Comparison of PET/CT vs. PET/MRI

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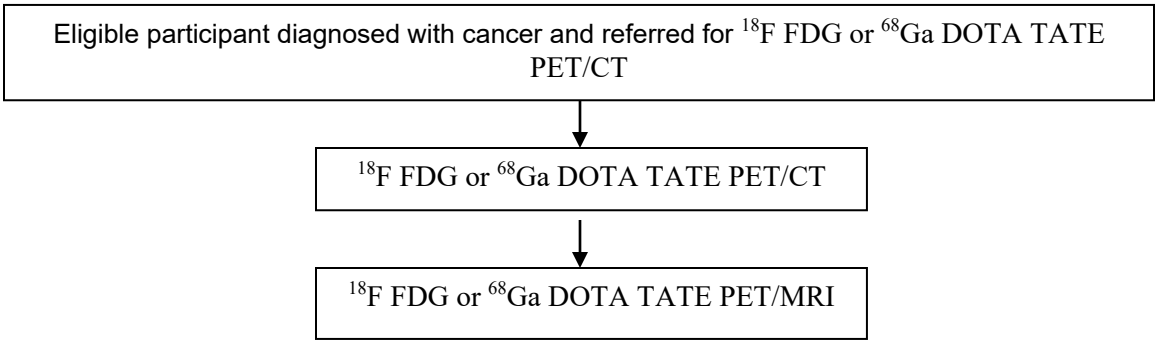
SCHEMA


Eligible participant diagnosed with cancer and referred for ^{18}F FDG or ^{68}Ga DOTA TATE PET/CT
^{18}F FDG or ^{68}Ga DOTA TATE PET/CT
^{18}F FDG or ^{68}Ga DOTA TATE PET/MRI

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

FDG	Fluorodeoxyglucose
IRB	Institutional Review Board
IV	Intravenous
PET/CT	Positron emission tomography – computed tomography
PET/MRI	Positron emission tomography – Magnetic resonance imaging
ROC	Receiver-Operative-Characteristic
SUV	Standardized Uptake Value

1. OBJECTIVES

1.1 Primary Objective

- To evaluate if PET/CT and PET/MRI scanners provide equivalent results for evaluation of cancer patients

2. BACKGROUND

2.1 Preliminary information

The recent introduction of hybrid PET/MRI scanners in clinical practice (*1-3*) showed promising initial results for several clinical scenarios (*4, 5*). More than a decade ago, multimodality imaging was introduced into clinical routine with the development of the PET/CT. Since then, PET/CT has been widely accepted in clinical imaging and has emerged as one of the main cancer imaging modalities. With the recent development of combined PET/MRI systems for clinical use, a promising new hybrid imaging modality is now becoming increasingly available. The combination of functional information delivered by PET with the morphologic and functional imaging of MR imaging (e.g., diffusion-weighted imaging, dynamic contrast-enhanced MR imaging and MR spectroscopy) offers exciting possibilities for clinical applications as well as basic research. However, the differences between CT and MR imaging are fundamental. This also leads to distinct differences between PET/CT and PET/MRI not only regarding image interpretation but also concerning data acquisition, data processing and image reconstruction. PET/MRI is expected to show advantages over PET/CT in clinical applications in which MRI is known to be superior to CT due to its high intrinsic soft tissue contrast. However, as of now, only assumptions can be made about the future clinical role of PET/MRI, as data about the performance of PET/MRI in the clinical setting are still limited (*6*).

2.2 Study Agent

We will use ^{18}F FDG and ^{68}Ga DOTA TATE as the PET radiopharmaceuticals.

2.3 Clinicaltrials.gov

^{18}F FDG is an FDA-approved product. Therefore no registration on clinicaltrials.gov is required. ^{68}Ga DOTA TATE PET/CT is already registered on clinicaltrials.gov.

2.4 Rationale

The Division of Nuclear Medicine and Molecular Imaging at Stanford has two of the most modern PET/CT scanners from GE Healthcare, the Discovery 600 PET/CT and Discover 690 PET/CT scanners. There will be a novel GE PET/MRI scanner installed at the Lucas Imaging Center. This will be the first of this kind to be produced by GE Healthcare. Therefore it is important to determine if PET/CT and PET/MRI scanners provide equivalent results for evaluation of cancer patients.

2.5 Study Design

This is a non-randomized prospective trial. Patients who are referred to Nuclear Medicine for evaluation of extent of cancer and are scheduled to undergo the ^{18}F FDG or ^{68}Ga DOTA TATE PET/CT will be asked to have the scan repeated on the same day using PET/MRI scanner. There will be a single injection of ^{18}F FDG or ^{68}Ga DOTA TATE followed by the PET/CT scan and immediately after by the PET/MRI scan. There will be no additional radiation to the patient. This is because only one injection of ^{18}F FDG or ^{68}Ga DOTA TATE will be given and the MRI uses non-ionizing radiation.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1 Inclusion Criteria

- Patient is ≥ 18 years old at the time of the scan
- Patient provides written informed consent
- Patient is diagnosed with cancer
- Patient is capable of complying with study procedures
- Patient is able to remain still for duration of imaging procedure (approximately 90 minutes total for PET/CT and PET/MRI)

3.2 Exclusion Criteria

- Patient is < 18 years old at the time of the drug administration
- Patient is pregnant or nursing
- Metallic implants (contraindicated for MRI)
- Renal function impairment preventing administration of MRI contrast

3.3 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

3.4.1 Primary Completion:

The study will reach primary completion 24 months from the time the study opens to accrual.

3.4.2. Study Completion:

The study will reach study completion 48 months from the time the study opens to accrual.

4. IMAGING AGENT INFORMATION

4.1 Study Agent

We will use ^{18}F FDG or ^{68}Ga DOTA TATE as the PET radiopharmaceuticals. These will be used as standard of care. The administered dosage is 10-12 mCi iv for ^{18}F FDG and 5-7 mCi for ^{68}Ga DOTA TATE.

4.2 Specify the source of the study agent.

Molecular Imaging Program at Stanford
Lucas Cyclotron Radiochemistry Facility
1201 Welch Road, Room PS049
Stanford, CA 94305-5484

4.3 Describe how the agent will be requested and provide mailing address and phone number.

Ordered in Radiology Information System (RIS), address per above.

4.4 Agent Accountability

RIS is password protected and part of the electronic medical records.

5. IMAGING SPECIFICS

5.1 Modality or Modalities to be used

PET/CT & PET/MR

5.2 Details of Imaging (i.e. dynamic, static, number of scans, etc.)

Whole-body (skull base to mid-thighs) PET/CT images will be obtained using the GE PET/CT 600 and 690 scanners (GE Healthcare) per standard oncologic protocols (*7*). In brief, PET/CT images will be acquired in 3D mode at 45-60 minutes after injection of 10-12 mCi of ^{18}F FDG or 5-7 mCi of ^{68}Ga DOTA TATE. The PET emission scan is corrected using segmented attenuation data of the CT scan. The PET images are reconstructed with a standard iterative algorithm (OSEM, two iterative steps, 28 subsets) using GE software release 5.0. All images are reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (AW, GE Medical Systems).

Immediately after completion of the PET/CT exam, the patients will be transferred to the PET/MRI suite at the Lucas Imaging Center and undergo the PET/MRI image acquisition with the least delay. Acquisition will start in the pelvic region and move toward the head. First, a localizer MRI scan will be performed to define the table positions. After correct positioning of the spatial acquisition windows will be ensured, the combined PET/MRI acquisition will be initiated with 3–5 table positions at a 4-min acquisition time per table position. First, a coronal 2-point Dixon 3-dimensional volumetric interpolated breath-hold T1-weighted MRI sequence will be acquired at each table position and used for the generation of attenuation maps and for anatomic allocation of the PET results. Simultaneously with the start of the Dixon MRI sequence, the PET acquisition will start at the same table position, thus ensuring optimal temporal and regional correspondence between MRI and PET data. The PET acquisition time will be 4 min per table position, taking delayed acquisition times and radioactive decay into account. After completion of the PET acquisition, the table will be moved to the next table position and the procedure will be repeated. In the thorax and abdomen regions, the MRI scans will be acquired during breath-hold in shallow inspiration, similarly to the acquisition of the low-dose CT (*8*). Other sequences may also be used as needed (*9*). Multiplanar pre- and post-contrast MR images may be obtained at multiple stations as needed. Images will be reformatted into axial, coronal, and sagittal views and viewed with the software provided by the manufacturer (AW, GE Medical Systems).

5.3 Details of processing/analysis

The PET/CT scans will be interpreted by ABNM certified Nuclear Medicine physicians, while the PET/MRI scans will be reviewed by ABNM certified Nuclear Medicine physicians and ABR certified Radiologists. All these investigators have significant clinical experience and will be blinded to the participants' medical history and the results of other imaging

modalities. Consensus read will be obtained for each scan. Each lesion will be tabulated and a comparison of lesion detection by each scanner will be conducted.

6. STUDY PROCEDURES

6.1 Criteria for Removal from Study

The Protocol Director may withdraw subjects from the study for one or more of the following reasons: failure to follow the instructions of the Protocol Director and/or study staff; determination that continuing the participation could be harmful to the subject; the study is cancelled or other administrative reasons.

6.2 Alternatives

The alternative is to not participate in the study.

7. STUDY CALENDAR

	Pre-Study	Week 1	12 Months
Informed consent	X		
Demographics	X		
Medical history	X		
^{18}F FDG or ^{68}Ga DOTA TATE PET/CT and PET/MRI done on the same day		X	
Data analysis			X

8. ADVERSE EVENTS AND REPORTING PROCEDURES

8.1 Potential Adverse Events

The administration of the radioactive substance will feel like a slight pinprick if given by intravenous injection. Patients who are claustrophobic may feel some anxiety while positioned in the scanner. Also, some patients find it uncomfortable to hold one position for more than a few minutes. The subjects will not feel anything related to the radioactivity of the substance in their body. Because the radioactivity is very short-lived, the radiation exposure is low. The substance amount is so small that it does not affect the normal processes of the body.

There will be a single injection of ^{18}F FDG or ^{68}Ga DOTA TATE followed by 1 PET/CT scan and 1 PET/MR scan. There will be no additional radiation to the patient. This is because only one injection of ^{18}F FDG or ^{68}Ga DOTA TATE will be given and the MRI uses non-ionizing radiation.

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. All such metallic objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means the patient should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. There is a possibility that the patient will experience a localized twitching sensation due to the magnetic field changes during the scan. This is expected and should not be painful. If the patient had a previous reaction to gadolinium-based contrast agents, a history of severe allergies, or a history of kidney disease, he/she should notify the operator/investigator.

8.2 Adverse Event Reporting

We do not anticipate hazardous situations for the subjects as a result of this protocol. However, procedures will be in place for verification of correct radiopharmaceutical dose and route of administration (i.e., each dose will be double checked for dosimetry and quality by a researcher and technologist). The study Principal Investigator (PI) or his designee will report unanticipated AEs related to the Stanford CCTO Safety Coordinator within 10 working days of becoming aware of the event (5 days if the event is life-threatening or resulted in death) using the Adverse Events Communication Form. If the principal investigator determines the unanticipated adverse device effect presents an unreasonable risk to subjects, the study will be terminated as soon as possible, but no later than 5 working days after the PI makes the determination and no later than 15 working days after first receiving notification of the effect.

9. REGULATORY CONSIDERATIONS

9.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

9.2 Data Management Plan

The CRFs will be stored in a locked office in the Nuclear Medicine clinic. Records will be kept using OnCore.

During the clinical investigation, the Protocol Director will evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome. Monitoring of the trial will occur every 8 weeks and a record of monitoring activities will be maintained by the study team.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will audit study related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC audits will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

10. MEASUREMENTS

10.1 Primary outcome measure

We will evaluate the maximum standardized uptake value (SUV_{max}) of ^{18}F FDG or ^{68}Ga DOTA TATE in the lesions detected with both scanners. There are now several papers based on other vendors' scanners (no GE PET/MRI scanner built yet). The authors showed that in oncologic patients examined with PET/CT and PET/MRI, the SUV_{max} values generally correlate well in normal organ tissues. SUV_{max} derived from PET/MRI can be used reliably in clinical routine. Differences observed between MRI and CT derived SUV values may be attributed to the time-delay between the PET/CT and PET/MRI scans or biologic clearance of radiotracer (*10, 11*).

10.2 Measurement Methods

Regions of interest will be placed around the lesions using the AW software (GE Healthcare) and the SUV_{max} values from the images acquired with both scanners will be recorded.

10.3 Measurement Time Points

SUV_{max} values of the lesions will be measured after the scan completion.

10.4 Response Review

The SUV_{max} values will be analyzed by Nuclear Medicine and Radiology physicians blinded to the diagnosis and results of the other scan, in a randomized order to avoid bias. Two physicians will review all scans independently. Both scans of a given patients will be analyzed by one physician, then separately by the second physician.

11. STATISTICAL CONSIDERATIONS

11.1. Statistical Design

Single arm prospective study of paired imaging studies.

11.2. Randomization

This study is to compare the images from two different scanners: PET/CT and PET/MR and patients are scanned with both scanners. No randomization will be done.

11.3. Interim analyses

No interim analyses are planned.

11.4. Descriptive Statistics and Exploratory Data Analysis

(see below)

11.5. Primary Analysis

11.1.1. Analysis Population

Analysis population: all lesions identified by either modality (per-lesion analysis).

11.1.2. Analysis Plan

Normal quantile plots of SUV_{max} for each scanner will be prepared to assess to what extent the distribution can be approximated by the normal distribution, and to suggest a suitable transformation if not. The distribution of SUV_{max} for each scanner will be summarized with means, standard deviations, range, median and upper and lower quartiles. The distribution of the difference (SUV_{max}_PET/CT – SUV_{max}_PET/MRI) (difference of transformed values if applicable) will likewise be summarized. Cumulative distribution (waterfall plots) may be prepared to assist in the evaluation of the results. Patient clinical and demographic characteristics will be summarized using relevant summaries (proportions for categorical variables, means and standard deviations for continuous variables.

The mean difference plus or minus twice the standard deviation of the difference will be calculated as a measure of absolute accuracy. The relative accuracy will be calculated by dividing the preceding interval by the arithmetic average of the mean SUV_{max} of the two scanners. The interpretation of these intervals is that we can expect that approximately 95% of future differences to lie in these intervals. A paired t-test will be used to aid in the interpretation of the results. Sensitivity analyses may be conducted using linear mixed effects models to account for possible clustering of lesions within patients.

The difference of SUV_{max} measures will be correlated with patient and lesion characteristics and with time after injection using the appropriate method (Pearson correlation for continuous variables such as age and time from injection, two-sample t-tests for binary attributes (sex) and analysis of variance for categorical variables).

11.6. Sample Size

Data from Kershah (*10*) shows coefficients of variation between SUV measurements between PET/CT and PET/MRI ranging from 0.21 to 0.51, about 0.33 for CT attenuation correction and 0.38 for MR attenuation correction. We present calculations assuming a CV of 0.38 for both modalities and a Pearson correlation of 0.5 (moderate scenario) and 0.9 (optimistic scenario). Assuming a Pearson correlation of 0.5 on the log scale, 200 subjects provide 80% power to detect a relative difference of 8% between the SUV_{max} values using the two modalities. With an optimistic assumption of a Pearson correlation of 0.9, 200 patients provide 80% power to detect a relative difference of 3.4%. These differences do not seem minute, they will be a bit larger with only 100 subjects: assuming a Pearson correlation of 0.5 on the log scale, 100 subjects provides 80% power to detect a relative difference of 11% between the SUV_{max} values using the two modalities. With an optimistic assumption of a Pearson correlation of 0.9, 200 patients provide 80% power to detect a relative difference of 5%.

11.7. Accrual estimates

We expect the accrual of 100 patients. There are approximately 4500 patients scanned each year using PET/CT for cancer, of which approximately 100 patients are Ga68 DOTA TATE PET/CT patients. We plan to enroll 15 participants/year and this is easily achievable given our experience with other protocols.

11.8. Criteria for future studies

At this time there are no future studies planned beyond the initial 100 participants.

Appendix: Inclusion/Exclusion Criteria Checklist

Subject Initials	**Inclusion Criteria** (From IRB approved protocol)	**Yes**	**No**	Supporting Documentation*
	1. Patient is ≥ 18 years old at the time of the drug administration	☐	☐	
	2. Patient provides written informed consent	☐	☐	
	3. Patient is diagnosed with cancer	☐	☐	
	4. Patient is capable of complying with study procedures	☐	☐	
	5. Patient is able to remain still for duration of imaging procedure (about one hour)	☐	☐	
	Exclusion Criteria (From IRB approved protocol)			
	1. Patient is < 18 years old at the time of the drug administration	☐	☐	
	2. Patient is pregnant or nursing	☐	☐	
	3. Metallic implants (contraindicated for MRI)	☐	☐	
	4. Renal function impairment preventing administration of MRI contrast (only for patients receiving contrast)	☐	☐	

IV. Statement of Eligibility

This subject is ☐ **eligible** / ☐ **ineligible** for participation in the study.

Signature:	Date:
Printed Name:	

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