Somatostatin Receptors and Analogs in Pheochromocytoma and Paraganglioma: Old Players in a New Precision Medicine World

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Neuroendocrine tumors overexpress somatostatin receptors, which serve as important and unique therapeutic targets for well-differentiated advanced disease. This overexpression is a well-established finding in gastroenteropancreatic neuroendocrine tumors which has guided new medical therapies in the administration of somatostatin analogs, both “cold”, particularly octreotide and lanreotide, and “hot” analogs, chelated to radiolabeled isotopes. The binding of these analogs to somatostatin receptors effectively suppresses excess hormone secretion and tumor cell proliferation, leading to stabilization, and in some cases, tumor shrinkage. Radioisotope-labeled somatostatin analogs are utilized for both tumor localization and peptide radionuclide therapy, with ⁶⁸Ga-DOTATATE and ¹⁷⁷Lu-DOTATATE respectively. Benign and malignant pheochromocytomas and paragangliomas also overexpress somatostatin receptors, irrespective of embryological origin. The pattern of somatostatin receptor overexpression is more prominent in succinate dehydrogenase subunit B gene mutation, which is more aggressive than other subgroups of this disease. While the Food and Drug Administration has approved the use of ⁶⁸Ga-DOTATATE as a radiopharmaceutical for somatostatin receptor imaging, the use of its radiotherapeutic counterpart still needs approval beyond gastroenteropancreatic neuroendocrine tumors. Thus, patients with pheochromocytoma and paraganglioma, especially those with inoperable or metastatic diseases, depend on the clinical trials of somatostatin analogs. The review summarizes the advances in the utilization of somatostatin receptor for diagnostic and therapeutic approaches in the neuroendocrine tumor subset of pheochromocytoma and paraganglioma; we hope to provide a positive perspective in using these receptors as targets for treatment in this rare condition.

Keywords: pheochromocytoma, paraganglioma, somatostatin receptors, somatostatin analog, peptide receptor radionuclide therapy, ⁶⁸Ga-DOTATATE, theranostic, PET/CT
INTRODUCTION

The theranostic revolution began over three decades ago, following the medical conception of somatostatin receptors (SSTRs) and their analogs (SSA). The identification of specific tumor targets for diagnosis and therapy of advanced diseases has been a continuing trend in oncology since its innovation. Neuroendocrine tumors (NETs) with the overexpression of SSTRs are ideal cancer models for discovering the dual ability of diagnosis and treatment using SSAs.

Two decades after the identification of somatostatin (SST) as the central regulator of neuroendocrine cell physiology in the early seventies, five SSTR subtypes were discovered (1–4). The discovery of SSTRs led to the successful introduction of somatostatin analogs (SSAs), initially as antisecretory agents, and recently as antiproliferative agents based on the results of two large phase III trials (5–7).

Through recognition of the SST molecular pathway, we can extrapolate how SSAs exert these physiologic functions. SST inhibits the secretion of neuroendocrine hormones by activating seven-transmembrane somatostatin receptors, a type of G-protein coupled receptor (GPCR). Activation of GPCR initiates a cascade of inhibiting adenyl cyclase, lowering intracellular cAMP, decreasing protein kinase A (PKA) activity, and inhibiting/activating Ca2+ and K+ channels, respectively. This sequence leads to a decrease in exocytosis of peptides, effectors, or ligands resulting in a reduction of hormone secretion (8–17). SST antiproliferative effect has been much more difficult to elucidate, involving various pathways that result in a global imbalance toward increased apoptosis, cell growth modulation, and decreased angiogenesis. Besides the reduction in growth factors (GF) release, SST exerts the effect through SSTR2 triggering and subsequent activation of phosphotyrosine phosphatases (PTPs). This causes a downregulation of the mitogen-activated protein kinase (MAPK) pathway and of tyrosine kinase receptor (TKR) phosphorylation, inducing cell cycle arrest and decreased cell proliferation (18–27).

Moreover, clinical imaging using radiolabeled SSAs to target SSTRs, known as somatostatin receptor imaging (SRI), became a prominent method in the diagnosis and management of NETs. The earliest success of SRI was pivotal in gastroenteropancreatic (GEP)-NETs and glomus paraganglioma (PGL) localization using 111In-pentetreotide (Octreoscan®) (28, 29). The progression of SRI in NETs increased with the introduction of radiolabeled isotope 68Ga-SSAs for positron emission tomography (PET) imaging. Then, Lutetium-177 (177Lu)-SSA was developed for peptide receptor radionuclide therapy (PRRT). A particular SST-based PRRT, 177Lu-DOTA0-Tyr3-Octreotate (177Lu-DOTATATE), was shown to be superior to other modalities in terms of progression-free survival (PFS) in a subset of GEPNETs (30). In 2018, based on the results of the NETTER-1 trial, 177Lu-DOTATATE (Lutathera®) was approved by the FDA for foregut, midgut, and hindgut GEPNET treatment. Current management algorithms for GEPNET patients use radiolabeled, and “cold” or unlabeled SSAs for their antiproliferative and cytotoxic abilities.

The discovery of SSTR overexpression in pheochromocytomas and paragangliomas (PPGLs) occurred in the 1990s (31), predicting a limitless therapeutic potential of SSA; however, its role in PPGL management was not developed in parallel with GEPNETs. Initial efficacy testing of SSAs, both cold and radiolabeled, was futile, mostly due to small clinical trials without any clear accrual of therapeutic benefits (32–34) in PPGLs. Despite the therapeutic responses of SSAs in GEPNETs showing significant success (35–39), the application of cold and radiolabeled SSA in PPGL was prematurely abandoned. In the last decade, there was a rise in the use of octreotide and radiolabeled SSA for recommended therapies approved by the FDA for both functioning and nonfunctioning GEPNETs, without enough studies confirming the clinical benefits of these compounds in PPGLs for federal approval. Figure 1 is a timeline comparing important findings and trials in SSTRs and 121 SSAs between NETs and PPGLs.

The primary therapy of choice for PPGL is surgical resection, but not in the case of unresectable advanced and metastatic tumors. A significant proportion of patients with PPGL is due to an inheritable genetic component, where the incidence of metastatic PPGL (mPPGL) occurs due to succinate dehydrogenase subunit B (SDHB) germline mutation patterns (49). Interestingly, SDHB-related PPGLs overexpress SSTRs, mainly SSTR2 (48). To advance and expand the clinical utilization of SSAs in this PPGL, it is imperative to view the SDHB subgroup as a prime example of clinical benefits that these analogs could provide.

This review summarizes the studies on the role of SSTRs focusing on PPGLs. We detail the discovery of PPGL receptors and the creation of diagnostic and therapeutic radionuclide-bound moieties to target these receptors. We also explore future perspectives for SSTRs and SSAs in driving precision-based care of PPGL patients.

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

PPGLs are rare NETs arising from neural crest cells, specifically chromaffin cells. Differentiated based on anatomic locations, tumors from the adrenal medulla are defined as pheochromocytoma (PCC), whereas tumors from the sympathetic and parasympathetic ganglia are known as paraganglioma (PGL). While both these tumors present with similar molecular findings on pathology, they vary in manifested symptoms based on their biochemical profile (50).

More than 20 susceptibility genes (SDHA, SDHB, SDHC, SDHD, SDHAF2, FH, VHL, EPAS1, CSDE1, MAML3, RET, NF1, MAX, HRAS, TMEM127, HIF2A, PHD1/2) indicate predisposition to PPGLs (50). SDHB-related PPGLs are considered aggressive, causing more than 40% of all the metastatic cases (47). The risk of metastatic progression necessitates early diagnosis and intervention for obtaining good outcome in patients. It is important to identify symptoms and perform laboratory tests using plasma or urine metanephrines to confirm the diagnosis, followed by tumor localization through imaging.
FIGURE 1 | Timeline of important events in the development of somatostatin receptors and targeting analogs in neuroendocrine tumors and Pheochromocytoma and Paragangliomas (1–7, 30, 40–48).
Imaging allows personalized therapy by assisting clinicians in deciding whether surgical interventions can render the patient disease-free. PPGLs occur in a wide range of anatomical locations, from the base of the skull to the bladder, making computed tomography (CT) with intravenous contrast the initial choice of imaging modality. However, magnetic resonance imaging (MRI) with or without gadolinium is recommended if there are contraindications to CT imaging, for example contrast allergy, pregnancy, young age, and surgical clip artifacts (51).

Several predictors increase the risk of metastases: PPGL tumor > 5 cm, noradrenergic phenotype, dopaminergic phenotype, familial PPGLs (especially SDHB and SDHA), young age at initial diagnosis, multiple tumors, and recurrent disease (52, 53). PPGLs are more likely to metastasize to the lungs, liver, bones, and lymph nodes (54). While MRI has high sensitivity and specificity for PPGLs, functional imaging has shown to surpass it (55, 56). The advent of functional imaging utilizing SSTRs dramatically improved PPGL localization and identification, enabling clinicians to guide precision medicine.

ADVENT OF SSTR-BASED IMAGING IN PHEOCHROMOCYTOMA AND PARAGANGLIOMA

Success in nuclear imaging of PPGLs was achieved in 1990, when Lamberts et al. conducted a study on three NETs, including one PGL, by labeling Tyr3-octreotide with radioisotope 123Iodine (123I-Tyr3-octreotide) to target SSTRs and capturing them using gamma cameras to produce single photon emission computed tomography (SPECT) and planar images. Results showed that 29 of the 31 possible PGLs were identified, and the two missed lesions were less than 5 mm in size (40). Although it was a relatively small study in terms of patient number, these findings on SRI-related PGLs could not be ignored. Subsequent studies improved the radiolabeled nucleotide by substituting 123Iodide with 111Indium in octreotide (111In-pentetreotide), chelated by a diethylene triamine penta-acetic acid (DTPA) group, thus solving the problems of short half-life half-life: 13 hours for 123Iodide versus 24-48 hours for 111Indium and obscured pathology identification due to biliary excretion with subsequent accumulation in the intestines (57). A study detected 94% of PGLs in 25 patients, and an additional 36% of tumors that were not recognized with conventional imaging [CT, ultrasound, 123I-metaiodobenzylguanidine (123I-MIBG), MRI, and bone scanning] were detected using 111In-pentetreotide. The study showed that using 111In-pentetreotide could identify the PGLs identified by conventional imaging and others that were not initially visualized (58). In PCCs, 123I-MIBG significantly outperformed 111In-pentetreotide in detection (57). 111In-pentetreotide had higher sensitivity than 123I-MIBG in detecting head and neck PGLs (HNPGLs) (59–61) and mPPGL (62, 63). The ability of 111In-pentetreotide to bind with SSTRs, especially SSTR2, provided an additional diagnostic tool for clinicians to identify PPGL; however, their sole gamma-emitting capability allows the application of only SPECT to visualize them. SPECT images do not provide spatial resolution to pinpoint the precise anatomical location of PPGL.

68Ga-BASED-SSA: A PREFERRED IMAGING RADIOISOTOPE IN PPGL

PET, which captures emitted positrons from radiotracers and combines them with low dose CT (PET-CT) for targeted receptor localization, was developed in the late nineteenth (64). Not only does PET have better spatial resolution than SPECT, it can also quantify radiotracer uptake in the form of a standardized uptake value (SUV) (65). To utilize PET-CT hybridized imaging, radiotracers -emitting positrons and targeting SSTRs were created. The first discovered radiotracer was a somatostatin analog 1-Nal3-octreotide (NOC) combined with 68Gallium (68Ga)-labeled 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), better known as 68Ga-DOTANOC. 68Ga-DOTANOC targets SSTR2,3, and 5 (66, 67) subtypes, while another moiety, 68Ga-labeled DOTA-Tyr3-octreotide (68Ga-DOTATOC), showed affinity for SSTR5, which is not specific to PPGLs. The last moiety of the three 68Ga-labeled DOTA peptides is 68Ga-DOTA-Tyr3-octreotide (68Ga-DOTATATE), which showed a strong tendency to bind with SSTR2 and is ideally suited for PPGLs because of the preferential expression of these SSTR subtypes (68). These three radiolabeled somatostatin analogs were compared with previous somatostatin-targeting 111In-pentotreotide. The overall sensitivities for NET detection, including metastatic lesions, were much higher with 68Ga-labeled DOTA-peptides by PET imaging than 111In-pentetreotide by SPECT imaging (69–75). While these studies were not specific to PPGL tumors, one study found 16 and 12 additional PGLs on 68Ga-DOTATATE compared to only two on 111In-pentetreotide (71). The other study included two patients with PGLs, comparing 68Ga-DOTATOC to 99mTechnetium-labeled hydrazinonicotinyl-Tyr3-octreotide (99mTc-HYNIC-TOC). While the study proved that 68Ga-labeled DOTA-peptide was superior, individual details of these PGL patients cannot be inferred from the analysis because it was performed on a regional basis, and on other NETs (75). There were no studies comparing the efficiency of 68Ga-DOTATATE to that of its predecessor, 111In-pentetreotide, but it was widely shown to be effective in tumors that express SSTRs. In an individual case of metastatic PGL with SDHD germline mutation, 68Ga-DOTATATE PET/CT produced higher resolution of tumors than Octreoscan (6), as seen in Figure 2.

Among the three radiolabeled somatostatin analogs, 68Ga-DOTATATE provided a brighter outlook for PPGL evaluation. SSTR expression by PPGLs, mainly extra-adrenal PGLs and mPPGLs, was found to be the subtype 2 variety (76). This subtype was the preferred target of 68Ga-DOTATATE (68). 68Ga-DOTATATE was shown to be superior to alternative PET radiotracers in imaging for genotypes, phenotypes, metastases, and PGL-predominant diseases. The two alternative PET radiotracers used to diagnose PPGLs,
18 Fluorine-fluorodeoxyglucose (18 F-FDG) and 18 F-fluorodihydroxyphenylalanine (18 F-FDOPA), were inferior to 68Ga-DOTATATE in the following cohorts of patients with:

i. sporadic metastatic PPGL (77)
ii. PGLs (78)
iii. HNPGLs (78, 79)
iv. metastatic SDHB PPGL (47)
v. SDHA PPGL (80)
vi. SDHD PPGL (81)
vii. pediatric SDHx PPGL (82).

At a molecular level, the utility of 68Ga-based SRI in these patient cohorts can be explained by the current knowledge that SDHx-based lesions and extra-adrenal PGLs have higher proportions of SSTR2 than other PPGL types. Even though 68Ga-DOTATATE has lower sensitivity in other types of PPGLs than 18 F-FDOPA, it remains the secondary radiopharmaceutical of choice in the evaluation of PPGL genotypic and phenotypic subtypes that do not fit in the cohorts mentioned above.

In two recent meta-analyses, 68Ga-DOTA-SSA had outperformed several radiotracers, including 18 F-FDOPA and 18 F-FDG. The pooled detection rate of unknown genetic mutational status in 68Ga-DOTA-SSA was 93% ([95% CI, 91%-95%], P < 0.005), higher than 80% in 18 F-FDOPA ([95% CI, 69%-88%], P < 0.005) or 74% in 18 F-FDG PET ([95% CI, 46%-91%], P < 0.005). The analyses showed that while genetic mutations can help select the type of radiotracers to be used in staging and diagnosing PPGL, it was not always required prior to the selection of 68Ga-DOTATATE, 68Ga-DOTATOC, and 68Ga-DOTANOC PET exams (83). A second meta-analysis pooled results of mPPGLs with germline mutational status, and the outcomes showed that 68Ga-DOTA-SSA PET/CT (0.97 [95% CI: 0.94-0.98]) detected more lesions than 18 F-FDG PET/CT (0.79 [95% CI: 0.69-0.87]) (84).

68Ga-DOTATATE PET/CT proved to be more than a complementary imaging modality to traditional CT and MRI imaging modalities. 68Ga-DOTATATE PET/CT has taken the place of 111In-pentetreotide (Octreoscan®) in becoming the SRI modality of choice in PPGLs, subject to the availability of a PET/CT scanner and radiotracer. It also outperformed 18 F-FDOPA and 18 F-FDG for detection of PGLs, mPGLs, HNPGLs, and SDHx PPGLs in adults and children. Figure 3 illustrates the superiority of 68Ga-DOTATATE PET/CT compared to 18 F-FDOPA and 18 F-FDG of metastatic lesions in a PPGL patient with a SDHB mutation. While 68Ga-DOTATATE PET/CT effectively localizes PPGL tumors, the benefit was ultimately attributed in conversion of the 68Ga radiometal to a stronger beta-emitting one for therapeutic purposes.

EXPERIENCES WITH PEPTIDE RECEPTOR RADIONUCLIDE THERAPY USING SOMATOSTATIN ANALOGS IN PPGLS

An interchange of radiolabeling on a chelated SSA (e.g., DOTATRA SSA) caused a functional switch of the molecular compound from diagnostic to therapeutic capabilities. 68Ga-DOTA-SSA precisely located SSTRs on the surface of PPGL lesions through the capture of 68Ga-beta emissions by PET/CT scanners. A change in radiometal to 177Lutetium (177Lu) or 90Yttrium (90Y) gave radiolabeled DOTA-SSA the ability to emit not only imageable radiations but also deliver beta radiations to the target lesions. Lutathera® was approved by the FDA for GEPNET treatment; hopefully, it is only a matter of larger-model experiences and extensive reporting until its approval in surgically unamenable or metastatic PPGLs. More trials and research are needed to determine its actual applicability in PPGLs and to support the studies mentioned in this section.

177 Lu-Based-SSA PRRT

A recent 2020 report by Basu et al. reviewed 1000 patients with NETs treated with 177 Lu-DOTATATE; 15 were diagnosed with
PPGL. A particular case of metastatic HNPPGL was detailed in the review, displaying stabilization of the disease after two cycles of $^{177}$Lu-DOTATATE on $^{68}$Ga-DOTATATE PET/CT (85) and should be considered in metastatic HNPPGL with associated SDHB mutations (86). The same team recently published a retrospective study highlighting disease control of progressive mPGL in 6 out of 9 patients treated with $^{177}$Lu-DOTATATE with negative $^{131}$I-MIBG scans. These patients tolerated treatment without any significant adverse events (87).

A retrospective study in 2019 by Vyakaranam et al. involved 22 PPGL patients (nine with progressive disease and 13 with stable disease at the start of PRRT) and their responses to $^{177}$Lu-DOTATATE. The response rates of the therapy, such as biochemical response, scintigraphy, response evaluation criteria in solid tumors (RECIST), overall survival (OS), and progression-free survival (PFS) showed favorable outcomes. $^{177}$Lu-DOTATATE showed that only one of the 19 patients reviewed with SPECT/CT had progressive disease, while with CT, according to RECIST 1.1, all patients either had stable disease (n=20) or partial response (n=2). The median OS calculated was 49.6 months and median PFS was 21.6 (88); these were not established in other recent studies (87, 89, 90).

Another retrospective study focused on 30 patients with either parasympathetic PGL, sympathetic PGL, or PCC; after four cycles of $^{177}$Lu-DOTATATE, results showed either stable disease or partial response in 90% of these patients. Among these patients, 20 had progressive disease prior to the start of $^{177}$Lu-DOTATATE, of which 85% showed the disease controlled post-treatment (91).

$^{90}$Y-Based-SSA PRRT

The alternative beta-emitting radiometal, $^{90}$Y, was utilized and studied in SSA-based PRRT. $^{90}$Y had shorter half-life, longer path length, and greater emitted energy compared to $^{177}$Lu (92, 93). $^{90}$Y also cannot be imaged using gamma cameras post-therapy because of its inherent property of being a sole beta emitter (93). With longer half-life, shorter path length, lower beta emission, and partial gamma emission, $^{177}$Lu had a significant advantage over $^{90}$Y; however, studies showed the therapeutic benefit of $^{90}$Y-labeled SSA as PRRT.

In a prospective study from 2019 by Kolansinska-Cwikla et al., 13 patients with metastatic SDHB and SDHD (n=5 and 8, respectively) were treated with $^{90}$Y-DOTATATE, with an 82% response of stable disease after 1 year. The median OS and PFS were 68 months and 35 months, respectively, with no difference in the endpoints in patients who were either secretory or non-secretory (94). A retrospective study assessing $^{90}$Y-DOTATATE and $^{131}$I-MIBG concluded that mPGLs were best suited for treatment by SSA-based PRRT. The study reviewed the treatment responses of 22 patients with mPCC or mPGL after three different targeted radionuclide therapies. While only two patients received $^{177}$Lu-DOTATATE, $^{90}$Y-DOTATATE performed better in terms of median PFS and RECIST 1.1 base response to treatment compared to $^{131}$I-MIBG (these were the two statistically significant findings) in mPGL with no significant difference observed when considering all the mPPGL patients (95).

These studies showed some positive responses to either $^{177}$Lu- or $^{90}$Y-based SSA therapy (Table 1, summarizing experiences using SSA-based PRRT therapies in PPGL). There are still insufficient data for FDA approval of these therapies for PPGLs.

**CLINICAL SIDE EFFECTS OF SOMATOSTATIN ANALOG BASED PEPTIDE RECEPTOR NUCLEOTIDE THERAPY**

The clinical side effects of SSA-based PRRT include nausea, vomiting, fatigue, and abdominal pain (106). Nausea and
| Study Authors | Type of SSA-based PRRT | Type of study | PPGL patients | Progression at baseline | Response assessment data | Partial Responders (%) | Stable Disease (%) | Total Response (%) | PFS in months (median) | OS in months (median) | Concomitant Therapy |
|---------------|------------------------|---------------|---------------|-------------------------|--------------------------|------------------------|-------------------|-------------------|----------------------|---------------------|---------------------|
| Parghane et al. (87) | 177Lu-DOTATATE | Retrospective | 9 | 7 | Morphological, biochemical, clinical, and SSA PET/CT | 1/9 | 3/9 | 6/9 | N.A. | N.A. | - |
| Jaiswal et al. (89) | 177Lu-DOTATATE | Retrospective | 15 | 8 | Morphological, biochemical, clinical, and SSA PET/CT | 1/15 | 8/15 | 12/15 | N.A. | N.A. | - |
| Roll et al. (90) | 177Lu-DOTATATE | Retrospective | 7 | 1 | Morphological, clinical, and SSA PET/CT | 4/7 | 3/7 | 7/7 | N.A. | N.A. | - |
| Kolasinska-Cwikla et al. (94) | 90Y-DOTATATE | Prospective | 13 | 13 (100%) | Morphological | 1/12 | 9/12 | 10/12 | 35.0 | 68.0 | - |
| Vyakaranam et al. (88) | 177Lu-DOTATATE | Retrospective | 22 | 9 (41%) | Morphological, biochemical, and clinical data | 2/22 | 20/22 | 22/22 | 21.6 | 49.6 | - |
| Zandee et al. (91) | 177Lu-DOTATATE | Retrospective | 30 | 20 (67%) | Morphological and clinical data | 7/30 | 20/30 | 27/30 | 30.0 | N.A. | - |
| Yadav et al. (96) | 177Lu-DOTATATE | Retrospective | 25 | 21 (84%) | SSA PET/CT, morphological, biochemical, and clinical data | 7/25 | 14/25 | 21/25 | 32.0 | N.A. | Chemotherapy (100%) |
| Garske-Roman et al. (97) | 177Lu-DOTATATE | Prospective | 5 | 2 | Morphological, clinical, and biochemical data | 0/5 | 5/5 | 5/5 | 14.0 | 37.0 | - |
| Demirci et al. (98) | 177Lu-DOTATATE | Retrospective | 12 | NR | Morphological and SSA PET/CT | 4/8 | 2/8 | 6/8 | 31.4 | 51.8 | - |
| Hamiditabar et al. (99) | 177Lu-DOTATATE | Prospective | 5 | NR | Morphological, clinical, and biochemical data | 0/5 | 4/5 | 4/5 | N.A. | N.A. | - |
| Kong et al. (34) | 177Lu-DOTATATE | Retrospective | 20 | 6 (30%) | SSA PET/CT, morphological, biochemical, and clinical data | 8/17 | 7/17 | 15/17 | 39.0 | N.A. | Chemotherapy (45%) |
| Nastos et al. (95) | 177Lu-/90Y-DOTATATE | Retrospective | 13 | 13 (100%) | Morphological, biochemical, and clinical data | NR | NR | 13/13 (100) | 38.5 | 60.8 | Chemotherapy, Radiation Therapy, or Cold SSA |
| Pinato et al. (100) | 177Lu-DOTATATE | Case series | 5 | 5 (100%) | SSA PET/CT and morphological data | 1/5 | 3/5 | 4/5 | 17.0 | N.A. | - |
| Estevao et al. (101) | 177Lu-DOTATATE | Retrospective | 14 | 4 (29%) | SSA PET/CT and clinical data | N.A. | N.A. | 10/14 (71) | N.A. | N.A. | - |
| Purank et al. (102) | 177Lu-/90Y-DOTATATE/DOTATOC | Prospective | 9 | NR | SSA PET/CT, morphological and clinical data | 4/9 | 5/9 | 9/9 | N.A. | N.A. | - |
| Zovato et al. (33) | 177Lu-DOTATATE | Case series | 4 | 4 (100%) | SSA scintigraphy, morphological and clinical data | 2/4 | 2/4 | 4/4 | N.A. | N.A. | - |
| Imhof et al. (103) | 90Y-DOTATOC | Prospective | 39 | 39 (100%) | Morphological, biochemical, and clinical data | NR | NR | 7/39 (18) | N.A. | N.A. | - |
| Forrer et al. (104) | 177Lu-/90Y-DOTATOC | Retrospective | 28 | 28 (100%) | Morphological, biochemical, and clinical data | 7/28 | 13/28 | 20/28 | N.A. | N.A. | - |
| van Essen et al. (45) | 177Lu-DOTATATE | Retrospective | 12 | 4 (33%) | Morphological, biochemical, and clinical data | 2/11 | 6/11 | 8/11 | N.A. | N.A. | - |

*adapted from Roll et al. (90). ‡adapted from Satapathy et al. (105). The remaining studies were adapted from Taieb et al. (92).

^All 9 patients had mPGL, no PCC. *3 patients had concomitant PNETs of which 2 patients had VHL.

NR, not reported; PFS, progression-free survival; OS, overall survival.
vomiting have been attributed to commercial amino acid infusion for renal protection prior to infusion of the selected PRRT. The occurrence of nausea and vomiting can be reduced by substituting the commercial amino acid infusion with an alternative containing L-lysine and L-arginine. More serious side effects include neutropenia, lymphopenia, thrombocytopenia, and nephrotoxicity. In a review of 45 PPGL patients treated with PRRT, 3% had grade 3/4 neutropenia, 9% had thrombocytopenia, 11% had lymphopenia, and 4% had nephrotoxicity. A long-term complication of myelodysplastic syndrome was also observed in an unreported number of PPGL patients receiving the therapy (105). In a case report by Wolf et al., a dangerous side effect of Lutathera® in two mPGL patients was hyperprogression of mPGL disease after three cycles of 90Y177Lu-DOTATOC (cycle one was 90Y, and cycle two and three were 177Lu-DOTATATE in patient A and two cycles of 177Lu-DOTATATE in patient B (107). Future reporting of adverse effects of SSA-based PRRT is important in assessing the safety of this therapy in PPGL patients to determine whether the therapy can be effectuated in patients, without life-threatening side effects.

FUTURE AVENUES OF SOMATOSTATIN-BASED THERAPY IN PPGLS

The following section will focus on ongoing studies that focus on the targeting of SSTRs by SSA based therapeutic compounds.

Ongoing PRRT Clinical Trials

An ongoing phase II study at the National Institutes of Health (NIH), NCT03206060, could make a strong case for federal approval. The study is using Lutathera® for treating progressive and inoperable PPGL patients with either germline SDHx mutation or sporadic disease. This prospective clinical trial will identify important clinical benefits of this treatment, focusing on the primary endpoint of PFS and several secondary endpoints, such as safety profile, OS, and quality of life. There are two other trials on Lutathera® currently recruiting children (NCT03923257 in Iowa, USA) and adults (NCT04029428 in Warsaw, Poland) with nonresectable or treatment-refractory SSTR-positive PPGLs. Similar prospective clinical studies should be conducted to uncover the therapeutic potential of SSTR-targeting radiotherapy.

Ongoing Lanreotide Clinical Trial

The long history of adoption and trial of SSA with good outcomes perpetuated an environment of ongoing clinical research and investigation. This culminated in large studies, such as the PROMID and CLARINET trials, which showed the clinical benefit of SSAs in GEPNETs (6, 7). However, the subset of NETs focused on in this review did not have extensive trials for testing the efficacy of cold SSA. There are reports of clinical stabilization of surgically unamenable PPGLs, two of which were patient experiences observed by our clinical team (80, 108), but there were no prospective or retrospective studies to either strengthen or refute these claims (80, 108–111). A prospective clinical trial (NCT03946527 in New York, USA) will evaluate the effectiveness of lanreotide in mPPGLs (LAMPARA) by observing tumor growth rate, overall survival, overall response rate, progression-free survival, and biochemical response.

Next Generation Cold SSAs

Overexpression of SSTRs on the cell surfaces of PPGLs has led to ongoing investigations that target and manipulate these receptors. The antiproliferative and apoptotic effects of somatostatin and its analogs upon binding with SSTRs were identified through extensive and detailed studies (112, 113). Targeting SSTR2 due to their preferential expression is the current and future direction of therapeutic management in these tumors (93, 114, 115). Cold SSAs, such as octreotide and lanreotide, have a proclivity to target SSTR2, which have been studied and utilized in various endocrine-related diseases, including GEPNETs and acromegaly (116). Pasireotide, a second-generation SSA, targets five SSTR subtypes, unlike octreotide and lanreotide. Although it was not superior to octreotide in terms of therapy or safety profile, it could be beneficial in tumors with broader expression of SSTR subtypes, including SSTR1, SSTR3, SSTR5, and SSTR6 (117, 118). Somatoprim, another second-generation SSA, is a multi-receptor targeting analog with a preference for SSTR2, SSTR4, and SSTR5, which was trialed in vitro on growth hormone (GH)-secreting pituitary adenomas. The results showed that it had anti-secretory effects on GH adenomas that were not controlled by octreotide (119). It would be worthwhile to investigate whether somatoprim has the same antisecretory effect in PPGLs. Dopastatin, a novel chimeric analog with dual binding ability to SSTR2 and dopamine receptors (D2), also exhibited an antisecretory effect on GH in acromegaly patients (120), and antitumor effects in midgut carcinoid cells in vitro (121). D2 receptors were expressed in larger amounts in 52 PPGL patients than 35 GEPNET patients (122), providing another targetable receptor for dopastatin analogs through radiopeptide imaging and therapy.

SSTR Antagonists

Development and research on SSA, which were recognized to antagonistically bind to SSTRs, are ongoing. According to an in vitro study by Ginj et al. (123), SSTR antagonists (SSTR-ANs) bound to NET SSTRs (especially SSTR2 and SSTR3) better than agonists but did not undergo subsequent internalization. These antagonists, sst3-ODN-8 and sst2-ANT were chelated to In by DOTA to create a receptor-targeting radioligand. These findings captured by gamma cameras were impressive in displaying antagonist-based radioligands, which bound more receptors for longer durations than their counterparts (123). The study caused a shift from the traditional theory that better binding and more benefits are derived from agonist-based analogs, mainly due to their ability to internalize the compound. A subsequent clinical comparison showed an antagonist-based ST ligand, 111In-DOTA-BASS, which allowed better visualization and had higher uptake in NETs than 111In-pentetreotide (124). Based on the impressive results from first-generation SSTR-ANs, second-generation ones, such as LM3, JR10, and JR11, were developed. These second-generation SSTR-ANs were further improved in their SSTR binding capacity by using the chelator NODAGA.
A comparative study showed that $^{68}$Ga-NODAGA-JR11 had higher tumoral uptake despite its lower affinity to SSTR$_2$ than $^{68}$Ga-DOTATATE (126). The benefits were just as clear when $^{177}$Lu-DOTA-JR11 was used for treating four patients with 18 advanced NETs, with a ten-fold higher dose than $^{177}$Lu-DOTATATE and with reversible adverse events (127). A phase I/II study (NCT 02592707) focusing on the endpoints of safety, tolerability, efficacy, biodistribution, and dosimetry of $^{177}$Lu-OPS201 (also known as $^{177}$Lu-DOTA-JR11) in unresectable GEPNETs, lung carcinoids, and PPGLs is currently underway. This study could provide an additional research perspective to identify therapeutic options for PPGLs.

**Alpha Emitting $^{225}$Ac-DOTATATE PRRT**

Alpha-emitting radiometals are also being explored in the treatment of GEPNETs and PPGLs. A study explored the utility of $^{225}$Actinium ($^{225}$Ac)-DOTATATE, a targeted alpha therapy (TAT), in 32 patients with metastatic GEPNETs refractory or stable after $^{177}$Lu-DOTATATE therapy. Four patients with paraganglioma received TAT but were excluded from the analysis. Of the 32 GEPNET patients, 24 were assessed by RECIST 1.1 and found to have either stable or partial response. A positive biochemical response in chromogranin A (CgA) was observed as well, showing stable or decreased levels in 32 patients. There were also minimal grade III/IV toxicities reported in patients, which included gastritis in 7, weight loss in 5, flushing in 3, and headaches in 2 (128). Another study used $^{225}$Ac-DOTATATE as compassionate care in two patients with progressive PCC after 3 cycles of $^{177}$Lu-DOTATATE; however, results on the effectiveness and toxicity were not published (89).

**Cytotoxic Compounds Conjugated to SSA**

Another frontier of therapeutic innovation in SSTR targeting was that of compounds linking SSA and cytotoxic agents. The SSA, Tyr$^3$-octreotate, was conjugated with a microtubule-targeting agent, DM1, creating PEN-221. SSTR$_2$ targeting of this agent was accomplished by the Tyr$^3$-octreotate analog of the compound; after endocytosis, the DM1 portion induced a toxic payload within the targeted cells (129). A current phase I/II study (NCT 02936323) is ongoing for investigating the utility of PEN-221 in advanced NETs, including PPGLs.

**CONCLUSION**

The “Old Players” in the title of this review shows that SSAs have a historic role in treating and managing NETs. The review hopes to restore clinical awareness of these analogs through successes achieved in PPGLs. The theranostic utility of SSAs in PPGLs can be realized once federal approval is achieved. However, research and innovation should not be halted once an approval of Lutathera® for unresectable PPGLs is garnered. Research should be continued for targeting SSTRs with second-generation SSAs, SSTR-ANs, chimeric dual receptor-targeting peptides, chemotactic delivery through SSTRs, and other novel methods.

**AUTHOR CONTRIBUTIONS**

MP and IT share first co-authorship; they contributed to the conception of the idea, creation of the outline, writing, reviewing, and editing. AJ contributed to creating an outline, conceptualization, reviewing, and editing. DT contributed to reviewing. KP contributed to creating an outline, conceptualization, review, and edit of the manuscript. All authors contributed to the article and approved the submitted version.

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**REFERENCES**

1. Patel YC. Somatostatin and its receptor family. Front Neuroendocrinol (1999) 20(3):157–98. doi: 10.1006/frne.1999.0183
2. Krenning EP, Valkema R, Kooij PP, Breeman WA, Bakker WH, deHerder WW, et al. Scintigraphy and radionuclide therapy with [indium-111]-labelled diethyl triamine penta-acetic acid-D-Phe1]-octreotide. Ital J Gastroenterol Hepatol (1999) 31(Suppl 2):S219–23.
3. Vanetti M, Koub M, Wang X, Vogt G, Holl T. Cloning and expression of a novel mouse somatostatin receptor (SSTR2B), FEBS Lett (1992) 311(3):290–4. doi: 10.1016/0014-5793(92)81122-3
4. Krenning EP, Bakker WH, Breeman WA, Koper JW, Kooij PP, Ausema L, et al. Localisation of endocrine-related tumours with radiolabeled analogue of somatostatin. Lancet (1989) 1(8632):242–4. doi: 10.1016/0140-6736(89)91258-0
5. Rinke A, Muller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol (2009) 27(28):4656–63. doi: 10.1200/JCO.2009.22.8510
6. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med (2014) 371(3):224–33. doi: 10.1056/NEJMoa1316158
7. Rinke A, Wittenberg M, Schade-Brittinger C, Aminossadati B, Ronicke E, Gross TM, et al. Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors (PROMID): Results of Long-Term Survival. Neuroendocrinology (2017) 104(1):26–32. doi: 10.1159/000443612
8. Kagimoto S, Yamada Y, Kubota A, Someya Y, Ihara Y, Yasuda K, et al. Human somatostatin receptor, SSTR2, is coupled to adenylyl cyclase in the presence of Gi alpha 1 protein. Biochem Biophys Res Commun (1994) 202(2):1188–95. doi: 10.1016/bbrc.1994.02.043
9. Kubota S, Yamada Y, Kagimoto S, Seino S, Seino Y. Effector coupling of somatostatin receptor subtypes on human endocrine tumors. Metabolism (1996) 45(8 Suppl 1):42–5. doi: 10.1006/metb.1995.0078-5
10. Law SF, Yasuda K, Bell GL, Reisine T. Gi alpha 3 and Gi(o) alpha selectively associate with the cloned somatostatin receptor subtype SSTR2. J Biol Chem (1993) 268(15):10721–7. doi: 10.1074/jbc.268.15.10721
11. Tintner JJ, Hadcock JR, Gutierrez-Hartmann A. Somatostatin acts by inhibiting the cyclic 3',5'-adenosine monophosphate (cAMP)/protein
kinase A pathway, cAMP response element-binding protein (CREB) phosphorylation, and CREB transcription potency. Mol Endocrinol (1997) 11(7):589–66. doi: 10.1210/endo.11.7.5943
12. Tomura H, Okajima F, Akbar M, Majid MA, Sho KM, Kondo Y. Transfected Human Somatostatin Receptor Type 2, SSTR2. Not Only Inhibits Adenylate Cyclase but Also Stimulates Phospholipase C and Ca2+ Mobilization. Biochem Biophys Res Commun (1994) 200(2):986–92. doi: 10.1006/ birc.1994.1547
13. Yang SK, Parkington HC, Blake AD, Keating DJ, Chen C. Somatostatin receptors 1, 2, and 5 cooperate in the somatostatin inhibition of C6 glioma cell proliferation in vitro via a phosphotyrosine phosphatase-eta-dependent inhibition of extra cellularly regulated kinase-1/2. Invest Ophthalmol Vis Sci (2008) 149(9):4736–47. doi: 10.1167/iovs.08-3038-C
14. Van Op den Bosch J, Adriaensen D, Van Nassauw L, Timmermans JP. The role(s) of somatostatin, structurally related peptides and somatostatin receptors in the gastrointestinal tract: a review. Regul Pept (2009) 156(1-3):1–8. doi: 10.1016/j.regpep.2009.04.003
15. Koch BD, Schonbrunn A. Characterization of the cyclic AMP-independent actions of somatostatin in GH cells. II. An increase in potassium conductance initiates somatostatin-induced inhibition of prolactin secretion. J Biol Chem (1988) 263(1):226–34. doi: 10.1002/s00021-9258(19)57382-3
16. Pace CS, Tarvin JT. Somatostatin: mechanism of action in pancreatic islet beta-cells. Diabetes (1981) 30(10):836–42. doi: 10.2337/diabetes.30.10.836
17. Yamashita N, Shibuya N, Ogata E. Hyperpolarization of the membrane potential caused by somatostatin in dissociated human pituitary adenoma cells that secrete growth hormone. Proc Natl Acad Sci U S A (1986) 83(16):16198–202. doi: 10.1073/pnas.83.16.16198
18. Sellers LA, Alderton F, Carruthers AM, Schindler M, Humphrey PP. Receptor isomers mediate opposing proliferative effects through gbetagamma-activated p38 or Akt pathways. Mol Cell Biol (2000) 20(16):5974–85. doi: 10.1128/MCB.20.16.5974-5985.2000
19. Reubi JC, Laissue JA. Multiple actions of somatostatin in neoplastic disease. Trends Pharmacol Sci (1995) 16(3):110–5. doi: 10.1016/0166-6851(95)88992-0
20. Buscall L, Esteve JP, Saint-Laurant N, Bertrand V, Reine T, O’Carroll AM, et al. Inhibition of cell proliferation by the somatostatin analogue RC-160 is mediated by somatostatin receptor subtypes SSTR2 and SSTR5 through different signaling pathways. Proc Natl Acad Sci U S A (1995) 92(5):1580–4. doi: 10.1073/pnas.92.5.1580
21. Cattaneo MG, Amoroso D, Gussoni G, Sanguini AM, Vicentini LM. A somatostatin analogue inhibits MAP kinase activation and cell proliferation in human neuroblastoma and in human small cell lung carcinoma cell lines. FEBS Lett (1996) 397(2-3):164–8. doi: 10.1016/S0014-5793(96)01159-3
22. Fola S, Cattaneo MG, Vicentini LM. Anti-migratory and anti-invasive effect of somatostatin in human neuroblastoma cells involvement of Rac and MAP kinase activity. J Biol Chem (2003) 278(42):40601–6. doi: 10.1074/jbc.M306510200
23. Douziech N, Calvo E, Coulombe Z, Muradia G, Bastien J, Aubin RA, et al. Inhibitory and stimulatory effects of somatostatin on two human pancreatic cancer cell lines: a primary role for tyrosine phosphate shpping SHP-1. Endocrinology (1999) 140(2):765–77. doi: 10.1210/endo.140.2.6492
24. Barbieri F, Pattarozi A, Gatti M, Porcile C, Bajetto A, Ferrari A, et al. Somatostatin receptors 1, 2, and 5 cooperate in the somatostatin inhibition of C6 glioma cell proliferation in vitro via a phosphotyrosine phosphatase-eta-dependent inhibition of extracellularly regulated kinase-1/2. Endocrinology (2008) 149(9):4736–46. doi: 10.1210/en.2007-1762
25. Bouques C, Deleusque N, Lopez F, Saint-Laurent N, Esteve JP, Bedecs K, et al. st2 somatostatin receptor mediates negative regulation of insulin receptor signaling through the tyrosine phosphate shpping SHP-1. J Biol Chem (1998) 273(12):7099–106. doi: 10.1074/jbc.273.12.7099
26. Shimon I, Taylor JE, Dong JZ, Bitonte RA, Kim S, Morgan B, et al. Somatostatin receptor subtype specificity in human fetal pituitary cultures. Differential role of SSTR2 and SSTR5 for growth hormone, thyroid-stimulating hormone, and prolactin regulation. J Clin Invest (1997) 99(4):789–98. doi: 10.1172/JCI91225
27. Murray RD, Kim K, Ren SG, Chelly M, Umehara Y, Melmed S. Central and peripheral actions of somatostatin on the growth hormone-IGF-1 axis. J Clin Invest (2004) 114(3):349–56. doi: 10.1172/JCI19933
56. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei djs188.
57. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WA, Kooij PP, Oei djs188.
58. Kwekkeboom DJ, van Urk H, Pauw BK, Lamberts SW, Kooij PP, Hoogma RP, et al. Octreotide scintigraphy for the detection of paragangliomas.
59. Muros MA, Llamas-Elvira JM, Rodriguez A, Ramirez A, Gomez M, Arraez –.
60. Ilias I, Chen CC, Carrasquillo JA, Whatley M, Ling A, Lazurova I, et al. Comparison of 6-18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. J Nucl Cancer Invest (2012) 104:990–8. doi: 10.1093/jnci/djs188.
61. Schmidt M, Fischer E, Dietlein M, Michel O, Weber K, Moka D, et al. Clinical value of somatostatin receptor imaging in patients with suspected head and neck paragangliomas. Eur J Nucl Med Imaging (2002) 29 (12):1571–80. doi: 10.1007/s00259-002-0939-6.
62. van der Harst E, de Herder WW, Bruins HA, Bonjer HJ, de Krigger RR, Lamberts SW, et al. [1123]metaiodobenzylguanidine and [111In] octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metabol (2001) 86(2):685–93. doi: 10.1210/jc.86.2.685.
63. Patel et al. Somatostatin Receptor and Analogs.
87. Parghane RV, Talole S, Basu S. (131)I-MIBG negative progressive pheochromocytoma and paraganglioma. Front Oncol (2019) 9:53. doi: 10.3389/fonc.2019.00053

88. Jaiswal SK, Sarathi V, Memon SS, Garg R, Malhotra G, Verma P, et al. Comparative study of (68)Ga-DOTA-TOC and (18)F-FDG PET/CT in the detection of metastatic paraganglioma and paragangliomas with germline mutations: a meta-analysis. Acta Radiol (2019) 59(12):2466–74. doi: 10.1080/02841851.2018.1538238

89. Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of (68)Ga-DOTA-TATE PET/CT in metastatic/inoperable pheochromocytoma and paraganglioma. Acta Radiol (2018) 59(5):787–97. doi: 10.1080/02841851.2018.1449637

90. Jha A, de Luna K, Balili CA, Millo C, Paraiso CA, Ling A, et al. Clinical, diagnostic, and treatment characteristics of SDHA-Related Metastatic Pheochromocytoma and Paraganglioma. Front Oncol (2019) 9:53. doi: 10.3389/fonc.2019.00053

91. Iha A, Ling A, Millo C, Chen C, Gupta G, Viana B, et al. Superiority of (68)Ga-DOTATATE PET/CT to other functional and anatomic imaging modalities in the detection of SDHB-related pheochromocytoma and paraganglioma-A comparative prospective study. J Nucl Med (2018) 59(supplement 1):46–6.

92. Iha A, Ling A, Millo C, Gupta G, Viana B, Lin FL, et al. Superiority of (68)Ga-DOTATATE over (18)F-FDG and anatomic imaging in the detection of succinate dehydrogenase mutation (SDHx)–related pheochromocytoma and paraganglioma in the pediatric population. Eur J Nucl Mol Imaging (2018) 45(5):787–97. doi: 10.1007/s00259-017-3896-9

93. Han S, Suh CH, Woo S, Kim YJ, Lee JJ. Performance of (68)Ga-DOTA-Conjugated Somatostatin Receptor-Targeting Peptide PET in Detection of Pheochromocytoma and Paraganglioma: A Systematic Review and Metaanalysis. J Nucl Med (2019) 60(3):369–76. doi: 10.2967/jnumed.118.111706

94. Han Y, Zhang S, Wang W, Liu J, Yang J, Wang Z. (68)Ga-somatostatin receptor analogs and (18)F-FDG PET/CT in the localization of metastatic pheochromocytomas and paragangliomas with germline mutations: a meta-analysis. Acta Radiol (2018) 59(12):2466–74. doi: 10.1080/02841851.2018.1538238

95. Nastos K, Cheung VTF, Toumpanakis C, Navalkissoor S, Quigley AM, Dimitriou E, et al. In vitro melanoma, breast, prostate and lung cancer cells: a panel of human tumour xenografts. Eur J Nucl Med Mol Imaging (2018) 45(6):970–88. doi: 10.1007/s00259-018-3945-z

96. Demirci E, Kabasakal A, Toklu T, Ocak M, Sahin OI, Altun-Selcuk N, et al. 177Lu-DOTATATE therapy in patients with neuroendocrine tumours including high-grade (WHO G3) neuroendocrine tumours: response to treatment and long-term survival update. Nucl Med Commun (2018) 39(8):789–96. doi: 10.1097/NMN.0000000000000874

97. Garske-Roman U, Sandstrom M, Fross Baron K, Lundin L, Hellman P, Welin S, et al. Prospective observational study of (177)Lu-DOTA-octreotide therapy in 200 patients with advanced metastasized neuroendocrine tumours (NETs): feasibility and impact of a dosimetry-guided study protocol on outcome and toxicity. Eur J Nucl Med Mol Imaging (2018) 45(5):787–97. doi: 10.1007/s00259-017-3896-9

98. Yadav MP, Ballal S, Bal C. Concomitant (177)Lu-DOTATATE and capcitabine therapy in malignant paragangliomas. EJNMMI Rev (2019) 9(1). doi: 10.1186/s13550-019-0484-y

99. Hamidibasar M, Ali M, Rois J, Wolin EM, O’Dorisio TM, Ranganathan D, et al. Peptide Receptor Radionuclide Therapy With 177Lu-Octreotate in Patients With Somatostatin Receptor Expressing Neuroendocrine Tumors: Six Years’ Assessment. Clin Nucl Med (2017) 42(6):436–43. doi: 10.1097/RLU.0000000000001629

100. Pinato DJ, Black JR, Ramaswami R, Tan TM, Adjogatse D, Sharma R. Peptide receptor radionuclide therapy for metastatic paragangliomas. Med Acta (2019) 8(2019)34–43.

101. Estevao R, Duarte H, Lopes F, Fernandes J, Monteiro E. Peptide receptor radionuclide therapy in head and neck paragangliomas - Report of 14 cases. Rev Laryngol Otol Rhinol (Bord) (2015) 136(4):155–8.

102. Puranik AD, Kulkarni HR, Singh A, Baum RP. Peptide receptor radionuclide therapy with (90)Y/(177)Lu-labelled peptides for inoperable head and neck paragangliomas (glomus tumours). Eur J Nucl Med Mol Imaging (2015) 42(8):1223–30. doi: 10.1007/s00259-015-3029-2

103. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabelled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. Clin Oncol (2011) 29(17):2416–23. doi: 10.10120/ JCO.2010.33.7873

104. Forrer F, Riedweg I, Maecke HR, Mueller-Brand J. Radionuclide DOTATOC in patients with advanced paraganglioma and pheochromocytoma. Q J Nucl Med Mol Imaging (2008) 52(4):334–40.

105. Satapathy S, Mittal BR, Bhansali A. ‘Peptide receptor radionuclide therapy in the management of advanced pheochromocytoma and paraganglioma: A systematic review and meta-analysis’. Clin Endocrinol (Oxf) (2019) 91 (6):718–27. doi: 10.1111/cen.14106

106. Taieb D, Pacak K. Molecular imaging and theranostic approaches in pheochromocytoma and paraganglioma. Cell Tissue Res (2018) 372(2):393–401. doi: 10.1007/s00441-018-2791-4

107. Wolf KI, Iha A, van Berkel A, Wild D, Janssen I, Millo CM, et al. Eruption of Metastatic Paraganglioma After Successful Therapy with (177)Lu/(90)Y-DOTATOC and (177)Lu-DOTATATE. Nucl Med Mol Imaging (2019) 53(3):223–30. doi: 10.1016/j.jnme.2019.01-00579-w

108. Jha A, Patel M, Baker E, Gonzales MK, Ling A, Millo C, et al. Role of (68)Ga-DOTATATE PET/CT in a Case of SDHB-Related Pterygopalatine Fossa Paraganglioma Successfully Treated with Octreotide. Nucl Med Imaging (2020) 53(4):1223–30. doi: 10.1016/j.jnme.2019.01-00579-w

109. van Hulstijn LT, van Duinen N, Verbit BM, Jansen VC, van der Klauwa AA, Smit JW, et al. Effects of octreotide therapy in progressive head and neck paragangliomas: case series. Head Neck (2013) 35(12):E391–6. doi: 10.1002/hed.23348

110. Narayan V, Fishbein L, Nathanson K, Bennett B, Pryma D, Cohen D. Use of Somatostatin Analog Therapy in Patients With Advanced Pheochromocytoma/Paraganglioma. Somatostatin-Receptor Avid Disease. Paper presented at: PANCReAS (2018).

111. Moller LN, Sidsen CE, Hartmann B, Holst JJ. Somatostatin receptors. Biochim Biophys Acta (2003) 1616(1):1–84. doi: 10.1016/S0005-2736(03)00235-9
113. Florito T. Molecular mechanisms of the antiproliferative activity of somatostatin receptors (SSTRs) in neuroendocrine tumors. *Front Biosci* (2008) 13:222–40. doi: 10.2741/2722

114. Unger N, Serdiuk I, Sheu SY, Watz MK, Schulz S, Saeger W, et al. Immunohistochemical localization of somatostatin receptor subtypes in benign and malignant adrenal tumours. *Clin Endocrinol (Oxf)* (2008) 68 (6):850–7. doi: 10.1111/j.1365-2265.2007.03124.x

115. Ziegler CG, Brown JW, Schally AV, Erler A, Gebauer L, Treszl A, et al. Expression of neuropeptide hormone receptors in human adrenal tumors and cell lines: antiproliferative effects of peptide analogues. *Proc Natl Acad Sci U S A* (2009) 106(37):15879–84. doi: 10.1073/pnas.0907843106

116. Hofland LJ, Lamberts SW. The pathophysiological consequences of somatostatin receptor internalization and resistance. *Endocr Rev* (2003) 24 (1):28–47. doi: 10.1210/eur.2000-0001

117. Stueven AK, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci* (2019) 20(12):1–13. doi: 10.3390/ijms20123049

118. Vitale G, Dicitore A, Sciammarella C, Di Molfetta S, Rubino M, Faggiano A, et al. Pasireotide in the treatment of neuroendocrine tumors: a review of the literature. *Endocrine-related cancer* (2018) 25(6):R351–64. doi: 10.1530/ERC-18-0010

119. Plockinger U, Hoffmann U, Geese M, Lupp A, Buchfelder M, Flitsch J, et al. DG3173 (somatoprim), a unique somatostatin receptor subtypes 2-, 4- and 5-selective analogue, effectively reduces GH secretion in human GH-secreting pituitary adenomas even in Octreotide non-responsive tumours. *Eur J Endocrinol* (2012) 166(2):223–34. doi: 10.1530/EJE-11-0737

120. Tzompanakis C, Caplim ME. Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. *Semin Oncol* (2013) 40(1):36–68. doi: 10.1053/j.seminoncol.2012.11.006

121. Zitzmann K, Andersen S, Vlotides G, Spottl G, Zhang S, Datta R, et al. Expression of somatostatin receptors, dopamine D(2) receptors, noradrenaline transporters, and vesicular monoamine transporters in 52 pheochromocytomas and paragangliomas. *Endocrine-related cancer* (2011) 18(2):287–300. doi: 10.1530/ERC-10-0175

122. Saveant A, Muresan M, De Micco C, Taieb D, Germanetti AL, Sebag F, et al. Expression of somatostatin receptors, dopamine D(2) receptors, noradrenaline transporters, and vesicular monoamine transporters in 52 pheochromocytomas and paragangliomas. *Endocrine-related cancer* (2011) 18(2):287–300. doi: 10.1530/ERC-10-0175

123. Ginj M, Zhang H, Waser B, Cescato R, Wild D, Wang X, et al. Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. *Proc Natl Acad Sci U S A* (2006) 103 (44):16436–41. doi: 10.1073/pnas.0607761103

124. Wild D, Fani M, Behe M, Brink I, Rivier JE, Reubi JC, et al. First clinical evidence that imaging with somatostatin receptor antagonists is feasible. *J Nucl Med* (2011) 52(9):1412–7. doi: 10.2967/jnumed.111.088922

125. Fani M, Del Pozzo L, Abiraj K, Mansi R, Tamma ML, Cescato R, et al. PET of somatostatin receptor-positive tumors using 64Cu- and 68Ga-somatostatin antagonists: the chelate makes the difference. *J Nucl Med* (2011) 52(7):1110–8. doi: 10.2967/jnumed.111.087999

126. Fani M, Braun F, Waser B, Beetschen K, Cescato R, Erchegyi J, et al. Unexpected sensitivity of sst2 antagonists to N-terminal radiometal modifications. *J Nucl Med* (2012) 53(9):1481–9. doi: 10.2967/jnumed.112.102764

127. Wild D, Fani M, Fischer R, Del Pozzo L, Kaul F, Krebs S, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. *J Nucl Med* (2014) 55(8):1248–52. doi: 10.2967/jnumed.114.138834

128. Ballal S, Yadav MP, Bal C, Sahoo RK, Tripathi M. Broadening horizons with (225)Ac-DOTATATE targeted alpha therapy for gastroenteropancreatic neuroendocrine tumour patients stable or refractory to (177)Lu-DOTATATE PRRT: first clinical experience on the efficacy and safety. *Eur J Nucl Med Mol Imaging* (2020) 47(4):934–46.

129. White BH, Whalen K, Kriksciukaite K, Alargova R, Au Yeung T, Bazinet P, et al. Discovery of an SSTR2-Targeting Maytansinoid Congjugate (PEN-221) with Potent Activity in Vitro and in Vivo. *J Med Chem* (2019) 62(5):2708–19. doi: 10.1021/acs.jmedchem.8b02036

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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