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Is there a clinical usefulness for radiolabeled somatostatin analogues beyond the consolidated role in NETs?

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Abstract

The somatostatin (SS) receptor scintigraphy (SRS), using octreotide radiolabelled with ^{111}In (Ocreoscan©, OCT), is a consolidated diagnostic procedure in patients with neuroendocrine tumors (NET) because of an increased expression of somatostatin receptors (SS-R) on neoplastic cells. Uptake of SS analogues (SSA) can also be due to SS-R expression on nonmalignant cells when activated as lymphocytes, macrophages, fibroblasts, vascular cells. Because of this uptake, clinical indications can be found either in neoplasms not overexpressing SS-R, as nonsmall cell lung cancer, and in active benign diseases. Nevertheless, clinical application of SRS has not found clinical relevance yet. In this paper, we discuss the nononcologic fields of clinical interest in which SRS could play a clinical role such as diagnosis, prognosis, and therapy of benign and chronic diseases such as sarcoidosis, histiocytosis, rheumatoid arthritis, idiopathic pulmonary fibrosis, and Graves' ophthalmopathy.

Key words: Autoimmune diseases; diagnostic imaging; Graves' ophthalmopathy; octreotide; osteomalacia; paraneoplastic syndromes; sarcoidosis; somatostatin

Introduction

Somatostatin (SS) is a proteic hormone of 14 amino acids produced in various organs and tissues, mainly in the central nervous system, with a particularly short half-life (approximately 3 minutes), which practically precludes its use as exogenous drug.[1] It inhibits numerous physiological processes including secretion of certain hormones [(e.g., growth hormone (GH), thyroid stimulating hormone (TSH), insulin, glucagon], gastrointestinal motility, production of gastric acid, and bile secretion. With respect to neuroendocrine tumors (NETs), it has an inhibitory effect on cellular growth, angiogenesis and response to tumor growth factors.[2] It explicates its function through interaction with somatostatin receptors (SS-R) that belong to the superfamily of G-protein coupled receptors. Specific molecular studies reported five subtypes of SS-R, SS-R1, SS-R2, SS-R3, SS-R4, and SS-R5, which appear to be expressed with some degree of tissue specificity and show differences in the binding affinity of somatostatin analogues compared to the native molecule.[3] In particular, the most represented subtype in tumor cell lines is SS-R2, followed by SS-R1 to SS-R4 that are variably expressed according to the primary site of tumor such as central nervous system, colon, liver, pancreas and lung. SS-R5 has been found with greater frequency in anterior pituitary tumor cells and smooth muscle cells of the gastrointestinal tract and recently its expression has also been demonstrated in thyroid tumors.[4]

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Due to their physiological presence in a vast majority of normal neuroendocrine cells and their overexpression in different types of tumors, these receptors have been accurately studied as potential targets for diagnosis and treatment in oncological scenarios.[5] However, as many studies pointed out, SS-R expression can also be found in peritumoral vessel endothelial cells, inflammatory cells and in immune system cells such as activated lymphocytes, monocytes and epithelioid cells, thus, suggesting a potential regulatory function of SS and its receptors in immune cell activity [Table 1].[6] Therefore, radiolabeled somatostatin analogues may have a role not only in oncology but also in the diagnosis, prognosis, and therapy of benign and chronic diseases such as sarcoidosis, histiocytosis, rheumatoid arthritis, inflammatory bowel disease, idiopathic pulmonary fibrosis and Graves' ophthalmopathy.[7]

Basic Premises

The most used radiolabeled SS analogue (SSA) is ^{111}In-DTPA-octreotide (^{111}In-Pentetreotide, Octreoscan©, OCT),[7] an octapeptide with longer half-life (several hours) than that of SS, which presents a higher binding affinity for SS-R2 and SS-R5. It is by now the most widely adopted tracer for somatostatin receptor scintigraphy (SRS), a technique that plays a crucial role in diagnosis, staging and follow-up of NETs [Figure 1].[8-10] After intravenous administration, ^{111}In-DTPA-octreotide shows specific areas of physiological uptake which include pituitary gland, thyroid, liver, spleen, kidneys, and bladder, along with the radiotracer that is excreted via urinary system.[11] The examination is carried out with whole-body acquisition, which may be integrated with an analysis based on kinetic comparison at 4 and 24 hours after intravenous injection. By adding tomographic images via SPECT acquisitions, or even better, by carrying out the study with a hybrid system (SPECT-CT), higher overall sensitivity and specificity values of the test could be achieved.[12] SRS proved to be positive in patients with inflammation, especially in chronic inflammatory processes such as granulomatous diseases.[13] The exact uptake mechanism has not been completely clarified yet but is probably due to overexpression of SS-R in the immune cells activated in tissues and activated by blood vessels.[14] In addition, SS probably has an important regulatory role in the immune system by regulating the development of immature immune cells.[15] Some authors found a constant expression of somatostatin-receptor subtype 3 in human peripheral lymphocytes, whereas subtype 5 was over-expressed only after activation.[16] These aspects may partially explain the uptake of OCT at inflammation sites. However, regardless of the mechanism responsible for uptake, OCT is a reliable imaging tracer for the diagnosis and assessment of chronic inflammation in the active phase, with significant implications in terms of prognosis and therapeutic management.[17] With respect to radio-compounds, during the last few years, a new family of SSAs, which took advantage of new labelling techniques, has been developed.[18] Using positron-emitting radionuclides such as 68-Gallium, the Gallium-peptides[19] have been synthesized, enabling us to achieve high sensitivity and specificity not only in the identification of NETs but also in the recognition of all diseases that overexpress SS-R.

Table 1: Target cells and effects of somatostatin analogues (SS-A) in inflammatory processes; pathophysiological premise for SRS utilization in chronic inflammatory diseases

Targets	Effects
Vascular smooth muscle cells	Inhibition of vasodilation
Vascular endothelial cells	Inhibition of plasma protein extravasation, inhibition of intimal hyperplasia
T and B lymphocytes	Inhibition of cytokine (IFN-γ) release and Ig production
Monocytes/macrophages	Inhibition of IL-1, IL-6, TNF-α secretion, reduction of reactive oxygen species secretion
Mast Cells	Inhibition of degranulation
Fibroblasts/synovial cells	Inhibition of cell proliferation
Intestinal epithelial cells	Inhibition of cytokine production
Sensory nerve terminals	Inhibition of nociception and sensory neuropeptide release
Neurons	Inhibition of neural transmission

In contrast with most common positron-emitting isotopes used for positron emission tomography (PET), which require production by a cyclotron, ^{68}Ga can be easily eluted from a ^{68}Ge/^{68}Ga generator. Several factors can be found to explain why the development of these generators was so pronounced in most recent years.[20] In particular, with respect to corresponding gamma-emitting tracers as OCT, SSA labeled with ^{68}Ga showed better sensitivity and specificity, shorter examination times and lower patient dosimetry; furthermore, although with some limitations, they allowed the quantification of tracer's uptake in a specific region of interest via Standardized Uptake Value (SUV) assessment. In addition, ^{68}Ge, which represents the parent radionuclide of ^{68}Ga, has a half-life of about 270 days, thus allowing the generator to last for long periods (9–12 months or even longer); ^{68}Ga itself has a

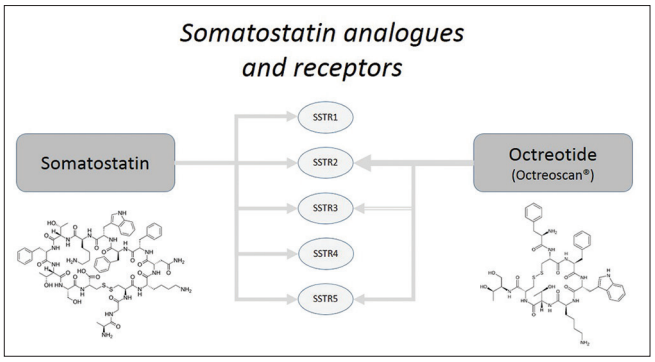

Figure 1: Comparison between somatostatin and octreotide affinity to SSTR subtypes

half-life of 68 minutes allowing adequate manipulation and linkage with different peptides and other small molecules. In fact, after the elution process, ^{68}Ga can be coupled to different SSAs through a chelating agent, more frequently 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA).

Owing to the recent introduction of ^{68}Ga-DOTA peptides, such as ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TOC, and ^{68}Ga-DOTA-TATE, there has been a significant improvement in the overall PET imaging quality respect to OCT due to higher and more specific receptor-mediated uptake and to a great extent *in-vivo* stability and favorable pharmacokinetic properties. This allowed better performances because of the superiority of the so called DOTA-PET with respect to SPECT with OCT, which is also evident when hybrid SPECT/CT is available.

The radiotracers used for DOTA-PET show variable affinity for SS-R subtypes. In particular, they bind to SS-R2, the predominant receptor subtype in NET, and to SS-R5; however, ^{68}Ga-DOTA-NOC has a good affinity for SS-R3. PET/CT images are acquired 45–60 min after injection[21] from the skull to the proximal third of the thigh, and the areas of physiological uptake are represented by the spleen that shows the highest tracer uptake.[22] However, liver uptake is variable, followed by pituitary gland, salivary glands, thyroid, liver, spleen, adrenals, pancreas, kidneys, ureters, and bladder.[23]

In this paper, we focused on some non-neuroendocrine diseases in which OCT and Gallium-peptides could have a decisive role in the management of patients such as sarcoidosis, Graves' ophthalmopathy, paraneoplastic syndromes, meningiomas, tumor-induced osteomalacia and rheumatoid arthritis [Table 2].

Sarcoidosis and Idiopathic Pulmonary Fibrosis

Sarcoidosis is an example of systemic chronic inflammatory disease in which OCT has been used to demonstrate levels of disease activity.[24] Sarcoidosis is an idiopathic multisystemic disease that affects connective tissue and presents typical non-necrotic granulomas, mainly composed of fibrotic tissue, with most frequent localization in lungs, skin, or eyes even if sarcoidosis-related lesions have been documented in almost any organ.

Table 2: Established and potential indications of both ^{111}In-DTPA-Octreotide and ^{68}Ga-DOTA-peptides

	Established Indications	Potential Indications
^{111}In-DTPA-octreotide (Octreoscan®)	Neuroendocrine tumors Chronic inflammatory processes Granulomatous diseases, in active phase Sarcoidosis Idiopathic pulmonary fibrosis Graves' ophthalmopathy	Rheumatoid arthritis (RA) Radio-guided surgery
^{68}Ga-DOTA-peptides (^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-TATE)	Neuroendocrine tumors Tumor-induced osteomalacia Meningiomas	Paraneoplastic syndromes Cushing's syndrome

SRS can locate sarcoid granuloma with high sensitivity and specificity.[25] In 1998, Kwekkeboom *et al*. published one of the first reports on this topic and defined the clinical usefulness in the evaluation of post-therapy nodal activity, where SRS proved its value in 34 of 46 patients, compared to X-ray and CT that showed an efficacy in only 29 patients.[26] Lebtahi *et al*.[25] instead, evaluated patients with untreated sarcoidosis and demonstrated that OCT could identify a greater number of lesions compared to Gallium-67 citrate.

In a recent study, Kamphuis *et al*.[24] retrospectively studied SRS in 218 patients suspicious for sarcoidosis, taking into consideration both intensity uptake degrees and localization of sarcoidosis-associated lesions. Comparing the results with conventional radiological techniques, namely chest X-ray and CT, SRS was unable to demonstrate the disease in only one case out of 175 affected patients; in contrast, SRS increased the yield of visualization and/or the definition of activity with respect to chest X-ray and CT in about 30% of the patients, considering either histologically proven or unproven lesions, thus confirming the usefulness of this technique in the diagnosis and follow-up of patients with sarcoidosis.

Sarcoidosis and rheumatoid arthritis (see below) are long-term chronic diseases that should be treated with a different and more effective approach when they are in the active phase. While it is impossible to reliably define disease activity using morphostructural techniques, useful information may be obtained by functional procedures utilizing ultrasound or, with a higher consistency, with MRI. These procedures may have the capability to individuate changes in blood flow, blood volume, permeability, and cellular density (mainly intended as variation of the tissue water/fluid content), recognizing the presence of necrosis and fibrosis. Nevertheless, it is not possible with these techniques to directly image activated cells, such as granulocytes, macrophages, lymphocytes, and fibroblasts, involved in tissue damage and/or associated with an active disease. Therefore, although functional ultrasound and MRI may have a high negative predictive value in excluding the presence of active inflammation, in these patients F-18 fluorodeoxyglucose (FDG) may be considered the tracer of choice due to the increased glucose metabolism present in activated cells. Another possibility can be found in SSA-based imaging, which is capable of detecting active disease in patients with chronic inflammation in a more specific way, thanks to a higher expression of somatostatin receptors on activated lymphocytes, macrophages, monocytes and so on (i.e. in cells directly involved in the pathophysiological event).

In this sense, the detection of active disease granted by ^{18}F-FDG or SSA-based imaging can avoid unjustified therapies and possible collateral negative effects in subjects with sarcoidosis or rheumatoid arthritis. Thus, their clinical role may be considered as second line approach after MRI. In fact, neither dynamic contrast-enhanced (DCE) nor diffusion-weighted (DW) MRI can be used to define the presence of active disease as radionuclide procedures do, although the formers are suited to measure functional changes in tissues. In particular, DCE-MRI characterizes regional uptake and washout of gadolinium-based contrast agents (Gd-CAs). DW-MRI instead, can represent, both qualitatively and quantitatively, the diffusion of water molecules by apparent diffusion coefficient, which indirectly reflects tissue cellularity. For these reasons, we foster the use of a radionuclide approach when MRI suggests an active disease; more specifically, radiolabeled somatostatin analogues should be preferred to FDG.

In idiopathic pulmonary fibrosis (IPF), an excessive proliferative activity of fibroblasts results in collagen deposition in the interstitial space. Activated fibroblasts overexpress SS-R, which is the rationale for the use of SS-R imaging in the evaluation of this disease. Lebtahi *et al*.[27] analyzed SRS in 11 patients with IPF, demonstrating a significant increase in lung uptake compared to healthy controls in all patients. In addition, the intensity of pulmonary uptake of OCT was correlated with clinical disease activity determined by lung function tests such as counts of inflammatory cells in bronchoalveolar lavage (BAL) fluid, breathing tests and with HRCT.[28,29]

In conclusion, the role of radiolabeled SSA could be connected with the clinical interest in individuating active disease or in individuating the presence of a cellular target in inflammation. Thus, waiting for further studies comparing different procedures, at present, radiolabeled SSA may be suggested as second line procedure for patients in whom MRI has individuated the presence of inflammation, when it could be useful to discriminate the presence of a cellular target for therapy.

Graves' ophthalmopathy

Graves' ophthalmopathy (GO) is a common ocular complication of the most classical form of hyperthyroidism, Graves' disease. From a pathogenetic point of view, it is caused by an autoimmune-based thickening of ocular muscles and it is characterized by bulging of the eyes anteriorly (proptosis), which may be associated with either irritation and conjunctivitis or functional problems such as diplopia, thus affecting patient's normal eyesight.[30] All cellular elements involved in active GO express SS-R; a positive SRS may be useful in choosing a standard medical therapy or a receptor-based therapy, rather than surgery or radiotherapy, that should be considered in the presence of nonactive GO, which is negative at SRS.[31] In addition, several studies showed that OCT might be important in the assessment of GO stage because orbital uptake is determined by number and activity of reactive cells.[32] Starting from these premises, two main different issues arise in patients with GO that need to be carefully analyzed: the correlation between intensity of uptake with clinical stage and disease activity, as well as the possibility to predict the effectiveness of medical treatment and/or to analyze therapeutic response.[33] Postema *et al*.[34] in 1996 reported a positive correlation between clinical activity and uptake of OCT in 32 patients with GO, using a semi-quantitative scoring system (skull/orbit ratio) calculated on SPECT images obtained 5 hours after tracer injection. The orbital uptake was significantly higher in patients with active GO than in those with nonactive disease. Furthermore, a significant reduction of orbital uptake during or after steroid therapy and/or radiotherapy was observed. Mansi *et al*.[35] also supported the hypothesis of SRS positivity as an expression of active GO by using a different kinetic model considering thyroid and orbital uptake up to 24 hours. A distinct kinetics was observed between orbital uptake, which decreased across 24 hours and thyroid concentration, which instead increased with time [Figure 2].[36] The reasons behind this different kinetic behavior may be partially explained with the presence of a subpopulation of "moving" cells at orbital level that leave the eye during the 24-hour period of observation [Figure 3]. On the other hand, the increased thyroid uptake over time can be linked to the presence of resident cells. It has also been proven how OCT negativity could be associated with

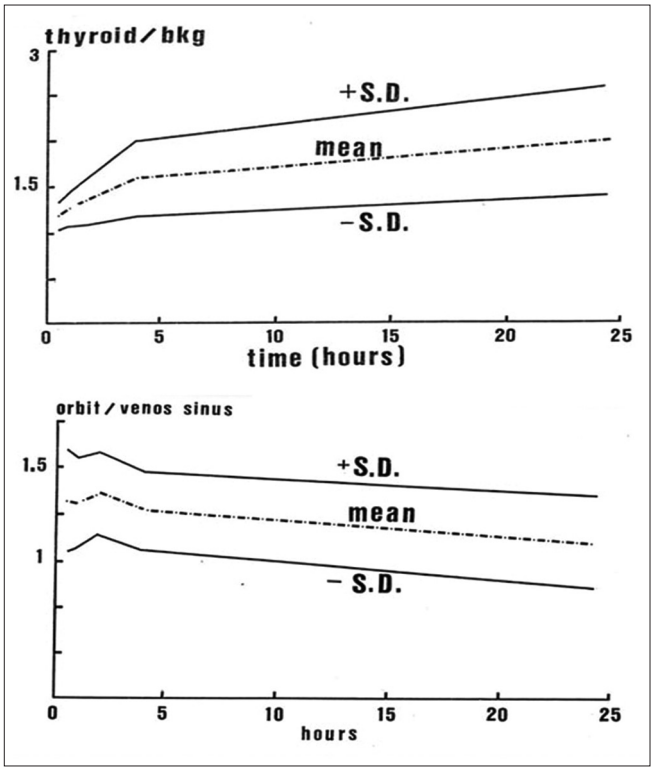

Figure 2: Different kinetics between thyroid concentration and orbital uptake in patient of Figure 3B

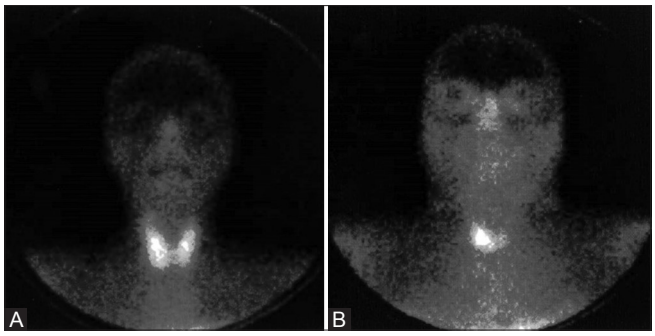

Figure 3 (A and B): (A) Intense thyroid uptake in patient with inactive GO. (B) Post-surgical thyroid uptake and typical orbital uptake in patient with active GO. Modified by Mansi *et al*, Q J Nucl Med. 1995[35]

inactive GO, whereas OCT positivity may support the choice of a medical therapy. Therefore, in patients with GO, SRS could become a crucial step either in the diagnostic algorithm or in assessing the response to corticosteroid or SS-R based therapy. Krassas prospectively recruited patients with GO and positive SRS.[37] After corticosteroid treatment, they underwent a second scan, in which uptake levels were compared with clinical activity to define an effective therapeutic response, evidenced by reduction in OCT uptake. Using a semi-quantitative method based on orbit/brain relationship, further increase in predictive value was obtained, with final positive and negative predictive (PPV and NPV) values of 87% and 100%, respectively. In patients with a ratio higher than 10 in SPECT scans at 4 hours, the response rate after corticosteroids or radiotherapy reached 90%. In contrast, none of the patients with a ratio lower than 10 were responsive to treatment. It has also been proposed to treat patients with GO with SS-A to obtain a clinical improvement. Experimental studies have shown that SS-A, given as long-acting formulations, determine a statistically significant reduction of active disease and of OCT uptake compared with placebo in patients with moderately-severe GO. However, given the high cost of this therapeutic approach, SS-A cannot be currently recommended for routine treatment of GO, being only feasible in patients positive for SRS. Nonetheless, OCT, especially if associated with SPECT acquisitions, could be used as a diagnostic tool to highlight GO in the active phase and help to define the best therapeutic strategies and prognosis.[38]

Paraneoplastic Syndromes

A paraneoplastic syndrome (PNS) is a set of signs and symptoms that result from the presence of cancer in the body but at the same time are not strictly related to the local presence of cancer cells.[39] In fact, these phenomena are mediated either by factors such as hormones and/or cytokines, which are excreted by tumor cells or consequent to host's immune response against the tumor, thus leading to metabolic changes in specific tissues. This inappropriate production of hormones can be detected either in the first phase with an unknown primary tumor where PNS may also represent the manifestation of onset, or after its diagnosis not being related to its stage and prognosis.[40] Due to the high frequency of PNS in patients with SS-R overexpressing tumors, great interest has been developed regarding SS-A molecular imaging. In fact, in a high number of patients suffering from these conditions, SRS may have a role in helping to identify and characterize the primary tumor at the base of the syndrome, especially when it is located in extrathoracic sites, which are known to be not easily detected with conventional CT (and MRI).[41]

Four major endocrine-PNS have been reported: Cushing's syndrome, hypoglycemia, hypercalcemia, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). The most common is Cushing's syndrome, which is most frequently associated with NETs of the lung, with a high incidence in carcinoid and SCLC. From a clinical point of view, a PNS may be suspected and distinct from a pituitary dysfunction whenever high doses of dexamethasone cannot suppress or reduce to less than 50% 17hydroxy-corticosteroid levels. High-resolution CT and MRI have low sensitivity (50%) in locating tumors characterized by ectopic ACTH production because many lesions are either small-sized or extrathoracic.[42] Therefore, it is more advantageous to use OCT/SPECT or ^{68}Ga-DOTA PET that allow whole-body acquisitions.[43] In particular, SRS allows diagnosis of a paraneoplastic Cushing's syndrome induced by bronchial carcinoid tumors in 75% of the cases. False negative results may be due to an unfavorable tumor-to-background ratio in case of small-sized lesions, especially when they are in close proximity to areas that show nonspecific uptake. Because paraneoplastic syndromes are mostly associated to well-differentiated tumors, a greater number of tumors can be detected by DOTAPET with ^{68}Ga-peptides; scarce results are obtained with FDG-PET which present a low sensitivity in detecting differentiated NETs.[6,8,44] Regarding the location of the ACTH-secreting tumor, the authors recommend an integrated approach of SRS with morphological imaging (CT and/or MRI).[45] In conclusion, despite sensitivity values, functional imaging reduces false-positive results, because it exploits specific characteristics of cancerous cells rather than focusing on their anatomical features. Currently, there are no validated studies on the use of PET with ^{68}Ga in paraneoplastic syndromes such as Cushing's, but probably the use of this approach could improve diagnostic accuracy. In this manner, molecular imaging could find further and wider fields of application in endocrinological diseases of strong multidisciplinary interest.[46]

Tumor-induced Osteomalacia

Tumor-induced osteomalacia (TIO) is a paraneoplastic syndrome characterized by renal phosphate atrophy, hypophosphatemia, and low calcitriol, along with clinical symptoms such as widespread muscle and bone pain, stress fractures, or increased risk of fractures.[39] Often,

conventional imaging fails to detect small tumors; however, their localization may significantly improve owing to SS-R-based imaging, such as SRS or OCT SPECT/CT.[47] Unfortunately, recent studies revealed that even this approach could not detect a large number of cancers, whereas ^{68}Ga-DOTA-TATE PET/CT proved to be effective in the localization of tumor in patients with TIO. A study by Breer *et al*.[48] was conducted in 5 patients with TIO who underwent both SRS-SPECT/CT and ^{68}Ga-DOTA-TATE PET/CT. Athough ^{68}Ga-DOTA-PET could localize lesions in all the patients, SRS was positive in only one of them. Therefore, the study demonstrated that ^{68}Ga-DOTA-PET is an effective and promising diagnostic tool in the diagnosis of TIO, even in patients negative at SRS.[49,50]

Meningiomas

A potential use of ^{68}Ga DOTA-PET has been proposed in the diagnosis and radiotherapy planning of meningiomas.[51,52] Henze *et al*. conducted a dynamic study with ^{68}Ga-DOTA-TATE in 21 patients with meningioma to evaluate kinetic parameters before radiotherapy.[53] They found significant differences in average SUVs (10.5 vs 1.3, $P < 0.05$) between meningiomas and reference tissues (nasal mucosa), showing a clear differentiation of lesions, especially those located at the base of the skull. This type of kinetic model allows a more complete assessment of tumor biology, which can be used to evaluate the state of SS-R meningiomas after radiotherapy. Other authors[54] evaluated the utility of ^{68}Ga-DOTA-TOC in planning of radiotherapy treatment in 26 patients by obtaining a PET scan and diagnostic CT or MRI before fractionated stereotactic radiotherapy (FSRT). They found that ^{68}Ga-DOTA-TOC PET provided additional information regarding the extent of the tumor in all patients; in one case, ^{68}Ga-DOTA-TOC PET was the only method that correctly located the lesion. Thus, they concluded that a ^{68}Ga-DOTA-TOC-PET fused with diagnostic CT or MRI led to changes in planning radiotherapy in 73% of the cases.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder characterized by chronic and symmetric inflammation of several joints (besides possible extra-articular involvement), which determines progressive erosions and gradual deformity.[55] Through the formation of the so-called synovial pannus, fostered by the presence of proliferative synovial membranes and by neovascularization, there is progressive destruction of bone and cartilages. In this context, radiolabeled (and/or unlabeled) SS-A may have a possible role not only in assessing disease activity but also for possible therapeutic implications.[56] In fact, RA synovitis presents a massive leukocyte infiltration, which may be evidenced due to the persistent immunological activity in all affected joints despite the presence of clinical manifestations.[57] As stated above, this condition promotes the expression of SS-R on the surface of such cellular types involved in inflammation, which consequently become a primary imaging target, especially in patients with an early stage of RA; in these patients, SRS may allow an earlier diagnosis compared to X-ray that can only detect cartilage damage, thus providing a late diagnosis. In addition, owing to the detection of leukocyte infiltration, SRS could even become the first diagnostic step before performing therapies with SSA, beyond its possible use as profitable monitor of anti-inflammatory treatment.[58]

With respect to currently used tests, MRI is useful as an imaging modality to visualize the inflamed synovia in RA patients, as well as to detect volume changes and changes in contrast enhancement in the synovia post anti-inflammatory drug therapy. Intravenous contrast is necessary to estimate the degree of synovial inflammation and to differentiate the enhancing synovia from surrounding tissues. Dynamic MRI, instead, which is based on repeated imaging of the same few MRI slices with few seconds interval immediately after intravenous contrast injection, correlates closely to synovial vascularity and inflammation. As reported above when discussing sarcoidosis, radionuclide procedures could be helpful in the identification of cellular targets, in order to guide therapeutic decisions and to avoid the administration of highly toxic and/or expensive therapies.[59]

Interstitial lung disease (ILD) is a common pulmonary manifestation of RA that whose etiology may be related to the inflammatory process itself, to infectious complications or even to the treatments used. The most frequent patterns in RA patients with ILD seem to be usual interstitial pneumonia and nonspecific interstitial pneumonia. Although there are no specific studies regarding this topic, either PET-FDG or SRS and DOTA-PET could be suggested in this situation because both techniques could allow an early detection of a pulmonary involvement in RA when compared to X-ray, even if an increased uptake may be not considered pathognomonic.

Conclusions

Undoubtedly, the main advantage of SS-A is their versatility, which allows them to be properly manipulated for either diagnostic or therapeutic purposes, including peptide receptor radionuclide therapy (PRRT)[60] and radio-guided surgery (RGS).[61] Today, the most common field of application for SS-A based methods is represented by NETs where different techniques, including SRS with Octreoscan©, SPECT/CT, and ^{68}Ga-peptides PET/CT, may be applied to increase the number of detected and treatable lesions. However, as different study groups already showed, significant uptake of radiolabeled SS-A can be proved in many benign and non-neuroendocrine diseases, especially when in active phase, owing to the presence of reactive cells overexpressing SS-R, even if the application of such

procedure did not find its place in most of diagnostic algorithms yet.[62]

This paper tried to point out the possible role of SS-A for indications beyond NETs suggesting some of the most promising fields of application for both benign and malignant conditions, in which radiolabeled SS-A can be used despite the presence of these receptors on the surface of tumor cells.

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Conflicts of interest
There are no conflicts of interest.

References

1. Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. Semin Nucl Med 2002;32:84-91.
2. Reubi JC, Waser B, Schaer JC, Laissue JA. Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001;28:836-46.
3. Patel YE. Somatostatin and its receptor family. Front Neuroendocrinol 1999;20:157-98.
4. Reubi JC, Laissue JA, Waser B, Steffen DL, Hipkin RW, Schonbrunn A. Immunohistochemical detection of somatostatin sst2a receptors in the lymphatic, smooth muscular, and peripheral nervous systems of the human gastrointestinal tract: Facts and artifacts. J Clin Endocrinol Metab 1999;84:2942-50.
5. Barnett P. Somatostatin and somatostatin receptor physiology. Endocrine 2003;20:255-64.
6. Cuccurullo V, Cascini GL, Tamburrini O, Mansi L, Rotondo A. Less frequent requests for In-111 pentreotide and its brothers of endocrinological interest. Minerva Endocrinol 2011;36:41-52.
7. Van der Lely AJ, de Herder WW, Krenning EP, Kwekkeboom DJ. Octreoscan radioreceptor imaging. Endocrine 2003;20:307-11.
8. Cascini GL, Cuccurullo V, Tamburrini O, Rotondo A, Mansi L. Peptide imaging with somatostatin analogues: More than cancer probes. Curr Radiopharm 2013;6:36-40.
9. Krenning EP, de Jong M, Kooij PP, Breeman WA, Bakker WH, de Herder WW, *et al*. Radiolabelled somatostatin analogue (s) for peptide receptor scintigraphy and radionuclide therapy. Ann Oncol 1999;10(Suppl 2):S23-9.
10. Cuccurullo V, Faggiano A, Scialpi M, Cascini GL, Piunno A, Catalano O, *et al*. Questions and answers: What can be said by diagnostic imaging in neuroendocrine tumors? Minerva Endocrinol 2012;37:367-77.
11. Rufini V, Calcagni ML, Baum RP. Imaging of neuroendocrine tumors. Semin Nucl Med 2006;36:228-47.
12. Mansi L, Cuccurullo V. Diagnosticimaging in neuroendocrine tumors. J Nucl Med 2014;55:1576-7
13. Reubi JC. Peptide receptors as molecular targets for cancer diagnosis and therapy. Endocr Rev 2003;24:389-427.
14. Cuccurullo V, Mansi L. Toward tailored medicine (and beyond): The phaeochromocytoma and paraganglioma model. Eur J Nucl Med Mol Imaging 2012;39:1262-5.
15. 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 2003;30:781-93.
16. Rambaldi PF, Cuccurullo V, Briganti V, Mansi L. The present and future role of (111) Inpentetreotide in the PET era. Q J Nucl Med Mol Imaging 2005;49:225-35.
17. Cascini GL, Cuccurullo V, Mansi L. The non tumour uptake of (111) In-octreotide creates new clinical indications in benign diseases, but also in oncology. Q J Nucl Med Mol Imaging 2010;54:24-36.
18. Velikyan I. 68Ga-Based radiopharmaceuticals: Production and application relationship. Molecules 2015;20:12913-43.
19. Ambrosini V, Nanni C, Fanti S. The use of gallium-68 labeled somatostatin receptors in PET/CT imaging. PET Clin 2014;9:323-9.
20. Ambrosini V, Morigi JJ, Nanni C, Castellucci P, Fanti S. Current status of PET imaging of neuroendocrine tumours ([18F] FDOPA, [68Ga] tracers, [11C]/[18F]-HTP). Q J Nucl Med Mol Imaging 2015;59:58-69.
21. Rambaldi PF, Cuccurullo V, Cascini GL, Mansi L. Our experience in thymic hyperplasia using 67Ga-citrate, 111In-pentetreotide and 201Tl-chloride. Eur J Nucl Med Mol Imaging 2010;37:1616.
22. Briganti V, Matteini M, Ferri P, Vaggelli L, Castagnoli A, Pieroni C. Octreoscan SPET evaluation in the diagnosis of pancreas neuroendocrine tumors. Cancer Biother Radiopharm 2001;16:515-24.
23. Cascini GL, Cuccurullo V, Tamburrini O, Mansi L, Rotondo A. Nuclear medicine in multiple myeloma -- more thandiagnosis. Nucl Med Rev Cent East Eur 2010;13:32-8.
24. Kamphuis LS, Kwekkeboom DJ, Missotten TO, Baarsma GS, Dalm VA, Dik WA, *et al*. Somatostatin receptor scintigraphy patterns in patients with sarcoidosis. Clin Nucl Med 2015;40:925-9.
25. Lebtahi R, Crestani B, Belmatoug N, Daou D, Genin R, Dombret MC, *et al*. Somatostatin receptor scintigraphy and gallium scintigraphy in patients with sarcoidosis. J Nucl Med 2001;42:21-6.
26. Kwekkeboom DJ, Krenning EP, Kho GS, Breeman WA, Van Hagen PM. Somatostatin receptor imaging in patients with sarcoidosis. Eur J Nucl Med 1998;25:1284-92.
27. Lebtahi R, Moreau S, Marchand-Adam S, Debray MP, Brauner M, Soler P, *et al*. Increased uptake of 111In-octreotide in idiopathic pulmonary fibrosis. J Nucl Med 2006;47:1281-7.
28. Cuccurullo V, Cascini G, Rossi A, Tamburrini O, Rotondo A, Mansi L. Pathophysiological premises to radiotracers for bone metastases. Q J Nucl Med Mol Imaging 2011;55:353-73.
29. Cuccurullo V, Cascini GL, Tamburrini O, Rotondo A, Mansi L. Bone metastasesradiopharmaceuticals: An overview. Curr Radiopharm 2013;6:41-7.
30. Bahn RS. Graves' ophthalmopathy. N Engl J Med 2010;362:726-38.
31. Smith TJ. Pathogenesis of Graves' orbitopathy: A 2010 update. J Endocrinol Invest 2010;33:414-21.
32. Förster GJ, Krummenauer F, Nickel O, Kahaly GJ. Somatostatin-receptor scintigraphy in Graves' disease: Reproducibility and variance of orbital activity. Cancer Biother Radiopharm 2000;15:517-25.
33. Kahaly G, Diaz M, Hahn K, Beyer J, Bockisch A. Indium-111-pentetreotide scintigraphy in Graves' ophthalmopathy. J Nucl Med 1995;36:550-4.
34. Postema PT, Krenning EP, Wijngaarde R, Kooy PP, Oei HY, van den Bosch WA, *et al*. [111In-DTPA-D-Phe1] octreotide scintigraphy in thyroidal and orbital Graves' disease: A parameter for disease activity? J Clin Endocrinol Metab 1994;79:1845-51.
35. Mansi L, Rambaldi PF, Bizzarro A, Panza N, Di Martino S, De Bellis A, *et al*. E. Indium-111 octreotide in Graves' disease and in the evaluation of active exophthalmos. Q J Nucl Med 1995;39:105-10.
36. Santini M, Rambaldi PF, Di Lieto E, Cuccurullo V, Vicidomini G, Di Crescenzo VG, *et al*. Role of radio-guided surgery with 111In-octreotide in the treatment of thoracic neoplasms. Minerva Endocrinol 2001;26:285-8.

37. Krassas GE, Dumas A, Pontikides N, Kaltsas T. Somatostatin receptor scintigraphy and octreotide treatment in patients with thyroid eye disease. Clin Endocrinol 1995;42:571-80.
38. Mansi L, Cuccurullo V. Diagnostic imaging in neuroendocrine tumors. J Nucl Med 2014;55:1576-7.
39. Dadoniene J, Miglinas M, Miltiniene D, Vajauskas D, Seinin D, Butenas P, *et al*. Tumour-induced osteomalacia: A literature review and a case report. World J Surg Oncol 2016;14:4.
40. Teves DA. Clinical Approach of Cushing Syndrome Resulting From ACTH-Producing Metastatic Neuroendocrine Tumor. Endocrinologist 2005;15:401-4.
41. Witek P, Witek J, Zieliński G, Podgajny Z, Kamiński G. Ectopic Cushing's syndrome in light of modern diagnostic techniques and treatment options. Neuroendocrinol Lett 2015;36:201-8.
42. Doppman JL, Travis WD, Nieman L, Miller DL, Chrousos GP, Gomez MT, *et al*. Cushing syndrome due to primary pigmented nodular adrenocortical disease: Findings at CT and MR imaging. Radiology 1989;172:415-20.
43. Pelosof LC, Gerber DE. Paraneoplastic syndromes: An approach to diagnosis and treatment. Mayo Clin Proc 2010;85:838-54.
44. Kulkarni HR, Singh A, Baum RP. Advances in the Diagnosis of Neuroendocrine Neoplasms. Semin Nucl Med 2016;46:395-404.
45. Zemskova MS, Gundabolu B, Sinaii N, Chen CC, Carrasquillo JA, Whatley M, *et al*. Utility of various functional and anatomic imaging modalities for detection of ectopic adrenocorticotropin-secreting tumors. J Clin Endocrinol Metab 2010;95:1207-19.
46. Mansi L, Ciarmiello A, Cuccurullo V. PET/MRI and the revolution of the third eye. Eur J Nucl Med Mol Imaging 2012;39:1519-24.
47. Drezner MK. Tumorinducedosteo-malacia. In: Favus MJ, editor. Primer on metabolic bone disease and disorders of mineral metabolism. 4th ed. Philadelphia: Lippincott-Raven; 1999. pp 319-37.
48. Breer S, Brunkhorst T, Beil FT, Peldschus K, Heiland M, Klutmann S, *et al*. 68Ga DOTA-TATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative 111In-octreotide SPECT/CT. Bone 2014;64:222-7.
49. Seufert J, Ebert K, Müller J, Eulert J, Hendrich C, Werner E, *et al*. Octreotide therapy for tumor-induced osteomalacia. N Engl J Med 2001;345:1883-8.
50. Paglia F, Dionisi S, Minisola S. Octreotide for tumor-induced osteomalacia. N Engl J Med 2002;346:1748-9.
51. Nathoo N, Ugokwe K, Chang AS, Li L, Ross J, Suh JH, *et al*. The role of 111indium-octreotide brain scintigraphy in the diagnosis of cranial, dural-based meningiomas. J Neurooncol 2007;81:167-74.
52. Grzbiela H, Tarnawski R, D'Amico A, Stąpór-Fudzińska M. The Use of 68Ga-DOTA-(Tyr3)-Octreotate PET/CT for Improved Target Definition in Radiotherapy Treatment Planning of Meningiomas. Curr Radiopharm 2015;8:45-8.
53. Henze M, Dimitrakopoulou-Strauss A, Milker-Zabel S, Schuhmacher J, Strauss LG, Doll J, *et al*. Characterization of 68Ga-DOTA-D-Phe1-Tyr3-octreotide kinetics in patients with meningiomas. J Nucl Med 2005;46:763-9.
54. Combs SE, Welzel T, Habermehl D, Rieken S, Dittmar JO, Kessel K, *et al*. Prospective evaluation of early treatment outcome in patients with meningiomas treated with particle therapy based on target volume definition with MRI and 68Ga-DOTATOC-PET. Acta Oncol 2013;52:514-20.
55. Haugen IK, Hammer HB. A need for new imaging modality to detect inflammation in rheumatoid arthritis and osteoarthritis? Ann Rheum Dis 2016;75:479-80.
56. Vanhagen PM, Markusse HM, Lamberts SW, Kwekkeboom DJ, Reubi JC, Krenning EP. Somatostatin receptor imaging. The presence of somatostatin receptors in rheumatoid arthritis. Arthritis Rheum 1994;37:1521-7.
57. Weinmann P, Crestani B, Tazi A, Genereau T, Mal H, Aubier M, *et al*. 111In-pentetreotide scintigraphy in patients with Langerhans' cell histiocytosis. J Nucl Med 2000;41:1808-12.
58. Dalm VA, van Hagen PM, Krenning EP. The role of octreotide scintigraphy in rheumatoid arthritis and sarcoidosis. Q J Nucl Med 2003;47:270-8.
59. Kierans A, Parikh N, Chandarana H. Recent Advances in MR Hardware and Software. Radiol Clin North Am 2015;53:599-610.
60. Baum RP, Kulkarni HR, Carreras C. Peptides and receptors in image-guided therapy: Theranostics for neuroendocrine neoplasms. Semin Nucl Med 2012;42:190-207.
61. Adams S, Baum RP, Hertel A, Wenisch HJ, Staib-Sebler E, Herrmann G, *et al*. Intraoperative gamma probe detection of neuroendocrine tumors. J Nucl Med 1998;39:1155-
62. Kitson SL, Cuccurullo V, Moody TS, Mansi L. Radionuclide antibody-conjugates, a targeted therapy towards cancer. Curr Radiopharm 2013;6:57-71.