^{68}Ga-DOTAXXX Positron Emission Tomography (PET) for Diagnosis, Staging and Measurement of Response to Treatment in Somatostatin Receptor-Positive Neuroendocrine Tumors

IMAGING MANUAL

1.0 Purpose and Background

It is the explicit purpose of this document to help harmonize radiochemical syntheses, imaging, analysis practices, and the collection of safety, efficacy, and change of management data for clinical trials with ^{68}Ga-DOTAXXXX in the United States. Through strict harmonization and documentation practices, it is anticipated that data collected from different trials may be effectively combined (i.e., to simulate a multi-center trial) for regulatory filing(s) that may aid in the more rapid approval of these clinically important PET radiopharmaceuticals.[1,2]

This imaging manual has been prepared to guide the use of ^{68}Ga-DOTAXXXX within the context of single- and multicenter clinical trials for the diagnosis, staging and measurement of response to treatment in somatostatin receptor-positive neuroendocrine tumors (NETS). Information taken from the approved INDs being held by the University of Iowa (DOTATOC: IND# 114,398) and Vanderbilt University (DOTATATE: IND# 111,972) are referenced in this manual. Reference is also made to the EANM Procedure Guidelines for PET/CT tumor imaging with ^{68}Ga-DOTA-conjugated peptides.[3]

For all ^{68}Ga-DOTAXXXX imaging performed in the United States, the DOTA agent must be obtained from a source that holds an FDA-approved IND for that agent.

2.0 Patient Selection Criteria

Patients may remain on their somatostatin therapies throughout the study. All pertinent dosing information must be collected and reported.

2.1 Inclusion Criteria

- Known or suspected somatostatin receptor positive tumor such as: neuroendocrine tumor (carcinoid, pancreatic neuroendocrine tumors, etc); pheochromocytoma; neuroblastoma; medulloblastoma; ectopic Cushing syndrome/non-pituitary ACTH elevation; tumor-induced osteomalacia. Supporting evidence may include MRI, CT, biochemical markers, and or pathology report.
- Karnofsky performance status of $\geq$50 (or ECOG/WHO equivalent)
- Not pregnant. A negative serum pregnancy test is required for all female subjects with child-bearing potential
- Able to provide informed consent
- At least 18 years of age

2.2 Exclusion Criteria

- Patients exceeding the weight limitations of the scanner or are not able to enter the bore of the PET/CT scanner due to Body Mass Index (BMI)
- Inability to lie still for the entire imaging time (e.g. cough, severe arthritis, etc.)
- Inability to complete the needed investigational and standard-of-care imaging examinations due to other reasons (severe claustrophobia, radiation phobia, etc.)
- Any additional medical condition, serious intercurrent illness or other extenuating circumstance that, in the opinion of the Investigator, may significantly interfere with study performance or interpretation.

- Previous systemic or radiation treatment for another cancer of any type within the last 2 months

3.0 Use of ^{68}Ga-DOTAXXXX

3.1 Preparation, Labeling and Dosing

^{68}Ga-DOTAXXXX is produced by qualified personnel who are experienced in clinical and investigational radiochemical syntheses for human use. Radiochemistry staff perform syntheses, conduct quality control tests and approve the final preparation following USP <823> standards. Before final release of the agent for administration, verification based on the release criteria (Appendix B) developed by SNMMI's Clinical Trials Network Gallium Users Group for ^{68}Ga-DOTAXXXX injection is required. Reference is also made to the European Pharmacopoeia.[4]

Each unit dose will be made close to the time of use due to the 68 minute half-life of the Gallium-68 and labeled in accordance with the usual and customary practice of the radiopharmacy at the facility. The standard label must meet local radiopharmaceutical labeling requirements that typically includes calibration date and time, expiration data and time, activity at time of calibration, volume, and identity of the radiopharmaceutical.

The amount of radioactivity injected into the patient's IV is recorded immediately prior to injection, with residual activity in the syringe recorded immediately after injection. Dose calibrators used must be regularly maintained and calibrated in accordance with current NRC or agreement state standards. An investigational record is maintained with a copy of each drug label, documentation on time of injection, pre- and post-injection activity, time and date of injection and patient identification information.

This single IV injection should contain a maximum mass dose of ^{68}Ga-DOTAXXXX of ≤50 µg. The total volume administered is typically between 2 and 20 mL.

3.2 Administration

3.2.1 Patient Preparation

3.2.1.1 There are no dietary restrictions for or nor activity limitations prior to ^{68}Ga-DOTAXXXX scans.

3.2.1.2 Octreotide (Sandostatin)[5] or Lanreotide (Somatuline) Treatments: Patients should remain on their prescribed treatment regimen. The scan should not impact the treatment regimen; however, the ^{68}Ga-DOTAXXXX PET/CT scan should be scheduled such that the scan is performed at the tail-end of the treatment cycle.

- Long-Acting (Sandostatin or LAR/Somatuline): Schedule scan at 4-6 weeks from last injection
- Short-Acting (Sandostatin): Schedule scan at least 12 hours after last Sandostatin injection.

3.2.1.3 Anxiety Medications: Patients who suffer from anxiety or claustrophobia may have Alprazolam or other medication as prescribed by physician. Patients

receiving these anti-anxiety drugs must arrange for a driver to take them home after the study.

3.2.2 Recommended Injected Dose

3.2.2.1 The injected dose should be 111-259 MBq (3-7 mCi) of ^{68}Ga-DOTAXXXX with a maximum peptide dose as described in the CMC section. The body weight of the patient should be taken into account (a dose of 185MBq [5 mCi] per 70 kg is recommended).

3.2.2.2 Injection: ^{68}Ga-DOTAXXXX should be administered intravenously through a large bore (≥21 gauge) indwelling catheter, preferably in an antecubital vein. Intravenous ports should not be used, unless no other venous access is available. If a port is used, additional flush volume should be used. As reproducible and correct administration of ^{68}Ga-DOTAXXXX is required for quantification purposes, extravasation or paravenous administration should be avoided. If an infiltration is suspected, the event and expected quantity should be recorded and the infiltration site should be imaged. The approximate amount of infiltration should be estimated from the images where possible. If the infiltration is greater than 5% of the administered dose and the quantitative result from the ^{68}Ga-DOTAXXXX PET/CT study is a primary or secondary endpoint, the data point might be censored from review or the subject might not be included in the study. The injection site should be documented on the appropriate case report form.

3.3 Monitoring and Quality Control

All study related data including the informed consent process, safety, efficacy, and patient treatment/management plan data should be recorded in the patient's permanent record. Sample data collection forms or case report forms are included in Appendix D.

To ensure that all study data is collected uniformly across all study sites, Good Clinical Practices should be followed according to ICH Guidelines for all patients (http://www.ich.org/products).

3.3.1 Patient Monitoring

Toxicity is graded according to the National Cancer Institute's (NCI) Common Toxicity Criteria for Adverse Events (CTCAE, v4). The principal investigator is responsible for determining the attribution of toxicity as it is relates to the investigational drug. All grades of toxicity are noted and reported appropriately.

The patient is carefully observed and monitored in the PET area from pre-injection work-up until approximately 45 minutes after completion of the scan. Vital signs (blood pressure, heart rate, body temperature) are measured and recorded prior to injection and again after the scan before the patient leaves the PET area. Laboratory testing includes serum creatinine pre- and post-scan if x-ray contrast is used. The patient is called 24 hours post-injection to determine if any adverse reactions occurred. Results of the phone call

are recorded. All adverse events are recorded in the patient's medical chart and in the study file.

A key component of the trial is the collection of the change in patient management data. For purposes of eventual reimbursement by CMS should the agent be approved by FDA, the careful documentation and timely collection of this data is critical. See Appendix D for Change in Management data collection pages.

3.3.2 Drug QA/QC

Investigational radiopharmaceutical Quality Control (QC) information is maintained for each unit dose for at least two years after a regulatory filing for the agent or a decision not to file a regulatory application. These data provide important information should there be a need to perform a root cause analysis for a failure-to-perform in a given investigational PET/CT scan.

3.3.3 Record Retention

The investigator should retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures.

If an NDA will be filed for ^{68}Ga-DOTAXXXX, and the data derived from this study is to be included, you must retain all study documents for a period of two years following successful approval and denial of the application. The organization filing the NDA will notify you when the study records are no longer needed.

If the investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Documentation of such transfer will be given in writing to the NDA sponsor.

4.0 Imaging Specifications

4.1 Acquisition and Reconstruction

4.1.1 Uptake Period

^{68}Ga-DOTAXXXX uptake into both tumors and other body tissues is a dynamic process that may differ significantly from patient to patient. Therefore, it is extremely important that (1) the time interval between ^{68}Ga-DOTAXXXX administration and the start of emission scan acquisition is consistent and (2) when repeating a scan on the same subject, it is essential to use the same interval between injection and acquisition in scans performed at different times.

The uptake time for ^{68}Ga-DOTAXXXX imaging should be 60 minutes. While the "target" tracer uptake time is 60 minutes, the "acceptable" window is from 55 to 70 minutes. The exact time of injection must be recorded; the time of injection initiation should be used as the time to be recorded as the radiotracer injection time. The injection and flush should

be completed within one minute with the rate of injection appropriate to the quality of the vein accessed for ^{68}Ga-DOTAXXXX administration so as to avoid compromising the integrity of the injection vein. When repeating a scan on the same subject, especially in the context of therapy response assessment, it is essential to apply the same time interval with target window of +/- 10 minutes provided that the scan must not begin prior to 55 minutes after the injection of ^{68}Ga-DOTAXXXX. If a limited anatomy scan is obtained at follow-up after a whole body scan was performed at baseline, the timing should be adjusted to be congruent with the timing for the same anatomic region as achieved during the baseline study.

4.1.2 CT Imaging Protocol

The ^{68}Ga-DOTAXXXX PET scan should be performed with a standard low-dose CT scan for attenuation correction (typically 10-40 mAs for a 70 kg adult patient),[6] but can and should conform to an institution's standard CT attenuation correction scan protocol. A second clinical quality CT with IV or oral contrast (using standard clinical dilute oral contrast protocol since many NETs and neuroblastoma involve the GI tract) can be performed following the ^{68}Ga-DOTAXXXX scan on the PET/CT scanner. For each subject, the same approach should be followed for all later imaging time points.

4.1.3 Subject Positioning

During the PET/CT, subjects should be positioned in the center of the field of view (FOV), preferably with the subjects' arms positioned overhead for whole-body imaging (to minimize beam hardening and FOV truncation artifacts). If the subject is physically unable to maintain arms above head for the entire whole-body examination, then the arms can be positioned along the side before the start of the scan. Arm positioning in a particular subject should be consistent between the PET emission and CT transmission scans at each time point and should be as consistent as possible for all later imaging time points.

The patient should be asked to empty their bladder just before placement on the imaging table.

4.1.4 Scanning Coverage and Direction

Anatomic coverage should include the top of head to the mid-thigh. Scanning direction is recommended to be caudal-cranial as a matter of convention, as this is typical for oncology scans – even though bladder filling is not a significant problem with ^{68}Ga-DOTAXXXX. Regardless, it is critical that for a given subject, scanning direction on baseline scans be duplicated for all later imaging time points.

4.1.5 Min/Bed Position

The actual scanning time is dependent on the make and model of the scanner, injected dose and patient body habitus. A minimum of 3 minutes per bed position is recommended for scanners with high efficiency and/or time-of-flight capabilities (e.g., 3D), but can and should be longer (typically 5 minutes per bed position) for scanners with

lower sensitivities (e.g., 2D), protocols with a lower injected dose and patients with larger Body Mass Indexes.

4.1.6 Imaging Data Reconstruction

- PET emission data must be corrected for geometrical response and detector efficiency (normalization), system dead time, random coincidences, scatter and attenuation.
- Data acquired in the 3D mode can be reconstructed directly using a 3D reconstruction algorithm or re-binned into 2D data and subsequently be reconstructed with a 2D reconstruction algorithm.
- Iterative reconstruction algorithms are current standard for PET (rather than filtered back projection) and should be used to reconstruct all PET images.
- Reconstructions should be performed with and without attenuation correction.
- Scanners must be properly normalized and calibrated to ensure uniformity and accuracy of SUV measurements within the limits of the spatial resolution

4.2 Image Interpretation

To maintain the rigor of a registration trial, the methods for image interpretation need to be clearly defined prospectively in the final study protocol. Adherence to the minimum criteria below is essential.

4.2.1 Treatment Planning Studies

For studies conducted under an expanded access IND, the ^{68}Ga-DOTAXXXX PET/CT scan will be evaluated as a clinical read with patient care decisions possibly based on the results. The scan should be read by an experienced board-certified and credentialed nuclear medicine physicians or equivalent, with adequate experience in PET/CT.

4.2.2 Blinded Studies

Readers of the investigational ^{68}Ga-DOTAXXXX PET/CT scan are blinded to the patient's identity. All investigational scans are independently read without discussions with other healthcare providers and without correlation with other imaging by at least one additional experienced board-certified and credentialed nuclear medicine physicians with at least 5 years of established expertise in PET/CT.

After the investigational ^{68}Ga-DOTAXXXX PET/CT has been independently interpreted, comparison is then made with other conventional imaging (CI), clinical, and laboratory data, as available.

Areas of data analysis specific to imaging include:

- Whether or not areas of tumor involvement are visible on the investigational ^{68}Ga-DOTAXXXX PET/CT scan that are not otherwise visible prospectively on CI.
- Whether or not the ^{68}Ga-DOTAXXXX PET/CT scan result caused the clinical care givers to change treatment, e.g. change within modality (e.g. change chemotherapy, change planned surgery) or across modalities (e.g. add molecular therapy [kinase inhibitors], Octreotide analogues, chemotherapy or radiation therapy to surgery, etc.). In discussion with clinical staff, impact on care is accessed for value added by the investigational ^{68}Ga-

DOTAXXXX PET/CT scan similar to assessment for impact on care as in the National Oncology PET registry, such as (1) Change in stage; (2) Change in treatment; (3) Change in prognosis.

- Whether previously identified lesions are growing or shrinking (post-therapy)
- Whether the scan identified the location of a previously unknown primary tumor
- Whether new lesions are appearing

4.3 Quantitative Image Analysis

For quantitation to be most robustly applied, images must meet the image acquisition guidelines as outlined within the UPICT Protocol[7] including, but not limited to,

- similar tracer uptake times (see Section 5.3 of FDG-PET/CT UPICT protocol)
- same scanner and reconstruction algorithm (see Section 7 of FDG-PET/CT UPICT protocol)
- similar injected dose (see Section 5.2 of FDG-PET/CT UPICT protocol)

Additionally, the same software and workstation model and version should be used for a given subject across all time points (and for central analysis for all sites and all subjects and all time points) for the analyses described in this section. Stability and acceptability guidelines have been articulated in the PERCIST 1.0 guidelines.[8]

Image analysis and interpretation also presumes that the image datasets to be used are corrected for attenuation, scatter, dead time, randoms, geometry, and normalization (see Section 7.3 of FDG-PET/CT UPICT protocol).[7]

In studies that require quantification, it is recommended that size and uptake of up to five "target" lesions (a maximum of 2 lesions per organ) should always be performed. For uptake, SUV_{max} measurements on the five hottest lesions as described above should be collected. In addition, SUV_{peak} measurements may be made if such measurements are available on the analysis workstation.

For size, CT-based measurements should be made per RECIST 1.1 criteria on the five target lesions is they are all visualizable on the CT. If measured, PET-based volume measurements should be made with 3D threshold-based VOI's with a 50% of maximum threshold.

If a follow-up ^{68}Ga-DOTAXXXX PET/CT scan is performed, the SUV_{max} measurements for the same five lesions should be collected. If a new lesion is now the hottest lesion, this SUV_{max} measurement and lesion location should be collected and documented.

5.0 Risk and Radiation Dosimetry

5.1 Radiation Exposure

5.1.1 Overall Radiation Risk Statement for ^{68}Ga-DOTAXXXX PET/CT Scan

The radiation dose associated with the administration of the ^{68}Ga-DOTAXXXX and the CT scan(s) should be tuned to result in the lowest radiation dose necessary to achieve the diagnostic objective.

The actual radiation dose resulting from the ^{68}Ga-DOTAXXXX PET/CT scan is dependent on the radiopharmaceutical, the injected ^{68}Ga-DOTAXXXX dose, and the CT parameters used. However, on average, a one-time dose of 5 mCi administered to the patient for the investigational ^{68}Ga-DOTAXXXX PET/CT results in approximately 5 mSv (500 mR) from the ^{68}Ga-DOTAXXXX injection. For comparison, the radiation dose for a 10 mCi administered dose of FDG is about 7.0 mSv. There is an additional 1.5 to 5.9 mSv[9] from the low-dose CT(10-40 mAs), for an average body habitus.

In total, this results in approximately 6.5 to 10.9 mSv. This is more than the 3 mSv (300 mR) of radiation that the average person in the United States gets each year from natural sources like the sun, outer space, air, food and soil. It is less than the 50 mSv (5000 mR) of radiation that is allowed each year for people who are exposed to radiation in their jobs.[9]

Although there are no proven short-term harmful effects from this amount of radiation, long-term effects such as cancer cannot be ruled out with certainty.

5.1.2 Radiation Dosimetry for ^{68}Ga-DOTAXXXX

A summary of radiation dosimetry for ^{68}Ga-DOTAXXXX and other related radiopharmaceuticals is listed below in Table 1. References for each of the table entries are provided beneath the table. The values in the table represent averages of the estimated male and female exposures as calculated by the original authors.

Table 1: Selected Organ and Effective Dose for Various ^{68}Ga-labeled Somatostatin Analogs, ^{111}In-DTPA-octreotide and ^{18}F- FDG[9]

Organs	^{68}Ga-DOTATATE[8]	^{68}Ga-DOTATOC[1a]	^{68}Ga-DOTANOC[2a]	^{111}In-DTPA-octreotide[3a]	^{18}F-FDG[4a]
Kidneys	9.21E-02	2.2E-01	8.97E-02	4.5E-01	1.7E-02
Liver	4.50E-02	7.4E-02	3.38E-02	7.0E-02	2.1E-02
Spleen	2.82E-01	2.4E-01	7.25E-02	3.2E-01	1.1E-02
Urinary bladder wall	1.25E-01	7.0E-02	8.36E-02	1.8E-01	1.3E-01
ED (mSv/MBq)*	2.57E-02	2.3E-02	1.67E-02	8.0E-02	1.9E-02
Units	mSv/MBq	mSv/MBq	mSv/MBq	mSv/MBq	mSv/MBq
Typical IA** MBq (mCi)	185 (5)	185 (5)	185 (5)	74 (2)	370 (10)
Estimated ED per exam (mSv)	4.8	4.3	3.1	5.9	7.0

*ED = effective dose
**IA = injected activity for an adult scan

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4a. Brix G, Lechel U, Glatting G, et al. Radiation exposure of patients undergoing whole-body dual-modality 18F-FDG PET/CT examinations. *J Nucl Med*. 2005;46:608-613.

5.1.3 CT Scan

The "low-dose" CT scan for anatomic localization and attenuation correction results in additional radiation dose. Ideally, the radiation exposure from the CT scans is minimized by the use of low tube current and the automated radiation exposure limiting features of the PET/CT scanner, which adjusts the tube current for each patient according to body habitus to minimize exposure for the CT portion of the PET/CT. The actual radiation dose from the CT scan should be calculated by a qualified medical physicist based upon the actual CT acquisition parameter used in the study.[10]

5.1.4 ^{68}Ga-DOTAXXXX Drug Mass Effects

The summary of human experience using ^{68}Ga-DOTAXXXX provides strong evidence that the mass quantity of the investigational drug (≤50 µg) is within the acceptable range for patients with life-threatening malignancies whose treatment may benefit from the use of the proposed PET/CT imaging procedure.

APPENDICES

APPENDIX A: Glossary

Item/Term	Definition
^{68}Ga-DOTAXXXX	generic term used to represent any of the three recognized investigational DOTA agents
^{68}Ga-DOTATATE	Gallium-labeled DOTA-(Tyr^3)-octreotate
^{68}Ga-DOTATOC	Gallium-labeled DOTA-(Tyr^3)-octreotide
^{68}Ga-DOTANOC	Gallium-labeled DOTA-(1-Nal^3)-octreotide
ACTH	adrenocorticotropic hormone
BMI	Body Mass Index
Ci	curie
cm	centimeter
CMC	chemistry manufacturing controls
CI	conventional imaging
CT	computed tomography
CTCAE	Common Toxicity Criteria Adverse Event
CTN	Clinical Trials Network
DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
EANM	European Association of Nuclear Medicine
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	[F-18]fluorodeoxyglucose
FOV	field of view
IND	Investigational New Drug
ID	identification
IV	intravenous
kg	kilogram
MBq	megabecquerel
mCi	millicurie
mL	milliliter
mm	millimeter
MRI	magnetic resonance imaging
mR	milliRem
mSv	millisievert
NCI	National Cancer Institute
NDA	New Drug Application
NETS	neuroendocrine tumors
NIH	National Institutes of Health
PERCIST	PET Response Criteria in Solid Tumors
PET	positron emission tomography
QA/QC	quality assurance / quality control
RECIST	Response Evaluation Criteria In Solid Tumor
rem	roentgen equivalent in man

SNMMI	Society of Nuclear Medicine and Molecular Imaging
SUV	standard uptake value
µg	microgram
US	United States
USP	United States Pharmacopoeia
UPICT	Uniform Protocols for Imaging in Clinical Trials
VOI	Volume of Interest
WHO	World Health Organization

APPENDIX B. Release Criteria (CTN Gallium Users Group)

Test	Suggested Acceptance Criteria
Appearance Visual Inspection	Clear, colorless solution; no visible foreign matter
pH	4 – 8
Endotoxins	<175 EU per dose or < 17.5 EU/mL whichever is lower
Radiochemical Purity	>90% Ga-68 DOTA-XXX
Radioisotope Identity and purity	Target half-life of 68 min (64-72)
Filter Integrity Test	Meets or exceeds filter manufacturer's defined testing specifications
Sterility	Sterile

APPENDIX C. Process Qualification and Periodic Verification

Testing performed during Process Qualification and Periodic Verification (3 consecutive lots) + annual or for each new batch of DOTA-XXX or Ga-Generator	
Upper limit of injected peptide mass of DOTA-XXX content	≤ 50 µg / injected dose based on Kit CoA (or calibrated balance and documented batch records)
Radiochemical Identity	HPLC: Retention matches reference standard (i.e., cold Ga-DOTA-XXX) or ITLC: >90% activity stays at origin
Heavy Metals	USP <233> (ICP-MS): Pb≤0.1µg/g; Hg ≤ 0.15 µg/g; As≤0.15 µg/g; Sb≤0.2µg/g; Sn≤150 µg/g; Fe≤150 µg/g (based on CoA of components)
Residual solvents - Acetonitrile (if used in process)	Meets USP specifications for any class 2 solvents used (GC)
Residual solvents - Acetone or Ethanol (if used in labeling process)	≤ 5 mg/mL for any Class 3 solvents used (GC-MS)
Upper limit for contamination by Ge-68 Breakthrough[3]	<0.001% of the total radioactivity is 68-Ge at the time of product expiration.

APPENDIX D. Acknowledgement and References

Acknowledgement:
Information found in various sections of this imaging manual was borrowed from the UPICT FDG-PET/CT Protocol Working Group Effort: http://qibawiki.rsna.org/index.php?title=FDG-PET_tech_ctte

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APPENDIX E. Data Collection Forms (*see separate attachment)*