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# Prognostic Implications, Modifications & Therapeutic Strategies Targeting Somatostatin Receptor-2 Expression in Gastroenteropancreatic Neuroendocrine Tumors

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## ABSTRACT

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) are a diverse group of tumors often characterized by somatostatin receptor type 2 (SSTR2) positivity. The objective of this article is to review basic information on GEP NETs and somatostatin receptors (SSTR) with a focus on SSTR2. The prognostic implications of the receptor, how epigenetic modifications play a role, and the diagnostic and therapeutic strategies available that rely on the somatostatin receptor including somatostatin analogs (SSAs), SSTR-based imaging, and peptide receptor radionuclide therapy (PRRT) are explored. While surgery is the only curative option, current therapy for SSTR2 positive GEP NETs is based on the use of SSAs which have been shown to both control symptoms and exert antiproliferative effects in SSTR2 positive GEP NETs. SSTR-based imaging offers numerous benefits over standard imaging techniques including revealing additional metastases, assessing response to therapy, and by demonstrating sufficient SSTR expression in tumors to render patients eligible for PRRT. PRRT has been shown to be an effective treatment in low grade, SSTR2 positive GEP NETs. Adjuncts are being investigated to synergize with PRRT and improve patient outcomes. Complete responses to SSA and PRRT are rare and SSTR2 negative tumors have limited treatment options. Given that GEP NETs have a low frequency of mutations and no mutations in SSTR2 have been identified, efforts are being made to investigate epigenetic regulations influencing SSTR2 expression as a future therapeutic option.

**Keywords**: Somatostatin receptor, somatostatin analog, neuroendocrine tumor, epigenetics

## Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP NETs) arise from neuroendocrine cells along the digestive tract and are the most common neuroendocrine tumor (NET) subtype [1]. GEP NETs are known for their ability to produce and secrete peptides, hormones, and neuroamines, and can be functional or non-functional which often influences patient presentation [2]. The majority of GEP NETs are non-functional and are thus identified at later stages secondary to tumor burden, mass effect or metastases [2]. In the minority, functional tumors tend to present earlier as localized lesions in the setting of symptoms related to secretory function [2]. GEP NETs can also be classified by genomic characteristics [3]. These tumors arise either sporadically or in association with hereditary predisposition syndromes including multiple endocrine neoplasia type 1 (MEN1), Von Hippel-Lindau's disease (VHL), or neurofibromatosis type 1 (NF1) [4]. Using histology, mitotic count, and expression of Ki-67, they are classified as well-differentiated grade 1, 2 or 3 NETs, or poorly differentiated grade 3 neuroendocrine carcinomas (NECs) [5]. Both the incidence and prevalence of these lesions have increased over time and while most possess an indolent, benign pathology there is a subset of highly proliferative, therapy-resistant tumors that still pose a challenge to clinicians and scientists [4]. While surgical resection is the only curative therapy, only a small subset of patients are candidates for surgery due to the presence of metastatic disease at initial diagnosis [6]. Consequently, great effort has been made into the identification of novel diagnostic and therapeutic targets for NETs.

A significant area of focus in GEP NET research is the somatostatin receptor (SSTR) family of transmembrane G-protein coupled receptors (GPCRs). Somatostatin itself is an inhibitory peptide, regulating endocrine and exocrine hormone secretion in normal physiologic states [7]. Although a heterogenous group of tumors, SSTR expression is a shared feature amongst NETs and therefore a desirable candidate for diagnosis and therapy [7]. High SSTR expression is associated with well-differentiated tumors and is more common amongst gastroenteric NETs than pancreatic NETs [8]. Currently, there are five described subtypes of the SSTR, SSTR 1-5, which vary in structure, distribution, and signaling effects [9]. Qian et al. discovered in examination of 112 small intestine NETs, 19 pancreatic NETs, and 42 NETs from other locations, that 65%, 76%, 90%, 86% and 93% of all cases were recognized by the expression of SSTR1, SSTR2, SSTR3, SSTR4, and SSTR5, respectively [10]. Further evaluation showed that SSTR type-2 (SSTR2) was expressed most frequently and that 51% of examined NETs were recognized by high SSTR2 levels [10]. SSTR2 subtype is prevalent amongst GEP NETs and are a particular area of clinical focus [6]. Consequently, somatostatin analogs (SSAs) have become increasingly utilized to diagnose and treat SSTR expressive NETs through radiolabeling [11].

## Somatostatin Signaling

Somatostatin is a cyclic neuroendocrine peptide, widely functioning as inhibitory to exocrine function and hormonal homeostasis [12]. Somatostatin has two isoforms, somatostatin-14 and -28, each with 14 and 28 amino acids respectively [6]. These isoforms result from post-translational modification of pro-somatostatin and have a short plasma half-life of less than three minutes [13-15]. Somatostatin-14 is secreted from pancreatic β-cells, and somatostatin-28 largely from gastrointestinal D-cells, with each peptide's functions specifically mediated by the SSTR subtype it binds to [16]. Somatostatin-14 has higher affinity to SSTRs 1-4, while somatostatin-28 preferentially binds to SSTR5 [17]. SSTR subtypes can be co-expressed in various cell types and share common signaling pathways.

As SSTRs 1-5 are types of GPCRs, their structures and signaling are largely conserved with up to 61% of conserved amino acid identity despite being encoded for by different genes [18,19]. GPCRs are the largest family of cell surface signaling receptors, and mediate most of our physiologic responses to hormones, neurotransmitters, lipids, and peptides. GPCRs play a critical role in normal cellular function, and their dysregulation has been implicated in a variety of diseases and cancers [20]. Composed of a single subunit polypeptide chain, seven α-helical segments span the plasma membrane, with an extracellular component binding to an agonistic molecule [21]. The intracellular component of the receptor incorporates the "G protein" portion of the receptor which upon agonistic stimulation of the extracellular receptor an alpha subunit exchanges GDP for GTP, allowing for its dissociation from beta and gamma subunits [21]. The ligand-binding pockets are what make each SSTR subtype distinct, and their functionality critical to various organ processes [22]. These processes result in inhibition of adenylyl cyclase, reduction of intracellular Ca2+, and inhibition of cellular proliferation and secretory signaling [23].

## Somatostatin Receptors

SSTR1 is encoded by SSTR1 on chromosome 14q13 [24]. Compared to other SSTR subtypes, studies report SSTR1 expression is more difficult to detect through immunohistochemistry (IHC) and may be more reliably analyzed using reverse transcriptase-polymerase chain reaction (RT-PCR) [25]. SSTR1 is naturally found in neuroendocrine cells [26], cerebral cortex [27], blood vessels [28], retinal cells [29], as well as normal, benign, and malignant thyroid cells [30]. In the pancreas, SSTR1 has been identified on glucagon secreting α- cells and somatostatin secreting δ-cells [31]. Functionally, activation of SSTR1 inhibits growth hormone (GH), prolactin (PL), and calcitonin. It has been shown to inhibit the cell cycle and angiogenesis. SSTR1 is thought to also regulate cardiac and vasomotor tone due to its presence in vascular tissue [32].

In cancer, SSTR1 has been identified as highly expressed in neuroblastomas, and correlates with improved prognosis [33]. Additionally, SSTR1 is expressed in GEP NETs, and has been shown to be highly expressed in lower grade tumors [34]. Pharmacologically, octreotide, a somatostatin analog used in a variety of therapeutic treatments, has no affinity for SSTR1 [9]. Newer agents, including pasireotide, a cyclic hexapeptide, has 30 times higher binding affinity for SSTR1 compared to

octreotide, but its utility in NET treatment has yet to be demonstrated [35].

SSTR3 is encoded by SSTR3 on chromosome 22q13.1 [24]. It is expressed throughout the gastrointestinal tract, exocrine pancreas, salivary glands, and nervous system [36]. Within the pancreas, SSTR3 is expressed mostly on δ and β -cells [37]. Activation of SSTR3 inhibits cellular proliferation and induces apoptosis in various cell types, including in models of pituitary NET [38], neuronal injury [39], and breast cancer [40]. Like its comparable subtypes, SSTR3's presence in NETs has been established, albeit in lower abundance than SSTR2A and SSTR5 [25]. SSTR3 expression is also associated with lower grade NETs [34] . SSTR3 is highly expressed both in normal pituitary and in gonadotroph pituitary adenomas, making it of therapeutic interest in this group of neoplasms as well [41]. In terms of pharmacologic targeting, octreotide has low affinity for SSTR3, while newer somatostatin analog pasireotide has a 5-fold stronger binding affinity [35].

SSTR4 is encoded by SSTR4 on chromosome 20p11.2 and found in lung, heart, placenta, and intestinal cells [42]. Interestingly, SSTR4 is the most rarely expressed in NETs amongst all SSTR subtypes, and its function is less understood [25,43]. SSTR4 has been shown to mediate analgesic effects by inhibiting nociceptive signaling [44], while also mediating pro-inflammatory effects of somatostatin in murine intestine [42,45,46]. It is implicated in mediating neurogenic inflammatory conditions, Alzheimer's disease, and depression, setting it apart from the other subtypes [47,48].

SSTR5 is encoded by SSTR5 on chromosome 16p13.3 [49]. Along with SSTR2, it is the most abundantly expressed somatostatin receptor [50]. SSTR5 is highly expressed in the pituitary and has been shown to be crucial in the modulation of pituitary hormone release [51]. In GEP NETs its expression is correlated with lower grade, well differentiated tumors [52]. There is conflicting evidence whether SSTR5 expression is correlated with better [50,53] or worse [54] survival but it is generally regarded as a positive prognosticator. Similar to SSTR2, SSTR5 is detectable in circulating tumor cells in NET patients, proving a useful prospective biomarker [55]. Additionally, SSTR5 has high binding affinity to somatostatin analogs octreotide and lanreotide, regulating symptoms from functional tumor secretion and resulting in delayed tumor proliferation [56-58].

Epigenetic and post transcriptional regulation of SSTR5 has been shown to downregulate its expression in pancreatic NETs, influencing tumor biology and treatment responsiveness [59]. An alternatively spliced SSTR5 variant sst5TMD4 has been reported in glioblastoma [60], breast cancer [61], and prostate cancer [62] with overexpression associated with more aggressive disease [60].

## Somatostatin Receptor 2

SSTR2 is encoded by SSTR2 located on chromosome 17q24 [42]. SSTR2 RNA is subject to alternative splicing which can produce two variants, SSTR2a and SSTR2b [6]. SSTR2 plays a role in cell cycling, angiogenesis, apoptosis, as well as growth factor signaling via inhibition of adenylate cyclase, inhibition of calcium influx, augmentation of p53 influx and downstream signaling through kinases such as mitogen activated protein kinase (MAPK) and protein kinase B (AKT) [63]. Given its upregulation in GEP-NETs and wide-reaching functions, this receptor has been the focus of research on its diagnostic and therapeutic implications.

## Implications in Other Cancers

While SSTR2 is of particular interest in GEP NETs, it is also expressed in other malignancies with various functional and therapeutic implications. Small-cell lung cancer (SCLC) comprises approximately 15% of lung cancers, is highly morbid and lacks effective therapeutic treatment. Significantly, these tumors possess neuroendocrine features; and SSTR2 has been found to be most prevalent as determined by IHC and sequencing analyses [64,65]. As seen in GEP NETs, decreased expression of SSTRs (except SSTR5) occurs in more poorly differentiated tumors [65]. Although SSTR2 expression is correlated with worse tumor differentiation, studies have failed to demonstrate predictive capacity for overall survival (OS) or progression free survival (PFS) [66]. Congruently, SSTR expression as determined by $^{68}$Ga-DOTATATE radio-imaging and in vitro assays can elucidate options for treatment, including $^{177}$Lu-DOTATATE PRRT alone or in combination therapy as second- or third-line treatment options [67,68].

In meningioma, SSTR2 is widely expressed [69] and utilized as a biomarker of disease [70]. While expression has not been demonstrated to correlate with meningioma grade, it has been correlated to the meningothelial subtype, which can guide prognostication and treatment [71]. Like in GEP NET, $^{68}$Ga-DOTATATE-PET can be utilized for diagnosis of meningioma and has proven useful in identifying tumor recurrence versus post-treatment change [72,73]. While surgery is the mainstay treatment for meningioma, the utility of somatostatin analogs and SSTR2-directed PRRT within the treatment paradigm is currently under investigation [74].

Another neurologic tumor of which SSTR2 is of significant relevance is gliomas. There are various subtypes of gliomas, of which differential SSTR2 expression has been shown [75,76]. High grade gliomas (grade III and IV) are the most common primary malignant brain tumors and have poor prognosis [77]. Glioblastoma (grade IV) is the most aggressive subtype of glioma and rarely expresses SSTR2, while oligodendroglioma, astrocytoma, and anaplastic oligodendrogliomas have been shown to have more significant expression [76]. In addition to variable expression amongst glioma subtypes, there exists discrepancy between ability to assess glioma SSTR2 expression in vivo versus in vitro. While IHC and western blot techniques have demonstrated increased expression of SSTR1-3 [75], in vivo somatostatin receptor scintigraphy has not shown clear binding of somatostatin analogs [78-80]. Furthermore, there are reports of $^{68}$Ga-DOTATATE uptake misrepresenting glioma tumor recurrence in the setting of treatment related changes, which is thought to be due to SSTR2 expression in proinflammatory macrophages and other immune cell populations [81]. Like in GEP NETs, a truncated alternatively spliced SSTR5

variant, sst5TMD4, has been associated with more aggressive disease in glioblastoma [60,82]. Overall, SSTR2 expression is correlated with improved outcomes in glioma, while the utility of $^{68}$Ga-DOTATATE imaging amongst various glioma subtypes is still under investigation.

Head and neck squamous cell carcinoma (HNSCC) are a prevalent and heterogenous group of cancers originating from mucosal epithelium of various anatomic structures including oral cavity, oropharynx, lip, nasal cavity, sinuses, nasopharynx, and larynx [83], and caused by different inciting agents [84]. In contrast to the aforementioned cancer types, SSTR2 expression is correlated with worse prognosis of HNSCC [83]. SSTR2 expression is highly sensitive and specific for Epstein Barr Virus-positive nasopharyngeal carcinoma, likely mediated via virally induced changes in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathways [85], making it a valuable biomarker for this disease [86]. Concordant with the degree of SSTR2 expression amongst HNSCC, $^{68}$Ga-DOTATATE was shown to be an effective imaging modality with comparable results to traditional 18F-FDG-PET/CT [87].

SSTR2 is somewhat expressed amongst lymphoma subtypes, with immunopositivity predominantly shown in dendritic cells and follicular centers of lymph nodes. IHC analysis performed by Juntikka et al. demonstrated approximately 50% of cells staining positive for SSTR2 in diffuse large B-cell lymphoma, Hodgkin lymphoma, and follicular lymphoma [88]. SSTR3 and 5 were not expressed in diffuse large B-cell and follicular subtypes but were expressed in Hodgkin lymphoma within cytoplasmic domains. Interestingly, CXCR4 was co-expressed with SSTR2, pointing to potential future targeted co-therapeutic options. Largely, studies analyzing SSTR2 in lymphomas show too little expression to make them suitable candidates for somatostatin receptor radio-imaging and therapy [89,90]. An exception to this conclusion has been found in differentiating gastric versus extra-gastric MALT-type lymphomas, as somatostatin receptor scintigraphy has better uptake in extra-gastric MALT-type lymphomas [91].

## Somatostatin Receptor 2 in Gastroentero-pancreatic Neuroendocrine Tumors

With the heterogeneity of this spectrum of disease in GEP NETs, efforts are being made to identify biomarkers for predicting response to treatment and outcomes. 90% of GEP NETs express SSTR2 on tumor surface [92]. Okuwaki et al. studied 79 pancreatic NETs and found that negative SSTR2 staining was a significant independent predictor of poor outcome [93]. Wang et al. looked at SSTR2 and SSTR5 expression among 143 GEP NETs, finding that positive expression for these two receptors was associated with improved survival compared to negative expression [53]. Conversely, van Adrichem et al. in a study of 73 GEP NETs, found that negative SSTR2 staining was not significantly related to OS, disease stage, or tumor grade [94]. Despite an unclear relationship between SSTR2 expression and outcomes, expression of these receptors has implications in the diagnosis and treatment of GEP NETs.

Radiolabeled SSAs, including $^{68}$Ga-DOTA-SSA and $^{111}$In-pentetrotide, are used as radiopharmaceuticals in PET/CT imaging for NET diagnosis and staging [5,11]. Further, radiolabeled SSAs and unlabeled SSAs are employed in peptide receptor radionuclide therapy (PRRT) which has been shown to prolong PFS in metastatic GEP NETs [56,95,96]. Utilizing these mechanisms has proved beneficial in some patients, however, there is a subset, albeit small, of patients that do not express SSTR2. Few have sought to delineate differences between SSTR2 positivity and negativity in these lesions. Hu et al. examined 223 cases of non-functional pancreatic NETs, of which 23 were negative for SSTR2 and found that SSTR2 negativity was significantly associated with earlier onset, larger, more advanced lesions, peripheral aggression, metastasis to liver and lymph nodes (LN), and worse PFS [11]. Refardt et al. examined 69 SSTR2 positive and 69 SSTR2 negative propensity score matched patients with well-differentiated NETs and found that those negative for the receptor had a worse prognosis despite receiving more aggressive treatment [5].

With no known mutations affecting its expression [97], it has become clear that SSTR2 loss in advanced tumors is chiefly mediated through epigenetic mechanisms [6]. Simply put, epigenetics is the study of heritable gene expression alterations that do not involve changes to the underlying DNA sequence. Examples of epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling and non-coding RNAs [98]. Preclinical work from several labs, including ours, have identified broad-based epigenetic silencing mechanisms, such as DNA CpG methylation and histone deacetylation, in negatively controlling SSTR2 expression [6,99]. DNA methylation involves the covalent addition of a methyl group to cytosines, just upstream of a guanine nucleotide (CpG), by a family of enzymes called, DNA methyltransferases [100]. DNA CpG methylation causes compaction of chromatin, impeding transcription factor binding, resulting in gene silencing [101]. CpG sites occur at increased frequencies in regions called CpG islands, which are often concentrated in gene regulatory elements, such as promoters and enhancers [102]. CpG islands are routinely found to be hypermethylated in cancers, often leading to silencing of tumor suppressor genes. Importantly, the SSTR2 gene was found to have a CpG island in its promoter, upstream of the transcription start site [103]. As expected, increased promoter CpG methylation has been correlated with decreased expression of SSTR2 gene transcript [99,103,104]. In addition to CpG methylation, histone deacetylation also plays a major role in regulating SSTR2 expression. Enzymes termed histone acetyltransferases (HATs) attach acetyl groups to select lysine residues on histone protein N-terminal tails. Histone acetylation acts to open chromatin, leading to increased transcription factor binding and gene transcription [105]. Opposite to that of HATs, histone deacetylases (HDACs) remove acetyl groups from histone protein tails, facilitating chromatin compaction, resulting in decreased gene expression [106]. Performing chromatin immunoprecipitation (ChIP) experiments, it was shown that promoter histone acetylation levels correlate with SSTR2 gene expression levels [103]. Unique to epigenetics is the plasticity of their marks. While direct damage to DNA and its base pairs is permanent, epigenetic changes and

their marks are not. The focused clinical goal regarding SSTR2-based epigenetic studies is to ultimately turn back on its expression, resulting in improved patient responses to SSTR2-focused radioligand imaging and therapy modalities. With that in mind, numerous preclinical NET cell culture studies have demonstrated that epidrug treatment, with either DNA methyltransferase inhibitors (DNMTi) or histone deacetylase inhibitors (HDACi), increases SSTR2 expression levels [6,99,107-110]. Thus, these studies, and others, have shown the utility of epigenetic targeting to increase expression of SSTR2.

## Prognostic Implications & Modifications

SOMATOSTATIN ANALOGS

Current therapy for SSTR2 positive GEP NETs is based on the use of somatostatin analogs (SSAs). Natural somatostatin peptides have a half-life of a few minutes – thus, octreotide was developed with a half-life of several hours [4]. Octreotide has a high affinity for both SSTR2 and SSTR5 and can be administered by subcutaneous injection or through intravenous infusion with a maximum daily dose of 3000 µg [4]. Lanreotide is another SSA that can be administered by subcutaneous injection every 28 days [111]. These drugs are typically well-tolerated with side-effects being dose-dependent [111]. SSAs are useful in the symptomatic control of functioning NETs given their antisecretory effect. Both octreotide and lanreotide can be used to address carcinoid syndrome and one meta-analysis found that they provided symptomatic improvement in 65-72% of patients [112]. However, with long-term use of these medications, decreased response has been observed which may be attributable to tumor progression, tachyphylaxis or treatment resistance [111]. Multiple studies have found that SSAs also exert antiproliferative effects on these tumors in addition to symptom control. The PROMID trial investigated eighty-five patients with well-differentiated metastatic neuroendocrine midgut tumors in a placebo-controlled, prospective, randomized study where patients received either octreotide or placebo with a primary endpoint of time to tumor progression. Those that received octreotide had significantly longer time to tumor progression (14.3 months) compared to those receiving the placebo (6 months) and at the 6 month mark, they also had significantly lower tumor progression rates (37% vs 66%) [56]. The CLARINET trial investigated the antiproliferative effect of lanreotide in 204 patients with grade 1/2 differentiated, nonfunctioning, SSTR positive NETs of the foregut, midgut, pancreas and unknown primary with a primary endpoint of PFS [113]. Those that received lanreotide had significantly prolonged PFS compared to placebo (32.8 months vs 18 months) [113]. Further, the CLARINET FORTE trial investigated the safety and efficacy of increasing the frequency of dosing of lanreotide autogel (LAN) in ninety-nine patients with pancreatic or midgut NETs that had progression in the previous two years while on standard dosing of LAN with a primary endpoint of PFS. They found that the median PFS in midgut NETs was 8.3 months and 5.6 months in pancreatic NETs with increased dosing frequency of LAN and that it was well tolerated and safe [114]. Thus, lack of response with standard dosing does not necessarily mean a new treatment has to be pursued. More recently, another SSA was developed, pasireotide, which has high affinity for SSTR1-3 and SSTR5 [115]. Though not statistically significant, a randomized double-blind phase III study compared pasireotide long-acting release with octreotide long-acting repeatable in managing symptoms of NETs of the digestive tract refractory to first-generation SSAs and found that those on pasireotide had better tumor control rate than those on octreotide [115]. In a *post hoc* analysis of these study participants, pasireotide had a five month longer PFS than patients on octreotide which was statistically significant [115]. In summary, SSAs provide both symptom control and antiproliferative benefits to patients with SSTR2 positive GEP NETs.

SOMATOSTATIN RECEPTOR-BASED IMAGING

SSTR-based imaging is a useful adjunct to standard imaging techniques that allows enhanced sensitivity for most types of NETs and is an integral part of tumor staging and preoperative imaging [116]. Computed tomography (CT) and magnetic resonance imaging (MRI) are often employed to detect NETs but have a sensitivity between 50-80% [117]. SSTR-based imaging offers numerous benefits – it can reveal additional metastases compared to conventional imaging, assess response to therapy, and by demonstrating sufficient SSTR expression in tumors it deems patients eligible for peptide receptor radionuclide therapy (PRRT) [116]. Currently, $^{68}$Ga-DOTA-SSA and $^{111}$In-pentetrotide are the radiopharmaceuticals of choice for SSTR-based imaging. $^{68}$Ga is an isotope normally chelated to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) which is then bound to a peptide: DOTATATE, DOTATOC, or DOTANOC [118]. DOTATATE is the most common and has the highest affinity to SSTR2 [118]. The most avid uptake of $^{68}$Ga-DOTATATE occurs in the spleen, adrenal glands, kidneys and pituitary gland which is attributed to the presence of SSTR2 [118]. Uptake in the liver and salivary glands is related to nonspecific clearance of the tracer [118]. DOTATOC has high affinity for SSTR2 and SSTR5 while DOTANOC has the widest receptor binding profile, binding SSTR2, SSTR3, and SSTR5 [119]. Numerous studies have identified benefits to these imaging modalities compared to standard techniques [120-123].

SSTR-based imaging is not without pitfalls. Tumors must express SSTRs to be visualized on these modalities which is less common among poorly differentiated lesions. False negative results are often related to tumor heterogeneity [118]. False positives can occur secondary to physiologic reasons, osteoblastic lesions, inflammatory processes, and incidentally. For example, the uncinate process of the pancreas can demonstrate increased activity due to higher expression of SSTR2, often presenting as ill-defined enhancement [124]. Accessory spleens can be a source of false positives as well. Any process that leads to increased osteoblastic activity can create foci with increased uptake secondary to high SSTR2 expression in osteoblasts [124]. Macrophages and leukocytes also express SSTR2 therefore, active inflammatory processes can contribute to false positives [124].

Treatment with SSA does not preclude clinicians from using SSTR-based imaging. Investigations into the use of long-acting octreotide and these imaging modalities have found that the use of SSAs diminished physiologic uptake

in the liver, spleen and thyroid [125,126]. These medications did not compromise tracer uptake in primary tumors or metastatic lesions and tended to improve tumor-to-background ratio [125,126].

## Peptide Receptor Radionuclide Therapy

$^{177}$Lu-dotatate therapy was approved by the United States Food and Drug Administration (FDA) in 2018 for the treatment of SSTR positive, well-differentiated, GEP NETs. The radionuclide, $^{177}$Lu, is attached to a SSA, DOTATATE, to target tumor cells that express SSTR and deliver ionizing radiation to them which induces apoptosis through single and double-stranded DNA breaks [127]. Numerous studies have investigated the benefit of this therapy. In the NETTER-1 global phase 3 trial, 229 patients with SSTR positive, grade 1 or 2 midgut NETs who progressed on standard dosing of long-acting octreotide were assigned to receive either four cycles of 7.4 GBq $^{177}$Lu-DOTATATE with intramuscular long-acting octreotide 30 mg every 4 weeks or long-acting octreotide 60 mg every 4 weeks [96]. Results of this study demonstrated longer PFS and higher response rate in the PRRT group than high-dose long-acting octreotide in patients with advanced midgut NET [96]. Follow up from this trial showed that these patients also experienced a longer time to deterioration in the $^{177}$Lu-dotatate group and that 36% of the patients in the control group had to crossover to $^{177}$Lu-dotatate therapy [128,129]. Thus, there is both a survival benefit and symptom control provided by this treatment. The NETTER-2 trial was another randomized multicenter phase 3 trial that enrolled 226 patients with newly diagnosed grade 2 or 3, SSTR positive GEP NETs to evaluate $^{177}$Lu-dotatate with 30 mg intramuscular long-acting octreotide followed by 30 mg long-acting octreotide every 4 weeks with patients receiving just high dose 60 mg long-acting octreotide every 4 weeks [130]. $^{177}$Lu-dotatate therapy plus long-acting octreotide significantly extended median PFS by 14 months in patients with grade 2 or 3 advanced GEP NETs [130]. Currently ongoing, is the COMPOSE trial which aims to evaluate PFS in patients receiving a different radioligand, $^{177}$Lu-DOTATOC, with chemotherapy in patients with grade 2 or 3 GEP NETs and a Ki-67% between 15-55%.

Chromogranin A (CgA) levels are often used as a biochemical marker in NETs with an elevated level correlating to hepatic tumor burden, rapid tumor progression and shorter overall survival (OS) [131]. In patients who undergo PRRT, 25-52% of them exhibit a drop in CgA >50% - such a drop has been associated with prolonged PFS and OS [132]. CgA can, however, be increased by both tumor progression and cell damage or lysis from PRRT and is thus unreliable [132].

PRRT is contraindicated in pregnant or breastfeeding patients, those with severe cardiac impairment or those with a life expectancy less than 3 months [133]. The most common side effects include hematologic toxicity, commonly lymphopenia, nephrotoxicity secondary to renal excretion of radiolabeled SSAs, and hepatotoxicity [132].

Efforts to improve the efficacy of this treatment modality are ongoing. PRRT is known to induce double and single-stranded DNA breaks – most of these breaks are single-stranded which require poly-[ADP-ribose]-polymerase 1 (PARP-1) activity for repair [134]. Without repair, these single-stranded breaks cause replication fork arrest and thus double-stranded break formation during replication [134]. Olaparib is a PARP-1 inhibitor and has been found to synergistically sensitize SSTR2-expressing human tumor cells to $^{177}$Lu-DOTATATE treatment [134]. Investigations have also shown that inhibition of heat shock protein 90 (Hsp90) with ganetespib can enhance the anti-tumor effect of $^{177}$Lu-DOTATATE therapy in an SSTR expressing xenograft model [135]. Hsp90 expression is higher in small intestine NETs relative to tumor stroma [135]. Investigations are also underway exploring alternative radionuclides to use in PRRT [132].

## Epigenetic Therapeutic Implications & Future Directions

Although epidrug treatment has been shown to increase expression of SSTR2, evidence of therapeutic benefit from this re-expression is necessary to drive novel SSTR2-directed therapies to the clinic. To date, several GEP-NET cell culture studies have demonstrated increased uptake of $^{68}$Ga-radiolabeled somatostatin analogs after either DNMTi or HDACi epidrug treatment [108-110,136,137]. While in vitro epidrug therapy can both increase expression of SSTR2 and radiolabeled somatostatin analog uptake, the results from limited in vivo studies have been mixed. Studies using DNMTi or HDACi treatment of mice, harboring NET cell line xenografts, have shown increased uptake of radiolabeled $^{68}$Ga somatostatin analogs [108,110,136]. One in vivo study demonstrated uptake of $^{177}$Lu-DOTATATE PRRT in NET cell line tumor xenografts [138]; unfortunately, no effects on tumor size or therapeutic benefit was seen. Additional in vivo studies demonstrated contradictory results, depending on the specific HDACi employed, regarding SSTR2 expression increases and $^{177}$Lu-DOTATATE uptake [139,140]. Lack of functional effects or therapeutic benefit from the limited in vivo studies to date may hint at necessary changes or finetuning in epidrug selection or dosing regimen parameters. A recent publication from our group, using an SSTR2-low PNET cell line xenograft tumor model, demonstrated that HDACi treatment led to increased tumor uptake of $^{177}$Lu-DOTATATE and resulted in significant antitumor response, compared to $^{177}$Lu-DOTATATE treatment alone [99]. Currently, human studies combining epidrug and radiolabeled somatostatin analogs are also limited. One study showed no tumor uptake of $^{68}$Ga-DOTATATE after dual DNMTi and HDACi treatment in advanced NET patients having low baseline levels of SSTR2 expression [141]. In contrast, a study of metastatic midgut NET patients revealed increased $^{68}$Ga-DOTATOC after HDACi treatment [142]. Future GEP-NET patient trials combining novel epidrug therapy and somatostatin radioligand regimens are eagerly anticipated. Currently, participants are being recruited for a Phase 1 trial in the United Kingdom investigating whether pre-treatment with ASTX727 (cedazuridine 100 mg + decitabine 35 mg) results in re-expression of SSTR2 in patients with metastatic neuroendocrine tumors [143].

Recent research endeavors from our lab have delved deeper into the finer details of SSTR2 epigenetic

regulation, beyond just broad-based DNA CpG methylation and histone deacetylation events. Our unpublished work, using functional genomic and chemical screens, has identified various repressor complexes responsible for silencing of SSTR2 expression and further demonstrates the unique interconnectedness of various epigenetic mechanisms. Ultimately, our clinical research goal is to formulate the optimal epidrug treatment regimen. This epidrug regimen would have negligible patient toxicity and would increase SSTR2 cell surface expression in SSTR2 low/negative GEP-NET patients, resulting in augmented somatostatin radioligand imaging and therapeutic efficacy.

## Conclusion

In summary, GEP NETs encompass a heterogeneous group of tumors often characterized by SSTR2 positivity. Though surgery is the only curative option, most patients at the time of diagnosis are not candidates and must instead rely on treatment based on the use of SSA. SSA provide both symptoms control and antiproliferative properties. PRRT is a newer therapeutic modality that takes advantage of SSTR2 positivity to target ionizing radiation. SSTR2 expression is associated with well-differentiated tumors and the loss of expression in more advanced ones is attributed to epigenetic silencing [6]. Efforts are now being made to employ epidrugs to increase the expression of SSTR2 in poorly differentiated GEP NETs so that SSTR-based imaging, SSA, and PRRT can be utilized in this subset of patients.

## Conflicts of Interest

The authors have no conflicts of interest to declare.

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## Author Contributions

LFR and SMS contributed to the manuscript conception. LFR, RMS, JPM, and SMS prepared the article. LFR, RMS, and SMS provided critical revisions to the article. LFR, RMS, JPM and SMS reviewed the article.

## References


1. Das S, Dasari A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? *Curr Oncol Rep*. Mar 14 2021;23(4):43. doi:10.1007/s11912-021-01029-7
2. Kos-Kudla B, Cwikla J, Ruchala M, et al. Current treatment options for gastroenteropancreatic neuroendocrine tumors with a focus on the role of lanreotide. *Contemp Oncol (Pozn)*. 2017;21(2):115-122. doi:10.5114/wo.2017.68619
3. Forsythe SD, Pu T, Andrews SG, Madigan JP, Sadowski SM. Models in Pancreatic Neuroendocrine Neoplasms: Current Perspectives and Future Directions. *Cancers (Basel)*. Jul 25 2023;15(15)doi:10.3390/cancers15153756
4. Diez M, Teule A, Salazar R. Gastroenteropancreatic neuroendocrine tumors: diagnosis and treatment. *Ann Gastroenterol*. 2013;26(1):29-36.
5. Refardt J, Zandee WT, Brabander T, et al. Inferior outcome of neuroendocrine tumor patients negative on somatostatin receptor imaging. *Endocr-Relat Cancer*. Nov 2020;27(11):615-624. doi:10.1530/Erc-20-0340
6. Klomp MJ, Dalm SU, de Jong M, Feelders RA, Hofland J, Hofland LJ. Epigenetic regulation of somatostatin and somatostatin receptors in neuroendocrine tumors and other types of cancer. *Rev Endocr Metab Disord*. Sep 2021;22(3):495-510. doi:10.1007/s11154-020-09607-z
7. Rogoza O, Megnis K, Kudrjavceva M, Gerina-Berzina A, Rovite V. Role of Somatostatin Signalling in Neuroendocrine Tumours. *Int J Mol Sci*. Jan 27 2022;23(3)doi:10.3390/ijms23031447
8. Zamora V, Cabanne A, Salanova R, et al. Immunohistochemical expression of somatostatin receptors in digestive endocrine tumours. *Dig Liver Dis*. Mar 2010;42(3):220-5. doi:10.1016/j.dld.2009.07.018
9. Kulaksiz H, Eissele R, Rossler D, et al. Identification of somatostatin receptor subtypes 1, 2A, 3, and 5 in neuroendocrine tumours with subtype specific antibodies. *Gut*. Jan 2002;50(1):52-60. doi:10.1136/gut.50.1.52
10. Qian ZR, Li T, Ter-Minassian M, et al. Association Between Somatostatin Receptor Expression and Clinical Outcomes in Neuroendocrine Tumors. *Pancreas*. Nov 2016;45(10):1386-1393. doi:10.1097/MPA.0000000000000700
11. Hu HF, Hu YH, Xu XW, et al. Role of Somatostatin Receptor 2 in Nonfunctional Pancreatic Neuroendocrine Tumors: Clinicopathological Analysis of 223 Cases and Whole Exome Sequencing of a Multifocal Case. *Pancreas*. Nov-Dec 01 2022;51(10):1404-1410. doi:10.1097/MPA.0000000000002199
12. Stueven AK, Kayser A, Wetz C, et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci*. Jun 22 2019;20(12)doi:10.3390/ijms20123049
13. Brazeau P, Vale W, Burgus R, et al. Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science*. Jan 5 1973;179(4068):77-9. doi:10.1126/science.179.4068.77
14. Pradayrol L, Jornvall H, Mutt V, Ribet A. N-terminally extended somatostatin: the primary structure of somatostatin-28. *FEBS Lett*. Jan 1 1980;109(1):55-8. doi:10.1016/0014-5793(80)81310-x
15. Warren TG, Shields D. Expression of preprosomatostatin in heterologous cells: biosynthesis, posttranslational processing, and secretion of mature somatostatin. *Cell*. Dec 1984;39(3 Pt 2):547-55. doi:10.1016/0092-8674(84)90461-6
16. Francis BH, Baskin DG, Saunders DR, Ensinck JW. Distribution of somatostatin-14 and somatostatin-28 gastrointestinal-pancreatic cells of rats and humans. *Gastroenterology*. Nov 1990;99(5):1283-91. doi:10.1016/0016-5085(90)91151-u
17. Patel YC, Greenwood MT, Warszynska A, Panetta R, Srikant CB. All five cloned human somatostatin receptors (hSSTR1-5) are functionally coupled to adenylyl cyclase. *Biochem Biophys Res Commun*. Jan 28 1994;198(2):605-12. doi:10.1006/bbrc.1994.1088
18. Bell GI, Yasuda K, Kong H, Law SF, Raynor K, Reisine T. Molecular biology of somatostatin receptors. *Ciba Found Symp*. 1995;190:65-79; discussion 80-8. doi:10.1002/9780470514733.ch5
19. Costanzi E, Simioni C, Conti I, et al. Two neuroendocrine G protein-coupled receptor molecules, somatostatin and melatonin: Physiology of signal transduction and therapeutic perspectives. *J Cell Physiol*. Apr 2021;236(4):2505-2518. doi:10.1002/jcp.30062
20. Chaudhary PK, Kim S. An Insight into GPCR and G-Proteins as Cancer Drivers. *Cells*. Nov 24 2021;10(12)doi:10.3390/cells10123288
21. Alexander SP, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2017/18: G protein-coupled receptors. *Br J Pharmacol*. Dec 2017;174 Suppl 1(Suppl Suppl 1):S17-S129. doi:10.1111/bph.13878
22. Li YG, Meng XY, Yang X, et al. Structural insights into somatostatin receptor 5 bound with cyclic peptides. *Acta Pharmacol Sin*. Jun 26 2024;doi:10.1038/s41401-024-01314-8
23. Gunther T, Tulipano G, Dournaud P, et al. International Union of Basic and Clinical Pharmacology. CV. Somatostatin Receptors: Structure, Function, Ligands, and New Nomenclature. *Pharmacol Rev*. Oct 2018;70(4):763-835. doi:10.1124/pr.117.015388
24. Yamada Y, Stoffel M, Espinosa R, 3rd, et al. Human somatostatin receptor genes: localization to human chromosomes 14, 17, and 22 and identification of simple tandem repeat polymorphisms. *Genomics*. Feb 1993;15(2):449-52. doi:10.1006/geno.1993.1088
25. Papotti M, Bongiovanni M, Volante M, et al. Expression of somatostatin receptor types 1-5 in 81 cases of gastrointestinal and pancreatic endocrine

tumors. A correlative immunohistochemical and reverse-transcriptase polymerase chain reaction analysis. *Virchows Arch*. May 2002;440(5):461-75. doi:10.1007/s00428-002-0609-x
26. Olias G, Viollet C, Kusserow H, Epelbaum J, Meyerhof W. Regulation and function of somatostatin receptors. *J Neurochem*. Jun 2004;89(5):1057-91. doi:10.1111/j.1471-4159.2004.02402.x
27. Piwko C, Thoss VS, Schupbach E, et al. Pharmacological characterisation of human cerebral cortex somatostatin SRIF1 and SRIF2 receptors. *Naunyn Schmiedebergs Arch Pharmacol*. Feb 1997;355(2):161-7. doi:10.1007/pl00004927
28. Bocci G, Culler MD, Fioravanti A, et al. In vitro antiangiogenic activity of selective somatostatin subtype-1 receptor agonists. *Eur J Clin Invest*. Sep 2007;37(9):700-8. doi:10.1111/j.1365-2362.2007.01848.x
29. Thermos K. Functional mapping of somatostatin receptors in the retina: a review. *Vision Res*. Aug 2003;43(17):1805-15. doi:10.1016/s0042-6989(03)00169-x
30. Atkinson H, England JA, Rafferty A, et al. Somatostatin receptor expression in thyroid disease. *Int J Exp Pathol*. Jun 2013;94(3):226-9. doi:10.1111/iep.12024
31. Kumar U, Sasi R, Suresh S, et al. Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. *Diabetes*. Jan 1999;48(1):77-85. doi:10.2337/diabetes.48.1.77
32. Voros I, Saghy E, Pohoczky K, et al. Somatostatin and Its Receptors in Myocardial Ischemia/Reperfusion Injury and Cardioprotection. *Front Pharmacol*. 2021;12:663655. doi:10.3389/fphar.2021.663655
33. Watanabe N, Nakanishi Y, Kinukawa N, et al. Expressions of Somatostatin Receptor Subtypes (SSTR-1, 2, 3, 4 and 5) in Neuroblastic Tumors; Special Reference to Clinicopathological Correlations with International Neuroblastoma Pathology Classification and Outcomes. *Acta Histochem Cytochem*. 2014;47(5):219-29. doi:10.1267/ahc.14024
34. Kaemmerer D, Trager T, Hoffmeister M, et al. Inverse expression of somatostatin and CXCR4 chemokine receptors in gastroenteropancreatic neuroendocrine neoplasms of different malignancy. *Oncotarget*. Sep 29 2015;6(29):27566-79. doi:10.18632/oncotarget.4491
35. Cives M, Kunz PL, Morse B, et al. Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors. *Endocr Relat Cancer*. Feb 2015;22(1):1-9. doi:10.1530/ERC-14-0360
36. Kumar U, Singh S. Role of Somatostatin in the Regulation of Central and Peripheral Factors of Satiety and Obesity. *Int J Mol Sci*. Apr 7 2020;21(7)doi:10.3390/ijms21072568
37. Somvanshi RK, Jhajj A, Heer M, Kumar U. Characterization of somatostatin receptors and associated signaling pathways in pancreas of R6/2 transgenic mice. *Biochim Biophys Acta Mol Basis Dis*. Feb 2018;1864(2):359-373. doi:10.1016/j.bbadis.2017.11.002
38. Di Muro G, Catalano R, Treppiedi D, et al. The Novel SSTR3 Agonist ITF2984 Exerts Antimitotic and Proapoptotic Effects in Human Non-Functioning Pituitary Neuroendocrine Tumor (NF-PitNET) Cells. *Int J Mol Sci*. Mar 23 2024;25(7)doi:10.3390/ijms25073606
39. Yao Q, Liu Q, Xu H, et al. Upregulated Expression of SSTR3 is Involved in Neuronal Apoptosis After Intracerebral Hemorrhage in Adult Rats. *Cell Mol Neurobiol*. Nov 2017;37(8):1407-1416. doi:10.1007/s10571-017-0471-7
40. War SA, Kim B, Kumar U. Human somatostatin receptor-3 distinctively induces apoptosis in MCF-7 and cell cycle arrest in MDA-MB-231 breast cancer cells. *Mol Cell Endocrinol*. Sep 15 2015;413:129-44. doi:10.1016/j.mce.2015.06.019
41. Lee M, Lupp A, Mendoza N, et al. SSTR3 is a putative target for the medical treatment of gonadotroph adenomas of the pituitary. *Endocr Relat Cancer*. Feb 2015;22(1):111-9. doi:10.1530/ERC-14-0472
42. Patel YC. Somatostatin and its receptor family. *Front Neuroendocrinol*. Jul 1999;20(3):157-98. doi:10.1006/frne.1999.0183
43. Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumours: molecular basis for in vivo multireceptor tumour targeting. *Eur J Nucl Med Mol Imaging*. May 2003;30(5):781-93. doi:10.1007/s00259-003-1184-3
44. Borzsei R, Zsido BZ, Balint M, Helyes Z, Pinter E, Hetenyi C. Exploration of Somatostatin Binding Mechanism to Somatostatin Receptor Subtype 4. *Int J Mol Sci*. Jun 21 2022;23(13)doi:10.3390/ijms23136878
45. Van Op den Bosch J, Torfs P, De Winter BY, et al. Effect of genetic SSTR4 ablation on inflammatory peptide and receptor expression in the non-inflamed and inflamed murine intestine. *J Cell Mol Med*. Sep 2009;13(9B):3283-95. doi:10.1111/j.1582-4934.2009.00760.x
46. Van Op den Bosch J, van Nassauw L, Lantermann K, van Marck E, Timmermans JP. Effect of intestinal inflammation on the cell-specific expression of somatostatin receptor subtypes in the murine ileum. *Neurogastroenterol Motil*. Jul 2007;19(7):596-606. doi:10.1111/j.1365-2982.2007.00931.x
47. Sandoval KE, Farr SA, Banks WA, et al. Chronic peripheral administration of somatostatin receptor subtype-4 agonist NNC 26-9100 enhances learning and memory in SAMP8 mice. *Eur J Pharmacol*. Mar 1 2011;654(1):53-9. doi:10.1016/j.ejphar.2010.12.013
48. Kecskes A, Pohoczky K, Kecskes M, et al. Characterization of Neurons Expressing the Novel Analgesic Drug Target Somatostatin Receptor 4 in Mouse and Human Brains. *Int J Mol Sci*. Oct 21 2020;21(20)doi:10.3390/ijms21207788
49. Patel YC. Molecular pharmacology of somatostatin receptor subtypes. *J Endocrinol Invest*. Jun 1997;20(6):348-67. doi:10.1007/BF03350317

 

50. Corleto VD, Falconi M, Panzuto F, et al. Somatostatin receptor subtypes 2 and 5 are associated with better survival in well-differentiated endocrine carcinomas. *Neuroendocrinology*. 2009;89(2):223-30. doi:10.1159/000167796
51. Taboada GF, Luque RM, Bastos W, et al. Quantitative analysis of somatostatin receptor subtype (SSTR1-5) gene expression levels in somatotropinomas and non-functioning pituitary adenomas. *Eur J Endocrinol*. Jan 2007;156(1):65-74. doi:10.1530/eje.1.02313
52. Srirajaskanthan R, Watkins J, Marelli L, Khan K, Caplin ME. Expression of somatostatin and dopamine 2 receptors in neuroendocrine tumours and the potential role for new biotherapies. *Neuroendocrinology*. 2009;89(3):308-14. doi:10.1159/000179899
53. Wang YH, Wang W, Jin KZ, et al. Somatostatin receptor expression indicates improved prognosis in gastroenteropancreatic neuroendocrine neoplasm, and octreotide long-acting release is effective and safe in Chinese patients with advanced gastroenteropancreatic neuroendocrine tumors. *Oncol Lett*. Mar 2017;13(3):1165-1174. doi:10.3892/ol.2017.5591
54. Mehta S, de Reuver PR, Gill P, et al. Somatostatin Receptor SSTR-2a Expression Is a Stronger Predictor for Survival Than Ki-67 in Pancreatic Neuroendocrine Tumors. *Medicine (Baltimore)*. Oct 2015;94(40):e1281. doi:10.1097/MD.0000000000001281
55. Childs A, Vesely C, Ensell L, et al. Expression of somatostatin receptors 2 and 5 in circulating tumour cells from patients with neuroendocrine tumours. *Br J Cancer*. Dec 6 2016;115(12):1540-1547. doi:10.1038/bjc.2016.377
56. Rinke A, Muller HH, Schade-Brittinger C, 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*. Oct 1 2009;27(28):4656-63. doi:10.1200/JCO.2009.22.8510
57. Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. Oct 16 2014;371(16):1556-7. doi:10.1056/NEJMc1409757
58. Khan MS, El-Khouly F, Davies P, Toumpanakis C, Caplin ME. Long-term results of treatment of malignant carcinoid syndrome with prolonged release Lanreotide (Somatuline Autogel). *Aliment Pharmacol Ther*. Jul 2011;34(2):235-42. doi:10.1111/j.1365-2036.2011.04693.x
59. Pedraza-Arevalo S, Ibanez-Costa A, Blazquez-Encinas R, et al. Epigenetic and post-transcriptional regulation of somatostatin receptor subtype 5 (SST(5) ) in pituitary and pancreatic neuroendocrine tumors. *Mol Oncol*. Feb 2022;16(3):764-779. doi:10.1002/1878-0261.13107
60. Fuentes-Fayos AC, ME GG, Perez-Gomez JM, et al. Somatostatin Receptor Splicing Variant sst5TMD4 Overexpression in Glioblastoma Is Associated with Poor Survival, Increased Aggressiveness Features, and Somatostatin Analogs Resistance. *Int J Mol Sci*. Jan 20 2022;23(3)doi:10.3390/ijms23031143
61. Gahete MD, Rincon-Fernandez D, Duran-Prado M, et al. The truncated somatostatin receptor sst5TMD4 stimulates the angiogenic process and is associated to lymphatic metastasis and disease-free survival in breast cancer patients. *Oncotarget*. Sep 13 2016;7(37):60110-60122. doi:10.18632/oncotarget.11076
62. Hormaechea-Agulla D, Jimenez-Vacas JM, Gomez-Gomez E, et al. The oncogenic role of the spliced somatostatin receptor sst5TMD4 variant in prostate cancer. *FASEB J*. Nov 2017;31(11):4682-4696. doi:10.1096/fj.201601264RRR
63. Lehman JM, Hoeksema MD, Staub J, et al. Somatostatin receptor 2 signaling promotes growth and tumor survival in small-cell lung cancer. *Int J Cancer*. Mar 1 2019;144(5):1104-1114. doi:10.1002/ijc.31771
64. Sagie N, Romanov E, Kezerle Y, Meirovitz A, Sheva K. Expression Analysis of SSTR 1, 2 and 3 in Small-cell Lung Cancer Patients as Targets for Future Peptide Receptor Radionuclide Therapy. *Anticancer Res*. Sep 2024;44(9):3807-3812. doi:10.21873/anticanres.17206
65. Tsuta K, Wistuba, II, Moran CA. Differential expression of somatostatin receptors 1-5 in neuroendocrine carcinoma of the lung. *Pathol Res Pract*. Aug 15 2012;208(8):470-4. doi:10.1016/j.prp.2012.05.014
66. Lapa C, Hanscheid H, Wild V, et al. Somatostatin receptor expression in small cell lung cancer as a prognostic marker and a target for peptide receptor radionuclide therapy. *Oncotarget*. Apr 12 2016;7(15):20033-40. doi:10.18632/oncotarget.7706
67. Sen F, Sheikh GT, von Hinten J, et al. In-Vivo Somatostatin-Receptor Expression in Small Cell Lung Cancer as a Prognostic Image Biomarker and Therapeutic Target. *Cancers (Basel)*. Jul 13 2023;15(14)doi:10.3390/cancers15143595
68. Rauch H, Kitzberger C, Janghu K, et al. Combining [(177)Lu]Lu-DOTA-TOC PRRT with PARP inhibitors to enhance treatment efficacy in small cell lung cancer. *Eur J Nucl Med Mol Imaging*. Jul 18 2024;doi:10.1007/s00259-024-06844-1
69. Menke JR, Raleigh DR, Gown AM, Thomas S, Perry A, Tihan T. Somatostatin receptor 2a is a more sensitive diagnostic marker of meningioma than epithelial membrane antigen. *Acta Neuropathol*. Sep 2015;130(3):441-3. doi:10.1007/s00401-015-1459-3
70. Anis SE, Lotfalla M, Zain M, Kamel NN, Soliman AA. Value of SSTR2A and Claudin - 1 in Differentiating Meningioma from Schwannoma and Hemangiopericytoma. *Open Access Maced J Med Sci*. Feb 15 2018;6(2):248-253. doi:10.3889/oamjms.2018.062
71. Durand A, Champier J, Jouvet A, et al. Expression of c-Myc, neurofibromatosis Type 2, somatostatin receptor 2 and erb-B2 in human meningiomas: relation to grades or histotypes. *Clin Neuropathol*. Sep-Oct 2008;27(5):334-45. doi:10.5414/npp27334


 

72. Rachinger W, Stoecklein VM, Terpolilli NA, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. *J Nucl Med*. Mar 2015;56(3):347-53. doi:10.2967/jnumed.114.149120
73. Ivanidze J, Roytman M, Lin E, et al. Gallium-68 DOTATATE PET in the Evaluation of Intracranial Meningiomas. *J Neuroimaging*. Sep 2019;29(5):650-656. doi:10.1111/jon.12632
74. Wu W, Zhou Y, Wang Y, et al. Clinical Significance of Somatostatin Receptor (SSTR) 2 in Meningioma. *Front Oncol*. 2020;10:1633. doi:10.3389/fonc.2020.01633
75. Mawrin C, Schulz S, Pauli SU, et al. Differential expression of sst1, sst2A, and sst3 somatostatin receptor proteins in low-grade and high-grade astrocytomas. *J Neuropathol Exp Neurol*. Jan 2004;63(1):13-9. doi:10.1093/jnen/63.1.13
76. He JH, Wang J, Yang YZ, et al. SSTR2 is a prognostic factor and a promising therapeutic target in glioma. *Am J Transl Res*. 2021;13(10):11223-11234.
77. Ostrom QT, Bauchet L, Davis FG, et al. The epidemiology of glioma in adults: a "state of the science" review. *Neuro Oncol*. Jul 2014;16(7):896-913. doi:10.1093/neuonc/nou087
78. Reubi JC, Lang W, Maurer R, Koper JW, Lamberts SW. Distribution and biochemical characterization of somatostatin receptors in tumors of the human central nervous system. *Cancer Res*. Nov 1 1987;47(21):5758-64.
79. Tarkin JM, Calcagno C, Dweck MR, et al. (68)Ga-DOTATATE PET Identifies Residual Myocardial Inflammation and Bone Marrow Activation After Myocardial Infarction. *J Am Coll Cardiol*. May 21 2019;73(19):2489-2491. doi:10.1016/j.jacc.2019.02.052
80. Bhanat E, Koch CA, Parmar R, Garla V, Vijayakumar V. Somatostatin receptor expression in non-classical locations - clinical relevance? *Rev Endocr Metab Disord*. Jun 2018;19(2):123-132. doi:10.1007/s11154-018-9470-3
81. Li L, Tian Y, He Y. Late Pseudoprogression: A Potential Pitfall in 68Ga-DOTATATE PET/CT for Glioma. *Clin Nucl Med*. Apr 1 2023;48(4):e207-e208. doi:10.1097/RLU.0000000000004511
82. Sampedro-Nunez M, Luque RM, Ramos-Levi AM, et al. Presence of sst5TMD4, a truncated splice variant of the somatostatin receptor subtype 5, is associated to features of increased aggressiveness in pancreatic neuroendocrine tumors. *Oncotarget*. Feb 9 2016;7(6):6593-608. doi:10.18632/oncotarget.6565
83. Fan S, Zheng H, Zhan Y, et al. Somatostatin receptor2 (SSTR2) expression, prognostic implications, modifications and potential therapeutic strategies associates with head and neck squamous cell carcinomas. *Crit Rev Oncol Hematol*. Jan 2024;193:104223. doi:10.1016/j.critrevonc.2023.104223
84. Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. *Nat Rev Dis Primers*. Nov 26 2020;6(1):92. doi:10.1038/s41572-020-00224-3
85. Lechner M, Schartinger VH, Steele CD, et al. Somatostatin receptor 2 expression in nasopharyngeal cancer is induced by Epstein Barr virus infection: impact on prognosis, imaging and therapy. *Nat Commun*. Jan 5 2021;12(1):117. doi:10.1038/s41467-020-20308-8
86. Viswanathan K, Sadow PM. Somatostatin receptor 2 is highly sensitive and specific for Epstein-Barr virus-associated nasopharyngeal carcinoma. *Hum Pathol*. Nov 2021;117:88-100. doi:10.1016/j.humpath.2021.08.004
87. Patel R, Marano G, Joseph J, Chung J, Plata A, Vos JA. (18) F-fludeoxyglucose positron emission computed tomography ((18) F-FDG-PET/CT) versus (68) Ga-DOTATATE-PET/CT in patients with head and neck cancer: Comparisons and implications for treatment. *Head Neck*. Feb 2023;45(2):347-354. doi:10.1002/hed.27243
88. Juntikka T, Vaittinen S, Vahlberg T, Jyrkkio S, Minn H. Somatostatin Receptors and Chemokine Receptor CXCR4 in Lymphomas: A Histopathological Review of Six Lymphoma Subtypes. *Front Oncol*. 2021;11:710900. doi:10.3389/fonc.2021.710900
89. Dalm VA, Hofland LJ, Mooy CM, et al. Somatostatin receptors in malignant lymphomas: targets for radiotherapy? *J Nucl Med*. Jan 2004;45(1):8-16.
90. Ferone D, Semino C, Boschetti M, Cascini GL, Minuto F, Lastoria S. Initial staging of lymphoma with octreotide and other receptor imaging agents. *Semin Nucl Med*. Jul 2005;35(3):176-85. doi:10.1053/j.semnuclmed.2005.03.001
91. Priyadarshini S, Allison DB, Chauhan A. Comprehensive Assessment of Somatostatin Receptors in Various Neoplasms: A Systematic Review. *Pharmaceutics*. Jul 1 2022;14(7)doi:10.3390/pharmaceutics14071394
92. Gatto F, Hofland LJ. The role of somatostatin and dopamine D
receptors in endocrine tumors. *Endocr-Relat Cancer*. Dec 2011;18(6):R233-R251. doi:10.1530/Erc-10-0334
93. Okuwaki K, Kida M, Mikami T, et al. Clinicopathologic Characteristics of Pancreatic Neuroendocrine Tumors and Relation of Somatostatin Receptor Type 2A to Outcomes. *Cancer-Am Cancer Soc*. Dec 1 2013;119(23):4094-4102. doi:10.1002/cncr.28341
94. van Adrichem RC, Kamp K, van Deurzen CH, et al. Is There an Additional Value of Using Somatostatin Receptor Subtype 2a Immunohistochemistry Compared to Somatostatin Receptor Scintigraphy Uptake in Predicting Gastroenteropancreatic Neuroendocrine Tumor Response? *Neuroendocrinology*. 2016;103(5):560-6. doi:10.1159/000441604
95. Caplin ME, Pavel M, Cwikla JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. Jul 17 2014;371(3):224-33. doi:10.1056/NEJMoa1316158
96. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. Jan 12 2017;376(2):125-135. doi:10.1056/NEJMoa1607427


 

97. Di Domenico A, Wiedmer T, Marinoni I, Perren A. Genetic and epigenetic drivers of neuroendocrine tumours (NET). *Endocr Relat Cancer*. Sep 2017;24(9):R315-R334. doi:10.1530/ERC-17-0012
98. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. *Nat Rev Genet*. Aug 2016;17(8):487-500. doi:10.1038/nrg.2016.59
99. Sharma R, Earla B, Baidoo KE, et al. Upregulation of Somatostatin Receptor Type 2 Improves 177Lu-DOTATATE Therapy in Receptor-Deficient Pancreatic Neuroendocrine Tumor Model. *Mol Cancer Ther*. Sep 5 2023;22(9):1052-1062. doi:10.1158/1535-7163.MCT-22-0798
100. Mensah IK, Norvil AB, AlAbdi L, et al. Misregulation of the expression and activity of DNA methyltransferases in cancer. *NAR Cancer*. Dec 2021;3(4):zcab045. doi:10.1093/narcan/zcab045
101. Nishiyama A, Nakanishi M. Navigating the DNA methylation landscape of cancer. *Trends Genet*. Nov 2021;37(11):1012-1027. doi:10.1016/j.tig.2021.05.002
102. Angeloni A, Bogdanovic O. Sequence determinants, function, and evolution of CpG islands. *Biochem Soc Trans*. Jun 30 2021;49(3):1109-1119. doi:10.1042/BST20200695
103. Torrisani J, Hanoun N, Laurell H, et al. Identification of an upstream promoter of the human somatostatin receptor, hSSTR2, which is controlled by epigenetic modifications. *Endocrinology*. Jun 2008;149(6):3137-47. doi:10.1210/en.2007-1525
104. Klomp MJ, Refardt J, van Koetsveld PM, et al. Epigenetic regulation of SST(2) expression in small intestinal neuroendocrine tumors. *Front Endocrinol (Lausanne)*. 2023;14:1184436. doi:10.3389/fendo.2023.1184436
105. Marmorstein R, Zhou MM. Writers and readers of histone acetylation: structure, mechanism, and inhibition. *Cold Spring Harb Perspect Biol*. Jul 1 2014;6(7):a018762. doi:10.1101/cshperspect.a018762
106. Seto E, Yoshida M. Erasers of histone acetylation: the histone deacetylase enzymes. *Cold Spring Harb Perspect Biol*. Apr 1 2014;6(4):a018713. doi:10.1101/cshperspect.a018713
107. Taelman VF, Radojewski P, Marincek N, et al. Upregulation of Key Molecules for Targeted Imaging and Therapy. *J Nucl Med*. Nov 2016;57(11):1805-1810. doi:10.2967/jnumed.115.165092
108. Guenter RE, Aweda T, Carmona Matos DM, et al. Pulmonary Carcinoid Surface Receptor Modulation Using Histone Deacetylase Inhibitors. *Cancers (Basel)*. Jun 3 2019;11(6)doi:10.3390/cancers11060767
109. Klomp MJ, Dalm SU, van Koetsveld PM, Dogan F, de Jong M, Hofland LJ. Comparing the Effect of Multiple Histone Deacetylase Inhibitors on SSTR2 Expression and [(111)In]In-DOTATATE Uptake in NET Cells. *Cancers (Basel)*. Sep 29 2021;13(19)doi:10.3390/cancers13194905
110. Veenstra MJ, van Koetsveld PM, Dogan F, et al. Epidrug-induced upregulation of functional somatostatin type 2 receptors in human pancreatic neuroendocrine tumor cells. *Oncotarget*. Mar 13 2018;9(19):14791-14802. doi:10.18632/oncotarget.9462
111. Del Olmo-Garcia MI, Prado-Wohlwend S, Andres A, Soriano JM, Bello P, Merino-Torres JF. Somatostatin and Somatostatin Receptors: From Signaling to Clinical Applications in Neuroendocrine Neoplasms. *Biomedicines*. Dec 1 2021;9(12)doi:10.3390/biomedicines9121810
112. Hofland J, Herrera-Martinez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. *Endocr Relat Cancer*. Mar 2019;26(3):R145-R156. doi:10.1530/ERC-18-0495
113. Caplin ME, Pavel M, Cwikla JB, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer*. Mar 2016;23(3):191-9. doi:10.1530/ERC-15-0490
114. Pavel M, Cwikla JB, Lombard-Bohas C, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. *Eur J Cancer*. Nov 2021;157:403-414. doi:10.1016/j.ejca.2021.06.056
115. Wolin EM, Jarzab B, Eriksson B, et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. *Drug Des Devel Ther*. 2015;9:5075-86. doi:10.2147/DDDT.S84177
116. Sundin A, Arnold R, Baudin E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. *Neuroendocrinology*. 2017;105(3):212-244. doi:10.1159/000471879
117. Wong KK, Waterfield RT, Marzola MC, et al. Contemporary nuclear medicine imaging of neuroendocrine tumours. *Clin Radiol*. Nov 2012;67(11):1035-50. doi:10.1016/j.crad.2012.03.019
118. Malan N, Vangu MD. Normal Variants, Pitfalls and Artifacts in Ga-68 DOTATATE PET/CT Imaging. *Front Nucl Med*. 2022;2:825486. doi:10.3389/fnume.2022.825486
119. Xu C, Zhang H. Somatostatin receptor based imaging and radionuclide therapy. *Biomed Res Int*. 2015;2015:917968. doi:10.1155/2015/917968
120. Etchebehere EC, de Oliveira Santos A, Gumz B, et al. 68Ga-DOTATATE PET/CT, 99mTc-HYNIC-octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors: a prospective trial. *J Nucl Med*. Oct 2014;55(10):1598-604. doi:10.2967/jnumed.114.144543
121. Gabriel M, Decristoforo C, Kendler D, et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med*. Apr 2007;48(4):508-18. doi:10.2967/jnumed.106.035667
122. Sharma P, Arora S, Mukherjee A, et al. Predictive value of 68Ga-DOTANOC PET/CT in patients with suspicion of neuroendocrine tumors: is its routine use


 

justified? *Clin Nucl Med*. Jan 2014;39(1):37-43. doi:10.1097/RLU.0000000000000257
123. Sadowski SM, Neychev V, Millo C, et al. Prospective Study of 68Ga-DOTATATE Positron Emission Tomography/Computed Tomography for Detecting Gastro-Entero-Pancreatic Neuroendocrine Tumors and Unknown Primary Sites. *J Clin Oncol*. Feb 20 2016;34(6):588-96. doi:10.1200/JCO.2015.64.0987
124. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. *Radiographics*. Mar-Apr 2015;35(2):500-16. doi:10.1148/rg.352140164
125. Haug AR, Rominger A, Mustafa M, et al. Treatment with octreotide does not reduce tumor uptake of (68)Ga-DOTATATE as measured by PET/CT in patients with neuroendocrine tumors. *J Nucl Med*. Nov 2011;52(11):1679-83. doi:10.2967/jnumed.111.089276
126. Ayati N, Lee ST, Zakavi R, et al. Long-Acting Somatostatin Analog Therapy Differentially Alters (68)Ga-DOTATATE Uptake in Normal Tissues Compared with Primary Tumors and Metastatic Lesions. *J Nucl Med*. Feb 2018;59(2):223-227. doi:10.2967/jnumed.117.192203
127. Paluri RK, Killeen RB. Neuroendocrine Tumor Lu-177-Dotatate Therapy. *StatPearls*. 2024.
128. Strosberg J, Wolin E, Chasen B, et al. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With (177)Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol*. Sep 1 2018;36(25):2578-2584. doi:10.1200/JCO.2018.78.5865
129. Strosberg JR, Caplin ME, Kunz PL, et al. (177)Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. Dec 2021;22(12):1752-1763. doi:10.1016/S1470-2045(21)00572-6
130. Singh S, Halperin D, Myrehaug S, et al. [(177)Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. Jun 29 2024;403(10446):2807-2817. doi:10.1016/S0140-6736(24)00701-3
131. Arnold R, Wilke A, Rinke A, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. *Clin Gastroenterol Hepatol*. Jul 2008;6(7):820-7. doi:10.1016/j.cgh.2008.02.052
132. Becx MN, Minczeles NS, Brabander T, de Herder WW, Nonnekens J, Hofland J. A Clinical Guide to Peptide Receptor Radionuclide Therapy with (177)Lu-DOTATATE in Neuroendocrine Tumor Patients. *Cancers (Basel)*. Nov 24 2022;14(23)doi:10.3390/cancers14235792
133. Hicks RJ, Kwekkeboom DJ, Krenning E, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. *Neuroendocrinology*. 2017;105(3):295-309. doi:10.1159/000475526
134. Nonnekens J, van Kranenburg M, Beerens CE, et al. Potentiation of Peptide Receptor Radionuclide Therapy by the PARP Inhibitor Olaparib. *Theranostics*. 2016;6(11):1821-32. doi:10.7150/thno.15311
135. Hofving T, Sandblom V, Arvidsson Y, et al. 177Lu-octreotate therapy for neuroendocrine tumours is enhanced by Hsp90 inhibition. *Endocr Relat Cancer*. Apr 1 2019;26(4):437-449. doi:10.1530/ERC-18-0509
136. Guenter R, Aweda T, Carmona Matos DM, et al. Overexpression of somatostatin receptor type 2 in neuroendocrine tumors for improved Ga68-DOTATATE imaging and treatment. *Surgery*. Jan 2020;167(1):189-196. doi:10.1016/j.surg.2019.05.092
137. Sun L, Qian Q, Sun G, et al. Valproic acid induces NET cell growth arrest and enhances tumor suppression of the receptor-targeted peptide-drug conjugate via activating somatostatin receptor type II. *J Drug Target*. 2016;24(2):169-77. doi:10.3109/1061186X.2015.1066794
138. Evans JS, Beaumont J, Braga M, et al. Epigenetic potentiation of somatostatin-2 by guadecitabine in neuroendocrine neoplasias as a novel method to allow delivery of peptide receptor radiotherapy. *Eur J Cancer*. Nov 2022;176:110-120. doi:10.1016/j.ejca.2022.09.009
139. Klomp MJ, Hofland LJ, van den Brink L, et al. The Effect of VPA Treatment on Radiolabeled DOTATATE Uptake: Differences Observed In Vitro and In Vivo. *Pharmaceutics*. Jan 12 2022;14(1)doi:10.3390/pharmaceutics14010173
140. Klomp MJ, van den Brink L, van Koetsveld PM, et al. Applying HDACis to increase SSTR2 expression and radiolabeled DOTA-TATE uptake: from cells to mice. *Life Sci*. Dec 1 2023;334:122173. doi:10.1016/j.lfs.2023.122173
141. Refardt J, Klomp MJ, van Koetsveld PM, et al. Effect of epigenetic treatment on SST(2) expression in neuroendocrine tumour patients. *Clin Transl Med*. Jul 2022;12(7):e957. doi:10.1002/ctm2.957
142. Pollard JH, Menda Y, Zamba KD, et al. Potential for Increasing Uptake of Radiolabeled (68)Ga-DOTATOC and (123)I-MIBG in Patients with Midgut Neuroendocrine Tumors Using a Histone Deacetylase Inhibitor Vorinostat. *Cancer Biother Radiopharm*. Oct 2021;36(8):632-641. doi:10.1089/cbr.2020.4633
143. Sharma R. Lutathera and ASTX727 in Neuroendocrine Tumours (LANTana). Updated 03/20/2024. Accessed 10/30/2024, 2024. https://www.clinicaltrials.gov/study/NCT05178693