HHS Public Access

Author manuscript

PET Clin. Author manuscript; available in PMC 2015 October 23.

Published in final edited form as:

PET Clin. 2015 October ; 10(4): 477–486. doi:10.1016/j.cpet.2015.06.001.

Application and dosimetric requirements for ^{68}Ga-labeled somatostatin analogues in targeted radionuclide therapy for gastroenteropancreatic neuroendocrine tumors

David Taïeb[1,2,3], **Philippe Garrigue**[4], **Manuel Bardiès**[5], **Abdullah Ahmad Esmaeel**[1], and **Karel Pacak**[6]

[1]Department of Nuclear Medicine, La Timone University Hospital, Aix-Marseille University, Marseille, France

[2]European Center for Research in Medical Imaging, Aix-Marseille University, Marseille, France

[3]Inserm UMR1068 Marseille Cancerology Research Center, Institut Paoli-Calmettes, Marseille, France

[4]Department of Radiopharmacy, La Timone University Hospital, Aix-Marseille University, Marseille, France

[5]UMR 1037 Inserm/UPS, Cancer Research Center of Toulouse, France

[6]Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD), National Institutes of Health, Bethesda, Maryland, 20892 USA

Abstract

Neuroendocrine tumors (NETs) are associated with variable prognosis, with grade 1 and 2 NETs having a more favorable outcome than G3 ones (also called carcinoma). GEP-NET patients need highly individualized interdisciplinary evaluations and treatment. New treatment options have become available (i.e., sunitinib, mTOR inhibitors) with significant improvements in progression-free survival. Peptide receptor radionuclide therapy (PRRT) using ^{90}Y or ^{177}Lu-labeled somatostatin analogs has also shown promise in the treatment of advanced progressive NETs but randomized clinical trials comparing with other modalities are still lacking. SST-targeting represents the essence of theranostics. ^{68}Ga-DOTA-SSTa can be used as companion imaging agents to assist in such a radionuclide therapy selection. ^{68}Ga-DOTA-SSTa PET/CT might also provide critical information for prognosis, tumor response assessement to PRRT, and internal dosimetry. It is also expected that the development of novel receptor-targeting radiopharmaceuticals will contribute to the development of molecular-based personalized medicine approaches.

Corresponding author: David Taïeb, MD, PhD, Biophysics and Nuclear Medecine, La Timone University Hospital, European Center for Research in Medical Imaging, Aix-Marseille University, 264, rue Saint-Pierre - 13385 Marseille, France, david.taieb@ap-hm.fr, PHONE/FAX: +33 (0) 4-91-38-44-06.

Disclosure summary: The authors have nothing to disclose.

Keywords

positron emission tomography; gallium radioisotopes; somatostatin; gastroenteropancreatic; neuroendocrine

1. Current views on molecular origins of GEP-NETs

Neuroendocrine tumors are neural crest-derived neoplasms with predominant neuroendocrine differentiation and arise in most organs of the body. They account for 0.5% (incidence 2/100,000) of all malignancies. The most frequent primary sites are the pancreas (PanNET), gastrointestinal tract, and lungs. They share some common biological features such as overexpression of somatostatin receptors (SST) in 70–100% of cases.

The pathogenesis of most NETs starts with inherited or somatic driver mutations in the genes that specifically regulate neuroendocrine cell proliferation [1]. Exonomic studies of sporadic pancreatic NETs (PanNETs) demonstrate somatic mutations in the MEN1 gene in 44% of these tumors, Daxx (death-domain-associated protein) and ATRX (α thalassemia/mental retardation syndrome X-linked) in 43%, and mTOR pathway genes (PTEN and TSC2) in 14% [2]. Some of the mutations are related to a loss in the integrity of telomere chromatins [3]. Recently, PHLDA3, a repressor of Akt activity, was proposed as a novel tumor suppressor of PanNETs [4].

The genetic pathogenesis of small intestine neuroendocrine tumors (midgut NETs) is less well understood. In contrast to PanNETs, exonomic studies demonstrate that somatic mutations are rare in midgut NETs [5].

2. Current management of metastatic GEP-NETs

The management of these tumors relies on several factors such as the presence of hormones/peptide hypersecretion-related symptoms, tumor stage, and grade. According to the ENETS recommendations, tumors are graded as follows: grade 1 (<2 mitoses/10 HPF i.e high power field on microscope and <3% Ki67 index), grade 2 (2–20 mitoses/10 HPF or 3–20% Ki67 index), and grade 3, also called NE carcinomas (>20 mitoses/10 HPF or >20% Ki67 index). In the case of disseminated disease, many treatment options are possible, with potential associations between systemic and locoregional approaches.

The systemic therapy of patients with progressive metastatic GEP-NETs has historically relied mainly on cytotoxic chemotherapy with some positive responses when using a combination of streptozotocin, 5FU, and doxorubicin (especially in PanNETs). In contrast, these treatments were found to have limited efficacy in midgut NETs. There has been breakthrough research in the last few years that has made rapid strides in the targeted therapies of NETs. Since most NETs are hypervascular, they can be targeted by antiangiogenic agents. Furthermore, they may also exhibit an activation of the mTOR signaling pathways and be treated with mTOR inhibitors.

In RADIANT-3, 410 patients with advanced PanNETs and progressive disease were randomly assigned to treatment with oral everolimus 10 mg/day or a placebo. Octreotide

LAR was administered at the discretion of the investigator [6]. Everolimus showed improved survival (11.0 months with everolimus compared to 4.6 months with the placebo) in the advanced, low-grade (Grade 1) or intermediate-grade (Grade 2) PanNETs with radiological progression [6]. In the RADIANT-2 study, 429 patients with advanced progressive midgut NETs were randomized to receive everolimus 10 mg/day plus octreotide LAR 30 mg/month or octreotide LAR plus a placebo [7]. In the study, the pre-defined threshold for statistical significance was not achieved. Therefore, the precise therapeutic activity of everolimus in advanced progressive midgut NETs has not been demonstrated [7]. However, if the tumor was somatostatin receptor positive, the CLARINET trial group has shown that Lanreotide is associated with prolonged progression-free survival among patients with metastatic midgut and pancreatic NETs of Grade 1 or 2 [8]. Sunitinib has also been proven to improve progression free survival and overall survival among patients with advanced PanNETs [9]. In summary, Grade 1 and 2 PanNETs and midgut NETs exihibit strikingly different drug response profiles.

3. SST PET/CT using ^{68}Ga-labeled somatostatin analogues

Well-differenciated neuroendocine tumors (NETs) often overexpress somatostatin receptors (SSTR) on their cell surfaces that could be targeted for diagnostic and therapeutic purposes by radiolabeling somatostatin analogs. Octreoscan® (^{111}In-DTPA-octreotide, Octreoscan®, Mallinckrodt), a synthetic octapeptide labeled with indium-111 was the first radiolabeled SST analog to be approved for scintigraphy of NETs and has been shown to be well suited for the scintigraphic localization of primary and metastatic NETs [10].

Beyond tumor localization, radionuclide imaging using radiolabeled peptides that target SST may be used to select who is likely to benefit from PRRT and to assess therepeutic responses to PRRT.

Scanning with Octreoscan® is usually performed at 4 and 24 hours after tracer injection. Repeat imaging may be required later. The sensitivity of Octreoscan® is widely dependent on SST density, tumor grade, and size. Also, in recent years, SPECT/CT has become more widely available and has the advantage of simultaneous acquisition of both anatomical and functional data, increasing diagnostic confidence in image interpretation and enhancing sensitivity in some cases. Octreoscan® scintigraphy is associated with practical constraints such as long imaging times, GI tract artifacts requiring bowel cleansing in some cases. The main disadvantage is the still low-resolution of the SPECT image, limiting the ability to detect tiny lesions. SPECT also does not provide a quantifiable estimate of the SST expression. Thus, PET imaging has been growing rapidly in the localization of paragangliomas (PGLs), paralleled by great efforts towards the development of new tracers.

The design of the radiotracer (isotope, chelator, peptidic sequence) dramatically affects the SST affinity (Figure 1). The generator-produced, positron-emitting gallium-68 (^{68}Ga) is a diagnostic trivalent radiometal with convenient labeling characteristics and is also easily available for the daily routine synthesis of ^{68}Ga-labeled radiopharmaceuticals.

1,4,7,10-Tetraazacyclodecane-1,4,7,10-tetraacetic acid (DOTA) was identified as a better chelator compared to pentetic acid (DTPA), increasing stability and SST targeting.

Numerous ^{68}Ga DOTA-conjugated SST analogs have been designed in order to increase affinity of these compounds to SST receptors, but three are mostly described: ^{68}Ga-DOTA$_0$-[Tyr^3]octreotide (^{68}Ga-DOTATOC), ^{68}Ga-DOTA$_0$-1-NaI^3-octreotide (^{68}Ga-DOTANOC) and [^{68}Ga-DOTA$_0$-Tyr^3]octreotate (^{68}Ga-DOTATATE). All of these bind to SST2. ^{68}Ga-DOTATATE has been shown to have the highest affinity for STT2 (IC50= 0.2 nM vs 2.5 nM for and DOTATOC and 1.9 nM for DOTANOC (Figure 1). DOTA-NOC also binds specifically to SST3, SST4 and SST5 receptors. DOTA-TOC binds to SST5 although with lower affinity than DOTA-NOC) [11–13]. In direct comparisons between ^{68}Ga-DOTA-SSTa PET/CT and ^{99m}Tc-HYNIC-Octreotide/^{111}In-pentetreotide SPECT(/CT), ^{68}Ga-DOTA-SSTa has performed better than other functional imaging technique, providing a compelling reason for switching from SPECT/CT to PET/CT imaging. PET/CT is also more suitable than SPECT/CT for quantifying the disease at a molecular level.

3. ^{68}Ga-labeled somatostatin analogues as theranostics for GEP-NETs

Peptide receptor radionuclide therapy (PRRT) has shown promise in the treatment of metastatic Grades 1 and 2 NETs [14,15]. ^{90}Y-octreotide and ^{177}Lu-octreotate (Lutathera®), have been shown to be efficient and effective therapeutic modalities [16] (Table 1). Response rates (mainly partial responses) have been 30–60% on average. Disease stabilization is frequent (20–50%) but more difficult to interpret [17–23]. Independent predictors of survival in advanced grade 1/2 PanNETs treated by ^{177}Lu-octreotate are the tumor proliferation index, the patient's performance status, tumor burden, and baseline plasma NSE level [23]. For advanced NET of the small intestine, tumor functional status and high plasma chromogranin A appeared to be independent predictors of unfavorable patient outcome [24].

Randomized clinical trials comparing with other modalities are still lacking [25].

It is worth noting the ongoing trials that compare the use peptide receptor radionuclide therapy with ^{177}Lu-octreotate in GEPNETS against a range of other molecules. These were obtained from the database of clinicaltrials.gov.

The (CONTROL NETS) is an open label phase two study that involves two parallel trials, the first comparing PRRT therapy (^{177}Lu-octreotate) plus Capecitabine/Temozolomide (CAP/TEM) against: (a) Lu177-DOTATATE alone in the treatment of low to intermediate grade mid gut neuroendocrine tumours; (b) CAP/TEM alone in the treatment of low to intermediate grade pancreatic neuroendocrine tumours. A further study is comparing treatment with ^{177}Lu-octreotate against Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours (NETTER-1).

The french OCLURANDOM study is a randomized, open-label, multicenter trial that assesses the safety and efficacy of ^{177}Lu-octreotate versus Sunitinib in pre-treated progressive well differentiated pancreatic neuroendocrine tumours and is expected to be finalised in 2023. Another study is comparing ^{177}Lu-octreotate against interferon α-2b in progressive non-pancreatic gastrointestinal neuroendocrine tumors that are non-resectable and resistant to therapy with somatostatin analogues, its estimated completion date is the end of 2016.

In 2014, the FDA defined a companion diagnostic device (CDD) as an "*in vitro* […] or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product" publishing an exhaustive list of consequent examples. Most of these were *in vitro* diagnostic devices like immunohistochemistry and FISH/CISH kits, with the aim of predicting the utility of therapeutic monoclonal antibodies upon one target (or more) expressed by the tumor. CDDs in imaging, and particularly in PRRT, are emerging.

PET/CT using gallium-68-labeled SST analogs is a prime example of a PET-based theranostic approach. A close correlation was found between SUVmax and immunohistochemical scores used for the quantitative assessment of the density of subtypes of SST [26]. Until present, the Krenning scale remains the unique validated scoring system for selecting good candidates for PRRT [27]. Validation of a new scoring system adapted to ^{68}Ga-DOTA-SSTa PET/CT would be of particular interest.

DOTANOC/TOC/TATE can be radiolabelled with lutetium-177 for PRRT with a lower energy deposit and a shorter tissue penetration than ^{90}Y. It has to be underlined that exactly the same peptide should be used for CDD imaging to avoid potential discordances [28–30](Figure 2).

4. Prognostic value and tumor response assessement to PRRT

PET/CT with ^{68}Ga-DOTA-SSTa might also provide prognostic information. Increased tumor avidity for ^{68}Ga-DOTA-SSTa was found to be associated with prolonged survival [31]. Sequential evaluation of metastatic NET patients by ^{68}Ga-DOTA-SSTa PET/CT and ^{18}F-FDG PET/CT that is often also complementary and points towards aggressiveness of these tumors should be recommended at baseline for comprehensive NET grading of patients with these tumors. It was found that patients with high tumor ^{68}Ga-DOTA-SSTa avidity and low ^{18}F-FDG uptake have a better prognosis and are good candidates for PRRT (27). Decrease in tumor-to-spleen SUV ratio (and not SUVmax) after the first PRRT cycle is associated with a longer progression-free survival [32], although additional confirmatory studies are needed. However, PRRT in these tumors, in contrast to other tumor types, usually results in smaller tumor size responses compared to functional status responses (e.g., done by monitoring secretory status of these tumors), which are often very substantial. Thus, response evaluation criteria in solid tumors (RECIST) and World Health Organization criteria for classifying tumor response is less adapted to the evaluation of targeted therapies and PRRT since only a small percentage of patients show a significant decline in tumor size despite their clinical and biochemical improvements. Furthermore, it is widely recognized that molecular/functional responses precede morphological responses and therefore enable an earlier evaluation of overall therapy response.

5. Internal dosimetry

Internal dosimetry enables a personalized approach to patient treatment. The dream of a common dosimetry protocol applicable to all targeted radionuclide therapy (TRT) procedures is a widespread misconception, possibly derived from the wish to standardize therapeutic applications in nuclear medicine.

TRT dosimetry must be implemented in order to answer a clinical question. The fact is that dosimetry implementations, as seen in the literature, are diverse and depend on the clinical context (the aim of the therapy) and the radiopharmaceutical and its mode of administration. In addition, the isotope attached to the biological vector will impact the methodology that can be implemented. In other words, safety-related dosimetry will focus of organs at risk (OARs) whereas efficacy-related dosimetry will focus on tumors [33].

This is consistent with legal requirements, derived from EURATOM Directive 97/43 and the more recent 2013/59 that states: “For all medical exposure of patients for radiotherapeutic purposes, exposures of target volumes shall be individually planned and their delivery appropriately verified taking into account that doses to non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.” In that respect, *dosimetry that works* should establish the relation between injected activity and observed biological or clinical effect: “The objective of dosimetry in targeted radionuclide therapy is to provide information that will help improve patient care. With this objective, estimated absorbed dose is useful to the extent that it relates to response” [34]. In that sense, dosimetry is the missing link that allows for real treatment personalization.

The current administration scheme of ^{177}Lu-labeled peptides is based on repeated administrations of fixed activities, most often 4 to 6 cycles of 7.4 GBq of radiophamarceutical.

- The front-line OAR is the kidney, as toxicity has been observed in that kind of treatment, even though initially with ^{90}Y-labelled peptides. This explains why the renal function is followed during the course of the treatment. Suspicion of kidney toxicity may lead to a decrease injected activities or even stop the treatment.
- The second OAR is bone marrow.
- Tumor dosimetry has been reported, even though to-date more as a way to document the therapy than as a means to define the posology. However, a significant correlation between absorbed dose and tumor reduction was reported [35].

D*osimetry that works* in PRRT should aim at assessing kidneys, bone marrow, and tumor absorbed doses, with the aim of establishing the relationship between absorbed dose and observed effect.

Regarding clinical dosimetry, the well-known ^{90}Y-DOTATOC trial yielded very important conclusions [36]:

- Activity quantification (and cumulated activity determination) is of paramount importance. ^{86}Y-DOTATOC was used to assess pharmacokinetics [37], a far from trivial task as ^{86}Y is a “dirty isotope” with low positron abundance and emits a high proportion of single gammas in the range of the coincidence window [38].
- The model used for absorbed dose calculation also has a major impact: By moving from a “standard” kidney model for all patients to a better accounting of patient-

specific kidney volume, the correlation between absorbed dose and kidney toxicity significantly improved.

- Accounting for radiobiological parameters (computation of the Biologic Equivalent Dose – BED) allowed to further improve the correlation. It is remarkable that this was accomplished by deriving BED values from parameters issued from External Beam Radiotherapy, thereby illustrating the fact that a quite robust phenomenon is supporting that absorbed dose effect correlation [39].
- In a retrospective study, Walrand et al. also demonstrate a good correlation between red marrow absorbed dose and platelet count reduction at the nadir.

For ^{177}Lu-labelled PRRT, kidney toxicity is far less frequent [20], a fact that can be explained partly by the different range of radiation emitted by ^{177}Lu as compared to ^{90}Y [40]. This makes the determination of the absorbed dose (or surrogate)–effect relationship more difficult to characterize.

Dosimetry with ^{177}Lu-labelled peptides, when performed, is usually meant to insure that the absorbed dose (or surrogate) delivered to kidney will not exceed a certain threshold (safety). Nephrotoxicity is increased in patients with baseline impaired renal function and is more frequently observed in those who develop hematotoxicity during PRRT. Nephroptection by using positively charged molecules such as L-lysine and/or L–arginine (which competitively inhibit the proximal tubular reabsorption of the radiopeptide) is recommended.

There is usually no pre-therapeutic dosimetry: absorbed dose is assessed for every therapy cycle, in order to insure that the next cycle can be safely administered. This “conservative” approach relies on the hypothesis that intra-patient pharmacokinetics variability is inferior to inter-patient variability.

On principle, that scheme could be used to modulate injected activity—as is done, for example, in ^{131}I-mIBG neuroblastoma Molecular Radiotherapy where the absorbed dose assessed for the first, fixed injection (444 MBq/kg) is used to derive the activity to administer for the second injection, under the constraint of limiting the whole body absorbed dose below 4 Gy [41].

The fact is that ^{177}Lu-labelled PRRT, as currently delivered, is not very toxic: the maximum tolerated absorbed dose has probably not been reached, and therefore absorbed dose–toxicity correlations are difficult to put in evidence. In that context, it is difficult to conclude: a potential reason for that apparent absence of correlation could lie in methodological flaws in the dosimetric protocol implemented, but a more trivial reason could be that the lack of effect limits the possibility of evaluating the dose-response relationship.

The dosimetric protocols implemented suffer from a very high heterogeneity, and the comparison and appraisal of uncertainties is very difficult to get [42].

Most protocols implement 2D whole body dosimetry at different times after injection (3 to 7 time-points), even though this approach is known to be limited, essentially due to the overlap of source contribution in Ant-Post projections and the difficulty of correcting for

background. Time sampling is also very variable, and this is known to markedly impact the determination of cumulated activities [43]. Even for 3D approaches, protocols can hardly be compared.

A discussion of the current means to derive dosimetry for PRRT is given in an article from Cremonesi [42]. In figure 2, they present the various possibilities offered for pre- and post-therapeutic dosimetry. The possibility of using ^{68}Ga as a surrogate isotope for quantitative imaging PET studies is mentioned. However, due to the very short physical half-life of ^{68}Ga (68 min) compared to ^{90}Y and ^{177}Lu, data collection can only be performed for up to a few hours after the injection (Table 1). This, on principle, should rule out ^{68}Ga for dosimetric studies. However, some recent studies highlighted the potential of ^{68}Ga for assessing the response to PRRT [32,44]. This means that the “effect” of the absorbed dose–effect relationship can be identified. It is therefore tempting to see how ^{68}Ga could be used in a dosimetric context. Velikyan proposed an elegant concept for combining the good activity quantification obtained from ^{68}Ga PET imaging with late data acquisition from ^{177}Lu blood sampling or quantitative SPECT imaging. This approach certainly deserves to be studied. Beyond internal dosimetry, there are also unidentified individual susceptibilities to radiation-associated disease [45].

Conclusion

Theranostics of GEP-NETs based on ^{68}Ga-labeled-SSTa PET imaging and targeted therapy applying PRRT with ^{90}Y and/or ^{177}Lu-labeled SSTa has paved the way to personalized medicine (Figure 3). Future directions include the clinical use of somatostatin antagonists as targeting peptides for imaging and therapy [46] and the development of novel receptor-targeting radiopharmaceuticals that will offer exciting perspectives for theranostics of NETs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Lewis MA, Yao JC. Molecular pathology and genetics of gastrointestinal neuroendocrine tumours. Curr Opin Endocrinol Diabetes Obes. Feb; 2014 21(1):22–27. [PubMed: 24310147]
2. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. Mar 4; 2011 331(6021):1199–1203. [PubMed: 21252315]
3. Marinoni I, Kurrer AS, Vassella E, et al. Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology. Feb; 2014 146(2):453–460. e455. [PubMed: 24148618]
4. Ohki R, Saito K, Chen Y, et al. PHLDA3 is a novel tumor suppressor of pancreatic neuroendocrine tumors. Proc Natl Acad Sci U S A. Jun 10; 2014 111(23):E2404–2413. [PubMed: 24912192]
5. Banck MS, Kanwar R, Kulkarni AA, et al. The genomic landscape of small intestine neuroendocrine tumors. J Clin Invest. Jun 3; 2013 123(6):2502–2508. [PubMed: 23676460]
6. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. The New England journal of medicine. Feb 10; 2011 364(6):514–523. [PubMed: 21306238]
7. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2):

a randomised, placebo-controlled, phase 3 study. Lancet. Dec 10; 2011 378(9808):2005–2012. [PubMed: 22119496]

8. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. The New England journal of medicine. Jul 17; 2014 371(3):224–233. [PubMed: 25014687]
9. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. The New England journal of medicine. Feb 10; 2011 364(6):501–513. [PubMed: 21306237]
10. Baum RP, Kulkarni HR, Carreras C. Peptides and receptors in image-guided therapy: theranostics for neuroendocrine neoplasms. Semin Nucl Med. May; 2012 42(3):190–207. [PubMed: 22475428]
11. Wild D, Macke HR, Waser B, et al. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. Eur J Nucl Med Mol Imaging. Jun.2005 32(6):724. [PubMed: 15551131]
12. Wild D, Schmitt JS, Ginj M, et al. DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. Eur J Nucl Med Mol Imaging. Oct; 2003 30(10):1338–1347. [PubMed: 12937948]
13. Reubi JC, Schar JC, Waser B, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. Mar; 2000 27(3):273–282. [PubMed: 10774879]
14. Ezziddin S, Opitz M, Attassi M, et al. Impact of the Ki-67 proliferation index on response to peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging. Mar; 2011 38(3):459–466. [PubMed: 20852858]
15. Ezziddin S, Attassi M, Yong-Hing CJ, et al. Predictors of long-term outcome in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors after peptide receptor radionuclide therapy with 177Lu-octreotate. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. Feb; 2014 55(2):183–190.
16. Bodei L, Cremonesi M, Kidd M, et al. Peptide receptor radionuclide therapy for advanced neuroendocrine tumors. Thoracic surgery clinics. Aug; 2014 24(3):333–349. [PubMed: 25065935]
17. Waldherr C, Pless M, Maecke HR, et al. Tumor response and clinical benefit in neuroendocrine tumors after 7.4 GBq (90)Y-DOTATOC. J Nucl Med. May; 2002 43(5):610–616. [PubMed: 11994522]
18. Kwekkeboom DJ, de Herder WW, Kam BL, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol. May 1; 2008 26(13):2124–2130. [PubMed: 18445841]
19. Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. Jun 10; 2011 29(17):2416–2423. [PubMed: 21555692]
20. Bodei L, Cremonesi M, Grana CM, et al. Peptide receptor radionuclide therapy with (1)(7)(7)Lu-DOTATATE: the IEO phase I-II study. Eur J Nucl Med Mol Imaging. Dec; 2011 38(12):2125–2135. [PubMed: 21892623]
21. Danthala M, Kallur KG, Prashant GR, Rajkumar K, Raghavendra Rao M. (177)Lu-DOTATATE therapy in patients with neuroendocrine tumours: 5 years' experience from a tertiary cancer care centre in India. Eur J Nucl Med Mol Imaging. Jul; 2014 41(7):1319–1326. [PubMed: 24570096]
22. Paganelli G, Sansovini M, Ambrosetti A, et al. 177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study. Eur J Nucl Med Mol Imaging. Oct; 2014 41(10):1845–1851. [PubMed: 24615468]
23. Ezziddin S, Khalaf F, Vanezi M, et al. Outcome of peptide receptor radionuclide therapy with 177Lu-octreotate in advanced grade 1/2 pancreatic neuroendocrine tumours. Eur J Nucl Med Mol Imaging. May; 2014 41(5):925–933. [PubMed: 24504504]
24. Sabet A, Dautzenberg K, Haslerud T, et al. Specific efficacy of peptide receptor radionuclide therapy with Lu-octreotate in advanced neuroendocrine tumours of the small intestine. Eur J Nucl Med Mol Imaging. Mar 26.2015
25. van der Zwan WA, Bodei L, Mueller-Brand J, de Herder W, Kvols L, Kwekkeboom D. GEP-NETS update: Radionuclide therapy in neuroendocrine tumors. European journal of endocrinology/European Federation of Endocrine Societies. Aug 12.2014

26. Kaemmerer D, Peter L, Lupp A, et al. Molecular imaging with (6)(8)Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours. Eur J Nucl Med Mol Imaging. Sep; 2011 38(9):1659–1668. [PubMed: 21626438]
27. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [111In-DTPA-D-Phe1]- and [123I-Tyr3]-octreotide: the Rotterdam experience with more than 1000 patients. Eur J Nucl Med. Aug; 1993 20(8):716–731. [PubMed: 8404961]
28. Wild D, Bomanji JB, Benkert P, et al. Comparison of 68Ga-DOTANOC and 68Ga-DOTATATE PET/CT within patients with gastroenteropancreatic neuroendocrine tumors. J Nucl Med. Mar; 2013 54(3):364–372. [PubMed: 23297077]
29. Basu S, Abhyankar A, Kand P, et al. 'Reverse discordance' between 68Ga-DOTA-NOC PET/CT and 177Lu-DOTA-TATE posttherapy scan: the plausible explanations and its implications for high-dose therapy with radiolabeled somatostatin receptor analogs. Nucl Med Commun. Jul; 2011 32(7):654–658. [PubMed: 21654355]
30. Damle NA, Bal C, Gupta S, Singhal A. Discordance in 68Ga-DOTANOC and 177Lu-DOTATATE uptake in diagnostic and post-therapy scans in patients with medullary thyroid cancer-likely reasons. J Cancer Res Ther. Oct-Dec;2013 9(4):754–755. [PubMed: 24518738]
31. Campana D, Ambrosini V, Pezzilli R, et al. Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. J Nucl Med. Mar; 2010 51(3):353–359. [PubMed: 20150249]
32. Haug AR, Auernhammer CJ, Wangler B, et al. 68Ga-DOTATATE PET/CT for the early prediction of response to somatostatin receptor-mediated radionuclide therapy in patients with well-differentiated neuroendocrine tumors. J Nucl Med. Sep; 2010 51(9):1349–1356. [PubMed: 20720050]
33. Strigari L, Konijnenberg M, Chiesa C, et al. The evidence base for the use of internal dosimetry in the clinical practice of molecular radiotherapy. Eur J Nucl Med Mol Imaging. Oct; 2014 41(10): 1976–1988. [PubMed: 24915892]
34. Sgouros G. Toward patient-friendly cell-level dosimetry. J Nucl Med. Apr; 2007 48(4):496–497. [PubMed: 17401083]
35. Ilan E, Sandstrom M, Wassberg C, et al. Dose response of pancreatic neuroendocrine tumors treated with peptide receptor radionuclide therapy using 177Lu-DOTATATE. J Nucl Med. Feb; 2015 56(2):177–182. [PubMed: 25593115]
36. Barone R, Borson-Chazot F, Valkema R, et al. Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship. J Nucl Med. Jan; 2005 46(Suppl 1):99S–106S. [PubMed: 15653658]
37. Walrand S, Jamar F, Mathieu I, et al. Quantitation in PET using isotopes emitting prompt single gammas: application to yttrium-86. Eur J Nucl Med Mol Imaging. Mar; 2003 30(3):354–361. [PubMed: 12634962]
38. Walrand S, Flux GD, Konijnenberg MW, et al. Dosimetry of yttrium-labelled radiopharmaceuticals for internal therapy: 86Y or 90Y imaging? Eur J Nucl Med Mol Imaging. May; 2011 38(Suppl 1):S57–68. [PubMed: 21484382]
39. Wessels BW, Konijnenberg MW, Dale RG, et al. MIRD pamphlet No. 20: the effect of model assumptions on kidney dosimetry and response--implications for radionuclide therapy. J Nucl Med. Nov; 2008 49(11):1884–1899. [PubMed: 18927342]
40. Konijnenberg M, Melis M, Valkema R, Krenning E, de Jong M. Radiation dose distribution in human kidneys by octreotides in peptide receptor radionuclide therapy. J Nucl Med. Jan; 2007 48(1):134–142. [PubMed: 17204710]
41. Flux GD, Chittenden SJ, Saran F, Gaze MN. Clinical applications of dosimetry for mIBG therapy. Q J Nucl Med Mol Imaging. Apr; 2011 55(2):116–125. [PubMed: 21386786]
42. Cremonesi M, Ferrari M, Di Dia A, et al. Recent issues on dosimetry and radiobiology for peptide receptor radionuclide therapy. Q J Nucl Med Mol Imaging. Apr; 2011 55(2):155–167. [PubMed: 21386788]
43. Guerriero F, Ferrari ME, Botta F, et al. Kidney dosimetry in (1)(7)(7)Lu and (9)(0)Y peptide receptor radionuclide therapy: influence of image timing, time-activity integration method, and risk factors. Biomed Res Int. 2013; 2013:935351. [PubMed: 23865075]

44. Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [(68)Ga]DOTATOC-PET/CT Predicts Response Probability of PRRT in Neuroendocrine Tumors. Mol Imaging Biol. Jun; 2015 17(3): 313–318. [PubMed: 25319765]

45. Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. Eur J Nucl Med Mol Imaging. Jan; 2015 42(1):5–19. [PubMed: 25273832]

46. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for Peptide receptor radionuclide therapy: a pilot study. J Nucl Med. Aug; 2014 55(8):1248–1252. [PubMed: 24963127]

Key points

- Peptide receptor radionuclide therapy (PRRT) using ^{177}Lu-labeled somatostatin analogs has also shown promise in the treatment of advanced progressive grades 1 and 2 NETs with response rates (mainly partial responses) observed in approximately 30% of cases.
- PET/CT using gallium-68-labeled SST analogs is a prime example of a PET-based theranostic approach by providing prognostic information, selecting good candidates for PRRT and enabling tumor response assessement to PRRT.

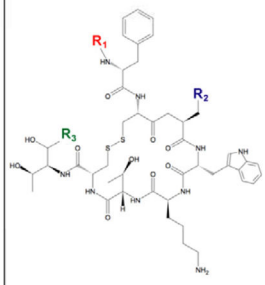
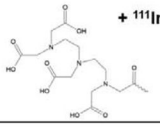
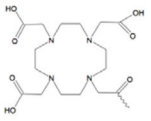
Octreotide derivative	R_1	R_2	R_3	Radiotracer	sst1	sst2	sst3	sst4	sst5
	+ ^{111}In 		H	^{111}In-pentetreotide	>10,000	22 ±3.6	182 ±13	>1,000	237 ±52
	+ ^{68}Ga or ^{90}Y or ^{177}Lu 		H	^{68}Ga-DOTANOC	>10,000	1.9 ±0.4	40 ±5.8	260 ±74	7.2 ±1.6
			H	^{68}Ga-DOTATOC	>10,000	2.5 ±0.5	613 ±140	>1,000	73 ±21
			O	^{68}Ga-DOTATATE	>10,000	0.2 ±0.04	>1,000	300 ±140	377 ±18

Figure 1.

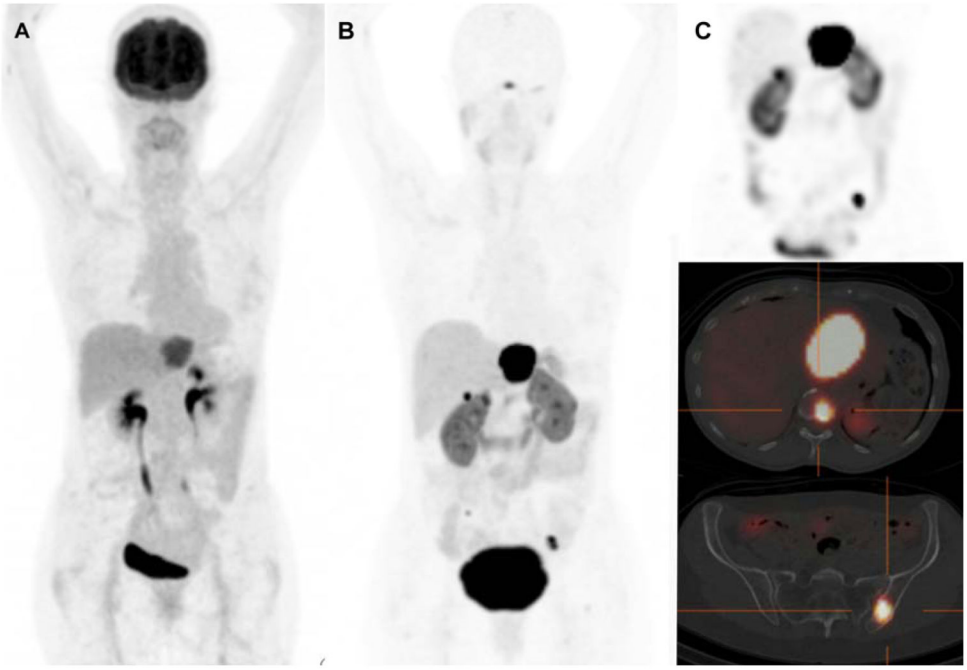


Figure 2.

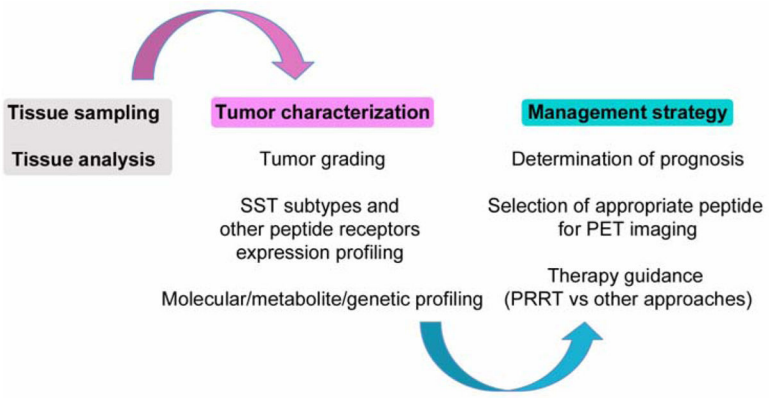


Figure 3.

Table 1

Type of intervention	Pooled number of patients	Number of studies	Complete remission CR	Partial response PR	Minor response MR	Stable disease SD	Favourable outcome CR+PR+MR+SD	Progressive disease PD	Median Progression Free Survival in months	Toxicity
177Lu-DOTATATE	988	12	14 (1.4%)	310 (31.4%)	112 (11.3%)	390 (39.5%)	826 (83.6%)	162 (16.4%)	32	• Nausea (29–35%) • Vomiting (10–18%) • Abdominal discomfort (6–11%) • Reversible hematotoxicity (5.9–22%) • Severe nephrotoxicity 1.3 %
Re-treatment with 177Lu-DOTATATE	88	3	3 (3.4%)	10 (11.4%)	7 (8%)	37 (42%)	57 (64.8%)	31 (35.2%)	18.5	• Reversible hematotoxicity 21.2 %
Dual tx 90Y-DOTATATE + 177Lu-DOTATATE	88	2	2 (2%)	26 (30%)	-	45 (51%)	73 (83%)	15 (17%)	18	• Reversible hematotoxicity (7–15%) • G1 renal toxicity 12%
177Lu-DOTATATE combined with chemotherapy	86	2	6 (7%)	28 (32%)	-	48 (56%)	82 (95%)	4 (5%)	39.5	**1** ***With Capecitabine*** **1.1** Transient hematoxicity G3/4 7% **1.2** Mild hand foot syndrome 9% **1.3** Thrombocytopenia G3 3% **2** ***With Temozolomide+Capecitabine*** **2.1** Nausea 21% **2.2** Transient hematotoxicity G3/4 16.2 % **2.3** Neutropenia G3 6% **2.4** Thrombocytopenia G2 24% **2.5** MDS 3% **3** ***With 5-FU*** **3.1** Thrombocytopenia G3/4 6% **3.2** Hepatotoxicity 11.5 % **3.3** Mean yearly reduction in GFR (with renal protection protocol) 2.2 ml/y

Table 2

	$T_{1/2}$ (h)	Eβmax (Mev)	Max tissue penetration range (mm)
^{68}Ga	1.08	1.9	10
^{90}Y	64.1	2.3	12
^{177}Lu	160.4	0.5	<2