ACR–ACNM–ARS–SNMMI PRACTICE PARAMETER FOR LUTETIUM-177 (Lu-177) DOTATATE THERAPY

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[1]. 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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1 *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 not establish the standard of care.*

I. INTRODUCTION

This practice parameter was developed collaboratively by the American College of Radiology (ACR), the American College of Nuclear Medicine (ACNM), the American Radium Society (ARS) , and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

The practice parameter, initially drafted and evaluated in 2020 [1], provided a set of comprehensive guidelines for appropriately trained and licensed physicians to perform therapy with lutetium-177 (Lu-177) DOTATATE. Such therapies require close cooperation and communication between the physicians who are responsible for the clinical management of the patient, those who administer radiopharmaceutical therapy and those who manage

the attendant side effects. Adherence to this parameter should help to maximize the efficacious use of these procedures, maintain safe conditions, and ensure compliance with applicable state and federal regulations. Since then, applications and needs for Lu-177 DOTATATE have significantly expanded, and the number of patients receiving this parenterally radioactive therapy have increased. A full Committee on Practice Parameters and Technical Standards has been convened, and completed a detailed clinical update as reported below.

Application of this parameter should be in accordance with the ACR–AAPM–ACNM–SNMMI–SPR Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals [2], in so far as that standard relates to the handling of radiopharmaceuticals, radiation safety, and radiation protection of patients, personnel, and the public. There must also be compliance with applicable laws and regulations.

The goal of therapy with Lu-177 DOTATATE is to slow disease progression, to palliate symptoms, and/ or to possibly improve overall survival [3], while minimizing side effects and potential complications. The US Food and Drug Administration approved Lu-177 DOTATATE radiopharmaceutical therapy in 2018.

The most common utilization of Lu-177 DOTATATE therapy is in patients with neuroendocrine tumors (NETs), which are relatively rare and typically slow-growing neoplasms originating in neuroendocrine tissue distributed throughout the body. The most common site of origin is from the gastroenteropancreatic (GEP) region. They may secrete bioactive amines and hormones, giving rise to variable clinical presentations [4]. Surgical resection of the tumor is the preferred initial therapy because it is potentially curative[5, 6]; however, because of the indolent course and nonspecific presentation of the disease, many patients present initially with locally advanced or metastatic disease, making curative resection difficult or impossible[7]. Other regularly used conventional treatments include use of nonradioactive somatostatin analogues that take advantage of the overexpression of somatostatin receptors (SSRs) by these NETs. Use of other agents, including cytotoxic chemotherapy such as capecitabine and temozolomide [8], is often suboptimal because of side effects and smaller magnitudes of clinical effectiveness in certain grades of tumor including well-differentiated grade 3 NETS [9] and progressive cases, which are refractory to somatostatin therapies [10, 11]. Despite use of these currently available conventional treatments, many patients continue to progress with life-altering signs and symptoms, such as unrelenting diarrhea, flushing, or right-sided heart disease [12, 13]. Uncontrolled and treatment-resistant NETs can lead to significant morbidity as well as mortality.

Lu-177 DOTATATE is an effective therapy for patients with inoperable, locally advanced, or metastatic NETs that progress on conventional treatments [12-16]. Data demonstrating improvement in disease control rates, progression-free survival, although not statistically significant there was a trend for overall survival improvement following the final analysis of the NETTER I trial and[3] quality of life suggest that this therapy may be considered as first-line therapy [17]. Lu-177 DOTATATE specifically binds to the SSRs that are overexpressed on the cell surfaces of most NETs, with highest affinity for subtype 2. The complex formed is chemically stable and is internalized into the cell resulting in a favorable position to irradiate the nucleus and induce DNA damage–related inhibition of growth and death [18]. This treatment is also called peptide receptor radionuclide therapy (PRRT). Beta (ß-) emission from Lu-177 has a maximum energy (Q-value) of 0.5 MeV, range in soft tissues of 2 mm, and half-life of 6.7 days. Lu-177 also emits low-energy gamma rays at 208 keV (11% abundance) and 113 keV (6.4% abundance) that can be used for gamma camera imaging and dosimetry if desired [19]. The potential indications for Lu-177 DOTATATE have expanded significantly over the past few years. A large prospective study from Spain enrolled 522 patients, including pancreas, midgut, bronchopulmonary, pheochromocytoma, paraganglioma, and other non-GEP originating NETs; the median survivals ranged from 17.6 to 31.3 months [20] with the use of 4 cycles of Lu-177 DOTATATE, which are comparable to the NETTER-1 study [3]. A large number of pilot and retrospective studies have demonstrated clinical efficacies in patients with high cellular proliferative indices (Ki-67 15-55%); [21-25] other tumor types such as medullary thyroid carcinoma neuroblastoma, paraganglioma, and meningioma that may be PRRT-sensitive[25]. Results from the prospective randomized NETTER-2 trial, indicated that Lu-177 DOTATATE is more efficacious than high-dose octreotide LAR in metastatic or inoperable G2 (Ki67>10%) and G3 NETs as first or second line, PFS 28 vs 8 months[26]. Recently, international and US-based investigators have also been actively evaluating the use of Lu-177 DOTATATE as retreatments, for patients with recurrent or progressive NET[27]. Prospective clinical trials, including the indication for rechallenging patients with progressive intestinal NETs using 2 additional cycles of Lu-177 DOTATATE, are ongoing[28]. Another pivotal study, titled COMPOSE, will compare Lu-177-Edotreotide versus

best standard of care including chemotherapy in patients with well-differentiated grade 2-3 NETs.

Although PRRT with Lu-177 DOTATATE has been proven to be effective in NETs, there are adverse side effects and safety issues that must be understood and taken into consideration by treating physicians so that appropriate plan and required interventions can be instituted [14]. In a US-based population, 63% of patients developed 1 or more grade 2+ adverse effects, during or after receiving Lu-177 DOTATATE-based PRRT [29].

Side effects associated with PRRT with Lu-177 DOTATATE can be categorized as acute, subacute, or delayed [14]. It is highly advisable that a multidisciplinary team coordinate the care of a patient being considered for treatment with Lu-177 DOTATATE [15].

General: Abdominal pain, nausea, and vomiting can occur typically within 24 hours of treatment. In addition, patients can also experience fatigue, diarrhea, alopecia, and cough [17]. In most cases, these symptoms are self-limiting and rarely require more than supportive therapy. Careful evaluation of the pretreatment scan should be performed to evaluate potential for small-bowel obstruction related to peritoneal disease. Patients deemed at risk may be prescribed a steroid course to minimize risk likelihood of bowel obstruction [30].

Nephrotoxicity: Lu-177 DOTATATE is excreted by the kidneys through glomerular filtration and is reabsorbed by the proximal tubules where radiation damage can occur [19]. Reduction of proximal tubular reabsorption has been effectively achieved with use of other ligands that can competitively bind to the receptors in the proximal tubular cells without affecting the SSR targets of Lu-177 DOTATATE in the circulation [31]. The most efficacious solution to date to reduce renal uptake of somatostatin analogues consists of a combination of basic amino acids lysine (25 g) and arginine (25 g) [19, 32]. Renal toxicity is generally mild and well-tolerated with amino acid coinfusions. However, grade 1 nephrotoxicity in 20% and grade 2 nephrotoxicity in 4% of patients has been reported [14, 17]. Higher-grade toxicities are rare (0% to 0.4%) and are observed in individuals with baseline compromised renal function [13, 14]. Many studies have shown improvement of renal function over time, but long-term renal impairment remains one of the clinical concerns in patients with renal compromise at baseline, since reporting an annual decrease in creatinine clearance of 3.4% to 3.8% has been reported [33, 34]. Novel strategies in preventing nephrotoxicities and understanding renal dosimetry with peptide-receptor radionuclide therapy (PRRT) are urgently needed, as it is a critical step for maximizing the therapeutic ratio and potentials of Lu-177 DOTATATE in future clinical trials [35]. Details on administration are provided in the "Specific Procedures" section of this document (IV.B).

Hematologic: The bone marrow is an organ with rapidly dividing hematopoietic cells and is thus radiosensitive. Mild subacute myelosuppression can be seen in the first days to weeks after treatment and typically reverses within weeks after cessation of treatment [14]. The most common side effects include anemia, thrombocytopenia, and leukopenia. Six weeks after the first dose of Lu-177 DOTATATE, a rare and potentially life-threatening case of hemorrhagic disseminated intravascular coagulation associated with anemia and thrombocytopenia was reported [36, 37] Grade 3 and 4 bone marrow toxicity are seen less frequently and are generally reversible without intervention within 2 to 3 months but may take up to 12 months [13, 38, 39]. Bone metastases can increase the likelihood of myelotoxicity [39, 40]. In approximately 2% of patients, especially those heavily pretreated with myelosuppresive therapies before receiving PRRT, a preleukemic condition, myelodysplastic syndrome or more rarely acute myeloid leukemia, can develop which requires specific chemotherapeutic regimens and can lead to a fatal outcome [13, 14, 34, 38].

Hepatic: Liver dysfunction has been noted with increases in bilirubin and transaminases. A few patients have developed grade 3 toxicity that progressed to liver failure and death within one year after PRRT [14]. On the other hand, patients with GEP-NET can still present with very high liver tumor burden, with cancer comprising more than 75% of the native liver. In a small series of 15 patients with very high liver tumor burden, only 1 patient experienced hepatotoxicity, and none developed a grade 3, 4, or 5 hepatoxicity (clinical hepatic failure, death). [[41].

Hormonal Crisis: This is a rare complication that presents as flushing and significant diarrhea and, less frequently, heart failure, emesis, and bronchoconstriction. It typically occurs within 48 hours of infusion, with greater likelihood in patients with large tumor burden [42, 43]. This is a serious adverse side effect requiring prompt in-

hospital care for continuous somatostatin analogue infusion and supportive care.

Risk of Infertility: The recommended cumulative activity of 800 mCi (29.6 GBq) Lu-177 DOTATATE results in radiation absorbed dose to the testis and ovaries within the range in which temporary or permanent infertility may ensue, such as seen following pelvic external-beam radiotherapy [13, 15, 17, 44]. Two pediatric patients, ages 8 and 13, respectively, with metastatic NET being treated by Lu-177 DOTATATE have been reported in the literature. This toxicity must be discussed and counseled with patients of reproductive age, for family planning purposes [45].

Facilities and their responsible staff should consult with their radiation safety officer to ensure that there are policies and procedures specific to Lu-177 DOTATATE that address 1) required instrumentation, calibration, and calibration frequency and 2) ordering and receiving, recordkeeping, safe use, and waste disposal in compliance with the applicable laws and regulations as described in ACR–AAPM Radiation Safety Officer Resources [44].

II. INDICATIONS

Lu-177 DOTATATE is indicated for the treatment of SSR-bearing GEP-NETs, including foregut, midgut, and hindgut NETs in adults [15]. Other disease indications (see Section I. above) can also be considered, at the discretion of the responsible physician for treatment, as recommended by the National Comprehensive Cancer Network guidelines. It also appears to be safe and efficacious in geriatric patients who are 70 years in age or older with maintained health-related quality of life. There is usually no age limit for Lu-177 DOTATATE therapies [46]. On April 23, 2024, the FDA approved Lu177 DOTATATE for pediatric patients aged 12 and older with somatostatin positive GEP NET tumor including foregut, midgut and hindgut[47].

III. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

The qualifications and responsibilities of physicians and other personnel performing these therapeutic procedures should be in accordance with the ACR–AAPM–ACNM–SNMMI–SPR Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals and/or the ACR–ARS Practice Parameter for Radiation Oncology [2, 48].

In addition, training and experience must be in compliance with the applicable laws and regulations.

IV. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

A. Clinical Evaluation

The treating physician's initial evaluation of the patient must include review of the patient's history, physical examination, pertinent diagnostic studies, laboratory reports, and complete history of all available records of previous pertinent therapies, including, but not limited to, myelosuppressive systemic therapy and/or radiotherapy.

1. Verification of Pathology and Indication for Therapy: A pathology report confirming the diagnosis should be reviewed and included in the patient's record. Efficacy of Lu-177 DOTATATE is well documented, particularly in well-differentiated NET with a Ki-67 index of <20% (G1-2)[49]. Other subtypes of NETs, medullary thyroid carcinoma[50], [51], and well-differentiated grade 3 NET tumors (based on NETTER-2 [26, 52]) may also be considered on an individual patient basis [24, 25, 50, 52-54]. Because Lu-177 DOTATATE localizes to NET expressing SSR, it is necessary to confirm that the NET being treated expresses SSRs with a SSTR PET/CT (see ACR–ACNM–SNMMI–SPR Practice Parameter for the Performance of Neuroendocrine Tumor Scintigraphy and ACR–ACNM–SNMMI Practice Parameter for the Performance of Gallium-68 and Copper-64 DOTATATE PET/CT Imaging for Neuroendocrine Tumors) [55, 56]. Indium-111 octreotide scan should only be used if PET is unavailable.

2. Discontinuation of Somatostatin Analogue Therapy with Baseline Laboratory Evaluation: If the patient is being treated with long-acting somatostatin analogue, this should be stopped 4 weeks before Lu-177 DOTATATE infusion. Short-acting analogues may be stopped 24 hours before PRRT. In anticipation of possible side effects, each patient should have a complete blood count with

differentials and metabolic panel including renal and hepatic function tests. Such monitoring should be performed before each infusion and as needed for hematologic monitoring in between treatments. Dose reduction based on laboratories is discussed in Section IV.B.2. Although institution and patient-specific considerations take precedence, grade 1 to 2 or less hepatic enzyme elevation or myelosuppression is sufficient to allow therapy, creatinine clearance at least 30 mL/min. Below this threshold, no safety data are available, as per FDA label. Women of childbearing age should undergo pregnancy testing [15, 57].

3. Special Populations: Lu-177 DOTATATE has not been tested in lactating patients, and these patients should be advised to cease breastfeeding while receiving treatment and for 2.5 months after the last treatment fraction, as effects on infants have not been determined. For patients of reproductive potential, discussion should be carried out to use effective contraceptive measures during and after PRRT. For female patients, because of the possibility of fetal harm, effective contraception should be continued for 7 months following the last treatment fraction of PRRT. For male patients with female partners, contraception should be continued until 4 months following the last treatment fraction [15]. Sexual activity should be avoided following therapy for 7 days. .

4. Quality Management: To use radiopharmaceuticals as unsealed sources for therapy, including Lu-177 DOTATATE, a "quality management" program must be in place as required by applicable state and federal regulations. (An Agreement State is any state with which the Nuclear Regulatory Commission (NRC) or the US Atomic Energy Commission has entered into an effective agreement under subsection 274.b of the Atomic Energy Act of 1954 as amended, 73 Stat, 689). Key elements of such a program include written directives, duplicative procedures for identifying patients, careful record keeping to ensure prescribed administered activity, minimization of the possibility of infiltration for radiopharmaceuticals that are administered intravenously (IV), procedures for minimizing radiation exposure or radiopharmaceutical contamination of personnel, family members of patients, and the public (eg, alerts regarding possible current or future pregnancy), procedures for containment of radioactivity; and an audit mechanism to ensure compliance with the program[58].

5. Informed Consent: Informed consent must be obtained and documented. See the ACR-ARS Practice Parameter on Informed Consent – Radiation Oncology [59].

6. Treatment: The procedure and follow-up should be performed according to an established system of procedural steps unique for Lu-177 DOTATATE [60].

7. Radiation Precautions: Radiation precautions and patient release criteria may be regulated federally by the NRC in many states or by the state (with regulations that are closely patterned on the federal regulations and may be more restrictive). The radiation safety officer, medical physicist, or health physicist for the local facility can provide information on the applicable regulations. Details on the federal regulations can be obtained at the NRC website (nrc.gov) [61-63].

   Under the guidelines of federal code 10 of the Code of Federal Regulations (CFR) 35.75 [64] and key sections of NUREG-1556 [65], a patient may be released to the public if the total effective dose equivalent to any other individual (including any caregiver or family member) who is exposed to the patient is not likely to exceed 5 mSv (0.5 rem). If the total effective dose equivalent is likely to exceed 1 mSv (0.1 rem) to any individual, instructions (including written instructions) must be provided to the patient on actions to limit radiation exposure to others by using the "as low as reasonably achievable" (ALARA) principle. Some states may have specific rules and regulations regarding the release of patients with significant residual activity.

   The dose limits specified by the National Council on Radiation Protection and Measurements (NCRP) differ somewhat from the NRC regulations [66]. Because the fetus and children are more sensitive to radiation injury than adults, the NCRP specifies that children and pregnant women, whether or not they are members of the patient's household, should be limited to 1 mSv (0.1 rem). Any individual

who has no familial connection to the patient and whose presence offers no emotional benefit should also be limited to 1 mSv, which is also the NRC dose limit to a member of the public.

Many radiation meters measure exposure rates in milliroentgens per hour (mR/h). For purposes of radiation protection and for low linear energy transfer radiation (including beta particles and most x-rays and gamma rays), the authors of this document accept the approximation that 1 mR, 0.01 mSv, and 1 mrem are equivalent. Thus, an exposure rate of 7 mR/h at 1 m is an adequate approximation to the dose rate, 0.07 mSv/h (7.0 mrem/h) at 1 m.

Specific Considerations During Lu-177 DOTATATE Therapy and Patient Release:
According to radiation exposure calculations based on whole-body clearance data, patients may need to be kept in radiation isolation for 4 to 5 hours following the administration of the typical dose of 200 mCi (7.4 GBq) Lu-177 DOTATATE [67], which overlaps with the time needed to complete the amino acid administration. A postinfusion survey by physics or other radiation safety may be performed to determine an acceptable maximum exposure rate that conforms to the 10 CFR 35.75 requirement of <5 mSv exposure anticipated to other individuals. An established protocol for documenting this survey result should be used and available. Until the patient has been released, the patient must be kept in an area to protect others from unnecessary exposure. An administration of 200 mCi Lu-177 DOTATE typically results in exposure levels on the order of 2 mR/h at 1 m immediately after administration, declining to 1 mR/h after 24 hours, allowing outpatient treatment in most cases with appropriate training, protocols, infrastructure, and patient counseling. The procedures and practical example guidance for instruction of patients on discharge have been reviewed in published literature [68]. For further information, see Appendix A.

Modeling per the NUREG-1556 assumption of 0.25 occupancy factor estimates 1.8 mSv exposure dose to other individuals, thus requiring written instructions be given to the patient on ALARA principles. During therapy, involvement of trained radiation safety personnel qualified in safe management of unsealed sources, waste, accidental contamination, and counseling of patients is important. The patient and, as relevant, caregivers should be compliant with all radiation safety precautions and instructions. Education should occur before treatment, preferably at the time of consultation so that the patient and caregivers can plan ahead. Inability to comply with the precautions may require an admission or other special accommodations to account for the realities of patient life at home, as determined by the authorized user. The specific instructions and considerations for admission or other special accommodations will vary from institution to institution, but key features are summarized below.

Urinary Contamination:
Specific concern is paid to disposal of urine as the most common potential source of contamination. During therapy, a dedicated toilet is recommended, and although lead shielding is not necessary because of the short range of beta emission, disposable lining of the floors and toilet/sink surfaces is encouraged to contain radioactive urine or other contamination [68]. Urinary incontinence, if present, would require catheterization before administration and for at least 2 days thereafter to minimize radiation contamination. Other simple measures used to minimize urinary contamination on discharge include:

Use of private room with its own bathroom
Washing of hands for 20 seconds after each use of the restroom
Instructing the patient to urinate while seated
Flushing 2 to 3 times with the toilet lid closed
Rinsing of sinks and showers after use
Cleanup of urinary spills with damp toilet paper that can be flushed down the toilet (to minimize accumulation of waste product trash requiring long-term storage). Should patients use pads, they must be instructed on how to store the pads before placing in the general waste
Other Potential Sources of Contamination:

Peritoneal and hemodialysis are not contraindications for treatment, but they may impact the administered activity of Lu-177 given the prolonged residence time within the patient and complicate handling of hemodialysis machines because of the likelihood of retained radioactivity after use, thus requiring logistics planning with dialysis facilities and the patient. A case report showed that a patient required therapeutic paracenteses clinically, and the radioactivity in ascites was already very low (175 Bq/mL), after 3 days of a standard dose of Lu-177 DOTATATE (7.4 GBq) therapy [69]. Another infrequent but special consideration for Lu-177 DOTATE therapy given its target population is in patients with indwelling drains, such as biliary drains, which require confirmation of ability of caregivers to safely manage disposal of waste with the same precautions applied to urine. When possible, these sources of waste should be flushed down the toilet similar to urine, with use of disposable gloves by the caregiver when handling and cleaning drain equipment and collection bags.

Release to Health Care Facility/Admission to Hospital Considerations:
If confinement in a health care facility is needed, it is not usually necessary to store body effluents, such as urine, stool, or vomitus. In general, for patients who have been released to the public, precautions for the patient should be according to ALARA principles and universal precautions. A discussion should be had in such cases with a facility or hospital's radiation safety department and/or involved parties (clinical leadership) to determine any additional precautions that will be taken for care workers. Furthermore, should a patient receiving Lu-177 DOTATATE require admission to a hospital or transfer to an emergency department, it is highly recommended that the administering team contact the receiving personnel for a "sign-out."

Although not explicitly required, examples of "extra" precautions include the following. For effluent disposal where acceptable under state or federal regulations, the toilet can be flushed two or three times after each use to ensure sufficient dilution of radioactivity. Food trays, linens, and all other contaminated products may be stored in the patient's room until monitored and cleared by radiation safety staff. The patient must stay in the room except in a medical or nonmedical (eg, fire) emergency, and access by personnel and visitors can be limited. All trash and residual nondisposable items can be monitored after the patient's release and stored until radiation levels reach the statutory level defined for safe disposal or reuse. In some jurisdictions, items in decay storage must reside there for 10 half-lives (67 days for Lu-177) or until radiation levels are indistinguishable from background. Once all known contamination is removed from the room, the room must be surveyed to verify that the radiation levels and removable contamination are sufficiently low to permit its general use. The room may not be used until this survey is performed and safe level documented. Individual institution's radiation safety procedures may vary somewhat.
If the admitting physician is different from the physician who administers the radiopharmaceutical, there must be a mechanism to prevent premature discharge or release of the patient from confinement.

Waste Disposal:
As previously mentioned, trash and nondisposable items contaminated by patient fluids must be stored and monitored until their radiation levels reach safe disposal limits, which may vary between institutions and jurisdictions, with one prominent guideline being 10 half-lives (67 days for Lu-177).

Distance of Caregivers and Considerations for Travel:
There is no specific regulation on required distance of caregivers following discharge. However, to meet guidance from NUREG-1556's use of a 0.25 occupancy factor for estimating exposure of public allowing safe discharge of patients after administration, it is assumed that exposed persons will maintain a distance of 1 m (3 ft) for at least 3 days and not sleep in the same bed as the patient for 7 days. There is a further assumption of following ALARA principles to minimize exposure to potential contamination, such as may occur during use of the same toilet facilities.

Prolonged use of personal or public transportation (bus, train, etc) in the company of others for more

than 1 hour is discouraged for the first 3 days following therapy. Although Title 10 of the CFR, part 35.75, does not expressly prohibit release of a radioactive patient to a location other than a private residence such as a hotel, the NRC strongly discourages this practice because it can result in radiation exposure to members of the public for which the licensee may not be able to assess full compliance with the code.

Nonetheless, when travel is unavoidable in the first 3 days after therapy, the patient should be instructed to discuss the matter with treating personnel.

Furthermore, although patients are recommended to travel immediately home, it is acknowledged that some patients may need to reside in a hotel or other public facility. Again, precautions to maximize distance from other members of the public are recommended (>1 m at a minimum) in the 3 days after Lu-177 DOTATATE administration.

Postmortem Handling of a Deceased Patient:

In a case report, a patient received 194 mCi of Lu-177 DOTATATE in the year 2017. He was admitted into a different hospital and died from his NET 2 days later. He was cremated 5 days after the lutetium treatment. Multiple crematory equipment's registered very-low-dose counts and exposure by a Geiger radiation detector, and a low activity of technetium Tc 99m was found in the crematory operator's urine (as a result of handling the deceased patient). Although there is no current mandate regarding evaluation of radio-activities in deceased patients who just received Lu-177 DOTATATE or how funeral homes and facilities could get notified, cremation (versus other methods, such as burial) may not be a suitable method if the deceased patient was just exposed radioactive pharmaceuticals hours or days ago. These scenarios need to be handled on a case-by-case basis [70].

IV. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

B. Treatment Procedures for Infusion on Lu-177 DOTATATE

1. Preparation:
   Before ordering Lu-177 DOTATATE solution for PRRT, confirm that treatment with Octreotide analogs has been discontinued [71] for at least 4 weeks for long-acting preparation and for 24 hours for short-acting preparation before scheduled therapy.
   Lu-177 DOTATATE is a radiopharmaceutical that requires effective radiation shielding before handling. The vial containing the radiopharmaceutical is delivered in a lead- or Plexiglas-shielded container. It is advised that the personnel assigned to prepare or infuse the radiopharmaceutical wear double gloves.
   Before the actual administration of Lu-177 DOTATATE, patients should be started on a renal protective amino acid infusion and may be premedicated with antiemetics according to institutional/physician preference. Depending on institutional preferences and resources, coordination should be made between all involved staff, including the referring physician and the physician administering the radiopharmaceutical to ensure that the steps and processes involved with PRRT are conducted. Two separate IV access sites are preferred: one for the amino acid infusion and one for Lu-177 DOTATATE infusion, although infusion can be performed with one IV in patients with limited IV access.

2. Dosage:
   The recommended dosage is 200 mCi (7.4 GBq) Lu-177 DOTATATE, administered every 8 weeks for a total of 4 doses as tolerated in patients 12 and older. Dosage can be halved, according to the FDA-approved clinical notes, in special clinical situations, such as hematological toxicity [72].

   Prophylaxis: Amino Acid Solution and Antiemetics:
   The Lu-177 DOTATATE solution needs to be administered with concomitant amino acid infusion to reduce radiation absorbed dose and toxicity to the kidneys. Amino acid infusion should be initiated 30 minutes prior to infusion of Lu-177 DOTATATE and continued for a total of 4 hours. There are different amino acid

formulations available. The extemporaneously compounded formulation contains only 25 g lysine HCl and 25 g arginine HCl with 1 L of appropriate sterile solvent (eg, water for injection). This formulation has lower osmolality and less patient emetic side effects. The commercially available amino acid solutions have a lysine content between 18 and 24 g and arginine content between 18 and 25 g in a volume of 1.5 - 2.2 L of solution having <1,050 mOsmol/L. Aminosyn II 10% used in clinical trials in the United States contained additional essential and nonessential amino acids as well as electrolytes resulting in osmolality of 1,040 mOsmol/L. This preparation was associated with a high incidence of nausea and vomiting. Choice of amino acid formulations depends on institutional resources.

Because of nausea with or without vomiting observed in some patients receiving amino acid infusion, it is advised that the use of prophylactic antiemetic medications be considered, as used in each institution with any chemotherapy, 30 minutes before commencing amino acid solution administration. Other adjunct treatment for persistent vomiting is reasonable depending on physicians' experiences.

3. Infusion Methods:
It is highly preferred that the IV access for administration of Lu-177 DOTATATE solution be separate from IV access for amino acid infusion. Separate access allows removal of the radiopharmaceutical access materials from the patient after PRRT, ensuring no radioactive medical line leaves the confines of the administering facility. Before infusion, measure the source activity to confirm prescribed activity. In some centers, a double lumen peripherally inserted central catheter line can be used for infusion to avoid delivery failures.

Lu-177 DOTATATE is delivered in a vial under positive pressure. It can be administered via gravity method, infusion pump method or via automated syringe pump injector, as detailed with illustrative figure at the available link: https://jnm.snmjournals.org/content/60/7/937/F3 [60]. Each institution can choose the best technique of radiopharmaceutical administration.

Gravity Method:

- Insert a 2.5-cm-long, 20-gauge needle (short needle) into the Lu-177 DOTATATE vial, ensuring that the beveled tip inside the vial does not touch the solution at any time during the infusion. The hub of the short needle is fastened to the IV tubing of a previously prepared 500-mL sterile 0.9% sodium chloride solution. Keep the IV tubing clamp closed until the entire setup has been completed and is ready for infusion.
- Insert a second needle that is 9 cm long, 18 gauge (long needle) into the Lu-177 DOTATATE vial, ensuring that the beveled tip of this long needle touches and is secured to the bottom of the vial during the entire infusion. Fasten a connecting tube prefilled with sterile 0.9% sodium chloride to the hub of the long needle, ensuring that there are no air bubbles inside the plastic tubing. Check the designated IV access for Lu-177 DOTATATE to ensure patency; once confirmed, fasten the male Lauer lock of the connecting tube to the IV access, keeping clamp closed.
- Do not remove the needles to reposition once the seal is punctured, as this may make the seal ineffective and prevent dose delivery by this method.
- Open the clamp in the connecting tube from the vial to the patient, and then open the clamp of the tubing from the bag of normal saline solution. Regulate the flow of the sodium chloride solution via the short needle into the Lu-177 DOTATATE vial at a rate of 50 mL/h to 100 mL/h for 5 to 10 minutes and then 200 mL/h to 300 mL/h for an additional 25 to 30 minutes. During infusion, ensure that the level of solution in the Lu-177 DOTATATE vial remains constant and that the vial does not fill up completely. Total duration of infusion is about 30 to 40 minutes.
- Do not administer Lu-177 DOTATATE as an IV bolus.
- Clamp the saline line once the level of radioactivity is stable for at least five minutes.
- Clamp the connecting line from the vial and disconnect from the long needle, taking care that no fluid spills out. Open the connecting tube again and flush with 25 mL of 0.9% sterile sodium chloride to wash off any radiopharmaceutical remaining within the tubing into the patient.
- Remove the IV access used. Measure the remaining activity in the setup, including the vial, and subtract from the measured preinfusion activity to obtain the net activity administered.

Infusion Pump Method:
For the infusion pump method, the short and long needles are also used. The tubing that connects to the long needle should be primed with normal saline solution before attachment to an infusion pump. The other end of this tubing is attached to the IV access of the patient. A 3-way stopcock is connected to the hub of the short needle before it is inserted into the vial with a filter attached to the vent tip. Again, the tip of the short needle should stay above the fluid level, whereas the tip of the long needle is at the bottom of the vial. The positive pressure within the Lu-177 DOTATATE vial drives fluid into the patient and is controlled by the infusion pump, which is usually programmed to deliver 0.8 to 0.9 mL/min for total infusion time of 25 to 30 minutes. Remove the IV access used. Measure the remaining activity in the setup, including the vial, and subtract from the measured preinfusion activity to obtain the net activity administered.

Automated Syringe Pump Injector Method:
Another method involves drawing the Lu-177 DOTATATE solution from inside the vial into a sterile lead-shielded syringe that is then mounted on an automated syringe pump injector to administer the Lu-177 DOTATATE. This method exposes the individual drawing the solution to radiation risk. A connecting tube prefilled with sterile 0.9% sodium chloride solution is used to connect the syringe containing the radiopharmaceutical to the IV access of the patient. Before starting the infusion, confirm patency of patient's IV access. The pump is programmed to deliver the contents of the syringe over 30 minutes, eg, 30 mL at 60 mL/h. Once infusion is completed, the connecting tube can be flushed with 25 mL of 0.9% sterile sodium chloride to wash off any radiopharmaceutical remaining within the tubing into the patient. Attention is required to safely handle the setup to avoid spillage as well as minimize radiation exposure by using tongs. Remove IV access, use and measure remaining radioactivity in the setup and vial, and subtract it from preinfusion activity to determine net activity administered.

IV. SPECIFICATIONS OF THE EXAMINATION AND TREATMENT

C. Post-Therapy Management

All personnel involved with Lu-177 DOTATATE therapy should perform a survey of their hands and clothing for any contamination, and appropriate measures should be performed if such contamination is discovered. The room used for infusion should be surveyed for contamination before releasing the room to another patient. All medical wastes associated with the PRRT should be stored as required by radiation safety procedures, making sure that they are separated from other wastes associated with short-acting radiopharmaceuticals [73, 74].

Care of the patient after Lu-177 DOTATATE therapy follows established institutional protocol for care of patient after radionuclide therapy with special consideration to ALARA principles. Therapy with octreotide LAR or lanreotide is usually given 4 to 24 hours after Lu-177 DOTATATE at the discretion of the attending oncology physician and stopped 4 weeks before subsequent PRRT. Short-acting octreotide maybe given for symptomatic management during PRRT cycles and withheld 24 hours before next dose of Lu-177 DOTATATE after determination by treating team of physicians.

If desired, posttherapy 3-D imaging may be obtained for the purposes of dosimetry. Personalized dosimetry may be used to assess and estimate potential risk to organs for the individual patient, as data collection for correlative studies seeking to establish maximum organ dose thresholds or lesion treatment efficacy thresholds, or for dose reporting in case of future radiation treatments [60]. In addition, postinfusion single-photon emission CT imaging may influence management decisions and provide additional dosimetric evaluation [75].

V. DOCUMENTATION

Reporting should be in accordance with the ACR–ARS Practice Parameter for Communication: Radiation Oncology [76].

A summary of the patient's history, pathologic findings, imaging results and laboratory findings should be included in the report to document the indication and tolerability for treatment with Lu-177 DOTATATE. The report should include the radiopharmaceutical used, the administered activity, site and route of administration,

safety precautions for other staff involved in the patient's care, and any associated incident encountered during therapy. If dosimetry is performed, salient organ absorbed dose values, both in directly calculated dose and in equivalent dose, should be reported, and, if available, a dose map in DICOM format with the associated CT. On subsequent PRRT, interval history should include a summary of previous Lu-177 DOTATATE treatments, interval imaging to assess treatment efficacy, and pertinent laboratory findings to determine and confirm appropriateness and safety of additional therapy [60].

VI. STATEMENT OF THERAPEUTIC USE OF UNSEALED RADIOPHARMACEUTICAL SOURCES

On the basis of their education, training pathway(s), initial board certification(s), and maintenance of certification(s), NRC or Agreement State Authorized User (AU) status, and clinical work experience, diagnostic radiologists (DRs), nuclear radiologists (NRs), nuclear medicine physicians (NMs), and radiation oncologists (ROs) may have the qualifications to supervise and perform therapy with Lu-177 DOTATATE. Although it is recognized that individual physician variations and state and federal regulatory requirements may, of necessity, dictate site-specific practice patterns, these physicians may best participate in the practice according to their special interests and qualifications. In most clinical settings, one of the following common practice paradigms generally applies:

- Physicians who are NRC and/or Agreement State recognized, board-eligible or board-certified in DR, NR, NM, or RO but do not hold AU status. These physicians may participate in the practice of PRRT under the supervision of an AU. Although they may not issue written directives for Lu-177 DOTATATE, they may administer such a dosage as designated and supervised by an AU.
- Physicians who are NRC and/or Agreement State–recognized and board certified in DR, NR, NM, or RO and hold AU status based on that certification and site-specific credentialing: These physicians may administer Lu-177 DOTATATE therapy under their own AU qualifications and licensure.
- Physicians who are NRC and/or Agreement State–recognized and board certified in DR, NR, NM, or RO and hold the appropriate AU statuses and site-specific credentialing. These physicians may practice parenteral Lu-177 DOTATATE therapy as permitted by their own specific training leading to such AU statuses.

VII. EQUIPMENT SPECIFICATIONS

Equipment performance monitoring should be in accordance with the ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras [77].

VIII. RADIATION SAFETY

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

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®, 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® for children (www.imagegently.org) and Image Wisely® for adults (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).

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION

Policies and procedures related to quality control and improvement, 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 *ACR Position Statement on Quality Control and 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).

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REFERENCES

1. Love C, Desai NB, Abraham T, et al. ACR-ACNM-ASTRO-SNMMI Practice Parameter for Lutetium-177 (Lu-177) DOTATATE Therapy. American Journal of Clinical Oncology. 45(6):233-242, 2022 06 01.
2. American College of Radiology. ACR-AAPM-ACNM-SNMMI Technical Standard for Therapeutic Procedures Using Radiopharmaceuticals. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=153+&releaseId=2
3. Strosberg JR, Caplin ME, Kunz PL, et al. 177Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol. 2021 Dec;22(12):S1470-2045(21)00572-6.
4. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 Jun 20;26(18):3063-72.
5. Perri G, Prakash LR, Katz MHG. Pancreatic neuroendocrine tumors. Curr Opin Gastroenterol. 2019 Sep;35(5):468-477.
6. Sulciner ML, Clancy TE. Surgical Management of Pancreatic Neuroendocrine Tumors. Cancers (Basel). 2023 Mar 28;15(7):2006.
7. Kandathil A, Subramaniam RM. Gastroenteropancreatic Neuroendocrine Tumor Diagnosis: DOTATATE PET/CT. PET Clin. 2023 Apr;18(2):S1556-8598(22)00088-8.
8. Kesavan M, Grover P, Lam WS, Claringbold PG, Turner JH. Long-term hematologic toxicity of 177Lu-octreotate-capecitabine-temozolomide therapy of GEPNET. Endocr Relat Cancer. 2021 Jun 20;28(7):521-527.
9. Zamfir G, Rugina V, Mihail G. The role of certain socio-sanitary factors in conditioning the quality of man's life. Part One. Sante Publique (Bucur). 1984;27(2):125-40.
10. Espinosa-Olarte P, La Salvia A, Riesco-Martinez MC, Anton-Pascual B, Garcia-Carbonero R. Correction to: Chemotherapy in NEN: still has a role?. Rev Endocr Metab Disord. 2022 Oct;23(5):1103-1104.
11. Agarwal P, Mohamed A. Systemic Therapy of Advanced Well-differentiated Small Bowel Neuroendocrine Tumors Progressive on Somatostatin Analogues. Curr Treat Options Oncol. 2022 Sep;23(9):1233-1246.
12. Hamiditabar M, Ali M, Roys J, et al. Peptide Receptor Radionuclide Therapy With 177Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors: Six Years' Assessment. Clin Nucl Med. 2017 Jun;42(6):436-443.
13. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. 26(13):2124-30, 2008 May 01.
14. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. 2015 Jan;42(1):5-19.
15. Garske-Román U, Sandström M, Fröss Baron K, et al. Prospective observational study of 177Lu-DOTA-octreotate therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and

impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging. 2018 Jun;45(6):970-988.
16. Clement D, Navalkissoor S, Srirajaskanthan R, et al. Efficacy and safety of 177Lu-DOTATATE in patients with advanced pancreatic neuroendocrine tumours: data from the NETTER-R international, retrospective study. European Journal of Nuclear Medicine & Molecular Imaging. 49(10):3529-3537, 2022 08.
17. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017;376:125-35.
18. Kam BL, Teunissen JJ, Krenning EP, et al. Lutetium-labelled peptides for therapy of neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2012 Feb;39 Suppl 1(Suppl 1):S103-12.
19. Vegt E, de Jong M, Wetzels JF, et al. Renal toxicity of radiolabeled peptides and antibody fragments: mechanisms, impact on radionuclide therapy, and strategies for prevention. J Nucl Med. 2010 Jul;51(7):1049-58.
20. Mitjavila M, Jimenez-Fonseca P, Belló P, et al. Efficacy of [177Lu]Lu-DOTATATE in metastatic neuroendocrine neoplasms of different locations: data from the SEPTRALU study. Eur J Nucl Med Mol Imaging. 2023 Jul;50(8):2486-2500.
21. Patel M, Tena I, Jha A, Taieb D, Pacak K. Somatostatin Receptors and Analogs in Pheochromocytoma and Paraganglioma: Old Players in a New Precision Medicine World. [Review]. Frontiers in Endocrinology. 12:625312, 2021.
22. Liu Q, Kulkarni HR, Zhao T, et al. Peptide Receptor Radionuclide Therapy in Patients With Advanced Progressive Medullary Thyroid Cancer: Efficacy, Safety, and Survival Predictors. Clin Nucl Med. 2023 Mar 01;48(3):221-227.
23. Urso L, Nieri A, Uccelli L, et al. Lutathera® Orphans: State of the Art and Future Application of Radioligand Therapy with 177Lu-DOTATATE. Pharmaceutics. 2023 Mar 31;15(4):1110.
24. Richter S, Steenblock C, Fischer A, et al. Improving susceptibility of neuroendocrine tumors to radionuclide therapies: personalized approaches towards complementary treatments. Theranostics. 2024;14(1):17-32.
25. Trautwein NF, Hinterleitner C, Kiefer LS, et al. Radiosensitizing Favors Response to Peptide Receptor Radionuclide Therapy in Patients With Highly Proliferative Neuroendocrine Malignancies: Preliminary Evidence From a Clinical Pilot Study. Clin Nucl Med. 2024 Mar 01;49(3):207-214.
26. Singh S, Halperin D, Myrehaug S, et al. [177Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. Lancet. 2024 Jun 29;403(10446):S0140-6736(24)00701-3.
27. Neumann HG. Biomonitoring of aromatic amines and alkylating agents by measuring hemoglobin adducts. Int Arch Occup Environ Health. 1988;60(3):151-5.
28. Deshayes E, Assenat E, Meignant L, Bardiès M, Santoro L, Gourgou S. A prospective, randomized, phase II study to assess the schemas of retreatment with Lutathera® in patients with new progression of an intestinal, well-differentiated neuroendocrine tumor (ReLUTH). BMC Cancer. 2022 Dec 22;22(1):1346.
29. Kipnis ST, Hung M, Kumar S, et al. Laboratory, Clinical, and Survival Outcomes Associated With Peptide Receptor Radionuclide Therapy in Patients With Gastroenteropancreatic Neuroendocrine Tumors. JAMA Netw Open. 2021 Mar 01;4(3):e212274.
30. Strosberg JR, Al-Toubah T, Pellè E, et al. Risk of Bowel Obstruction in Patients with Mesenteric or Peritoneal Disease Receiving Peptide Receptor Radionuclide Therapy. J Nucl Med. 2021 Jan;62(1):69-72.
31. Hammond PJ, Wade AF, Gwilliam ME, et al. Amino acid infusion blocks renal tubular uptake of an indium-labelled somatostatin analogue. Br J Cancer. 1993 Jun;67(6):1437-9.
32. Jamar F, Barone R, Mathieu I, et al. 86Y-DOTA0)-D-Phe1-Tyr3-octreotide (SMT487)--a phase 1 clinical study: pharmacokinetics, biodistribution and renal protective effect of different regimens of amino acid co-infusion. Eur J Nucl Med Mol Imaging. 2003 Apr;30(4):510-8.
33. Bodei L, Cremonesi M, Ferrari M, et al. Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with 90Y-DOTATOC and 177Lu-DOTATATE: the role of associated risk factors. Eur J Nucl Med Mol Imaging. 2008 Oct;35(10):1847-56.
34. Valkema R, Pauwels SA, Kvols LK, et al. Long-term follow-up of renal function after peptide receptor radiation therapy with (90)Y-DOTA(0),Tyr(3)-octreotide and (177)Lu-DOTA(0), Tyr(3)-octreotate. J Nucl Med. 2005 Jan;46 Suppl 1():83S-91S.
35. Geenen L, Nonnekens J, Konijnenberg M, Baatout S, De Jong M, Aerts A. Overcoming nephrotoxicity in peptide receptor radionuclide therapy using [177Lu]Lu-DOTA-TATE for the treatment of neuroendocrine tumours. Nucl Med Biol. 2021;102-103():S0969-8051(21)00488-1.
36. Worbe N, Damian L, Le Cam-Duchez V, Levesque H, Michel P, Quak E. Hemorrhagic disseminated intravascular

coagulation after 177Lu-Dotatate in metastatic midgut neuroendocrine tumor: A case report. Medicine (Baltimore). 2021 Oct 08;100(40):e27455.
37. Naveed Ahmad JA, Schroeder BB, Ruhoy SM, Kennecke HF, Lin BS. Severe Thrombocytopenia in Patients With Advanced Neuroendocrine Tumor Treated With Peptide Receptor Radioligand Therapy. Clinical Nuclear Medicine. 47(5):409-413, 2022 May 01.
38. Bergsma H, Konijnenberg MW, Kam BL, et al. Subacute haematotoxicity after PRRT with (177)Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging. 2016 Mar;43(3):453-63.
39. Bodei L, Modlin IM, Luster M, et al. Myeloid neoplasms after chemotherapy and PRRT: myth and reality. Endocr Relat Cancer. 2016 Aug;23(8):C1-7.
40. Bodei L, Mueller-Brand J, Baum RP, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. 2013 May;40(5):800-16.
41. Gococo-Benore DA, Kuhlman J, Parent EE, et al. Evaluation of Hepatotoxicity from Peptide Receptor Radionuclide Therapy in Patients with Gastroenteropancreatic Neuroendocrine Tumors and a Very High Liver Tumor Burden. J Nucl Med. 2023 Jun;64(6):880-884.
42. de Keizer B, van Aken MO, Feelders RA, et al. Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [177Lu-DOTA0,Tyr3]octreotate. Eur J Nucl Med Mol Imaging. 2008 Apr;35(4):749-55.
43. Huang K, Brenner W, Prasad V. Tumor Lysis Syndrome: A Rare but Serious Complication of Radioligand Therapies. J Nucl Med. 2019 Jun;60(6):752-755.
44. American College of Radiology. ACR-AAPM radiation safety officer resources. Available at: https://edge.sitecorecloud.io/americancoldf5f-acrorgf92a-productioncb02-3650/media/ACR/Files/Clinical/Radiology-Safety/ACR-AAPM-Radiation-Safety-Resources.pdf.
45. Foster JH, Sher A, Seghers V, et al. Peptide receptor radionuclide therapy for treatment of metastatic neuroendocrine tumors in children. Pediatric Blood & Cancer. 68(7):e29056, 2021 07.
46. Chen L, Navalkissoor S, Quigley AM, et al. 177Lu-DOTATATE in older patients with metastatic neuroendocrine tumours: safety, efficacy and health-related quality of life. Eur J Nucl Med Mol Imaging. 2021 Oct;48(11):3582-3594.
47. 2024, FDA approves lutetium Lu 177 dotatate for pediatric patients 12 years and older with GEP-NETS. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lutetium-lu-177-dotatate-pediatric-patients-12-years-and-older-gep-nets.
48. American College of Radiology. ACR-ARS Practice Parameter for Radiation Oncology. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=200+&releaseId=2
49. Ezziddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-octreotate. J Nucl Med. 55(2):183-90, 2014 Feb.
50. Hertelendi M, Belguenani O, Cherfi A, Folitar I, Kollar G, Polack BD. Efficacy and Safety of [177Lu]Lu-DOTA-TATE in Adults with Inoperable or Metastatic Somatostatin Receptor-Positive Pheochromocytomas/Paragangliomas, Bronchial and Unknown Origin Neuroendocrine Tumors, and Medullary Thyroid Carcinoma: A Systematic Literature Review. [Review]. Biomedicines. 11(4), 2023 Mar 27.
51. García-Bragado F, Genesca J, Allende H, Jardí R, Lima J. [Replication of the hepatitis B virus in 5 cases of essential mixed cryoglobulinemia]. Gastroenterol Clin Biol. 1986 Nov;10(11):772.
52. Raj N, Coffman K, Le T, et al. Treatment Response and Clinical Outcomes of Well-Differentiated High-Grade Neuroendocrine Tumors to Lutetium-177-DOTATATE. Neuroendocrinology. 112(12):1177-1186, 2022.
53. Camus B, Cottereau AS, Palmieri LJ, et al. Indications of Peptide Receptor Radionuclide Therapy (PRRT) in Gastroenteropancreatic and Pulmonary Neuroendocrine Tumors: An Updated Review. J Clin Med. 2021 Mar 18;10(6):1267.
54. Strosberg JR, Al-Toubah T, El-Haddad G, Reidy Lagunes D, Bodei L. Sequencing of Somatostatin-Receptor-Based Therapies in Neuroendocrine Tumor Patients. J Nucl Med. 2024 Mar 01;65(3):340-348.
55. American College of Radiology. ACR-ACNM-SNMMI-SPR Practice Parameter for the Performance of Neuroendocrine Tumor Scintigraphy. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=92+&releaseId=2
56. American College of Radiology. ACR–ACNM–SNMMI Practice Parameter for the Performance of Gallium-68 and Copper-64 DOTATATE PET/CT Imaging for Neuroendocrine Tumors. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=18+&releaseId=2
57. Alsadik S, Gnanasegaran G, Chen L, et al. Safety of Peptide Receptor Radionuclide Therapy with 177Lu-

DOTATATE in Neuroendocrine Tumor Patients with Chronic Kidney Disease. Journal of Nuclear Medicine. 63(10):1503-1508, 2022 10.
58. Mittra ES, Wong RKS, Winters C, Brown A, Murley S, Kennecke H. Establishing a robust radioligand therapy program: A practical approach for North American centers. [Review]. Cancer Medicine. 13(3):e6780, 2024 Feb.
59. American College of Radiology. ACR-ARS Practice Parameter on Informed Consent- Radiation Oncology. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=141+&releaseId=2
60. Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI Procedure Standard for Somatostatin Receptor-Based Peptide Receptor Radionuclide Therapy with 177Lu-DOTATATE. J Nucl Med. 2019 Jul;60(7):937-943.
61. Hendifar AE, Mehr SH, McHaffie DR. Best Practices for the Coordinated Care of Patients With Neuroendocrine Tumors Undergoing Peptide Receptor Radionuclide Therapy. Pancreas. 2022 Mar 01;51(3):213-218.
62. Soulek DK, Mastascusa NJ, Martin ME, Graves SA. Practical Considerations for Implementation of 177Lu-DOTATATE Neuroendocrine Tumor Treatment Programs. J Nucl Med Technol. 2022 Jun 14;():jnmt.122.263813.
63. Bennett B, Gardner L, Ryan P. Peptide Receptor Radionuclide Therapy Using 177Lu-DOTATATE: Nursing Roles in Managing Patients With Gastroenteropancreatic Neuroendocrine Tumors. Clin J Oncol Nurs. 2024 Jan 18;28(1):79-87.
64. United States Nuclear Regulatory Commission. NRC policy on release of iodine-131 therapy patients under 10 CFR 35.75 to locations other than private residences. RIS 2011-01. Available at: https://www.nrc.gov/docs/ML1036/ML103620153.pdf.
65. United States Nuclear Regulatory Commission. Consolidated guidance about materials licenses: program-specific guidance about medical use licenses (NUREG-1556, Volume 9, Revision 2). Available at: http://www.nrc.gov/reading-rm/doc-collections/nuregs/staff/sr1556/v9/r2/.
66. National Council on Radiation Protection and Measurements. NCRP No. 155, management of radionuclide therapy patients. Available at: https://ncrponline.org/publications/reports/ncrp-reports-155/. .
67. Bakker WH, Breeman WA, Kwekkeboom DJ, De Jong LC, Krenning EP. Practical aspects of peptide receptor radionuclide therapy with [177Lu][DOTA0, Tyr3]octreotate. Q J Nucl Med Mol Imaging. 2006 Dec;50(4):265-71.
68. Mittra ES.. Neuroendocrine Tumor Therapy: 177Lu-DOTATATE. [Review]. AJR Am J Roentgenol. 211(2):278-285, 2018 08.
69. Tipnis S, Rieter WJ, Henderson-Suite V, Gordon L. Risk of Radiation Exposure to Clinical Staff from Paracenteses of Large-Volume Chylous Ascites After 177Lu-DOTATATE Infusion. Journal of Nuclear Medicine Technology. 50(3):274-277, 2022 Sep.
70. Yu NY, Rule WG, Sio TT, Ashman JB, Nelson KL. Radiation Contamination Following Cremation of a Deceased Patient Treated With a Radiopharmaceutical. JAMA. 2019 Feb 26;321(8):803-804.
71. Lodge MA, Solnes LB, Chaudhry MA, Wahl RL. Prospective Within-Patient Assessment of the Impact of an Unlabeled Octreotide Pre-dose on the Biodistribution and Tumor Uptake of 68Ga DOTATOC as Assessed by Dynamic Whole-body PET in Patients with Neuroendocrine Tumors: Implications for Diagnosis and Therapy. Mol Imaging Biol. 2021 Oct;23(5):766-774.
72. Advanced Accelerator Applications. Highlights of prescribing information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208700s000lbl.pdf.
73. Halfdanarson TR, Mallak N, Paulson S, et al. Monitoring and Surveillance of Patients with Gastroenteropancreatic Neuroendocrine Tumors Undergoing Radioligand Therapy. Cancers (Basel). 2023 Oct 02;15(19):4836.
74. Fazio N, Falconi M, Foglia E, et al. Optimising Radioligand Therapy for Patients with Gastro-Entero-Pancreatic Neuroendocrine Tumours: Expert Opinion from an Italian Multidisciplinary Group. Adv Ther. 2024 Jan;41(1):113-129.
75. Yadav S, Lawhn-Heath C, Paciorek A, et al. The Impact of Posttreatment Imaging in Peptide Receptor Radionuclide Therapy. J Nucl Med. 2024 Mar 01;65(3):409-415.
76. American College of Radiology. ACR-ARS Practice Parameter for Communication: Radiation Oncology. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=199+&releaseId=2
77. American College of Radiology. ACR–AAPM Technical Standard for Nuclear Medical Physics Performance Monitoring of Gamma Cameras. Available at https://gravitas.acr.org/PPTS/GetDocumentView?docId=196+&releaseId=2

Appendix A

Post Treatment Instructions to Patient Following Lu-177 DOTATATE Therapy

Name of Patient: _____ Medical Record Number: _____

Last name, First name

Date of Treatment: _____ Isotope: Lu-177 Activity: _____

Before this date: _____, please show this form to every physician, healthcare worker or emergency personnel that provide you care.

Special Precautions

1. Maintain a distance of at least 3 feet (1 meter) from others for 3 days since radiation exposure decreases with distance, the further away you are from others, the less radiation they get.
2. Minimize visits by family or friends for 3 days. If you have visitors, try to stay at least 3 feet away.
3. Minimize close contact with others at work for 3 days.
4. For woman of childbearing age (<55 years old), pregnancy must be excluded before initiating the treatment. Both men and women of child-bearing potential must refrain from procreation by using effective contraceptive methods during the treatment and for 6 months after.
5. For women who are breastfeeding, discontinue breast feeding for this child.
6. Sleep alone for at least 7 nights. Sleeping together with another adult exposes them to the radiation coming from you. Sexual activity is not advised for 7 days after LUTATHERA administration.
7. No children should sleep with you for 7 days. No pregnant person should sleep with you for 15 days. Children and fetuses are much more sensitive to radiation than adults, and special care is needed. Limit close contact to brief periods for 7 days.
8. Take particular care when urinating for 3 days. Toilets must be used in a seated position, even for men. Use private bathroom or flush 2 to 3 times and clean any spills with disposable gloves and damp cloth after each use. Wash hands thoroughly. The radiation leaves your body mainly from your urine.
9. Wash dishware and utensils and bathroom accessories separately for 3 days.
10. Do not travel by public transportation (bus, train, plane) for more than 1 hour for 3 days. If you are planning to travel while radiation safety precautions are in effect, please inform Nuclear Medicine or Radiation Facility personnel at (area code) ____-_____.

**For flights, travelers may call TSA Cares toll free at 1-855-787-2227 prior to traveling with questions about screening policies, procedures, and what to expect at the security checkpoint. For more information, visit https://www.tsa.gov/travel/special-procedures.

1. No prolonged car trip (more than 1 hour) with others for 3 days.
2. Drink plenty of fluid (4-8 glasses) per day for 3 days.

If you are admitted to the ER or hospitalized while radiation safety precautions are in effect, inform the hospital staff to notify the above contact person immediately. During off-hours, contact Nuclear Medicine or Radiation Facility via the operator at _____.

Instructions for Radioactive Trash Generated by patient

Please be aware that the following items that may be contaminated with urine and blood cannot be disposed into regular trash:

1. Pads, tampons
2. Toilet papers, tissue
3. Towels, linens, sheets
4. Any other items that are contaminated with urine, blood, and wound or drainage secretions for the first 3 days post treatment

Towels, linens and sheets can be washed separately and reused.
Toilet paper and tissue need to be flushed down the toilet.
Any other contaminated items that cannot be washed or flushed down the toilet needs to be kept for at least 70 days or bring it to the Nuclear Medicine or Radiation Oncology Facility to be stored.

I have read the above precautions and instructions and have spoken with the Nuclear Medicine or Radiation Facility personnel and agree to comply.

Patient (print name): _____

Signature: _____ Date/time: _____

Witness (print name) _____

Signature: _____ Date/time: _____

Authorized User or Supervised Designee (print name) _____

Signature: _____ Date/time: _____

*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.

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