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Practical Considerations for Implementation of ^{177}Lu-DOTATATE Neuroendocrine Tumor Treatment Programs

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Abstract

The 2018 FDA approval of ^{177}Lu-DOTATATE for the treatment of somatostatin receptor-positive (SSTR) neuroendocrine tumors (NETs) represents a paradigm-shifting approach to cancer treatments around the globe. Gastroenteropancreatic (GEP) NETs overexpress the somatostatin subtype receptor 2, which is now exploited for receptor-based imaging and therapy, thus generating significant progress in the diagnosis and treatment of this orphan disease. The recent FDA approval of receptor-based PET radiopharmaceuticals and a new peptide receptor radiopharmaceutical therapy (PRRT), ^{177}Lu-DOTATATE, has dramatically impacted NET patient management. The focus of this paper is to review

clinical considerations associated with implementing a ^{177}Lu-DOTATATE program. We review receptor-based NET radiopharmaceuticals, ^{177}Lu-DOTATATE patient selection criteria, administration methods, clinical, regulatory, and radiation safety considerations, technical factors, tissue dosimetry, and reimbursement guidelines.

Key Words: neuroendocrine tumor, ^{177}Lu-DOTATATE, somatostatin receptor, PRRT, dosimetry

1. Introduction

It is estimated the annual incidence of neuroendocrine tumors is 7 per 100,000 persons, resulting in approximately 23,000 new cases each year in the United States (*1*). Neuroendocrine tumors (NETs) are slightly more common in women (52.7%) with 5-year overall survival depending strongly on the grade and stage of disease. At the time of diagnosis, approximately half of patients present with localized disease while the other half have already progressed to regional disease or distant metastases. Localized disease is often well-managed by surgery alone (*2*) with median overall survivals in the range of 4 – 30 years depending on site and grade (*1*).

Neuroendocrine tumors of gastroenteropancreatic (GEP) origin often secrete serotonin and a variety of other peptide hormones which can cause characteristic symptoms known as carcinoid syndrome, or other symptoms related to the tumor's site of origin. Shortly following the discovery of somatostatin receptors (SSTR) in 1972 (*3*), it was observed that agents targeted to the somatostatin subtype receptor 2 (SSTR-2 or SSR2) resulted in potent anti-secretory effects in neuroendocrine tumors, providing significant palliative benefit in patients with secreting GEP-NETs. These SSTR-targeted somatostatin analogue agents were initially available in short-acting immediate-release formulations (octreotide acetate, 1988) and were later made available in long-acting formulations (octreotide, lanreotide; 1998 – 2001) (*4*). In addition to the palliative therapeutic benefit of somatostatin analogues, these agents were found to exhibit anti-tumor effects (*5,6*), resulting in their clinical use as primary interventions for metastatic GEP-NETs regardless of hormone secretion status.

Expression of SSTR is observed in many cancer types, and this receptor is highly over-expressed in low-grade (G1/G2) NETs (mitotic rate ≤ 20, Ki-67 index ≤ 20%), and to a lesser extent in high-grade (G3) NETs (mitotic rate > 20, Ki-67 index > 20%) (*7,8*). Based on the high degree of overexpression, as well as the known molecular structures with high-affinity binding to this receptor, research into the use of radiolabeled somatostatin analogues for imaging and therapy began in the early 1990s. The first proof

of concept nuclear imaging studies utilized [^{123}I-Tyr3]-octreotide (*9,10*); shortly thereafter, use of ^{111}In-pentetreotide (an octreotide analogue labeled with DTPA chelator for complexation of indium-111) gained traction for neuroendocrine tumor imaging, receiving FDA approval in 1994 (*11,12*). In subsequent years, somatostatin analogues with macrocycle chelators (DOTATOC, DOTANOC, DOTATATE) were developed and shown to have improved stability, biodistribution, and clearance for a variety of radiometal labels (*13,14*). Among these, ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{64}Cu-DOTATATE have thus far received FDA approval and are in current clinical use, whereas ^{111}In-pentetreotide is being phased out in favor of the newer PET-based imaging agents.

Early success in the diagnostic imaging of GEP-NETs led to the development of somatostatin receptor-targeted radiotherapeutics, often referred to as peptide receptor radionuclide therapy (PRRT) in this context. The first therapeutic agent to be studied was ^{90}Y-DOTATOC, which was shown to have significant oncologic benefit in small animals and humans (*13,15,16*). Trials with ^{90}Y-DOTATOC demonstrated some renal and hematologic toxicity, and these off-target effects were found to be dose-limiting for this agent. Most recently, lutetium-177 ($t_{1/2}$: 6.6 d) labeled DOTATATE has been favored due to increased retention time in tumors, an apparent reduction in nephrotoxicity, as well as logistical considerations associated with these agents. In the phase 3 NETTER-1 trial, ^{177}Lu-DOTATATE was evaluated in patients with well-differentiated, unresectable or metastatic, progressive midgut NETs (*17*). In comparison to long-acting octreotide, ^{177}Lu-DOTATATE was associated with improved response rate (18% vs. 3%, $p<0.001$) and progression-free survival (65.2% vs. 10.8% at 20 months). These data led to the FDA approval of ^{177}Lu-DOTATATE (LUTATHERA®; Advanced Accelerator Applications USA Inc) (AAA) in 2018 for treatment of patients with SSTR-positive GEP-NETs. This therapeutic agent is now widely available and frequently used in the treatment of patients with NETs. As of 2021, AAA reports ^{177}Lu-DOTATATE is available at more than 230 treatment centers in the United States.

The purpose of this paper is to review the practical clinical considerations associated with the use of ^{177}Lu-DOTATATE, with an emphasis on what the care team members (technologists, nurses, pharmacists, physicists) need to know for successful application of this newly approved PPRT agent.

2. Patient Selection

^{177}Lu-DOTATATE is not currently considered a first-line therapy for NET. Instead, patients with surgically unresectable, metastatic, or locally advanced midgut NET may be treated with first-line somatostatin analog (SSA) therapy. If disease progression occurs during SSA therapy and SSTR positivity is confirmed with functional imaging, the patient may be considered for ^{177}Lu-DOTATATE therapy (*18*). A multidisciplinary team (nuclear medicine, medical oncology, endocrinology, surgical oncology, interventional radiology, radiation oncology) should evaluate the patient's performance status, clinical and imaging data, potential alternative treatments, and PRRT contraindications before deciding to proceed with PRRT. Adequate bone, liver, and renal function should be verified with European Neuroendocrine Tumor Society exclusion criteria detailed in Table 1, and the patient's Karnofsky performance, a measure of patient health status, should be ≥ 60% (*19*).

Fundamental to patient selection is the clinical behavior of the GEP-NET, often determined by the tumor's primary site, grade, and differentiation. NET grade reflects the proliferative activity of cells, measured by mitotic rate and/or Ki-67 index, and differentiation describes the extent to which tumor cells resemble their healthy endogenous cell line (*20*). GEP-NENs (neuroendocrine neoplasms) were recently subdivided in the 2019 WHO (World Health Organization) classification system (*21*) and are summarized in Table 2. NET tumor grade inversely correlates with SSTR density and prognosis; in general, the lower the grade, the higher the SSTR density. A high SSTR density thus correlates with an improved response to PRRT and better prognosis (*20*). Due to weak or absent SSTR expression, as well as being generally more aggressive, higher-grade NETs and poorly differentiated neuroendocrine cancers

(NECs) have a worse prognosis (*22*). SSTR positivity for all lesions should be confirmed with SSTR imaging before ^{177}Lu-DOTATATE therapy; PET-based SSTR imaging (DOTATATE, DOTATOC, DOTANOC) has become the standard of care and is preferred over ^{111}In-pentetreotide scintigraphy due to the higher spatial resolution and dramatically improved lesion detectability of these agents (*23*). Lesions with uptake more intense than normal liver activity are deemed SSTR-positive and thus better candidates for PRRT (*24*).

Due to the frequent lack of SSTR expression in higher grade (G2/G3) and poorly differentiated NETs, these tumors are often examined with ^{18}F-fluorodeoxyglucose (FDG) PET imaging, in lieu of, or in addition to SSTR PET imaging. PRRT administration has historically been contraindicated in patients with sites of discordant or mismatched lesions (lesions with positive ^{18}F-FDG uptake, positive contrast-enhancement on CT or MRI, and negative SSTR expression). ^{18}F-FDG-positive lesions are known to be associated with a reduced likelihood of response to PRRT. In this patient population, multidisciplinary teams may consider the addition of concomitant chemotherapy to a PRRT regimen. Higher grade NETs (G2/G3) are currently being evaluated in the Phase III NETTER-2 trial, which is investigating PRRT as first-line therapy when used in combination with long-acting, high-dose octreotide (*22*). The Phase III COMPETE trial is currently comparing 4 cycles of 7.4 GBq (200 mCi) ^{177}Lu-DOTATOC to daily everolimus administration in patients with somatostatin receptor-positive disease (*25*). Further studies of ^{177}Lu-DOTATATE are being conducted in pediatric patient populations, including the NETTER-P study, as well as investigator-initiated studies (*26*).

3. Clinical Considerations

Patient preparation is a critical component to the success of PRRT. Many NET patients receive SSAs for symptomatic control of their disease, which elicit their therapeutic effect by binding to SSTRs. ^{177}Lu-DOTATATE also works by targeting SSTRs, and administration of SSAs should be carefully planned

during ^{177}Lu-DOTATATE treatment to prevent receptor saturation, which can interfere with the efficacy of PRRT (*24,27*). Long-acting SSAs should be discontinued at least 4 weeks before each ^{177}Lu-DOTATATE dose; short-acting SSAs may be used as needed up to 24 hours before each treatment. SSAs may be resumed 4 hours after administration of ^{177}Lu-DOTATATE for symptomatic management between therapeutic cycles and following completion of treatment (*24*).

During ^{177}Lu-DOTATATE administration, patients should be monitored for potential reactions to the infusion (*24,27*). Although infrequent, extravasation of the radiopharmaceutical may occur if the intravenous (IV) line becomes obstructed; patency of the line should be verified before the start of the infusion and monitored throughout the administration. Signs of extravasation, such as pain and swelling, should be immediately addressed to increase the clearance of the radiopharmaceutical from the infusion site. Steps to be taken include image acquisition to confirm and quantify the amount of extravasated radiopharmaceutical (whole-body planar scintigraphy and SPECT/CT of the affected area), elevation and exercise of the affected arm as much as possible for 24 hours, and application of a compression bandage with heated gel pads for 20 minutes every 6 hours to facilitate the redistribution of the radiopharmaceutical. Following the initial 24-hour period, imaging should be repeated. A qualified medical physicist should be consulted regarding the radiation dosimetry of this event, and referral to plastic surgery should be considered based on the dosimetry results. Additional information can be found in literature case reports and reviews (*28,29*).

In addition to the risk of extravasation, patients may experience neuroendocrine hormonal crisis during ^{177}Lu-DOTATATE administration due to excessive hormone released by the tumor (*30*). Symptoms include cutaneous flushing, diarrhea, bronchospasm, and hypotension, and generally occur during or within 24 hours of the initial ^{177}Lu-DOTATATE dose. Hormonal crisis can be treated by IV administration of SSAs and fluids, corticosteroids, and correction of electrolyte imbalances (*24,30*). Administration of ^{177}Lu-DOTATATE may occur in an outpatient setting not immediately equipped to deal

with carcinoid crisis. Institutional policies describing how to obtain additional medical support and/or transport the patient to an emergency clinic, if needed, should be in place.

Since kidneys receive significant radiation dose, amino acids should be given simultaneously with each cycle of ^{177}Lu-DOTATATE to decrease absorption through the proximal tubules, thus reducing the radiation dose to the kidneys (*27,31,32*). The amino acid solution must be infused over 4 hours and should contain 18-25 grams each of L-lysine HCl and L-arginine HCl in a total volume of 1-2 liters. Several commercial amino acid solutions are available that contain the required amounts of lysine and arginine. However, the presence of additional amino acids in these products may cause significant nausea and vomiting for the patient. Alternatively, a two amino acid solution containing only lysine and arginine may be compounded by the hospital or local pharmacy to improve patient tolerability (*33,34*). Figure 1 illustrates the timeline for administration of ^{177}Lu-DOTATATE PRRT. Antiemetics are administered first followed by the start of the amino acid infusion 30 minutes later. The amino acid infusion should run at a rate that allows for the entire volume to be infused over a total of 4 hours. Administration of ^{177}Lu-DOTATATE begins 30 minutes following the start of the amino acid infusion. If the ^{177}Lu-DOTATATE prescribed activity is decreased, the amount of amino acids administered is not altered (*24*).

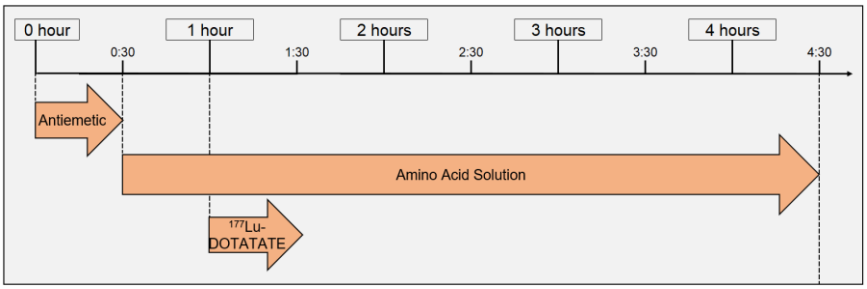

FIGURE 1: ^{177}Lu-DOTATATE PRRT administration timeline.

Long-term radiation effects of ^{177}Lu-DOTATATE treatment may occur and can include myelosuppression and renal toxicity (*24,27,31*). Laboratory values, including CBC and renal function tests, should be monitored throughout the treatment cycle and following the completion of PRRT to

assess for toxicity. Based on acute changes, typically myelosuppression, ^{177}Lu-DOTATATE prescribed activity can be reduced, withheld, or permanently discontinued (*24*).

The use of ^{177}Lu-DOTATATE in specific populations may require additional clinical considerations. Pregnancy status should be verified in patients with reproductive potential prior to initiation of therapy as ^{177}Lu-DOTATATE can cause fetal harm. All patients should be counseled on the use of effective contraception during and following treatment and advised of the potential for infertility. Patients who are lactating should be advised not to breastfeed during the treatment cycle and for 2.5 months following the conclusion of therapy.

Dose adjustment is not automatically necessary for mild to moderate renal impairment; however, renal function should be monitored more frequently in these patients. Decreased renal function can lead to longer residence time in the kidneys and higher exposure rates and may require dose adjustment for subsequent cycles. Limited data is available on the safety of ^{177}Lu-DOTATATE in patients with severe renal impairment or end-stage renal disease (*35*), but it is not a contraindication for treatment.

Caution should be exercised when considering PRRT in patients with extensive peritoneal carcinomatosis due to the risk of radiation-induced bowel obstruction. Patients with spontaneous urinary incontinence may make the safe administration of PRRT impossible. Additional PRRT clinical considerations can be found in consensus guidelines by Hicks et al., (*22*). Special situations can vary in complexity, so the multidisciplinary team should communicate and tailor the treatment plan to each patient's individual needs.

4. Regulatory and Radiation Safety Considerations

Before initiating a PRRT program, sites will need to ensure their radioactive materials license includes the possession and use of Lu-177 in sufficient quantities to cover ordered doses as well as

residual waste material (*36*). It is also important to review the waste disposal policy with the site Radiation Safety Officer (RSO). While the half-life of Lu-177 is relatively short ($t_{1/2}$ 6.6 d), ^{177}Lu-DOTATATE may contain small amounts (~0.1%) of the long-lived contaminant Lu-177m ($t_{1/2}$ 161 d). This contaminant can make waste storage and disposal difficult to comply with the < 120 d half-life requirement outlined in NRC 10 CFR 35.92. If decay-in-storage is not a viable option, the RSO or nuclear pharmacist can coordinate pickup and disposal with the local radiopharmacy or a third-party vendor (*36,37*).

NRC regulations require the authorized user physician to date and sign a written directive containing the patient's name, radiopharmaceutical, prescribed administered activity, and route of administration before the ^{177}Lu-DOTATATE is administered. Nuclear medicine staff should follow the site's procedure for administration of therapeutic radiopharmaceuticals, including verifying patient identity, verifying activity to be administered, and administration of the drug per the written directive (*36*).

Care should be taken when handling and administering ^{177}Lu-DOTATATE to keep radiation exposure as low as reasonably achievable (ALARA) for the staff and general public (*37*). Appropriate personal protective equipment should be worn, and the use of shielding and tongs for manipulation of the ^{177}Lu-DOTATATE vial should be employed. ^{177}Lu-DOTATATE is shipped by AAA/Novartis directly to the end-user site as a 7.4 GBq (200 mCi) quantity in a shielded vial. A variety of methods have been developed for direct infusion from the vial, or the activity may be drawn up into a shielded syringe for use in a syringe pump (*24*). For patients requiring a reduced 3.7 GBq (100 mCi) administration, the site can use an infusion pump to administer the correct volume of ^{177}Lu-DOTATATE from the unit dose vial. Alternatively, the vial can be adjusted by aseptically withdrawing the excess volume of ^{177}Lu-DOTATATE using a shielded syringe; the residual volume of ^{177}Lu-DOTATATE should be properly disposed of according to the site's waste disposal policy.

Except in the case of medical events, only the patient and nuclear medicine staff should be in the treatment room from the start of the infusion until the patient has been released. The patient should also have access to a single-user restroom during the visit as urine will be radioactive following infusion. If a medical event does occur, all necessary steps should be taken to ensure the medical safety of the patient without regard for personnel radiation exposure. Following the medical intervention, the qualified medical physicist or RSO may provide radiation dose estimates for un-badged personnel who participated in patient care. The patient may be released following therapy provided radiation dose to the maximally exposed member of the public is expected to be less than 5 mSv (0.5 rem). The patient must be provided with written instructions on how to follow ALARA principles, including interruption/discontinuation of breastfeeding, if applicable, restroom usage, interaction with household family members, and other considerations deemed relevant by the authorized user or RSO (*38*). ^{177}Lu-DOTATATE is usually administered as an outpatient procedure as exposure to the general public following the infusion is unlikely to exceed NRC regulatory limits (*39*).

5. Protocol/Technical Considerations

After a patient has been approved for treatment, the product is ordered through the manufacturer's web-based ordering system. Confirmation is supplied from the manufacturer via email, unless the desired treatment date is within 3 days, in which case the ordering facility must call the manufacturer to verify material availability. The manufacturer recommends subsequent treatments be scheduled when the

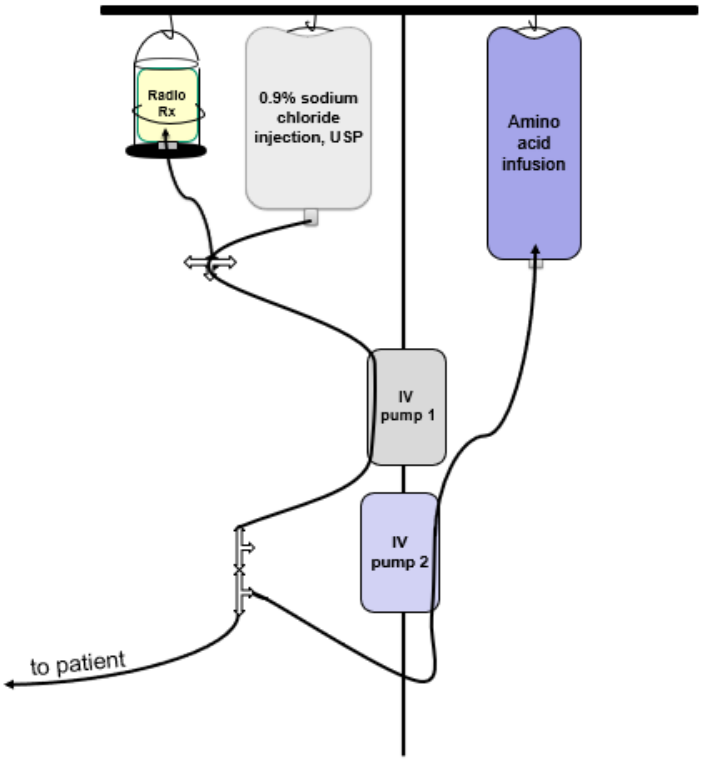

FIGURE 2. ^{177}Lu-DOTATATE Rotterdam secondary pump infusion method

first treatment is scheduled. After production, the manufacturer ships the radiopharmaceutical to the end-user under quarantine; the ^{177}Lu-DOTATATE cannot be infused into the patient until the batch release document from the manufacturer is received via email, thus releasing the lot from quarantine. The radiopharmaceutical is supplied in a 30 mL unit dose vial containing 7.4 GBq (200 mCi) ± 10% of ^{177}Lu-DOTATATE in 20.5-25 mL at a concentration of 370 MBq/mL (10 mCi/mL) calibrated to the time of infusion. The default Lu-177 dose calibrator setting may be used for measuring ^{177}Lu-DOTATATE, but it is recommended end-users obtain an annual calibration source from AAA/Novartis to determine a more precise dial setting. Currently, ^{177}Lu-DOTATATE approved labeling describes only a 3.7 or 7.4 GBq (100 or 200 mCi) administration, and there appears to be minimal dose calibrator geometry effect (*40,41*) for volume modification between these levels.

Several different radiopharmaceutical administration methods have been reported (*27,42*). The gravity method arose from the NETTER-1 clinical trial experience. This method involves a normal saline bag be hung and connected via an intravenous line to an upright shielded ^{177}Lu-DOTATATE vial with the needle tip above the level of the contents. A longer needle is inserted into and touches the bottom of the ^{177}Lu DOTATATE vial that is connected to the patient administration intravenous line. The saline entering the closed system at the top of the vial pushes the radiopharmaceutical out through the elongated needle placed at the bottom of the vial and into the patient. Further reading regarding the gravity infusion method is included in Hope TA, et al., (*27*) and the manufacturer's package insert (*24*). There have been issues reported with this technique (*43*), including loss of pressure in the vial to the room air from improper needle placement through the vial septum. Since United States Pharmacopeia (USP) general chapter <825> radiopharmaceutical guidelines were published in February of 2021 (*44*) and have already been adopted in some areas, it is imperative to follow USP guidelines for beyond-use times after puncturing a vial septum to ensure patient safety.

Our institution uses a ^{177}Lu-DOTATATE Secondary Pump Infusion method (*45*) similar to the Rotterdam method (Figure 2). For this method, the ^{177}Lu-DOTATATE vial is placed into a shield, spiked with a vial spike administration set, inverted, and infused with an IV pump. Using this simple and easily reproducible method, we have observed very little residual activity in the administration vial, essentially no contamination, and marginal additional exposure to the technical staff (*46*). Alternatively, the activity may be drawn up into a shielded syringe for administration via a syringe pump (*47*). Regardless of the ^{177}Lu-DOTATATE administration method utilized, the timing of antiemetics and amino acids infusion prior to and immediately following the ^{177}Lu-DOTATATE administration should not be modified with any alternative administration technique.

6. Dosimetry and Imaging

Imaging plays a major role in the management of patients with neuroendocrine tumors. During workup, patients undergo a PET/CT study (^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, or ^{64}Cu-DOTATATE) to assess for SSTR receptor positivity. Patients with low uptake of the SSTR-targeted radiotracer, in comparison to the liver or spleen, should not be considered eligible for treatment with ^{177}Lu-DOTATATE. In some cases, it can be helpful to also obtain a ^{18}F-FDG PET/CT study to identify lesions with increased metabolic rates. Determining lesion FDG positivity, as well as discordant tracer uptake (FDG positive and DOTATATE/TOC negative), provides prognostic value beyond what standard histopathological grading can provide (*48*). An example of ^{18}F-FDG and ^{68}Ga-DOTATOC discordance is shown in Figure 3**.** Although tumor uptake on pre-treatment SSTR PET imaging is weakly correlated with absorbed dose from ^{177}Lu-DOTATATE therapy and likelihood of response, it is not possible to accurately predict absorbed dose to tumors and normal organs from pre-treatment PET imaging. This is due to the short half-life of gallium-68 ($t_{1/2}$ 68 min), typically conducive to imaging ~1 hour after radiopharmaceutical administration. Peak tumor uptake of DOTATATE/TOC typically occurs several hours after administration, and the clearance kinetics must be

characterized for accurate absorbed dose determination. The half-life of copper-64 ($t_{1/2}$ 12.7 h) may be sufficient to obtain quantitative information at later PET imaging time-points (2-3 days) (*49*), but this has yet to be demonstrated conclusively in the literature. For these reasons, it is most common to perform dosimetry by SPECT/CT and/or planar gamma imaging following administration of the therapeutic quantity of ^{177}Lu-DOTATATE. An example of DOTATATE imaging, both pre-treatment PET/CT and post-treatment SPECT/CT, from our own institution is shown in Figure 4. In addition to providing quantitative information for dosimetry, post-treatment imaging is useful for rapid evaluation of whether any extravasation has occurred during infusion of the ^{177}Lu-DOTATATE. Although rare, extravasation can require immediate medical intervention to prevent excess radiation exposure at the site of injection.

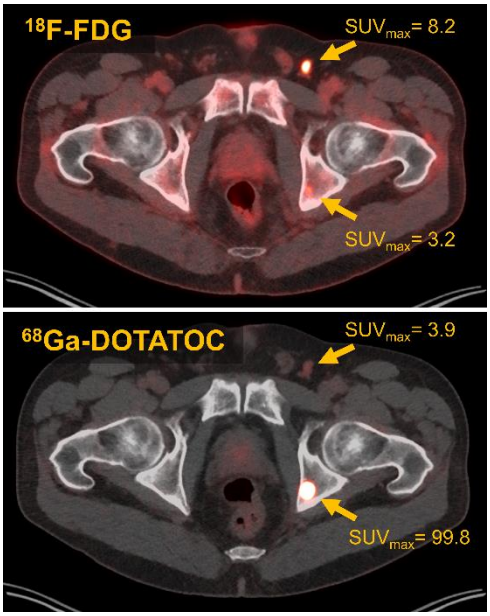

FIGURE 3. Example of discordant uptake on ^{18}F-FDG and ^{68}Ga-DOTATOC imaging. Two lesions are visualized: a left inguinal node (FDG positive, minimal DOTATOC uptake) and a left ischium bone lesion (DOTATOC positive, FDG negative).

Lutetium-177 emits two photons that can be used for imaging: 113 keV in 6.2% of decays and 208 keV in 10.4% of decays. Details regarding quantitative SPECT imaging of Lu-177 can be found in MIRD pamphlet no. 26 (*50*). Typical

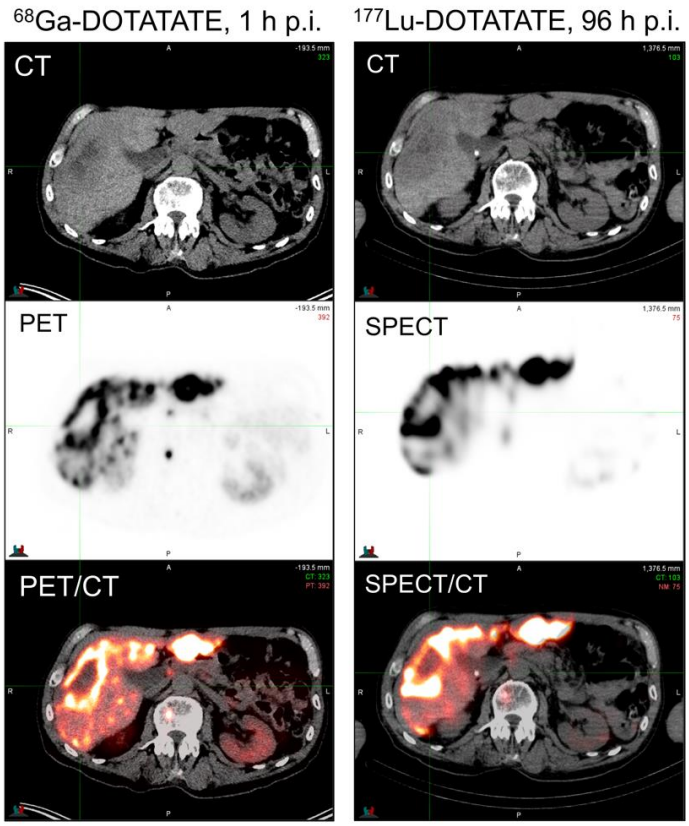

FIGURE 4. PET/CT imaging 1-hour post-administration of ^{68}Ga-DOTATATE (left) and SPECT/CT imaging 96 hours post-administration of ^{177}Lu-DOTATATE (right).

acquisition parameters include the use of a medium energy collimator; auto-contouring orbit; ≥ 60 views/head; 15-30 seconds/view; 128 x 128 or higher matrix size; 15-20% energy window on the 208 keV photopeak; and 5-10% scatter windows above and below the 208 keV photopeak. Images are typically reconstructed using iterative techniques with CT-based attenuation correction; triple energy window (TEW) scatter correction; collimator detector response (CDR) modeling; iterative updates adequate to achieve activity recovery convergence (e.g., 12i8s for typical OSEM3D); and minimal or no pre-or post-reconstruction filtering. In addition to these acquisition and reconstruction parameters, system sensitivity should be assessed via an appropriate phantom experiment (*51*), and dead time should be estimated from measured patient count rates during imaging (*52*).

Fully calibrated and corrected images can then be used to assess patient-specific dosimetry. Methods for determination of patient-specific absorbed dose vary in complexity and accuracy; there are an increasing number of software tools to facilitate dose calculation from radiopharmaceuticals (*53*). The interested reader can find pertinent dosimetry details in the papers by Siegel et al., Bolch et al., Graves et al., as well as the MIRD Primer for Absorbed Dose Calculations, revised (published in 1991, new edition expected in early 2022) (*54-57*). Tissues of relevance in dosimetry calculations for ^{177}Lu-DOTATATE often include bone marrow, kidneys, and occasionally liver in cases of prior/planned liver-directed therapy or extensive hepatic tumor burden. Details of normal tissue dose limits for radiopharmaceuticals can be found in the recent article by Wahl et al., (*58*).

7. Billing and Coding

The Centers for Medicare and Medicaid Services (CMS) issued ^{177}Lu-DOTATATE a Healthcare Common Procedure Coding System (HCPSC) code of A9513 on January 1, 2019. The A9513 code descriptor specifies billing as per 1 millicurie (mCi), and it is important to ensure the administered mCi amount for the therapy is accurately documented and submitted (*59*). If a portion of the ^{177}Lu-

DOTATATE activity is wasted due to personalized dosimetry or other reasons, a JW modifier should be utilized. The JW modifier is used to report discarded drug amounts still eligible for payment under Medicare's discarded drug policy (*60*). The HCPCS codes for antiemetics and amino acids (AA) will vary based on physician drug choice and AA procurement location. Current Procedural Terminology (CPT) codes are also used for ^{177}Lu-DOTATATE treatment. CPT code 79101, radiopharmaceutical therapy, intravenous (IV) administration, can be used for ^{177}Lu-DOTATATE administration. The first hour of IV AA administration can be coded with 96365, and subsequent hours can be coded with 96366. Coding for antiemetic pre-medication will vary based on the drug type and route of administration (*59*).

Medical billing and coding guidelines can vary by practice and region, and readers are encouraged to consult the SNMMI's Coding and Reimbursement website, manufacturer's reimbursement guide, and internal institutional reimbursement specialists. The accurate coding and classification of a patient's diagnosis and treatment are essential, and billing modifiers may be required. Billing codes and reimbursement rates are subject to change based on payer, date of service, and billing setting, and the information shared at the time of this publication is no guarantee of reimbursement. Billing and coding guidelines will continue to evolve with the growth of PRRT. Additionally, reimbursement approaches for dosimetry-guided radiopharmaceutical therapy are emerging, as detailed by Graves, et al., (*61*).

9. Conclusion

^{177}Lu-DOTATATE currently serves as a second-line treatment option for patients with surgically unresectable, metastatic, or locally advanced midgut NET that have failed first line SSA therapy and is a paradigm-shifting approach to cancer treatment. ^{177}Lu-DOTATATE is paving the way for the future of receptor-based therapy and personalized cancer treatment; this PRRT agent has yielded significant treatment progress for NETs and dramatically impacted patient management. Before offering a patient ^{177}Lu-DOTATATE therapy, a multidisciplinary team should evaluate patient-specific clinical

considerations, and SSTR positivity should be confirmed with functional imaging. Sites wanting to implement a ^{177}Lu-DOTATATE program are encouraged to consider the patient selection criteria, PRRT administration methods, clinical, regulatory, and radiation safety considerations, technical factors, tissue dosimetry, and reimbursement practices required with the use of this newly approved PRRT agent.

TABLE 1: PRRT Exclusion Criteria Considerations

• Serum creatinine > 150 µmol/L (>1.7mg/dL) or creatinine clearance (CrCl) < 50 mL/min*
• Hemoglobin (Hb) < 5.0 mmol/L (< 8.0 g/dL)
• White-cell count < 2,000/mm^3 (2x10^9/L)
• Platelet count < 75,000/mm^3 (75x10^9/L)
• Total bilirubin > 3x ULN
• Serum albumin ≤ 3.0g/dL, unless prothrombin time (PT) value was within normal range

ULN = upper limit of normal range

*Calculated by the Cockroft Gault method; confirmed by measured creatinine clearance or measured glomerular filtration rate (GFR) using plasma clearance methods, not gamma camera-based; < 50 mL/min (measured creatinine clearance/GFR required only has confirmatory exam)

Reference: (*19*)

TABLE 2: Classification and grading criteria for neuroendocrine neoplasms (NENs) of the GI tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic rate*	Ki-67 index*
NET, G1	Well-differentiated	Low	<2	<3%
NET, G2		Intermediate	2-20	3-20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High†	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated	Variable‡	Variable‡	Variable‡

LCNEC, Large-cell neuroendocrine carcinoma; MiNEN, Mixed neuroendocrine-non-neuroendocrine neoplasm; NEC, Neuroendocrine carcinoma; NET, Neuroendocrine tumor; SCNEC, Small-cell neuroendocrine carcinoma

*Mitotic rates are to be expressed as the number of mitoses/2mm^2 as determine by counting 50 fields of 0.2mm^2 (i.e., in a total area of 10mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.

†Poorly differentiated NECs are not formally graded but are considered high-grade.

‡In most MiNENS, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

Reference: (*21*)

Disclosures

NM has served as a consultant for Novartis Inc. and SG has a research proposal being reviewed by Novartis Inc. relating to ^{177}Lu-DOTATATE. The other authors have no potential conflicts of interest to disclose.

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