 calendar days. The UW HS-IRB will be notified in accordance with posted institutional policy.

Adverse Events: Serious and Non Serious Adverse events will be recorded, regardless of whether or not they are thought to be related to the investigational imaging tracer. While all adverse events will be tabulated and reported in the study final report, serious adverse events will be reported in the course of the trial. Adverse events that meet criteria of a serious adverse event listed above will also be recorded and reported.

The Investigator will inform the IRB of all adverse events attributed to the investigational imaging tracer in accordance with posted institutional policy.

8.0 PRIVACY AND CONFIDENTIALITY PROTECTIONS

Research procedures will be conducted in private areas and we are only collecting the minimum amount of information necessary to conduct the study. No sensitive data (HIV status, illicit drug use) will be collected. Identifiable records will only be available to study team members.

Data are not being shared outside of UW except through publications, in which case the data do not identify individual subjects. Study data will be managed by Drs. Barriohlet and Sadowski. Data will not be placed on unencrypted laptop computers. Coded electronic data will be kept on the Obstetrics and Gynecology and Radiology Department secure network drives. A separate file linking codes to subject identity will be kept in the same manner, in a folder separate from study data. At the end of 7 years study data will be de-identified by destroying the link to identifiable

information. Until that time data will remain coded and the file linking codes to subject identity kept as well.

All imaging will be performed for research purposes only and will be given a unique study number that cannot be linked to the patients' medical records in any way. Imaging research images will be stored on PACS under this study number only. The investigators will have access to the patients' electronic medical records that are relevant to this study. Study records will be kept for seven years. Study data will be managed by the PI and co-PI.

Subject's identifiable information will be linked to a study code. The study code will be used to identify the subject and research images. Research images may be used in scientific presentations, but all images will be de-identified. The data will be stored on the Principal Investigator's (PI or co-PI) password protected computer in her locked office. The code will be stored separate from the data on the PI's computer in her locked office.

9.0 DATA AND SAFETY MONITORING

Safety monitoring of research protocols investigating novel PET tracers utilize a combination of tools. These are framed to provide adequate clinical trial oversight ensuring that the research team is complying with the conditions of IRB approval and FDA requirements. The tools enable frequent evaluations of study-related activities, identification of deviations or noncompliance with the conduct of the study or protocol, review of adverse events tracking and reporting, and review of drug production and accountability.

These tools include:

- Study visit checklists – Research Coordinators use study visit checklists to ensure that all study required procedures and processes are met before, during and after the subject has been seen. Items listed on these checklists include informed consent obtained, consent questions answered (and by whom), vitals recorded, medications reviewed, MR safety form, etc. These checklists are reviewed by the study coordinator and are signed off for each study subject by the coordinator monitoring the study to ensure that protocols are followed accurately and include limited variance from protocol.

- Safety monitoring – The safety monitoring of subjects enrolled in the research includes both internal and external safety checks governing the administration of ^{18}F-DCFPyL. Internal monitoring is performed by co-investigators and external monitoring by a team of four physicians with the appropriate broad clinical and technical. The internal monitoring plan includes a brief review of each subject visit after it occurs. In this regard, the study team will discuss data quality, ^{18}F-DCFPyL production and administration, and subject compliance and tolerance of research procedures.

  The external monitoring plan will be coordinated by the Department of Radiology Medical Imaging Research Support (MIRS) administrative team. MIRS is a working group that provides investigators with the support needed to conduct clinical research that uses imaging as an outcome measure. Members include a core administrative group

(physicians, scientists, imaging modality managers, regulatory and administrative support) and ad hoc members recruited when their expertise is required for the review/monitoring of a research project. MIRS administrative team in addition to a 4-person committee of physicians/scientists will meet annually with representatives from the research team, to discuss research progress, AE/SAE reports, as well as other data reports compiled by the study team. If an AE/SAE occurs, an ad hoc committee meeting will be organized to discuss whether the event is considered serious, whether it can be attributed to research procedures, whether it constitutes non-compliance on the part of the study team, and the plan for resolution and a future remediation plan.

As part of this plan, the monitor(s) will verify that:

- The rights and well-being of human subjects are protected
- Reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol, GCPs, applicable regulatory requirements, and guidelines for clinical research studies at the University of Wisconsin-Madison and its affiliates

10.0 STATISTICAL CONSIDERATIONS

The goals of this study are to 1) record the normal distribution of PSMA in the body, 2) record the frequency that the normal fallopian tubes and ovarian are seen on high resolution MR imaging, 3) record the distribution of PSMA in cancer tissue, and 4) estimate the sensitivity, specificity, and accuracy of PSMA PET and MR imaging.

12 healthy controls and 40 subjects with known gynecologic cancer will be enrolled in this pilot study. With final IHC staining as the “gold standard” in detection of cancer, we will estimate the sensitivity, specificity, and accuracy of PSMA PET and MR imaging. The sample size was chosen based on logistical and financial considerations. The table below shows the precision with which we will be able to estimate the sensitivity and specificity of PSMA PET and MR imaging.

Sensitivity/Specificity	Width of 95% CI
65%	31.1%
70%	29.9%
72.5%	29.3%
75%	28.5%
77.5%	27.7%
80%	26.5%
82.5%	25.5%
85%	24.1%

Based on this pilot study, we plan to pursue further evaluation in larger, more appropriately powered studies if sensitivity and specificity are at least 80%.

11.0 DRUG FORMULATION AND PROCUREMENT

Investigation Product

The investigational product will be obtained from the University of Wisconsin Radiopharmaceutical Production Facility (RPF). The RPF is located in the Wisconsin Institute for Medical Research Building. The FDA IND for this protocol will be cross-filed with the current Johns Hopkins University IND for 18F-DCFPyL, IND # 121064 to reference the Pharmacology and Toxicology, dosimetry, and Previous Human Experience sections of that IND.

Common Name: DCFPYL

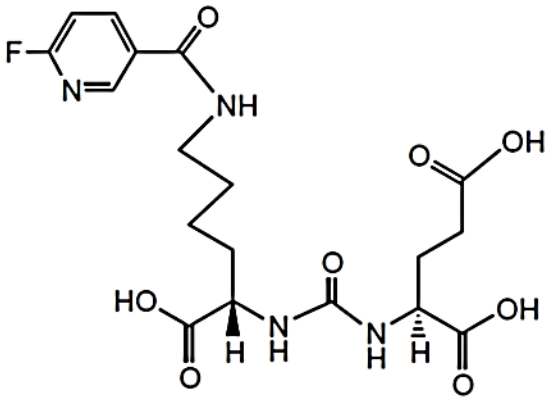
Chemical Names: 2-(3-{1-Carboxy-5-[(6-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid

Characteristics: hygroscopic white powder

Chemical Formula: $C_{18}H_{23}FN_4O_8$

C.A.S. Number: 1423758-00-2

Structure:



Molecular Weight: 442.40

Solubility: Soluble in DMSO, methanol, 1:1 acetonitrile:water

^{18}F-DCFPyL is eluted with 1 mL of ethanol followed by 10 mL of 0.9% sodium chloride, via a sterilizing 0.22μ filter into a sterile vial containing 4 mL 0.9% sodium chloride. Test radiopharmaceutical will be administered intravenously via slow I.V. push. The maximum mass dose of the ligand corresponding to the <9 mCi dose of ^{18}F-DCFPyL will be less than 3.98 μg per administration, although the actual dose will be significantly less depending on the specific activity achieved during each radiosynthesis run. The lowest limit for specific-activity (SA) we will use at the time of injection is 1000 mCi/μmole, although the validation and phase I study radiosynthesis SA was significantly higher than 1000 mCi/μmole.

Preclinical Toxicology

A toxicity report "*14-Day Study to Determine Toxicity of DCFPyL from a Single IV Dose in Sprague Dawley Rats*" was prepared by SoBran Inc. (Study No. SB-MP-001). The following summary is taken from that report.

The purpose of this study was to evaluate the toxicity of DCFPyL three and fifteen days following a single intravenous dose in rats. This study consisted of two test article treatment groups of ten male and female Sprague-Dawley rats per group dosed with DCFPyL at 0.1 and 0.5 mg/kg. An additional group of ten males and ten females received the vehicle, 5% Dextrose, and served as the control. All rats received a dose volume of 5 mL/kg. The rats were dosed intravenously once on Study Day 1. Five male and five female rats from each group were bled on Study Day 3 and the remaining rats were bled on Study Day 15. All animals were euthanized and necropsied following blood collection. Parameters evaluated for test article effect included survival, clinical observations, body weight, body weight gain, clinical pathology, gross pathology, organ weights, and microscopic pathology.

All rats survived to the scheduled termination and remained bright, alert and responsive during the study. No abnormal findings were indicated during cageside or hands-on observations. One female rat treated with the vehicle control and one female rat treated with 0.1 mg/kg DCFPyL lost weight between Days 8 and 15. All rats treated with 5% Dextrose or DCFPyL gained weight during the course of the study. There were no treatment related changes seen in the hematology, coagulation, or clinical chemistry data. Organ weights showed some variance but microscopic findings in the Day 3 and Day 15 rats were considered incidental and not directly related to the test article. Under the conditions of this study, there were no treatment related findings in Sprague Dawley rats three or fifteen days after a single intravenous dose of DCFPyL at 0.1 mg/kg and 0.5 mg/kg.

Organ	30 min	60 min	120 min	240 min
Blood	1.53 ± 0.19	0.24 ± 0.05	0.43 ± 0.37	0.03 ± 0.01
Heart	0.68 ± 0.07	0.20 ± 0.11	0.06 ± 0.01	0.02 ± 0.00
Lung	1.91 ± 0.47	0.55 ± 0.17	0.18 ± 0.02	0.06 ± 0.00
Liver	3.88 ± 0.74	2.87 ± 0.92	2.14 ± 0.11	1.80 ± 0.39
Stomach	1.50 ± 1.12	0.35 ± 0.34	0.08 ± 0.03	0.02 ± 0.00
Pancreas	1.02 ± 0.53	0.26 ± 0.13	0.08 ± 0.00	0.03 ± 0.01
Spleen	7.59 ± 3.56	2.70 ± 1.28	0.69 ± 0.11	0.23 ± 0.09
Kidney	74.1 ± 6.6	42.3 ± 19.0	15.7 ± 3.3	7.42 ± 0.89
Muscle	0.39 ± 0.05	0.61 ± 0.92	0.04 ± 0.00	0.05 ± 0.05
Bone	0.82 ± 0.16	0.42 ± 0.15	0.33 ± 0.08	0.43 ± 0.06
sm. Intest	0.79 ± 0.11	0.31 ± 0.12	0.11 ± 0.07	0.05 ± 0.01
lrg. Intest	0.73 ± 0.04	0.40 ± 0.17	0.12 ± 0.05	0.06 ± 0.01
Bladder (empty)	18.6 ± 18.1	9.88 ± 4.92	6.44 ± 4.42	1.54 ± 1.79
PSMA+ PIP	46.7 ± 5.8	44.2 ± 9.7	39.4 ± 5.4	36.6 ± 4.3
PSMA⁻flu	1.17 ± 0.41	0.36 ± 0.14	0.11 ± 0.02	0.03 ± 0.01
PIP/flu	40	123	358	1220

[a]Values are in% ID/g SD; $n = 4$.

^{18}F-DCFPyL was assessed for its ex-vivo pharmacokinetics in non-obese diabetic severe-combined immunodeficient (NOD-SCID) mice bearing both PSMA positive PC3-PIP and PSMA negative PC3-flu xenografts. Table below shows the percent injected dose per gram of tissue (%ID/g) of ^{18}F-DCFPyL activity in selected organs.

^{18}F-DCFPyL PSMA-dependent uptake within PSMA positive PC3 PIP xenografts, reaching a value of 46.7 ± 5.8%ID/g at 30 minutes post-injection (p.i.), which decreased by only about 10% over the ensuing 4 hours. At 60 minutes p.i. the kidney, liver, and spleen displayed the highest uptake. By that time, the urinary bladder also showed relatively high uptake. However, that uptake includes excretion at all-time points. Rapid clearance from the kidneys was shown, decreasing from 74.1 ± 6.6%ID/g at 30 minutes to 7.4 ± 0.9%ID/g at 4 hours. The relatively high values noted in kidney are partially due to high expression of PSMA within proximal renal tubules. The ratio of uptake within PSMA positive PIP to PSMA negative flu tumors ranged from 40:1 to more than 1,000:1 over the 4-hour time period of the study. A possible explanation for that increased tumor uptake of radiochemical over time could be due to ligand-mediated PSMA internalization within tumor cells. Less retention in kidney relative to tumor over time could be due to a lower degree of internalization in this (normal) tissue and/or different metabolism of ^{18}F-DCFPyL, which does not promote retention of radiochemical in kidney. Relatively low bone uptake (<1% ID/g at all-time points) suggests little metabolic defluorination of ^{18}F-DCFPyL. The total effective dose for 333 MBq (9 mCi) of ^{18}F-DCFPyL was calculated to be 5.93 mGy (0.593 rem) based on animal models.

Initial Phase I Study Adverse Events:
An initial phase I study of the biodistribution and dosimetry of ^{18}F-DCFPyL found that in nine patients there were no severe adverse events. One patient reported two adverse events that were classified as unlikely to be attributable to the radiotracer (mild headache and mild nose bleed, both of which resolved without treatment and were considered Grade I by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0). Another participant experienced a decrease in platelet count on routine assessment during the post-imaging follow up which, at the time of publication, had not resolved but which was attributed to the participant starting treatment for prostate cancer. This was also a NCI CTCAE Grade I adverse event. There were no radiotracer-related adverse events with monitored heart rate or blood pressure.

Human dosimetry: 18F-DCFPyL human dosimetry reported in Risks/Benefits section.

12.0 REFERENCES

1. Elattar, A., et al., *Optimal primary surgical treatment for advanced epithelial ovarian cancer.* Cochrane Database Syst Rev, 2011(8): p. Cd007565.
2. Mohaghegh, P. and A.G. Rockall, *Imaging strategy for early ovarian cancer: characterization of adnexal masses with conventional and advanced imaging techniques.* Radiographics, 2012. **32**(6): p. 1751-73.
3. Lee, S.I., O.A. Catalano, and F. Dehdashti, *Evaluation of gynecologic cancer with MR imaging, 18F-FDG PET/CT, and PET/MR imaging.* J Nucl Med, 2015. **56**(3): p. 436-43.
4. Sala, E., et al., *The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know.* Radiology, 2013. **266**(3): p. 717-40.
5. deSouza, N.M., A. Rockall, and S. Freeman, *Functional MR Imaging in Gynecologic Cancer.* Magn Reson Imaging Clin N Am, 2016. **24**(1): p. 205-22.
6. Jacobs, I.J., et al., *Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial.* Lancet, 2016. **387**(10022): p. 945-56.
7. Kinoshita, Y., et al., *Expression of prostate-specific membrane antigen in normal and malignant human tissues.* World J Surg, 2006. **30**(4): p. 628-36.
8. Silver, D.A., et al., *Prostate-specific membrane antigen expression in normal and malignant human tissues.* Clin Cancer Res, 1997. **3**(1): p. 81-5.
9. Lindenberg, L., P. Choyke, and W. Dahut, *Prostate Cancer Imaging with Novel PET Tracers.* Curr Urol Rep, 2016. **17**(3): p. 18.
10. Shetty, D., et al., *Elevated 68Ga Prostate-Specific Membrane Antigen Activity in Metastatic Non-Small Cell Lung Cancer.* Clin Nucl Med, 2016. **41**(5): p. 414-6.
11. Rowe, S.P., et al., *Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted (1)(8)F-DCFPyL PET/CT.* Ann Nucl Med, 2015. **29**(10): p. 877-82.
12. Barbieri, C.E., et al., *The Emergence of Precision Urologic Oncology: A Collaborative Review on Biomarker-driven Therapeutics.* Eur Urol, 2016.
13. Cho, Steve, et al., *Biodistribution, Tumor Detection, and Radiation Dosimetry of 18F-DCFBC, a Low-Molecular-Weight Inhibitor of Prostate-Specific Membrane Antigen, in Patients with Metastatic Prostate Cancer.* JNM, 2012. **53**: p.1883-1891
14. Szabo, Z., et al. *Initial Evaluation of [18F]DCFPyL for Prostate-Specific Membrane Antigen (PSMA)-Targeted PET Imaging of Prostate Cancer.* Molecular Imaging and Biology, 2015.