SNMMI Procedure Standard/EANM Practice Guideline for SSTR PET: Imaging Neuroendocrine Tumors

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PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. Its 18,000 members are physicians, technologists, and scientists specializing in the research and practice of nuclear medicine. In addition to publishing journals, newsletters, and books, the SNMMI also sponsors international meetings and workshops designed to increase the competencies of nuclear medicine practitioners and to promote new advances in the science of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional nonprofit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985.

The SNMMI/EANM will periodically define new standards/guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients. Existing standards/guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated. Starting February 2014, the SNMMI guidelines have been referred to as procedure standards. Any practice guideline or procedure guideline published before that date is now considered an SNMMI procedure standard.

Each standard/guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI/EANM recognizes that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document.

The EANM and SNMMI have written and approved these standards/guidelines to promote the use of nuclear medicine procedures with high quality. These standards/guidelines are intended to assist practitioners in providing appropriate nuclear medicine care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, the SNMMI/EANM cautions against the use of these standards/guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgment regarding the propriety of any specific procedure or course of action must be made by medical professionals taking into account the unique circumstances of each case. Thus, there is no implication that an approach differing from the standards/guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the standards/guidelines when, in the reasonable judgment of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the standards/guidelines.

The practice of medicine involves not only the science but also the art of dealing with the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment. Therefore, it should be recognized that adherence to these standards/guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these standards/guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION

Somatostatin receptor (SSTR) imaging using PET has replaced scintigraphic imaging using ^{111}In-pentetreotide (OctreoScan), unless PET is unavailable. Several benefits of SSTR PET compared with ^{111}In-pentetreotide have driven this change: improved sensitivity of lesion detection; lower radiation dose; and shorter and more convenient study duration. Three SSTR PET radiotracers are currently available: ^{68}Ga-DOTATATE approved by the Food and Drug Administration (FDA) in 2016, ^{68}Ga-DOTATOC approved by the European Medicines Agency in 2016 and the FDA in 2019, and ^{64}Cu-DOTATATE approved by the FDA in 2020. ^{68}Ga-DOTANOC is also used at some institutions, although has not been approved by either the FDA or the EMA. The use of ^{68}Ga-DOTA-NOC generally mirrors that of ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE and has similar accuracy at detecting SSTR-positive disease.

SSTRs are overexpressed on a wide range of neuroendocrine tumor (NET) cells and can be targeted using somatostatin analogs (SSAs). Initially, SSAs were used not only for treatment of hormone-based symptoms but also to prevent disease progression (*1,2*). The first imaging agent to target the SSTR was ^{111}In-pentetreotide, and imaging included the use of SPECT or SPECT/CT. Imaging protocols typically required imaging 4 and 24 h after injection.

The development of the next generation of SSAs (DOTATATE and DOTATOC) resulted in faster tumor targeting and therefore enabled the use of positron emitters such as ^{68}Ga for radiolabeling. [68]Ga is most commonly produced using a [68]Ge/^{68}Ga generator, which can yield several doses per synthesis. More recently, SSAs have been labeled with ^{64}Cu, which is produced using a cyclotron.

II. GOALS

The goal of providing guidelines is to assist physicians in recommending, performing, interpreting and reporting the results of SSTR PET imaging studies for patients with NETs. This document aims to provide clinicians with the best available evidence, to inform where robust evidence is lacking, and to help them to deliver the best possible diagnostic efficacy and study quality for their patients. This guideline also presents standardized quality control/quality assurance (QC/QA) procedures and imaging procedures for SSTR PET. Adequate precision, accuracy, repeatability, and reproducibility are essential for the clinical management of patients and the use of SSTR PET within multicenter trials. A standardized imaging procedure will help to promote the appropriate use of SSTR PET and enhance subsequent research.

III. DEFINITIONS

Definitions are based on the EANM procedure guidelines for tumor PET imaging, version 2.0 (*3*):

PET/CT: An integrated or multimodality PET/CT system is a physical combination of PET and CT that allows sequential acquisition of PET and CT portions. The patient remains in the same position within both examinations. SSTR PET/CT examination may cover various coaxial imaging ranges. These are described as follows:

- Whole-body PET: From the top of the head through the feet.
- Skull base to midthigh PET: Base of the skull to midthigh. Covers most of the relevant portions of the body in many oncologic diseases (standard for both Europe and the United States). If indicated, cranially extended imaging may also cover the brain in the same scan (vertex to midthigh). In PET/CT studies,

attenuation correction and scatter correction are performed using the CT data.

CT: a combined x-ray source and detector rotating around the patient to acquire tomographic data. CT generates 3-dimensional images of tissue density, which allows for attenuation correction of PET and tumor visualization with a high spatial resolution.

A PET/CT examination can include different types of CT scans depending on the CT characteristics, the dose, and the use (or not) of oral or intravenous contrast agents.

- Low-dose CT scan: CT scan that is performed only for attenuation correction (CT-AC) and anatomic correlation of PET findings (with reduced voltage or current of the x-ray tube settings), that is, a low-dose CT is not intended a priori for a dedicated radiologic interpretation.
- Diagnostic CT scan: CT scan with or without intravenous or oral contrast agents, commonly using higher x-ray doses than low-dose scans. Diagnostic CT scan should be performed according to applicable local or national protocols and guidelines.

IV. COMMON CLINICAL INDICATIONS

Clinical indications for the use of SSTR PET have been previously discussed in the Appropriate Use Criteria (AUC) for SSTR PET, which has recently been updated (*4*). Common indications include initial staging at diagnosis, localization of primary tumor, staging before surgery, and selection of patients for peptide receptor radionuclide therapy (PRRT). Recently, the SSTR PET AUC was updated to include a post-PRRT study to serve as a new baseline 9–12 mo after the completion of treatment for future comparisons (*5*). Some NETs have lower expression of the SSTR, and therefore imaging using ^{18}F-FDG PET may be more beneficial. Neuroendocrine neoplasms are broken down into NETs and neuroendocrine carcinomas (NECs). NETs are well differentiated and are classified based on Ki-67 staining, which is a marker of cellular proliferation: grade 1 with $\leq$ 2% Ki-67 staining, grade 2 with 3%–20% Ki-67 staining, and grade 3 with $>$ 20% Ki-67 staining (*6*). Poorly differentiated NECs typically have a Ki-67 greater than 55%. Although ^{18}F-FDG uptake in well-differentiated NETs is only increased in part of the patients, the loss of differentiation and loss of SSTR expression in G3 NECs is generally associated with a significant increase in glycolytic metabolism and tumor aggressiveness. In general, G3 NECs rarely overexpress the SSTR and ^{18}F-FDG PET is usually preferred, whereas in G3 NENs, SSTR PET may be helpful.

Additionally, benign, localized insulinomas usually lack SSTR overexpression. In such cases, SSTR PET may not be useful and alternative tracers, such as glucagonlike peptide-1 receptor PET and 6-[^{18}F]-l-fluoro-l-3,4-dihydroxyphenylalanine (^{18}F-FDOPA) PET, are being tested in clinical trials (*7*). Also, medullary thyroid carcinomas frequently exhibit low-density and heterogeneous SSTR expression, resulting in a suboptimal imaging performance of SSTR PET, which is surpassed by that of ^{18}F-FDOPA PET (*8*).

V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

A. Physician

SSTR PET examinations should be performed by, or under the supervision of, a physician specialized in nuclear medicine and certified by accrediting boards. Physicians who interpret SSTR

PET results should also complete appropriate training programs provided by the manufacturers of approved radiotracers.

B. Technologist

SSTR PET examinations should be performed by qualified registered or certified nuclear medicine technologists. (see (9) for further details). According to location of practice, additional qualifications may be requested for technologists to use the CT and MR component of the scanner.

C. Medical Physicist

PET systems should comply with the international standard of quality, including dosimetry and radiation protection procedure, to limit the irradiation exposure of patients and health care personnel. A medical physicist should optimize protocols, ensuring that the established standards are met. A medical physicist can assist physicians to adhere to and maintain good practice, by monitoring and optimizing radiation dose and developing algorithms to reduce the radiation exposure of the CT component.

VI. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

As of the publication of this document, 3 SSTR-targeted radiotracers (including ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{64}Cu-DOTA-TATE) have been approved by the FDA and a ^{68}Ga-DOTATOC kit has been approved by the EMA for imaging of SSTR-positive malignancies. Although these radiotracers share a common imaging target and similar imaging characteristics, SSTR PET radiotracers can differ in their binding affinity and optimal imaging parameters. Overall, these radiotracers can be considered equivalent in terms of their ability to detect SSTR-positive disease.

A. Request

The nuclear medicine imaging facility should check with its local nuclear pharmacy provider as to the availability of the radiotracer before scheduling the examination. Advanced notice may be required for radiotracer delivery. The study requisition should include clinical information about the patient to justify the study and to allow coding of the examination or study, information about the ability of the patient to cooperate with the test, and information about current medications in case mild sedation is necessary. It is also helpful to know if the patient needs to be accompanied by a guardian.

B. Patient Preparation and Precautions

1. Prearrival and Patient Instructions. It is generally recommended that before SSTR PET imaging, patients discontinue all short-acting SSAs 12 h prior. Referring physicians should be instructed to schedule SSTR PET imaging just before dosing with long-acting SSAs. The EANM procedure guidelines for SSTR PET suggest an interval of 3–4 wk after administration of long-acting SSAs to avoid potential SSTR blockade (10). However, a recent prospective study with lanreotide (somatuline) showed that treatment immediately before SSTR PET had minimal effect on normal organ and tumor uptake (11). Therefore, it may be less important to have a prolonged interval from the most recent administered SSA than previously thought in patients receiving stable doses of long-acting SSAs, although it is unclear if this is true with octreotide acetate LAR (sandostatin) as compared with lanreotide (11–13).

Patients should drink water to ensure adequate oral hydration before administration of SSTR-targeted radiotracers and to continue to drink and void frequently during the first hours after administration to reduce radiation exposure to the bladder. The procedure should be carefully explained to the patient in an easily understandable manner, and patients may require reminders of the need for their cooperation during the scan from the technologist (i.e., limiting motion). For a variety of reasons, some patients may require sedation for the scan. The sedation method will vary by patient and may need to be determined on the basis of the information provided by the referring physician. Sedation should be arranged at the time an SSTR PET examination is scheduled so that the procedure will go smoothly and without delay.

It is not known whether SSTR PET radiotracers have harmful fetal effects. SSTR PET should be performed on a pregnant woman only if there is a clear clinical benefit. It is not known if SSTR PET tracers have harmful effects on infants or breast tissue. However, for caution in this rare instance and because of the potential for radiotracer excretion in human milk and potential radiation exposure to infants, either avoid performing SSTR PET imaging on a breastfeeding mother or have the mother interrupt breastfeeding for 24 h after administration of the radiotracer. SSTR PET is safe in the pediatric patient population (14,15), although in many countries pediatric use may be outside the marketing authorization.

C. Radiopharmaceuticals

Several SSTR-targeting radiotracers have been investigated: ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{64}Cu-DOTATATE. Although these radiotracers share a common imaging target and similar imaging characteristics, they can differ in their binding affinity and optimal imaging parameters, and hence have different recommended injected activities, times to initiate imaging after injection, and scan durations. Each radiotracer should be prepared according to good manufacturing practice or other applicable good practices within national regulations; QC procedures should follow the pharmacopoeia standards or provisions of the competent pharmaceutical authorities. Recommendations for kit-based radiolabeling methods are outside the scope of this document.

D. Administered Activity

All SSTR PET radiotracers are administered as an intravenous bolus injection. In adult patients, for ^{68}Ga-DOTATOC the prescribed activity is 148 MBq (4 mCi), with a range of 111–185 MBq (3–5 mCi) based on the FDA prescribing information (16) and 100–200 MBq (2.7–5.4 mCi) based on the EMA product information (17). For ^{68}Ga-DOTATATE, the prescribed administered activity is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi) (18), and for ^{64}Cu-DOTATATE the administered activity is 148 MBq (4 mCi) (19). ^{68}Ga-DOTATOC has a separate weight-based dosing for pediatric patients: 1.59 MBq/kg (0.043 mCi/kg), with a range of 11.1 MBq (0.3 mCi) to 111 MBq (3 mCi).

E. Uptake Time

In general, uptake times are similar for the 3 available SSTR-targeted radiotracers. The uptake times reported in the prescribing information for ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{64}Cu-DOTATATE are 55–90 min, 40–90 min, and 45–90 min, respectively (16–19). It should be noted that ^{64}Cu has a longer half-life than ^{68}Ga (12.7 h vs. 68 min), and therefore a later imaging time point with ^{64}Cu may be feasible, although this is not acknowledged in the package insert. It is currently unclear if delayed imaging with ^{64}Cu-DOTATATE provides benefit compared with standard imaging times, but it has recently been shown that imaging at 1 and 3 h have comparable lesion detection rates (20).

F. Image Acquisition

Imaging should start at the vertex and extend to the midthighs. Although a small lesion seen on PET may be better characterized with a diagnostic-quality CT, both CT and PET acquisition parameters will be scanner- and institution-dependent. Intravenous CT contrast is optional; however, it can improve characterization of hepatic metastases and other soft-tissue lesions. If diagnostic CT is performed, water should be used as oral contrast, since it will not obscure the CT identification of gastrointestinal lesions.

Time-of-flight PET with a reconstruction method including modeling of resolution degradation, often referred to as point spread function reconstruction, may help with the detection of small lesions. PET data should be fused with both standard and bone CT reconstructions.

PET/MRI may be used instead of PET/CT and may be beneficial for patients with liver-dominant NETs due to the ability to perform hepatobiliary phase imaging. Details about acquisition protocol and reconstruction for PET/MRI are beyond the scope of this guideline. For details, see relevant literature (21).

G. Impact of [64]Cu Versus [68]Ga

The range of the positrons is one of several components that will affect the spatial resolution of PET images. The amount of image blurring due to the positron range depends on the energies of the positrons emitted from the particular isotope. Positron emitters such as ^{18}F and ^{64}Cu emit positrons of relatively low-energy (250 and 278 keV, average energy, respectively) and the amount of resolution loss from the positron range is 0.2 mm in full width half maximum (FWHM) or 1.3 mm in full width tenth maximum (FWTM). The energy of the positrons from ^{68}Ga is significantly higher (836 keV, average energy) and the loss in spatial resolution is 0.8 mm FWHM or 4.7 mm FWTM. Any loss in spatial resolution will affect quantification and will underestimate activity concentration and SUV, particularly for small lesions. It is difficult to generalize how much of the greater positron range of ^{68}Ga will affect quantification in small lesions compared with [64]Cu. The reason for this is the complex interplay of the components that contributes to the final image resolution (i.e., the intrinsic detector resolution, system diameter, image reconstruction algorithm, and spatial filtering). Under typical clinical imaging conditions, it is expected that there will be an additional 10%–20% underestimation in small lesions (10–15 mm diameter) when imaging with ^{68}Ga compared with [64]Cu.

Additionally, the positron emission yield of 17.4% for ^{64}Cu is significantly lower than the yield 88.9% for [68]Ga. To achieve the same number of counts in the study, it would be necessary to image for approximately 5 times longer, assuming the same injected activity. However, when taking into account the longer physical half-life of [64]Cu (12.7 h) compared with [68]Ga (68 min), the difference in scan time 55–90 min after injection for the same injected dose is reduced to approximately 2 times longer. However, for practical reasons the scan time is not increased as this may to lead to patient motion during imaging. In theory, the injected activity could be increased instead, but one hesitation to doing this may be the dosimetry of ^{64}Cu-DOTATATE as the radiation dose per injected activity for ^{64}Cu-DOTATATE is 20%–25% higher than for ^{68}Ga-DOTATATE (Table 1). The expected increase in image noise due to the lower positron yield of ^{64}Cu can be reduced by applying a smoother spatial filter compared with the filter used for [68]Ga. Nonetheless, using standard image acquisitions, the ^{64}Cu-DOTATATE produces diagnostic scans equivalent to the 2 gallium-labeled compounds.

One of the main advantages of using ^{64}Cu over ^{68}Ga is the longer half-life. This makes the distribution logistics easier and delivery times less critical. Furthermore, the long half-life makes the ^{64}Cu less susceptible to delays in imaging after a patient has been injected compared with ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC.

VII. DOCUMENTATION AND REPORTING

A. Study Identification

The final report should include the full name of the patient, sex assigned at birth, medical record number, date of birth, and date of the examination.

B. Clinical Information

As a minimum, a summary of relevant clinical history should include reason for referral and the specific clinical question to be answered. If known, the primary location and grade of the tumor should be provided. The type and date of comparison studies should

TABLE 1
Dosimetry for ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, ^{64}Cu-DOTATATE, and ^{18}F-FDG

Organ	^{68}Ga-DOTATATE (22)	^{68}Ga-DOTATOC (48)	^{64}Cu-DOTATATE (49)	^{18}F-FDG (50)
Organ (mSv/MBq)				
Kidneys	9.2E–02	2.2E–01	1.4E–01	1.7E–02
Liver	4.5E–02	7.4E–02	1.6E–01	2.1E–02
Spleen	2.8E–01	2.4E–01	1.2E–01	1.1E–02
Bladder wall	1.3E–01	7.0E–02	3.7E–02	1.3E–01
Dose				
ED (mSv/MBq)	2.6E–02	2.3E–02	3.2E–0.2	1.9E–02
Typical IA				
MBq	200	185	148	370
mCi	5.4	5	4	10
Estimated ED per scan (mSv)	5.2	4.3	4.7	7.0

ED = effective dose; IA = injected activity.

be stated. If no comparison studies are available, a statement should be made to that effect. Finally, whether the patient is on SSA therapy and which therapy and duration of therapy should be noted.

C. Technical Details

Study-specific information should include the radiopharmaceutical, the amount of injected activity in megabecquerels (MBq) or millicuries (mCi), the route (intravenous) and anatomic site of administration, and the date and time of administration. If extravasation is seen, it should also be noted. The uptake time interval between the administration of the radiopharmaceutical and the start time of the acquisition should be reported. The body parts covered by imaging should be described. Any nonstandard position of the patient should be stated.

The direction and range the patient image was acquired should be stated (i.e., "images were acquired from the vertex to the midthigh"). If a nonoptimized CT was performed for attenuation correction and anatomic registration of the emission images only, the description may be limited to a short statement including the mAs and kVp. If a diagnostic CT was performed, then a more detailed description of the CT protocol and anatomic findings should be provided. Dosimetry parameters should be included if required by national or local regulations. The report should state whether contrast-enhanced or nonenhanced CT was used for attenuation correction.

D. Description of Findings

Quality issues of the PET, for example, motion artifacts, halo artifacts due to high activity in the collecting urinary system, or attenuation artifacts (from attenuating materials), should be reported.

E. Interpretation

1. Biodistribution. Physiologic uptake is present and most intense in the kidneys and bladder, spleen, and liver (Fig. 1). Normal uptake is also seen in the pituitary, adrenal glands, salivary glands, and the thyroid ([22]). ^{64}Cu-DOTATATE allows for late imaging. At 3 h after injection, ^{64}Cu-DOTATATE uptake decreases for kidney and bladder, remains unchanged for spleen, and increases for liver, although differences in early versus late biodistribution do not impact lesion detection ([20]). At early time-point
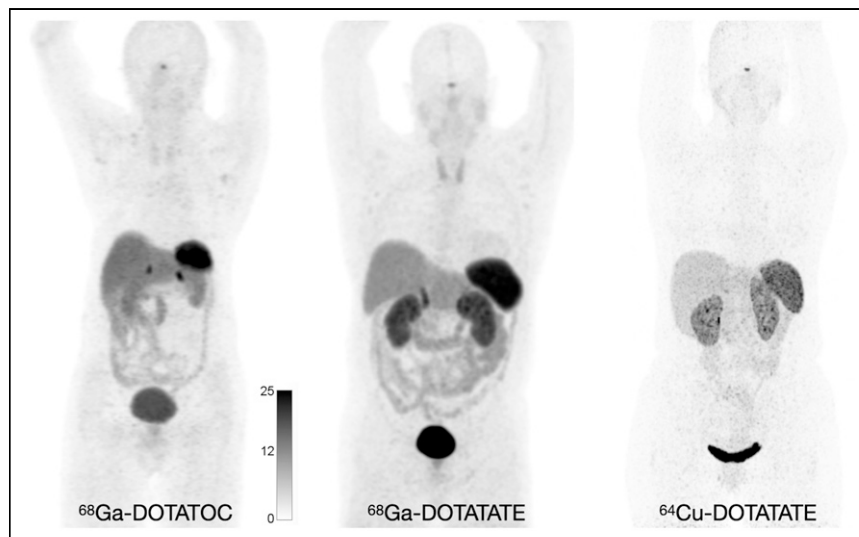

FIGURE 1. Normal biodistribution of ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{64}Cu-DOTATATE.

acquisition, no clinically meaningful difference in organ uptake was demonstrated for ^{68}Ga-DOTATOC versus ^{64}Cu-DOTATATE ([23]) or ^{68}Ga-DOTATATE versus ^{68}Ga-DOTATOC, respectively ([20]). There are no major differences between physiologic uptake of ^{64}Cu-DOTATATE and ^{68}Ga-labeled DOTATATE (Table 2) ([24]).

2. General Interpretation. Images should be interpreted by a physician trained in SSTR PET/CT imaging and informed about the clinical context of the scan indication (e.g., staging, assessment for PRRT, restaging). Focal tracer uptake that cannot be explained by physiologic biodistribution or that is higher than organ background activity is to be considered pathologic, especially if there is a correlating abnormal structure on CT. Consistent qualitative grading of uptake (mild = blood pool, moderate = liver, intense = clearly above liver) can be used in addition to SUV-related measurements and modified Krenning score.

3. Incidental Findings, Normal Variants, and Important Pitfalls. Increased uptake on SSTR PET does not make the diagnosis of a NET, and care should be taken in interpretation. For example, physiologically increased uptake in the head/uncinate process of the pancreas is observed in a large portion of patients (diffuse or focal) and usually remains stable over time ([25]). This physiologic uptake in the head/uncinate process of the pancreas is thought to be caused by a higher concentration of pancreatic polypeptide producing cells in this region. There is a significant overlap between

TABLE 2
Comparison of physiologic uptake of ^{68}Ga-DOTATATE and ^{64}Cu-DOTATATE

Organ SUV$_{mean}$ - mean (SD)	^{68}Ga-DOTATATE (60–80 min after injection) ([20])	^{68}Ga-DOTATOC (50–70 min after injection) ([51])	^{64}Cu-DOTATATE (43–80 min after injection) ([24])
Liver	4.5 (1.5)	5.7 (1.6)	4.0 (1.1)
Spleen	15.5 (5.5)	—	8.9 (3.4)
Pituitary gland	6.8 (2.3)	4.1 (1.8)	12.9 (6.1)
Adrenal gland	10.1 (3.7)	7.2 (3.1)	9.5 (4.4)
Uncinate process of pancreas	6.7 (2.2)	—	3.2 (0.5)

*Median.

the SUVs of the physiologic pancreas and tumoral lesions of the head/uncinate process (26), which can result in false-positive interpretations. Correlation with MRI or multiphase CT, with subsequent follow-up with SSTR PET, may be useful in challenging cases.

Splenules demonstrate high levels of physiologic uptake, similar to the spleen (27). Avoiding a false-positive interpretation can be especially challenging in the setting of intrapancreatic splenules, or in differentiating peritoneal splenosis from new tumor deposits after a splenectomy. In these cases, heat-damaged red blood cell or sulfur colloid SPECT/CT may be useful to confirm the locations of ectopic splenic tissue.

Finally, SSTR2 is expressed by normal osteoblasts (28) and white blood cells including macrophages (29), which can lead to false-positive interpretations. Areas of high osteoblastic activity can have increased osseous uptake on SSTR PET and include degenerative changes, fractures, and benign lesions such as fibrous dysplasia (27). In challenging cases, correlation with dedicated CT or MRI can help distinguish tumor from nontumor pathology. Areas of high leukocyte activity can have increased uptake on SSTR PET and may be seen in postradiation changes and reactive lymphadenopathy including sarcoidosis and infections such as tuberculosis (27).

4. Semiquantitative Analysis. Quantification of uptake using PET is typically defined using SUV, but it should be noted that SUV measurements may not be reproducible across scanners and institutions without standardization of image protocols, scanner qualifications, and cross-calibrations. In addition, SUV can be affected by lesion size and uptake time among other issues. The Krenning score is the most common approach to qualitative interpretation and was originally developed for planar or SPECT imaging with ^{111}In-pentetreotide. When using SSTR PET, lesional uptake is characterized using the modified Krenning score (24,27). Identical to the Krenning score, the modified Krenning score is based on the lesion with the highest SSTR uptake: 0, no uptake; 1, very low uptake; 2, uptake less than or equal to that of the liver; 3, uptake greater than the liver; and 4, uptake greater than that of the spleen. SSTR PET leads to higher Krenning scores than with ^{111}In-pentetreotide, particularly in patients with small SSTR-avid lesions (<2 cm) (30). Additional SSTR PET–based lesion assessment methodologies described in the literature include the use of tumor-to-liver ratios (31) and the proposed SSTR-RADS reporting system (32). It should be noted that an increase or decrease in uptake within a lesion should not be taken as an indicator of response or progression as seen with other radiotracers.

5. SSTR PET as a Predictive Biomarker for PRRT. The indication for PRRT relies on sufficient target expression. SSTR PET can be used to assess the SSTR expression level based on the modified Krenning score. In the NETTER-1 trial, patients with a Krenning score > 2 were eligible, but the study used ^{111}In-pentetreotide for enrollment and it is unclear how SSTR PET should be used for patient selection for PRRT (33). In general, the higher the uptake on SSTR PET, the better the expected response to PRRT (31,34).

6. Disease Heterogeneity and False-Negatives. SSTR expression generally correlates with the degree of tumor differentiation, with well-differentiated G1/G2 and even well-differentiated G3 tumors expressing the SSTR while poorly differentiated G3 NECs lack the SSTR (35,36). The heterogeneity of SSTR expression appears to be a poor prognostic factor in patients treated with PRRT (37–39). However, within grades, tumor behavior of NET can vary widely. Ki-67 is frequently determined based on a single metastatic lesion that may not reflect intrapatient tumor heterogeneity. In contrast, PET imaging provides a whole-body assessment of the SSTR expression. ^{18}F-FDG PET provides information complementary to SSTR PET by helping identify lesions that have lost SSTR expression (40). ^{18}F-FDG positivity is not rare in G1/G2 NET and is a stronger predictor of progression and prognosis than tumor grade (41,42). In particular, ^{18}F-FDG PET can be useful in patients with a negative SSTR PET result or a well-differentiated G3 tumor (43). Combining ^{18}F-FDG and SSTR PET imaging can identify the highest-grade, most aggressive lesion (i.e., ^{18}F-FDG–positivity and SSTR-negative) that may lead to better selection of biopsy site to identify the highest-grade disease (44). Of note, a combined ^{18}F-FDG and SSTR PET grading system (NETPET grade) has been developed that relies not only on the lesion with the highest SSTR PET uptake but also on the SSTR/^{18}F-FDG phenotype across the entire tumor burden (41).

False-negatives, although uncommon, can occur. For example, G3 NECs (44), generally have lower uptake than well-differentiated G1/G2 tumors. The term "false-negative" in this case is relative, because the tumor has been accurately characterized versus being detected by SSTR PET. Medullary thyroid cancer and insulinomas also have variable expression of SSTR. Nonfunctional tumors may be more likely than functional NETs to be negative on SSTR PET (45). Like other radiotracer studies, lesions may be false-negative on SSTR PET due to small size or being within or in proximity to organs with high physiologic uptake. The higher sensitivity of SSTR PET compared with ^{111}In-pentetreotide planar or SPECT(/CT) imaging has helped to overcome these limitations (46,47).

VIII. DOSIMETRY

The estimated absorbed and effective radiation doses for adult patients after intravenous injection of ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{64}Cu-DOTATATE are shown in Table 1. For an adult weight of 75 kg based on the prescribing information, the effective radiation dose is 3.2 mSv for ^{68}Ga-DOTATATE for a 150-MBq (4.1 mCi) administration, 3.1 mSv for ^{68}Ga-DOTATOC for a 148-MBq (4 mCi) administration, and 4.7 mSv for a 148-MBq (4 mCi) administration of ^{64}Cu-DOTATATE (16,18,19).

IX. ACKNOWLEDGMENTS

X. REFERENCES

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