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Chapter 4

Gastroenteropancreatic and pulmonary neuroendocrine tumors

Authors

Javier Ardila Manjarrez
Amaia Mari Hualde
Julián Ardila Mantilla
Juan Enrique Montalvá Pastor
Aitana Calvo Ferrándiz
Rebeca Pérez Pascual

4

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summary

Functional diagnosis:

- Whenever possible, it is preferable to perform PET/CT-STRS over scintigraphy-STRS.
- Well-differentiated tumors (G1 and G2) have greater expression of STRS and therefore greater PET/CT-STRS activity than poorly differentiated ones.
- PET/CT-STRS and PET/CT-FDG should be performed as a comprehensive imaging strategy in high-grade G3 and G2 NETs, in order to assess the dedifferentiation process.

PET/CT utility in NET-GEP:

- PET/CT-STRS is essential for the diagnosis and extension of conventional GEP-NETs, especially useful for the localization of mesenteric lymph node lesions and liver metastases, compared to other imaging techniques.
- In small intestine GEP-NETs, PET/CT-DOPA may be useful.
- Insulinomas are difficult to diagnose due to their small size. Both PET/CT-STRS and PET/CT-[^{18}F]F-DOPA have very limited sensitivities. Premedication with carbidopa improves the sensitivity of [^{18}F]F-DOPA PET/CT.

Usefulness of PET/CT in pulmonary NETs:

- PET/CT-STRS has excellent sensitivity for diagnosis of typical and atypical carcinoid.
- PET/TC-FDG is the technique of choice for CNCP and CNCG.

PET STRS-teragnosis:

- Confirmation of high tumour STRS expression, demonstrated in functional imaging studies, is a *sine qua non* condition for the administration of TRPR.
- Functional imaging, mainly the combination of PET/CT-FDG and PET/CT-STRS, is the main prognostic factor for PRRT.

PRRT indication:

- Gastroenteropancreatic neuroendocrine tumours (GEP) WHO grade 1 and 2, locally advanced or metastatic, well differentiated and with proven pathological expression of somatostatin receptors.

- The current trend is to treat patients with G3 NETs who have a Ki-67% < 55%, achieving disease control rates between 30-80%.

Side effects:

- Acute: during hospital events.
- Subacute: mainly hematological toxicity.
- Late: nephrotoxicity, hepatotoxicity, temporary impairment of fertility, hair loss, asthenia or decreased appetite.

Predictive factors:

- Greater tumor volumes, assessed in 68Ga-DOTATOC PET/CT, correlate with lower PFS.
- NETPET (dual imaging) score correlates well with disease grade, overall survival, and patient prognosis.

CLINICAL INTRODUCTION

Gastroenteropancreatic neuroendocrine tumours (GEP NETs) comprise well-differentiated tumours grades 1, 2 and 3, which constitute different nosological entities with very different prognoses and treatments.

The incidence ranges between 2.5 and 8.5 cases per 100,000 inhabitants, although the registration methodology and classification of tumours has traditionally been very variable between different countries[1], especially if the studies were carried out before of the World Health Organization (WHO) classification of 2017 and 2019[2]. In Spain, the most frequent NETs seem to be those of the small intestine (55%), pancreatic (36.3%) and unknown primary (9.1%), with 44% of the total being metastatic and 36% localized[3]. They can release hormones and therefore be functional, but they can also be non-functional if they are not associated with any hormonal syndrome (independent of the immunohistochemistry identified in the biopsy and hormonal detection in the blood). It is also important to keep in mind that they can produce several hormones simultaneously, although the symptoms of one of them will predominate over others, and that the functional status can change throughout the evolution of the disease.

Most NETs are sporadic, although they can be associated with NEM1, NEM2, NEM4, SDH and von Hippel-Lindau mutations, among others.

The prognosis of the disease is primarily determined by the degree of differentiation and the Ki-67 of the tumour. Well-differentiated low-grade tumours have a mitotic index of less than 2/10 high-power fields and/or a rate of less than 3%, while well-differentiated grade 2 tumours have 2-20 mitoses per 10 high-power fields. and a Ki-67 of 3 to 20%, and in grade 3 both indices are higher[2].

Regarding symptoms, local symptoms and symptoms derived from hormonal secretion may occur. In the case of pancreatic tumours, refractory hypoglycaemia (insulinomas), hyperglycaemia, diarrhea, dermatitis and hypercoagulability (glucagonoma), secretory diarrhea (VIPoma), hyperglycaemia, cholelithiasis and diarrhea (somatostatinoma) or peptic disease and diarrhea (gastrinoma) may occur, NETs with these last two characteristics being located not only in the pancreas but also in the duodenum. NETs located in the gastrointestinal tract are frequently located in the small intestine and appendix, and infrequently in other locations of the digestive tract. Carcinoid syndrome (diarrhea, flushing, symptoms of heart failure due to valvular fibrosis, etc.) will only occur in the case of extensive liver metastases.

Clinical diagnosis

The pathological diagnosis will include histological analysis and immunohistochemical markers when it was necessary (chromogranin A, synaptophysin, etc.). In the case of tumours of unknown origin, other markers such as CDX2 (GE) or Isl1 and PAX8 (pancreatic) can be used. The degree of differentiation, the mitotic index and the Ki-67 must be recorded in the pathology report. In case of discrepancy between one or several factors, the index that is higher should be taken[2].

The patient's symptoms will guide the completion of the hormonal study, although some locations are more frequently associated with certain syndromes. In case of carcinoid syndrome, a determination of 5-hydroxyndoleacetic acid should be carried out in 24-hour urine after a diet free of certain fruits and vegetables (avocado, banana, eggplant, pineapple, plum, tomatoes, kiwis, grapefruit, dates, etc., of at least 48 hours). In case of hypoglycaemia, endogenous insulin, proinsulin and C-peptide will be determined, while in case of hyperglycaemia and diarrhea, plasma glucagon should be determined if it is also associated with flushing, dermatitis or hypercoagulability, while if the associated symptoms are cholelithiasis and steatorrhea, somatostatin determination may be considered. Only if it is hypersecretory diarrhea with associated hypokalemia would serum vasoactive intestinal peptide (VIP) be considered. In case of associated peptic disease, the determination of gastrin in plasma may be performed.

The patient's functional status will depend on different factors, including the degree of tumour differentiation, tumour burden and stage, and the presence of a hormonal syndrome.

Current, systemic treatments and local (to contextualize and give way to radiometabolic treatment)

In case of localized disease with lesions larger than 2 cm, removal of the lesion with sufficient margins and regional lymphadenectomy should be considered; although the final decision will be determined by the location of the tumour, the age of the patient, the presence or absence of functional symptoms that are difficult to control despite the establishment of medical treatment and of course the degree of differentiation of the tumour and its proliferation index. Furthermore, recent data suggest that surgery for tumours between 1 and 2 cm could be beneficial in terms of survival, and not only in terms of symptom control in cases of functioning tumours, although tumours smaller than this size they would not benefit[4]. Regarding metastatic disease, cytoreduction surgery has traditionally been considered for symptomatic control in the case of obstructive tumours or those that produce other local symptoms or in casesof functioning tumours, although recently a possible benefit in overall survival (OS) has also been identified. Other types of hepatic locoregional treatments can be used in cases of predominantly hepatic disease.

Regarding systemic treatment as antitumor treatment, extended-release somatostatin analogues are the first choice due to their favourable toxicity profile and symptomatic control in the case of functioning tumours. The PROMID trial demonstrated a treatment benefit with octreotide LAR for midgut NETs compared with placebo (time to progression for octreotide LAR and placebo 14.3 and 6 months, respectively; hazard ratio [HR] 0.34; 95% confidence interval [CI]: 0.20 to 0.59; P = 0.000072)[5], with no long-term survival benefit detected[6]. However, the CLARINET clinical trial demonstrated the benefit of lanreotide in well-differentiated GEP NETs grades 1 and 2 (progression-free survival [PFS] not achieved vs. 18.0 months; P < 0.001; HR 0.47; CI 95%: 0.30 to 0.73)[7]. The CLARINET FORTE study has explored higher doses with good results[8]. The safety profile of these drugs is particularly favourable, highlighting only diarrhea in up to 26% of patients. In case of progression, treatment with everolimus (NET GEP), sunitinib (NET P) or treatment with ^{177}Lu-dotatate can be considered in case of NET with expression of somatostatin receptors. In the case of everolimus, the RADIANT3 and RADIANT4 trials were conducted in patients with P-NETs and GI and pulmonary NETs, respectively. In the first, an increase in PFS from 11 months to 4.6 months on median was demonstrated in the everolimus groups versus placebo in case of progression to analogues (HR 0.35; 95% CI: 0.27 to 0. 45; P < 0.001)[9]. In the second, an increase in PFS of 11.0 months was demonstrated in the experimental arm, compared to 3.9 months in the control arm (95% CI: 9.2-13.3)[10]. Everolimus produces diarrhea, anemia, asthenia, hyperglycaemia and, very characteristically, stomatitis. For sunitinib, the median PFS was 11.4 months in the sunitinib arm versus 5.5 in the placebo arm (HR, 0.42; 95% CI, 0.26 to 0.66; P < 0.001) in the registration trial. The safety profile of sunitinib was diarrhea, nausea, vomiting, asthenia, fatigue, and hypertension[11]. Other options may be treatment with temozolomide-capecitabine or classic chemotherapy treatments such as streptozocin-doxorubicin, 5-FU-doxorubicin, FOLFOX, XELOX,

TABLE 1. 2019 WHO classification. Adapted from Prado-Wohlwend et *al.*[61]

NET classification gastroenteropancreatic	Differentiated	Histological grade	Mitotic rate (mitosis/ 2 mm^2)	Ki-67
NET G1	Well differentiated	Low	2	< 3%
NET G2	Well differentiated	Medium	2-20	3-20%
NET G3	Well differentiated	High	> 20	> 20%
Small cell type NSC	Poorly differentiated	High	> 20	> 20%
High cell type NSC	Poorly differentiated	High	> 20	> 20%

etc., usually reserved for patients with more undifferentiated tumours. Belzutifan, a HIF2-α inhibitor, was recently approved in the United States and has not been submitted for registration in Europe for the treatment of tumours in patients with von Hippel-Lindau disease, including NETs. P. The authorization of registration in the territory of the US Food and Drug Administration (FDA) was based on the response rate (83% in the 12 patients with NET included; with a duration of response greater than 12 months in 50% of respondents). The safety profile includes anemia, hypoxia, asthenia, elevated creatinine, headache, dizziness, hyperglycemia, and nausea; the first two being particularly relevant[12]. Confirmatory clinical trials are underway.

DIAGNOSTIC IMAGING

NETs share many diagnostic similarities, as they are often hypervascular and more than 80% overexpress somatostatin receptors (STRS) on their surface. This allows the use of STRS images for staging and selection of patients amenable to specific STRS-targeted therapies (TRPR).

Morphological image

Anatomical imaging, mainly ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), has traditionally been used for the initial staging and follow-up of NETs, providing excellent anatomical detail and good diagnostic accuracy.

Primary and metastatic NET lesions generally show intravenous contrast enhancement in the arterial phase. The average sensitivity of CT is 73% for primary tumours and 80% for the detection of liver metastases, with a moderate decrease, to 75%, in secondary extrahepatic disease. MRI is considered the best imaging modality for the evaluation of liver metastases, with a reported sensitivity of 95.2%.

However, the precision of anatomical imaging techniques is limited, both in initial diagnosis and in the assessment of response to treatment, due to its exclusive assessment of variations in size and morphology.

Functional image

Radiopharmaceuticals that detect the expression of somatostatin receptors

The intense overexpression of STRS in the cell membrane of most NETs constitutes the basis for the use of functional imaging studies for their diagnosis and for the proposal of TRPR.

STRS functional imaging studies can be:

- SPECT/CT scintigraphy of somatostatin receptors (SPECT/CT-STRS).
- PET/CT of somatostatin receptors (PET/TC-STRS) with [^{68}Ga]Ga-DOTA-TOC/TATE/NOC.

Somatostatin receptor scintigraphy and SPECT/CT (SPECT/CT-STRS)

[^{111}In]In-pentetreotide (OctreoScan®) and [^{99m}Tc]Tc-HYNIC-TOC (Tektrotyd®)

For years, scintigraphy and SPECT/CT STRS have been considered the gold standard in the diagnosis of NETs using functional imaging, although numerous limitations regarding PET/CT STRS studies are currently known.

The first STRS scans were performed in 1989, using [^{123}I]I-Tyr3-octreotide to study pancreatic carcinoid tumours and NETs. [^{111}In] In-pentetreotide, with imaging at 4 and 24 hours, became the most widely used radiotracer with a

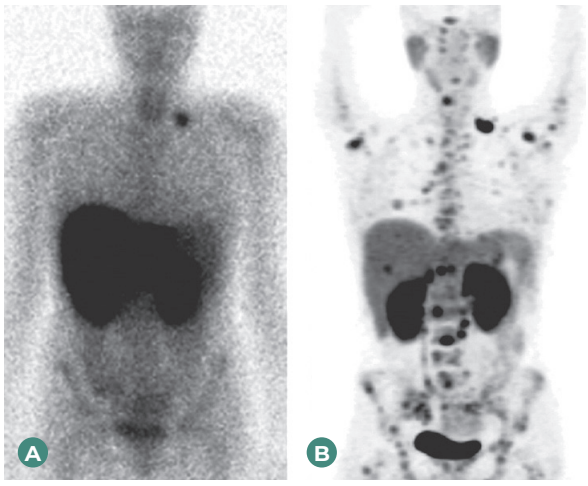

FIG. 1. Advantages of STRS PET over conventional STRS scintigraphy. TNE G1. [^{111}In] In-pentetreotide scintigraphic study with evidence of left supraclavicular lesion (A). [^{68}Ga]Ga-DOTA-peptide (B) PET from the same patient at 4 days, where extensive metastatic disease was seen, not visible in a previous study[14].

highly variable sensitivity (67-100%). Currently, a benefit has been demonstrated from the use of [^{99m}Tc]Tc-HYNIC-TOC (Tektrotyd®) compared to [^{111}In]In-pentetreotide, providing better image quality, more effective compliance with the principle ALARA, lower cost and better efficiency when performing patient images.

The superiority of SPECT over planar imaging has been demonstrated, both to specify the location of lesions and to rule out confusing foci of physiological activity. Furthermore, with the use of hybrid equipment (SPECT/CT), a modification of clinical management has been described in up to 64% of cases.

In the first comparative studies between [^{68}Ga]Ga-DOTATATE and [^{111}In]In-pentetreotide in patients with NETs, an evident superiority in the image sensitivity of [^{68}Ga]Ga-DOTATATE was demonstrated (96% versus 60%). Regarding specificity, no differences were found between both techniques (97% versus 99%)[13].

There are numerous limitations of scintigraphic studies compared to the available [^{68}Ga]Ga-DOTA-peptide PET/CT studies, including lower image quality, biliary/intestinal physiological activity (which may decrease the ability to detect small lesions, abdominal), in addition to a higher radiation dose to the patient and the prolonged image acquisition time.

NET G1. [^{111}In]In-pentetreotide scintigraphic study with evidence of left supraclavicular lesion (**A**). [^{68}Ga]Ga-DOTA-peptide (**B**) PET from the same patient at 4 days, where extensive metastatic disease was seen, not visible in a previous study[14].

PET/CT of somatostatin receptors (PET/CT-STRS) with [^{68}Ga]Ga-DOTA-TOC/TATE/NOC

The analogues TOC and TATE show a high affinity for STRS2 and STRS5, while NOC has a lower affinity for STRS2, but has additional binding to them. STRS3 and STRS5. The TATE analogue is more selective for STRS2 and has an affinity for the receptor one hundred times greater than [^{111}In]In-pentetreotide[15].

PET/CT-STRS studies require less waiting and acquisition time, reduce patient dosimetry, allow quantification of uptake and, when performed earlier, present less biliary elimination. For the patient's preparation, a special diet or restriction in physical activity is not necessary. Some authors recommend prior suspension of octreotide therapy to eliminate possible STRS blockade: –1 day for short-acting analogues and –3-4 weeks for long-acting analogues. However, it is a controversial topic and currently not standardized in clinical practice.

The current PET/CT protocol involves image acquisition 60 minutes after intravenous injection of the radiopharmaceutical, from the base of the skull to the middle third of the thighs.

The use of intravenous contrast has been shown to increase the detection rate of liver metastases and may aid in the detection of primary small bowel tumours, so its use is recommended whenever possible. Furthermore, additional CT studies could be avoided in the same patient.

Once the greater diagnostic capacity of PET/CT-STRS has been demonstrated compared to the rest of conventional techniques, both functional and morphological, it is essential to keep in mind that the location of more extensive disease should not always have an impact on clinical management, and that it may exclusively represent a more precise staging with evidence of disease not visible in less precise techniques.

Therefore, progression should be assessed only by comparisons between PET/CT-STRS studies over the course of over time.

Biodistribution

[^{68}Ga]Ga-DOTA-peptide is rapidly eliminated from the bloodstream, with no evidence of radioactive metabolites within 4 hours, in serum or urine. The maximum accumulated activity in the tumour is reached 70 ± 20 minutes postinjection. Elimination is practically complete through the kidneys.

STRSs are expressed in various cells of the body, neuroendocrine and non-neuroendocrine, so physiological activity is

observed in the pituitary gland, spleen, liver, adrenal glands and urinary tract; while the thyroid, salivary glands and parotid show moderate activity.

All five types of STRS are expressed in the pancreas, with STRS2 found preferentially located in the islets. The accumulation of islets in the head and the pancreatic uncinate process causes a focal deposit of greater intensity capable of simulating a tumor lesion at that level. This must be known and assessed, since it is the main cause of false positives in this diagnostic test. [^{68}Ga]Ga-DOTA-peptide is excreted by the kidneys due to its hydrophilic properties.

Management of functional imaging in neuroendocrine tumour

Most neuroendocrine tumours express STRS and can be assessed using STRS functional imaging, mainly those located in the gastrointestinal tract and the lungs.

The degree of uptake in PET/CT-STRS is strongly correlated with the expression of STRS2, therefore, it is higher in well-differentiated NETs (G1 and G2), compared to poorly differentiated ones (G3 or carcinomas). The STRS image should not be the only functional image to be evaluated in NETs, since there are other molecular and metabolic targets useful in the diagnostic process, such as the increase in carbohydrate metabolism, assessed by PET/CT-FDG, useful in the dedifferentiation process and eventually in the prognostic assessment. PET/CT-STRS and PET/CT-FDG should be performed as a comprehensive imaging strategy in those NETs that are not low grade (G1). Furthermore, significant tumour heterogeneity can occur in the same patient, with the coexistence of well-differentiated and poorly differentiated lesions.

TABLE 2. List of tumors visualized with each radiotracer

PET/CT-STRS	PET/CT-DOPA	PET/CT-FDG
– NET GEP – Functional and non-functional – Pulmonary NET – Systemic tumors – Sympathetic-adrenal (paraganglioma) – Meningioma	– Midgut NET (jejunum and ileum) – Pheochromocytoma – Paraganglioma – Neuroblastoma – Medullary thyroid	– NET G2 and G3 with aggressive behavior – Neuroendocrine carcinomas – Medullary thyroid carcinoma

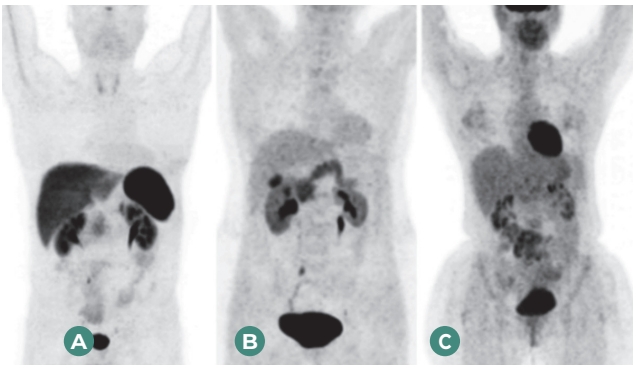

FIG. 2. Physiological biodistribution of [^{68}Ga]Ga-DOTATATE, [^{18}F]F-DOPA and [^{18}F]F-FDG. PET ^{68}Ga-DOTA-PEPTIDES. B) PET ^{18}F-DOPA. C) PET ^{18}F-FDG.

One of the most controversial issues in NET imaging is the suitability of each radiotracer, depending on the tumour characteristics, specifically when PET/CT-FDG should be added to detect more aggressive cell clones. Both the guidelines of the European NeuroEndocrine Tumours Society (ENETS) and the European Association of Nuclear Medicine (EANM). They consider it unnecessary to perform PET/CT-FDG in G1 tumours (particularly in the small intestine) and suggest its performance in high-grade G2 NETs (Ki-67 10-20%), G3 NETs and neuroendocrine carcinomas (NECs).

On the other hand, the guidelines of the European Society Medical Oncology (ESMO 2020) consider it optimal to perform both tests from the beginning in G2 and G3 NETs. Furthermore, not only should their diagnostic capacity be assessed, but various studies refer to the usefulness of imaging dual STRS and FDG as a prognostic factor. Likewise, considering that some originally well-differentiated tumours may present dedifferentiation throughout the course of the disease, the role of FDG-PET/CT continues to be the subject of debate even in well-differentiated strains[16].

[^{18}F]F-DOPA is a tracer of the catecholamine metabolic pathway and is of special interest in tumour lesions with little or variable expression of STRS, such as insulinomas, and its usefulness has been demonstrated in midgut NETs (jejunum and ileum). Additionally, it will be discussed extensively in the next chapter for diagnosis of medullary thyroid cancer, pheochromocytomas/paraganglioma, and neuroblastomas.

Performing a PET/CT-STRS study allows the visualization of possible synchronous tumours, which may present variable expression of STRS (breast cancer, melanoma, lymphoma, prostate, head and neck cancer, sarcoma, renal cell carcinoma, differentiated cancer thyroid and astrocytoma).

Utility of PET/CT-STRS in gastroenteropancreatic neuroendocrine tumors

PET/CT-STRS in classic gastroenteropancreatic neuroendocrine tumours

GEP-NETs arise from the stomach, small intestine, appendix, colon, rectum, or pancreas. They have a variable malignant potential with a clinical behaviour determined by proliferative activity according to the Ki-67 index and tumour differentiation. STRS expression in GEP lesions allows STRS images to be obtained in practically all its locations, with small nuances in the midgut (jejunum and ileum) and in pancreatic insulinomas.

The evaluation of the location and extent of the disease is crucial for its treatment.

A better overall accuracy of PET/CT-STRS has been demonstrated compared to CT, with special interest in lymph node disease, identifying greater sensitivity (92% vs. 64%) and specificity (83% vs. 59%), respectively. This is especially relevant in mesenteric lymph node disease, which is very common in small intestine NETs and which can vary the surgical behaviour. However, it must be taken into account that reactive lymph nodes may show activity, behaving as a false positive, as well as micrometastases, which, if not visualized, may generate a false negative.

Patients with GEP-NET may present with metastatic disease (20-40%), whose evaluation is crucial for the therapeutic approach, with the most common locations of dissemination being the liver, peritoneum, lung and bone. PET/CT-STRS has good diagnostic accuracy for detecting distant metastases with a significant impact on patient management. In liver assessment, similar performance has been demonstrated with respect to MRI, although there are data that demonstrate modifications in management strategies, including the suspension of liver surgeries due to the appearance of extrahepatic lesions not visible using other techniques. morphological.

PET/CT-STRS in gastroenteropancreatic neuroendocrine tumours: particularities

Midgut NET (jejunum and ileum)

Mid-small intestine NETs derive from serotonin-producing enterochromaffin cells, so, among other characteristics, the use of PET/CT-DOPA may have a place in their diagnosis. The biology of these tumours is different from that of other GEP NETs, characterized by a low proliferation rate, and most of them can be classified as grade 1 and 2 (exceptional

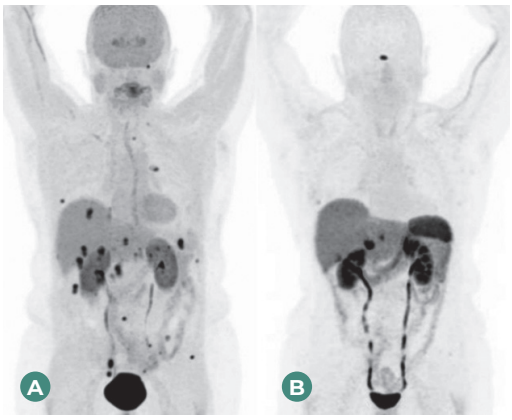

FIG. 3. Superiority of ^{18}F-DOPA (A) over ^{68}Ga-DOTATOC (B) in a patient with small intestine neuroendocrine tumor. Image from Veenstra EB, *et al.*

G3). They are usually diagnosed at an advanced stage with regional disease in 36% and metastatic disease in 48%[17].

PET/CT-STRS is clearly superior to PET/CT-DOPA for some NETs, mainly for pancreatic NETs (except insulinoma), and although it is currently the recommended technique, its superiority in small intestine NETs is not clear.

PET/CT-DOPA is more specific, shows better spatial resolution and has less physiological activity in the small intestine compared to PET/CT-STRS.

The group of Imperiale *et al.* analyzed the results of well-differentiated ileal NETs, after resection of the primary one, with both tracers: STRS and DOPA (carbidopa). PET/CT-DOPA achieved a better detection rate than PET/CT-STRS (96% vs. 80%). In a total of 605 lesions, 458 (76%) were positive in both modalities, 25 (4%) exclusively in PET/CT-STRS and 122 (20%) in PET/CT-DOPA corresponding to liver metastases, peritoneal and lymphadenopathy[18].

Emile B. Veenstra *et al.*, in a study proposed to assess the usefulness of pre-PRRT DOPA PET/CT, they demonstrated the usefulness of this technique in the diagnosis and localization of NET lesions, finding even more lesions than PET/CT-STRS, mostly liver metastases[19].

Taking into account various studies analyzed, we assume that both PET/CT-STRS and PET/CT-DOPA are excellent radiopharmaceuticals for the staging and restaging of G1 and G2 small intestine NETs, although PET/CT-DOPA seems be more sensitive, mainly in the detection of liver lesions, with a higher lesion/background ratio. These findings are of special interest in the face of a cytoreduction surgical approach, although more studies are necessary for an adequate conclusion.

FDG-PET/CT studies are not recommended in small intestine NETs unless high-grade G2/G3 disease is evident. These indications are in line with the 2017 European

Association of Nuclear Medicine guidelines for PET/CT imaging of NETs[15].

Pancreatic NETs

Pancreatic NETs are a very heterogeneous group with various peculiarities. Up to 10% develop in the context of clinical syndromes such as NEM1, Von Hippel-Lindau, tuberous sclerosis complex and neurofibromatosis type 1 (NF1). Most pancreatic NETs are non-functioning and are usually diagnosed by their mass effect. On the other hand, there is another percentage of functioning pancreatic NETs, which present early due to symptoms related to hormone production.

80-100% of pancreatic NETs are well differentiated. Overexpress STRS (STRS2>STRS5, STRS3). Current guidelines and expert reviews (ENETS, North American Neuroendocrine Tumour Society [NANETS]), recommend STRS imaging in the majority of pancreatic-NET patients, with the exception of some hereditary syndromes and benign insulinoma.

The diagnostic accuracy with PET/CT-STRS is similar in pancreatic NETs (except insulinoma) with respect to other NETs, finding values in various meta-analyses of sensitivity of 86% to 100%, and specificity of 79% to 100%. It seems that precision may be lower in functioning variants such as gastrinoma[15,20].

Pancreatic NETs: insulinoma

The location of insulinoma can represent a diagnostic challenge, due to its small size (up to 40% < 1 cm in some series). The symptoms of hypoglycaemia can be severe and are not always easily controlled with medical treatment, although approximately 90-95% are of benign origin and are potentially curable if the tumour can be located.

Its small size hinders the sensitivity of conventional morphological images (CT 55%, MRI 61% and US 21%), which is why the use of functional imaging techniques is necessary. However, there is no clear diagnostic protocol, and precision values are relatively low in all techniques.

Molecular imaging with [^{111}In]In-pentetreotide with SPECT/CT has not been successful, obtaining detection rates of 33-60%, probably due to little or no expression of STTR type 2. PET/CT imaging-STRS are contradictory, with very variable data (32-90%).

PET/CT-[^{18}F]F-DOPA, likewise, has a relatively low sensitivity (25-50%) for detecting insulinomas.

Based on the few case series, it seems that premedication with carbidopa, a peripheral aromatic amino acid decarboxylase inhibitor (100-200 mg 1 hour before injection) would achieve a low residual activity in the pancreatic parenchyma, preserving the activity tumour in more than 70% of patients and, therefore, achieving an increase in diagnostic sensitivity[21]. The decrease in peripheral decarboxylation of [^{18}F]FDOPA causes a decreased renal clearance of the radiotracer, which increases its availability and absorption by target tissues. However, more studies are necessary to clarify the need for premedication with carbidopa[22].

Furthermore, the usefulness of an early abdominal image at 5 minutes post-injection and subsequently a full body image at 30 minutes is proposed.

The use of agonists of the GLP1 receptor (GLP1R) overexpressed by insulinomas seems promising (^{68}Ga DOTA exendin-4, ^{111}In-DTPA-exendin-4), with sensitivities of 95-100%.

Pancreatic NETs: gastrinoma

Patients with Zollinger-Ellison syndrome show symptoms caused by excessive secretion of gastric acid and can be well controlled medically (proton pump inhibitors or H2 antagonists).

Gastrinomas, as with insulinomas, are difficult to locate. The lesions are usually small in size (<1 cm), and are located mainly in the duodenum.

They are malignant in 60-90% of cases and frequently metastasize to adjacent lymph nodes, liver and, less frequently, bone, which makes extension study from the initial stages essential.

Radiological imaging studies detect a minority of small duodenal gastrinomas, while they are able to visualize a large proportion of pancreatic gastrinomas, which are generally larger.

PET/CT-STRS is currently the most sensitive technique for staging patients with Zollinger-Ellison syndrome; however, it can miss a significant number of small duodenal gastrinomas, achieving good detection of adjacent lymph nodes and metastatic disease. Given the difficulty of imaging techniques in locating small gastrinomas at the duodenal level, surgical exploration plays an important role in their diagnosis[21].

PET/CT-STRS in lung neuroendocrine tumors

Neuroendocrine neoplasms of the lung encompass pulmonary NETs composed of typical carcinoids, atypical

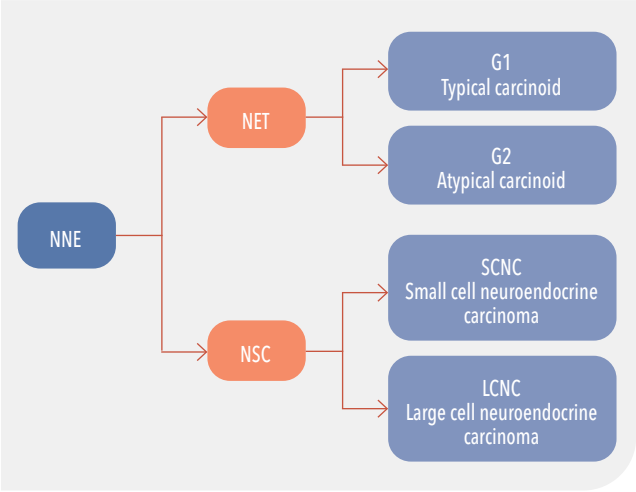

FIG. 4. Classification of bronchopulmonary NETs.

carcinoids, and NSCs, including large cell neuroendocrine carcinoma (LCNC) and small cell carcinoma (SCNC).

The term carcinoid resembles NET in GEP[23] variants.

Neuroendocrine neoplasms represent approximately 20% of primary lung tumours (SCNC: 15%, LCNP: 3% and carcinoids 2%, with an evident higher incidence of the typical variant).

The WHO criteria for differentiating typical from atypical carcinoid are based mainly on the mitotic count. However, this does not occur to differentiate carcinoid from carcinoma, where, although there are differences in mitotic criteria, they seem to be considered biologically different entities, as supported by recent molecular studies.

Although Ki-67 is a marker to differentiate grades in GEP-NETs, in pulmonary NETs the differentiation is based exclusively on the mitotic count[24].

Lung carcinoid tumours can be asymptomatic, depending on their location. Up to 90% of patients with central tumours develop nonspecific symptoms, while peripheral tumours are generally found incidentally. The most common symptoms are: cough, wheezing, dyspnoea, stridor or post-obstructive pneumonia.

Approximately 40% of cases can be detected incidentally on a chest x-ray, but currently the gold standard is CT with VSD and multiphase CT in the arterial and portal phases for the detection of metastases. For liver metastatic disease, MRI[25] should be used.

Like the rest of NETs in other locations, the majority of pulmonary NETs express STRS, mainly the subtype 2. PET/CT-STRS is a tool for the evaluation of NETs with a sensitivity of 100% for typical carcinoid and 83% for atypical carcinoid. In pulmonary pathology, the superiority of PET imaging over SPECT is also demonstrated and should be replaced whenever possible.

PET/CT-FDG is the technique of choice for SCNC and LCNP with greater proliferative activity. Its usefulness has also been explored in typical and atypical carcinoids, which also correlates with cell proliferation. In heterogeneous disease, both PET radiopharmaceutical can be combined.

Following a collaboration between CommNET and NANETS, the ENETS statements were modified, confirming the role of PET/CT-STRS in the detection of metastatic disease, but with limited usefulness for the diagnosis of small primary lung lesions, without evidence of metastatic disease on imaging anatomical.

Furthermore, they added the importance of having a positive PET/CT-STRS for the selection of patient's candidates for TRPR[25-29].

TABLE 3. 2015 WHO classification[28]

TNE classification pulmonary	Morphology	Citology	Mitosis
Typical carcinoid	Carcinoid	–	< 2
Atypical carcinoid	Carcinoid	–	2-10
Large cell NSC	Neuroendocrine	Large cell (> 20 µm)	> 10 (± 70)
Small cell carcinoma	Neuroendocrine	Small cell (<20 µm)	> 10 (± 80)

TABLE 4. KRENNING SCORE

Krenning Score	Catchment	STRS-RADS	Findings
0	Absence	1	Benign lesion by biopsy or imaging
1	Very low	2	White parts or bone lesion atypical for metastatic NET
2	Slightly less than or equal to hepatic	3	Doubtful malignant lesion in soft tissues or bone
3	Greater than the liver	4	Intense uptake in a typical location of NET without findings on conventional imaging
4	Greater than the splenic	5	Intense uptake in a typical location of NET with findings on conventional imaging

PET STRS-teragnosis

A necessary condition for TRPR is confirmation of high STRS expression on the tumour surface, demonstrated in functional imaging studies.

To characterize the intensity of uptake, both in SPECT/CT and PET/CT scintigraphic studies, it is common to use of the qualitative scale (Krenning), with numerical values of 0-4, in relation to hepatic and splenic activity.

The scale was initially developed for planar STRS scintigraphy studies and was subsequently validated for PET/CT-STRS.

A structured reporting system has been proposed, called STRS Reporting and Data System (STRS-RADS)[30], which is applied in NET theragnosis and which integrates the Krenning scale with diameter, tumour extension, and findings after biopsy. This system aims to optimize the selection of TRPR candidates. Patients with a Krenning scale greater than or equal to 3 and STRS-RADS greater than or equal to 4 are candidates for PRRT[31].

The main prognostic factor for PRRT is the heterogeneity of STRS expression between lesions; however, at the present time there are no clear predictors of response to it.

Clinical evidence suggests that lesions that show a mismatch between PET/CT-STRS PET/CT-FDG will progress throughout the history of the disease, at the expense of the more aggressive undifferentiated lesions, positive in PET- FDG, so there is no clear consensus on whether PRRT should be performed.

Therefore, in the evaluation prior to PRRT treatment (in high-grade G2 and G3 NETs), the combination of high FDG avidity and lack of avidity in PET/CT-STRS indicates that it is a high-grade NET more aggressive, not a candidate for PRRT and with a worse prognosis. On the contrary, a PET/CT-STRS with activity in all lesions, but without glucose craving, probably corresponds to a low-grade disease, with a more indolent course, a candidate for TRPR and a better prognosis.

In 2016, a grading scale was published that described, in a single value, the combination of PET/CT-FDG and PET/CT-STRS, which was called NETPET. A categorical scale of 0-5 was used, based on the uptake activity in both studies, which could vary from P1 (STRS+ and FDG–) to P5 (STRS– and FDG+). According to the results of this scale and in subsequent studies that support the process, it has been shown that the discordance between images and the results of the dual image (STRS and FDG) are more accurate as a prognostic factor than the European classification, the differentiation cellular and immunohistochemistry[32].

The Pauwels working group performed a post-hoc analysis on the usefulness of tumour uptake and volumetric parameters (pretherapeutic and early intermediate, at 7 weeks) in PET/CT-STRS for TRPR (^{90}Y-DOTATOC) in the setting of a prospective phase II trial. Response was analyzed by CT using RECIST 1.1.

The median PFS and OS were 13.9 and 22.3 months, respectively. In baseline PET/CT-STRS a higher mean SUV a 13.7 (75th percentile) was associated with longer OS, while a [^{68}Ga]Ga-DOTATOC metabolic tumour volume greater than 578 cm^3 (75th percentile) was associated with lower OS. These associations were not found with PFS. They conclude, therefore, that high tumour uptake of [^{68}Ga]Ga-DOTATOC predicts a better outcome in patients with NETs treated with TRPR; however, a high tumour metabolic volume (TMV) worsens the prognosis, and these factors can be considered for the personalization of treatment[33].

Opalinska performed PET/CT-STRS in a group of patients before and after TRPR and analyzed the SUVmax and mean values of 76 lesions. The results were correlated with the clinical outcome stratified as progression, stable disease or partial response. The mean follow-up period was 19.9 months.

Among patients with partial response, the mean decrease in SUVmax was 66.3%, with stable disease 30.3%, and with progressive disease the mean increase in SUVmax was 9.1%. They concluded, therefore, that the decrease in SUVmax in the lesions predicts a better response and lower risk of progression after PRRT and may constitute an additional and independent parameter for estimating the overall risk of disease progression[34].

Indications for PET/CT-STRS

PET/CT-STRS has demonstrated significant improvement over conventional STRS imaging and should preferably be used for NET imaging whenever possible. PET/CT-STRS is recommended as the first option for the diagnosis of all NETs, with the exception of adrenal pheochromocytoma, medullary thyroid carcinoma, benign insulinoma, neuroblastoma and abdominal paraganglioma (PGL) (all characterized by variable expression of STRS[35].

Appropriate use criteria (AUC) for PET/CT-STRS for NETs were published in January 2018 to help referring physicians in the appropriate use of this technique.

Representatives of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the American College of

Radiology (ACR), the American Society of Clinical Oncology (ASCO), the North American Neuroendocrine Tumor Society (NANETS), the European Association of Nuclear Medicine (EANM), the Endocrine Society, the Society of Surgical Oncology, the National Comprehensive Cancer Network (NCCN), the American College of Physicians (ACP), the American Gastroenterological Association (AGA), and the World Conference on Interventional Oncology (WCIO) They met to develop the following AUC.

The indications were evaluated in well-differentiated NETs and 12 clinical scenarios were defined for the use of the test.

Information on the role of PET/CT-STRS in G3 NETs and CNE and other subtypes of NETs such as paraganglioma and pheochromocytoma is scarce. There is little data available on its use in the paediatric population.

Of the twelve clinical scenarios evaluated, nine were rated as appropriate:

- *Scenario 1*: Initial staging after histological diagnosis of NET. The systematic review clearly demonstrated the superiority of PET/CT-STRS over conventional morphological imaging and STRS scintigraphy. The type (degree and location) and size of the NETs must be taken into account in order to optimize resources.
- *Scenario 2:* Location of the primary tumour in patients with known metastatic disease, but unknown primary. Up to 20% of patients with metastatic NETs have unknown primary tumours at initial staging. The location of the primary tumour is important, as treatment options vary depending on the origin of the tumour. In a prospective study, the primary tumour was found in 38% of patients who underwent PET/CT-STRS imaging.
- *Scenario 3:* Selection of patients for PRRT directed at STRS. PRRT is becoming an important component of the NET therapeutic algorithm and requires a positive STRS image prior to its administration. Virtually all TRPR trials have required STRS imaging (PET or scintigraphy) as an eligibility criterion. Furthermore, PET/CT-STRS uptake may be predictive of therapeutic response to PRRT.
- *Scenario 4:* Staging of NET before surgery. PET/CT-STRS should be used to guide surgical planning and rule out extensive extra-abdominal disease before undergoing hepatic cytoreduction procedures.
  Numerous series report on the usefulness of hepatic cytoreduction in NET metastases without curative purposes, but with improved survival, therefore, the presence of extrahepatic disease is not necessarily an absolute contraindication to surgery.
  With the increase in functional information due to PET/CT-STRS, more precise and extensive staging is being achieved, without achieving a clear consensus on how to manage patients with more extensive disease from a surgical point of view. Surgery may be justified with predominant liver disease or at least abdominal lymph node disease. In cases of bone, mediastinal or cervical metastases, the benefits of hepatic cytoreduction are less clear, especially in those patients with deteriorated functional status and high-grade tumours.
- *Scenario 5:* Evaluation of mass suggestive of NET no amenable to endoscopic or percutaneous biopsy. PET/CT-STRS shows great usefulness to demonstrate the presence of STRS in a non-invasive way, when the biopsy is not easily obtained, either due to technical limitations such as lack of access or greater risk of invasive biopsy (injury). hypervascular, next great vessels). In addition, another lesion could be located that is susceptible to biopsy.
- *Scenario 6:* Monitoring of NETs studied predominantly with PET/CT-STRS. In cases where the disease is not reliably visualized on conventional imaging (particularly in metastatic bone disease), PET/CT-STRS can be used for routine imaging and follow-up.
- *Scenario 7:* Evaluation of patients with biochemical evidence and symptoms of NET without evidence of this on conventional imaging and without prior histological diagnosis. Although diagnosis is unlikely in this situation, it is important to locate a positive result. Likewise, a negative result can be important to complete diagnostic tests and therefore have greater profitability.
- *Scenario 8:* Restaging at the time of clinical or analytical progression without progression on conventional imaging. PET/CT-STRS allows better evaluation of the disease than conventional imaging, and therefore in the face of clinical or biochemical progression, the location of tumour tissue is important to select the appropriate therapy.
- *Scenario 9:* New lesion on conventional morphological imaging and doubtful progression. The presence of STRS is an important finding to demonstrate the existence of a NET in a lesion demonstrated by conventional imaging and also to assess whether it represents progression or recurrence. On the other hand, it is possible that NETs dedifferentiate, changing from well-differentiated to poorly differentiated NETs over time, and PET/CT-STRS is an indirect indicator of tumour grade.

There are three other scenarios in which the use of PET/CT-STRS could be appropriate, but in which there was disagreement among the experts.

summary

- *Scenario 10*: Restaging in patients with NET in the initial follow-up after resection with curative intent. This indication could lead to excessive use of the technique in patients without theoretical evidence of disease. Furthermore, it does not condition a change in the impact of the treatment, because the visualization of small-volume residual disease is unlikely to change management. It was suggested that it would be more appropriate to wait for biochemical recurrence or radiological recurrence before the PET/CT-STRS study.
- *Scenario 11:* Selection of patients with NETs that do not work for treatment with somatostatin analogues. Although it is very likely that STRS expression correlates with the benefit of somatostatin administration (SSA), it has not been definitively proven in clinical trials. The CLARINET trial, which demonstrated the antiproliferative activity of lanreotide in GEP NETs, required evidence of STRS expression with ^{111}In-pentetreotide. The PROMID study, which evaluated octreotide in midgut NETs, did not require evidence of STRS expression; However, only 12% of patients had negative imaging results with [^{111}In]In-pentetreotide. The benign profile of SSA does not make evidence of STRS necessary for its application. Furthermore, in symptomatic patients, SSAs are started independently of the STRS image.
- *Scenario 12:* Monitoring of patients with NETs seen both on conventional imaging such as PET/CT-STRS with active disease, but without evidence of clinical progression. If conventional imaging detects metastatic disease, PET/CT-STRS should not be used for routine imaging. Intermittent PET/CT images can be performed every 2-3 years to assess progression, if conventional imaging remains stable, but not as routine monitoring[36].

At the European level, EANM Focus 3, published in 2021, in collaboration with ENETS, describes various

Utility of PET/CT-STRS in the management of NETs

Clinical suspicion

- PET/CT-STRS and CT-VIC can be performed in cases of suspected NET; This scenario is not clearly contemplated in clinical guidelines, although a careful clinical judgment of the pretest probability of disease must be made using symptoms and biochemical markers. A positive expression of STRS is not per se diagnostic of NETs, since infectious/inflammatory processes and some non-neuroendocrine tumours can express STRS physiologically.

Diagnosis/staging

- PET/CT-STRS is useful in the staging of NETs as a complement to conventional imaging. In addition to STRS imaging, CT and/or MRI are considered necessary in all patients in initial staging.
- PET/CT-STRS is the preferred technique for patients with NET and metastatic disease, but location of unknown primary.
- PET/CT-FDG is recommended in patients with G2 (high grade), G3 and CNE NETs and for those with any of the lesions on CT/MRI that are negative on PET/CT-STRS.

Follow-up

- Follow-up can be performed using CT-VIC and/or MRI.
- In case of clinical or laboratory progression, the first-choice imaging test proposed in NETs with positive STRS expression is PET/CT-STRS plus CT and/or MRI.
- The detection of a new lesion by PET/CT-STRS, associated with a CT that demonstrates stable disease, was considered a sufficient finding to define progression, when clinical and laboratory findings are also suggestive of progression.
- PET/TC-FDG is considered useful in some selected patients based on grade (particularly for G2, G3, and CNE NETs) on conventional imaging, e.g., CT/MRI that did not show STRS expression at staging.

Restaging

- PET/CT-STRS is considered necessary in restaging after potentially curative surgery, but limited to patients with significant clinical risk of residual disease or development of metastatic disease, as a complement to conventional imaging.
- PET/CT-STRS is considered necessary in restaging after non-curative surgery in all patients as a complement to conventional imaging.
- PET/CT-FDG was considered necessary in restaging in a minority of selected patients, if it was considered positive at the beginning of the study or in patients with rapid progression (< 6 months) of the disease despite having been considered the disease low grade initial.

Pretreatment

- PET/CT-STRS is required before initiation of PRRT in patients with unresectable or disseminated NET to confirm the expression of target receptors.
- FDG-PET/CT should be performed in patients with unresectable or disseminated NET, candidates for PRRT, in patients with G2 and G3 NET, complementary to STRS images, to exclude patients with non-matching lesions (FDG predominance + and STTR –) and as a prognostic factor. The evidence suggests that lesions with mismatch between FDG and STRS can progress at the expense of the dedifferentiated component after PRRT treatment in the natural history of NETs in G2 and G3, as well as in a minority of G1.

consensuses. Currently, between clinical guidelines and expert consensus, we can reach these conclusions on the usefulness of functional imaging in the management of NETs.

THE PATH TOWARDS THERAPY WITH RADIONUCLIDES DIRECTED AT PEPTIDE RECEPTORS

Historically, the treatment of NETs was limited to chemotherapy, radiotherapy and surgery, obtaining considerably improved results in the follow-up of the patients.

Octreotide was one of the first therapeutic agents used in the management of TNE-GEP and continues to be a fundamental pillar at the present time. Different studies have shown that patients with GEP-NET treated with octreotide show resolution or, at least, improvement of the most common symptoms such as diarrhea and flushing. Furthermore, in a high percentage of patients, biochemical responses are observed due to inhibition of hormonal hypersecretion.

In response to the results observed in the PROMID study, the National Comprehensive Cancer Network (NCCN) updated the recommendations for octreotide LAR, highlighting it as an option for the management of recurrent or unresectable metastatic NETs, regardless of functional status, symptoms, and progression status[5].

Although octreotide rapidly and effectively improves symptoms in patients with carcinoid syndrome, the effective duration of treatment varies due to the development of escape responses. Although the mechanisms underlying this effect remain unclear, it has been suggested that it may be related to a loss of sensitivity due to the growth of a clone of SST2-poor tumour cells.

^{123}I-octreotide

In the 1980s, it was discovered that multiple binding sites existed in NETs, with a high affinity for somatostatin and, therefore, for octreotide. This opened the possibility of scintigraphically localizing NETs using a radiolabeled SST derivative. They were Lamberts *et al.* who in 1989 showed for the first time the visualization of neuroendocrine tumour lesions using a gamma camera[37].

Octreotide cannot be easily labelled with a gamma-emitting radionuclide, so another synthetic analogue of STT (Tyr-3-octreotide) was generated in which phenylalanine has been replaced by tyrosine, allowing radioiodination of the molecule (Reubi *et al.*). This composition was successfully used as ^{123}I, a useful radioligand in the study of lesions with the presence of STRS[37].

Since its application to obtain scintigraphic images, multiple methodological changes were made, although it was observed in different studies that, after intravenous administration of the radiopharmaceutical, ^{123}I-Tyr-3-octreotide presented a rapid washout of the blood circulation, showing an approximate time of 2 minutes to reach 50% of maximum radioactivity in the bloodstream.

^{111}In-octreotide e ^{90}Y-octreotide

^{111}In-DTPA-octreotide shows less hepatic accumulation and is excreted mainly through the kidneys (elimination of 90% of the dose 24 hours after injection), therefore, the interpretation of the abdominal scintigraphic image is less artifacted by intestinal activity.

A wide variety of clinical studies, as well as abundant documentation on ^{111}In-DTPA-octreotide, have demonstrated the effectiveness of this radiopharmaceutical in the diagnosis and staging of NETs and metastatic lesions. It is capable of binding with high affinity to SST2 and SST5 receptors, moderate affinity to SST3 receptors and does not bind to SST1 and SST4 receptors.

In 1992, another octreotide analogue, ^{111}In-DOTA-DPhe1-Tyr3-octreotide, was created, the purpose of which was to create a ligand that could be stably labelled for therapeutic purposes. ^{111}In was not the ideal isotope to carry out NET treatments due to its short range of tissue penetration. Therefore, in 1996 another SST analogue was developed that will show more favourable results. This was ^{90}Y-DOTA^{0}-Tyr3-octreotide. The ^{90}Y is a pure β-emitter with a maximum energy of 2.3 MeV, a maximum range of 12 mm, and a half-life of 64 hours. This targeted form of systemic radiotherapy allows targeted delivery of radionuclides directly against tumour cells.

Later, in 1998, a study was published comparing DOTA^{0}-Tyr3-octreotide with DOTA^{0}-Tyr3-octreotate (in which the C-terminal threoninol is replaced with threonine), showing improved tissue binding. with overexpression of SST[38] receptors. Furthermore, DOTA^{0}-Tyr3-octreotate labelled with the radionuclide lutetium-177 (^{177}Lu) was found to have great impact on tumour tissue regression as well as survival.

On the other hand, that same year, octreoscan was also compared with gallium-67 (^{67}Ga) (^{67}Ga-DOTA-Tyr3-octreotide) in a preliminary study. The usefulness of this was seen when acquiring PET/CT images, since it demonstrates

better visualization of the NETs due to the improvement in the affinity of ^{67}Ga to the SST2 and SST5 receptors, greater resolution of the lesions, in addition to quantify the disease with SST analogues labelled with ^{68}Ga[39].

As a result of the results obtained in the aforementioned studies, and in view of the advantages they provided SST analogues in this type of tumours, it was decided to study patients with positivity for SST receptors with DOTA^{0}-Tyr3-octreotate using ^{177}Lu as the isotope.

Lutetium-177 (^{177}Lu) is a beta (0.497 MeV) and gamma (0.208 MeV) emitting radionuclide that allows imaging, as well as providing therapeutic options, with a maximum penetration range of 2 mm and a half-life of 160 hours (6.7 days). This is favourable for the treatment of small lesions, where isotopes such as ^{90}Y will lose a large part of their radiation dose in the surrounding tissues, while ^{177}Lu will have greater penetration into the tumour tissue.

In this way, some lines of research were launched, which studied different aspects of metabolic therapy with SST analogues and which are, today, the studies thanks to which treatment with ^{177}Lu-oxodotreotide (Lutathera®) is currently approved).

The most relevant studies are:

ERASMUS MC study (2008)[40]: single-center, open-label, phase I/II, non-comparative study, which included patients with histologically confirmed GEP-NETs or bronchial carcinoid tumours who presented uptake demonstrated in the study of SST receptors (of at least similar intensity to normal hepatic uptake on planar scintigraphy with ^{111}In-pentetreotide in the previous 6 months). The objective was to evaluate the toxicity, efficacy and survival of the included sample.

Life expectancy had to be at least 12 weeks. Patients with: brain metastases (unless they had been previously treated and stabilized), candidates for surgery with curative intent, patients who had undergone systemic treatment with short-term octreotide without tolerance to interruption treatment greater than 12 hours and in the case of octreotide and greater than 6 weeks in octreotide LAR were excluded. Patients who underwent surgery, radiotherapy, chemotherapy or other investigational treatment in the 3 months prior to receiving the radiopharmaceutical were also excluded.

A total of 1214 patients were included who received a maximum of four doses of 7400 MBq of ^{177}Lu-oxodotreotide with an interval of 8 weeks each, together with an amino acid solution.

The selected dosage was based on estimates to restrict the maximum radiation dose to the bone marrow as 2 Gy and 23 Gy to the kidney.

51% of patients presented disease progression (clinically or radiologically), 52% received octreotide LAR concomitant with treatment with ^{177}Lu-oxodotreotide.

The PFS was 30.3 months (median) in pancreatic tumours (n = 133), 28.5 months in midgut (n = 183), and 29.4 months in hindgut (n = 13).

NETTER-1 study[41,42]: multicenter, randomized, stratified, open-label, controlled, parallel-group trial comparing ^{177}Lu-oxodotreotide (a total of four injected infusions of 7400 MBq with each infusion separated by 8 weeks and co-administered with amino acid solution) with high doses of octreotide extended-release (octreotide LAR) (60 mg every 4 weeks intramuscularly). It was planned to include adults with histologically confirmed grade 1 and 2 GEP-NETs, located in the midgut, well-differentiated coma, unresectable, metastatic or locally advanced and with demonstrated radiological progression in the previous 36 months (according to RECIST 1.1 criteria) who had received 20 or 30 mg of octreotide LAR every 3-4 weeks for at least 12 weeks before randomization. In addition, they had to present at least one lesion on CT or MRI, and in all of them the presence of SST receptors had to be previously confirmed by planar scintigraphy with indium (^{111}In) pentetreotide.

Progression-free survival (PFS) for 76 weeks after starting ^{177}Lu-oxodotreotide was the primary endpoint of the study. Secondary endpoints include: objective response rate, OS, time to tumour progression and duration of response and quality of life.

A total of 231 patients were randomized into two groups: the group administered ^{177}Lu-oxodotreotide (n = 117) and the group administered octreotide LAR (n = 114).

The primary tumour, diagnosed 46 months earlier (median), was most frequently located in the ileum (n = 86), although there were cases in the jejunum, appendix, proximal colon, and other organs. All had metastases diagnosed 43 months previously (median) in different locations, except in the brain: liver (85%) and lymphatic (66%), mostly.

Time to first progression from diagnosis initial period was 20 months (median), the most had undergone prior surgery at least 3 years previously.

After analyzing the results, a significant improvement in PFS of 19.9 months was observed (28.4 months for ^{177}Lu-oxodotreotide and 8.5 months for octreotide).

The percentage of patients who died or had disease progression at 76 weeks was almost 3 times lower (25.6%

in patients with ^{177}Lu-oxodotreotide and 68.4% in patients with octreotide) associated with a 79% reduction. in the risk of progression or death.

The OS showed a trend in favour of ^{177}Lu-oxodotreotide, with a reduction in the risk of progression or death of 54% and 46%, respectively.

The objective response rate and time free from tumor progression were higher in the group that received ^{177}Lu-oxodotreotide, as was the duration of response.

The phase I and II studies, the cohort studies and, above all, the NETTER-1 study, yielded very relevant results that caused scientific societies to incorporate ^{177}Lu-DOTA-TATE as the first radiopharmaceutical for peptide receptor radionuclide therapy (PRRT) in NETs in their clinical guidelines. It was approved in September 2017 in Europe by the European Medicines Agency (EMA) and in January 2018 by the FDA[43].

Current clinical trials

Different lines of research are currently open (NETTER-2, COMPETE, COMPOSE), which include inclusion criteria different from those contemplated in previous studies such as high-grade NET (G3) and other locations (pancreatic).

INDICATIONS OF THERAPY WITH RADIONUCLIDES DIRECTED AT PEPTIDE RECEPTORS

The heterogeneous spectrum of NETs, added to their relative low incidence, requires an approach from a multidisciplinary committee that provides optimal and comprehensive management of their pathology. Treatment with radionuclides in the form of PRRT, and specifically: ^{177}Lu-oxodotreotide, which is currently approved, must arise from a consensus decision by said committee. This committee must be made up of medical professionals from the different specialties involved in the diagnosis and treatment of the patient (pathological anatomy, general surgery, digestive, endocrinology, nuclear medicine, oncology, and radiology), with a view to determining suitability as a candidate to receive this treatment (Fig. 5).

According to ENETS[44], as well as what was approved by the EMA in 2018 and the Spanish Medicines Agency, the main indication of ^{177}Lu-oxodotreotide, the only drug currently approved for PRRT, and in accordance with current scientific evidence (A) would be:

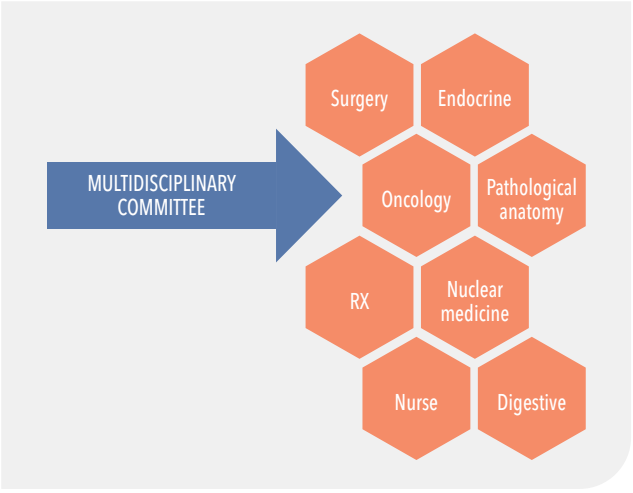

FIG. 5.

- GEP-NETs WHO grades 1 and 2 are locally advanced or metastatic, well differentiated[13,44-47] and the pathological expression of somatostatin receptors has been proven.

Other suitability criteria that the patient must meet are the following[47]:

- Adequate marrow reserve: hemoglobin >8g/dL, red blood cell count >3,000,000/µL, platelets >75,000/µL, leukocytes >3,000/µL.
- Glomerular filtration rate >50 mL/min. Patients on dialysis may be candidates for treatment, in coordination with the nephrology service.
- Adequate liver function: bilirubin <3 times the upper limit of normal, albumin >30 g/L, prothrombin time 1.5 times the limit of normal.
- Time elapsed since the administration of other therapies (chemotherapy and/or radiotherapy, interferon, mTOR inhibitors, antiangiogenics): 4-6 weeks.
- The patient must have a life expectancy of more than 6 months.
- Must be independent for basic activities of daily living, Karnofsky index >60 or ECOG <2).

All patients who are candidates for treatment with PRRT must have an imaging test that confirms the pathological presence of somatostatin receptors in the lesions, either through a somatostatin receptor scintigraphy (sensitivity: 62%, specificity: 99%) with SPECT-CT to increase the sensitivity of said test or directly with PET-CT for the detection of somatostatin receptors (PET/CT-STRS). The most used currently is ^{68}Ga (sensitivity 96% and specificity 97%)[13].

It is recommended that the imaging test does not exceed, on average, 3-6 months older than the treatment. Currently, the superiority of ^{68}Ga-STRS PET/CT over somatostatin receptor scintigraphy/SPECT-CT is recognized. However, your choice it will depend on the availability and opportunity to access each of them (*see diagnosis section*).

According to the results of the imaging tests, a patient is considered to be a good candidate for treatment with ^{177}Lu-oxodotreotide when he or she has a score on the Krening scale >4 (see the diagnosis section). In patients in whom there are doubts about the level of uptake (which indicates the pathological presence or not of STRS2 somatostatin receptors); It would be desirable to complement the imaging tests with a PET-CT/FDG, to determine the possible degree of dedifferentiation that the tumour presents. What was previously mentioned becomes especially important in patients with G3 tumour, or in G2, from a Ki-67% >5. Also, in patients with no or low uptake in ^{68}Ga-STRS PET/CT, regardless the degree they have, or patients with a G2 who, despite having a Ki-67% <5, present a rapid progression in a time period of less than 6 months[14].

Indication in neuroendocrine tumours of bronchopulmonary origin

Lung NETs or carcinoid tumours (typical and atypical) represent 1-2% of lung neoplasms. One third of all patients with lung carcinoid tumours, both typical and atypical, have distant metastases at the time of diagnosis and the median survival for these patients is approximately 24 months. Currently, there is only one FDA-approved therapy for patients with typical and atypical advanced pulmonary carcinoids, everolimus, indicating a clear need for more treatment options in this patient population[48,49].

Kanakis *et al.*[50] carried out a study (n = 119; typical cos: 100, atypical: 19), in which they reported the presence of the SST2-A receptor in 72% of the cases studied, being moderately higher in the case of typical carcinoid tumours (74%), over atypical (66%), rising to 82% in metastatic lesions.

Treatment with radionuclides would be indicated as a third line of treatment in tumours of bronchopulmonary origin, based on experience and other studies in series of significant size (Zidan *et al.* 2021, n = 48, and Brabender *et al.* 2017, n = 23)[41,51], in all of them with PFS over 20 months. This has demonstrated an adequate safety profile, as is the case of the study carried out by the Rotterdam group (ERASMUS)[41], with more than 1,200 patients treated with PRRT between the years 2000-2015; among them, 23 NETs of bronchial origin (PFS: 29 months and OS: 63 months).

Treatment with ^{177}Lu in some patients with grade 3 neuroendocrine tumours

The 2019 WHO classification for GEP-NETs already recognizes grade 3 tumours as an entity differentiated from CNE, given the better prognosis of the former, as well as the probability of expression of somatostatin receptors. This makes them a target for treatment with radionuclides such as PRRT-^{177}Lu-oxodotreotide.

Currently, and as is being done in multiple centers, treatment with ^{177}Lu is being administered in patients with NET-G3. The 2020 ESMO guidelines[16] report up to four retrospective studies, with 280 patients treated, all of them with Ki-67% >20%, and disease control rates between 30-80%, with PFS (9-23 months). The results were significantly better in patients with Ki-67% <55%. These results demonstrate that treatment with ^{177}Lu can be used in this type of patients safely and with acceptable results, after being carefully chosen, and pending prospective comparative studies that allow for greater scientific evidence than the current one.

Currently, clinical trials are being carried out that aim to cover this type of patients, among them the most notable:

- NETTER-2 (multicenter, randomized, open-label phase III study): its objective is to determine whether treatment with ^{177}Lu-oxodotreotide, in combination with long-acting octreotide, increases PFS in patients with GEP-NET with high proliferation rate (G2 and G3), when administered as first-line treatment compared to high-dose long-acting octreotide treatment (60 mg). Patients naïve to somatostatin analogues are eligible, as are patients previously treated with somatostatin analogues in the absence of progression.
- COMPOSE[52]: prospective, randomized, controlled, open-label, multicenter phase III study in patients with high-grade (G2 and G3) well-differentiated tumors (Ki-67 index 15-55%), STRS+, NET-GEP. This trial aims to evaluate the efficacy, safety and outcomes of ^{177}Lu-edotreotide compared to chemotherapy ([CAPTEM or FOLFOX]/everolimus, depending on the investigator's choice).

Indications for retreatment with radionuclide therapy directed at peptide receptors

In the case of tumour progression after a good initial response (clinical and/or radiological), retreatment with TRPR represents an alternative. In this sense, disease control rates of 70-85% have been reported, but with limited tumours response[53].

On the basis of multiple retrospective studies, as well as case series, we can conclude the efficacy and, more reliably, the safety of treatment with ^{177}Lu-oxodotreotide in patients who have already been treated and who have presented a clinical and/or radiological response, who have also had a PFS >12-18 months.

In these patients, the current trend is to give a shortened treatment, consisting of two treatment cycles with 177 Lu (7.4 GBq) spaced 8 weeks. Retrospective studies with a significant number of patients (n = 181), such as that published by the Dutch group of Van der Zwan *et al.*[48], report a significant level of safety with cumulative doses of up to 69 GBq (8 cycles), since within the cohort they include patients treated 1 and 2 times (with 2 cycles in each of them), with a disease control rate of 70% (partial response + stable disease, as best response) up to in 126 of the 181 patients included; without a significant increase in adverse effects. The total incidence of acute myeloid leukemia and myelodysplastic syndrome was 2.2%.

Similarly, Strosberg *et al.*[54] carried out a meta-analysis of 567 studies, with a total of 414 patients extracted from 13 studies, observing results similar to those of the other large series, with a good safety profile and level of reported adverse effects (hematological grades 3-4: myelodysplastic syndrome, acute myeloid leukemia: 0-1%), with a PFS >12 months (12.52 months) and a disease control rate around 71%.

Based on current evidence, and pending larger studies with a higher level of scientific evidence, the possibility of safe use of retreatment with ^{177}Lu-oxodotreotide in carefully selected patients who meet the eligibility criteria for retreatment: presence of clinical and/or radiological response with the first cycles of treatment, and a PFS >12 months, verifying that the patient continues to meet the suitability criteria (clinical, analytical and imaging) mentioned for the first cycle of treatments.

Treatment goals

Once the optimal patients have been selected to receive the treatment, the therapeutic objectives must be explained, emphasizing the results provided by the scientific evidence to date (phase III NETTER-1 clinical trial), where the fundamental thing is time free of progression (average of 28.4 months), when compared to the alternative (high-dose somatostatin analogues)[42], as well as the significant improvement in quality of life, as the most expected results of this technique. This study also reported a 79% reduction in the risk of progression or death compared to octreotide, and a higher overall response rate in the TRPR group (18%) compared to 3% in the control group[42].

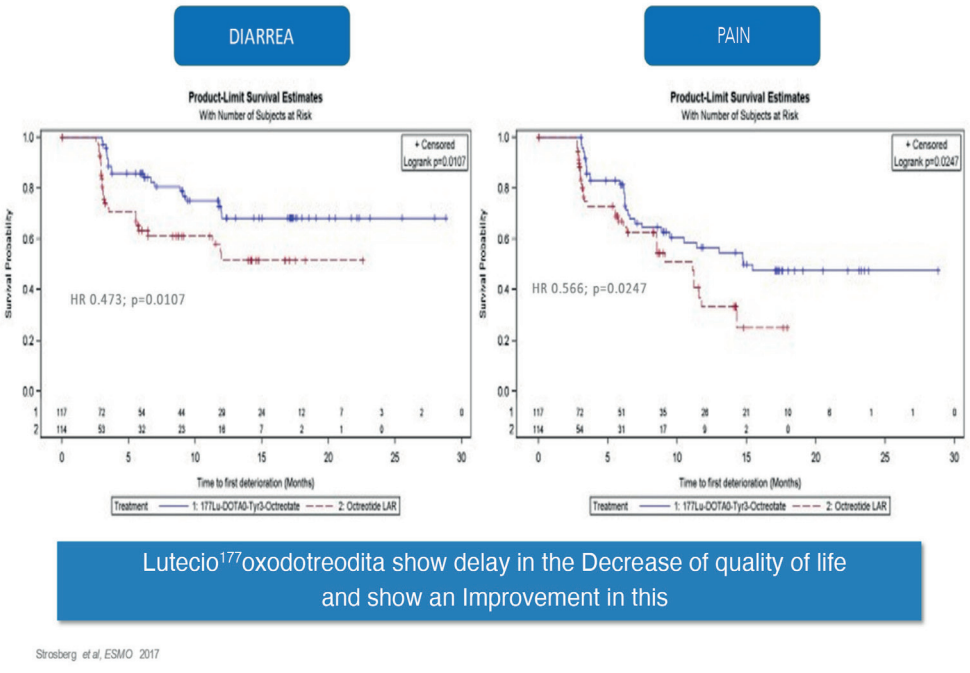

FIG. 6. Netter-1 study, impact of treatment with ^{177}Lu-Oxodotreotide on the patient's clinical and quality of life.

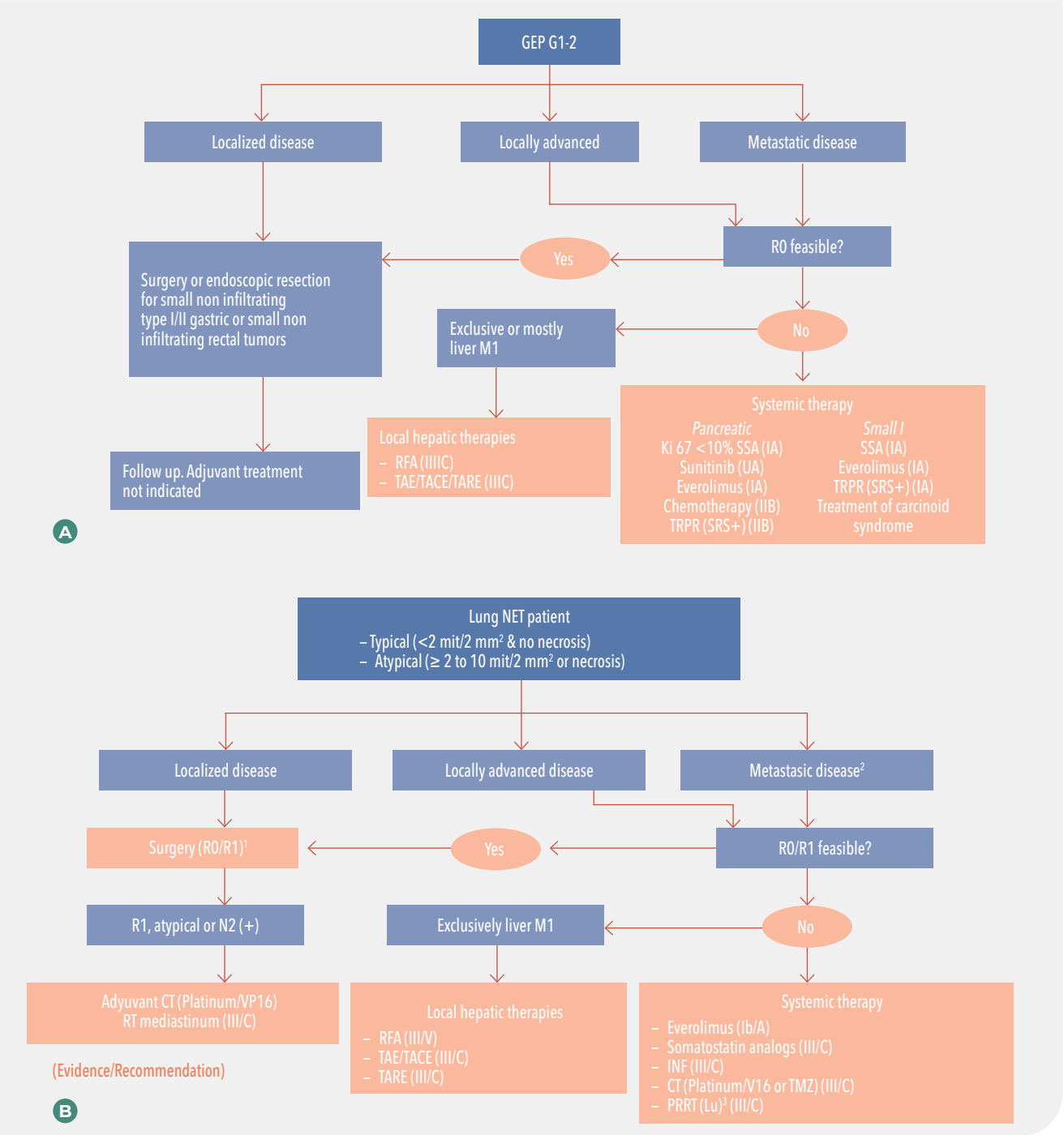

FIG. 7. SEOM clinical guidelines for the diagnosis and treatment of gastroenteropancreatic and bronchi neuroendrocrine neoplasms (NENs) (2018)[20]. [1] Consider somatostatine analogs (SA) therapy "presurgery" to avoid carcinoid syndrome. [2] Consider SA in all patients with functioning tumors (carcinoid syndrome). [3] Only in somatostatin positive tumors. A: algoritmo terapéutico para los NET GEP gi-2; B: algoritmo terapéutico para NET pulmonares típicos y atípicos. CT: chemotheraty; RT: radiotherapy; PRRT: Peptide Receptor Radionuclide Therapy.

In the final report of the phase III NETTER-I clinical trial, published in December 2021, it was concluded that there is an improvement in OS that may have clinical relevance (11.7 months) in the treatment arm with ^{177}Lu-oxodotreotide, although this did not reach a statistically significant difference with respect to the control group [20,55,56].

Contraindications to treatment with ^{177}Lu-oxodotreotide

Once the indications have been mentioned, it is important to determine the suitability of the patient, according to the contraindications of the technique[45-47]:

- Pregnancy or breastfeeding.
- Glomerular filtration rate: < 40 mL/min.
- Hemoglobin < 8 g/dL.
- Platelets < 75,000.
- Leukocytes < 2000.
- Bilirubin > 3 ULN (upper limit of normal).
- Albumin < 30 g/L.
- Prolonged prothrombin time.
- Severe congestive heart failure, New York Heart Association (NYHA) grade III-IV.

In addition to the aforementioned contraindication during pregnancy and lactation, patients of both sexes must be explained the need for contraception during the 6 months following the end of treatment. Genetic counselling is recommended at the end of treatment.

PRACTICAL ASPECTS OF THE TECHNIQUE

Nuclear medicine consultation

Once the multidisciplinary committee has decided that the patient is a candidate for treatment with PRRT-^{177}Lutetium, the patient will be scheduled for consultation at the nuclear medicine service within 15 days, preferably with an imaging test (PET-CT-STRS-^{68}Ga and/or scintigraphy with somatostatin receptors + SPECT-CT), no more than 3-6 months (prior to treatment), blood analysis with hemogram, kidney and liver function, ionogram and coagulation no more than 15 days.

Due to the general lack of knowledge of nuclear medicine techniques and treatments, it is necessary to explain in understandable and direct language what it consists of, with a view to reducing the anxiety that it can generate in the patient, as well as in their families. Any doubts that may arise must be resolved, making it clear what the possible side effects may be, as well as the real probability that they will occur. This consultation will also explain its exact indications, as well as the expectations that may be generated regarding it; it is important to make known that the main purpose of the treatment is to significantly improve the quality of life, as well as survival free of tumour progression, thus avoiding generating false expectations in the patient.

It should also be clear what the treatment administration logistics are:

- The treatment consists of 4 cycles.

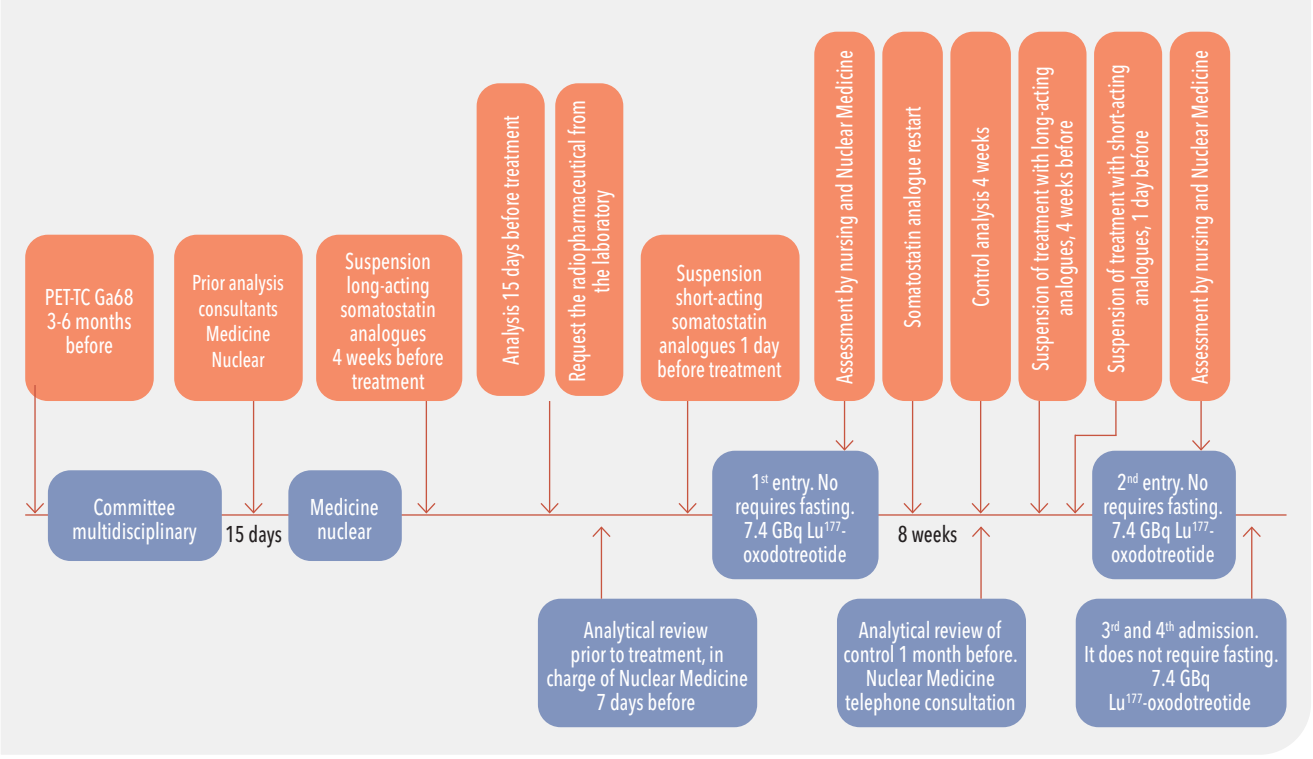

FIG.8. Schedule and treatment line.

summary

- They must be spaced a minimum of 8 weeks[42], which can be extended up to 16 weeks in case of toxicity after its administration.

The nuclear doctor will have the patient's clinical history, which must include: allergies, the treatments she is currently receiving, as well as the treatments already received specifically for their underlying pathology (chemotherapy or other systemic treatments), surgeries to which they have been subjected and anatomopathological results if they exist.

Once the initial part has passed, the administration date must be agreed (taking into account the times of each laboratory for the delivery of the drug, which on average can be around 14 days), it is suggested to adjust the times, by the type of treatment with somatostatin analogues that the patient is receiving. It is recommended that long-term medications be discontinued around 4 weeks before the administration of the radiopharmaceutical. With short-acting ones, 24 hours would be enough[45-47,57]. Currently, there is a tendency, in some particular cases—patients with extreme symptoms or those whose primary tumour originates in the small intestine—to consider not discontinuing the analogue, even providing a possible protective effect by maintaining it[58].

It is also important in this initial consultation, once what the treatment consists of, as well as its possible side effects and radioprotection measures, is explained to the patient, giving the patient the form corresponding to the informed consent, so that he and his surroundings have the possibility of reading and analyzing it with sufficient time at home; explaining the need to deliver it duly signed on the day of admission.

Prior preparation and entry

Given the physical characteristics of the radiopharmaceutical, and in accordance with current legislation in Spain, the patient may be treated on an outpatient basis, since within 6 hours his activity will have decreased by 50%, allowing 24 hours to pass. hours at a distance of one-meter acceptable exposure levels are present. It should be noted that said regulations may vary depending on the country or territory where the radiopharmaceutical is administered.

However, in many places it is decided to admit patients for a minimum of 24 hours for clinical reasons, since in this way adequate surveillance is maintained over the patient

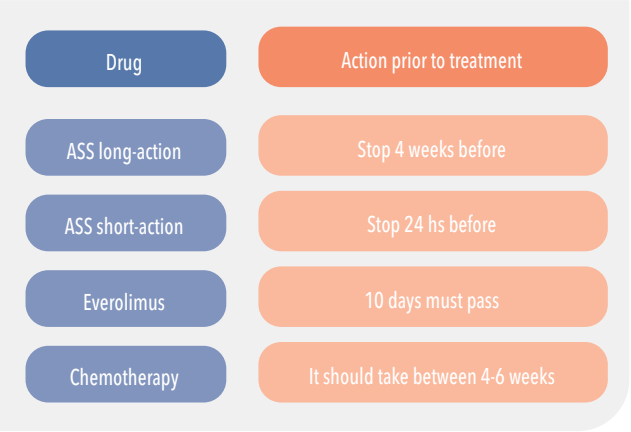

FIG. 9. Management of medication prior to treatment. SAA: somatostatin analogues.

and their vital signs, as well as on the appearance of possible side effects. The latter is important in certain patients with a high tumour burden, patients with a history of previous carcinoid crisis, or in those over 70 years of age. It is also recommended in patients who have some degree of heart failure and in those with blood pressure levels that are difficult to control.

The administration of the radiopharmaceutical must be carried out in a facility that meets the requirements required by the competent authority in the management of ionizing radiation in each country or territory. It is not strictly necessary that the administration of ^{177}Lu be carried out in a lead-lined room, since being negative beta particles they have a short range[45,59]. The toilet and the surrounding floor must be prepared with a coating to contain radiation from possible splashes of urine or other body secretions [45,47,60].

It is recommended to perform a blood test in the 15 days prior to the administration of the next treatment cycle, which must be reviewed by the nuclear medicine doctor before its administration (a review is recommended 8 days before, in case it is necessary to extend or suspend the treatment, with a view to being able to notify the supplying laboratory).

There is a wide debate regarding the use or not of corticosteroids (dexamethasone) as routine premedication before each cycle of ^{177}Lu-oxodotreotide, since, although it can help in the prevention of nausea, vomiting, post-treatment hormonal crises or possible inflammation and subsequent intestinal obstruction in patients with extensive peritoneal and mesenteric involvement[61], these drugs significantly reduce the presence of STRS2 receptors, with a subsequent decrease in the effectiveness of the treatment[25,26].

For these reasons, it is suggested to select the patient carefully. Selective administration of dexamethasone (4 mg i.v.) and selective 5-hydroxytryptamine 3 receptor antagonists may be considered in high-risk patients, in agreement with their treating physician.

In order to reduce the possibility of carcinoid crisis occurring, a bolus dose of 250-500 µg of octreotide can be administered subcutaneously 1 or 2 hours before the procedure[62].

On the day of admission, the patient can attend without fasting, and in some cases, it is even desirable that he or she have had breakfast, as is the case of patients with insulinomas or diabetic patients. Upon arrival at the hospital, the patient must be monitored with vital signs by nursing, and a blood glucose determination is optimal, especially in diabetic patients. In patients with potassium levels at the upper limits of normal, an electrocardiogram is suggested, due to the possibility of elevation of this ion with the administration of the amino acid solution. The nuclear medicine doctor must come to verify the general condition of the patient, and resolve any doubts that may arise prior to the administration of the medication.

The administration of ^{177}Lu-oxodotreotide must be carried out by health personnel accredited in the handling of radioactive substances by the corresponding competent authority in the management of ionizing radiation in accordance with the legislation in force in each country or territory[60].

Technical indications:

- If possible, two peripheral lines will be canalized, preferably in the antecubital fossa, ensuring a good caliber, to the extent that the patient's physical characteristics allow it. If it is not possible to have two venous accesses, a single line using a three-way stopcock would suffice.
- Administration of premedication, such as antiemetics (metoclopramide, ondansetron). It is key to ask the patient about the presence of nausea or not, as well as take into account any anxiety that may occur.
- The infusion of amino acids (lysine + arginine, see Amino Acids) should be started after the nursing review and medical visit; this infusion should last approximately 4-6 hours.
- 30 minutes after starting the infusion of amino acids (lysine + arginine), the infusion of ^{177}Lutetium-oxodotreotide can be started. This should be done in an approximate time of 30 minutes, its infusion should never be done as a bolus. It can be administered through an infusion pump or by a simple gravity drip system.

TABLE 5. Composition of the amino acid solution (60)

Compound	Amount
L-lisine HCl	25 g*
L-arginine HCl	25 g**
Sodium chloride 9 mg/ml (0.9%) solution for injection or water for injection	1 l

*Equivalent to 20.0 g of lysine. ** Equivalent to 20.7 g of arginine.

Composition of the compound amino acid solution[60]

The elimination of the radiopharmaceutical is primarily through the kidneys, so amino acids are administered as a measure of radioprotection of the kidneys and urinary tract, since their objective is to reduce the reabsorption of ^{177}Lutetium at the level of the proximal renal tubules[63].

The mixture of 2.5% lysine + 2.5% arginine is preferred because it significantly reduces the presence of nausea and vomiting compared to commercial preparations that they include more amino acids and, therefore, have a higher osmolarity[62]. Commercially available amino acid solutions should be used only if they have an osmolarity < 1050 mOsmol, since those with values greater than this are related to a large amount of emesis that is difficult to control[49].

Presentation and mechanism of action

^{177}Lutetium-oxodotreotide was approved for use in Spain since 2018. It is composed of a synthetic analogue of somatostatin that shows high affinity for STRS2 receptors, associated with ^{177}Lu and a chelator, which allows adhesion to tumour cells. NETs, which are characterized by a high expression of this type of receptors (STRS2).

This radiopharmaceutical is presented as a solution for infusion. Each vial contains 7.4 GBq at the infusion date and time, with a fixed activity of 370 MBq/mL at the calibration date and time. ^{177}lutetium is a radionuclide that decays to stable hafnium ^{177}through the emission of negative beta particles, with an average energy of approximately 0.13 MeV, with the most abundant emission being 0.497 MeV. The radioactive decay of ^{177}Lu and the consequent beta emission led to damage to the DNA chains, causing the death of the affected cell, with a maximum range in the tissues

Drug	Start time (minutes)	Infusion rate (ml/hour)	Duration
Antiemetic	• Start at minute 30 of the start of amino acid perfusion	–	–
Amino acid solution (lysine + arginine)	• Past 30 minutes of antiemetic, start infusion	• 200-500, depending on the volume*	• 4-5 hours
Lu^{177}-oxodotreotide with solution sodium chloride injection 9 mg/ml (0.9%)	• They must pass 10 days	• Till 400	• 30 ± 10 min

FIG. 10. Drugs and types of treatment. *Consider reducing volume in patients with CHF.

of 2.2 mm (average range of 0.67 mm), causing the death of tumour cells, with a limited effect on healthy neighbouring cells, giving an adequate safety profile for its use. ^{177}Lu also emits low-energy gamma radiation, 113 keV (6.2%) and 208 keV (11%), allowing the acquisition of scintigraphic + SPECT-CT images. This radionuclide has a half-life of 6.65 days[45,57,60].

Taking into account that the elimination of the radiopharmaceutical is mainly through the kidneys, patients should be recommended to urinate as many times as possible after administration of the radiopharmaceutical. They will be instructed to that they drink a large amount of water (one glass every hour) on the day of the infusion and the next day to facilitate its elimination. They will also be recommended to defecate every day and use laxatives, guaranteeing at least one defecation daily, if necessary. Urine and faeces will be disposed of in accordance with national regulations[60].

Discharge criteria

The patient may be discharged approximately 6 hours after the infusion of the radiopharmaceutical, as long as he or she meets tolerable exposure levels (< 20 µSv/h at 1 meter)[47].

One of the advantages offered by hospital admission for a period of 24 hours, in addition to those already mentioned of a clinical nature, they are of a logistical type, since it is possible to perform scintigraphic images before hospital discharge, avoiding a second visit by the patient to the hospital, and allowing better image quality by having less

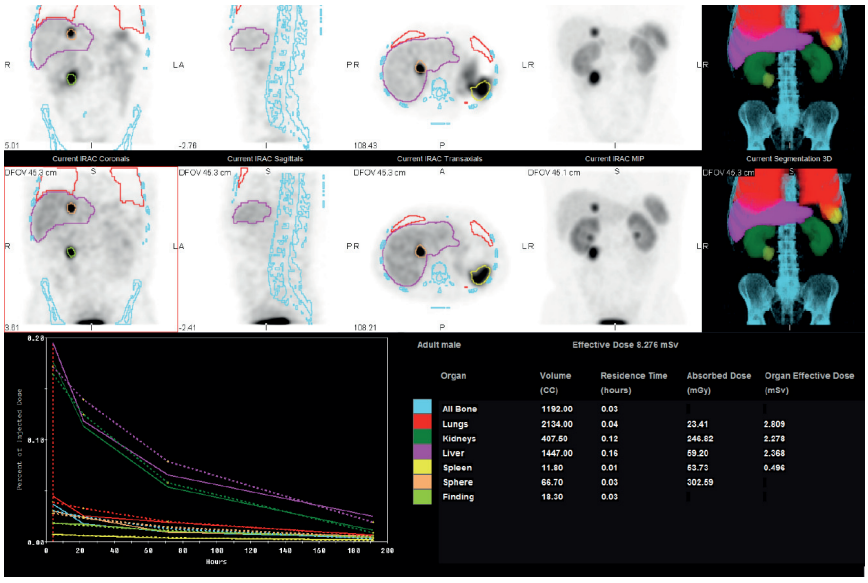

FIG. 11. Dosimetric study in a patient with NET of the pancreas and liver metastasis performed with Q.Thera Software (GE).

background noise. This image should preferably be accompanied by SPECT-CT in order to perform the respective dosimetry, in addition to checking the distribution of the radiopharmaceutical with respect to the diagnostic images available.

Dosimetry[60]

In the dosimetric evaluations carried out in clinical trials, the following conclusions were obtained regarding treatment with ^{177}Lu-oxodotreotide:

- The critical organ is the bone marrow. However, at the recommended cumulative dose of ^{177}Lu-oxodotreotide of 29.6 GBq (4 administrations of 7.4 GBq), in the phase I/II ERASMUS trial and the phase III NETTER-1 trial, no correlations were observed between haematological toxicity and the total activity administered or the dose absorbed in the bone marrow.
- The kidney is not a critical organ if an appropriate amino acid perfusion is administered concomitantly. In general, the results of the dosimetric analyzes carried out in the NETTER-142 and ERASMUS dosimetry substudy are concordant and indicate that the ^{177}Lu-oxodotreotide dosing regimen (4 administrations of 7.4 GBq) is safe.

Currently, according to the new regulations, studies are beginning to calculate absorbed doses to healthy organs, with software that has automatic contouring of organs at risk, as well as tumour volumes.

To obtain the activity-time curves it is necessary to have a post-treatment SPECT/CT image at different time-points. At present, this practice is not standardized, and the possibility of performing imaging is being evaluated genes at 6, 24 and 76 hours.

Care after hospital discharge

Before the patient is discharged, the nuclear medicine doctor will explain the radioprotection measures, in addition to the general precautions that must be followed in his daily activities after treatment. Close contact (less than one meter) with other people should be limited for 7 days following administration of the radiopharmaceutical. For children and/or pregnant women, close contact will be limited to less than 15 minutes daily. Patients should sleep in a separate room for 7 days after each administration of ^{177}Lu-oxodotreotide. In the case of children or pregnant women, it is advisable to increase the number of days to 15.

The patient should be explained that, once 24 hours have passed after the treatment infusion, they must restart their usual treatment with somatostatin analogues, and that they will continue to be monitored in the medical oncology consultations, pending the follow-up analysis (3-4 weeks) and the telephone consultation by nuclear medicine (fourth week post-treatment) for planning the next cycle.

Likewise, possible side effects and the measures to be taken in each case should be warned.

Response to certain situations in patients treated with ^{177}Lu

Extravasation

Although it is a rare situation, it can cause potentially serious injuries at the injection site, so once detected, the perfusion of the radiopharmaceutical must be immediately suspended, removing the administration route[47,59,63].

All equipment, including syringes and catheters, should be retained for measurement and documentation of residual activity. It can be helped with physical measures that facilitate vasodilation, such as warming the affected region, applying massages, and elevating the arm.

The perfusion of the radiopharmaceutical may continue through a new route, preferably in the contralateral arm. No other medication may be administered to the same side as the extravasation.

Urinary incontinence

In patients with urinary incontinence, hospital admission for 24 hours should be considered, in addition to considering the use of disposable diapers or bladder catheterization as an alternative. Both diapers and collected urine must be treated as radioactive waste[47,60].

Hemodialysis patients

Patients on hemodialysis are not excluded from receiving treatment with ^{177}Lutetium-oxodotreotide, which must be coordinated with the nephrology service to perform hemodialysis at the end of treatment.

Patients with heart failure

It should be remembered that in patients with severe heart failure (NYHA grade III and IV) treatment with ^{177}Lu-oxodotreotide is contraindicated. However, in patients with mild heart failure who are going to receive treatment, it is advisable to reduce the amount of volume to be perfused with the amino acid solution.

Hyperkalemia

Hyperkalemia is the most common biochemical alteration in patients treated with ^{177}Lu-oxodotreotide[61]. In patients with high potassium levels, or those close to the upper limit of normality before treatment, it is advisable to perform an electrocardiogram before starting the amino acid infusion.

Breastfeeding

It is currently unknown whether ^{177}Lu-oxodotreotide is excreted in breast milk. The absence of risk for the infant cannot be reliably excluded. Breastfeeding will be avoided during treatment. Breastfeeding should be interrupted if treatment with ^{177}Lu-oxodotreotide is necessary during the breastfeeding period, in addition to maintaining the necessary radioprotection measures mentioned in the previously described post-natal care section[60].

Acute side effects

Commons

Among the most common side effects is the presence of nausea and possible vomiting, which have a multifactorial origin, and which may be related to the infusion of amino acids, as well as the burden of anxiety and nervousness that the patient may present. Therefore, the routine application of antiemetics is recommended before starting amino acids.

Hyperkalemia

Due to the clinical implications of this hydroelectrolyte alteration, it is necessary to determine the levels of this ion in the previous analysis, since it can compromise the hydroelectrolyte balance with important alterations at the renal and cardiac levels.

With the infusion of the amino acid preparation (arginine and lysine) a transient increase in serum potassium levels may occur, which usually return to normal within 24 hours after starting the amino acid infusion. Hyperkalemia should be corrected before starting the infusion. In case of pre-existing clinically significant hyperkalemia, a second check should be performed before the infusion of the amino acid solution to confirm that the hyperkalemia has been satisfactorily corrected. The patient should be closely monitored to detect

Look for signs and symptoms of hyperkalemia such as paresthesia, dyspnea, weakness, numbness or chest pain, and cardiac manifestations (behavioral disturbances and cardiac arrhythmias).

In all patients with hyperkalemia, an electrocardiogram should be performed before discharge, to detect the presence of possible changes in the tracing. Patients should be instructed to drink plenty of water (at least one glass every hour) on the day of the infusion to stay hydrated and facilitate excretion of excess serum potassium. Should symptoms of hyperkalemia develop during amino acid infusion, appropriate corrective measures should be taken. In case of severe symptomatic hyperkalemia, discontinuation of the amino acid solution infusion should be considered taking into account the risk/benefit of renal protection against acute hyperkalemia.

Carcinoid crisis

The hormonal storm is known as a carcinoid crisis, product of the intense release of vasoactive amines, although the cause could have a multifactorial origin, since it is also related to alterations in fluid dynamics and extensive vasodilation.

The real rate of carcinoid crisis and acute hemodynamic instability during or after treatment with PRRT^{177} Lu isn't known precisely, but if one looks at what has been published in the literature, an average of around 1% would be considered, although some authors have described rates of 1-10%[45,63]. The prevalence may be considerably higher in patients who have undergone surgery.

It is important to recognize the clinical manifestations, which include: skin redness, diarrhea, bronchospasm, hypertension, cardiac arrhythmias, metabolic acidosis, and low level of consciousness.

Once symptoms are recognized, the hormonal crisis should be addressed with high doses of intravenous somatostatin analogues, intravenous fluids, corticosteroids and correction of hydroelectrolyte alterations, especially in patients with diarrhea or vomiting. Pretreatment of patients at high risk of seizures has been suggested, although this is not done in most centers.

It is necessary to know what type of patients may have a higher risk of presenting carcinoid crises:

- Patients with high tumour burden.
- Important presence of liver metastases.
- High levels of chromogranin A and urinary 5-hydroxyndolacetic acid.
- Patients with previous carcinoid syndrome who have had episodes of heart failure; these patients should be admitted for an interval of 24 hours for optimal monitoring and management.

In case of carcinoid crisis with hypotension or any symptom of hemodynamic and potential impairment mortality, during or immediately after the infusion of PRRT-^{177}Lu, the administration of bolus somatostatin analogues (500-1000 µg of octreotide) is recommended, repeating the treatment at 5-minute intervals, until the control of symptoms[63]. A continuous infusion of octreotide can be performed at a dose of 50-100 µg per hour. These patients may require admission to an intensive care unit.

ASSESSMENT OF THE RESPONSE TO THE TREATMENT. FOLLOW-UP AND SIDE EFFECTS

Prediction of response to treatment

Clinical benefit to therapy requires both appropriate patient selection and accurate assessment of response to PRRT. Knowledge of the histopathological and molecular characteristics of tumours, as well as the availability of more precise diagnostic tools and therapeutic options, allows a personalized approach to these diseases, with potential benefits in response to treatment and survival.

The identification of biomarkers to evaluate the effectiveness of PRRT and avoid patient toxicity is crucial, but also challenging in a heterogeneous group of tumours such as neuroendocrine tumours, which is why this type of approach is required.

Current parameters (biomarkers, such as chromogranin A and RECIST 1.1) used for evaluation of PRRT response are considered suboptimal, due to variability in somatostatin receptor expression, histology, and characteristic slow growth. of these tumours.

Functional imaging in particular and new approaches in image analysis could play a key role as prognostic biomarkers and for the evaluation of response to therapy. Therefore, standardization is advisable[64].

According to the guidelines for the appropriate use of PET studies with somatostatin receptors, this study would have an appropriate indication for the initial staging of the disease, location of the primary or metastatic tumour and mainly in the selection of patients for treatment with PRRT, leaving as its use prediction and monitoring of response to treatment is probably appropriate, given its lower scientific evidence[35]. Studies have recently been published in which Ga-DOTATOC-PET/TC, FDG-PET/TC and especially the joint assessment of these two tests, play a fundamental role not only in the appropriate selection of patients for treatment, but as isolated predictors of response and monitoring.

Lisa Bodei Kratochwil *et al.* investigated the ability of ^{68}Ga-DOTATOC-PET to predict the response of liver metastases to PRRT in 30 patients. Significant differences were observed in SUVmax at the beginning of the study between lesions that responded and those that did not respond[65]. This is in line with studies that show an association between the tumour absorbed dose and the therapeutic response. Öksüz *et al.* defined an SUVmax > 17.9 on PET with [^{68}Ga]Ga-DOTA-TOC as a cut-off point for a favourable prognostic PRRT result in a cohort of 40 patients with advanced NET treated with [^{90}Y]Y-DOTATOC[66]. On the other hand, in 2009 Gabriel *et al.* found no benefit of an SUVmax analysis in [^{68}Ga]Ga-DOTA-TOC-PET for the prediction of response to individual therapy[67].

Kratochwill *et al.*[65] evaluated three different prognostic parameters in [^{68}Ga]Ga-DOTA-TOC-PET: SUVmax > 16.4 (sensitivity 95%, specificity 60.0%, AUC = 0.87), tumour-spleen ratio (T/S) > 0.67 (sensitivity 95%, specificity 20%, AUC = 0, 78) and a tumour/liver ratio (T/L) > 2.17 (sensitivity 95%, specificity 20%, AUC = 0.73) as cut-off points for a favourable prognostic result for PRRT. In 2019, Sharma *et al.* evaluated four [^{68}Ga]Ga-DOTA-TATE PET-CT parameters in a cohort of 55 patients with metastatic NETs treated with [^{177}Lu]Lu-PRRT: SUVmax in single lesion, tumour-spleen and tumour-lesion ratios, and SUVmax-av (defined as the average SUVmax of up to five target lesions at multiple organ sites) at baseline and on follow-up PET/CT at the end of PRRT. Baseline single lesion SUVmax (SUVmax > 13.0) predicted both response (sensitivity 83%, specificity 84%, AUC = 0.78) and PFS (patients with SUVmax > 13.0 had median PFS of 45.1 months compared to 19.9 months in SUVmax patients < 13.0). A baseline SUVmax-av > 10.2 predicted response (sensitivity 80%, specificity 83%, AUC = 0.78). Neither the tumour-spleen and tumour-lesion proportions were predictive of the PRRT[68] response.

summary

Toriihara *et al.* found prognostic value of volumetric parameters calculated from ^{68}Ga-DOTATATE PET/CT in patients with well-differentiated NET demonstrating an association between "[^{68}P Ga] Ga-DOTA-TATE ∑SRETV" > 11.29 mL and a shorter PFS. For this, two volumetric parameters were calculated; somatostatin receptor-expressing tumour volume (SRETV) and total lesion somatostatin receptor expression (TLSRE), which represent the known metabolic tumour volume and total lesion glycolysis, respectively, from PET -FDG. Subsequently, the sum of SRETV (∑SRETV) and TLSRE (∑TLSRE) was calculated for all lesions detected by the patient and found a significant PFS difference for ∑SRETV ($P < 0.05$). There were no significant differences in age, sex, SUVmax and ∑TLSRE ($P > 0.05$). They thus concluded that the calculation from PET/CT with ^{68}Ga-DOTATATE may have prognostic value for PFS in patients with well-differentiated NETs, since larger tumour volumes showed a correlation with shorter PFS[69].

Three prospective studies demonstrated that FDG positivity is not rare in well-differentiated metastatic G1/G2 NETs, and is a stronger predictor of progression and prognosis than existing WHO groups[8-10]. In the study by Garin *et al.,* in 30 patients with well-differentiated metastatic NET, FDG-PET was positive in a visual analysis in 7 patients and 6 of them progressed within 6 months, while only 2 of 23 PET negative patients showed early progression ($p < 0.001$)[70]. When considering only the subgroup of patients with G1/ G2 tumours and positive PET-DOTATOC, FDG positivity was present in 3/23 cases and correlated with significantly lower PFS and overall survival. Binderup *et al.* investigated 98 patients with advanced NET[71]. FDG was positive (focal uptake) in 40% of G1 patients, 70% of G2 patients, and 93% of G3 patients. Among the 14 patients who died, 13 had a positive FDG scan (hazard ratio 10.3). Five of 47 patients in the G1 group died, 4 of whom had a positive FDG-PET. In the study recently published by Johnbeck *et al.*, 88 patients had well-differentiated advanced NET[72]. Treatment strategies were based on the standard of care. FDG was positive in 39% of G1 patients and 50% of G2 patients. In these patients with well-differentiated NETs, only FDG positivity was a significant prognostic factor with a hazard ratio of 2.4 for PFS ($P = 0.003$) and 5.3 for OS ($P = 0.001$). In a retrospective analysis, Ezziddin *et al.* reviewed the data of 89 patients with metastatic NET and identified three prognostic groups based on the relationship between the SUVmax of the lesion with the highest FDG uptake and the normal liver parenchyma (ratio ≤1; >1 to 2.3; > 2.3). These groups were associated with significant differences in overall survival (median OS was not reached after 114 months vs. 55 months vs. 13 months)[73].

Other prognostic markers have been identified using a dual-marker approach consisting of initial [^{68}Ga]Ga-DOTA-STRS PET/CT and 2-[^{18}F]FDG PET/CT in patients with NETs before PRRT. There is a flip-flop phenomenon in which GaTate PET/CT and FDG PET/CT findings are inversely related at either end of the NET spectrum. G2 tumours, which represent the middle of the spectrum, can show uptake of both GaTate and FDG. This is known as tumour heterogeneity in the FDG PET/CT-GaTate PET/CT combination.

Some authors found that FDG has a greater prognostic value than SRI[70], while others found that SRI is better than FDG in terms of its prognostic value[74,75] or its overall impact on management. However, many authors now view SRI and FDG not as competitors, but as complementary diagnostic tools. For example, Nilica *et al.* used dual-tracer imaging in the setting of PRRT in 66 patients with metastatic NETs. All patients were ^{68}Ga-DOTATOC-PET positives initially and at follow-up. FDG-PET showed more and/or larger metastases than ^{68}Ga-DOTATOC-PET in 5 patients at baseline and in 4 patients during follow-up. In all 9 patients, the disease progressed[76]. Some teams are investigating dual-marker imaging for preoperative prognosis and risk stratification in pancreatic tumours or lung carcinoids. Lococo et al. showed that a relationship ≥1.19 between the SUVmax in SRI-PET and the SUVmax FDG-PET can differentiate between a typical or atypical carcinoid[77]. Preoperative biopsy has difficulty distinguishing between these entities. In total, somatostatin receptor expression and differentiation status (SRI-PET) and glycolytic activity and metabolic reprogramming (FDG-PET) are important prognostic factors.

Considering the dual marker approach, Chan *et al.* developed the "NETPET score", based on a qualitative evaluation of different intralesional and interlesional uptakes with the two radiotracers [^{68}Ga] Ga-DOTA-SSTa and 218F] FDG[78].

The NETPET score correlates well with disease grade, OS, and patient prognosis. The NETPET score ranges from 1 ([^{68}Ga]Ga-DOTA-SSTa+ and 2-[18F]FDG) to 5 ([^{68}Ga] Ga-DOTA-SSTay 2-[^{18}F] FDG+), where score 1 indicates the best prognosis and score 5 indicates the worst prognosis.

In their study, subjects classified as NETPET score 1 or NETPET score 2-4 did not reach median OS, while for subjects classified as NETPET score 5, median OS was 11

months (p = 0.0018). Furthermore, their study highlights the heterogeneity of NETs due to the number of patients with G1 NETs but with a NETPET score greater than 1[79].

Treatment follow-up

To properly monitor the treatment of these patients, three key aspects must be taken into account , clinical symptoms, analytical findings and markers of tumour recurrence, as well as imaging techniques. This follow-up, according to the proposed guidelines, for both patients with GEP-NET and G1-G2 pulmonary NETs, should be carried out every 3 months until stable disease or confirmed slow growth is confirmed after 15 months after treatment. This follow-up could be carried out through image control every 6 months and clinical and biomarker control between 3 to 6 months. Patients with more aggressive or rapidly progressive lesions, as well as patients with risk factors (high-grade tumours, extensive disease, severe endocrine symptoms) or patients with clinical worsening and chromogranin A levels above the normal value for 10 months it is recommended that imaging checks be every 3 months along with clinical and analytical control[80].

Clinical follow-up

- Follow-up within the treatment cycles: the EANM guidelines recommend carrying out an analytical control 2,4 or 6 weeks after each treatment to assess liver function, kidney function and blood count, as well as assessment clinic (by oncology or nuclear medicine) to consider the administration of the next dose. Since, as we will see later, certain adverse reactions could delay or contraindicate the next dose[15,61].
- Follow-up after completing the 4th cycle: controls are recommended every 8 to 12 weeks during the first 12 months and annually thereafter. Follow-up should be carried out with routine tests, as well as tumour markers:
  - Chromogranin A: may reflect changes in tumour burden, which is why it is the most common in G1 and G2 at the time of follow-up.
  - Chromogranin B: mainly in monitoring rectal and pulmonary NETs.
  - 5-Hydroxyndolacetic acid: its use is more common in NETs of the small intestine, appendix and serotonin-producing lungs.
  - Gastrointestinal hormones: mainly used in functioning pancreaticoduodenal tumours.
  - Brain natriuretic peptide: monitoring of carcinoid syndrome to detect the appearance of carcinoid heart disease.

Clinical follow-up

According to recommendations, the preferred study for follow-up is abdominopelvic CT with liver study in three phases. Likewise, abdominal MRI may be considered to monitor liver lesions and in young patients. Radioisotopic techniques can also be used, depending on the patient's characteristics, mainly indicated in suspected recurrence. The main indication for the use of molecular tests in the follow-up of these tumours is the presence of a clinical-biochemical-radiological dissociation and the treatment approach, with the aim of optimizing the imaging tests and the radiation administered.

The assessment of the response to treatment is difficult due to the particularities of this tumour; the RECIST criteria may be suboptimal taking into account the high vascularization of the tumours and may not show the postsurgical or necrotic changes that occur within the tumour. As an alternative, the Choi criteria have been proposed, which in addition to size include tumour HU attenuation, which has shown a greater relationship with OS in patients with a response to PRRT[81,82].

The last expert consensus carried out by the ENETS in 2021 did not reach an agreement on the choice of the imaging technique to monitor the response to treatment in patients with unresectable or disseminated NETs and treated with PRRT[36].

Several standardized quantitative criteria have been developed for the evaluation of 2-[^{18}F]FDG PET/CT therapy, as well as for morphological imaging. In 1999, the European Organization for Research and Treatment of Cancer (EORTC) criteria were the first PET scoring system created. Subsequently, in 2009, these criteria were replaced by more reproducible criteria, the positron emission tomography response criteria in solid tumours (PERCIST). However, PERCIST criteria are not currently standardized to assess response using PET.

Both the EORTC and PERCIST criteria use the standardized uptake value (SUV) as a key parameter. Furthermore, the PERCIST criteria introduce the concept of metabolic tumour volume, which represents a measure of tumour volume with increased glucose consumption, and the total glycolysis of the lesion, which is the product of metabolic tumour volume and mean SUV[83].

In the retrospective study by Huizing *et al.* before mentioned[82], a reliable correlation between the change in SUV in FDG-PET after PRRT and the response to treatment has not yet been demonstrated. In 2010, Haugh *et al.* evaluated SUVmax, T/S ratio, and its delta between baseline and follow-up PET/CT 3 months after PRRT in a cohort of 33 patients. They showed that an early decrease in the T/S ratio after the first cycle of treatment was correlated with longer PFS, while delta SUVmax and delta chromogranin A were not significant prognostic factors. However, these data need to be validated in future prospective studies with larger cohorts.

The expert consensus considered that dosimetry should be performed only as part of clinical trials and, for better disease control, PRRT should be performed following the dosimetry estimate or adapting the administered activity to the patient's clinical data. (for example, tumour burden, body mass, comorbidities, laboratory values)[82].

Likewise, post-treatment scans carried out after each dose could be considered within the patient's follow-up, since said test, although it would not be diagnostic, could be indicative of progression. Since if new lesions are observed in the sequential post-dose scans, it could be secondary to treatment failure, so it is recommended to perform a diagnostic imaging study (by image or biomarkers and always in the multidisciplinary context) and in this way we can offer the patient another alternative that could be more effective.

Side effects

Treatment with PRRT is generally well tolerated by patients, and the adverse effects are mostly mild and self-limiting; only in a few cases can serious adverse effects be perceived that require intensive treatments.

Acutes

Acute adverse effects are those that appear during hospital admission and are mainly related to the infusion of amino acids. They have already been specifically treated in previous sections, so we will focus on subacute and delayed adverse effects.

Subacute

Subacute adverse effects occur in most cases between each treatment cycle.

Haematological toxicity: if it appears, it occurs 4 or 8 weeks after treatment and mainly and most frequently affects platelets. Like acute events, they generally tend to be mild and transient in nature, simply requiring periodic control through blood count or delay the next treatment cycle. If this toxicity persists after waiting between 6 to 8 weeks for the next cycle, half a dose of treatment could be given in the next cycle (depending on the assessment and clinical status of the patient), agreed with the oncology Department. In case of persistence after half a dose, suspension of treatment is indicated. Hematological toxicity could become severe in around 2-3% of cases; cases of acute leukemia or myelodysplastic syndromes have been described, however, this has been described in less than 2% of treatments and mainly affects patients over 70 years of age, patients who have been previously treated with alkylating agents or radiotherapy (who have received multiple previous lines of therapy[61,84].

Late

They are the least frequent and are usually related to previous treatments or lines of treatment. They usually appear after finishing the four cycles.

- Nephrotoxicity: this is an adverse event frequently observed at the beginning of treatment and has recently been rare due to the use of amino acid formulas at the time of admission. When it appears, it is associated with patients with a history of ureteropelvic obstruction, diabetes, high blood pressure or previous renal failure. It usually only requires periodic monitoring of kidney function.
- Hepatotoxicity: it can be common in patients with extensive liver involvement, and can even cause ascites. Its treatment requires a low-salt diet, treatment with diuretics in case of ascites, and may even require paracentesis or peritoneum-venous shunt.
- Temporary alteration in fertility: usually temporary in nature; depending on each patient, sperm banks should be considered prior to therapy. It mainly affects men due to the involvement of Sertoli cells.

Hair loss, asthenia, or decreased appetite may also occur as a delayed side effect.

Modification, suspension or extension dose interval

Although in the majority of cases in which adverse reactions occur, they are usually mild, there is the possibility

(although low) to present serious or intolerable adverse reactions, so its management may require temporary interruption of the dose, extension of the dosing interval from 8 weeks to 16 weeks, reduction of the dose or suspension of the treatment.

Likewise, there may be other clinical situations that require considering the interruption, whether temporary or total, of the treatment, such as the appearance of another disease that requires more immediate attention (for example, the appearance of a second primary tumour with a worse prognosis), the appearance of entities that may increase the risks associated with the administration of the treatment and that must be resolved or stabilized before continuing with it (for example, urinary tract infection) or even in the case of requiring major surgery between doses, in which case treatment should be interrupted for 12 weeks after the date of surgery. It should be taken into account that if the modification, suspension or extension of the dose interval is required, it must be agreed upon by a multidisciplinary tumour committee.

To modify the dose, there is an instruction scheme that generally proposes two scenarios, where after detecting serious adverse reactions (haematological, renal toxicity, hepatotoxicity or others), the first step to follow must consider the increase of the dose administration interval, delaying the administration of the next cycle even up to 16 weeks, taking into account that periodic clinical and analytical monitoring must be carried out to prevent worsening or detect improvement. If toxicity persists after 16 weeks, treatment should be discontinued. If the toxicity is resolved, treatment will be continued at half the dose and close monitoring will be done for possible reappearance of this toxicity. These scenarios are summarized in Figure 12[85].

Likewise, there is a specific protocol for each type of adverse reaction and, depending on its degree of severity, a specific modification guideline must be available; these recommendations are outlined in Table 6.

New radiotracers, future perspective

There are currently several studies underway whose objective is to improve the response rate and survival to treatment with PRRT. As well as the synthesis of new radionuclides, mainly alpha emitters that provide a linear energy absorbed by the tumour that is significantly greater than beta type emitters (such as lutetium). This greater energy results in a greater number of DNA chain breaks, so it would be related to greater cellular apoptosis, associated, thanks to its better penetration, with less damage to healthy tissue. Currently, these alpha emitters do not have clinical trials that can assess toxicity and efficacy; they are mostly studies with Bismuth-213 (^{213}Bi), Actinium-225 (^{225}Ac) and Lead-212 (^{212}Pb). In the particular case of bismuth, with studies in a more advanced phase, long-lasting treatment responses have been observed in humans, with moderate chronic renal toxicity and less pronounced acute haematological toxicity compared to beta emitters[84,86].

Studies are also being carried out in which the radiation-emitting isotope is not changed, but rather the ligand is directly changed, using somatostatin antagonists instead of agonists. Preclinical studies have shown that antagonists have greater tumour uptake compared to agonists, as well as a longer OS. However, it has been described that they may increase the risk of uptake in the bone marrow and kidney, which could result in greater toxicity. [^{177}Lu]-DOTA-JR11 showed promising results with a tumour dose 1.7-10.6 times higher than with the agonist [^{177}Lu]Lu-DOTA-TATE[87,88].

Likewise, studies have recently been carried out modifying the route of administration, performing intrahepatic arterial administration in patients with mainly hepatic

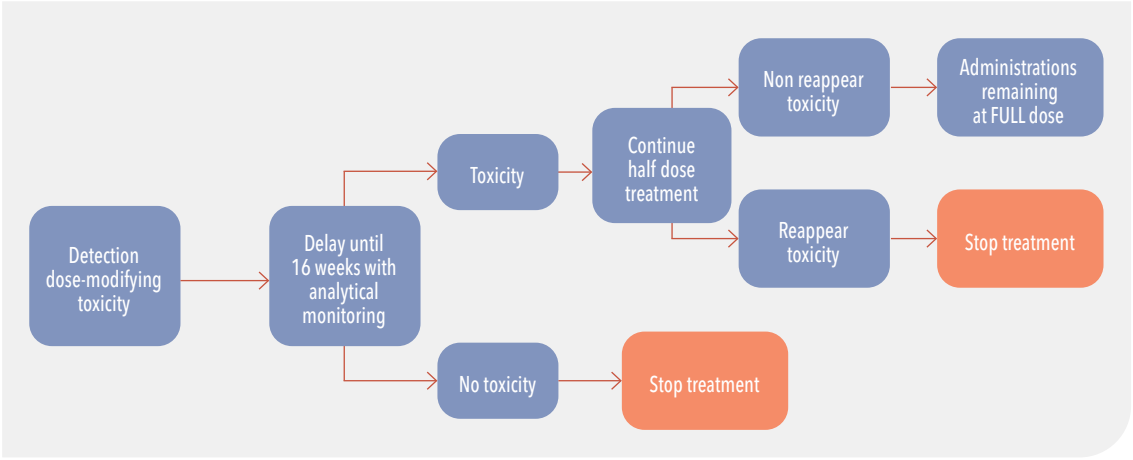

FIG. 12. Instructions for dose modification.

TABLE 6. Recommended dose modifications due to adverse drug reactions

Side effects	Severity	Change of the doses
Thrombocytopenia	• Grade 2 (platelets < 75-50 × 10^9/L)[1] • Grade 3 (platelets < 50-25 × 10^9/L) • Grade 4 (platelets < 25 × 10^9L)	1. Interrupt dose until complete or partial resolution (grade 0 to 1) 2. Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If the reduced dose does not produce grade 2, 3, or 4 thrombocytopenia, administer treatment at 7,400 MBq (200 mCi) at the next dose. 3. Permanently discontinue treatment for grade 2 or higher thrombocytopenia requiring treatment delay for 16 weeks or more
	Grade 2, 3 or 4 recurrence	Grade 2, 3 or 4 recurrence
Anemia and neutropenia	• Grade 3 (Hb < 8.0 g/dL)[1]; indicated transfusion • Grade 4 (fatal consequences) • Grade 3 (absolute count of neutrophils [ANC]) < 1.0-0.5 × 10^9/L) • Grado 4 (ANC < 0,5 × 10^9/L)	1. Interrupt dose until complete or partial resolution (grade 0, 1 or 2) 2. Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If the reduced dose does not produce grade 3 or 4 anemia or neutropenia, administer treatment at 7,400 MBq (200 mCi) at the next dose. 3. Permanently discontinue treatment for grade 3 or higher anemia or neutropenia that requires delaying treatment for 16 weeks or more
	Grade 2, 3 or 4 recurrence	Permanently stop treatment
Kidney toxicity	Defined as: creatinine clearance less than 40 mL/min1, or 40% increase in baseline serum creatinine, or 40% decrease in baseline creatinine clearance	1. Interrupt the dose until complete resolution or return to baseline. 2. Resume treatment at 3,700 MBq (100 mCi) in patients with complete resolution or return to baseline. If the reduced dose does not produce renal toxicity, administer treatment at 7,400 MBq (200 mCi) at the next dose. 3. Permanently discontinue treatment due to renal toxicity requiring postponement of treatment for 16 weeks or more
	Grade 2, 3 or 4 recurrence	Permanently stop treatment
Hepatotoxicity	Defined as: bilirubinemia greater than 3 times the upper limit of normal (grade 3 or 4)[2], hypoalbuminemia[2] less than 30 g/L with a decrease in prothrombin time below 70%	1. Interrupt the dose until complete resolution or return to baseline. 2. Resume treatment at 3,700 MBq (100 mCi) in patients with complete resolution or return to baseline. If the reduced dose does not cause liver toxicity, administer treatment at 7,400 MBq (200 mCi) at the next dose. 3. Permanently discontinue treatment due to liver toxicity requiring postponement of treatment for 16 weeks or more
	Grade 2, 3 or 4 recurrence	Permanently stop treatment
Any other CTCAE* with grade 3 or grade 4 toxicity	Grade 3 or grade 4	1. Interrupt the dose until complete or partial resolution (grade 0 to 2) 2. Resume treatment at 3,700 MBq (100 mCi) in patients with complete or partial resolution. If the reduced dose does not produce grade 3 or 4 toxicity, administer treatment to 7,400 MBq (200 mCi) in the next dose 3. Permanently discontinue treatment for grade 3 or higher toxicity requiring postponement of treatment for 16 weeks or more
	Grade 2, 3 or 4 recurrence	Permanently stop treatment

[1]The same thresholds also apply to baseline values at the start of treatment.
[2]If the same thresholds are observed at baseline, initiation of treatment should be considered after performing a benefit-risk assessment.
*NCICTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events

involvement with [^{177}Lu]Lu-DOTA-TATE through the hepatic artery. In this way, side effects can be reduced, since radiation to target organs is reduced as there is a smaller amount of circulating radiopharmaceutical and thus increasing the concentration in liver lesions[89].

Following this line of treatment, the combination of two techniques used in nuclear medicine has been proposed, such as PRRT and therapy with labeled microspheres with ^{90}Y or ^{166}Ho, which appears to be an effective alternative in patients with exclusively or predominantly hepatic metastatic involvement, especially in very symptomatic cases or voluminous hepatic tumour burden, given that treatment with PRRT shows a lower response in larger liver lesions. Where treatment with microspheres can be useful[90].

CLINICAL CASE NET-GEP

A 74-year-old female patient at diagnosis, who began with non-specific symptoms (anal pain), in CT and MRI studies, found a tumour in the left pararectal region above the levator ani 25 × 27mm, with AP of well-differentiated infiltrating neuroendocrine tumour (G2) Ki67: 5%. Octreoscan was performed, which confirmed the pathological expression of somatostatin receptors in the lesion described with secondary involvement in the lung and mediastinum, which underwent surgery 6 months later.

The PET/CT-STRS study 1 year after surgery (A) is compatible with liver metastases (segment III and VI), a single bone metastasis at C6 from a neuroendocrine tumour.

It was decided to continue treatment with somatostatin analogues and perform a new control with PET/TC-Ga68- DOTATOC. In the control PET/CT-STRS at 6 months, persistence of known lesions in C6 and liver parenchyma (Segments III and VI) was observed with the appearance of a new lesion in segment VIII (Fig. 13).

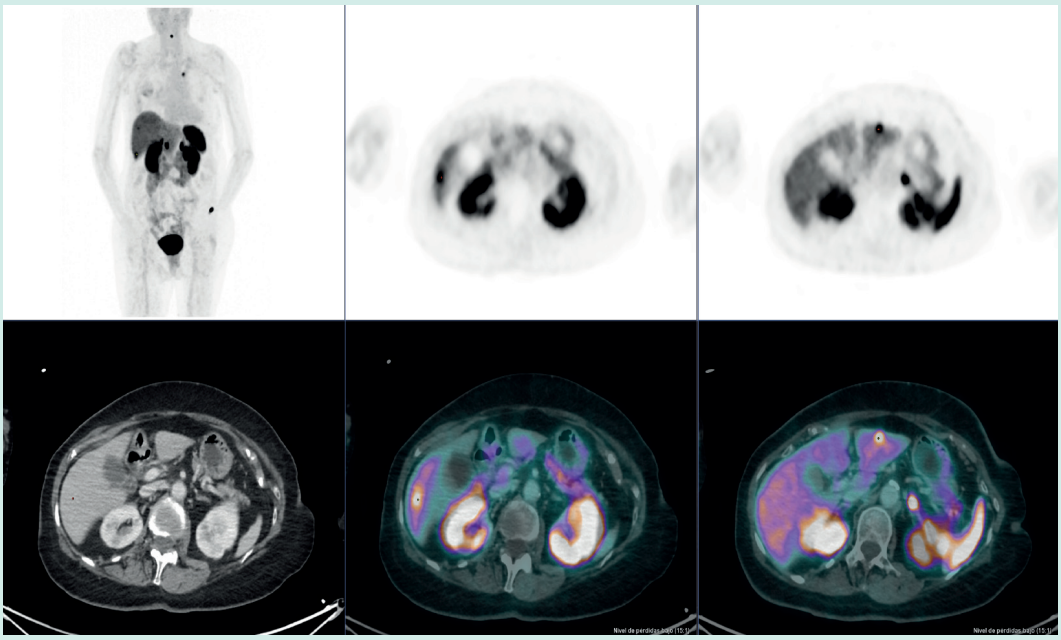

FIG. 13.

Given the progression, the multidisciplinary tumour committee decided on PRRT treatment with Lu^{177}.

4 doses of Lu^{177}-Oxodotreotide of 7.4 GBq are administered; presenting marked lymphopenia between the 3rd and 4th cycle, so it is necessary to extend the time between doses from 8 to 12 weeks. The 4th cycle was administered without significant complications.

A post-treatment control study was carried out with PET/CT-Ga68-DOTATOC(C), in which persistence of two hepatic space-occupying lesions was observed that did not show pathological expression of somatostatin receptors and disappearance of the rest of the lesions, in relation with complete response to treatment with ^{177}Lu-DOTATATE from a functional point of view.

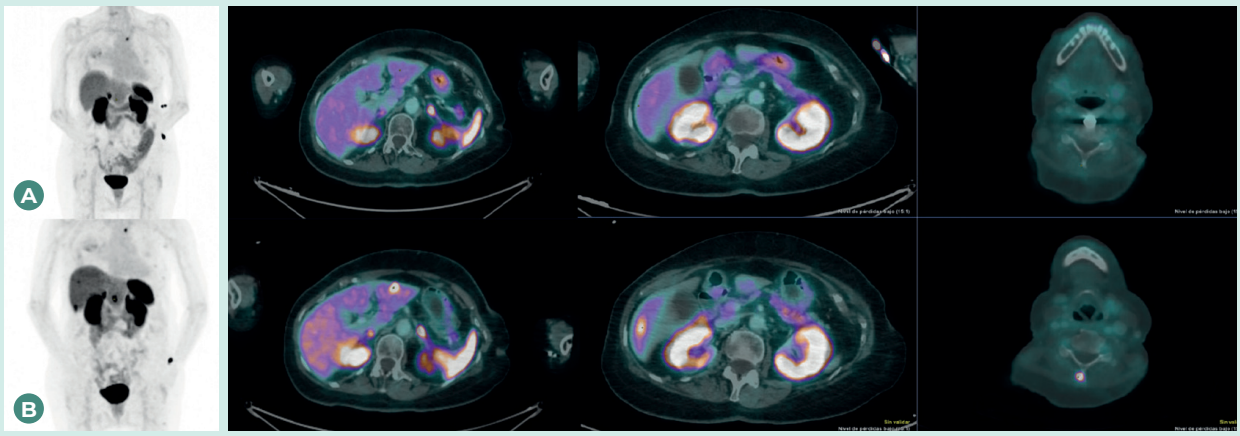

FIG. 14. Response to treatment: (A) Control Ga^{68} DOTATOC PET/CT, disappearance of the pathological deposits of the radiopharmaceutical is observed. (B) PET/CT Ga^{68} DOTATOC pretreatment

These changes reflected in the imaging studies were accompanied by a clear clinical and symptomatic improvement and in the patient's quality of life.

CLINICAL CASE NET-GEP

A 47-year-old man diagnosed with intestinal NET G2 (Ki-67 15%) stage IV due to lymph node and liver involvement and tumour implantation in the left gluteus at diagnosis. Among the diagnostic and staging imaging tests prior to the start of treatment, it was decided to perform dual imaging using PET/CT-STRS and PET/CT-FDG, Fig. 15), where well-differentiated disease with a predominance of expression of somatostatin receptors in primary tumour of the small intestine, as well as lymphadenopathy in the mesentery, retroperitoneum, mediastinum, subcutaneous/muscular implants and extensive liver and bone involvement. However, in the FDG image a heterogeneous behaviour is observed with evidence of some lesions without glucose avidity and others with avidity for both radiopharmaceuticals (FDG and somatostatin analogues). The joint assessment of both PET studies suggests a greater component of differentiated cellularity; However, there is a lesion in the right hepatic lobe that shows mismatch behaviour, due to greater uptake intensity in the PET/CT-FDG study (SUVmax 6.1) compared to the PET/CT-STRS study.

These findings correspond to a NETPET score of 4.

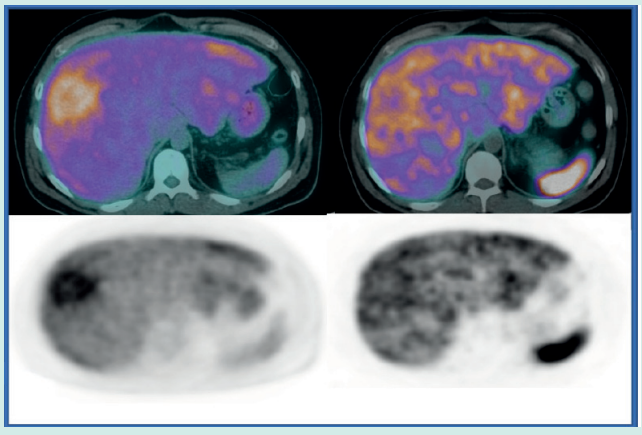

FIG. 15.

The patient meets clinical trial criteria to be treated first-line with lutetium, receiving a total of 4 doses. The post-treatment scan after the last dose shows a pathological expression of somatostatin receptors in known lesions and the appearance of new deposits in bone structures and the hiliomediastinal region, suggestive of incipient tumour progression, so it was decided to perform a new dual study with PET/CT.

When comparing both PET imaging tests with somatostatin receptors (pre- and post-treatment), disease progression is observed at the expense of new-appearing bone and liver lesions, as well as pulmonary metastases (Fig. 16). It was decided to treat with monthly octreotide LAR.

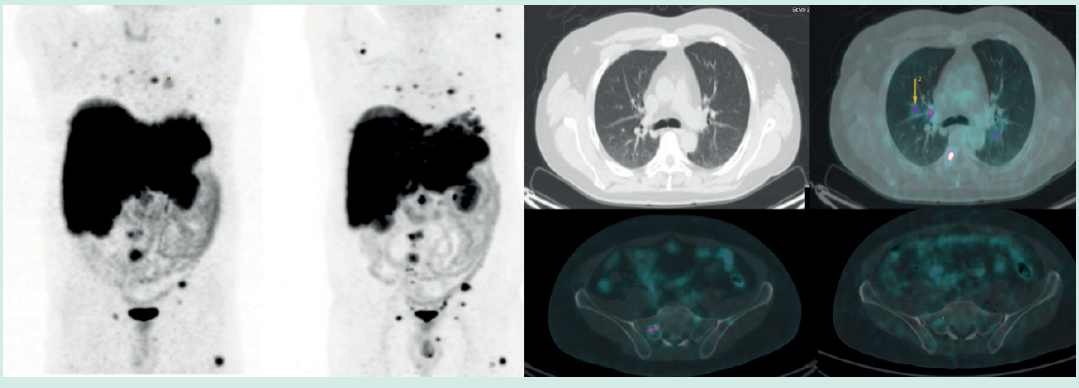

FIG. 16.

In the post-treatment assessment of the metabolic component (PET/CT-FDG) we observed that there are signs of partial response in most of the tumour involvement and in some locations (multiple liver lesions) a complete metabolic response (Fig. 17). However, most lesions are not identifiable in the FDG study due to their degree of differentiation and not due to response to treatment. We consider that the patient is progressing due to well-differentiated lesions (PET/CT-STRS and postlutecium scan).

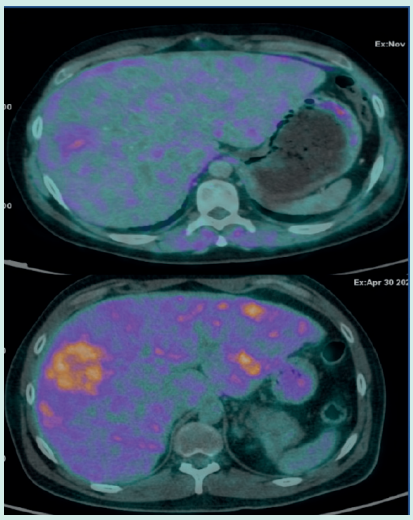

FIG. 17.

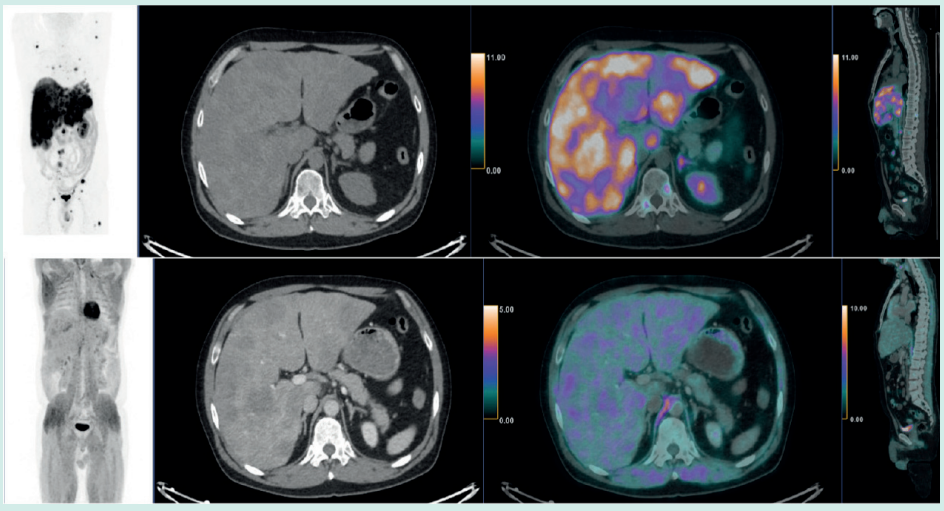

FIG. 18.

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