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REVIEW

Italian Association of Nuclear Medicine, Molecular Imaging and Therapy (AIMN) practical guide for peptide receptor radionuclide therapy (PRRT) with [^{177}Lu]Lu-Oxodotreotide in gastroenteropancreatic neuroendocrine tumors (GEP-NET)

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Abstract

Somatostatin receptors (SSTR) are overexpressed by most neuroendocrine tumors (NETs), and patients with SSTR-positive disease can be identified by DOTA-peptide PET. Phase II and III studies proved SSTR-targeted radiopharmaceutical therapy safe and effective in metastatic gastroenteropancreatic (GEP) NETs progressed after SST analogues. Additional data indicate that [^{177}Lu]Lu-oxodotreotide peptide receptor radionuclide therapy (PRRT) also has high potential in earlier clinical situations. The purpose of this Italian procedural guideline is to assist the nuclear medicine personnel in the delivery of [^{177}Lu]Lu-DOTA-peptide therapy, from patient selection to end-of-therapy follow-up, and to facilitate the management of possible side effects and their clinical management. The current document is based upon the current best practice and knowledge of experienced Centers and Nuclear Medicine Physicians in Italy.

Keywords DOTA-peptide · Gastroenteropancreatic neuroendocrine tumor · Lutathera · Lutetium · Peptide receptor radionuclide therapy · RPT

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Introduction

Although peptide receptor radionuclide therapy (PRRT) has been used for about 30 years in clinical trials, it was not until 2019 (after the publication of the NETTER-1 phase III study [1]) that the Italian Medicine Agency (AIFA) approved [^{177}Lu]Lu-Oxodotreotide for well-differentiated, inoperable, grade 1 and 2, gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) progressive to somatostatin (SST) analogue therapy.

Although NETs are not considered rare tumors anymore, the therapeutic algorithms for metastatic disease continue to exhibit substantial heterogeneity, with national, societal and institutional differences. The procedural recommendations on the use of [^{177}Lu]Lu-Oxodotreotide by the Italian Association of Nuclear Medicine (AIMN) were, therefore, designed to standardize the use of this radiopharmaceutical in the PRRT of GEP-NETs [2].

The purpose of this paper is to highlight the practical part which is essential for those preparing (and not only) to deliver [^{177}Lu]Lu-Oxodotreotide therapy.

For this document, we considered three sources of information: the summary of product characteristics of [^{177}Lu]Lu-Oxodotreotide [3], which has been partially provided here; a review of the literature; and, finally, the clinical experience of a few Italian referral Centers, which provided treatments for thousands of patients with NETs over two decades, prior to the availability of NETTER-1 results, as part of phase I and II clinical trials.

The paper is intended as a practical management document, designed and developed in a chronological description, of the necessary diagnostic and therapeutic steps to deliver PRRT with [^{177}Lu]Lu-Oxodotreotide to patients.

Patient's selection

In Europe, [^{177}Lu]Lu-Oxodotreotide is currently approved for the treatment of adult patients with metastatic or inoperable, well-differentiated, grade 1 and 2 GEP-NET exhibiting high expression of SST receptor (SSTR) 2, progressing after somatostatin analogues [3]. It should be reminded, however, that the joint International Atomic Energy Agency (IAEA), European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) guidelines also indicated patients with bronchial NET or with pheochromocytoma, paraganglioma, neuroblastoma or medullary thyroid carcinoma as potential candidates for PRRT [4, 5], which are currently treatable only within experimental protocols. Recently, the SNMMI also approved the use of PRRT in GEP-NET patients older than 12 years old.

Adult GEP-NET individuals who are affected by inoperable or metastatic, well-differentiated, G1 and G2, progressing at diagnostic imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and are considered potential candidates for [^{177}Lu]Lu-Oxodotreotide, should be evaluated by a dedicated multidisciplinary team or tumor board. The ENETS guidelines [4] and the NANETS/SNMMI consensus statement [6], indicate that candidate patients should have adequate performance status (PS), i.e. Karnofsky index > 50.

Patients should undergo prior DOTA-peptide positron emission tomography (PET)/CT or PET/MRI ([^{68}Ga]Ga-DOTATATE/DOTATOC, [^{64}Cu]Cu-DOTATATE) to document adequate expression of SSTR by disease localizations [7]. The minimum receptor expression to support the candidacy for PRRT was established with [^{111}In]pentetreotide scintigraphy as lesions with uptake equal to or greater than normal liver [8]. No clear cut-off relative to PET uptake with [^{68}Ga]Ga-DOTA-peptide has been defined, although background hepatic uptake again represents a typical reference for receptor expression quantification. A more favourable response to therapy has, in fact, been noted in patients with lesions uptake (expressed as maximum Standardized Uptake Value, SUV_{max}) twice as high as hepatic uptake [9]. [^{18}F]FDG PET/CT is not part of the standard patient selection protocol before PRRT, although it has been suggested that it might play a role especially in G2 GEP-NETs to rule out SSTR-negative/FDG-positive disease [10].

Patients enrolled for PRRT with [^{177}Lu]Lu-Oxodotreotide must have adequate bone marrow reserve confirmed by complete blood tests. These examinations should include complete blood count (hemoglobin, white blood cells with leukocyte formula, platelets), renal (creatinine and creatinine clearance) and liver function (alanine aminotransferase - ALT - aspartate aminotransferase - AST - serum albumin, total bilirubin), alkaline phosphatase, and additional laboratory tests as needed.

In patients with functioning NETs, carcinoid syndrome is the most common condition that can cause abdominal pain with recurrent episodes of flushing and/or diarrhea, symptoms due to the secretion of vasoactive compounds such as serotonin. Symptoms generally occur only after the tumor metastasizes to the liver or other sites, as vasoactive peptides produced by localized tumors are metabolized in the portal circulation. In these patients, it may be useful to perform other tests. The more accurate biomarker for the initial evaluation of suspected carcinoid syndrome is the measurement of 5-HIAA in a 24-hour urine sample, which is the product of serotonin metabolism [11].

In agreement with the joint NANETS/SNMMI procedural guidelines [12], the following values (Table 1) can be considered as a reference to consider treatment eligibility.

Table 1 PRRT enrollment serum values (readapted from [12])

Laboratory examinations	Recommended threshold for the I PRRT cycle
Hemoglobin (Hb)	> 8 g/dL
White blood cell (WBC)	> 2,000/mm^3
Platelets (PLT)	> 70,000/mm^3
Glomerular filtration rate (GFR) / creatinine clearance	> 40mL/min
Total bilirubin	≤ 3 x ULN
Serum albumin	> 3 g/dl

PRRT contraindications

Absolute

1) Pregnancy.
2) Concomitant severe acute comorbidities.
3) Concomitant severe psychiatric comorbidities.
4) Age < 18 years.

Relative

1) Breastfeeding (if not interrupted).

2) Severe renal dysfunction (GFR/creatinine clearance < 40mL/min at enrollment or < 30mL/min inter-cycles).

3) Reduced bone marrow reserve.

An unimpaired hematologic reserve should be present before PRRT. Suggested reference values are provided in Table 1. Such cutoffs must be considered in the context of the other therapeutic options available, the patient's life expectancy and whether the intent of treatment is symptom palliation or oncological control.

4) Bulky mesenteric disease, peritoneal carcinomatosis, and pretreated liver disease.

The NANETS guidelines indicate these subgroups of patients as being at potentially higher risk if treated with [^{177}Lu]Lu-Oxodotreotide. In cases of peritoneal carcinosis, irradiation could induce mesenteritis and potentially exacerbate the risk of bowel obstruction. Premedication with low-dose steroids and continued for 2–4 weeks after PRRT could play a role in preventing such complications. One study recently reported a 5% rate of bowel obstruction among patients with mesenteric or peritoneal disease at baseline [13]; in another study, bowel obstruction or ascites occurred in 28% of patients with diffuse peritoneal carcinomatosis treated with [^{177}Lu]Lu-Oxodotreotide [14]; a retrospective study found higher rates of liver toxicity in a population of patients who had undergone previous liver embolization [15].

Specific information for patients of childbearing age who are candidates for PRRT

If PRRT is planned in a patient of childbearing age, treatment may be administered only upon the verification of a recent (within 5 days) negative pregnancy test, preferably from blood. Men and women of childbearing age should use effective contraceptive methods throughout the treatment period and avoid pregnancy for 4–6 months after the last cycle of PRRT. Breastfeeding should be interrupted. Considering the possible temporary impairment of fertility, patients should consider using cryopreservation of oocytes and sperm before undergoing PRRT [16]. It is, in addition, advisable to use a "patient's guide" which should contain: (A) A brief introduction to the treatment and administration procedure; (B) Information on precautions that the patient should take before, during and after administration, in the hospital and at home, to reduce/limit any radiation exposure to themselves or third parties; (C) Information regarding possible serious side effects that should be reported to the physician.

PRRT practical considerations

The pharmacovigilance reporting of any adverse reactions that may occur during treatment with [^{177}Lu]Lu-Oxodotreotide is of paramount importance, as it allows continuous monitoring of the benefit/risk ratio of the drug. Healthcare professionals in Italy are required to report any certain or suspected adverse reactions through the dedicated reporting system of the Italian Medicine Agency (AIFA).

[^{177}Lu]Lu-Oxodotreotide is prescribed by the nuclear physician and is authorized by the Center's Pharmacy. The radiopharmaceutical is shipped to the requesting Center, and calibrated to the date and time of administration. The radiopharmaceutical is contained in a plastic box provided with a seal and labels illustrating the characteristics of the contents; internally it contains a polystyrene casing divided into refrigerated niches in which are housed the lead containers containing the type I glass vials, transparent and colorless, closed with a bromobutyl rubber stopper and aluminium ring. The glass vial contains a volume that varies from 20.5 to 25.0 mL of solution, corresponding to an activity of 7400 MBq calculated based on the date and time of infusion.

It is necessary to store the kit at a temperature below 25 °C. Radiopharmaceutical storage must be under national regulations on radioactive materials. A visual inspection of the bottle and its contents within a handling cell must be conducted by the Nuclear Medicine Physician and the Radiopharmacist before use to check for damage to the container and/or particulate contamination, which, if present,

will preclude its use. It should also be noted that the vial must remain intact in all its components, must not be opened, and, for administration, the contents must not be transferred to other containers or vials. Before infusion, the amount of radioactivity in the vial should be measured by the Medical Physicist using an appropriate calibration system to confirm what is stated on the manufacturing certificate and packaging labels. Unused medicine and any waste derived from it should be disposed of by personnel under the supervision of a Medical Physicist, following applicable local regulations.

Outpatient vs. inpatient treatments

PRRT can be performed on either an inpatient or outpatient basis (European Directive 59/13 Euratom, DL 101/20) within a department staffed with personnel well-trained in the safety rules and precautions required for the therapeutic administration of radiopharmaceuticals. However, regional regulations may introduce some variability. If a combined approach is used—such as transporting the patient between different departments for various treatment steps—additional caution is necessary to ensure proper radiation protection. For outpatient treatment, patients should be informed about the possibility of an overnight hospital stay in case of complications such as a hormone release crisis, severe vomiting, abdominal pain, or other issues [3].

Facilities

The body fluids (mainly urine) of the patient after [^{177}Lu]Lu-Oxodotreotide administration are radioactive. Therefore, the preparation of the administration/delivery room is essential to minimize the risk of any potential contamination. As such, patient stretchers, chairs, and floors should be made of washable materials with protective coverings such as blotting paper or washable material. Dedicated treatment rooms with a dedicated toilet are used. It is also essential to provide for the possible need for dedicated assistance for each patient. Universal precautions (e.g. gloves, gowns, shoe covers) should be used by the staff, to avoid contamination with patient bodily fluids. If blood or urine samples are needed for laboratory tests, nursing staff should be advised to collect the minimum amount needed for testing. When testing with medical devices or other skin contact instruments (e.g., ECGs), it is recommended that the radioactivity level of the equipment be monitored after use. Nursing staff should be equipped with dosimeters, and radiation protection personnel should check the patient's room (bed, floor, and bathroom) to minimize any potential radioactive contamination from body fluids. Institutional guidelines on radiation protection should be developed with consideration of the nursing care of inpatients, including approaches to medical emergencies or deaths. Physicians responsible for treatment should have a general knowledge of the pathophysiology and natural history of the disease, be aware of treatment alternatives, and collaborate closely with other physicians involved in patient management. All healthcare personnel should limit the time of proximity with patients treated with [^{177}Lu]Lu-Oxodotreotide, and it is advisable to use monitor systems to check patients. It will be the responsibility of the local radiation protection office to ensure compliance with regulations regarding the collection/disposal of radioactive waste materials.

Radiation safety information

In the first 3 days following PRRT, there will be elevated levels of radioactivity in the urine. On the day of infusion and the following days, to facilitate the elimination of the radiopeptide, patients should be encouraged to drink plenty of water (1 glass every hour) and to ensure daily bowel movements. Laxatives should be considered as needed. Urine and stools should be eliminated following national standards. Patients should be instructed about observing strict hygiene to avoid contaminating people using the same toilets. It is recommended to flush twice after urination, which should be done in a sitting position for both sexes. Patients should wash their hands with special care after urination, and in case of contamination, they should use plenty of cold water and avoid heavy rubbing. Upon discharge and for one week after PRRT, patients should avoid soiling their underwear and areas around the toilet. Contaminated clothing should be washed separately. In case of urinary incontinence, the use of disposable underwear is recommended. In case of bladder catheter need (incontinence), the use of a Foley catheter with acrylic urine bag shielding is recommended to be removed 2 days after PRRT. Urine bags should be emptied frequently and contact personnel should use gloves and protective clothing.

[^{177}Lu]Lu-Oxodotreotide treatment

[^{177}Lu]Lu-Oxodotreotide is administered with an activity of 7.4 GBq (200 mCi) for 4 cycles for a total of 29.6 GBq. The recommended interval between administrations is 8 weeks, extendable up to 16 weeks in case of toxicity; if toxicity persists beyond week 16, PRRT should be discontinued. If toxicity returns before week 16, the patient can be treated with half a dose. If toxicity does not reappear thereafter, the subsequent treatment can be given at full dose; if toxicity reappears again, treatment should be discontinued. [^{177}Lu]Lu-Oxodotreotide is administered in combination with prophylactic infusions of amino acids, preceded by antiemetics.

Figure 1 summarizes the timeline of administration (adapted from [12]).

Management of "cold" somatostatin analogue therapy and other medications

Cold somatostatin analogue therapy is frequently used in NET patients (especially in those symptomatic) via short or long-acting formulations with depot administration every 4 weeks. Due to the potential receptor interference, such therapy should be discontinued close to the PRRT cycle: the duration of discontinuation depends on the half-life of the analogue used with withdrawal periods of at least 8 to 24 h for short-acting formulations and 4 weeks for long-acting formulations [5]. However, cold somatostatin analogue therapy can be resumed as early as a few hours after PRRT administration. If necessary, in symptomatic patients taking long-acting formulations, short-acting formulations can be co-administered during the first 7 to 10 days of resumption of long-acting somatostatin. During the various cycles and after completion of PRRT, it is generally accepted that both syndromic patients and patients with non-functional NET continue therapy with cold somatostatin analogue regardless of progression before PRRT [17]. In this regard, in the NETTER-1 study, all patients continued therapy with slow-release octreotide despite previous progression [1], and the [^{177}Lu]Lu-Oxodotreotide package insert also suggests that patients should continue cold analogue therapy for up to 18 months after treatment [3]. [^{177}Lu]Lu-Oxodotreotide therapy is currently planned as monotherapy, so it is necessary to discontinue any other ongoing cancer therapies with the exception of cold analogue therapy as just described. Results of trials in which [^{177}Lu]Lu-Oxodotreotide was combined with other oncology therapies, such as capecitabine/temozolomide [18], or Everolimus [19], have been published in the literature. Despite encouraging results, such therapeutic approaches are not currently approved and thus remain confined to experiences related to experimental trials.

Additional peripheral intravenous catheter(s)

The ideal location to use as venous access for administration is the antecubital fossa, preferably bilateral, to be used for the administration of the [^{177}Lu]Lu-Oxodotreotide and amino acid solution (contralateral to the radiopharmaceutical). If two venous accesses cannot be found, the radiopharmaceutical and amino acids can be infused through the same route (e.g., using a multiway tap). If peripheral venous access is difficult to find, central venous accesses can also be used for the administration of premedication and amino acid solution only, as there is not enough scientific evidence for [^{177}Lu]Lu-Oxodotreotide. The function of the venous access, the appearance of the surrounding skin tissue, and the regularity of the flow of the administered substances must be carefully monitored during all phases of intravenous administration, in particular: during (1) administration of amino acids to prevent possible local reactions caused by the high osmolarity of the solution but, most importantly, during (2) administration of [^{177}Lu]Lu-Oxodotreotide to prevent or limit possible extravasation of radiopharmaceuticals that may induce tissue necrosis.

Premedications

Hydration and administration of amino acid solution

Along with the bone marrow (critical organ), the kidneys are the organs to be safeguarded in terms of radiation exposure during PRRT. Indeed, proximal tubular reabsorption of radiopeptide and subsequent retention in the interstitium

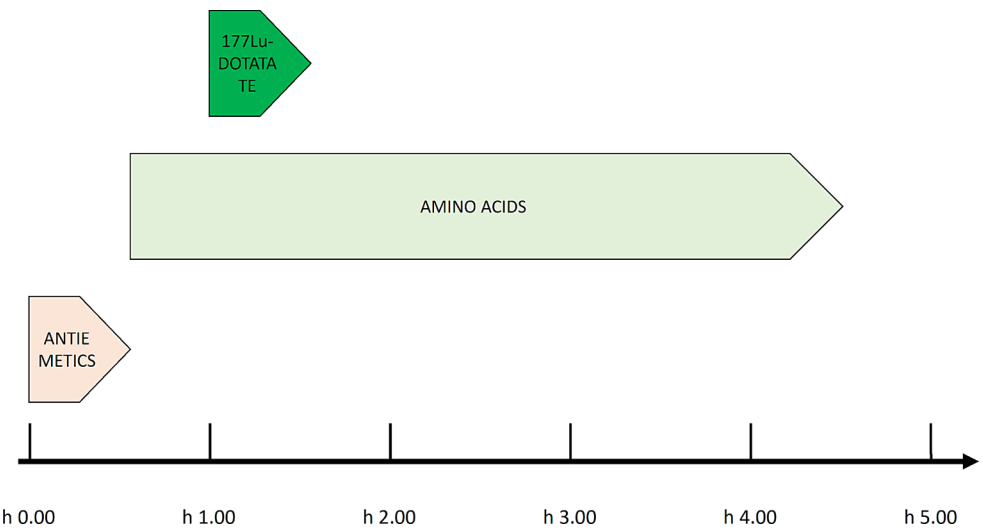

Fig. 1 [^{177}Lu]Lu-Oxodotreotide administration timeline

may result in excessive renal irradiation, which can be aggravated by preexisting risk factors such as hypertension or diabetes mellitus [20]. Therefore, administration of a positively charged amino acid solution with an appropriate concentration of lysine and arginine (in Table 2 the required characteristics of the amino acid solution) before, during and after infusion of [^{177}Lu]Lu-Oxodotreotide is standard practice, to decrease (up to 65%) the radiation exposure of the kidneys [21, 22].

Amino acid infusion should be started 30 min before radiopeptide administration and maintained for 4–6 h; lysine and arginine should be diluted appropriately in large volumes of saline (an appropriate dilution is 25 g amino acid in 1 L normal saline) to hydrate the patient. The ideal infusion rate of commercial amino acid solutions should be 320–400 mL/h, maintained during radiopeptide administration until amino acid administration is complete. [^{177}Lu]Lu-Oxodotreotide should generally not be administered until this infusion rate has been achieved or until 1/8 of the total volume of the amino acid solution has been infused. Starting at a moderate rate of administration (100 mL/h) and increasing slowly (e.g., by 20–50 mL/h every 15–20 min) has shown some success in reducing side effects related to nausea or vomiting. The most used amino acid formulation involves 25 g lysine and 25 g arginine diluted in 1 L of saline [4]. Such a solution composed of 2 amino acids appears to be more tolerable (less emetogenic) and can be infused in a shorter time (250 mL/h for 4 h, starting 30 min before radiopharmaceutical administration). Therefore, the use of formulations composed only of arginine and lysine appears preferable but is not always available in many centers due to licensing requirements and compounding regulations. Severe heart failure (e.g., carcinoid valvular disease) and nephrolithiasis, volume overload could cause acute insufficiency/heart failure or stone mobilization. Therefore, formulations with lower amounts of amino acids and reduced volumes such as 25 g of lysine or arginine diluted in up to 1 L of saline. In any case, it is recommended in these eventualities to follow close monitoring with the possible involvement of a cardiologist. In the case of phlebitis at the injection site associated with the hyperosmolarity of the amino acid solution, vasoprotective creams can be used. Particular attention should be paid to avoid possible electrolyte imbalances and consequent metabolic acidosis, nausea and vomiting [23]. Amino acid infusion may be associated with hyperkalemia/hypernatremia (onset of dyspnea, weakness, numbness, chest pain, and cardiac manifestations); therefore, it seems prudent to correct any electrolyte imbalances before PRRT or, in patients with K/Na in the upper part of the normal range, to increase renal electrolyte excretion by using a diuretic (e.g., in case of hyperkalemia use a loop diuretic). In case of an acute episode, it will be necessary to hydrate the patient with normal saline and possibly administer corticosteroids (e.g., 4 or 8 mg according to patient characteristics) and/or rapid-acting antiemetics (e.g., metoclopramide). Additional amino acid formulations can be found at [2].

Table 2 Characteristics of the amino acid solution

Component	Range
L-Arginine hydrochloride	18–25 g
L-Lysine hydrochloride	18–25 g
Volume	1–2 L
Osmolality	< 1,200 mOsmol/kg

Antiemetics

At least 30 min before starting the amino acid infusion, it is necessary to prevent possible nausea and vomiting by administering an intravenous premedication consisting of a 5-HT3 antagonist (e.g., ondansetron 4 mg but also granisetron, or palonosetron) sufficient for arginine- and lysine-only solutions. Such premedication can also be repeated using alternative drugs such as NK1 receptor antagonists [e.g., (fos)aprepitant] and H2 receptor antagonists (e.g., famotidine). When increasing the rate of administration of the amino acid solution to 320–400 mL/h, additional doses of 5-HT3 antagonist in combination with a D2 receptor antagonist (e.g., prochlorperazine) may be necessary. In cases of "anticipatory" (conditioned, learned, or psychological) nausea and vomiting, benzodiazepine drugs may also be used [24]. There are no known interactions between corticosteroids used intermittently to prevent nausea and vomiting during radiopeptide administration except in the case of patients at risk for carcinoid crisis [25]. Additional support against nausea and vomiting is through pressor aid strategies (e.g., avoid forward bending) and cooling of the environment. In this scenario, it appears critical to properly educate and prepare the patient before starting the procedure, ensuring that the patient understands the importance of avoiding the onset of these symptoms and their eventual containment.

[^{177}Lu]Lu-Oxodotreotide administration

The following minimal laboratory tests should be performed and checked for normality before each administration:

- CBC (hemoglobin, leukocyte count, platelet count).
- Renal function (creatinine and creatinine clearance).
- Liver function (ALT, AST, serum albumin, bilirubin).
- Serum electrolytes.

[^{177}Lu]Lu-Oxodotreotide should be administered over 30 min and not as a bolus. Regardless of the method of

administration (gravity or by use of infusion pump), appropriate radiation shielding and aseptic technique of radiopeptide preparation and administration should be used. Appropriate protective equipment for personnel should be used and appropriate forceps should be employed when handling the bottle containing [^{177}Lu]Lu-Oxodotreotide to minimize radiation exposure. Before administration, it will also be essential to quantify with a dose calibrator the radioactivity of the bottle containing the radiopeptide; also important will be a visual inspection of the product through appropriate shielding to detect any particulate matter and/or discoloration (the bottle must be closed and should not be used if particulate matter or discoloration is present). [^{177}Lu]Lu-Oxodotreotide should be administered via a stable catheter to ensure safe administration and prevent any possible extravasation/perivascular infiltration. The radiopeptide will be co-infused during the administration of amino acid solution (contralateral to the radiopharmaceutical) preferably using a multi-pathway tap. The [^{177}Lu]Lu-Oxodotreotide-related route will need to be flushed with the saline solution following the completion of the infusion (main steps, Fig. 2). At the end of each PRRT treatment, biodistribution whole-body imaging is recommended to document proper radiopharmaceutical distribution and assess/monitor functional response over time.

Pre-PRRT check

Once the patient is lying down, supine, in a comfortable position and with an empty bladder, check:

1) That the administration vial contains the prescribed radiopharmaceutical at the prescribed activity, and that the patient is recognized by name and date of birth.
2) That the patient has received the prescribed premedications.
3) That the patient has received/is receiving the prescribed amount of aminoacidic solution.
4) That peripheral venous catheters are well placed and that the flow is free.
5) The proper preparation and sealing of the devices that make up the afferent pathway, which should be filled with saline and closed (clamp).
6) The proper preparation and sealing of the devices that make up the efferent route, which should be completely filled with saline. A STOP (clamp) placed along the infusion tubing will prevent the saline from leaking from either end.
7) The integrity of the vial containing the radiopharmaceutical and its appropriate shielding.
8) That all the above materials are placed on an appropriate trolley (protected by waterproof, absorbent and properly shielded material) placed beside the patient.

PRRT Administration (highlighted in Fig. 3)

A) Connect the efferent route pre-filled with saline, without removing the STOP, to the patient's peripheral venous catheter.
B) Prepare the afferent route to the 250/500 mL saline bag by filling it with saline and closing the clamp.

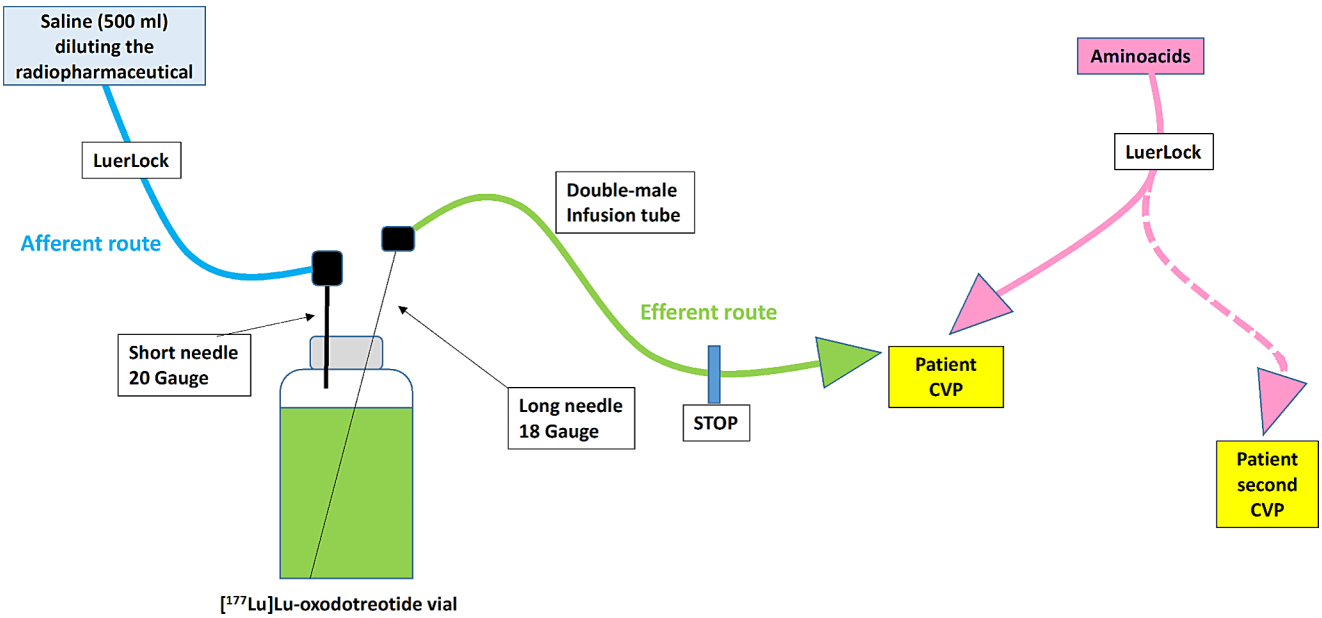

Fig. 2 Illustration of administration by gravity

C) Insert a 20-gauge short needle into the rubber septum of the radiopeptide bottle, taking care that it does not touch/reach the drug (constantly draw in the overlying air layer).
D) Connect the short needle to the afferent pathway prepared in step B while keeping the clamp closed.
E) Connect an 18-gauge long needle to the efferent route and insert it into the rubber septum of the vial containing the radiopharmaceutical until it touches the bottom of the vessel being sure that it is well spaced from the short needle already placed (we keep the clamp closed remembering that this is always pre-filled with saline and connected to the patient via CVP as described in step A).
F) Once both routes are positioned, open the clamp of the efferent route, and once equilibrium is reached, open the clamp of the afferent route.
G) Adjust the flow of saline through the short needle into the radiopeptide bottle to a flow rate of 50 to 100 ml/hr for 5 to 10 min and 200 to 400 ml/hr for another 25 to 30 min (the saline entering the bottle through the short needle will carry the radiopeptide from the bottle to the patient through the catheter connected to the long needle for a total duration of 30 to 40 min).
H) During the infusion, make sure that the fluidity of the radiopeptide and the level of the solution in the vial remain constant.
I) Shortly after the start of the infusion check the presence of [^{177}Lu]Lu-Oxodotreotide in the bloodstream by measuring the radioactivity on the patient's chest with a Geiger counter. Subsequent radioactivity emission checks should be performed approximately every 5 min at the patient's chest and vial. During the infusion, the radioactivity emission from the patient's chest should steadily increase, conversely that from the [^{177}Lu]Lu-Oxodotreotide vial should decrease.
J) Once the level of radioactivity emitted from the bottle is stable for at least five minutes (or after 2 consecutive measurements), disconnect the bottle from the long needle and clamp the route connected to the saline

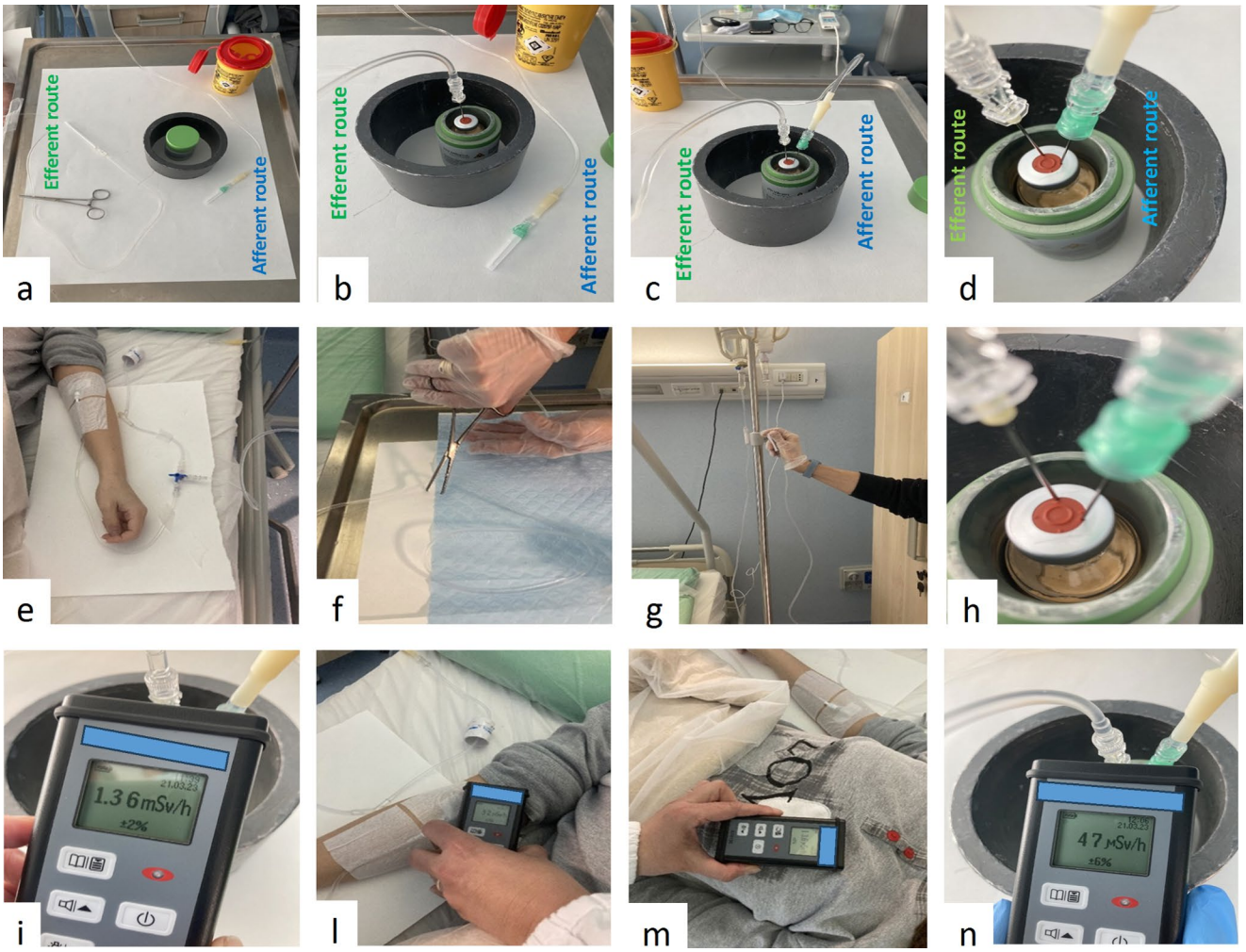

Fig. 3 Highlights of [^{177}Lu]Lu-Oxodotreotide administration

(connected to the short needle). The volume of saline needed to complete the infusion may vary. Measurements should be conducted with a calibrated detection system; the total activity administered will be equivalent to the activity in the vial before infusion minus the residual activity present in the vial after infusion.

K) Conclude the procedure with an intravenous flush of the patient's catheter with 2 ml of saline.

Further guidance on gravity administration can be found on pages 8–10 of [3]. Additional types of administration by infusion pumps are available in the supplementary material of [12].

Management of side effects

Acute and subacute toxicity

The risk of toxicity in patients undergoing PRRT is usually very low, especially if all appropriate precautions are taken. Side effects can be either acute, subacute or chronic. Acute toxicity is usually related to the administration of the amino acids or the radiopharmaceutical itself. The most common acute side effects despite premedication with antiemetics are nausea, headache, and vomiting and are due to metabolic acidosis induced by the administration of the amino acids [23, 26]. In this case, it is advisable to temporarily suspend the infusion to provide the patient with the necessary medical care, and then resume the radiopharmaceutical infusion as soon as the critical phase has passed. The physician may consider additional administration of other antiemetic drugs, for example, those that are fast-acting. Special attention should be paid to avoid possible electrolyte imbalance (hyperkalemia, hypernatremia), often due to a dehydrated condition of the patient. Related to PRRT is the risk of developing reversible acute bone marrow toxicity. In the case of patients who develop neutro/thrombocytopenia above grade 1 (incidence less than 5% [27]), the subsequent treatment can be delayed (with related dosimetric considerations), allowing the recovery of bone marrow function, or administer half activity (3.7 GBq = 100 mCi [3, 28]) or discontinue therapy permanently.

Renal and hepatic toxicity (bilirubin, albumin, AST, ALT, gamma-glutamyl transferase, alkaline phosphatase) are less frequent eventualities during PRRT, but if patients develop toxicity that is attributable to [^{177}Lu]Lu-Oxodotreotide (e.g., elevated bilirubin or decreased renal function), therapy should be discontinued until complete resolution. Therefore, slippage between treatments appears preferable. In the case of dose adjustment of [^{177}Lu]Lu-Oxodotreotide, a reduction in the amount of amino acids administered is not recommended. In case of reduced hematologic values (hemoglobin, platelets, white blood cells), we recommend specialized hematologic evaluation; blood transfusion or use of platelet concentrates; use of growth factors (granulocyte stimulants, romiplostim, or erythropoietin and derivatives) starting 10 days after PRRT; in patients with compromised bone marrow reserve before PRRT initiation, consider preemptive peripheral stem cell harvest and possible reinfusion post-PRRT. In case of impaired renal function (as assessed by creatinine clearance), we recommend: nephrologic evaluation; important pre-PRRT hydration (2–3 L of fluids, if clinically appropriate); use of diuretics (e.g., furosemide) in case of renal pelvis dilatation or delayed urinary outflow. In the case of peritoneal and mesenteric NET localizations, PRRT could aggravate symptoms (desmoplastic reaction) or cause potential bowel occlusions (in case of carcinomatosis). Therefore, post-PRRT corticosteroid medication might be useful in such patients [12]. In general, in patients with known renal, hepatic, or bone marrow dysfunction or those who develop toxicity during treatment, a decrease in administered activity or the use of longer time intervals between [^{177}Lu]Lu-Oxodotreotide administrations may be considered [28].

Hormonal release syndromes and carcinoid crises

During radiopeptide administration, the physician must remain nearby the patient, in the vicinity of an emergency cart and a trained team. Due to potential, sudden and massive hormonal release following PRRT, functional crises (carcinoid syndromes) may indeed occur, the main clinical manifestation of which will depend on the specific hormone involved (hypoglycemia, hypergastrinemia, hypo/hypertension, WDHA syndrome, electrolyte imbalances). Neuroendocrine hormone crises due to excessive release of hormones or bioactive substances develop in 1% of patients and typically occur during or within 2 days of treatment [29]. It is fundamental during the PRRT enrollment visit to identify patients at higher risk for carcinoid crises, assessing risk factors such as previous crises, high 5-HIAA and CgA values, heavy tumor burden (especially in the liver), presence of carcinoid heart disease (CHD), advanced age, stressed patients, use of sympatico mimetics and/or beta-2-agonists. For carcinoid crisis prevention, particular attention should be paid to correct any potential symptoms and unbalance in the electrolytes, protein and nutritional status, also avoiding possible triggers such as strenuous exercise, or tryptophane-rich nutriment (e.g., fruits), spicy food and alcohol [25, 30]. Particular attention must be paid to CHD patients (high NTproBNP values) who need to be evaluated by a cardiac surgeon and must undergo an echocardiogram, no less than 3 months before PRRT [31]. It is also important to

early identify potential carcinoid crises considering that the typical clinical manifestations include skin rash, diarrhea, bronchospasm, and hypertensive crisis. Also, in patients known to be symptomatic, monitoring vital parameters (at least blood pressure and heart rate) before and after PRRT infusion is recommended. According to ENETS guidelines, for high-risk patients starting PRRT and using short-acting SSA, this should be continued up to 8–24 h before administration and restarted 8–24 h after PRRT to prevent carcinoid crises [31]. However, in case of a carcinoid crisis, the same guideline suggests an aggressive treatment using iv octreotide (bolus and continuous infusion), fluids, corticosteroids and vasopressors, also correcting electrolyte disturbances. Other specific strategies can also be considered in high-risk patients such as administering the half PRRT dosage, prolonging the administration time and, as before, reducing the renal protection amount. More detailed and extensive prophylactic and carcinoid crisis treatment strategies have been suggested [25, 30], and will be soon deeply assessed by an Italian joint position paper. Personnel should be prepared (including in terms of radiation exposure) for these eventualities and undertake precise and prompt therapeutic interventions considering that radiation exposure to [^{177}Lu]Lu-Oxodotreotide is lower than that with 131I due to reduced energies and gamma emission rates. In the case of a medical emergency, staff concerns about radiation exposure should not hinder the prompt provision of appropriate medical care to the patient.

Management of radiopharmaceutical extravasation

Prevention of such an eventuality is critical and includes checking for patency of the intravenous route before administration of the radiopharmaceutical, direct observation of the site during administration, and prompt intervention in case of swelling or pain. In case of infiltration/extravasation, removal of the radiopeptide from the site of administration can be facilitated by extravasation aspiration, lavage injection, hot packs (vasodilatation), compression and elevation of the site to increase blood flow [12]. To continue radiopeptide infusion, it will be mandatory to use a new access, possibly contralateral. The area of extravasation should be demarcated with an indelible pen and, if possible, photographed. In addition, it is recommended to record the estimated time and volume of extravasation. Infiltration/extravasation should be reported to the radiation protection officer for monitoring and skin dose calculation and, depending on severity, reported as an adverse event.

Chronic toxicity

Despite the use of nephroprotective amino acid solutions, PRRT can (rarely) result in reduced renal function with loss of creatinine clearance (less than 4% annually; grade 3–4 incidence less than 5%) especially in patients with risk factors such as long-standing and poorly controlled hypertension and diabetes [32]. As mentioned earlier, acute bone marrow toxicity is mostly reversible and quite rare; however, sporadic cases of myelodysplastic syndrome or acute myeloid leukemia have been reported in the literature in less than 3% of patients at a median distance of about 2 and 4 years, respectively, after the end of PRRT [33]. Despite the presence of somatostatin receptors in normal pituitary, thyroid, adrenal, and Langerhans cells, no significant long-term alterations in endocrine function have been reported [34]. The potential toxicities of [^{177}Lu]Lu-Oxodotreotide are summarized in Table 3.

Biodistribution scintigraphic imaging after [^{177}Lu]Lu-Oxodotreotide: modalities and timing

Twenty-four hours after PRRT administration, planar total body scintigraphy in anterior and posterior projection should be performed. If possible, it would be appropriate to supplement the scintigraphy with a SPECT/CT acquisition of the regions affected by the disease. The main purpose of this imaging is to assess the biodistribution of the tracer (confirming the correct administration of the radiopharmaceutical), highlighting any/suspected disease progression. In addition, such scintigraphic acquisition is important to allow dosimetric estimation of absorbed dose to healthy organs and pathologic lesions (Fig. 4 shows an example of progression between cycles; Fig. 5 shows an example of SPECT/CT acquisition indicative of response to therapy).

For more precise and accurate dosimetric estimation, it would be advisable to perform several serial acquisitions over time, according to the characteristics of the center (type of hospitalization, diagnostic availability, etc.) and the patient. A possible scheme might be to perform a second acquisition at 48 h after radiopharmaceutical administration and another at 96–120 h. Planar scintigraphic images are critical for estimating biokinetics over time, while SPECT/CT images provide also morphological data about the three-dimensional distribution of radioactivity within the specific organ. Clearly, the acquisition of a SPECT/CT results in longer examination times and increased patient radiation exposure. Table 4 shows the absorbed doses by organ after [^{177}Lu]Lu-Oxodotreotide therapy.

A recent survey conducted in European centers performing radionuclide therapies showed that dosimetry is scarcely or never used in more than half of all centers [36]; even

Table 3 Summary of the main potential [^{177}Lu]Lu-Oxodotreotide toxicities

	Very common	Common	Uncommon
Hematopoietic system	Thrombocytopenia, lymphopenia, anemia, pancytopenia	Leukopenia, neutropenia	Refractory cytopenia with unilinear dysplasia, nephrogenic anemia, bone marrow failure, thrombocytopenic purpura
Gastrointestinal	Nausea, vomiting	Abdominal distension, diarrhea, abdominal pain, constipation, dyspepsia, gastritis	Dry cough, meteorism, ascites, gastrointestinal pain, stomatitis, hematochezia, intestinal blockage, colitis, acute pancreatitis
Oncological disorders		Myelodysplastic syndrome	Acute myeloid leukemia, acute leukemia
Hepatobiliary system		Hyperbilirubinemia	
Musculoskeletal and connective system		Muscle pain, muscle spasm	
Nervous system		Dizziness, dysgeusia, headache, lethargy, syncope, insomnia	Tingling, hepatic encephalopathy, paresthesias, parosmia, drowsiness, anxiety, hallucinations, disorientation
Endocrine system		Hypothyroidism	Diabetes mellitus, carcinoid crisis, hyperparathyroidism
Cardiovascular system		QT interval prolongation, hypertension, skin redness, flushing, hypotension	Atrial fibrillation, palpitations, myocardial infarction, angina pectoris, cardiogenic shock, pallor, cold extremities, phlebitis
Respiratory system		Dyspnea	Pleural effusion, increased sputum
Nephro-urinary system		Acute renal failure, hematuria, renal damage, proteinuria	Leukocyturia, urinary incontinence, reduced VFG, renal failure
Skin-subcutaneous system		Alopecia	Skin rash, dryness, swelling, hyperhidrosis, itching
Infections			Conjunctivitis, cystitis, pneumonia, Herpes Zoster, Influenza
Eye and Ear			Dizziness, eye disorders
Immune System			Hypersensitivity

in those centers where it is used, its usefulness is limited and does not influence the treatment itself. We can therefore conclude that dosimetric evaluation is not part of the standard feasibility protocol for PRRT with [^{177}Lu]Lu-Oxodotreotide; however, it would be advisable to perform it, especially in "frail" patients but not only. It would be ideal to carry it out in all patients to be able to collect data, albeit burdened with uncertainties, on the doses delivered to the organs most at risk and to the lesions, thus respecting the European directive described above.

Patient discharge guidelines after PRRT with [^{177}Lu]Lu-Oxodotreotide

Clinical and radioprotection prescriptions

The nuclear medicine physician, assisted by the physics, will need to determine when the patient can leave the controlled area of the Hospital, that is, the time when third-party radiation exposure does not exceed regulatory thresholds. The level of radiation emitted by PRRT with [^{177}Lu]Lu-Oxodotreotide is generally low (especially when compared with other therapeutic radiopharmaceuticals such as 131I) approximating about 2 mR/h (20 μSv/h) at a one-meter distance, decreasing after 24 h to about 1 mR/h (10 μSv/h) at a one-meter distance.

Patient monitoring during [^{177}Lu]Lu-Oxodotreotide

The monitoring of the patient undergoing PRRT should aim at assessing the efficacy of the therapy over time, checking the disease status to recognize any progressions or early relapses, monitor possible side effects and possible long-term toxicity while ensuring an acceptable quality of life. For this reason, certain laboratory and/or instrumental tests should be performed both after each cycle and at the end of the four cycles and in the subsequent follow-up. Instrumental investigations (morphological and/or functional) are not mandatory during treatments unless clinical progression, suspected progression on biodistribution imaging, or other clinical reasons are to be evaluated on a case-by-case basis.

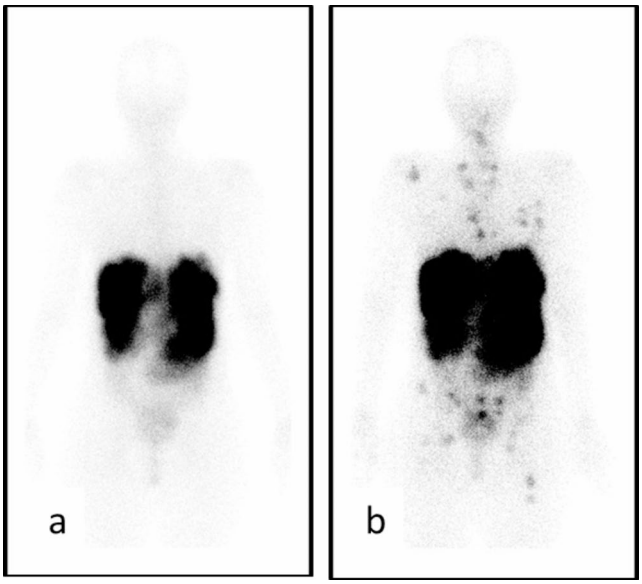

Fig. 4 [^{177}Lu]Lu-Oxodotreotide whole-body scintigraphic images, in anterior projection, were obtained approximately 16 h after the administration of the second (**a**) and third (**b**) cycles of PRRT. A comparison of the images highlights the appearance of several skeletal pathological radiopharmaceutical fixations as progressive disease

Table 4 Organs' mean absorbed dose after [^{177}Lu]Lu-Oxodotreotide [35]

	[^{177}Lu]Lu-Oxodotreotide Mean absorbed dose (Gy/GBq)
Bone marrow	0.02–0.07
Kidneys	0.32–1.67
Liver	0.13–0.21

It is at the discretion of the oncologist and/or nuclear physician whether to perform such instrumental examinations. For example, intermediate verification of disease status by CT or MRI one month after the end of the second cycle may be desirable to prevent disease progression and avoid subsequent treatment [37]. In case of evidence of instrumental disease progression or uncertain scenarios, it is also recommended to perform nuclear medical imaging PET with DOTA-peptides and possibly [^{18}F]FDG [7, 10].

Laboratory tests

After each cycle of PRRT and before the next, a complete blood count (hemoglobin, leukocyte and platelet counts), renal function tests (creatinine and creatinine clearance), liver function tests (AST, ALT, total bilirubin, serum albumin) and serum electrolytes should be performed. Patients

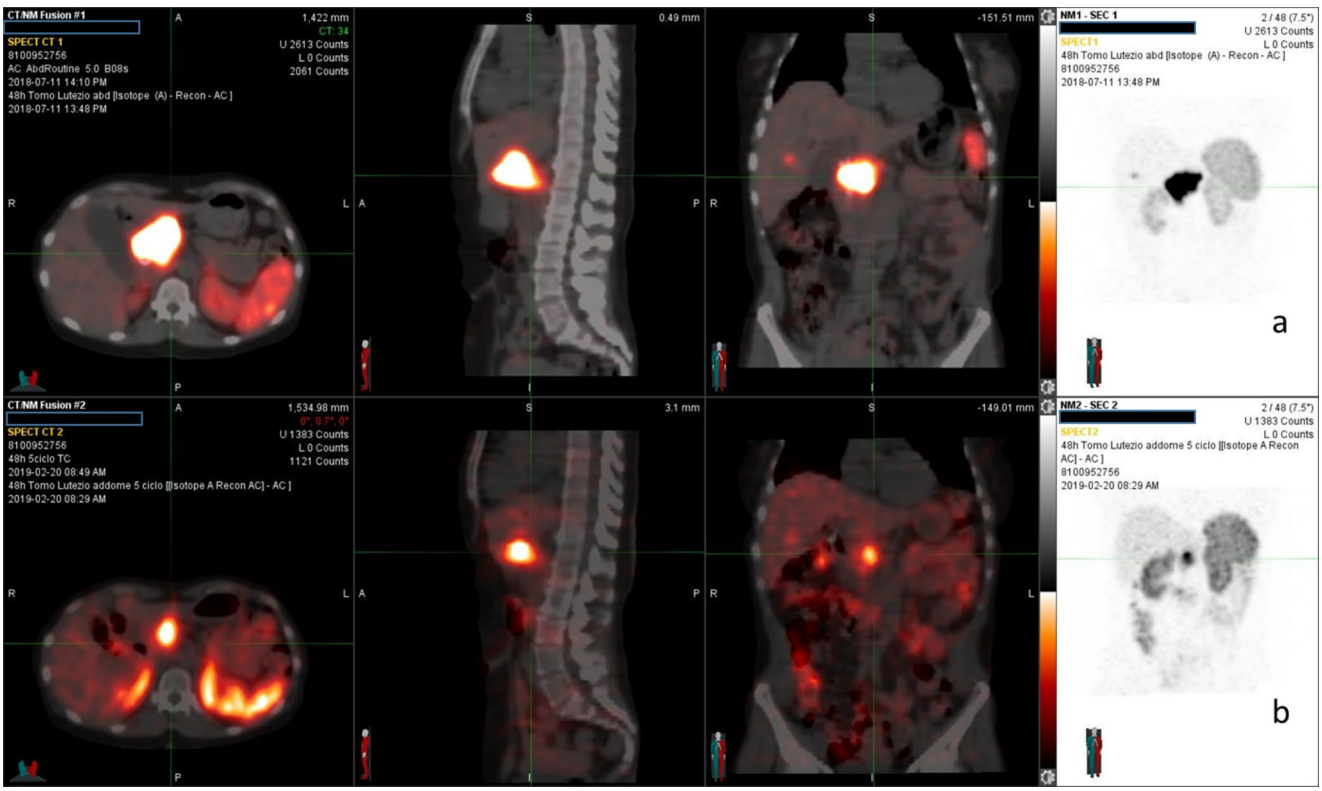

Fig. 5 SPECT/CT images of the abdominal region obtained approximately 16 h after administration of the first (**a**) and fourth (**b**) cycles of [^{177}Lu]Lu-Oxodotreotide. A comparison of the images highlights the reduction of pathological radiopharmaceutical fixation in the pancreatic head and in liver lesions indicating a good response to [^{177}Lu]Lu-Oxodotreotide, to be confirmed with morphological and functional diagnostic instrumental evaluations

with blood values below the indicated limits after the first cycle of PRRT should receive lower activity at the next cycle and/or interval deferral at the next cycle. In more severe cases, discontinuation of PRRT could be considered after appropriate multidisciplinary clinical evaluation.

Nonspecific or specific markers

There are no clear recommendations for measuring tumor markers (chromogranin A, 5-hydroxyindoleacetic acid, proinsulin, gastrin, NSE) after PRRT. If clinically applicable, tumor markers should be checked approximately every 3–12 months. Chromogranin A value should be monitored with caution because, in addition to limited accuracy (around 65%), there are known causes of false positives such as taking proton pump inhibitor drugs, the presence of gastric atrophy, and reduced renal and liver function.

Possible other tests

In patients with pre-existing risk factors for renal toxicity, sequential renal scintigraphy with clearance or GFR measurement should be considered before and after the four cycles, evaluating any changes.

Post PRRT follow-up

Laboratory tests

Since the kidneys and bone marrow (critical organ) are the healthy organs that receive the highest absorbed dose and therefore are most at risk of toxicity even in the long term, it appears essential to monitor renal function (serum creatinine and creatinine clearance) and blood counts even at the end of the four cycles of PRRT. It is advisable for a clinical evaluation including an objective examination of the patient within one month after the end of the four cycles and then quarterly or half-yearly as appropriate. Special attention should be paid to signs and symptoms that may reflect possible disease progression. Monitoring of laboratory tests (blood, kidney, and liver markers) every 4 weeks for at least 3 months after the last PRRT and every 6 months thereafter is also recommended to detect any late adverse reactions. Hematological values should always be monitored during standard oncologic follow-ups, and more frequent monitoring is recommended if altered blood values are present. Patients with mild-to-moderate renal impairment after PRRT need closer monitoring with frequent serum creatinine measurements. Patients with severe renal insufficiency or worsening renal function need specialist nephrology consultation.

Instrumental examinations

Three months after the last PRRT cycle it is of paramount importance to restage the patient. For evaluating the efficacy of PRRT, the gold standard examinations are CT and MRI to apply RECIST 1.1 criteria [38, 39]: the choice of the technique such as contrast-enhanced (ce) abdomen-pelvis CT or MRI and eventually thorax ceCT, will depend on the method used for staging before PRRT (based on the site of the disease and its characteristics); liver MRI with sodium gadoxetate should be considered as the first choice in cases of known liver disease [40]. The patient will also undergo a PET with DOTA-peptides allowing a functional restaging [41] also considering the eventuality (about 10%) of pseudoprogression due to a transient increase in tumor volume secondary to radiation edema and necrosis [42].

Thereafter, the follow-up timing will usually foresee morphological imaging every 6 months and a yearly functional assessment with DOTA-PET [43].

Furthermore, in the case of suspected progression and/or possible dedifferentiation, it is also appropriate to perform a metabolic PET study with [^{18}F]FDG useful for detecting possible mismatch lesions i.e., undifferentiated lesions that pick up only [^{18}F]FDG and not the receptor tracer, assuming an important prognostic value.

Conclusion

This practical guide summarizes the views and experience of the AIMN therapy committee with the indications from nationally and internationally published guidelines (AIOM, EANM and SNMMI). These procedural recommendations should be taken into the context of nuclear medicine good practice and do not substitute for national and international legal or regulatory provisions.

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Declarations

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