

# ACR–ACNM–SNMMI PRACTICE PARAMETER FOR THE PERFORMANCE OF GALLIUM-68 AND COPPER-64 DOTATATE PET/CT IMAGING FOR NEUROENDOCRINE TUMORS

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## PREAMBLE

This document is an educational tool designed to assist practitioners in providing appropriate radiologic care for patients. Practice Parameters and Technical Standards are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care<sup>1</sup>. For these reasons and those set forth below, the American College of Radiology and our collaborating medical specialty societies caution against the use of these documents 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 the practitioner considering all the circumstances presented. Thus, an approach that differs from the guidance in this document, standing alone, does not necessarily imply that the approach was below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in this document when, in the reasonable judgment of the practitioner, such course of action is indicated by variables such as the condition of the patient, limitations of available resources, or advances in knowledge or technology after publication of this document. However, a practitioner who employs an approach substantially different from the guidance in this document may consider documenting in the patient record information sufficient to explain the approach taken.

The practice of medicine involves the science, and 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 the guidance in this document will not assure 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 purpose of this document is to assist practitioners in achieving this objective.

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<sup>1</sup> *Iowa Medical Society and Iowa Society of Anesthesiologists v. Iowa Board of Nursing*, 831 N.W.2d 826 (Iowa 2013) Iowa Supreme Court refuses to find that the "ACR Technical Standard for Management of the Use of Radiation in Fluoroscopic Procedures (Revised 2008)" sets a national standard for who may perform fluoroscopic procedures in light of the standard's stated purpose that ACR standards are educational tools and not intended to establish a legal standard of care. See also, *Stanley v. McCarver*, 63 P.3d 1076 (Ariz. App. 2003) where in a concurring opinion the Court stated that "published standards or guidelines of specialty medical organizations are useful in determining the duty owed or the standard of care applicable in a given situation" even though ACR standards themselves do

## **I. INTRODUCTION**

This practice parameter was revised collaboratively by the American College of Radiology (ACR), the American College of Nuclear Medicine (ACNM), and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) to guide physicians requesting and interpreting oncologic positron emission tomography (PET) and computed tomography (CT) radiolabeled DOTA-Tyr3-octreotate ( DOTATATE) scans for adult and pediatric patients.

Radiopharmaceuticals targeting cell membrane expression of somatostatin receptors (SSTRs) are particularly useful in the evaluation of neuroendocrine tumors (NETs). Several PET radiopharmaceuticals targeting SSTRs have been investigated. A few of these include gallium-68 or copper-64 DOTATATE, DOTA-NaI3-octreotide, and DOTA-Tyl3-octreotide. These radiopharmaceuticals share a characteristic usefulness for imaging SSTR expressing tumors. Although they differ in their affinity for specific subtypes of the receptors, they are considered clinically equivalent [1]. This parameter will focus on the 2 commercially available agents in the United States, gallium-68 or copper-64 radiolabeled-DOTATATE , used for SSTR PET imaging, which is the most sensitive method of detecting, staging, characterizing, and monitoring well-differentiated NETs [2].

SSTR PET has been shown to have a high impact on the management of neuroendocrine patients compared to anatomical imaging. It has been shown to be significantly superior to gamma imaging (indium-111 diethylenetriaminepentaacetic acid DTPA-octreotide or Octreoscan) and has since essentially replaced these planar and/or single-photon emission computed tomography/CT techniques [3,4]. Radiolabeled DOTATATE and fluorodeoxyglucose (fluorine-18-2-fluoro-2-deoxy-D-glucose [FDG]) imaging are complementary to each other, with the degree of uptake varying depending on the degree of differentiation of the tumor. Well-differentiated tumors typically maintain their SSTR expression and have high DOTATATE uptake , whereas dedifferentiated tumors are less likely to demonstrate DOTATATE uptake but will demonstrate FDG uptake [5].

PET cameras are typically fused with either CT or magnetic resonance imaging (MRI). Combined PET devices [6,7] provide both the molecular information from DOTATATE PET and the anatomic information from CT or MRI in a single examination [8]. The information obtained by these combined, hybrid PET scanners has been shown to be more accurate in evaluating patients with known or suspected malignancy than either modality alone or with retrospective fusion techniques [9-11]. The advantages of both modalities in a single device have resulted in rapid dissemination of this technology in the United States and throughout the world. This practice parameter pertains only to hybrid PET devices.

Issues related to PET practice include equipment specifications, image acquisition protocols, supervision, interpretation, professional qualifications, and safety. A discussion of these issues by representatives of the ACR, the SNMMI, and the Society for Advanced Body Imaging (SABI) is available [12,13]. This document will focus on PET/CT imaging techniques, and specific technical details of PET/MR imaging are not included.

For additional information on Definitions, see Appendix A.

## **II. INDICATIONS AND CONTRAINDICATIONS**

Radiolabeled DOTATATE PET is indicated for localization of SSTR-expressing NETs in adult and pediatric patients. Examples of clinical indications include, but are not limited to, the following [14]:

1. Localization of the primary NET.
2. Helping to confirm the diagnosis in patients with anatomic lesions that are suspicious for NET on conventional imaging.
3. Detecting NETs in patients with strongly suggestive symptoms and laboratory evidence of NET but with no known primary tumor, although this role is not fully established.

4. Detection of NETs in patients with genetic syndromes such as multiple endocrine neoplasia type 1 or 2 and neurofibromatosis type 1.
5. Staging and evaluation of the extent of disease.
6. Identifying patients who are candidates for Peptide Receptor Radionuclide Therapy (PRRT) and as an adjunct to conventional imaging for response assessment after PRRT.
7. Radiolabeled DOTATATE PET/CT has been shown to be superior to indium-111 DTPA-octreotide scintigraphy in the evaluation of tumor induced osteomalacia and paraganglioma. Similarly, these have been shown to be superior to iodine-123 metaiodobenzylguanidine (MIBG) scintigraphy in the evaluation of neuroblastoma [15]. However, in select patients, iodine-123 MIBG can detect SSTR discordant lesions in patients who may benefit from iodine-131 MIBG radioligand therapy [16].

The [ACR–SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Patients with Ionizing Radiation](#) provides useful information on radiation risks to the fetus regardless of source. Information on managing pregnant or potentially pregnant patients undergoing nuclear medicine procedures is available from the International Commission on Radiological Protection [24].

### **III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL**

#### **A. Physician**

All PET examinations must be performed under the supervision of and interpreted by a physician who has the following qualifications:

Board certification or board eligibility in Radiology, Diagnostic Radiology, Interventional Radiology/Diagnostic Radiology (IR/DR), Nuclear Radiology, or Nuclear Medicine by the American Board of Radiology, American Board of Nuclear Medicine, American Osteopathic Board of Radiology, American Osteopathic Board of Nuclear Medicine, the Royal College of Physicians and Surgeons of Canada, or the Collège des Médecins du Québec.

or

At a minimum, completion of a formal Accreditation Council for Graduate Medical Education approved general nuclear medicine program.

If interpreting oncologic PET examinations, interpretation must include direct image correlation with relevant prior imaging. Knowledge of prior surgical, local, systemic and/or interventional radiological procedures related to the primary diagnosis is also pertinent.

Continuing Education

See the [ACR Practice Parameter for Continuing Medical Education \(CME\)](#) [25].

In addition, all physicians supervising and/or interpreting nuclear medicine examinations must satisfy all applicable state and federal regulations as well as any institutional policies that pertain to the in vivo use of radiopharmaceuticals, performance of imaging procedures, and safe handling of radioactive materials.

### **III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL**

#### **B. Qualified Medical Physicist**

For Qualified Medical Physicist qualifications, see the [ACR–AAPM Technical Standard for Medical Physics Performance Monitoring of PET/CT Imaging Equipment](#) [26].

### III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

#### C. Radiologic and Nuclear Medicine Technologist

Representatives of the SNMMI and the American Society of Radiologic Technologists (ASRT) met in 2002 to discuss the training and certification of technologists for PET imaging. The recommendations from that conference are outlined in the published consensus statement [27]. A key point is that technologists operating hybrid PET units would ideally be credentialed in both modalities. However, that is a goal and not a requirement. Subject to state licensure requirements, any registered radiographer with the credential R.T.(R), registered radiation therapist with the credential R.T.(T), registered nuclear medicine technologist with the credentials R.T.(N), or certified nuclear medicine technologist, C.N.M.T., may operate PET equipment after obtaining appropriate additional education or training and demonstrating competency. However, local regulations of hybrid PET imaging may require certification in both modalities, and facilities must comply with such regulations.

As a result of the consensus conference, a PET/CT Project Group meeting was convened by the ASRT and the Society of Nuclear Medicine Technologist Section to identify the skills and knowledge required for technologists performing PET/CT examinations and to recommend educational pathways for technologists to transition to PET/CT. The PET/CT curriculum was a product of this meeting (<https://www.asrt.org/educators/asrt-curricula>).

The Nuclear Medicine Technology Certification Board has developed PET and CT specialty examinations ([www.nmtcb.org](http://www.nmtcb.org)), and the American Registry of Radiologic Technologists offers a CT certification examination ([www.arrt.org](http://www.arrt.org)).

For more information regarding training and certification, see the [ACR Practice Parameter for Performing and Interpreting Diagnostic Computed Tomography \(CT\)](#) and the [ACR-ACNM-SNMMI-SPR Practice Parameter for the Use of Radiopharmaceuticals in Diagnostic Procedures](#) [28,29].

### III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

#### D. Radiation Safety Officer

The Radiation Safety Officer must meet applicable requirements of the Nuclear Regulatory Commission for training as specified in 10 CFR 35.50, or equivalent state regulations [30].

### IV. SPECIFICATIONS OF THE EXAMINATION

#### A. The written or electronic request for the examination

The written or electronic request for a gallium-68 or copper-64 DOTATATE PET examination should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation.

Documentation that satisfies medical necessity includes 1) signs and symptoms and/or 2) relevant history (including known diagnoses). Additional information regarding the specific reason for the examination or a provisional diagnosis would be helpful and may at times be needed to allow for the proper performance and interpretation of the examination.

The request for the examination must be originated by a physician or other appropriately licensed health care provider. The accompanying clinical information should be provided by a physician or other appropriately licensed health care provider familiar with the patient's clinical problem or question and consistent with the state scope of practice requirements. (ACR Resolution 35 adopted in 2006 – revised in 2016, Resolution 12-b)

See the [ACR-AAPM Technical Standard for Medical Physics Performance Monitoring of PET/CT Imaging Equipment](#), the [ACR-ASNR-SPR Practice Parameter for the Performance of Computed Tomography \(CT\) of the Extracranial Head and Neck](#), the [ACR-SCBT-MR-SPR-STR Practice Parameter for the Performance of Thoracic Computed Tomography \(CT\)](#), and the [ACR-SABI-SAR-SPR Practice Parameter for the Performance of Computed](#)

#### IV. SPECIFICATIONS OF THE EXAMINATION

##### B. Patient Preparation [37]

The major goals of patient preparation are to maximize the radiopharmaceutical uptake in the target tissues (neoplastic disease) and minimize patient radiation exposure. The preparation should include, but not be limited to, the following:

1. Prior to appointment:
  - a. Advise patients to drink enough water to ensure adequate hydration with a goal of 1 L (34 oz) in 2 hours prior to the appointment and urinate as often as possible during the first few hours following DOTATATE administration to reduce radiation exposure.
  - b. No need for strict fasting .
  - c. No need to restrict physical activity .
  - d.
2. Prior to DOTATATE injection:
  - a. Perform pregnancy testing when appropriate (see the [ACR–SPR Practice Parameter for Imaging Pregnant or Potentially Pregnant Adolescents and Women with Ionizing Radiation](#)) [24].
  - b. Obtain a focused history that includes:
    - i. Reason for examination (symptoms, diagnoses, biochemical test results, and recent imaging examinations)
    - ii. Absence or presence of functional symptoms
    - iii. Treatment
    - iv. Medications, specifically short-acting or long-acting somatostatin (SST) analogs and when last taken
    - v. Presence of concurrent infection
    - vi. Recent vaccination history (eg, COVID-19 vaccine), type of vaccination, and the site of administration because lymphadenopathy can often be associated with such vaccinations [38,39]
    - vii. Specific details and dates for the above should be obtained whenever possible
  - c. Consider premedication:
    - i. Anxiolytics can be administered in patients with claustrophobia or anxiety. Oral alprazolam (0.5 mg given 10 to 60 minutes prior to radiotracer injection), or similar medication, is an option, although patients must be counseled against driving given the medication’s sedative and motor-impairing effects.
  - d. Guidelines for patients on SST analogs therapy:
    - i. Some recommend withdrawing short-acting SST analogs for 1 day and long-acting SST analogs for 3 to 4 weeks prior to scanning. However, this issue is still controversial, with recent literature showing improved tumor to background ratios when the PET imaging is performed while continuing these agents [40-42].
    - ii. As such, most centers do not require octreotide therapy withdrawal before PET scanning.
3. Following injection (uptake period):
  - a. Patients should void immediately prior to being positioned on the PET table for imaging. This will reduce background noise as well as the radiation dose to the kidneys and bladder. In special circumstances, intravenous (IV) hydration, diuretic administration, and/or bladder catheterization can be used to reduce radiation burden and artifacts from accumulation of physiologic radiopharmaceutical activity in the ureters and urinary bladder.
  - b. Consider the use of sedation as necessary in younger children or developmentally delayed patients. (See the [ACR–SIR Practice Parameter for Minimal and/or Moderate Sedation/Analgesia](#) [43].)

#### IV. SPECIFICATIONS OF THE EXAMINATION

## C. Radiopharmaceutical

There are 2 radiolabeled DOTATATE agents currently available for clinical PET imaging. The gallium-68 labeled version was approved by the Food and Drug Administration (FDA) in 2016 and the copper-64 labeled version was approved in 2020. Copper-64 has the advantage of a longer half-life (12.7 hours) in comparison with gallium-68 (68 minutes) with a longer shelf life (>24 hours) and scanning window (at least 3 hours), which makes it easier to use for clinical imaging purposes. It has a shorter positron range (0.7 mm versus 3.5 mm), which provides better spatial resolution and a higher detection of small lesions, but has a lower positron fraction (18% versus 89%), which increases noise and acquisition time for a similar number of coincident counts [44,45]. The overall clinical diagnostic accuracy of the 2 radiotracers is comparable [45-49] if the scanner is properly optimized for the isotope being used.

For adults, the administered activity of gallium-68 DOTATATE ranges from 100–200 MBq (2.7–5.4 mCi), with an average of 150–185 MBq (4–5 mCi), given as a single IV bolus. The corresponding activity for copper-64 DOTATATE is approximately 148 MBq (4 mCi), given as a single IV bolus. The radiotracer should be administered via an angiocatheter (typically a 22- or 24-gauge angiocath) or butterfly needle. A right upper extremity vein is preferred to avoid confusion of persistent venous activity within a left supraclavicular (Virchow's) node. Additionally, when feasible, the radiopharmaceutical should be injected intravenously at a site away from sites of known or suspected disease.

Experience in the pediatric population is limited [15]. For children, the administered activity of gallium-68 DOTATATE should be based on body weight and should be as low as reasonably achievable (ALARA) for diagnostic image quality. Typically, the dosage range for children is 2 MBq/kg of body weight (0.054 mCi/kg), up to 200 MBq (5.4 mCi), given as an IV bolus, with a minimum of 18.5 MBq (0.5 mCi). The safety and efficacy of copper-64 DOTATATE have not been established in pediatric patients.

It is advised that a lactating patient should interrupt breastfeeding and pump and discard milk for 4 hours after gallium-68 DOTATATE and for 12 hours after copper-64 DOTATATE administration to minimize radiation exposure to a breastfed infant [50].

The specific administered activity typically depends upon the local imaging protocol. The local protocol may require a standard activity, or the activity may vary as a function of various parameters such as patient size, scanning mode (2-D versus 3-D), percentage of scan bed (slice) overlap, or clinical indication. For variable dosages, other means of determining the administered activity can be based upon a combination of factors, which use the patient's weight, duration of bed positions in minutes, and percentage of bed position overlap in certain PET systems (some systems do not use bed positions). The variable dose calculation's goal is to optimize a personalized dosage with the ALARA principle. Without a dedicated dosage injector with the ability to precisely elute a calculated dosage, a fixed dose with a range may be more practical for adults. To date, there are no clear data providing evidence of superiority of parameter-dependent administered activity protocols [51]. Imaging with copper-64 requires adjustment of imaging protocols and reconstruction parameters to account for the lower positron fraction of the radionuclide, such as extending the imaging time per bed position, and using noise reduction tools, which vary by manufacturer and by the capabilities of various PET scanners.

With PET/CT, the radiation dose to the patient is the combination of the administered activity from the PET radiopharmaceutical and the dose from the CT portion of the examination. Lower administered activities or changes in CT parameters resulting in decreased radiation dose may be appropriate with advances in PET/CT technology. However, the total effective dose from a typical gallium-68 or copper-64 DOTATATE PET (~5 mSv) is less than for indium-111 DTPA-octreotide (~6 mSv) or F-18 FDG (~7 mSv) scans [52,53]. The difference in effective dose between the 2 radiopharmaceuticals is marginal. Copper-64 DOTATATE has a slightly higher total effective dose than gallium-68 DOTATATE but is still lower than the other imaging modalities, described above. The critical organ for gallium-68 DOTATATE is the spleen and for copper-64 DOTATATE is the liver.

## IV. SPECIFICATIONS OF THE EXAMINATION

### D. Protocol for the CT Portion of the PET/CT Imaging

The technologist should ascertain that the radionuclide on the PET/CT scanner is set to gallium-68 or copper-64 and then change it again before scanning a patient with a different radionuclide (eg, fluorine-18). The CT performed as part of a PET/CT examination provides attenuation-correction information and diagnostic information that may be relevant to both PET interpretation and overall patient care. A variety of protocols exist for performing the CT scan in the context of PET/CT scanning. In some cases, low-dose CT scans are designed primarily to provide attenuation correction and anatomic localization. In other cases, the CT portion of the examination is performed with IV and/or oral contrast media and optimized CT parameters designed to lower image noise. If a diagnostic CT scan is requested as part of PET/CT, the CT protocol appropriate for the body region(s) requested should be used. If not previously performed, multiphase imaging of the abdomen including arterial, portal venous, and delayed phases may be considered for a diagnostic CT evaluation of NETs to optimize visualization of pancreatic tumors and liver metastases, which commonly portray arterial enhancement followed by hypoenhancement on the subsequent phases. Regardless of the CT technique used, a careful review of CT images is necessary for comprehensive interpretation of the PET/CT examination. Whether a diagnostic CT with IV contrast or a nondiagnostic CT for attenuation correction and anatomic localization is being performed, due to the common occurrence of primary or metastatic NETs in the gastrointestinal tract and peritoneal regions, either no oral contrast or "negative" oral contrast (water) use should be considered [54], because "positive" oral contrast may mask small bowel lesions. Highly concentrated barium may additionally result in attenuation-correction artifacts that can also obscure the presence of peritoneal and retroperitoneal tumor [11,54-57].

High intravascular concentrations of IV contrast media may cause a localized attenuation-correction artifact on the PET image [55,58], but the impact is usually limited [55,59].

Breathing patterns during CT acquisition should be optimized so that the positions of the diaphragm on the PET emission and the CT transmission images match as closely as possible.

#### **IV. SPECIFICATIONS OF THE EXAMINATION**

##### **E. Protocol for PET Emission Imaging**

After verifying that the scanner is set to the proper PET isotope, emission images are generally obtained 60 minutes following radiopharmaceutical administration. However, this time period may be shorter (no less than 45 minutes) or longer for certain trials or unique clinical situations. Note that the consistency of standardized uptake value (SUV) measurements depends on strict observance of the uptake time; therefore, when using a 60-minute interval, an acceptable range of injection-to-scan time is 55–75 minutes for gallium-68 DOTATATE and 45–90 minutes for copper-64 DOTATATE [60,61].

Emission image acquisition time typically varies from 1 to 5 minutes or longer per bed position for body imaging and is based on the administered activity, patient body weight, and sensitivity of the PET device (as determined largely by the detector composition and acquisition method). Acquisition time can be adjusted in certain clinical situations to provide higher count images in a given anatomic area. For gallium-68, the most used times per bed position are either 3 or 4 minutes in 3-D mode for current scanners, using similar filters and corrections for scanner and dead time as for FDG. When imaging with copper-64, imaging protocols and reconstruction parameters should be adjusted to account for the lower positron fraction, including longer imaging time per bed position.

Semiquantitative estimation of radiotracer accumulation using the SUV is based on local radioactivity concentration measured on images, corrected for attenuation, and normalized to the body weight, lean body mass, or body surface area. The accuracy of SUV measurements depends on the accuracy of the calibration of the PET device, among other factors. Because the SUV is becoming a standard for determining tumor response over time, measures should be taken to minimize the factors that may affect it. These include using the same radiotracer and scanner configuration on subsequent examinations (including reconstruction algorithms, attenuation maps, etc), maintaining the same interval between injection and scanning, avoiding infiltration of injected activity, and using the same measurement techniques, (eg, volume-of-interest (VOI) volumes, max/peak/mean measurements). Some factors that affect SUV currently remain beyond control, such as variations in patient motion/breathing–related attenuation-correction artifacts [62]. SUV measurements are not

directly comparable between gallium-68 and copper-64 DOTATATE, with SUVs being typically higher with the latter, particularly in liver lesions, lymph nodes, pancreatic lesions, intestinal tumors, and carcinomatosis lesions [45].

Krenning Score: Recording changes in the intensity of radiotracer uptake with semiquantitative measurements, expressed in absolute values and percent changes, may be appropriate in some clinical scenarios. However, the technical protocol and analysis of images need to be completely consistent in the 2 data sets, which can be difficult to achieve. Rather, a semiquantitative score that may be helpful to report is the "Krenning score." The Krenning score compares the uptake in sites of known or suspected tumor to the uptake in the liver, with the uptake scored as 0 (no uptake above background tissue), grade 1 (uptake greater than background tissue but less than liver), grade 2 (about the same uptake as liver), grade 3 (uptake greater than the liver but less than kidneys or spleen), and grade 4 (same as, or greater than, uptake in the kidneys or spleen) [63]. Although the Krenning score was validated in predicting response to PRRT with Lutetium-177 DOTATATE using indium-111 DTPA-octreotide scans, with a score of 3 or greater required for eligibility for PRRT treatment, the same concept can be adapted with DOTATATE PET imaging. The Krenning score also suggests that patients with a score of 3 or more are likely to respond to SST analog medications, such as LAR octreotide, for symptomatic control, because of the high density of SSTRs on their tumor.

#### IV. SPECIFICATIONS OF THE EXAMINATION

##### F. Interpretation

With integrated PET systems, the software packages typically provide a comprehensive platform for image review, including registered and aligned CT or MR images, PET images with and without attenuation correction, and PET/CT or PET/MR fusion images in the axial, coronal, and sagittal planes. In addition, maximum-intensity-projection images of the PET examination should be generated for review. PET images with and without attenuation correction should be available for review.

Although the pattern of radiopharmaceutical uptake and associated anatomical findings, as well as correlating with history, physical examination, laboratory results, and other imaging modalities, are usually the most helpful in differentiating benign from malignant lesions, semiquantitative estimates (eg, SUV) may also be of value. Unlike with F-18 FDG, in which high uptake generally identifies an aggressive tumor, high radiolabeled DOTATATE uptake generally indicates a well-differentiated tumor that is less aggressive, with low uptake suggesting a poorly differentiated tumor, typically with a poor prognosis. Patients with tumors of low uptake (Krenning score equal to or less than 2) may be better imaged with F-18 FDG PET.

The following issues should be taken into consideration while interpreting radiolabeled DOTATATE PET:

1. Physiologic distribution: Normal distribution is seen in the choroid plexus of the brain, pituitary gland, glandular tissues of the neck, liver, spleen, and adrenal glands. Kidneys and urinary tract are visualized due to renal excretion of the tracer. Uptake in islet cell clusters of the pancreas, typically seen in the uncinate process, is a common pitfall and not to be mistaken for NET. Normal biodistribution patterns are published and should be reviewed by physicians who are inexperienced with this radiopharmaceutical [2,52,53].
2. Intensity of radiotracer uptake relative to the liver (Krenning score) [63]: A presence of heterogenous uptake (eg, some areas of tumor with good uptake and others without) is important to note.
3. False-positive results: Tissues other than NETs may show substantial uptake, including, but are not limited to, the following:
  - a. Meningioma
  - b.
  - c. Benign tumors of the adrenal glands
  - d. Accessory spleens/splenosis (may require a heat-damaged red-cell scan to differentiate peritoneal/retroperitoneal nodules due to splenic tissue from metastatic disease)



- e. Areas of active infection/inflammation (most white cells express high levels of SSTRs), including inflammatory arthritis, fractures, healing surgical wounds, inflammatory response to radiation, and pneumonia or abscess, etc
  - f. Granulomatous reactions (especially if "active")
  - g. Osteoblastic activity including normal uptake (active epiphyseal plates) and bone disease (Paget disease, fibrous dysplasia, some bone islands, etc). These can be difficult to differentiate from bone metastases
  - h. Non-neuroendocrine cancers can have variable uptake, including a wide variety of epithelial tumors (head and neck, lung, esophageal, breast, colorectal, ovarian, testicular, lymphoma, etc) and primary brain tumors. Careful attention to the appearance on the CT or MR components of the imaging and pattern recognition of the overall context can assist in identifying second primary cancers
  - i. Atherosclerotic disease (inflammatory or unstable plaque)
  - j. Prostate (chronic prostatitis)
  - k. Hemangiomas (especially vertebral bodies, but also liver and other organs). At times, hemangioma uptake can be intense [65,66]
4. Tissues with moderate SST expression:
- a. Lacrimal and salivary glands
  - b. Thyroid
  - c. Liver
  - d. Breast tissue (variable), especially in pregnancy or with lactation
5. Artifacts
- a. Misalignment between PET and CT or MR data can cause attenuation correction artifacts. Fusion images and PET images without attenuation correction can be used to help identify these artifacts.
  - b. Inaccuracies in converting from polychromatic CT energies to the 511 keV energy of annihilation radiation can cause artifacts around implanted devices, metal, highly concentrated iodinated contrast, or dense barium, although these artifacts are less common with newer conversion algorithms.
6. Situations that can lead to false-negative interpretation
- a. Small lesions size (<2 times resolution of the system)
  - b. Low levels of SSTR expression (eg, poorly differentiated) tumor. F-18 FDG PET may be superior in this context
  - c. Recent treatment
    - i. Chemotherapy
    - ii. Radiation therapy
    - iii. Recent liver-directed therapy (eg, bland or chemoembolization, or embolization with radiolabeled microspheres)
    - iv. Recent PRRT
    - v. Postsurgical inflammation obscuring tumor
    - vi. Tumors occurring in areas with normal high physiologic uptake (eg, near the uncinated process of the pancreas the adrenal glands, or splenic hilum [tail of the pancreas], etc)

## V. DOCUMENTATION

Reporting should be in accordance with the [ACR Practice Parameter for Communication of Diagnostic Imaging Findings](#) [67].

The report should include the radiopharmaceutical, administered activity, and route of administration, as well as any other pharmaceuticals administered, along with dosage and route of administration.

The technique section of the report should include the radiopharmaceutical (eg, gallium-68 or copper-64

DOTATATE), the administered activity, the route and site of administration, and any pharmaceuticals administered (eg, diuretics, anxiolytics). Patient weight, height, and sex (to allow SUV normalization to lean body mass), time from injection to scanning, and technique for normalizing SUVs (eg, body weight, lean body weight, or body surface area) should also ideally be reported [68]. If possible, it should be noted if the patient is taking any short- or long-acting octreotide medications and the day/time of the last dose.

Details of oral or IV contrast agents, if used for the CT attenuation-correction portion of the examination, should also be reported to include the volume and route of administration. Other information relevant to contrast administration, such as steroid preparation, prehydration, or dialysis history, should be included. The report should also include documentation of contrast reactions and subsequent treatment, if observed during the examination.

The findings section should include a description of the location, extent, and intensity of abnormal radiotracer uptake in relation to normal comparable tissues and should describe the relevant morphologic findings on the CT images. Ideally, image and series numbers should also be included. Additionally, background activity (eg, normal liver) should be measured to help ensure comparable SUV values [69]. Often, injection-site infiltration, such as in arms, or attenuation-correction errors can significantly alter SUV values in lesions, leading to false conclusions. An estimate of the intensity of radiotracer uptake can be provided with the SUV; however, the intensity of uptake may be described as less than, about the same as, or greater than the liver and/or spleen (Krenning score).

If the CT scan was requested and performed as a diagnostic examination, the CT component of the examination should be reported separately to satisfy regulatory, administrative, or reimbursement requirements. In that case, the PET/CT report should refer to the diagnostic CT scan report for findings not related to the PET/CT combined findings [70-72]. Even if the CT scan was not requested as a diagnostic examination, clinically important nononcologic findings (eg, pneumothorax, aortic aneurysm, bowel obstruction, pneumoperitoneum, fracture) on the CT scan should be reported. Any critical findings should be conveyed in a timely manner as soon as possible to the health care provider responsible for the patient.

When radiolabeled DOTATATE PET is performed for monitoring therapy, a comparison of extent and intensity of uptake may be summarized as progressive disease, stable disease, partial response, or complete response using published criteria for these categories. However, it is imperative to remember that strong correlation with CT and, if available, MRI imaging is required to make these determinations. Radiolabeled DOTATATE uptake is based on SSTR receptor density, not metabolic activity, and loss of uptake may actually identify a tumor that has become less differentiated and likely more proliferative, not a tumor that is responding to treatment. Accordingly, strict use of appropriate objective treatment response criteria is strongly recommended for determining treatment effectiveness, especially following PRRT or liver-directed therapy [73-77].

## VI. EQUIPMENT SPECIFICATIONS

CT Performance monitoring should be in accordance with the [ACR–AAPM Technical Standard for Diagnostic Medical Physics Performance Monitoring of Computed Tomography \(CT\) Equipment](#) [78].

For specific issues regarding CT quality control (QC), see the [ACR–SPR Practice Parameter for Performing and Interpreting Diagnostic Computed Tomography](#) [28].

PET performance monitoring should be in accordance with the [ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras](#) [79] and the [ACR–AAPM Technical Standard for Medical Physics Performance Monitoring of PET/CT Imaging Equipment](#) [26].

### A. Performance Guidelines

For patient imaging, the PET/CT scanner should meet or exceed the following specifications:

1. For the PET scanner
  - a. In-plane spatial resolution: <6.5 mm
  - b. Axial resolution: <6.5 mm

- c. Sensitivity (3-D): >4.0 cps/kBq
  - d. Sensitivity (2-D): >1.0 cps/kBq
  - e. Uniformity: <5%
2. For the CT scanner
    - a. Helical scan time: <5 seconds (<2 seconds is preferable)
    - b. Slice thickness and collimation: <5 mm (<2 mm is preferable)
    - c. Limiting spatial resolution: >8 lp/cm for >32-cm display field of view (DFOV) and >10 lp/cm for <24-cm DFOV
  3. For the combined PET/CT scanner
    - a. Maximum co-scan range (CT and PET): >160 cm
    - b. Maximum patient weight: >350 lb
    - c. Patient port diameter: >59 cm

B. Appropriate emergency equipment and medications must be immediately available to treat adverse reactions associated with administered medications, to include iodinated contrast media. The equipment and medications should be monitored for inventory and drug expiration dates on a regular basis. The equipment, medications, and other emergency support must also be appropriate for the range of ages and sizes in the patient population.

C. A fusion workstation with the capability to display PET, CT, and fused images with different percentages of PET and CT blending should also be available. The workstation should also have the capability to measure SUV with volumetric regions of interest.

D. PET/CT scanning done specifically for radiation therapy planning should be performed with a flat tabletop, immobilization devices used as needed, with the use of appropriate positioning systems in order to best match patient positioning during radiation therapy.

The QC procedures for PET/CT should include both the PET procedures and the CT procedures according to the ACR Technical Standards. The QC procedures for PET should include a calibration measurement of activity in a phantom containing a known radiopharmaceutical concentration, generally as a function of axial position within the scanner field of view. The QC procedures for the CT should include air and water calibrations in Hounsfield units for a range of kilovoltage. A daily check on the stability of the individual detectors should also be performed to identify detector failures and drifts.

In addition, for PET/CT, the alignment between the PET and CT scanners should be checked periodically. Such a check should determine an offset between the PET and CT scanners that is incorporated into the fused image display to ensure accurate image alignment.

## VII. RADIATION SAFETY IN IMAGING

Radiologists, medical physicists, non-physician radiology providers, radiologic technologists, and all supervising physicians have a responsibility for safety in the workplace by keeping radiation exposure to staff, and to society as a whole, "as low as reasonably achievable" (ALARA) and to assure that radiation doses to individual patients are appropriate, taking into account the possible risk from radiation exposure and the diagnostic image quality necessary to achieve the clinical objective. All personnel who work with ionizing radiation must understand the key principles of occupational and public radiation protection (justification, optimization of protection, application of dose constraints and limits) and the principles of proper management of radiation dose to patients (justification, optimization including the use of dose reference levels). [https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775\\_web.pdf](https://www-pub.iaea.org/MTCD/Publications/PDF/PUB1775_web.pdf)

Facilities and their responsible staff should consult with the radiation safety officer to ensure that there are policies and procedures for the safe handling and administration of radiopharmaceuticals in accordance with ALARA principles. These policies and procedures must comply with all applicable radiation safety regulations and conditions of licensure imposed by the Nuclear Regulatory Commission (NRC) and by applicable state, local, or other relevant regulatory agencies and accrediting bodies, as appropriate. Quantities of radiopharmaceuticals should be tailored to the individual patient by prescription or protocol, using body habitus or other customized method when such guidance is available.

Nationally developed guidelines, such as the [ACR's Appropriateness Criteria](#)<sup>®</sup>, should be used to help choose the most appropriate imaging procedures to prevent unnecessary radiation exposure.

Additional information regarding patient radiation safety in imaging is available from the following websites – Image Gently<sup>®</sup> for children ([www.imagegently.org](http://www.imagegently.org)) and Image Wisely<sup>®</sup> for adults ([www.imagewisely.org](http://www.imagewisely.org)). These advocacy and awareness campaigns provide free educational materials for all stakeholders involved in imaging (patients, technologists, referring providers, medical physicists, and radiologists).

Radiation exposures or other dose indices should be periodically measured by a Qualified Medical Physicist in accordance with the applicable ACR Technical Standards. Monitoring or regular review of dose indices from patient imaging should be performed by comparing the facility's dose information with national benchmarks, such as the ACR Dose Index Registry and relevant publications relying on its data, applicable ACR Practice Parameters, NCRP Report No. 172, Reference Levels and Achievable Doses in Medical and Dental Imaging: Recommendations for the United States or the Conference of Radiation Control Program Director's National Evaluation of X-ray Trends; 2006, 2009, amended 2013, revised 2023 (Res. 2d).

## VIII. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control and Improvement, Safety, Infection Control, and Patient Education appearing under the heading *Position Statement on QC & Improvement, Safety, Infection Control, and Patient Education* on the ACR website (<https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Quality-Control-and-Improvement>).

Only licensed, properly credentialed and trained individuals who are familiar with reconstituting radiopharmaceuticals should perform the preparation of clinical doses. Specific kit manufacture instructions should be followed, and only FDA-approved gallium-68 generator(s) and gallium-68 DOTATATE kit(s) should be used.

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## Appendix A

For the purposes of this practice parameter, the following definitions apply:

**Neuroendocrine tumors (NETs):** Neuroendocrine tumors comprise a heterogeneous group of neoplasms that arise from endocrine cells within the glands (eg, adrenomedullary, pituitary, parathyroid) or from endocrine islets in the pancreas, thyroid, respiratory system, and gastrointestinal system [81].

**Somatostatin receptors (SSTRs):** SSTRs are present on the cell surface of essentially all cells, but with especially high expression on neuroendocrine cells, providing a unique and specific molecular target for imaging. There are 5 major subtypes of SSTRs, referred to as SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5. SSTR2 has 2 variants, SSTR2a and SSTR2b. The role of SSTR2b is poorly understood but is probably similar to SSTR2a. When SSTR2 is used in the context of medicine, it refers to SSTR2a, unless otherwise specified [1,82].

**Somatostatin (SST):** SST is the hormone ligand for SSTRs. SST is responsible for the "carcinoid" symptoms, such as wheezing, flushing, cramps, and diarrhea. Octreotide is an SST analog that binds with very high affinity to the SSTRs (especially subtypes 2 and 5) and can control these symptoms with very few, if any, side effects. Octreotide requires injection. Long-acting release (LAR) octreotide is very popular with patients because it lasts about 30 days with one intragluteal injection, obviating the need for daily injections with standard octreotide. Short-acting IV or sub-q octreotide is used to control "carcinoid crisis" and to supplement LAR octreotide if needed. A similar SST analog medication, lanreotide, has an LAR form given subcutaneously every 4 weeks. In addition to controlling symptoms, there is evidence that SST analogs can have antiproliferative effects on the NET.

**Peptide-receptor radionuclide therapy (PRRT):** A therapy used for neuroendocrine tumors with a high expression of SSTR2 using DOTATATE radiolabeled with lutetium-177 or yttrium-90 [83].

\*Practice parameters and technical standards are published annually with an effective date of October 1 in the year in which amended, revised or approved by the ACR Council. For practice parameters and technical standards published before 1999, the effective date was January 1 following the year in which the practice parameter or technical standard was amended, revised, or approved by the ACR Council.

### Development Chronology for This Practice Parameter

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