Peptide Receptor Radionuclide Therapy

Subjects: Oncology | Radiology, Nuclear Medicine & Medical Imaging

Contributor: Corrado Cittanti

The PRRT (Peptide Receptor Radionuclide Therapy) is a promising modality treatment for patients with inoperable or metastatic neuroendocrine tumors (NETs). Progression-free survival (PFS) and overall survival (OS) of these patients are favorably comparable with standard therapies. The protagonist in this type of therapy is a somatostatin-modified peptide fragment ([Tyr3] octreotide), equipped with a specific chelating system (DOTA) capable of creating a stable bond with β-emitting radionuclides, such as yttrium-90 and lutetium-177.

[Lu]Lu-DOTATOC [Y]Y-DOTATOC PRRT neuroendocrine tumors

1. Introduction

The success of therapy in nuclear medicine is based on the increasing availability of radionuclides with adequate chemical-physical characteristics and of molecular probes capable of selectively transporting the radiation source into the tumor tissue. In the last ten years, over 80% of the publications relating to therapeutic radionuclides concern preclinical and clinical research conducted with conventional radionuclides, among which the most cited are ^{131}I, ^{90}Y, and ^{177}Lu [1].

The key to their success lies in the recent and innovative nuclear medicine therapeutic strategy, which consists of the personalized theranostic approach.

Theranostics is the convergence point between diagnostic imaging and radiomolecular cancer therapy. There are several combinations of molecular targeting vectors and radionuclides suitable for theranostic use. Multi-element radiopharmaceuticals, consisting of two radioisotopes possessing similar chemical properties but having different physical emission properties, for example, ^{99m}Tc/^{188}Re [2][3][4], ^{68}Ga/^{177}Lu or ^{68}Ga/^{90}Y [5], used for the labeling of the same bioactive molecule, were the first and are still the most used in theranostic clinical practice. In this configuration, one radiopharmaceutical is used for therapeutic treatment of the tumor and the other one is used for diagnosis and response monitoring. [^{68}Ga]Ga-DOTATOC combined with [^{177}Lu]Lu-DOTATOC or [^{90}Y]Y-DOTATOC are used in the theranostic model of Neuro Endocrine Tumors (NETs) radioreceptor.

The nuclear medicine research, in this particular therapeutic field, is constantly evolving thanks to the strong multidisciplinary synergy. In particular, the close collaboration of specialists from different disciplines such as physics, chemistry, radiochemistry, biochemistry, pharmacology, and nuclear medicine has determined the possibility to offer targeted therapies against solid neoplasms, such as NETs.

NETs include a heterogeneous group of neoplasms, exhibiting a variable biological behavior, that can originate from various organs with an estimated incidence of about 5 new cases per 100,000 individuals per year [6].

Overall, the highest incidence of these neoplasms is affecting the organs of the digestive system, in particular ileum and pancreas and, less frequently, stomach, duodenum, colon and appendix, constituting the gastro-entero-pancreatic NET (GEP) and representing 60–70% of all NETs. In addition to GEP NETs, other histotypes, affecting, in particular, the respiratory system and bronchi (20–30%) or other organs (10%) such as skin, thyroid, parathyroid, thymus, paraganglia and adrenal glands, can be classified as non-GEP NETs [7][8][9].

The overall 5-year survival of NET patients is on average about 67.2% and can vary from 15% to 95% depending on the site of origin, the extent of the disease, and cellular biological characteristics [10]. The correct diagnostic approach of NETs is based on a careful evaluation of the clinical history, on the identification of general and specific biohumoral markers and on the localization of the primary tumor and any metastases through endoscopic and echo-endoscopic, morphological (CT or MRI), and functional (SPECT-CT with [^{111}In]In-pentetreotide or PET-CT with [^{68}Ga]Ga-SST-As) [5].

To date, there are no specific and consolidated therapeutic protocols to be routinely employed in the treatment of NETs. Nevertheless, there are many therapeutic options for this pathology and most patients with NET have the possibility of obtaining a good response to treatments and a good prognosis. Consequently, the management and therapy of these patients should be approached by clinicians with a multidisciplinary approach: a multimodal therapeutic strategy should be designed from the time of diagnosis and for each individual patient, rather than simply delivering an empirical sequence of treatments. The therapeutic approach will depend on the location of the primary tumor, the histological examination, the stage, and the grade of the neoplasm. Diagnosis of NETs often occurs in an advanced stage of the disease, given the non-specificity of the symptoms and the general slow progression, making the surgical approach for curative purposes applicable in the minority of cases.

Since the liver is the organ with the highest incidence of metastases, alternative treatments to surgery such as locoregional approaches including transarterial chemoembolization (TACE) [11] and Selective Internal Radiation Therapy (SIRT) [12] should be considered. In case of metastatic spreading, numerous systemic therapies are available including therapy with somatostatin analogues in long-acting release (LAR) form [13], chemotherapy [14], up to the most innovative target therapies such as biological therapies (e.g., mammalian target of rapamycin (mTOR) inhibitor drugs) and the peptide receptor radionuclide with radiolabeled somatostatin analogues (PRRT) [15][16][17][18].

NETs plasmalemma shares the expression of specific molecules, proteins and receptors that make up the neuroendocrine phenotype. Some of these biomarkers have been extensively studied as specific targets for targeted diagnostic and therapeutic approaches.

In particular, NETs almost constantly over-express membrane receptors capable of binding, with high affinity, somatostatin (SST) [19][20]. To date, five somatostatin receptor subtypes have been identified (SST-R1, SST-R2,

SST-R3, SST-R4, SST-R5), and the SST-R1, SST-R2, SST-R3 subtypes are the most expressed by NET cells [21][22].

However, the SST (cyclic neuropeptide consisting of 28 amino acids, secreted by neurons and cells of the endocrine system) cannot be used as a bio-probe for the aforementioned receptors due to its instability and its very short half-life.

The availability of synthetic analogues of SST (SST-As) and of synthesis strategies, allowing SST-As to be stably—in vitro—labelled to specific low and high energy radioisotopes, has allowed the development of specific radiopharmaceuticals and consequently innovative theranostic nuclear medical pathways. By these radiopeptides, it is currently possible to selectively convey radiation in tumor lesions expressing somatostatin receptors (SST-Rs), both for diagnostic and therapeutic purposes [23][24].

The most used radiopharmaceuticals in PRRT are those deriving from the combinations of the two isotopes yttrium-90 and lutetium-177 and of the two somatostatin analogues DOTATOC and DOTATATE: [^{90}Y]Y-DOTATOC, [^{90}Y]Y-DOTATATE, [^{177}Lu]Lu-DOTATATE, [^{177}Lu]Lu-DOTATOC. However, the greatest clinical experience (and the most abundant scientific literature) refers to the use of [^{90}Y]Y-DOTATOC, which represented the first generation radiopharmaceutical for NETs. More recently, the [^{177}Lu]Lu-DOTATATE was used in the phase 3 Netter-1 study [25], which prompted the production and commercialization of the Lutathera®. In recent years, a smaller number of trials involved the use of [^{90}Y]Y-DOTATATE while the interest and use of [^{177}Lu]Lu-DOTATOC is still growing [26][27].

In 2016, waiting for the availability of Lutathera®, our group designed an experimental protocol for therapeutic treatment that included all types of NETs, both GEP NETs and non-GEP NETs. Starting from the diagnostic phase performed with the SST analogue DOTATOC radiolabeled with ^{68}Ga ([^{68}Ga]Ga-DOTATOC), we proposed both [^{90}Y]Y-DOTATOC and [^{177}Lu]Lu-DOTATOC as therapeutic radiopharmaceuticals [28][29][30][31].

In order to obtain the necessary authorizations from the national competent authorities, the study protocol was accompanied by the specific Investigational Medicinal Product Dossier (IMPD) concerning the two radiopharmaceuticals included in the study protocol (FENET-2016, EUDRACT number: 2016-005129-35, NCT04790708). To address the various issues concerning the compilation of the IMPD, an extensive literature review of the last 25 years was necessary to allow us to retrace the main steps relating to the PRRT preclinical and clinical studies performed with DOTATOC labeled with high energy isotopes.

2. PRRT: Risks, Benefits, and Considerations

The nuclear physician who is preparing to treat a patient with PRRT must, in advance, carry out a careful analysis of the benefits and risks related to the treatment. To do this, it is necessary first of all: (i) to proceed to a correct selection of the patient to be treated and, therefore, (ii) carefully consider the type of radiopharmaceutical and the therapeutic scheme to be proposed based on the characteristics of the patient and a preliminary dosimetric evaluation, so as to guarantee personalized treatment, (iii) operate within a multidisciplinary group and in line with

the main national and international guidelines [32][33]. The appropriateness level of the initial choices will be decisive for obtaining adequate results in terms of efficacy, safety, and sustainability.

The PRRT benefits are based on its documented therapeutic efficacy which, in practical terms, manifests itself through the interference with tumor growth and the reduction/resolution of lesions, the increase in survival times and the improvement of the quality of life, in patients with NET and also with other histotypes expressing somatostatin receptors. PRRT has been used with benefit in clinical settings in which diffuse and metastatic lesions were present, in those characterized by residual lesions after surgical treatment (adjuvant purpose) and in situations in which an inoperable solitary primary lesion was present (neoadjuvant purpose). In certain situations, the PRRT has also documented greater therapeutic benefits compared to chemotherapy treatments and medical therapies based on the use of biological drugs. In other studies, however, a benefit of PRRT in combination with other drugs has been documented.

The risks of PRRT are related to its potential side effects, which, as already mentioned above, can be acute, subacute, and often reversible or chronic and, therefore, permanent.

The Council Directive 2013/59/Euratom fixes the need for personalized dosimetry to patients treated with radionuclide therapy. In order to fulfil such a directive, an absolute quantification of the activity in the targets of the treatment and the organs at risk for each subject is necessary. The personalization of radiometabolic therapy passes from the knowledge of the dose to the organs and therefore from their uptake.

The starting point for such aim is a precise estimate of the spatial resolution and the sensitivity of the gamma camera exploited for the SPECT-CT studies, as well as an improvement in the uncertainty assessment associated to the measurements and the image reconstruction. The critical organs to monitor and preserve during PRRT are the hematopoietic marrow and, above all, the renal parenchyma, which is unduly irradiated by the amount of radiopeptide that does not bind to the target and which, through a re-uptake mechanism, enters the cells tubular section of the proximal nephron. Patients with labile hepatic compensation will also need to be carefully evaluated before being treated with PRRT.

The factors that can lead to predicting a benefit obtainable with PRRT and the factors that, on the other hand, can be correlated with a potential risk of toxicity are summarized and commented on below.

PRRT benefit predictors are [18][32][34]:

(a) factors related to the biological characteristics of the tumor:In fact, a high receptor expression is essential to
(a1) Elevated lesional expression of SST-R2.ensure adequate accumulation of radiopharmaceuticals and a consequent adequate radiation dose to tumor lesions. Positive imaging with [^{111}In]In-pentetreotide and mostly [^{68}Ga]Ga-SS-As guarantee high accuracy to obtain this type of information. Numerous recent studies have confirmed that the lesion level uptake index (assessable by applying the Rotterdam scale in the monophotonic survey with [^{111}In]In-pentetreotide and in a semi-quantitative mode by measuring the SUV in the PET-CT

survey) is potentially correlated with the magnitude of the objective response (OR) and the efficacy of the treatment in terms of overall survival (OS) and progression-free survival (PFS), reductions in symptoms and, therefore, improved quality of life (QoL).

(a2) Histology positive for NET.NETs include the neoplasms that most frequently and most abundantly express SST-R2. Among these, the histological variants that statistically best respond to PRRT include those of the gastro-entero-pancreatic tract and the forms of broncho-pulmonary origin. NETs that originate in the remaining organs of the respiratory system and in other locations (skin, thyroid, CNS, meninges), as well as other histotypes with neuroendocrine phenotypes, generally have less responsiveness and efficacy to the treatment.

(a3) Well-differentiated low graded shapes (WHO) [35].The histotypes with a high degree of differentiation, i.e., G1 (Ki67 ≤ 3%) and G2 (Ki67 ≤ 10%), provide the best profiles of objective response and efficacy in terms of survival at PRRT. Some histotypes with G2 (Ki67 > 10%) and especially the well-differentiated G3 (Ki67 > 20%) forms may respond to treatment but have lower PFS and OS values.

(a4) Limited spread of disease.The extent of disease spread is inversely proportional to the degree of objective response and therapeutic efficacy in terms of PFS and OS. Very often the NETs are indolent and slowly progressive, and their diagnosis occurs frequently when the disease is already systemic due to the presence of diffuse metastases or in any case not surgically attacked. Where technically possible and the patient's general condition permits, surgical or interventional procedures aimed at eradicating or reducing the disease are recommended. Adjuvant post-surgical therapies, including PRRT, may be more successful after tumor debulking.

(a5) Hepatic and pancreatic localization.Secondary hepatic lesions from NET are those that most frequently respond to PRRT, but primary NETs of the pancreas also show good responses to treatment. More resistant to treatment are secondary lymph node lesions and, above all, skeletal ones. PRRT with intra-arterial administration of the radiopharmaceutical through the hepatic artery represents—in patients with localized liver disease—an alternative modality (compared to the classic systemic intravenous administration) capable of expanding the therapeutic response and outcome of patients.

(a6) Good performance status.A good general clinical status of the patient, a good life expectancy and the absence of comorbidities are potential factors directly related to the success of the treatment. In particular, the absence of risk factors for bone marrow toxicity (anemia, leukocytopenia, thrombocytopenia from previous chemotherapy or radiation treatments) and for renal toxicity (diabetes, hypertension, primary and secondary nephropathies) allows, in a context of greater tolerability by of these two critical organs, the administration of the highest levels of administrable radiopharmaceutical activity, which results in a higher absorbed dose to the tumor lesions.

(a7) Favorable genotype.It is known, in clinical practice, how similar clinical presentations of NETs can respond differently or even opposite to the various types of treatment, including PRRT. The evaluation of the cellular

genome, which can be performed with specific tests still in the experimental phase (NeTest), will, in the near future, describe the state of the disease and predict its prognosis and possible response to therapeutic treatments [36][37].

(b) Factors related to the therapeutic management of the patient to be treated:

(b1) Multidisciplinary evaluation. The preliminary discussion of each single clinical case, the collegial choice of treatment, the timing and sequencing between the different treatments that make up the patient's therapeutic plan, as well as the participatory evaluation of the follow-up, represent the ideal prerequisites for an efficient and effective management of the patient affected by NETs. Various studies correlate patient outcomes with how they are managed within structured specialized clinical paths and/or specialized and highly equipped Centers to respond to this type of patient.

(b2) Adherence to PRRT protocols (and guidelines).The shared guidelines IAEA-EANM-SNMMI [18], which draw from the numerous clinical dosimetric works reported in the previous paragraphs, provide specific indications about the treatment schemes to be used in PRRT. These reference documents explain the radiopharmaceutical activities (per cycle and cumulative) to be used in the various categories of patients (with or without risk factors), the interval between the various cycles, and the most suitable type of radiopharmaceutical. The various protocols are outlined that involve the use of somatostatin analogues (DOTATOC/DOTATATE) radiolabeled with ^{90}Y for large lesions, with ^{177}Lu for small lesions or combined or sequential treatments. By now, the hydration schemes to be performed collateral to the therapeutic treatment are known, including those relating to the infusion of nephroprotective molecules. Furthermore, personalized dosimetry is always recommended—in compliance with the optimization principle—in order to make the treatment as effective and safe as possible. The MIRD scheme provides the recognized and validated technical lines for dosimetry in nuclear medical therapy and, in particular, the OLINDA/EXM software is widely used to estimate the absorbed dose to the target and critical organs after administration of ^{90}Y and ^{177}Lu-labeled peptides.

PRRT risk predictors are [18][32][34]:

(a) Reduced bone marrow function.Adequate bone marrow reserve should be present in PRRT candidates. Reference values recommend: WBC > 3000/μL, with absolute neutrophil value >1000/μL, PLT > 75,000/μL for [^{177}Lu]Lu-DOTATOC and >90,000/μL for [^{90}Y]Y-DOTATOC, RBC > 3,000,000/μL. Previous myelotoxic chemotherapy treatments and extensive radiotherapy treatments on the bone marrow (to the pelvis and spine), especially if performed in the weeks preceding the PRRT, increase the risk of bone marrow toxicity after PRRT. In cases of suspected haematological compromise, it could be useful to perform a biopsy of the haematopoietic marrow to verify the pre-PRRT situation, in order to evaluate the possible risks that the PRRT itself could bring and therefore implement the precautions aimed at reducing potential risks (reduction of the activity to be administered, longer interval between one cycle and the next). In any case, the overall bone marrow dose should always be ≤2 Gy. In relation to the activities (^{90}Y or ^{177}Lu) administered, the persistence of low platelet values, after the first courses of treatment, could affect the ability to recycle within the scheduled time and administer the planned activities at the start of treatment. Severe acute toxicity, albeit reversible, was reported in less than 10–13% of

patients treated with ^{90}Y and in 2–3% of those treated with ^{177}Lu. In addition, sporadic cases of acute myelodysplasia and leukemia have been described.

(b) Reduced kidney function.The kidney represents the dose-limiting organ for radiopharmaceutical activities normally used in PRRT. Therapy with ^{90}Y is recommended in situations in which renal function (normalized for the patient's age) is preserved. Treatments with ^{177}Lu can also be admitted to patients with mild renal function impairment but, in any case, with creatinemia values ≤1.7 mg/dL. Renal parenchyma protection based on the administration of amino acids (L-Lysine and/or L-Arginine) before, during and after PRRT treatment is always recommended in all patients, regardless of starting renal function. For this concomitant treatment, attention should be paid to the possible hyperkalemia [38][39].

Some chronic diseases such as uncompensated diabetes, uncontrolled hypertension, obstructive nephropathies, as well as any previous nephrotoxic chemotherapeutic treatments (based on platinum) represent risk factors for the development of a potential toxicity induced by PRRT. On the basis of these observations, the absorbed dose to the kidney, in terms of BED (biological effective dose), was set at a threshold value of ≤40 Gy for the standard population and ≤28 Gy for subjects with a positive history of aforementioned pathologies favoring the onset of renal toxicity. Although the clinical experience accumulated in the last twenty years by the main PRRT centers has considerably reduced the occurrence of side effects, the most recent summary data confirm the possibility of a deterioration of renal function, more accentuated in the PRRT protocols in where ^{90}Y labeled peptides are used compared to those based on the use of analogues conjugated with ^{177}Lu.

Absolute contraindications to PRRT [32]: pregnancy; severe concomitant acute illness; severe psychiatric disorders.

According to what emerges from the literature and clinical experience, it can be said that PRRT constitutes an essential tool for the treatment of numerous patients with neuroendocrine neoplasia. In particular, taking into consideration the data concerning the potential toxicity and the documented therapeutic efficacy, the balance between the risks and the benefits clearly leans in favor of PRRT.

References

1. Uccelli, L.; Martini, P.; Cittanti, C.; Carnevale, A.; Missiroli, L.; Giganti, M.; Bartolomei, M.; Boschi, A. Therapeutic Radiometals: Worldwide Scientific Literature Trend Analysis (2008–2018). Molecules 2019, 24, 640.
2. Boschi, A.; Uccelli, L.; Pasquali, M.; Pasqualini, R.; Guerrini, R.; Duatti, A. Mixed Tridentate π-Donor and Monodentate π-Acceptor Ligands as Chelating Systems for Rhenium-188 and Technetium-99m Nitrido Radiopharmaceuticals. Curr. Radiopharm. 2014, 6, 137–145.
3. Boschi, A.; Martini, P.; Uccelli, L. 188Re(V) Nitrido Radiopharmaceuticals for Radionuclide Therapy. Pharmaceuticals 2017, 10, 12.

4. Uccelli, L.; Martini, P.; Pasquali, M.; Boschi, A. Monoclonal Antibodies Radiolabeling with Rhenium-188 for Radioimmunotherapy. BioMed Res. Int. 2017, 2017.
5. Werner, R.A.; Bluemel, C.; Allen-Auerbach, M.S.; Higuchi, T.; Herrmann, K. 68Gallium- and 90Yttrium-/177Lutetium: “theranostic twins” for diagnosis and treatment of NETs. Ann. Nucl. Med. 2014, 29, 1–7.
6. Kulke, M.H.; Siu, L.L.; Tepper, J.E.; Fisher, G.; Jaffe, D.; Haller, D.G.; Ellis, L.M.; Benedetti, J.K.; Bergsland, E.K.; Hobday, T.J.; et al. Future Directions in the Treatment of Neuroendocrine Tumors: Consensus Report of the National Cancer Institute Neuroendocrine Tumor Clinical Trials Planning Meeting. J. Clin. Oncol. 2011, 29, 934–943.
7. Modlin, I.M.; Lye, K.D.; Kidd, M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003, 97, 934–959.
8. Teunissen, J.J.M.; Kwekkeboom, D.J.; Valkema, R.; Krenning, E.P. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr. Relat. Cancer 2011, 18, S27–S51.
9. Yao, J.C.; Hassan, M.; Phan, A.; Dagohoy, C.; Leary, C.; Mares, J.E.; Abdalla, E.K.; Fleming, J.B.; Vauthey, J.-N.; Rashid, A.; et al. One Hundred Years After “Carcinoid”: Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J. Clin. Oncol. 2016, 26, 3063–3072.
10. Modlin, I.M.; Oberg, K.; Chung, D.C.; Jensen, R.T.; de Herder, W.W.; Thakker, R.V.; Caplin, M.; Fave, G.D.; Kaltsas, G.A.; Krenning, E.P.; et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008, 9, 61–72.
11. De Baere, T.; Deschamps, F.; Tselikas, L.; Ducreux, M.; Planchard, D.; Pearson, E.; Berdelou, A.; Leboulleux, S.; Elias, D.; Baudin, E. GEP-NETS UPDATE: Interventional radiology: Role in the treatment of liver metastases from GEP-NETs. Eur. J. Endocrinol. 2015, 172, R151–R166.
12. Rajekar, H.; Bogammana, K.; Stubbs, R.S. Selective Internal Radiation Therapy for Gastrointestinal Neuroendocrine Tumour Liver Metastases: A New and Effective Modality for Treatment. Int. J. Hepatol. 2011, 2011, 404916.
13. Jann, H.; Denecke, T.; Koch, M.; Pape, U.F.; Wiedenmann, B.; Pavel, M. Impact of Octreotide Long-Acting Release on Tumour Growth Control as a First-Line Treatment in Neuroendocrine Tumours of Pancreatic Origin. Neuroendocrinology 2013, 98, 137–143.
14. Bison, S.M.; Konijnenberg, M.W.; Melis, M.; Pool, S.E.; Bernsen, M.R.; Teunissen, J.J.M.; Kwekkeboom, D.J.; de Jong, M. Peptide receptor radionuclide therapy using radiolabeled somatostatin analogs: Focus on future developments. Clin. Transl. Imaging 2014, 2, 55–66.
15. Panzuto, F.; Rinzivillo, M.; Fazio, N.; de Braud, F.; Luppi, G.; Zatelli, M.C.; Lugli, F.; Tomassetti, P.; Riccardi, F.; Nuzzo, C.; et al. Real-World Study of Everolimus in Advanced Progressive

Neuroendocrine Tumors. Oncologist 2015, 20, 570.

16. Dong, M.; Phan, A.T.; Yao, J.C. New Strategies for Advanced Neuroendocrine Tumors in the Era of Targeted Therapy. Clin. Cancer Res. 2012, 18, 1830–1836.
17. Kulke, M.H.; Bendell, J.; Kvols, L.; Picus, J.; Pommier, R.; Yao, J. Evolving Diagnostic and Treatment Strategies for Pancreatic Neuroendocrine Tumors. J. Hematol. Oncol. 2011, 4, 1–8.
18. Zaknun, J.J.; Bodei, L.; Mueller-Brand, J.; Pavel, M.E.; Baum, R.P.; Hörsch, D.; O'Dorisio, M.S.; O'Dorisiol, T.M.; Howe, J.R.; Cremonesi, M.; et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. Eur. J. Nucl. Med. Mol. Imaging 2013, 40, 800–816.
19. Reubi, J.C.; Schaer, J.-C.; Laissue, J.A.; Waser, B. Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels. Metab.-Clin. Exp. 1996, 45, 39–41.
20. Kwekkeboom, D.J.; Krenning, E.P. Somatostatin receptor imaging. Semin. Nucl. Med. 2002, 32, 84–91.
21. Reubi, J.; Waser, B.; Schaer, J.-C.; Laissue, J.A. Somatostatin receptor sst1–sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur. J. Nucl. Med. 2001, 28, 836–846.
22. Reubi, J.C.; Schär, J.-C.; Waser, B.; Wenger, S.; Heppeler, A.; Schmitt, J.S.; Mäcke, H.R. Affinity profiles for human somatostatin receptor subtypes SST1–SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur. J. Nucl. Med. 2000, 27, 273–282.
23. Heppeler, A.; Froidevaux, S.; Mäcke, H.R.; Jermann, E.; Béhé, M.; Powell, P.; Hennig, M. Radiometal-Labelled Macrocyclic Chelator-Derivatised Somatostatin Analogue with Superb Tumour-Targeting Properties and Potential for Receptor-Mediated Internal Radiotherapy. Chem. Eur. J. 1999, 5, 1974–1981.
24. Ducreux, M.; Ruszniewski, P.; Chayvialle, J.-A.; Blumberg, J.; Cloarec, D.; Michel, H.; Raymond, J.M.; Dupas, J.-L.; Gouerou, H.; Jian, R.; et al. The Antitumoral Effect of the Long-Acting Somatostatin Analog Lanreotide in Neuroendocrine Tumors. Am. J. Gastroenterol. 2000, 95, 3276–3281.
25. Strosberg, J.; El-Haddad, G.; Wolin, E.; Hendifar, A.; Yao, J.; Chasen, B.; Mittra, E.; Kunz, P.L.; Kulke, M.H.; Jacene, H.; et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. N. Engl. J. Med. 2017, 376, 125–135.
26. Baum, R.P.; Kluge, A.W.; Kulkarni, H.; Schorr-Neufing, U.; Niepsch, K.; Bitterlich, N.; van Echteld, C.J. [177Lu-DOTA]0-D-Phe1-Tyr3-Octreotide (177Lu-DOTATOC) For Peptide Receptor Radiotherapy in Patients with Advanced Neuroendocrine Tumours: A Phase-II Study. Theranostics 2016, 6, 501–510.

27. Schuchardt, C.; Kulkarni, H.R.; Prasad, V.; Zachert, C.; Müller, D.; Baum, R.P. The Bad Berka Dose Protocol: Comparative Results of Dosimetry in Peptide Receptor Radionuclide Therapy Using 177Lu-DOTATATE, 177Lu-DOTANOC, and 177Lu-DOTATOC. Recent Results Cancer Res. 2013, 194, 519–536.
28. Teunissen, J.J.M.; Kwekkeboom, D.J.; de Jong, M.; Esser, J.P.; Valkema, R.; Krenning, E.P. Peptide receptor radionuclide therapy. Best Pract. Res. Clin. Gastroenterol. 2005, 19, 595–616.
29. De Jong, M.; Breeman, W.A.P.; Valkema, R.; Bernard, B.F.; Krenning, E.P. Combination Radionuclide Therapy Using 177Lu- and 90Y-Labeled Somatostatin Analogs. J. Nucl. Med. 2005, 46, 13S–17S.
30. Kunikowska, J.; Królicki, L.; Hubalewska-Dydejczyk, A.; Mikołajczak, R.; Sowa-Staszczak, A.; Pawlak, D. Clinical results of radionuclide therapy of neuroendocrine tumours with 90 Y-DOTATATE and tandem 90Y/177Lu-DOTATATE: Which is a better therapy option? Eur. J. Nucl. Med. Mol. Imaging 2011, 38, 1788–1797.
31. Seregni, E.; Maccauro, M.; Chiesa, C.; Mariani, L.; Pascali, C.; Mazzaferro, V.; De Braud, F.; Buzzoni, R.; Milione, M.; Lorenzoni, A.; et al. Treatment with tandem [90Y]DOTA-TATE and [177Lu]DOTA-TATE of neuroendocrine tumours refractory to conventional therapy. Eur. J. Nucl. Med. Mol. Imaging 2013, 41, 223–230.
32. Kwekkeboom, D.J.; De Herder, W.W.; Kam, B.L.; Van Eijck, C.H.; Van Essen, M.; Kooij, P.P.; Feelders, R.A.; Van Aken, M.O.; Krenning, E.P. Treatment With the Radiolabeled Somatostatin Analog [177Lu-DOTA0,Tyr3]Octreotate: Toxicity, Efficacy, and Survival. J. Clin. Oncol. 2008, 26, 2124–2130.
33. Pavel, M.; O'Toole, D.; Costa, F.; Capdevila, J.; Gross, D.; Kianmanesh, R.; Krenning, E.; Knigge, U.; Salazar, R.; Pape, U.-F.; et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016, 103, 172–185.
34. Ezziddin, S.; Attassi, M.; Yong-Hing, C.J.; Ahmadzadehfar, H.; Willinek, W.; Grünwald, F.; Guhlke, S.; Biersack, H.-J.; Sabet, A. Predictors of Long-Term Outcome in Patients with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors After Peptide Receptor Radionuclide Therapy with 177Lu-Octreotate. J. Nucl. Med. 2014, 55, 183–190.
35. Nagtegaal, I.D.; Odze, R.D.; Klimstra, D.; Paradis, V.; Rugge, M.; Schirmacher, P.; Washington, K.M.; Carneiro, F.; Cree, I.A. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020, 76, 182–188.
36. Modlin, I.M.; Frilling, A.; Salem, R.R.; Alaimo, D.; Drymousis, P.; Wasan, H.S.; Callahan, S.; Faiz, O.; Weng, L.; Teixeira, N.; et al. Blood measurement of neuroendocrine gene transcripts defines the effectiveness of operative resection and ablation strategies. Surgery 2016, 159, 336–347.

37. Bodei, L.; Kidd, M.; Modlin, I.M.; Severi, S.; Drozdov, I.; Nicolini, S.; Kwekkeboom, D.J.; Krenning, E.P.; Baum, R.P.; Paganelli, G. Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of peptide receptor radionuclide therapy (PRRT) in neuroendocrine tumors. Eur. J. Nucl. Med. Mol. Imaging 2016, 43, 839–851.
38. Lapa, C.; Werner, R.A.; Bluemel, C.; Lueckerath, K.; Muegge, D.O.; Strate, A.; Haenscheid, H.; Schirbel, A.; Allen-Auerbach, M.S.; Bundschuh, R.A.; et al. Prediction of clinically relevant hyperkalemia in patients treated with peptide receptor radionuclide therapy. EJNMMI Res. 2014, 4, 74.
39. Pfob, C.H.; Eiber, M.; Luppa, P.; Maurer, F.; Maurer, T.; Tauber, R.; D'Alessandria, C.; Feuerecker, B.; Scheidhauer, K.; Ott, A.; et al. Hyperkalemia in patients treated with endoradiotherapy combined with amino acid infusion is associated with severe metabolic acidosis. EJNMMI Res. 2018, 8, 1271.