Protocol Title: An Exploration of Gated and Non-Gated Dynamic PET/CT Imaging

NCT#: NCT04283552

Version Date: 11/20/2020

An Exploration of Gated and Non-Gated Dynamic PET/CT Imaging

Protocol Version: 1.2
HRPO #: 201910076
Version Date: 11/20/2020

Principal Investigator
Richard L Wahl, MD
Professor of Radiology and Radiation Oncology
Chairman: Department of Radiology
Director: Mallinckrodt Institute of Radiology
Washington University School of Medicine
Telephone: (314) 362-7100
Email: rwahl@wustl.edu

Sub-Investigators
Tyler J Fraum, MD
Assistant Professor of Radiology
Mallinckrodt Institute of Radiology
Washington University School of Medicine
Telephone: (314) 362-2928
Email: tylerjfraum@wustl.edu

I. Background

Positron emission tomography / computed tomography (PET/CT) imaging has become a crucial tool in the diagnosis, staging, and restaging of cancer patients (1,2,3). PET/CT imaging is generally performed by imaging a patient, following an uptake phase, after administration of a radiotracer, most commonly ^{18}F-fluorodeoxyglucose (FDG) (4). This 'uptake' period allows time for the radiotracer to accumulate in areas of interest and for a reduction in the ratio of normal tissue uptake to the uptake in tissue with disease. However, the uptake periods used in clinical protocols are somewhat arbitrary and are not expected to be optimal for all clinical cases. Dynamic tracer imaging during the uptake phase can provide considerably more information by delineating both the temporal and spatial pattern of tracer uptake. Dynamic imaging allows calculation of tissue uptake rate, whereas from static imaging only magnitude of tissue uptake can be calculated. In addition, several potential sources of error that occur in static imaging may be mitigated (5).

In order to fully assess the utility of dynamic PET imaging, an understanding of the test-retest repeatability of dynamic imaging is necessary. Generally, the standardized uptake value (SUV), a semi-quantitative measure of PET radiotracer uptake, has been shown to be a highly repeatable imaging biomarker (6). In recurrent ovarian cancer patients, one study found FDG uptake measurements to have repeatability coefficients of 16.3% and 17.3% for SUVmean and SUVmax, respectively (7). Using a mouse model, Whisenant et al found kinetic parameters extracted from dynamic PET images were sufficiently repeatable to be used for therapy response assessment (8). While several human studies have indicated PET metrics extracted from dynamic PET images also show a high degree of test-retest reliability, a complete evaluation of dynamic PET repeatability remains incomplete (9, 10, 11).

Since PET/CT imaging (dynamic or static) is performed over an extended period of time, patient motion (particularly respiratory motion) is inevitable and can cause significant image artifacts (12). Volume and SUVmax (vital metrics in PET/CT imaging) have been shown to be significantly impacted by movement during imaging. Motion has been shown to cause an underestimation of SUVmax by as much as 28% and an overestimation of volume by up to 130% (13). Different methods have been developed to manage the respiratory motion problem including breathhold procedures (14), respiratory gating (15), and other post-processing techniques (16). Respiratory gating involves sorting the PET data into different bins with respect to the respiratory status. Each bin thus contains only a part of total motion and will have reduced motion artifacts. Unfortunately, the bins contain only a part of the total number of events detected in the scanner, which leads to more noise. OncoFreeze is a novel approach to PET motion correction that utilizes 100% of events, which are corrected to an optimal gate image utilizing

an optical flow algorithm, creating the potential for motion corrected images without increasing image noise.

II. Objectives

1. Assess the technical feasibility of dynamic, whole-body multiparametic PET imaging
2. Assess the quantitative and clinical impacts of a novel approach to PET data motion correction (OncoFreeze), relative to more conventional static and respiratory-gated PET images.
3. Quantify the test-retest repeatability of quantitative metrics extracted from dynamic PET images.
4. Comparision of the early and late Patlak images to determine the optimal post-injection time period for dynamic PET imaging for Patlak analysis.

III. Eligibility

Main Cohort: Any patient 18 years of age or older, scheduled to undergo a clinical PET/CT scan with any clinically prescribed radiotracer* for known or suspected malignancy (pathologic confirmation not required), and able to provide informed consent is eligible to participate in this study.

Repeatability Cohort: Any patient 18 years of age or older, scheduled to undergo a clinical PET/CT scan with FDG or ^{68}Ga- DOTA-0-Tyr3-Octreotate (DOTATATE) for known or suspected malignancy (pathologic confirmation not required), and able to provide informed consent is eligible to participate in this study.

*NOTE: Some patients are evaluated clinically with multiple radiotracers prior to therapy. Patients scheduled to undergo multiple PET/CT imaging procedures will be eligible to have dynamic imaging performed during each of these procedures. However, these patients would only be eligible to have 1 repeat imaging procedure for research purposes.

IV. Patient Registration

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.
The following steps must be taken before registering patients to this study:
1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Confirmation of Patient Eligibility
Confirm patient eligibility by collecting the information listed below:
1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

Patient Registration in the Siteman Cancer Center Database
All patients must be registered through the Siteman Cancer Center database.

Assignment of UPN
Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

V. Patient Compensation

Patients will be compensated for their participation in this study. Upon successful completion of the study, patients will be paid $50.00 and given a parking voucher, if necessary, for research imaging performed on the day of their clinical scan. Patients who participate in a retest imaging session will be paid an additional $150.00, as well as a parking voucher, if they drove to campus.

VI. Methods

Main and Repeatability Cohorts

This protocol seeks to evaluate: (1) Metrics derived from dynamic positron emission tomography / computed tomography (PET/CT) imaging, (2) methods for achieving motion correction of PET/CT images, and (3) the repeatability of dynamic imaging. Clinical PET/CT imaging is normally performed by injecting a patient with a radiopharmaceutical (most commonly FDG) and collecting images using a PET scanner (preceded by a brief CT scan) after an uptake phase, which varies in duration depending on radiotracer. The data for this study will mostly be collected by asking patients to have PET images collected during the uptake phase (preceded by a low-dose research CT scan) in addition to the normal clinical images. We will also ask them to remain in the scanner for up to 20 minutes following the clinical scan in order to perform additional research PET imaging. The normal clinical scan (including radiation dose) will not be impacted by this study. However, the low-dose CT performed prior to the dynamic imaging will result in additional radiation exposure. All scans will be performed on a Siemens Vision scanner.

Ideally, participants will be positioned in the same way they'll be positioned for their clinical scan. However, as the research imaging takes a considerable amount of time, patients may be positioned differently (e.g. with arms by their sides) if the clinically-indicated position would prove too difficult.

Repeatability Cohort Only

A subset of patients (up to 30 scheduled to undergo FDG or DOTATATE PET/CT imaging) will be asked to return to the CCIR within 7 days for a repeat imaging study. This time-point will involve the same procedures performed during the initial imaging visit.

Study Procedures

Following the consent process, patients will be escorted to the PET/CT imaging suite where they will be positioned on the imaging bed. As part of the routine clinical PET/CT procedure, an IV will be placed. A low-dose CT will then be performed, followed by the administration of the [clinically-prescribed] radiotracer. Immediately following the tracer administration, PET imaging will begin and continue for approximately 40 - 60 minutes at which point the clinical PET/CT procedure will be performed. Patients will be asked to use the bathroom between the research and clinical imaging.

Specific Dynamic Imaging Procedure

1) Upon arrival, patients will be taken to a preparation room where they will be kept warm and they will have time to review the consent form and ask any questions they might have about the dynamic imaging study.
2) Patients will be asked to void immediately prior to the start of PET/CT imaging.
3) Patients will then be escorted to the scanner and have one IV placed.
4) A low-dose CT will be performed.
5) A single weight-based dose of a radiotracer will be administered.
6) Patients should be positioned comfortably so as to reduce the likelihood of movement during the scan.
7) Dynamic PET/CT imaging (utilizing multiple whole-body passes) will begin immediately following the radiotracer injection and will continue until approximately 10 – 20 minutes prior to the start of the clinical scan. These passes will be used to generate early Patlak images.
8) Upon completion of the dynamic scan, patients will be asked to use the bathroom to empty their bladders, and then the clinical scan procedure will begin.
9) During the clinical scan procedure, patients will wear an Anzai belt, a device that tracks respiratory motion.
10) Following the clinical imaging, patients will remain in the scanner for approximately 20 minutes while additional research PET images are

collected. These additional passes will enable the generation of late Patlak images for comparison with early Patlak images.

Repeat Dynamic Imaging

Patients who agree to participate in the repeatability sub-study will be asked to return to the CCIR within 7 days for an additional imaging study. This visit will involve the same procedures as the initial imaging visit and will be performed entirely for research purposes. The repeat visit should include approximately the same radiotracer and CT doses. In the case of imaging delays (i.e. an uptake time differing significantly from what is clinically recommended) during the initial imaging visit, the same delay should be incorporated into the repeat imaging visit.

VII. Data Analysis

The primary endpoint of this prospective study is the feasibility of multiparametric PET in a general oncology population. A total of 75 subjects will be recruited for the multiparametric PET portion of the study. If we observe a successful completion rate of 81.3% (i.e., 61 of 75 subjects), the exact 95% confidence interval for that proportion and sample size would be 71-89%. The lower limit of this confidence interval will effectively indicate that the true successful completion rate is highly likely to be ≥70% and that multiparametric PET is feasible in a general oncology population.

Primary aim: The feasibility of rapid, whole-body dynamic PET imaging will be assessed by evaluating the practicality of acquiring dynamic PET data in the clinic. The feasibility of multiparametric PET for oncologic imaging will be defined as successful completion of the study imaging component in at least 70% of cases. Successful completion of the study imaging component will be defined as: (1) patient remains on scanner for the full dynamic phase of PET imaging prior to the standard-of-care PET/CT and (2) automated scanner software is able to successfully generate valid parametric maps (requires at least three consecutive whole-body PET acquisitions without substantial motion between acquisitions). Feasibility is important to establish due to the added demands on patients arising from the long imaging period. In addition, novel quantitative metrics derived from dynamic PET acquisitions will be compared with standard semiquantitative metrics, such as SUV and metabolic tumor volume (MTV), obtained from the clinical PET/CT scan.

Secondary aim #1: The quantitative and clinical impacts of OncoFreeze (specifically, on semi-quantitative SUV metrics and on the number of detectable lesions) will be assessed by comparing motion-corrected images derived from OncoFreeze with standard static non-gated PET images and conventionally gated PET images. Two independent readers blinded to the

reconstruction approach will score image quality utilizing a standard Likert-type scale and will extract quantitative metrics (e.g., SUV-max, SUV-peak) for any apparent FDG-avid lesions. Results will be compared for (1) motion-corrected images derived from OncoFreeze, (2) standard static non-gated PET images, and (3) conventionally gated PET images.

Secondary aim #2: The repeatability of dynamic imaging will be evaluated by calculating the measurement agreement and relative differences in semi-quantitative PET metrics between test and retest dynamic images. Imaging metric agreement will be measured using Bland-Altman analysis. Groupwise differences between imaging time-points will also be assessed using t-tests or Mann-Whitney U tests, depending on normality.

Secondary aim #3: The early and late Patlak images (specifically: metabolic rate [slope] and volume of distribution [intercept] images) will be compared in a head-to-head fashion, both qualitatively and quantitatively. This aim will help to determine the optimal post-injection time period for dynamic PET imaging for Patlak analysis.

VIII. Study Risks and Benefits

1) IV Risks:

The risks from IV placement include bruising, pain, or infection at the injection site and possible leaking of IV fluid into nearby tissues. The risk of infection is quite low. There is a moderate risk of pain or bruising. Intravenous injections will be performed only by experienced staff and a physician will be available throughout the procedure in case of any infusion side effects.

2) FDG Risks:
FDG is FDA-approved and known to be very safe. There are few known side-effects associated with FDG. In a large cohort, less than 1% or less of patients experienced transient hypotension, hypo- or hyperglycemia, or transient increases in alkaline phosphatase. The package insert for FDG lists no warnings, interactions, or precautions. A review of the literature reveals no adverse effects.

3) DOTATATE Risks:
Risks associated with DOTATATE were assessed in 3 clinical trials and no serious adverse events were reported. In a small percentage of patients, nausea and/or vomiting have been reported following the administration of DOTATATE.

4) Radiation Risks:
This research involves exposure to radiation from PET/CT imaging. As part of the repeatability cohort, patients will receive 1 radiotracer dose (either FDG or DOTATATE) and 3 low-dose CTs as part of the research procedures. The risk from the radiation exposure in this study is too small to be measured. It is not a big risk when compared with other risks you take every day. For more information about radiation exposure, please see the "Radiation Fact Sheet" at https://hrpo.wustl.edu/participants/radiation-fact-sheet.

5) PET/CT Imaging Risks:

Patients may experience some discomfort having to lie still for an extended period of time. Patients who dislike small spaces may also find the PET/CT scanner uncomfortable.

IX. Regulatory and Reporting Requirements

The Principal Investigator is responsible for ensuring the safety of subjects who have enrolled in the study. The PI will monitor the study for adverse events directly attributable to participation in this study (i.e. events associated with the additional research PET/CT imaging, not events associated with the clinical PET/CT imaging, including radiopharmaceutical administration). If any breach of confidentiality were to occur, it would be reported according to the HRPO-recommended guidelines.

Reporting
Based on the half-lives of the tracers involved in this study, adverse event tracking will be performed for 24 hours starting at the time of radiotracer administration. Any reported events, anticipated or unanticipated, will be reviewed by the PI and reported per the WUSTL HRPO guidelines. These events will be followed until resolution.

Study deviations will be tracked and recorded throughout the study. Any serious deviations will be reported immediately to the IRB. Otherwise, study deviations will be reviewed by the PI and reported on an annual basis.

X. Data and Safety Monitoring Plan

The principal investigator will review all patient data at least every six months, and provide an annual report to the QASM Committee. This report will include 1. the protocol title, IRB protocol number, and the activation date of the study. 2. the number of patients enrolled to date 3. the date of first and most recent

patient enrollment 4. a summary of all adverse events regardless of grade and attribution 5. a response evaluation for evaluable patients 6. a summary of any recent literature that may affect the ethics of the study. The study principal investigator and clinical research associate will monitor for serious toxicities on an ongoing basis. Once the principal investigator or clinical research associate becomes aware of a serious adverse event, the SAE will be reported to the HRPO and QASM Committee [add other reporting requirements here if applicable, e.g. sponsor, FDA, collaborating institutions] within 10 working days.

Adverse Events

For the purposes of this protocol, an adverse event (AE) is any untoward medical occurrence within 24 hours of radiotracer administration (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding) that emerges or worsens relative to pre-imaging baseline. The Investigators will monitor the occurrence of adverse events during the course of 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 imaging procedure.
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 imaging procedure.

- 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 imaging procedure; 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 adverse effects will be documented and recorded in the medical record and will include:

- Specific reaction according to NCI Common Toxicity Criteria, version 4.0.
- Duration of the reaction
- Severity/grade according to NCI Common Toxicity Criteria, version 4.0. 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).
- Relation of reaction to study agent
- Management of reaction, including any interruption or dose modification of the study drugs.

Event Types

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 (From the time of consent until the completion of the repeat PET/MR scan). However, the Investigator also will assess the possible relationship between the adverse event and the investigational imaging tracer.

Serious Adverse Events

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 by telephone or fax to the Principle Investigator.

XI. References

1. M. E. Juweid and B. D. Cheson, "Positron-Emission Tomography and Assessment of Cancer Therapy," *The New England Journal of Medicine,* pp. 496-507, 2006.

2. B. Fischer, U. Lassen, J. Mortensen, S. Larsen, A. Loft, A. Bertelsen, J. Ravn, P. Clementsen, A. Høgholm, K. Larsen and T. Rasmussen, "Preoperative Staging of Lung Cancer with Combined PET–CT," *The New England Journal of Medicine,* vol. 361, pp. 32-39, 2009.
3. R. L. Wahl, H. Jacene, Y. Kasamon and M. A. Lodge, "From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors," *The Journal of Nuclear Medicine,* vol. 50, pp. 122-150, 2009.
4. Boellaard R, O'Doherty MJ, Weber WA, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. European Journal of Nuclear Medicine and Molecular Imaging. 2009;37:181.
5. Rahmim A, Lodge MA, Karakatsanis NA, et al. Dynamic whole-body PET imaging: principles, potentials and applications. Eur J Nucl Med Mol Imaging. 2019;46:501-518.
6. Lodge MA. Repeatability of SUV in Oncologic (18)F-FDG PET. *J Nucl Med.* 2017;58:523-532.
7. A. G. Rockall, N. Avril, R. Lam, R. Iannone, P. Mozley, C. Parkinson, D. Bergstrom, E. Sala, S.-J. Sarker, I. A. McNeish and J. D. Brenton, "Repeatability of Quantitative FDG-PET/CT and Contrast-Enhanced CT in Recurrent Ovarian Carcinoma: Test–Retest Measurements for Tumor FDG Uptake, Diameter, and Volume," *Clinical Cancer Research,* vol. 20, no. 10, pp. 2751-2760, 2014.
8. Whisenant JG, Peterson TE, Fluckiger JU, Tantawy MN, Ayers GD, Yankeelov TE. Reproducibility of static and dynamic (18)F-FDG, (18)F-FLT, and (18)F-FMISO MicroPET studies in a murine model of HER2+ breast cancer. *Mol Imaging Biol.* 2013;15:87-96.
9. Krak NC, Boellaard R, Hoekstra OS, Twisk JW, Hoekstra CJ, Lammertsma AA. Effects of ROI definition and reconstruction method on quantitative outcome and applicability in a response monitoring trial. Eur J Nucl Med Mol Imaging. 2005;32:294–301
10. Rahmim A, Lodge MA, Karakatsanis NA, et al. Dynamic whole-body PET imaging: principles, potentials and applications. *European Journal of Nuclear Medicine and Molecular Imaging.* 2019;46:501-518.
11. Menda Y, Ponto LLB, Schultz MK, et al. Repeatability of Gallium-68 DOTATOC Positron Emission Tomographic Imaging in Neuroendocrine Tumors. *Pancreas.* 2013;42.
6. Callahan J, Kron T, Schneider-Kolsky M, Hicks RJ. The clinical significance and management of lesion motion due to respiration during PET/CT scanning. Cancer Imaging. 2011;11:224-236.
7. Liu C, Pierce LA, 2nd, Alessio AM, Kinahan PE. The impact of respiratory motion on tumor quantification and delineation in static PET/CT imaging. Physics in medicine and biology. 2009;54:7345-7362.
8. Kawano T, Ohtake E, Inoue T. Deep-inspiration breath-hold PET/CT of lung cancer: maximum standardized uptake value analysis of 108 patients. J Nucl Med. 2008;49:1223-1231.
9. Pan T, Lee TY, Rietzel E, Chen GT. 4D-CT imaging of a volume influenced by respiratory motion on multi-slice CT. Med Phys. 2004;31:333-340.
10. Dawood M, Lang N, Jiang X, Schafers KP. Lung motion correction on

respiratory gated 3-D PET/CT images. IEEE Trans Med Imaging. 2006;25:476-485.