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Study Title:

Dual-Tracer Theranostic PET

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Imaging radiopharmaceuticals to be used:

- Fluorine-18 fluorodeoxyglucose (FDG)
  - ANDA # 204498
- Copper-64 dotatate (Cu64 DOTATATE)
  - Detectnet™
- Gallium-68 dotatate (Ga68 DOTATATE)
  - NETSPOT™
- Gallium-68 PSMA-11 (PSMA)

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the course of the study must first be approved by the IRB prior to implementation except when such notification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

Note: This document is signed electronically through submission and approval by the Principal Investigator in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system.

1.0 STUDY PURPOSES AND OBJECTIVES

This study is designed to obtain positron emission tomography with x-ray computed tomography (PET/CT) scan data according to the Specific Aims of Small Business Innovation Research (SBIR) grant 2R44CA257522 from the National Cancer Institute (PI=Kadrmas; consortium between MultiFunctional Imaging LLC and HCI). PET/CT exams will be acquired for three pairs of radiopharmaceuticals: FDG + Cu64-DOTATATE and FDG + Ga68-DOTATATE in patients with known or suspected neuroendocrine tumors; and FDG + Ga68-PSMA-11 in patients with known or suspected prostate cancer. All of these radiopharmaceuticals are FDA approved, and each radiopharmaceutical will be used according to its approved indications for use. The study data will be used by the sponsor company, MultiFunctional Imaging LLC (MFI) according to the aims of the grant to develop new techniques and algorithms for simultaneous dual-tracer PET imaging of these tracer pairs. **The overall objective is to obtain scan data for developing new techniques and algorithms for simultaneous dual-tracer imaging of these tracer pairs with PET**.

The PET scans will be acquired using specially-designed "multi-timepoint" scanning sequences that acquire more images than would be obtained in routine standard of care PET/CT scans. The study will be performed over three Arms. Each Arm will acquire separate, single-tracer scans of two tracers on separate days in each subject, and the 2nd tracer used for each Arm will differ as follows:

- Arm 1 = FDG and Cu64-DOTATATE PET/CT exams in 15 subjects with known or suspected neuroendocrine tumors (NETs);
- Arm 2 = FDG and Ga68-DOTATATE PET/CT exams in 15 subjects with known or suspected NETs; and
- Arm 3 = FDG and Ga68-PSMA PET/CT exams in 20 subjects with known or suspected prostate cancer with suspected metastasis or recurrence.

The PET/CT exams will be acquired at HCI, and the visual and semi-quantitative image assessments described in Section 5.0 will also be performed at HCI. The resulting images and assessment results will be de-identified and delivered to MFI, where the images will be analyzed and used for the Specific Aims of the research grant, including the analyses described in Section 6.0. Here, the separate-scan images obtained in each Arm will be combined to "synthesize" corresponding simultaneous dual-tracer images—enabling development and testing of various simultaneous dual-tracer processing algorithms, where the original single-tracer images provide "gold standard" references for recovering individual-tracer images from the combined dual-tracer ones. This is a well-established approach for developing rapid dual-tracer PET techniques [1-13], and in essence it allows for the data to act as their own controls.

This study is funded by National Cancer Institute grant 2R44CA257522, and it will be performed as part of a consortium agreement between MFI and the University of Utah under that grant. The overall goal is to develop techniques and algorithms for simultaneous dual-tracer imaging of these tracer pairs. This requires sets of dual-tracer PET data acquired using specially-designed multi-timepoint acquisition protocols that facilitate the development and study of simultaneous

dual-tracer PET imaging techniques. New algorithms for processing dual-tracer PET images will be developed and tested using these data. These algorithms are not part of any medical device, and the approach of using multi-timepoint dual-tracer PET scanning is novel and requires the development of new algorithms to process these data and recover individual-tracer PET images.

It is important to note that the primary goal is to develop new technologies, *not* to investigate the clinical value of the PET tracers being used. Indeed, all four PET tracers are FDA approved and will be used within their approved indications for use. Also note that this study is *not* an NIH-defined clinical trial. This distinction is clearly identified in the R44 grant application (PHS Human Subjects section; Clinical Trial Questionnaire: the study is *not* "designed to evaluate the effect of the intervention on the participates" and does *not* "evaluate a health-related biomedical outcome"). *I.e.*, the study is *not* designed to evaluate the efficacy of the PET tracers being used. Instead, the study is designed to develop new dual-tracer PET imaging techniques and evaluate whether or not individual-tracer PET images can be recovered from simultaneous dual-tracer PET scans.

1.1. Primary Objective

The primary objective is to obtain PET/CT imaging data suitable for developing new simultaneous dual-tracer PET techniques and processing algorithms for dual-tracer imaging of FDG + Cu64-DOTATATE, FDG + Ga68-DOTATATE, and FDG + Ga68-PSMA-11 PET/CT.

1.2. Secondary Objective

The data obtained may also provide insight into the combined value of dual-tracer PET/CT images with these tracers. The secondary objective of the study is to preliminarily assess the combined value of dual-tracer images with these tracers as compared to single-tracer images. The relative uptake of each tracer in tumors will be assessed to determine the potential for improved detection sensitivity and specificity for dual-tracer imaging as compared to single-tracer imaging. This secondary objective is <u>exploratory</u> in nature, and may result in preliminary data suitable for designing subsequent hypothesis-driven research studies in this area.

2.0 <u>BACKGROUND</u>

2.1. Dual-Tracer PET Technologies and MFI

MultiFunctional Imaging LLC (MFI) is a University of Utah spinoff company that is investigating technologies patented at the University for rapidly imaging multiple PET tracers in a single scan. Under research grant 2R44CA257522, MFI is investigating novel techniques for simultaneously imaging several tracer pairs. These include simultaneous imaging of FDG + Cu64-DOTATATE and FDG+ Ga68-DOTATATE for NETs, and of FDG + Ga68-PSMA for prostate cancer. The rationale for imaging these tracer combinations is provided below. The proof-of-concept for the new simultaneous dual-tracer PET techniques was established under a previous Phase I grant. The current Phase II grant will study the new simultaneous dual-tracer PET techniques in depth,

develop new algorithms for processing simultaneous dual-tracer PET images, and evaluate how well these algorithms can recover individual-tracer images from simultaneous dual-tracer PET datasets.

The clinical research study described by this protocol is designed to obtain dual-tracer PET/CT imaging data with each tracer pair according to the Specific Aims of the grant, providing the imaging data needed to develop new simultaneous dual-tracer imaging techniques and processing algorithms for these tracer pairs. The study design uses established physics/engineering principles, and it is based on two decades of research and development in dual-tracer PET by the investigators.

2.2. Theranostic Tracers and Dual-Tracer PET/CT

2.2.1. Value of Imaging Two Tracers

While FDG remains the primary workhorse tracer for general PET cancer imaging, a number of other PET tracers have recently received FDA approval and are experiencing increased utilization. Of particular importance are *theranostic* radiopharmaceuticals (*e.g.* PSMA, DOTATATE), which are PET tracers with therapeutic analogs that can predict radiotherapeutic efficacy. Since different PET tracers reveal different aspects of tumor function, concurrently imaging *multiple* PET tracers in each patient provides more complete diagnostic information imaging just single tracers. Such multi-tracer imaging can greatly improve the utility of PET for diagnosing and characterizing a variety of malignant tumors; it can improve staging and grading; and moreover it can provide improved image-guided selection of the most effective targeted therapies in individual patients when using combinations that include theranostic tracers.

2.2.2. Dual-Tracer Imaging of FDG + Theranostic Tracers

Several theranostic PET tracers have recently received FDA approval, including Cu64 DOTATATE (Detectnet™) and Ga68 DOTATATE (NETSPOT™) for localization of somatostatin receptor positive neuroendocrine tumors (NETs) [14-53], and Ga68 PSMA for imaging PSMA-positive lesions in men with prostate cancer [54-84]. Uptake of these theranostic tracers can predict response to targeted radionuclide therapy with Lu177-DOTATATE or Lu177-PSMA, respectively, and PET imaging with these tracers may be prerequisite before starting such therapies. However, diagnostic performance of these tracers varies with tumor grade. DOTATATE and PSMA provide high sensitivity for well-differentiated tumors, but they also experience low uptake in poorly-differentiated tumors. FDG, on the other hand, provides higher sensitivity for poorly-differentiated tumors and enhanced grading information. Combined dual-tracer imaging could improve sensitivity and staging over either tracer alone. It could enable improved grading by comparing the relative uptake of the two tracers (well-differentiated tumors will have high DOTATATE/PSMA uptake and low FDG update; and *vice versa* for poorly-differentiated, high-grade tumors). In addition, it could provide a more powerful means of predicting response to targeted radionuclide therapy, with uptake of the theranostic tracer predictive of response, but uptake of FDG being contraindicative.

2.2.3. FDG, DOTATATE, and Neuroendocrine Tumors

Neuroendocrine tumors, including gastrointestinal NET, pancreatic NET, pulmonary carcinoids, and other rare NET, have an annual incidence of about 5 per 100,000 in the US. Symptoms can be vague, diagnosis is often made at an advanced stage, and selecting the optimal treatment strategy is challenging. Patients with high uptake of DOTATATE (or other SSTR PET tracers) typically have a more indolent tumor and are more amendable to treatment with Lu177 DOTATATE (Lutathera™), while those with high FDG uptake are more aggressive and are best treated by other methods. Combined imaging of FDG and SSTR tracer avidity has previously been proposed for optimal characterization of NETs [34]. Current approaches use biopsies of the initial tumor to assess differentiation status of tumor cells, and then subsequently prescribe either DOTATATE or FDG imaging for well-differentiated and poorly-differentiated tumors, respectively. However, biopsies provide limited sampling, different groups of cells may exhibit different levels of differentiation, and tumors may initially present as well-differentiated but undergo transformation into higher grade over time with the development of treatment resistance [85]. NETs may also exhibit different degrees of differentiation *simultaneously* in the same patient. Combined imaging of FDG+DOTATATE can provide high sensitivity for both well- and poorly-differentiated NETs, improve staging and grading, and provide more accurate prognosis, and predicting effectiveness of targeted radionuclide therapy [26, 32, 86, 87]. Chan *et al.* [35] state *"it is clear that the time has come to think about FDG and SSRI in metastatic NET not as competitors but as complementary imaging modalities".* Proposed dual-tracer "NETPET scores" [34] and three-scale combined grading system [17] also highlight the need for combined dual-tracer FDG+DOTATATE of NETs.

There are currently 3 DOTA-conjugated peptide PET tracers with FDA approval for localization of somatostatin receptor positive NETs: Cu64-DOTATATE, Ga68-DOTATATE, and Ga68-DOTATOC [16, 20, 26, 27, 38, 48, 49, 88-93]. Each experiences similar uptake and distribution in the body, but have different radioisotopes: Cu64 ($T_{1/2}$=12.70h, cyclotron-produced, centrally distributed [94, 95]) *vs.* Ga68 ($T_{1/2}$=67.71m, generator-produced locally). We include both Cu64 DOTATATE (Arm 1) and Ga68 DOTATATE (Arm 2) in this study.

2.2.4. FDG, PSMA, and Prostate Cancer

An analogous situation exists for FDG + PSMA imaging of prostate cancer. Prostate cancer is the 2nd most common cancer in American men, with 248,530 new cases and 34,130 deaths in 2021 [cancer.org]. PSMA PET offers high sensitivity in well-differentiated tumors, and PSMA uptake is predictive of response to Lu177-PSMA therapy. Conversely, high FDG uptake in a tumor site indicates high-grade poorly-differentiated tumor, and suggests that Lu177-PSMA therapy may not be effective [96]. Again, dual-tracer FDG+PSMA imaging would provide higher sensitivity over all tumor grades and better staging than either tracer alone; it would provide enhanced grading using relative FDG:PSMA tracer uptake ratios; and it would provide improved prediction of response for Lu177-PSMA over all tumor sites.

Ga68-labeled PSMA-11 (PSMA) received FDA approval in Dec. 2020, and will be used for this study. A closely-related tracer, F18-PSMA, is also FDA approved; however, as an F18-labeled tracer, it has the radioactive half-life as FDG and would require different signal-separation approaches for dual-tracer imaging with FDG. As such is not included in this study.

2.2.5. Challenges of Dual-Tracer Imaging

Currently, obtaining FDG & DOTATATE or FDG & PSMA PET images in a given patient requires that separate scans be performed on separate days to allow for radioactive decay of the first tracer before imaging the second. This requires the patient to go to the imaging center twice (particularly burdensome for patients who must travel to reach the clinic), repeat pre-scan procedures, and undergo separate PET exams—each with its own CT component and associated radiation exposure. The time, logistical challenges, expense, and undue patient burden associated with bringing a patient back for separate PET scans on separate days has generally blocked patients from receiving both FDG and DOTATATE or PSMA PET/CT scans—especially considering that they also typically undergo other diagnostic procedures in the short time window before starting treatment.

The ability to image both tracers *simultaneously* in a *single* PET/CT exam would greatly improve the patient experience, require only a single trip to the imaging center, simplify scheduling demands, and reduce overhead. It would also reduce technologist workload: the patient would only need to be positioned once; only one CT scan would be needed for PET attenuation correction (thereby reducing radiation exposure to the patient). In addition, the images would be 'natively' co-registered since the patient remains ~motionless on the imaging table for all scans (frame-by-frame image co-registration may still be required in the event of patient motion while scanning). Simultaneous dual-tracer imaging would also benefit the imaging clinic by greatly increasing throughput and improving utilization of the PET/CT scanner resource.

2.2.6. Simultaneous Dual-Tracer Imaging Technique

These obstacles can be overcome by simultaneous dual-tracer imaging, where two tracers are administered to the patient and imaged in a single scan. The resultant dual-tracer images would then be processed to recover separate (corrected) images of each tracer. MFI has previously studied patented techniques for rapid *sequential* dual-tracer PET imaging. Under the prior Phase I project, a number of scanning approaches were studied for FDG+DOTATATE and FDG+PSMA imaging, ranging from a simultaneous multi-timepoint scans to sequential back-to-back dynamic scans with each tracer, and evaluated the feasibility and tradeoffs of each. It was found that these tracer pairs could potentially be accurately and robustly recovered from *simultaneous* multi-timepoint imaging as shown in Fig. 1. Here T1-T3 represent multi-timepoint "whole-body" (typically eyes-to-thighs) passes, providing images at 3 timepoints. Proprietary "signal-separation" algorithms at MFI utilize differences in radioactive decay and late tracer kinetics between tracers in order to process the dual-tracer images and recover separate (corrected) images of each tracer. Notably, the imaging characteristics of Cu64 DOTATATE, Ga68 DOTATATE, and PSMA *with respect to* simultaneous imaging with FDG are very similar, and the same signal-separation algorithms and processing can be used. As such, it is efficacious to include all three of these tracer pairs in this study.

If successful, this research will demonstrate the first-ever technique for simultaneous (not sequential) dual-tracer PET imaging of tracer pairs that are being used clinically.

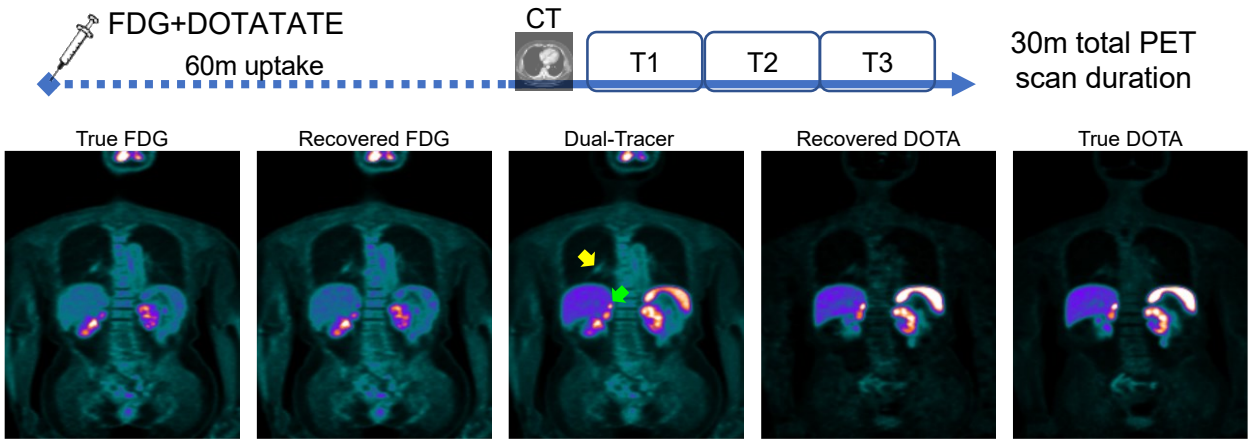


Figure 1. Simultaneous FDG+DOTATATE scan protocol (top) and example FDG and DOTATATE images for 30m simultaneous scan (bottom). The recovered FDG and DOTATATE images closely match the true images, with areas of focal uptake (arrows) effectively (but not perfectly) recovered for each tracer.

3.0 SAFETY and RADIATION DOSIMETRY

3.1. Safety

The following information was obtained from the FDA approved labels for each PET radiopharmaceutical.

3.1.1. FDG Contraindications, Warnings and Precautions, Adverse Reactions, and Use

FDG Contraindications and Use in Specific Populations

• Contraindications: None.

• Lactation: Temporarily discontinue breastfeeding. A lactating woman should pump and discard breastmilk for 9 hours after FDG administration.

• Pediatric Use: Safety and effectiveness in pediatric patients have not been established in the oncology and cardiology settings.

FDG Warnings and Precautions

• Radiation risks: use smallest dose necessary for imaging.

• Blood glucose abnormalities: may cause suboptimal imaging.

FDG Adverse Reactions

Hypersensitivity reactions have occurred; have emergency resuscitation equipment and personnel immediately available.

3.1.2. Cu64 DOTATATE (Detectnet™) Contraindications, Warnings and Precautions, Adverse Reactions, and Use

Cu64 DOTATATE Contraindications and Use in Specific Populations

• Contraindications: None.

• Lactation: Advise patients to interrupt breastfeeding for 12 hours after Cu64 DOTATATE administration.

Cu64 DOTATATE Warnings and Precautions

• Radiation risks: Ensure safe handling and preparation procedures to protect patients and healthcare workers from unintentional radiation exposure. Advise patients to hydrate before and after administration and to void frequently after administration.

• Risk for Image Misinterpretation: Uptake of Cu64 DOTATATE can be seen in a variety of tumor types other than NETs, in other pathologic conditions, and as a normal physiologic variant (*e.g.* uncinate process of the pancreas).

Cu64 DOTATATE Adverse Reactions

Reported adverse reactions include nausea, vomiting, and flushing.

3.1.3. Ga68 DOTATATE (NETSPOT™) Contraindications, Warnings and Precautions, Adverse Reactions, and Use

Ga68 DOTATATE Contraindications and Use in Specific Populations

• Contraindications: None.

• Lactation: Breast milk should be pumped and discarded for 12 hours after Ga68 DOTATATE administration.

Ga68 DOTATATE Warnings and Precautions

• Radiation Risks: Ga68 DOTATATE contributes to a patient's overall long-term cumulative radiation exposure. Ensure safe handling and preparation procedures to protect patients and healthcare workers from unintentional radiation exposure. Restrict close contact with infants and pregnant women during the first 12 hours after administration of Ga68 DOTATATE.

• Risk for Image Misinterpretation: The uptake of Ga68 DOTATATE can be seen in a variety of tumor types other than NETs (*e.g.* those derived from neural crest tissue), in sites of splenosis or other pathologic conditions, and as a normal physiologic variant (*e.g.* uncinate process of the pancreas).

Cu64 DOTATATE Adverse Reactions

Nausea, vomiting, and injection site pain and burning sensation were all reported during post-approval use.

3.1.4. Ga68 PSMA-11 Contraindications, Warnings and Precautions, Adverse Reactions, and Use

Ga68 PSMA-11 Contraindications and Use in Specific Populations

• Contraindications: None.

• Pregnancy, Lactation: PSMA is not indicated for use in females.

• Pediatric Use: PSMA is not indicated for use in the pediatric population.

• Geriatric Use: The efficacy in safety profiles of PSMA appear similar in adult and geriatric patients with prostate cancer, although the number of adult patients in the trials was not large enough to allow definitive comparison.

PSMA Warnings and Precautions

• Radiation risks: Ensure safe handling to protect patients and healthcare workers from unintentional radiation exposure.

• Risk for Misdiagnosis: Ga68 PSMA-11 uptake can be seen in a variety of tumor types and in non-malignant processes. Image interpretation errors can occur with Ga68 PSMA-11.

PSMA Adverse Reactions

The most commonly reported adverse reactions include nausea, diarrhea, and dizziness.

3.2. Human Radiation Dosimetry

The following sections summarize human radiation dosimetry for the PET/CT scans with each tracer. Note that the study will be performed in three Arms, and the subjects in each Arm will receive a total of two PET/CT exams performed on separate days.

3.2.1. Human Radiation Dosimetry of F18 Fluorodeoxyglucose

The amount of injected F18 FDG activity used in this protocol will be 555 MBq (15 mCi), which is the standard institutional dose. The radiation dosimetry estimates for F18 FDG are based on Publication 106 issued by The International Commission on Radiation Protection (ICRP) [International Commission on Radiological Protection; Radiation dose to patients from radiopharmaceuticals; Addendum 4 to ICRP Publication 53; ICRP Publication 106; Feb 24, 2014.]. The greatest organ absorbed doses for a 555 MBq (15 mCi) injection of F18 FDG are the bladder (72 mGy) and the heart (37 mGy), while the effective dose is 11 mSv. Organ dosimetry and effective dose for FDG is provided in Tables 1-3.

3.2.2. Human Radiation Dosimetry of Cu64-DOTATATE

The amount of injected Cu64-DOTATATE activity used in this protocol is based on the recommended dose of 148 MBq (4 mCi) in the FDA product label. Radiation dosimetry estimates for Cu64-DOTATATE are likewise based on the FDA product label, and are provided in Table 1. The greatest organ absorbed doses for a 148 MBq (4 mCi) injection of Cu64-DOTATATE are the liver (24 mGy), kidneys (21 mGy), adrenals (20 mGy), while the effective

dose is 4.7 mSv. Organ dosimetry and effective dose for Cu64 DOTATATE is provided in Table 1.

3.2.3. Human Radiation Dosimetry of Ga68-DOTATATE

The amount of injected Ga68-DOTATATE activity used in this protocol is based on the institutional dose of 185 MBq (5 mCi), which is within recommended range of the FDA product label. Radiation dosimetry estimates for Ga68-DOTATATE are likewise based on FDA product label. The greatest organ absorbed doses for a 185 MBq (5 mCi) injection of Ga68-DOTATATE are the spleen (20 mGy), bladder (18 mGy), kidneys (17 mGy), and adrenals (16 mGy) while the effective dose is 3.9 mSv. Organ dosimetry and effective dose for Ga68-DOTATATE is provided in Table 2.

3.2.4. Human Radiation Dosimetry of Ga68-PSMA-11

The amount of injected Ga68 -PSMA-11 activity used in this protocol is based on the maximum recommended dose in the tracer label, and will be 259 MBq (7 mCi). Radiation dosimetry estimates for Ga68-PSMA-11 are likewise based on the FDA product label, and are provided in Tables 3. The greatest organ absorbed doses for a 259 MBq (7 mCi) injection of Ga68-PSMA-11 are the kidneys (69 mGy), and bladder (18 mGy), and the effective dose is 4.4 mSv.

3.2.5. Human Radiation Dosimetry for CT Scans

CT scans are performed as part of PET/CT scans for both PET attenuation correction and anatomic localization. Each PET/CT exam performed in this study will include a CT scan. Since the subjects undergo 2 separate PET/CT exams, they will receive a total of 2 CT scans.

The study will be performed on research PET/CT scanners in the Molecular Imaging Suite at HCI. The previous scanner was a GE Discovery 710 PET/CT scanner and was used for dosimetry calcuclations. This scanner was replaced with a United Imaging uMI 780 PET/CT scanner and a uMI Panorama PET/CT. While this does not affect the dosimetry for the PET tracers, it may affect dosimetry for CT scans. The CT parameters for both new scanners have been adapted to achieve comparable dosimetry to those specified for the current GE D710 scanner. A helical CT scan will be acquired from the top of the head through the knees with moderate dose technique for both anatomical localization and attenuation correction. The original GE CT acquisition parameters for large patients receiving the greatest exposure were be 140 kVp, 0.5s rotation speed, 250 mA tube current, 64 x 1.25 mm collimation, and a pitch of 1.35 for the helical scan. Note that smaller patients will utilize 120 kVp but dosimetry estimates are based on larger patients at 140 kVp. Automatic tube current modulation is used for all CT exams but for the purpose of estimating maximum risk, a maximum fixed tube current of 250 mA is used for all calculations in order to provide a conservative estimate of maximum risk. In order to estimate the absorbed doses of individual organs and the resulting effective dose, the ImPACT Scan CT Patient Dosimetry Calculator (Version 1.0.4) was used with the specific acquisition parameters used in this protocol and the NRPB Monte Carlo dose data sets for the GE Lightspeed VCT scanner produced in report SR250 dosimetry tables.3-5 A correction factor has been applied to account for the difference in the CT Dose index (CTDIvol) derived from ImPACT Calculator and that reported on the GE scanner. Note that the topogram contributes a negligible radiation exposure to the helical CT exam and was not included in the dose

estimates. The greatest organ absorbed doses for a single helical body CT scan using the aforementioned acquisition parameters are bone surfaces (28 mGy) and thyroid (27 mGy), while the effective dose is 17 mSv (Tables 1-3).

3.2.6. Cumulative Dosimetry for PET/CT Exams in Each Arm

Tables 1-3 lists the individual scan dosimetry and cumulative radiation dosimetry for all PET/CT exams for each study Arm of the project. Each subject will undergo two single-tracer PET/CT exams, and each subject will receive two moderate dose CT scans as part of these exams.

3.2.6.1 Cumulative Dosimetry for PET/CT Exams in Arm 1

Arm 1 (15 subjects) will receive 2 single-tracer PET/CT exams – F18 FDG and Cu64-DOTATATE on separate days. A moderate dose CT scan will be performed for attenuation correction and anatomical localization as part of each single tracer PET/CT exam (2 CTs total). The greatest cumulative organ absorbed doses for the study are the bladder (113 mGy), heart (75 mGy), and liver (69 mGy), while the effective dose is 49 mSv (Table 1).

3.2.6.2 Cumulative Dosimetry for PET/CT Exams in Arm 2

Arm 2 (15 subjects) will receive 2 single-tracer PET/CT exams – F18 FDG and Ga68-DOTATATE on separate days. A moderate dose CT scan will be performed for attenuation correction and anatomical localization as part of each single tracer PET/CT exam (2 CTs total). The greatest cumulative organ absorbed doses for the study are the bladder (125 mGy), heart (76 mGy), and bone surfaces (66 mGy), while the effective dose is 48 mSv (Table 2).

3.2.6.3 Cumulative Dosimetry for PET/CT Exams in Arm 3

Arm 3 (20 subjects) will receive 2 single-tracer PET/CT exams – F18 FDG and Ga68-PSMA-11 on separate days. A moderate dose CT scan will be performed for attenuation correction and anatomical localization as part of each single tracer PET/CT exam (2 CTs total). The greatest cumulative organ absorbed doses for the study are the kidneys (141 mGy), bladder (133 mGy), and heart (76 mGy), while the effective dose is 49 mSv (Table 3).

Arm 1	FDG-PET	Cu64-DOTATATE-PET	Helical Body CT	PET/CT Total
Activity (mCi)	15	4	-	-
Number of Scans	1	1	2	-
Organ			Single Scan Absorbed dose (mGy)	Protocol Absorbed dose (mGy)
Adrenals	6.66	20.28	15.43	57.80
Bladder	72.15	5.48	17.77	113.16
Bone surfaces	6.11	5.03	28.05	67.24
Brain	21.09	1.92	18.23	59.48
Breasts	4.88	1.92	14.96	36.73
Gallbladder	7.22	5.92	16.36	45.86
Stomach	6.11	2.81	16.83	42.58
Small intestine	6.66	9.77	15.43	47.29
Colon	7.22	4.59	15.43	42.67
Heart	37.19	2.81	17.77	75.53
Kidneys	9.44	20.57	17.77	65.54
Liver	11.66	23.83	16.36	68.21
Lungs	11.10	2.52	18.70	51.02
Muscles	5.55	2.81	13.56	35.48
Oesophagus	6.66	2.22	20.11	49.09
Ovaries	7.77	2.81	14.96	40.51
Pancreas	7.22	13.76	14.96	50.90
Red marrow	6.11	4.00	13.09	36.28
Skin	4.33	1.78	12.62	31.35
Spleen	6.11	16.13	15.90	54.03
Testes	6.11	2.07	19.17	46.52
Thymus	6.66	2.22	20.11	49.09
Thyroid	5.55	2.07	26.65	60.92
Uterus	9.99	2.81	15.43	43.66
Effective dose (mSv)	10.55	4.74	16.83	48.95

Table 1. Radiation dosimetry for Arm 1 subjects in receiving 1 FDG PET, 1 Cu64-DOTATATE PET and 2 CT scans.

Arm 2	FDG-PET	Ga68-DOTATATE-PET	Helical Body CT	PET/CT Total
Activity (mCi)	15	5	-	-
Number of Scans	1	1	2	-
Organ			Single Scan Absorbed dose (mGy)	Protocol Absorbed dose (mGy)
Adrenals	6.66	15.91	15.43	53.43
Bladder	72.15	18.13	17.77	125.81
Bone surfaces	6.11	3.89	28.05	66.10
Brain	21.09	1.85	18.23	59.41
Breasts	4.88	1.85	14.96	36.66
Gallbladder	7.22	2.96	16.36	42.90
Stomach	6.11	2.41	16.83	42.17
Small intestine	6.66	4.63	15.43	42.14
Colon	7.22	3.41	15.43	41.48
Heart	37.19	3.33	17.77	76.05
Kidneys	9.44	17.21	17.77	62.17
Liver	11.66	9.25	16.36	53.63
Lungs	11.10	1.11	18.70	49.61
Muscles	5.55	2.22	13.56	34.89
Oesophagus	6.66	2.22	20.11	49.09
Ovaries	7.77	2.96	14.96	40.65
Pancreas	7.22	2.78	14.96	39.91
Red marrow	6.11	2.78	13.09	35.06
Skin	4.33	1.85	12.62	31.43
Spleen	6.11	20.17	15.90	58.06
Testes	6.11	1.85	19.17	46.30
Thymus	6.66	2.22	20.11	49.09
Thyroid	5.55	2.04	26.65	60.89
Uterus	9.99	2.78	15.43	43.62
Effective dose (mSv)	10.55	3.89	16.83	48.09

Table 2. Radiation dosimetry for Arm 2 subjects in receiving 1 FDG PET, 1 Ga68-DOTATATE PET and 2 CT scans.

Arm 3	FDG-PET	Ga68-PSMA-11-PET	Helical Body CT	PET/CT Total
Activity (mCi)	15	7	-	-
Number of Scans	1	1	2	-
Organ			Single Scan Absorbed dose (mGy)	Protocol Absorbed dose (mGy)
Adrenals	6.66	4.04	15.43	41.56
Bladder	72.15	25.43	17.77	133.12
Brain	21.09	2.69	18.23	60.25
Breasts	4.88	2.67	14.96	37.48
Gallbladder	7.22	4.06	16.36	44.00
Stomach	6.11	3.34	16.83	43.11
Small intestine	6.66	3.63	15.43	41.15
Colon	7.22	3.47	15.43	41.54
Heart	37.19	3.11	17.77	75.83
Kidneys	9.44	96.19	17.77	141.16
Liver	11.66	10.59	16.36	54.98
Lungs	11.10	2.87	18.70	51.38
Muscles	5.55	2.67	13.56	35.34
Oesophagus	6.66	2.72	20.11	49.59
Pancreas	7.22	3.81	14.96	40.95
Red marrow	6.11	2.95	13.09	35.24
Skin	4.33	2.36	12.62	31.93
Spleen	6.11	16.84	15.90	54.73
Testes	6.11	2.87	19.17	47.32
Thymus	6.66	2.72	20.11	49.59
Thyroid	5.55	2.69	26.65	61.55
Effective dose (mSv)	10.55	4.38	16.83	48.59

Table 3. Radiation dosimetry for Arm 3 subjects in receiving 1 FDG PET, 1 Ga68-PSMA-11 PET and 2 CT scans.

3.3. Patient Eligibility

Study patients: Adult patients with known or suspected neuroendocrine tumors or prostate cancer that would be eligible to receive PET/CT with FDG, DOTATATE, and/or PSMA as part of their standard of care, and who are willing and able to tolerate PET/CT imaging exams with two tracers. Subjects who have already received PET/CT exams as part of their standard of care are eligible (*i.e.*, previous PET/CT does not rule out eligibility). Oncologists, nuclear medicine physicians, and research staff at Huntsman Cancer Institute will identify and recruit patients for participation, and obtain informed consent.

The study duration is expected to be 2 years.

4.0 STUDY DESIGN

4.1. Inclusion Criteria

4.1.1 All Patients

- Adults aged 18 years or greater.
- All patients or legal guardians must be willing and able to sign a written informed consent and HIPAA authorization in accordance with local and institutional guidelines.
- Presence of at least 1 measurable lesion ≥ 1 cm in size.
- Patients must be willing to have their clinical records reviewed for at least 24 months after enrollment.
- Patients must be willing to lie flat on their back in the PET/CT scanner for up to one hour to allow for the imaging data to be obtained.
- Patients must be willing to undergo two separate PET/CT exams on different days within 2 weeks of each other.
- Determination of pregnancy status: Female patients who are not postmenopausal or surgically sterile will undergo a serum pregnancy test prior to baseline and the subsequent set of multi-tracer PET scans. The serum pregnancy test must be performed within 48 hours prior to research PET imaging. A negative test will be necessary for such patients to undergo research PET imaging. This only applies to Arms 1-2, since only males will be included in Arm 3 (only males can get prostate cancer).

4.1.2 Patients in Arms 1-2

- Patients with known or suspected somatostatin receptor-positive neuroendocrine tumor (NET) who could be considered for clinical use of DOTATATE PET/CT imaging under the approved indications for use of this radiopharmaceutical according to published appropriate use criteria [97]. These indications include: initial staging after the histologic diagnosis of NET; evaluation

of an unknown primary; evaluation of a mass suggestive of NET not amenable to endoscopic or percutaneous biopsy; staging of NET before planned surgery; monitoring of NET seen predominantly on SSTR PET; evaluation of patients with biochemical evidence and symptoms of a NET; evaluation of patients with biochemical evidence of a NET without evidence on conventional imaging or a prior histologic diagnosis; restaging at time of clinical or laboratory progression without progression on conventional imaging; and new indeterminate lesion on conventional imaging with unclear progression.

4.1.3 Patients in Arm 3

- Patients with known or suspected prostate cancer who could be considered for clinical use of PSMA PET/CT imaging under the approved indications for use of this radiopharmaceutical, including: patients with suspected metastasis and patients with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level.

4.2. Exclusion Criteria

- Patients with known intolerance or hypersensitivity to any somatostatin analogs will be excluded from the study Arms involving DOTATATE (Arms 1-2).
- Patients with known allergic or hypersensitivity reactions to previously administered radiopharmaceuticals
- Patients who require monitored anesthesia for PET/CT scanning.
- Patients who are too claustrophobic to undergo PET/CT scanning.
- Patients who exceed the 450 lb. weight limit of the PET/CT scanner.
- Patients who are pregnant or currently breast feeding.

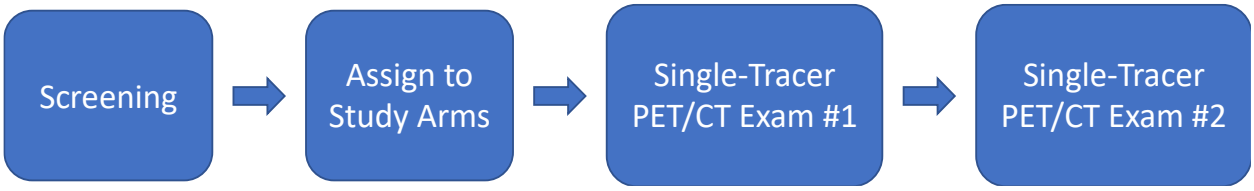
4.3. Patient Registration

Participants must meet all of the eligibility requirements listed above prior to registration. Following appropriate pre-registration evaluation, informed consent will be obtained by the study coordinator. The study coordinator will also record study data on all patients entered into the study and complete subsequent forms.

4.4. Study Procedures, Schedule of Events, PET Tracer Administration: Route and Dosing

Patients enrolled in this study will receive all standard of care procedures as determined by their oncologist. The PET/CT exams performed at part of this study will be interpreted a nuclear medicine physician (sub-investigator Matthew Covington, MD) and reported as a research note in the electronic health record. Identification of suspected lesions will be performed by the same physician and used for analysis as described below in the methods section.

Study Schema



The PET/CT exams may be performed in either order: FDG first or second, according to scheduling considerations and at the Investigator's discretion.

4.4.1. Initial Visit Prior to PET Imaging

Upon enrollment in the study, the patient will be evaluated by one of the HCI oncologists with verification of informed consent. The following additional patient data will be obtained: histological diagnosis (when available following biopsy or surgery), age, gender, and other treatment modalities used. Clinical (non-research related) PET/CT imaging studies as acquired according to standard of care will be retrieved and loaded into the research database.

4.4.2. Research PET/CT Exams

Patients will receive two research PET/CT exams with two PET tracers: FDG + Cu64-DOTATATE (Arm 1), FDG + Ga68-DOTATATE (Arm 2), or FDG + Ga68-PSMA-11 (Arm 3). The cost of these exams will be covered by the study. The order of the scans with each tracer is not important and will be determined according to scheduling considerations. Female patients who are not postmenopausal for a minimum of one year, or surgically sterile, must have a serum pregnancy test performed within 48 hours prior to each research PET/CT exam (Arms 1-2 only; no females will be enrolled in Arm 3).

4.4.3. Restrictions in 24 Hour Period Prior to PET/CT Exams

• FDG Scans: Patients will be asked to minimize physical activity 24 hours prior to scans with FDG. They will also be required to fast for 6 hours prior to the FDG injection. Patients can take all required medications with water.

• DOTATATE and PSMA Scans: There are no dietary restrictions for patients prior to receiving PET/CT scans with these tracers.

4.4.4. Day of Study: Single-Tracer FDG PET/CT Exam (all Arms)

FDG PET Tracer Administration:

The patient will be taken to the tracer uptake room, seated comfortably, and have the appropriate IV access placed for tracer administration. The PET technologist will administer approximately 15 mCi of FDG intravenously, and the patient will remain resting during the tracer uptake period (90 min. until start of PET scanning). The patient will be encouraged to hydrate and void their bladder. After the uptake period, the patient will be moved to the PET/CT scanner.

Topogram and CT Scan:

Patients will be position on the scanner bed, and will be instructed to remain motionless for the duration of the scan. A CT topogram will be obtained, and the PET imaging field-of-view (FOV) selected. The scanner bed position will be recorded. A CT scan for PET attenuation correction and anatomic localization will then be performed.

Multi-Timepoint PET Scan:

The PET scan will then be acquired, acquiring 5 back-to-back “whole-body” (eyes-to-thighs, or similar) scans, providing 5 sequential PET images. Each pass will take approx. 10 min., for a total scan time of approx. 50 min.

Patient Positioning:

The patient position, bed position, and PET scan FOV will be recorded from the first PET/CT exam. These data will be used to re-position the patient, bed, and FOV for the second PET/CT to match those for the first exam, as possible.

4.4.5. Day of Study: Single-Tracer Cu64-DOTATATE PET/CT Exam (Arm 1)

There are no dietary restrictions for patients prior to the Cu64-DOTATATE PET/CT exam. Patients will be injected with approximately 4 mCi Cu64-DOTATATE, and the tracer uptake time before initiation of PET scanning will be 75 min. All other aspects of the imaging will be identical to that for the FDG PET/CT scan.

4.4.6. Day of Study: Single-Tracer Ga68-DOTATATE PET/CT Exam (Arm 2)

There are no dietary restrictions for patients prior to the Ga68-DOTATATE PET/CT exam. Patients will be injected with approximately 5 mCi Ga68-DOTATATE, and the tracer uptake time before initiation of PET scanning will be 75 min. All other aspects of the imaging will be identical to that for the FDG PET/CT scan.

4.4.7. Day of Study: Single-Tracer PSMA PET/CT Exam (Arm 3)

There are no dietary restrictions for patients prior to the PSMA PET/CT exam. Patients will be injected with approximately 7 mCi Ga68-PSMA-11, and the tracer uptake time before initiation of PET scanning will be 80 min. All other aspects of the imaging will be identical to that for the FDG PET/CT scan.

4.4.8. After Study Procedures

All images will be reconstructed and processed using the same parameters in order to ensure that there are no differences in processing. The PET/CT images will transferred to the research DICOM database, and de-identified copies will be delivered to MultiFunctional Imaging LLC for processing and analysis according to the Specific Aims of the grant R44CA257522-02.

5.0 METHODS FOR ASSESSMENT OF PET IMAGES

The PET images for each tracer will be evaluated using qualitative visual assessment and semi-quantitative analysis techniques that have previously been used by us and other groups, and represent the standard and accepted means of evaluating static PET images. These assessments will be performed by investigators at HCI, and are described below.

5.1. Qualitative Visual Assessments

Visual assessment of the images for each tracer will be used to qualitatively assess for abnormal focal tracer uptake throughout the imaged body. Images will be reviewed in an unblinded manner to assess whether additional lesions are found when comparing with prior imaging. The coordinates of abnormal foci of uptake will be recorded and semi-quantitative assessments of these lesions will be computed as described below.

5.2. Semi-Quantitative Assessments

Tracer uptake in each lesion identified in the qualitative visual analysis will be quantified by calculating body-weight-corrected Standardized Uptake Values (SUVbw) as follows:

$$SUV_{max} = \frac{Amax}{injected\ activity\ (mCi)/_{BW}}$$

where A_{max} = radioactive concentration (mCi/mL)

BW = body weight BW (g)

Corrections for lean body mass will also be performed to calculate the SUVlean as follows:

SUVlean = (LBM/BW) X SUVbw

where SUVbw = the SUV measurements using body-weight corrections

LBM = the lean body mass estimated from the Janahasastian Formula [98]

A region-of-interest (ROI) will be drawn over the lesions (on all image slices with abnormal uptake). The mean value in each ROI will be computed to obtain the SUV_{mean} for each tracer, and the maximum value in each ROI will be computed to obtain the SUV_{max} for each tracer.

The location, ROI, SUV_{mean}, and SUV_{max} for each lesion will be recorded and used for data analysis.

6.0 DATA ANALYSIS AND STATISTICS

The de-identified images with marked lesion locations will be provided to MFI for further analysis according to the aims of grant 2R44CA257522. The imaging data will be used to develop dual-tracer PET scanning protocols and new processing algorithms for imaging FDG + Cu64-DOTATATE, FDG + Ga68-DOTATE, and FDG + Ga68-PSMA-11. Since a dual-tracer PET image is essentially the sum of two single-tracer PET images, this research will make use of the synthesized dual-tracer evaluation technique summarized below.

6.1. Synthesized Dual-Tracer Evaluation Technique

One challenge of evaluating rapid multi-tracer PET techniques is the need to know the ground truth when evaluating results. For example, one possible study design would be to obtain separate, single-tracer scans with each tracer on separate days, and then to obtain simultaneous dual-tracer scans on a 3rd day—all in the same patient. Here the separate-scan images of each tracer could be used as the standard for evaluating images of each tracer recovered from the dual-tracer scans. However, such an approach would pose many problems, in particular: (1) high cost, scheduling challenges, and patient compliance issues for performing 3 different PET/CT exams on 3 different days; (2) increased radiation exposure from 3 PET/CT exams (3 CTs and 4 total PET tracer administrations); (3) test-retest variability for PET is on the order of 10-15% [99-101]—differences that can be larger than the errors in recovered dual-tracer images and thus limit the value of the study; and (4) it would only allow for a single dual-tracer scanning protocol to be studied (rather than allowing for various scanning protocols to be studied and compared).

A better and widely-accepted approach, used by our group and others [2-8, 10-13] is to acquire separate, single-tracer PET scans with each tracer and then retroactively combine the images to “synthesize” dual-tracer images which are ~identical to the images that would have been obtained from actual dual-tracer scanning. When more than one PET tracer is present during a scan, the resulting image represents the sum of all tracer present. As such, the images from separate, single-tracer PET scans can be added together to create “synthesized” multi-tracer PET images. Aside from small differences in scanner deadtime and random coincidence rates (which are well-understood and accurately corrected by the PET scanner), such synthesized dual-tracer images accurately mimic actual multi-tracer PET images, which characteristics that closely match what would have been obtained from actual multi-tracer scanning.

The advantage of this approach is that the actual single-tracer components of the resulting dual-tracer images are known exactly — and they can be used to evaluate the accuracy of individual-tracer images recovered from the multi-tracer images. In effect, the data become their own controls when using this approach.

6.2. Dual- vs. Single-Tracer Performance Assessments

The PET images for each tracer pair will be co-registered and combined to synthesize corresponding dual-tracer images. Dual-tracer processing algorithms, based on modeling differences in radioactive decay rates and kinetic distributions for each tracer, will be developed that take simultaneous dual-tracer PET images as input and out separate, recovered images of each individual tracer. The performance of the dual-tracer scanning approach and processing algorithms will be evaluated by comparing output images for each tracer to the corresponding original single-tracer images for that tracer. A number of analyses will be performed on these data.

In the following paragraphs, "recovered" is used to denote measures (image pixel values, SUVs) for individual-tracer images recovered from the dual-tracer images, and "true" is used to denote the corresponding value from the original constituent single-tracer image. This analysis evaluates how accurately the simultaneous dual-tracer imaging technique can recover individual images of each tracer, as compared to the images from conventional single-tracer scans.

6.2.1. Qualitative Visual Assessments

The images of each tracer recovered from the dual-tracer images as processed and output by the new dual-tracer processing algorithms will be visually assessed side-by-side with the original "true" single-tracer images. Tracer uptake throughout the body will be visually assessed for the presence of any artifacts, and regions of abnormal focal tracer uptake will be identified and compared for differences between the recovered and "true" images for each tracer. Any artifacts or differences in visual lesions will be marked and documented, and any such differences will be evaluated for any potential effect on the clinical interpretation of the images. All lesions identified will be marked, and quantitative analyses for each will be performed as described below.

6.2.2. Quantitative Performance Measures

Pixelwise Linear Regression Analysis: The overall accuracy of image pixels for each tracer will be measured by performing linear regression analysis for recovered vs. true image pixel values over all image pixels. This will be computed for each tracer for each patient. The regression slope, intercept, and Pearson's correlation coefficient will be used as measures of bias between the recovered and true image pixels.

Linear Regression Analysis of ROIs: The accuracy of ROI values for lesions and normal background tissues will also be measured using linear regression analysis of the recovered vs. true values. The regression slope, intercept, and Pearson's correlation coefficient will be used as measures of bias between the recovered and true ROI values.

6.2.3. Quantitative Performance Targets

The following quantitative performance targets have been set in order to conclude that the new simultaneous dual-tracer techniques provide images of each tracer that are equivalent to images that would be obtained from separate, single-tracer scans of each tracer:

(1) dual-*vs.*-single correlation coefficients ≥ 0.95 for both image voxels and lesion SUVs;

(2) bias, as measured by the linear regression slope, to be within 5% of 1.0 ($0.95 \leq$ slope ≤ 1.05);

(3) bias, as measured by the linear regression intercept, to be within 5% (of mean voxel or SUV value) of zero; and

(4) tumor and background tissue SUVs for dual-tracer images within 0.05 of those for the separate-scan standard images (to 95% power).

These analyses will be repeated for all 3 tracer pairs.

6.3. Justification of Sample Size

The following sample size calculations are based on testing the hypothesis that differences in SUV_{mean} for lesions and normal tissue regions in images recovered from dual-tracer scanning for each tracer are less than 5% different than those from the single-tracer "standard" images, using a 2 sided *t*-test with alpha = 0.05 and desired power = 0.95. We also assume a standard deviation of 10% for SUV_{mean} measurements (based on PET test-retest variability). This gives a required sample size of N = 104. Assuming 5-7 regions/lesions per subject, this gives 15-20 subjects needed to obtain the desired statistical power, which supports our design of 15-20 patients each for each study Arm.

The study design and data analysis techniques were reviewed and approved by the NIH study section for grant 2R44CA257522, and no issues or concerns were noted.

7.0 REGULATORY AND REPORTING REQUIREMENTS

7.1. Human Subject Protections

The study will be conducted in accordance with the appropriate FDA, IRB, ICH GCP, and other federal and local regulatory requirements, as applicable. Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB-approved version. All patients must be at least 18 years of age to participate.

7.2. Institutional Review

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB for the protocol, consent form, subject recruitment materials (e.g., advertisements), and any other applicable patient-facing documents. The investigator or designee should provide the IRB with reports, updates and other information (*e.g.*, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

7.3. Data and Safety Monitoring Plan

As this study will be using FDA-approved radiopharmaceuticals, monitoring by the Huntsman Cancer Institute Data Safety and Monitoring Committee is not required. This study will be reported and monitored by the Principal Investigator using the ERICA and OnCore. Any serious adverse events that occur during the study will be reported to the IRB. The PI will review data

and documentation on a monthly basis with the clinical research manager and data research coordinator.

7.4. Protocol Amendments

Any amendments or administrative changes in the research protocol during the period, for which the IRB approval has already been given, will not be initiated without submission of an amendment for IRB review and approval.

These requirements for approval will in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial.

7.5. Protocol Deviations

A protocol deviation (or violation) is any departure from the defined procedures and treatment plans as outlined in the protocol version submitted and previously approved by the IRB. Protocol deviations have the potential to place participants at risk and can also undermine the scientific integrity of the study thus jeopardizing the justification for the research. Protocol deviations are unplanned and unintentional events.

Because some protocol deviations pose no conceivable threat to participant safety or scientific integrity, reporting is left to the discretion of the PI within the context of the guidelines below. The IRB requires the **prompt reporting** of protocol deviations which are:

• Exceptions to eligibility criteria.

• Intended to eliminate apparent immediate hazard to a research participant or

• Harmful (caused harm to participants or others, or place them at increased risk of harm – including physical, psychological, economic, or social harm), or

• Possible serious or continued noncompliance.

8.0 PET RADIOPHARMACEUTICAL PRODUCTION

All use of the FDA-approved PET radiopharmaceuticals under this study will be in accordance with the approved indications for use of each tracers' labeling. All PET radiopharmaceuticals will be purchased commercially from the Center for Quantitative Cancer Imaging (CQCI) program at HCI, from the Intermountain Radiopharmacy (IRP), or from Cardinal Health.

9.0 Resources and Responsibilities

This study is being done under grant 2R44CA257522 as part of a consortium agreement between HCI / University of Utah and MultiFunctional Imaging LLC. MFI is the primary awardee for the grant, with sub-award to the University. All human subjects research procedures will be entirely performed by the University, and MFI will not be involved in these procedures. The resultant data will be de-identified and delivered to MFI for subsequent use in performing the

specific aims of the grant. MFI will only receive de-identified data and will not have any means of identifying the study participants.

The protocol will be administered by the Principal Investigator, Jeffrey Yap, Ph.D., Director of the Center for Quantitative Cancer Imaging (CQCI) program at Huntsman Cancer Institute. The PET/CT exams will be performed by CQCI staff using CQCI equipment, and will be funded by the grant subaward. Dr. Yap will coordinate with the sub-investigators and CQCI staff in identifying and enrolling subjects, performing the initial image assessments, de-identifying the data and delivering it to MFI.

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11.0 APPENDIX A: Schedules of Events

Assessment / Procedure	Screening	Imaging Session #1	Imaging Session #2
Informed Consent	X		
Inclusion/ Exclusion Criteria	X		
Pregnancy Test		X[1]	
F18-FDG PET/CT Imaging		X[2]	
Cu64-DOTATATE PET/CT Imaging			X[3]

1) Patient must be postmenopausal for a minimum of one year, surgically sterile, or confirmed not to be pregnant by serum pregnancy test performed within 48hrs prior to PET imaging.

2) Subjects will be required to fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours of the scan if needed for administration of medications.

3) The Cu64-DOTATATE PET/CT imaging is performed on a separate day, either before or after the day of the FDG PET/CT imaging.

Assessment / Procedure	Screening	Imaging Session #1	Imaging Session #2
Informed Consent	X		
Inclusion/ Exclusion Criteria	X		
Pregnancy Test		X[1]	
F18-FDG PET/CT Imaging		X[2]	
Ga68-DOTATATE PET/CT Imaging			X[3]

1) Patient must be postmenopausal for a minimum of one year, surgically sterile, or confirmed not to be pregnant by serum pregnancy test performed within 48hrs prior to PET imaging.

2) Subjects will be required to fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours of the scan if needed for administration of medications.

3) The Ga68-DOTATATE PET/CT imaging is performed on a separate day, either before or after the day of the FDG PET/CT imaging.

Assessment / Procedure	Screening	Imaging Session #1	Imaging Session #2
Informed Consent	X		
Inclusion/ Exclusion Criteria	X		
F18-FDG PET/CT Imaging		X[1]	
Ga68-PSMA-11 PET/CT Imaging			X[2]

1) Subjects will be required to fast for at least 4 hours prior to the scan, drinking only sips of water within 4 hours of the scan if needed for administration of medications.

2) The Ga68-PSMA-11 PET/CT imaging is performed on a separate day, either before or after the day of the FDG PET/CT imaging.