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REVIEW ARTICLE

# Somatostatin receptor SPECT

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**Abstract** Somatostatin is a peptide with a broad distribution in the nervous system and acts as a neurotransmitter in several organs, having a wide range of mainly inhibiting effects, such as the suppression of growth hormone release, as well as the inhibition of pancreatic and gastrointestinal hormone release. Five somatostatin receptor subtypes have been cloned and demonstrated to have an emphasized expression in all human tumours. In particular, type 2 receptors were identified as the most frequently represented on the surface of neuroendocrine tumour cells, providing the molecular basis for many clinical applications of somatostatin analogues. Towards the end of the 1980s, the in vivo demonstration of somatostatin receptors on the surface of some tumours raised interest in receptor imaging, and indeed the peptide receptor overexpression on tumour cells, as compared to normal tissues, constitutes the basis for molecular imaging of these tumours. This review intends to illustrate the development of single photon emission radiopharmaceuticals for the study of somatostatin receptors and their application in diagnostic imaging.

**Keywords** Somatostatin · Somatostatin receptor scintigraphy (SRS) · Single photon emission computed tomography (SPECT) · Neuroendocrine tumours (NET) · Gastroenteropancreatic (GEP) tumours · Peptide receptor radionuclide therapy (PRRT)

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## Introduction

Somatostatin is a peptide with a broad distribution in the nervous system and acts as a neurotransmitter in several organs, having a wide range of mainly inhibiting effects, such as the suppression of growth hormone release, as well as the inhibition of pancreatic and gastrointestinal hormone release [1, 2]. Five somatostatin receptor subtypes have been cloned of which sstr 1 and 4 are grouped into one family and sstr 2, 3 and 5 into another. They all are G protein-coupled receptors located at the cell membrane [3].

Pangerl et al. [4] reported that only sstr3 seems to have an emphasized expression in all human tumours, whilst sstr2 appears to be the most frequently represented receptor over the surface of neuroendocrine tumour (NET) cells [5], providing the molecular basis for many clinical applications of somatostatin analogues [6].

Towards the end of the 1980s, the in vivo demonstration of somatostatin receptors on the surface of some tumours raised interest in receptor imaging [7], and indeed the peptide receptor overexpression on tumours cells, as compared to normal tissues [8, 9], constitutes the basis for molecular imaging of these tumours.

This review intends to be a "voyage" through the development of single photon emission radiopharmaceuticals for the study of somatostatin receptors and their application in diagnostic imaging.

We will describe the somatostatin analogues and the derived radiopharmaceuticals, describe the imaging technique and show the results and applications in the clinical scenario.

## Somatostatin analogues

Somatostatin is an acid polypeptide broadly distributed throughout different organs and tissues including the central

nervous system. Structural and functional studies on this peptide demonstrated the amino acid components that are considered fundamental for the peptide activity in the body; therefore, a number of peptides showing similarities in the binding affinity of the native somatostatin have been synthesized [10].

The most important octapeptides in clinical use are octreotide and lanreotide, registered in several countries for clinical use [11] (Table 1).

## Octreotide-based radiopharmaceuticals

The radiopharmaceutical that was first used in patients to study human NET is $^{123}$I-Tyr$^3$-octreotide, a radioiodinated somatostatin analogue with a Tyr substitution [12, 13]. Due to the costs of producing $^{123}$I, the need of special technology and skills for peptide iodination and the difficult interpretation of images due to the accumulation of the radiopharmaceutical in the bowel—a consequence of the predominantly biliary clearance of the product—led to the development of $^{111}$In-DTPA-D-Phe$^1$-octreotide (also called $^{111}$In-pentetreotide). This tracer became the first radioreceptor imaging tracer commercially available (OctreoScan, Mallinckrodt Medical, St. Louis, MO, USA) that was approved in 1994 by the US Food and Drug Administration as an imaging agent for somatostatin receptor-positive NET. $^{111}$In-pentetreotide has shown high accuracy for imaging NET [14–16] (Fig. 1).

Due to the affinity of $^{111}$In-pentetreotide to bind to sstr2 it has shown effectiveness in diagnosing and localizing NET. By means of this diagnostic ability staging of the disease through the detection of metastases has been made possible [17, 18].

As compared to $^{123}$I-Tyr-octreotide, it shows less intestinal accumulation as it is mainly cleared via the kidneys [19] and appears to be more suitable for late imaging thanks to its longer half-life, improving the interpretation of the scanning of the upper abdomen.

Given the importance and success of $^{99m}$Tc as a routine isotope in nuclear medicine imaging, it came as a logical consequence that $^{99m}$Tc-labelled somatostatin analogues have been developed, namely the $^{99m}$Tc-*N*-α-(6-hydrazinonicotinoyl)-octreotide ($^{99m}$Tc-EDDA/HYNIC OCT) [20, 21] (Fig. 2). At that time propagation of the tracer was hampered by proprietary rights on the peptide. For this reason it has remained a tracer for in-house use. Interestingly it is currently being offered as a routine product by POLATOM (Warsaw, Poland). Besides imaging of NET it has been used in the study of thyroid-associated orbitopathy [22].

Further improvements in the development of radioreceptor radiopharmaceuticals have been achieved with the introduction of DOTA a more universal chelator for metal ions, in the attempt to develop peptides that could be labelled to other isotopes such as $^{90}$Y with therapeutic rather than diagnostic aims. On the diagnostic side, $^{111}$In-DOTA-D-Phe$^1$-Tyr$^3$-octreotide shows similar biodistribution of $^{111}$In-DTPA-D-Phe$^1$-octreotide [23].

Three other tracers are $^{111}$In-DOTANOC (1-NaI$^3$-octreotide) [24], $^{111}$In-DOTANOC-ATE (1-NaI$^3$-Thr$^8$-octreotide) and $^{111}$In-DOTABOC-ATE, (Bz-Thi$^3$-Thr$^8$-octreotide), the applications of which are limited though and are not currently commercially available [25, 26]. The replacement of octreotide with octreotate has eventually shown a decrease of lipophilicity [27], boosting the affinity for the sstr2.

Among octreotate-based radiopharmaceuticals there are maltotriose-$^{123}$I-Tyr$^3$-octreotate ($^{123}$I-Mtr-TOCA) that however did not show major imaging advantages [28] and $^{99m}$Tc-Demotate for which preclinical evaluations are available [29–31].

It is interesting to mention that this Demotate peptide has been further developed into a positron emission tomography (PET) tracer in a more sophisticated combination with receptor-based reporter gene features [32].

The most recent contribution to $^{99m}$Tc-labelled peptides is Demotensin used for the detection of brain metastases [33].

**Table 1** sstr subtype selectivity to endogenous somatostatin and somatostatin analogues modified from Volante et al. [10]

| | *Ki* (n*M*) | | | | |
|---|---|---|---|---|---|
| Agonist | sstr1 | sstr2 | sstr3 | sstr4 | sstr5 |
| SS-14 | 1.1 | 1.3 | 1.6 | 0.53 | 0.9 |
| SS-28 | 2.2 | 4.1 | 6.1 | 1.1 | 0.07 |
| Octreotide | >1,000 | 0.6 | 34.5 | >1,000 | 7 |
| Lanreotide | >1,000 | 0.8 | 107 | >1,000 | 5.2 |
| Vapreotide | >1,000 | 5.4 | 31 | 45 | 0.7 |
| SOM-230 | 9.3 | 1.0 | 1.5 | >100 | 0.2 |

## Other analogue-based radiopharmaceuticals

The successful introduction of $^{111}$In-pentetreotide as a radiopharmaceutical for scintigraphic imaging coupled with the knowledge about other somatostatin analogues with different affinity profiles led as a consequence to efforts in developing new radiopharmaceuticals with higher sensitivity or a wider somatostatin receptor subtype affinity profile.

Some of these somatostatin analogues are characterized by the macrocyclic chelator DOTA instead of DTPA in their structure, suitable for the labelling not only with $^{111}$In for diagnostic use but also with beta emitters, namely $^{90}$Y and $^{177}$Lu, used for peptide receptor radionuclide therapy (PRRT).

An example is $^{111}$In-DOTA-lanreotide, known also as MAURITIUS (Multicenter Analysis of a Universal

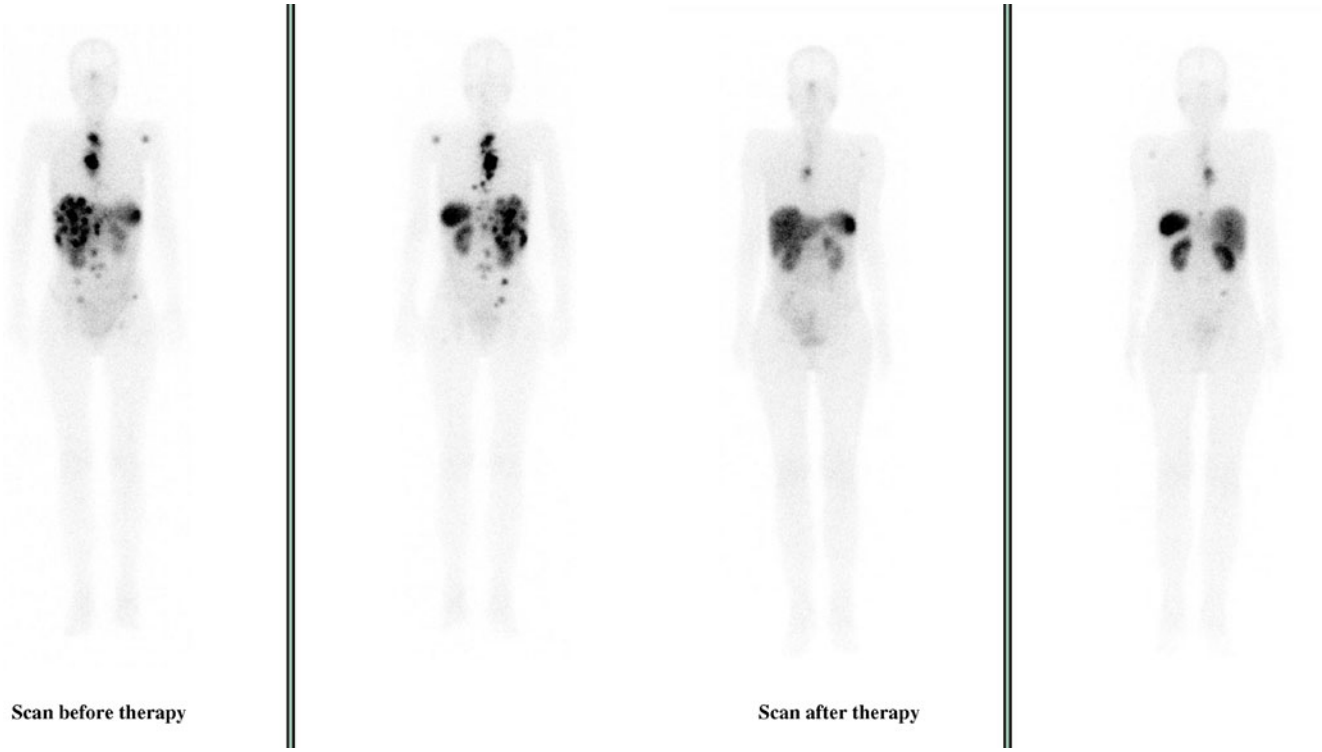


**Fig. 1** Imaging with $^{111}$In-pentetreotide. Patient affected by well-differentiated pancreatic NET. Diagnostic scan pre-therapy showed advanced disease with nodal, liver and bone metastases. After two cycles of treatment (one with $^{177}$Lu-DOTA-TATE and one with $^{90}$Y-DOTA-TATE) the post-therapy scan showed good response to treatment

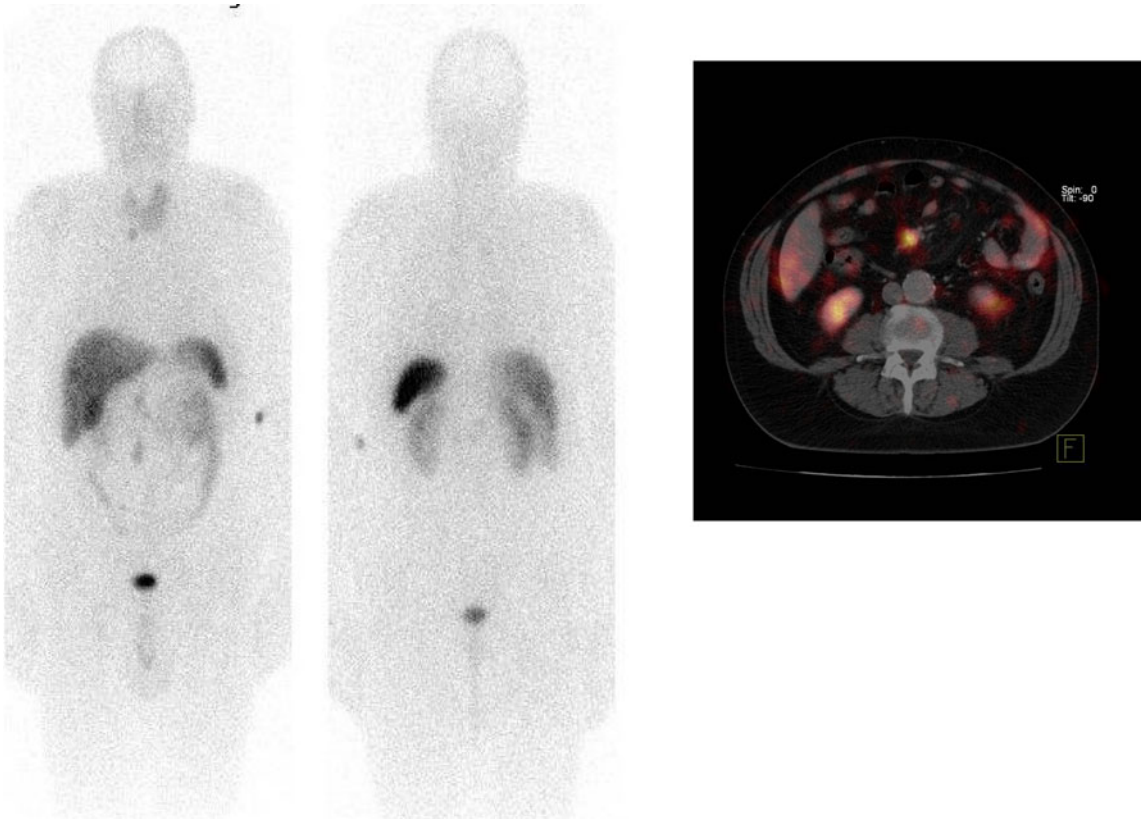

**Fig. 2** Imaging with $^{99m}$Tc-EDDA/HYNIC-TOC. Case of unknown primary. SRS imaging detected focal uptake in the ileum and a mediastinal node. CT fusion and registration was performed between separate scans

Receptor Imaging and Treatment Initiative: a European study), that has been used in Europe for dosimetry studies for therapy with $^{90}$Y-DOTALAN. Compared to $^{111}$In-DTPA-D-Phe$^{1}$-octreotide, it was shown to have lower affinity for NET but high affinity for intestinal adenocarcinoma and differentiated thyroid cancer [34]. One drawback of $^{111}$In-DOTA-lanreotide, however, is its affinity for bone marrow which makes diagnostic interpretation difficult.

$^{99m}$Tc-Depreotide, P829, commercially also known as NeoTect or NeoSpect, was approved for lung cancer studies [35]. Its applications for NET in the abdomen are reduced by the short half-life of the labelling isotope, thus not permitting late imaging to reduce the abdominal background [36].

$^{99m}$Tc-Vapreotide (RC-160 Octastatin) was developed for applications in gastroenterology and NET. It shows high binding affinity for sstr 2 and 5 and less for sstr 3 and 4 [37] (Table 2).

## Somatostatin receptor scintigraphic imaging

### Technique

Revised somatostatin receptor scintigraphy (SRS) guidelines have recently been published by the European Association of Nuclear Medicine (EANM) [38]. In an abridged way the method can be summarized as follows.

Previous to the moment of injecting the tracer preparation of the patient is needed. Any "cold" somatostatin analogues should be suspended 4 weeks before scintigraphy. In addition the administration of a mild oral laxative to reduce the abdominal interferences is recommended.

The preferred administered activity is 200 MBq [39–42] and a peptide amount of 10 μg, which is not expected to produce significant pharmacological effects.

The radiopharmaceutical is prepared according to the manufacturer's indications and undergoes quality controls during which the activity is measured in a calibrated ionization chamber and the radiochemical purity is verified with a thin-layer chromatography (TLC) method.

A gamma camera equipped with a medium-energy parallel-hole collimator with $^{111}$In photopeaks (172 and 245 keV) set for 20% windows is used to acquire 4-, 24- and also 48-h post-injection planar total body scans. Further single photon emission computed tomography (SPECT) images of the area of interest, neck, thorax or abdomen can also be acquired at both 4 and 24 h, but preferably at 24 h.

As we further explain in the following section, CT coregistration has been reported to improve the localization of the lesions, thanks to the attenuation correction [43–45].

The $^{99m}$Tc-labelled octreotide has also been used for image fusion studies [46].

Images are processed according to the preferences of each nuclear medicine department. Image viewing depends on the technology available on site.

### Normal findings and imaging pitfalls

Thyroid, spleen, liver, kidneys and sometimes pituitary gland are visualized as normal foci of uptake in SRS [19, 47]. The uptake in pituitary, thyroid, spleen and adrenals depends on receptor binding. The excretion via the liver may cause the visualization of bowel; therefore, the use of laxatives prior to late scanning (at 24–48 h) is recommended

**Table 2** Somatostatin receptor radiopharmaceuticals

| Radiopharmaceutical | | Availability |
|---|---|---|
| Full name | Abbreviation | |
| $^{123}$I-Tyr$^{3}$-octreotide | | Historical |
| $^{111}$In-DTPA-D-Phe$^{1}$-octreotide | $^{111}$In-DTPA-OCT ($^{111}$In-pentetreotide) | CCA |
| $^{111}$In-DOTA-D-Phe$^{1}$-Tyr$^{3}$-octreotide | $^{111}$In-DOTA-TOC | In house |
| $^{111}$In-DOTA-Tyr$^{3}$-octreotate | $^{111}$In-DOTA-TATE | In house |
| $^{111}$In-DOTA-NaI$^{3}$-octreotide | $^{111}$In-DOTA-NOC | In house |
| $^{111}$In-DOTA-NaI$^{3}$-Thr$^{8}$-octreotide | $^{111}$In-DOTANOC-ATE | Research |
| $^{111}$In-DOTA-Bz-Thi$^{3}$-Thr$^{8}$-octreotide | $^{111}$In-DOTABOC-ATE | Research |
| $^{99m}$Tc-EDDA/HYNIC-Tyr$^{3}$-octreotide | $^{99m}$Tc-EDDA/HYNIC-TOC | In house |
| $^{99m}$Tc-EDDA/HYNIC-Tyr$^{3}$-octreotate | $^{99m}$Tc-EDDA/HYNIC-TATE | In house |
| $^{123}$I-Mtr-TOCA-octreotate | | Research |
| $^{99m}$Tc-Demotate | | In house |
| $^{111}$In-DOTA-lanreotide | $^{111}$In-DOTA-LAN (MAURITIUS) | In house |
| $^{99m}$Tc-depreotide | | CCA |
| $^{99m}$Tc-vapreotide | | Research |

*CCA* currently commercially available

in order to differentiate aspecific areas of uptake [48]. The radiopharmaceutical is also excreted via the kidneys and is reabsorbed in the renal tubular cells: on the one hand this causes the possible visualization of the urinary bladder and on the other a higher radiation exposure of the kidneys, requiring a good hydration status and even infusion at therapeutically administered doses for renal protection.

A specific uptake in breast or in sites of recent surgery, the visualization of gallbladder or the presence of accessory spleens could lead to misinterpretation (Table 3).

There are also some other possible pitfalls emanating from other conditions such as inflammations and infections, granulomatous diseases, nodular goiter and cerebrovascular accidents [49].

Some of the SRS drawbacks related to the limited spatial resolution and the lack of anatomical landmarks may be overcome by the use of hybrid SPECT/low-energy CT integrated diagnostic systems. There is an interesting number of studies reporting an improvement in terms of diagnostic accuracy in general nuclear medicine when using a SPECT/CT device, and in particular the contribution of CT fusion to NET imaging has been reported by Krausz et al. [50] who found an incremental value of SPECT/CT over SPECT alone of 32%, with a subsequent change of patient management in 14% of cases. Similar results were described by Hillel et al. [44].

In a small series of patients studied by Moreira et al. [51] CT fusion imaging proved to be of additional value in NET imaging, and more recently Perri et al. [52] prospectively compared the performance of $^{111}$In-pentetreotide SPECT and SPECT/CT in patients with known or suspected NET and analysed the results on a patient-by-patient and lesion-by-lesion basis. SPECT/CT showed a 95.3% sensitivity and 92.1% specificity whilst for SPECT alone sensitivity was 95.3% and specificity was 71%, confirming that CT fusion improving the anatomical localization of the areas of uptake is useful in reducing equivocal findings.

**Table 3** Causes of potential misinterpretation of negative results with $^{111}$In-pentetreotide scintigraphy modified from Kwekkeboom et al. [54]

| Cause |
|---|
| Possible competitive effect against the tracer by the presence of unlabelled somatostatin |
| Different affinity profile of the analogue for the various sstr subtypes and variability of expression of the receptors: subtypes of receptors expressed and density of sstr expression over the tumour cells may influence the tumour detectability |
| Liver metastases may be taking up the tracer with a similar degree as the normal liver |

## Imaging results

The sensitivity of SRS by means of $^{111}$In-DTPA-octreotide scan is well documented in the diagnosis pathways for NETs but may vary depending on the type of tumour studied and on the site of the disease. As already said one of the major issues with the study of NETs is the heterogeneity of these neoplasms.

Somatostatin receptor-positive tumours include pituitary adenomas, gastroenteropancreatic (GEP) tumours, carcinoids, small cell lung cancers (SCLC), paragangliomas, phaeochromocytomas and neuroblastomas and medullary thyroid cancer. Some breast cancers have been reported and among the non-oncological diseases sarcoidosis can show positive results at SRS [10, 53]

Kwekkeboom et al. [54] recently listed the SRS results in tumours and other diseases (Table 4).

### Pituitary

Somatostatin receptors have been demonstrated in vitro in pituitary adenomas and positive results at SRS have been reported in patients affected by functioning and non-functioning pituitary adenomas, with the uptake higher in the first group of patients than in the second [55, 56]. However, in pituitary adenomas the role of SRS is still limited because of the physiological uptake in the same site that makes the diagnostic accuracy poorer [55].

### GEP NETs and carcinoids

GEPs and carcinoids are relatively rare diseases with a wide range of clinical presentations and therefore require a complex diagnostic workup in which scintigraphic imaging plays a relevant role both alone or in association with other instrumental examinations (Fig. 3).

The use of SRS in GEPs is largely diffused and there is nowadays quite a consolidated experience about it, supported by clinical data on its accuracy which is higher than conventional imaging (i.e. CT or MRI) with a sensitivity of 80–100% in localizing the primary tumour and disease burden [57, 58]. The association with other imaging techniques may improve the already high accuracy [59].

In a multicentre trial in Europe Krenning et al. [60] studied the sensitivity of histologically or biochemically proven pancreatic NET. The results were promising with a detection rate of 100% for glucagonomas, 88% for VIPomas, 72% for gastrinomas, 82% for non-functioning islet cell tumours and 87% for carcinoids.

Carcinoid tumour detection has been reported at nearly a 100% sensitivity and many authors describe the detection of unknown and unexpected sites of diseases that were not found at other imaging modalities [61]. This is very helpful

**Table 4** Sensitivity of somatostatin receptor imaging modified from Kwekkeboom et al. [54]

| Disease | Reference |
|---|---|
| High sensitivity (detection rate >75%) | |
| Pituitary tumours | Kwekkeboom et al. (1999) [55] |
| Gastrinomas | de Kerviler et al. (1994) [92]; Gibril et al. (1999) [49] |
| Non-functioning pancreatic NETs | Krenning et al. (1993) [13]; Lebtahi et al. (1997) [93] |
| Functioning pancreatic NETS except insulinomas | Krenning et al. (1993) [13]; Lebtahi et al. (1997) [93] |
| Carcinoids | Kwekkeboom et al. (1993) [94]; Westlin et al. (1993) [61]; Ahlman et al. (1994) [95]; Kälkner et al. (1995) [96] |
| Small cell lung cancer | Kirsch et al. (1994) [72]; Kwekkeboom et al. (1994) [71]; Bombardieri et al. (1995) [69]; Reisinger et al. (1998) [68] |
| Paragangliomas | Kwekkeboom et al. (1993) [81]; Telischi et al. (2000) [97]; Duet et al. (2003) [98] |
| Meningiomas | Haldemann et al. (1995) [99]; Schmidt et al. (1998) [100] |
| Sarcoidosis and other granulomatous diseases | Vanhagen et al. (1994) [101]; Kwekkeboom et al. (1998) [102] |
| Graves' disease and Graves' ophthalmopathy | Postema et al. (1994) [103]; Krassas et al. (1995) [104] |
| Intermediate sensitivity (detection rate ranging between 40 and 75%) | |
| Insulinoma | Krenning et al. (1993) [13]; Zimmer et al. (1996) [62]; Schillaci et al. (2000) [63]; Vezzosi et al. (2005) [64] |
| Medullary thyroid carcinoma | Kwekkeboom et al. (1993) [84]; Tisell et al. (1997) [105]; Adams et al. (1998) [106] |
| Differentiated thyroid carcinoma, including Hürthle cell carcinoma | Postema et al. (1996) [107]; Haslinghuis et al. (2001) [108] |
| Breast cancer | van Eijck et al. (1994) [109] |
| Lymphoma (NHL, HL) | Lugtenburg et al. (2001) [110, 111] |
| Phaeochromocytoma | van der Harst et al. (2001) [112] |
| Astrocytoma | Schmidt et al. (1998) [100] |

*NHL* non-Hodgkin's lymphoma, *HL* Hodgkin's lymphoma

as it can modify the therapeutic strategy in the management of the patient.

The reported sensitivity for the diagnosis of insulinomas is lower and ranges between 20 and 60%. [13, 62–64]. The density of expression of somatostatin receptor is different in benign and malignant insulinomas and a higher number of $^{111}$In-DTPA-pentetreotide-positive scans have been reported [65].

In patients affected by malignant insulinomas, uptake in the primary and in the metastatic foci has been demonstrated in several studies [64, 66], although the high sensitivity of endoscopic ultrasound [67] is well known and the real role of SRS in these tumours still needs further investigations.

## Small cell lung cancers

SRS positivity has been demonstrated in lung cancers and shows high sensitivity particularly in SCLC. In the multicentre study by Reisinger et al. [68] including 4 centres and 100 patients, $^{111}$In-pentetreotide scintigraphy yielded a sensitivity of 96% in diagnosing the primary tumour. Overall sensitivity in detecting the metastases was 54%, being higher for regional metastases (60%) and lower for distant metastases (45%). In an article published by Bombardieri et al. [69] the primary tumours were detected with a sensitivity of 95% and the metastases with a sensitivity of 80%. For the detection of the primary, Krenning et al. [13], O'Byrne et al. [70] and Kwekkeboom et al. [71] reported a sensitivity of 100%; Kirsch et al. [72] reported a sensitivity of 96% and Maini et al. [73] a sensitivity of 87%. The average sensitivity in the reported literature in detecting metastases is 59%.

Despite the limits in the detection of distant metastases, SRS by means of $^{111}$In-pentetreotide is a useful tool for the evaluation of the extent of disease and may upstage patients from a limited disease to an extensive disease status.

Leitha et al. [74] reported a sensitivity of 84% for the primary and 65% for the metastases in 20 patients affected by SCLC and evaluated with $^{123}$I-Tyr$^3$-octreotide.

$^{99m}$Tc-depreotide approved specifically for lung nodules has been reported with a sensitivity of 97% and a specificity of 73% [75].

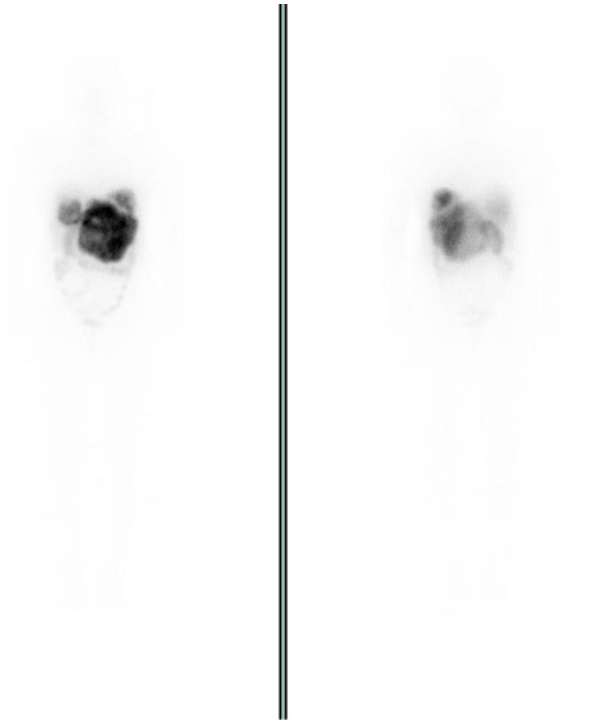

**Fig. 3** Imaging with $^{111}$In-pentetreotide of gastrinoma. Patient with gastrinoma metastases, showing multiple lesions to liver, lung and bone

Phaeochromocytomas and paragangliomas

Phaeochromocytoma is a neoplasm arising from the adrenal medulla occurring in 0.1% of patients with hypertension and is frequently associated with pallor, headaches and palpitations; 10% of phaeochromocytomas are bilateral, 10% are malignant and 10% arise outside the adrenals [76].

SRS sensitivity in phaeochromocytomas has been reported to be comparable to metaiodobenzylguanidine (MIBG) scintigraphy, ranging between 86 and 100% as in the papers by Tenenbaum et al. [77], Hoefnagel et al. [78] and Krenning et al. [13].

Paragangliomas, rare tumours most frequently originating from aorticosympathetic paraganglia including the organs of Zuckerkandl, produce catecholamine [79].

Telischi et al. [80] described $^{111}$In-pentetreotide scintigraphy having a high accuracy in the study of paragangliomas (90%), a 94% sensitivity and a specificity of 75%.

Ten per cent of paragangliomas are metastatic and the visualization in SRS can be of additional value to conventional imaging [81].

Phaeochromocytomas and paragangliomas show SRS-positive imaging, though $^{131/123}$I-MIBG imaging is usually preferred for the study of the adrenal region which can be difficult in SRS given the kidney excretion of the tracer and the consequent high background activity.

Medullary thyroid cancer

Different single photon emission radiopharmaceuticals have been proposed for the study of medullary thyroid carcinoma. $^{99m}$Tc(V)-DMSA showed an overall sensitivity of 69% as opposed to the 29% overall sensitivity shown by $^{111}$In-pentetreotide in a study by Kurtaran et al. [82], but according to other experiences, SRS has been compared to conventional imaging [83] and has been reported with a sensitivity of 50–70% for medullary thyroid carcinoma [84].

## Summary of clinical applications

The use of SRS in NET, above all in GEPs and carcinoids, is well established worldwide for the management of the patients and, as in the aforementioned $^{111}$In-pentetreotide EANM guidelines [38], suited to:

- Localize primary tumours and detect sites of metastatic disease (staging)
- Follow up patients with known disease to detect residual, recurrent or progressive disease (restaging)
- Monitor the effects of therapy (surgery, radiotherapy, chemotherapy or somatostatin analogue therapy)
- Select patients for PRRT
- Obtain prognostic parameters for the response to subsequent therapy

In NET a generally high level of sstr expression is expected, but the heterogeneity of their distribution can be responsible for some discrepancies in the clinical features and in the imaging results. However, the major advantages of the SRS seem to be the possibility of selecting patients for PRRT and providing prognostic information since the cellular differentiation is thought

**Table 5** Results of SRS, CT and US in the detection of primary and metastatic lesions from GEP NETs in 131 patients modified from Chiti et al. [89]

| | SRS | CT | US |
|---|---|---|---|
| Primary tumour | | | |
| Sensitivity (%) | 62 | 43 | 36 |
| Liver metastases | | | |
| Sensitivity (%) | 90 | 78 | 88 |
| Specificity (%) | 97 | 93 | 95 |
| Accuracy (%) | 93 | 83 | 91 |
| Other soft tissue lesions | | | |
| Sensitivity (%) | 90 | 66 | 47 |
| Specificity (%) | 98 | 98 | 100 |
| Accuracy (%) | 95 | 83 | 67 |

to be associated with high levels of sstr expression on the cell surface [85].

## Somatostatin receptor scintigraphy versus conventional imaging

The heterogeneity of NET has made clear the need for an integrated workup both in diagnosis and therapy: SRS has shown to be an accurate tool for diagnosis but of course conventional radiological imaging, including abdominal computed tomography (CT), ultrasound (US) and magnetic resonance imaging (MRI), is required as well.

There is not an extensive number of studies in which SSR and conventional imaging have been compared. Zimmer et al. [86] reported in metastasized NET of the upper gastroenteric tract a 52% detection rate for SRS, 36% for CT and 24% for MRI.

In another study by Zimmer et al. [62] ten gastrinoma patients and ten insulinoma patients were studied with SSR and conventional imaging. In a lesion-based analysis SRS showed an 86% sensitivity, whereas the combination of CT, US and MRI showed a 29% sensitivity.

In a study by Shi et al. [87] SRS, CT and MRI were compared in a group of 48 patients with known or clinically suspected NET. The sensitivity shown for SSR was 95%. In a lesion-based analysis SRS showed a detection rate of 87%, CT of 44% and MRI of 43%.

In 80 patients affected by Zollinger-Ellison syndrome studied by Gibril et al. [88], SRS succeeded in localizing the primary gastrinoma in 56% of patients, with a higher sensitivity than any conventional study including angiography.

We report here the interesting data from Chiti et al. [89]: in 131 patients with known or suspected NET of the GEP tract, the primary was identified by SRS with a sensitivity of 62%. The sensitivity in the detection of the primary fell to 43% for CT and to 36% for US. Considering the liver metastases there was a comparable sensitivity for SRS and US (90 vs 88%) and a lower one for CT (78%) (Table 5).

In a smaller series of patients in a more recent study, Schillaci [90] described a lower sensitivity for conventional imaging as compared to SRS in the detection of NET of the GEP tract.

However, we believe there is a need to compare the new improved conventional imaging technique with SRS in a larger series of patients.

## Future role and perspectives

The basic biochemistry and physiology of somatostatin and octreotide have been dealt with in a recent review [91]. It brings a series of challenges for both basic science researchers as well as for imaging experts. The "romantic" past of having one ligand and one receptor has to be re-evaluated in view of the complexities of receptor molecules (homodimers, heterodimers and truncated forms). This form of "socializing" might lead to the development of bivalent tracers and even to multi-agent diagnostic and therapeutic approaches. These thoughts might be applicable in many other systems based on other peptides. New theoretical models based on fractal dynamics that describe receptor interactions and OMICS might turn out to be the language of times to come and those who take up the challenge will write new reviews on this topic. A "brave new world" should come.

**Conflicts of interest** None.

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