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Review article

Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: the Rotterdam experience with more than 1000 patients

E.P. Krenning[1,2], D.J. Kwekkeboom[1], W.H. Bakker[1], W.A.P. Breeman[1], P.P.M. Kooij[1], H.Y. Oei[1], M. van Hagen[2], P.T.E. Postema[2], M. de Jong[1], J.C. Reubi[3], T.J. Visser[2], A.E.M. Reijs[1], L.J. Hofland[2], J.W. Koper[2], S.W.J. Lamberts[2]

[1] Department of Nuclear Medicine, University Hospital Dijkzigt, Rotterdam, The Netherlands
[2] Department of Internal Medicine III, University Hospital Dijkzigt, Rotterdam, The Netherlands
[3] Institute of Pathology, University of Berne, Switzerland

Abstract. Various tumours, classically specified as either neuroendocrine or non-neuroendocrine, contain high numbers of somatostatin receptors, which enable in vivo localization of the primary tumour and its metastases by scintigraphy with the radiolabelled somatostatin analogue octreotide. In addition granulomas and autoimmune processes can be visualized because of local accumulation of somatostatin receptor-positive activated mononuclear leucocytes. In many instances a positive scintigram predicts a favourable response to treatment with octreotide. It is tempting to speculate that octreotide labelled with an appropriate radionuclide might be used in cancer therapy. The successful application of radiolabelled octreotide in scintigraphy indicates the possible usefulness of other radiolabelled peptides, either native peptides or derivatives of these, in, for example, nuclear oncology. The small size of these peptides, e.g. bombesin and substance P, is of the utmost importance for a relatively fast blood clearance, thus leading to low background radioactivity. In this way peptides are powerful alternatives to (fragments of) monoclonal antibodies, the application of which to scintigraphic localization of specific cell surface antigen-bearing tumours is plagued by slow blood clearance and, hence, high background levels.

Key words: Somatostatin – Octreotide – Tumour targeting – Receptor imaging – Apudoma – Lymphoma

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Correspondence to: E.P. Krenning, Department of Nuclear Medicine, University Hospital Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands

Introduction

Somatostatin and somatostatin receptors

Somatostatin is a peptide hormone consisting of 14 amino acids (SS-14). It is present in the hypothalamus, the cerebral cortex, the brain stem, the gastrointestinal tract and the pancreas. Somatostatin receptors have been identified on many cells of neuroendocrine origin, including the somatotroph cells of the anterior pituitary, the thyroid C cells and the pancreatic islet cells [1, 2]. Also cells not known as classically neuroendocrine, such as lymphocytes [3], may possess these receptors (Fig. 1).

The information with regard to the interaction of somatostatin analogues with the reported somatostatin receptors is rather confusing. At the moment three subtypes of human somatostatin receptors have been cloned [4, 5], while another type has been identified in rat pituitary and brain [6, 7]. Somatostatin receptors are structurally related integral membrane glycoproteins. The human tissue distribution of cloned somatostatin receptors known so far is as follows: type I – stomach and jejunum; type II – brain, kidney and pancreatic islets; type III – pancreatic islets. On the basis of chemical characteristics the rat somatostatin receptor (type IV) is probably different from these human subtypes. The somatostatin analogue octreotide inhibits somatostatin binding to receptor type II in the low nanomolar range, in contrast to much higher values for types I and III. Conflicting results have been described for the effect of octreotide on somatostatin binding to type IV receptors, both sensitivity and non-sensitivity to octreotide having been reported [6, 7]. An explanation might be the existence of two type IV receptors with different affinities for octreotide. Among other things the reported differences in intracellular effector systems between type II and type IV receptors point to the existence of these two receptor subpopulations [8]. For in-

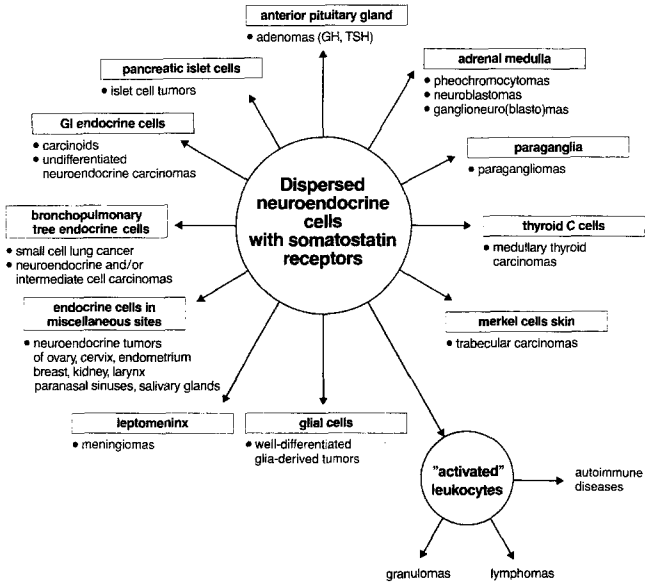

Fig. 1. Tumours and diseases with neuroendocrine cells and/or activated leucocytes with increased density of somatostatin receptors, which can be visualized with [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy [11]

stance, in contrast to type II (and type I), type IV (and type III) mediates its effects via inhibition of adenylyl cyclase activity. Since the effects of octreotide in human tissues seem to be related – at least in the pituitary and meningiomas – to inhibition of adenylyl cyclase activity [9], it is probable that a type IV-like somatostatin receptor also exists in man, which, in addition to the type II receptor, can be visualized with [^{125}I-Tyr^3]-octreotide autoradiography and octreotide scintigraphy.

Somatostatin effects in vitro and in vivo

In the central nervous system somatostatin acts as a neurotransmitter, whereas its hormonal activities include the inhibition of the release (physiological and tumorous) of growth hormone, insulin, glucagon and gastrin [10]. Other actions are (a) an antiproliferative effect on tumours, as has been found for instance in cultured breast cancer cell lines, in numerous animal tumour models and in neuroendocrine tumours in man and (b) specific regulation of immune responses (for a review, see [11]). The antiproliferative effect is ascribed to (a) inhibition of growth via induction of somatostatin receptors, (b) inhibition of the release of hormones and growth factors such as growth hormone and insulin-like growth factor I (IGF-I), (c) inhibition of angiogenesis and (d) modulation of immunological activity.

Distribution of somatostatin receptors in disease states

Besides in normal tissue, somatostatin receptors have been demonstrated in most neuroendocrine tumours, many of which are derived from cells belonging to the amine precursor uptake and decarboxylation (APUD) system [12, 13]. These neuroendocrine tumours contain secretory granules [14]. Recently, somatostatin receptors have also been identified in tumours of the central nervous system (CNS) [15, 16], breast [17], lung [18] and lymphoid tissue [19, 20]. Tables 1–3 show the incidence of somatostatin receptors in various tumours and diseases.

The affinity of somatostatin for its receptor on tumours and lymphomas is in the low nanomolar range. In general, neuroendocrine tumours, lymphomas and activated leucocytes have an increased density of somatostatin receptors, which enables their visualization with radiolabelled somatostatin (analogues).

[^{123}I-Tyr^3]-octreotide and [^{111}In-DTPA-D-Phe^1]-octreotide

In 1987 we introduced the somatostatin analogue [Tyr^3]-octreotide labelled with iodine-123 for the localization of primary and metastatic somatostatin receptor-rich tu-

Table 1. Incidence of somatostatin receptors in neuroendocrine tumours: results of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy, as compared to in vitro somatostatin receptor autoradiography. In vivo and in vitro data are from different patient groups

	In vivo scintigraphy		In vitro receptor status	
GH-producing pituitary tumour	7/10	70%	45/46	98%
TSH-producing pituitary tumour	2/2	100%	–	–
Non-functioning pituitary tumour	12/16	75%	12/22	55%
Gastrinoma	12/12	100%	6/6	100%
Insulinoma	14/23	61%	8/11	72%
Glucagonoma	3/3	100%	2/2	100%
Unclassified APUDoma	16/18	89%	4/4	100%
Paraganglioma	33/33	100%	11/12	92%
Medullary thyroid carcinoma	20/28	71%	10/26	38%
Neuroblastoma	8/9	89%	15/23	65%
Phaeochromocytoma	12/14	86%	38/52	73%
Carcinoid	69/72	96%	54/62	88%
Small cell lung cancer	34/34	100%	4/7	57%

Table 2. Incidence of somatostatin receptors in non-neuroendocrine tumours: results of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy as compared to in vitro somatostatin receptor autoradiography. In vivo and in vitro data are from different patient groups

	In vivo scintigraphy		In vitro receptor status	
Non-small cell lung cancer	36/36	100%	0/17	0%
Meningiomas	14/14	100%	54/55	98%
Breast cancer	37/50	74%	33/72	46%
Exocrine pancreatic tumours	0/24	0%	0/12	0%
Astrocytoma	4/6	67%	14/17	82%

Table 3. Incidence of somatostatin receptors in granulomatous and autoimmune diseases: results of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy as compared to in vitro somatostatin receptor autoradiography. In vivo and in vitro data are from different patient groups.

	In vivo scintigraphy		In vitro receptor status	
Non-Hodgkin's lymphoma	59/74	80%	26/30	87%
Hodgkin's disease	23/24	96%	2/2	100%
Sarcoidosis	23/23	100%	3/3	100%
Wegener's granulomatosis	4/4	100%	–	
Tuberculosis	6/6	100%	2/2	100%
Graves' disease: thyroid	9	[a]	1	
Graves' ophthalmopathy	25	[b]	–	

[a] Increased accumulation of radioactivity in the thyroid gland in untreated hyperthyroidism

[b] Correlation with clinical activity score of orbital inflammation

mours, such as neuroendocrine tumours [21–27]. Our experience in more than 100 patients points to several drawbacks of [^{123}I-Tyr^3]-octreotide for in vivo scintigraphy [28]. First, the labelling of [Tyr^3]-octreotide with ^{123}I is cumbersome and requires special skills which are only available in the larger departments of nuclear medicine. Second, Na^{123}I of high specific activity is expensive and is hardly available worldwide. Third, the timing of the labelling and scanning procedures is dependent on the logistics of the production and delivery of Na^{123}I. Finally, substantial accumulation of radioactivity is seen in the intestines, since a major part of [^{123}I-Tyr^3]-octreotide is rapidly cleared via the liver and biliary system. This makes the interpretation of planar and single-photon emission tomographic (SPET) images of the upper abdomen difficult. Some of these problems can be solved by replacing ^{123}I with indium-111, which also improves scintigraphy 24–48 h after application by virtue of its longer half-life [29]. Binding of ^{111}In to the somatostatin analogue octreotide has been carried out by complexing with a diethylene triamine penta-acetic acid (DTPA) group coupled to the αNH_2 group of the N-terminal D-Phe residue [30]. In rats, it appeared that [^{111}In-DTPA-D-Phe^1]-octreotide (a) is excreted via the kidneys, (b) shows only minor accumulation in the liver and (c) has an initial plasma half-life in the order of minutes [31].

[^{111}In-DTPA-D-Phe^1]-octreotide as a somatostatin analogue

In vitro receptor binding studies using [^{123}I-Tyr^3]-octreotide and [^{111}In-DTPA-D-Phe^1]-octreotide show affinities for the rat brain cortex in the low nanomolar range, with the highest affinity for the first radioligand [30].

The molecular weights of SS-14 and its chelated analogue [DTPA-D-Phe^1]-octreotide are 1.6 and 1.4 kDa, respectively. Thus the maximal peak blood level after intravenous injection of 10 μg [DTPA-D-Phe^1]-octreotide in man is 0.5 n*M*, assuming an instant passage into the interstitium and a complete distribution in an extracellular volume of 14 l. The simultaneous renal clearance of this analogue might prevent [DTPA-D-Phe^1]-octreotide from reaching a concentration at the membrane receptor which equals the receptor affinity. Pretreatment of rats bearing implanted somatostatin receptor-positive tumours with a high dose of unlabelled octreotide blocks the binding of injected radiolabelled octreotide, pointing to in vivo saturation of the receptor [31].

Metabolism in man

The metabolic properties of [^{111}In-DTPA-D-Phe^1]-octreotide turned out to be similar in rat and man. After intravenous administration, [^{111}In-DTPA-D-Phe^1]-octreotide is rapidly cleared from the circulation via the kidneys. However, the initial disappearance from the circulation is considerably slower than that of [^{123}I-Tyr^3]-octreotide [29]. This slower initial clearance, combined with the longer physical half-life of ^{111}In ($t_{1/2}$ = 2.8 days for ^{111}In vs 13.2 h for ^{123}I) results in a longer residence time of the radiopharmaceutical in the tissues. The presence of a lower total body radioactivity 24 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide leads to a lower background radioactivity [29]. The higher background radioactivity with [^{123}I-Tyr^3]-octreotide is due to much higher circulating levels of degradation products than is the case with [^{111}In-DTPA-D-Phe^1]-octreotide. Therefore, [^{111}In-DTPA-D-Phe^1]-octreotide is a more suitable radioligand to localize somatostatin receptor-rich tissues. Furthermore, using [^{111}In-DTPA-D-Phe^1]-octreotide, interpretation of scintigrams of the abdominal region is less affected by intestinal background radioactivity. This contrasts remarkably with [^{123}I-Tyr^3]-octreotide, because the hepato-biliary clearance of this compound results in a higher hepatic and intestinal accumulation of radioactivity, which scarcely can be overcome with laxatives (1.9%→2.2% dose/liver/4→24 h for [^{111}In-DTPA-D-Phe^1]-octreotide versus 28%→6% dose/liver/4→24 h for [^{123}I-Tyr^3]-octreotide, respectively) [28, 29].

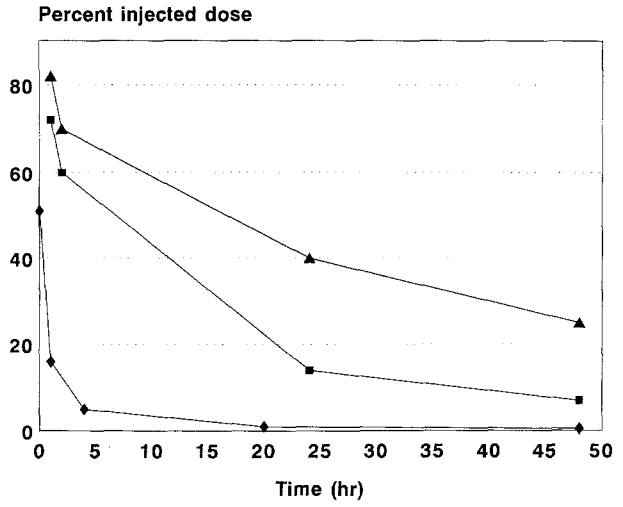

Fig. 2. Blood clearance in man of 10 μg [^{111}In-DTPA-D-Phe^1]-octreotide (♦) [29] and 1–10 mg F(ab)$_2$ (▲) and Fab (■) of anti-CEA monoclonal antibodies [65]

Analysis of the chemical status of plasma radioactivity during the first 4 h after injection shows mainly peptide-bound ^{111}In in the form of the original [^{111}In-DTPA-D-Phe^1]-octreotide. Similarly, analysis of radioactivity in the urine shows predominantly intact [^{111}In-DTPA-D-Phe^1]-octreotide during the first hours after injection. Furthermore, peptide-bound radioactivity in plasma and urine still possesses somatostatin receptor-binding properties as demonstrated by specific binding to rat brain cortex membranes. Degradation of [^{111}In-DTPA-D-Phe^1]-octreotide was observed only in plasma and urine samples obtained more than 4 h after intravenous injection of the radiopharmaceutical, when circulating radioactivity amounted to less than 10% of the administered dose (Fig. 2) [29]. The rapid appearance of intact [^{111}In-DTPA-D-Phe^1]-octreotide in the urine indicates an effective renal clearance of this radiopharmaceutical. The different metabolism of [^{111}In-DTPA-D-Phe^1]-octreotide compared with [^{123}I-Tyr^3]-octreotide indicates that the modification of octreotide with the ^{111}In-DTPA group inhibits hepatic clearance and/or facilitates renal clearance. Rat liver perfusion studies have indeed shown that [^{111}In-DTPA-D-Phe^1]-octreotide is cleared much more slowly by the liver than [^{123}I-Tyr^3]-octreotide (unpublished). The relatively long residence time of [^{111}In-DTPA-D-Phe^1]-octreotide in the kidneys suggests that following glomerular filtration part of the label is actively reabsorbed in the tubules [31].

Dosimetry

Since scintigraphy with [^{123}I-Tyr^3]-octreotide has the drawbacks mentioned previously, while [Tyr^3]-octreotide is not commercially available, the following part of this review will be focused on [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. The recommended doses are 111 and 222 MBq [^{111}In-DTPA-D-Phe^1]-octreotide for planar scintigraphy and SPET, respectively, with a high specific activity.

The effective dose equivalent of 111–222 MBq [^{111}In-DTPA-D-Phe^1]-octreotide (8–16 mSv), although somewhat higher than that of [^{123}I-Tyr^3]-octreotide (8–12 mSv/370–555 MBq) [28, 29], is comparable to values for other ^{111}In-labelled radiopharmaceuticals [32] and is acceptable in view of the clinical indications. Furthermore these radiation doses have to be compared with the values of commonly used imaging techniques for these clinical indications, e.g. CT (chest: 7–11 mSv) and angiography (5–25 mSv).

Imaging protocol for [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy

Planar and SPET images are obtained with a large field of view gamma camera, equipped with a medium-energy parallel-hole collimator. The pulse height analyser windows are centered over both ^{111}In photon peaks (172 keV and 245 keV) with a window width of 20%. Data from both windows are added to the acquisition frames. For planar images the acquisition parameters are as follows: (a) 128×128 word matrix, (b) images of head/neck: 300000 preset counts (or max. 15 min) at 24 h and 15 min preset time (≈200000 counts) at 48 h after injection, (c) images of the remainder of the body, with separate images of the chest (including as little as possible of the liver and spleen) and the upper (including liver/spleen and kidneys) and lower abdomen: 500 000 counts (or max. 15 min). For SPET with a single-head camera the aqcuisition parameters are: (a) 60 projections, (b) 64×64 word matrix and (c) 45–60 s acquisition time per projection, while for SPET with a three-head camera the corresponding parameters are (a) 120 projections, (b) 64×64 word matrix, and (c) 30 s acquisition time per step (45 s for SPET of the head). If a short counting time is required to obtain these numbers of counts, which especially tends to be the case when tissues with relatively high accumulation (e.g. abdominal organs) are included in the field of view, additional images with a longer counting time are recommended in order to visualize also lesions with low somatostatin receptor density. SPET analysis is performed with a Wiener filter on original data. The filtered data are reconstructed with a Ramp filter.

Planar and SPET studies are preferably performed 24 h after injection of the radiopharmaceutical. Planar studies after both 24 and 48 h can be carried out with the same protocol. Repeat scintigraphy after 48 h is especially indicated when 24-h scintigraphy shows accumulation in the abdomen, which can represent radioactive bowel content. Four-hour images of the abdomen are recommended by others since radioactive bowel content is almost always absent. One should realize, however, that the relatively high background radioactivity at 4 h might obscure the localization of lesions

with low receptor density. These lesions may be visible at 24 h because of a 6 times lower background radioactivity at 24 h after injection of the radioligand and a relatively long effective half-life in the tumour. This difference in results of 4- and 24-h images necessitates scanning after 48 h, since the interpretation of the difference in abdominal accumulation is twofold: radioactive bowel content or the accumulation in a lesion with low receptor density. If the abdomen is the region of interest the use of laxatives is highly recommended starting from the moment of injection.

Normal tissue accumulation

Accumulation of radioactivity after intravenous administration of [^{111}In-DTPA-D-Phe^1]-octreotide in man is observed in the pituitary (see "Arguments that [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy is receptor imaging") and thyroid gland, the spleen, the liver (low hepatobiliary clearance), the kidneys and the urinary bladder. The gallbladder is occasionally seen on the planar images and often on the 24-h SPET images, while the presence of intestinal radioactivity (mainly in the colon at 24 h) depends on the simultaneous use of laxatives. The relatively low clearance of the radioligand via the hepato-biliary system favours its use in SPET of the abdomen, which is strongly indicated for the localization of small pancreatic endocrine tumours. For instance, overprojection of kidney radioactivity can obscure lesions in the head and tail of the pancreas. The same is true for lesions in the stomach, which can be missed by overprojection of radioactivity of the left kidney and spleen. Furthermore hepatic receptor-positive tumours can be better localized with SPET.

At present, it is unclear what mechanism is responsible for the imaging of the thyroid (see "autoimmune diseases"). Binding studies with murine spleen cells and autoradiography of normal spleen tissue revealed the presence of somatostatin receptors [33; J.C. Reubi et al. unpublished]; however, the exact cell type (or types) bearing the somatostatin receptor has not yet been identified in man. Patients on octreotide treatment show a diminished (50%–100%, depending on the octreotide dose) accumulation of radioligand in the spleen, compatible with occupancy of spleen somatostatin receptors by the unlabelled octreotide. The accumulation in the urinary tract is explained by the metabolism (see above) of [^{111}In-DTPA-D-Phe^1]-octreotide.

For a correct interpretation of [^{111}In-DTPA-D-Phe^1]-octreotide scintigrams one must bear in mind the following:

1. During the typical season of epidemic common cold/influenza transient accumulation in the nasal region and lung hili has been observed. It is at present unknown whether this phenomenon is based on binding to increased numbers of activated lymphocytes in the respiratory tract, as has been described for human gut lymphoid tissue [20].
2. External irradiation of the lung can cause local pulmonary accumulation of [^{111}In-DTPA-D-Phe^1]-octreotide.
3. Bleomycin can likewise cause such local pulmonary accumulation.
4. Radioactivity may accumulate at sites of recent operation.

Octreotide scintigraphy

Introduction

Using autoradiography in most cases (see above), somatostatin receptors have been demonstrated in a variety of (neuroendocrine) tumours and in diseases with activated leucocytes. In virtually all cases the density of these receptors was high enough to allow in vivo visualization of these processes as well (Fig. 1 and Tables 1–3). Figure 3 illustrates the normal scintigraphic distribution of [^{111}In-DTPA-D-Phe^1]-octreotide radioligand in man.

Since 1989 1050 patients have undergone [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in our institution, of whom 735 have complete records, implying at least an unequivocal diagnosis and optimal anatomical information, whether provided by the usual imaging modalities, by histology and/or by autopsy. The data in the following are derived from the patients with complete records. In none of the patients has any side-effect been

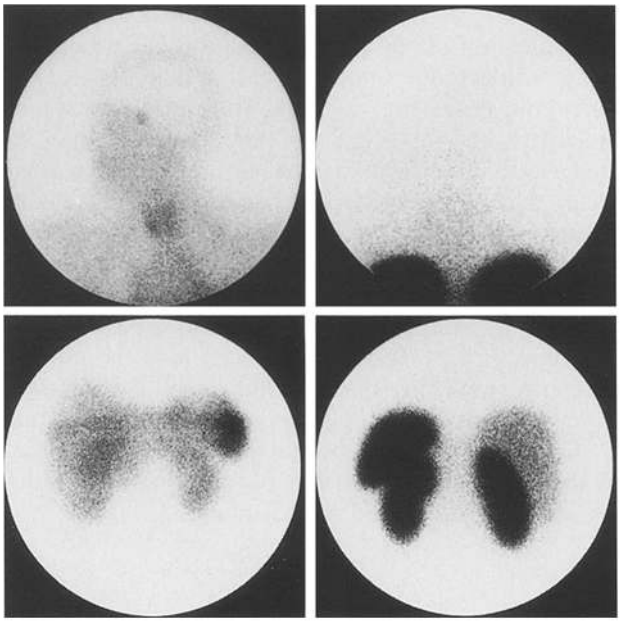

Fig. 3. Normal scintigraphic distribution of [^{111}In-DTPA-D-Phe^1]-octreotide in man 24 h after i.v. injection. Usually the pituitary, thyroid gland, liver, spleen, kidneys and urinary bladder are visualized. Visualization of intestinal radioactivity depends on time of scintigraphy (see text) and use of laxatives. Views: *top left*, left lateral part of the head; *top right*, anterior chest; *lower left*, anterior abdomen, *lower right*, posterior abdomen

noticed. To avoid paradoxical hypoglycaemia, the only precaution taken was a glucose infusion in the case of an insulinoma if the response to octreotide was unknown beforehand.

"Neuroendocrine" tumours

Pituitary tumours. Somatostatin receptors have been demonstrated in vitro on virtually all growth hormone (GH)-producing pituitary adenomas that have been investigated [34]. Also, in vivo somatostatin receptor imaging has been positive in most cases (see Table 1). A close correlation between the presence of somatostatin receptors on GH-producing pituitary tumours in vitro and the preoperative in vivo sensitivity of tumourous GH secretion to octreotide has been reported [34]. Likewise, the scan positivity or negativity during in vivo octreotide scintigraphy is linked to the sensitivity of GH release to suppression by octreotide [35, 36].

In cooperation with others we extensively studied a group of seven patients with clinically non-functioning pituitary adenomas. In six of the seven patients the adenomas were somatostatin receptor positive both in vivo and in vitro [37]. Long-term, high-dose octreotide treatment in four of these patients resulted in some reduction of tumourous gonadotropin secretion in two patients and improvement of visual field defects in three, but substantial tumour size reduction was not obseverd in any of the patients.

Not only GH-producing or clinically nonfunctioning pituitary adenomas but also TSH-secreting pituitary tumours can be visualized using octreotide scintigraphy (Table 2). In addition, other intra- or parasellar tumours, like pituitary metastases from somatostatin receptor-positive neoplasms, e.g. breast cancer or parasellar meningiomas and lymphomas, may be positive. Therefore, in our opinion, the differential diagnostic value of octreotide scintigraphy in pituitary tumours is limited.

Endocrine pancreatic tumours. The majority of peptide hormone-producing endocrine tumours originate from the islet cells of the pancreas, but they may also occur in the stomach, duodenum or intestines. These tumours are named after the hormones they secrete, e.g. gastrinomas, insulinomas, glucagonomas. Octreotide has been shown to be of special benefit in the treatment of the clinical syndromes caused by hypersecretion of these hormones [38, 39]. Though surgery is the treatment of choice in most patients, localization of the primary tumour as well as metastatic tumours may prove very difficult or even impossible with conventional imaging methods [40]. As is clear from Table 3, the majority of the endocrine pancreatic tumours can be visualized using [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. Therefore, octreotide scintigraphy can be of great value in localizing tumour sites in such patients, including in those cases where surgery is indicated but localization of the tumour is not possible with conventional imaging modalities.

Special mention should be made of the failure to visualize some insulinomas with [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. We previously described a patient whose insulinoma was not localized during [^{123}I-Tyr^3]-octreotide scintigraphy and in whom insulin levels did not respond to octreotide administration. Using in vitro techniques, however, high-affinity binding sites were demonstrated for SS-14 and SS-28, but not for octreotide. Also, SS-14 and SS-28, but not octreotide, suppressed insulin release from cultured cells in vitro [23]. This points to the existence of somatostatin receptor subclasses on this type of tumour. It should be emphasized, however, that on by far the majority of somatostatin receptor-positive tumours the receptors bind both native somatostatin and octreotide (analogues).

In contrast to endocrine pancreatic tumours, all human exocrine adenocarcinomas of the pancreas that we have so far investigated have been negative, both in vivo and in vitro (Table 2). Although occasionally a presumed exocrine pancreatic tumour was visualized during octreotide scintigraphy, careful re-examination of the tumour tissue, appropriate immunostaining and electron microscopy revealed the neuroendocrine origin of these tumours, thus leading to a revision of the original diagnosis.

Paragangliomas. Using [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy, 50 of 53 (94%) known localizations in 25 well-documented patients with paragangliomas were visualized [41]. In two patients, three localizations were missed during octreotide scintigraphy. Unexpected additional paraganglioma sites, not detected or not investigated with conventional imaging techniques, were found in 9 out of 25 patients (36%) with known paragangliomas. Only in four of these were the supposed tumour localizations subsequently also demonstrated with other imaging modalities.

High-resolution computed tomography (CT) scanning in combination with magnetic resonance imaging (MRI), with and without gadolinium-DTPA enhancement, is an effective imaging regimen for paragangliomas [42]. However, this type of imaging is usually limited to the site where a paraganglioma is clinically suspected. In our series, CT scanning or MRI of the site where a paraganglioma was primarily expected was in most cases combined with ultrasound of the neck, in order to detect multicentricity. With [^{111}In-DTPA-D-Phe^1]-octreotide total-body scintigraphy, however, unexpected additional paraganglioma sites, not detected or not investigated with conventional imaging techniques, were found in one-third of the patients with known paragangliomas. This finding is of special interest since multicentricity and distant metastases each may occur in 10% of cases [43]. In this respect, one of the major advantages of octreotide scintigraphy is that it provides information on potential tumour sites in the whole body.

It could thus be used as a screening test, to be followed by CT scanning, MRI, or ultrasound of the sites at which abnormalities are found.

Neuroblastomas and phaeochromocytomas. In eight out of nine patients with neuroblastoma [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy visualized the tumour deposits. Patients with somatostatin receptor-positive neuroblastomas seem to have a longer survival (L. Kvols, personal communication) compared with the receptor-negative ones.

Of 14 phaeochromocytomas, 12 were somatostatin receptor-positive in vivo. A drawback of the use of [^{111}In-DTPA-D-Phe^1]-octreotide for localization of this tumour in the adrenal gland is the relatively high radioligand accumulation in the kidneys. Metaiodobenzylguanidine (MIBG) scintigraphy is preferred for its localization in this region. Discrepancies between whole-body scintigraphy with [^{111}In-DTPA-D-Phe^1]-octreotide and MIBG in the staging of phaeochromocytomas have been observed (see comparison with MIBG). The importance of this complementary radioligand accumulation, both diagnostic and therapeutic, will have to be investigated in future studies.

Medullary thyroid carcinoma. In 11 of 17 well-documented patients with medullary thyroid carcinoma (MTC) (65%), tumour localizations were demonstrated using [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy [44]. However, seven patients with tumour localizations in the liver and one patient with the primary tumour still present in the thyroid showed a homogeneous distribution of radioactivity in these organs during [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. Thus, the amount of radioactivity in these tumours was visually undistinguishable from that in the surrounding organ tissue. It appeared that subtraction techniques with radiolabelled colloid and radioiodine, respectively, are of help in demonstrating the binding of [^{111}In-DTPA-D-Phe^1]-octreotide to these tumours, especially when [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy shows a homogeneous distribution of radioactivity in these organs. Somatostatin receptors were demonstrated in vitro on all five investigated tumours which had also been visualized in vivo, as well as on one tumour that had not. The ratio of serum calcitonin (CT) to carcino-embryonic antigen (CEA) concentrations was significantly higher in patients whose MTCs were visualized during octreotide scintigraphy than in those whose tumours were not.

From this study, we concluded that: (a) in the majority of patients with metastatic MTC, tumour sites can be visualized using octreotide scintigraphy, although this technique is insensitive in detecting liver metastases or intrathyroidal tumour when no subtraction techniques are applied; (b) the visualization of MTC during in vivo somatostatin receptor imaging correlates with the in vitro presence of somatostatin receptors; (c) higher serum CT to CEA ratios in patients whose MTCs are visualized during octreotide scintigraphy might imply that somatostatin receptors are present on the more differentiated forms of MTC.

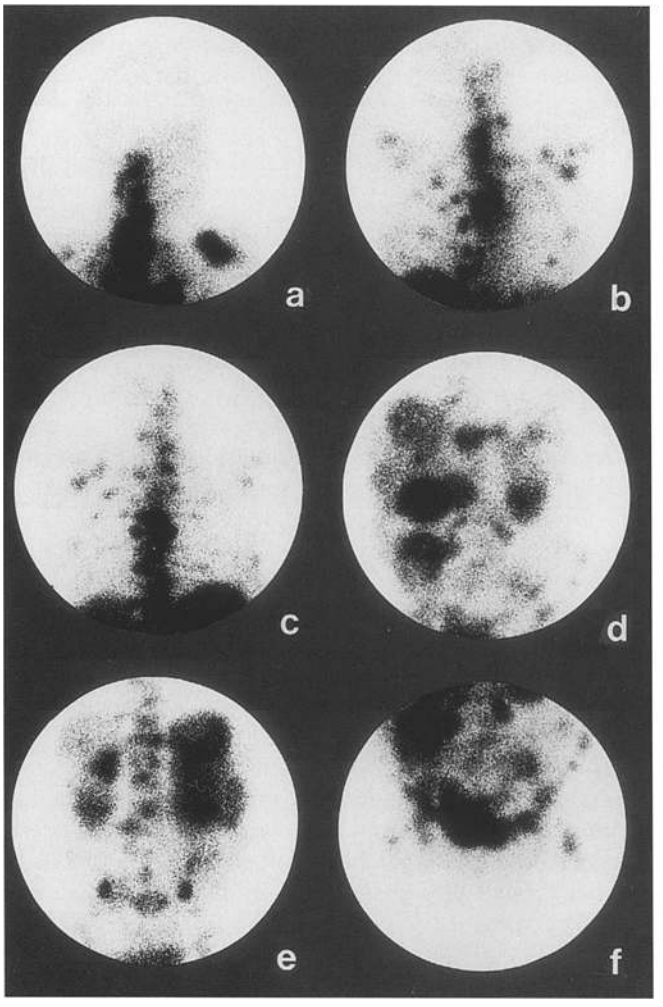

Fig. 4a–f. Octreotide scintigraphy in a patient with carcinoid syndrome, 24 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide. **a** Right lateral image of the head and neck, with abnormal accumulation of radioactivity along the right neck, in the mediastinum and in the left supraclavicular region. **b, c** Anterior (**b**) and posterior (**c**) images of the thorax. Note the many sites of abnormal accumulation of labelled octreotide, many of which represent bone metastases. **d** Anterior abdominal image, on which an irregular liver uptake can be seen, with many sites of abnormal accumulation of labelled octreotide. **e** Posterior abdominal image, showing prominent hot spots in the liver, spine and sacroileal joints. **f** Anterior lower abdominal image: Apart from normal accumulation of radioactivity in the bladder (medial spot in the image), many sites of abnormal accumulation of radioactivity are seen. Of special interest are the hot spots on the *lower left* and *right*, representing metastases in the femurs

Carcinoids Scintigraphy with [^{123}I-Tyr^3]-octreotide and [^{111}In-DTPA-D-Phe^1]-octreotide was performed in 52 patients diagnosed as, suspected of, or at risk of having carcinoid tumours [45]. In 32 of 37 (86%) patients in whom histologically proven carcinoids were still present, known tumour sites were visualized. Using [^{123}I-

Tyr^3]-octreotide, 24 of 40 (60%) known extrahepatic sites were visualized, whereas all 12 (100%) extrahepatic lesions were visualized after injection of [^{111}In-DTPA-D-Phe^1]-octreotide. An example in a patient not included in the cited study is given in Fig. 4. Known liver metastases were not visualized with octreotide scintigraphy in 12 of 24 patients. In all but two of these, a homogeneous distribution of radioactivity was observed in the liver. This was probably because these liver metastases accumulated about as much radioactivity as does normal liver tissue.

Previously unsuspected extrahepatic localizations or sites not recognized with other imaging techniques were found in 20 of the 37 patients. In 3 of 11 patients who were thought to have been surgically cured and in four of four patients who were suspected of having carcinoids, octreotide scintigraphy showed abnormal accumulation of radioactivity. Histological or radiological evidence that additional sites noticed on octreotide scintigrams indeed represented tumour tissue has so far been obtained in ten patients. Visualization of extrahepatic carcinoid localizations did not depend on the site of the tumour or on the presence or absence of hormonal hypersecretion, as measured by urinary 5-hydroxyindoleacetic acid (5-HIAA) and serum α-subunit concentrations.

Apart from its use for tumour localization, octreotide scintigraphy, as a consequence of its ability to demonstrate somatostatin receptor-positive tumours, could be used to select those patients with the carcinoid syndrome who are likely to respond favourably to octreotide treatment.

Comparison with results of other investigators

Using [^{123}I-Tyr^3]-octreotide scintigraphy, Faglia et al. [35] reported positive scans in three out of three patients with pituitary acromegaly and in two out of eight patients with clinically non-functioning pituitary tumours, but in none of three patients with prolactinomas. Ur et al. [36] found positive scans in 12 out of 15 patients with pituitary acromegaly and Becker et al. [46] described positive scans in 23 out of 35 patients with a variety of tumours, the majority of which were of neuroendocrine origin.

Using ^{111}In-octreotide scintigraphy, Bomjani et al. [47] found four out of five carcinoids, two out of three insulinomas and two out of two pituitary tumours to be somatostatin receptor positive in vivo. Also, Pauwels et al. [48] described the localization of 23 out of 26 gastro-entero-pancreatic (GEP) tumours and Van Dongen et al. [49] reported positive scans in four of four patients with carcinoids, one of one with MTC and one of one with an unclassified APUDoma using this technique. Ivancevic et al. [50] reported a sensitivity of 67%–83% in GEP tumours and carcinoids, while Joseph et al. [51], in a study of 38 patients, reported positive scans in 10 of 11 patients with gastrinomas, 10 of 11 patients with carcinoids, one of two patients with insulinomas and 10 of 14 patients with unclassified neuroendocrine tumours. The last two authors both mention the localization of tumour sites undetected with other imaging techniques.

Summarizing, it has been confirmed by various groups of investigators that most neuroendocrine tumours can be visualized in vivo using [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy.

Accumulation of [^{111}In-DTPA-D-Phe^1]-octreotide in neuroendocrine tumours

S. Pauwels and co-workers [UCL, Brussels, Belgium, unpublished] have calculated the accumulation of [^{111}In-DTPA-D-Phe^1]-octreotide in 47 GEP tumours in 22 patients. The mean value appeared to be 0.0123% dose per gram tumour tissue. The respective maximal and minimal values were 0.0527% and 0.0016% dose per gram tumour tissue. Our experience, although based on a lower number of selected patients, points to an accumulation of 0.0067% to 0.2% dose per gram tumour tissue (GEP tumours and paragangliomas). Tumour uptake percentages measured between 4 h and 168 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide decrease by about 25%. Given a blood-pool radioactivity at 4 h of 0.002% dose per ml blood [29] it seems, taking into account the measured minimum tumour value of 0.0016% dose per gram, that the tumour-to-background ratio, especially in endocrine tumours which are highly vascularized, might be about 1:1 at 4 h. Therefore these tumours with an apparently low receptor density can then be missed with [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy. Since the blood-pool radioactivity decreases sixfold from 4 h to 24 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide [29] the optimal time-point to localize these tumours is 24 h or later.

Possible factors interfering with the visualization of neuroendocrine tumours with [^{111}In-DTPA-D-Phe^1]-octreotide

Events and factors in the direct vicinity of the somatostatin membrane receptors can affect the results of the visualization of some processes with radiolabelled octreotide. These include the presence of unlabelled somatostatin e.g. by auto-, para- or endocrine production of somatostatin (eg. in phaeochromocytoma and medullary thyroid carcinoma) or after administration of a somatostatin (analogue) (e.g. in carcinoids). This may result in low or absent accumulation of the radioligand, because of occupancy of, competition with or down-regulation of the receptors by the unlabelled ligand.

The presence of different subtypes of somatostatin receptors with a different affinity for the radioligand

may also determine the result of the scintigram (e.g. in insulinomas and medullary thyroid carcinomas).

Lastly, variable differentiation grade of the primary tumour and its metastases and, therefore, variable expression of the somatostatin receptors have been observed in medullary thyroid carcinomas [52].

Results of somatostatin receptor imaging in various tumours and diseases

Brain tumours

All meningiomas have high numbers of somatostatin receptors and [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy localized this tumour in all 14 investigated patients. Meningiomas are tumours which arise outside the blood-brain barrier. This presumably allows them to be visualized so clearly. The high somatostatin receptor content of the normal brain cannot be visualized by scintigraphy because the normal blood-brain barrier is not penetrated by somatostatin and octreotide.

The majority of well-differentiated astrocytomas (grade I and II) are somatostatin receptor positive; in the undifferentiated glioblastomas (grade IV) somatostatin receptors are absent. An inverse relationship between the presence of somatostatin and epidermal growth factor (EGF) receptors has been observed. In grade III astrocytomas both types of receptor can be found [53]. Four out of six astrocytomas were visualized with radiolabelled octreotide scintigraphy. A prerequisite for the localization with this radioligand is a locally open blood-brain barrier. Especially in the lower grade astrocytomas this barrier might be unperturbed. It is tempting to speculate that, if somatostatin and EGF derivatives capable of passing the intact blood-brain barrier were to be developed, scintigraphy with a "cocktail" of such derivatives could form a new approach that would enable the grading of glia-derived brain tumours in vivo (for a review, see [54]).

Merkel cell tumours

Merkel cells are distributed throughout the normal skin and express a number of neuroendocrine characteristics. Trabecular carcinomas of the skin (Merkel cell tumours, cutaneous APUDomas, neuroendocrine carcinomas of the skin) are aggressive tumours of the skin with a high incidence of spread to regional lymph nodes (45%–91%) and distant metastases (18%–52%). In four out of the five patients studied with octreotide scintigraphy in whom tumour had also been detected by CT and/or ultrasound, these sites were recognized on the scintigrams. In one patient, a tumour with a diameter of less than 0.5 cm was missed with all these techniques. In two of these five patients octreotide scintigraphy demonstrated more metastatic tumour localizations than had previously been recognized [26].

Lung tumours

[^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy revealed the primary tumours and their metastases (e.g. in the brain) in all 34 patients with small cell lung cancer (SCLC), whereas only the primary tumours were visualized in all 36 patients with non-SCLCs. As somatostatin receptors are absent on most non-SCLCs investigated thus far, their in vivo visualization is probably due to uptake of radioactivity by the tissue surrounding the tumour. In theory one could consider the possibility of an accumulation of somatostatin receptor-positive immune cells and/or neuroendocrine cells in the immediate vicinity of the tumour. This is presently being investigated.

Breast cancer

In 74% of patients with stage I or II breast cancer the primary tumours can be visualized. Stages I and II (<2 cm and 2–5 cm, respectively) are nowadays the most common stages as a result of the introduction of population screening programmes. Axillary lymph node metastases have been visualized in four of 13 patients with impalpable axillary lymph nodes [C. van Eijck et al., unpublished]. The role of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in imaging breast cancer is at present unknown. It seems that in operated patients with somatostatin receptor-positive breast cancer, octreotide scintigraphy might be of use for the early detection of symptom-free recurrences [C. van Eijck et al., unpublished]. Furthermore, it has been reported from a retrospective study that 82% of patients with somatostatin receptor-positive tumours have a 5-year disease-free survival compared with 46% of patients with somatostatin receptor-negative breast cancer [55].

Other tumours and diseases

In addition to the neuroendocrine cells, APUD-cell derived tumours and breast cancer, somatostatin receptors have also been characterized on a variety of white blood cells [3, 33, 56] and human leukaemic cells in lymphoblastic leukaemia and non-lymphocytic leukaemia. Below, the results of in vivo somatostatin receptor imaging in some of these diseases are summarized.

Malignant lymphomas. In the first ten patients with Hodgkin's disease or non-Hodgkin's lymphoma who were investigated in our hospital, the lymphoma deposits were visualized with [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy [57]. In four patients, previously unrecognized additional tumour localizations were found. In four cases tissue biopsies were taken and confirmed by autoradiography to be somatostatin receptor positive.

Using in vitro autoradiography with [^{125}I-Tyr^3]-octreotide the somatostatin receptor status of surgically

removed malignant lymphoma samples has been evaluated [19]. Ten out of 11 low-grade B-cell lymphomas, all of the eight intermediate-grade lymphomas and seven out of ten high-grade B-cell lymphomas were somatostatin receptor positive. One T-cell lymphoma was positive. Thus overall out of these 30 non-Hodgkin's lymphomas, 26 (87%) were somatostatin receptor positive. This fact, together with our preliminary aforementioned in vivo results, points to [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy as a very promising localization technique for malignant lymphomas. The role of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in staging Hodgkin's disease and non-Hodgkin's lymphoma is presently being investigated in a prospective study.

Adenocarcinoma of unknown origin. [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy showed multiple lesions in nine out of 15 patients with metastases of an adenocarcinoma of unknown origin. Possible primary localizations of these tumours are, for instance, the breast (see "breast cancer"), kidney and colon. According to [^{125}I-Tyr^3]-octreotide autoradiography, 89% and 12% of renal cell carcinomas and colon cancers, respectively, express somatostatin receptors [13, 58].

Granulomatous diseases. In vivo somatostatin receptor imaging was positive in all cases of sarcoidosis investigated so far (Table 3). Our preliminary data indicate that other granulomatous diseases, such as tuberculosis, Wegener's granulomatosis, DeQuervain's thyroiditis and aspergillosis are also somatostatin receptor positive in vivo. It is expected that octreotide scintigraphy may contribute to a more precise staging and a better evaluation of granulomatous diseases. More importantly, it may be a sensitive indicator of the activity of sarcoidosis and of its response to corticosteroid therapy.

Autoimmune diseases. With radiolabelled somatostatin analogue autoradiography we have not so far been able to find somatostatin receptors in normal thyroid and differentiated thyroid carcinoma (papillary cancer) tissue slices [52, 59]. However, a high percentage of malignant medullary thyroid tumours (see "Neuroendocrine tumours") are somatostatin receptor positive by both autoradiography and [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy [52, 59], and the normal thyroid gland and several differentiated thyroid cancers and their metastases have also been found to be somatostatin receptor positive with the latter scintigraphic technique. In Graves' hyperthyroidism accumulation of radioactivity in the thyroid gland is markedly increased [60]. The presence of activated lymphocytes in the thyroid gland could explain this observation. Indeed, in one thyroid tissue sample of Graves' hyperthyroidism investigated with [^{125}I-Tyr^3]-octreotide autoradiography, a diffuse distribution of somatostatin receptors was found, although the type of cell which is positive has still to be established [J.C. Reubi, unpublished]. In most of the Graves' patients treated with methimazole the thyroidal uptake of octreotide remains elevated. In hypothyroidism after radioiodine treatment for Graves' disease there is no visible accumulation of radioactivity in the thyroid. In clinically active Graves' ophthalmopathy the orbits show accumulation of radioactivity 4 h and 24 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide (Fig. 5). SPET is required for a proper interpretation of this orbital scintigraphy. The value of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in Graves' disease has yet to be

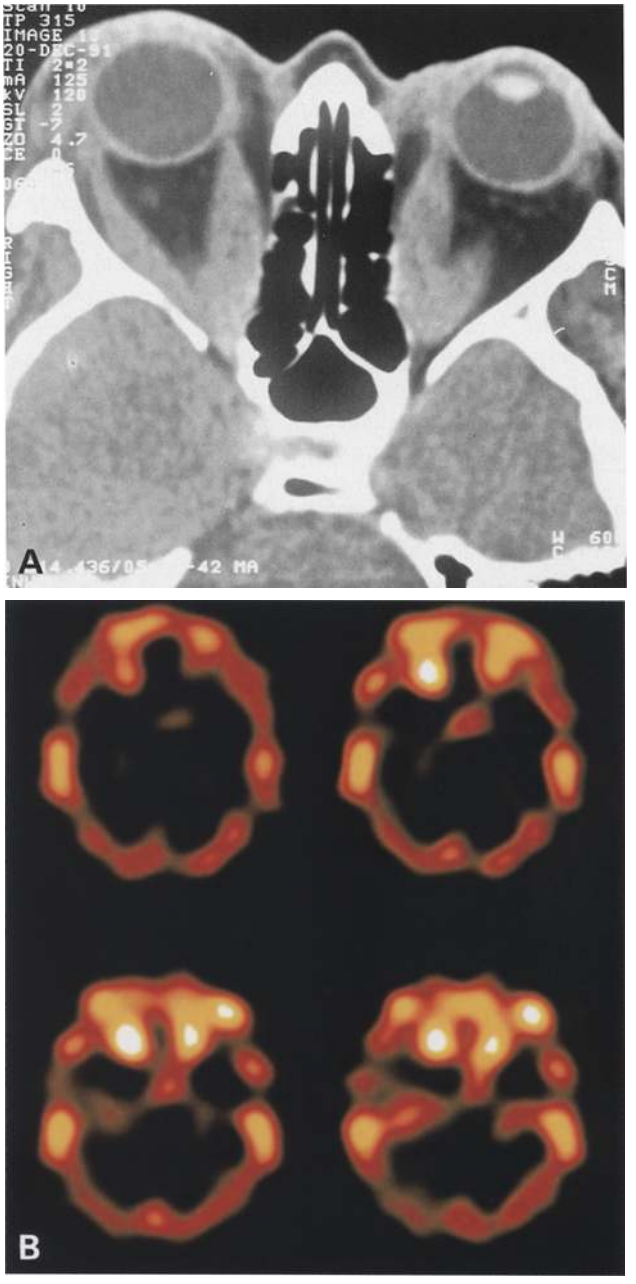

Fig. 5. a CT of the orbits in a patient with Graves' ophthalmopathy. **b** Orbital SPET transversal images (7 mm thickness each, the top-down diameter of an orbit is about 3 cm) of the same patient, 24 h after injection of [^{111}In-DTPA-D-Phe^1]-octreotide. Note the accumulation of radioactivity in the orbits in front of the pituitary

established. Possibly this technique could select those patients with Graves' ophthalmopathy who might benefit from treatment with octreotide [61].

Rheumatoid arthritis is another autoimmune disease with increased accumulation of radioactivity at the sites of inflammation. The joints which give rise to the most pronounced pain complaints also show the most intense uptake of [^{111}In-DTPA-D-Phe^1]-octreotide. Indeed, [^{125}I-Tyr^3]-octreotide autoradiography of the synovia of an affected joint points to the presence of somatostatin receptors [M. van Hagen and J.C. Reubi, unpublished]. It is of interest that a double-blind, placebo-controlled study in patients with rheumatoid arthritis of the knee has revealed an immediate reduction of pain with local injections of somatostatin [62].

Arguments that [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy is receptor imaging

It is indisputable that many of the neuroendocrine tumours which can be visualized by [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy contain somatostatin receptors. Yet many other diseases, which are generally not associated with the classic neuroendocrine characteristics, such as granulomas and lymphomas, also show increased uptake of labelled octreotide. Moreover, precise knowledge of which cells or mechanisms are responsible for the visualization of autoimmune diseases, spleen and thyroid by octreotide scintigraphy is lacking at present. In spite of this, there is ample evidence that octreotide scintigraphy represents somatostatin receptor imaging:

1. In rats bearing somatostatin receptor-positive tumours, tumour uptake of [^{111}In-DTPA-D-Phe^1]-octreotide is prevented by pretreating the animals with high doses of unlabelled octreotide [31].

2. Using ex vivo [^{111}In-DTPA-D-Phe^1]-octreotide autoradiography, i.e. after injection of this radioligand into the animal, only the anterior lobe of the rat pituitary, which is the only part of this organ with somatostatin receptors, showed specific binding of the radioligand [31].

3. A close correlation exists between the presence of somatostatin receptors, demonstrated with in vitro autoradiography and the visualization of tumours and diseases by in vivo octreotide scintigraphy. This pertains not only to an overall comparison between the in vitro and in vivo techniques as presented in Tables 1–3, but also to the results of both techniques applied to the same tumours (see above).

4. During octreotide treatment, the uptake of [^{111}In-DTPA-D-Phe^1]-octreotide in somatostatin receptor-positive tumours and the spleen is diminished. This is analogous to the blocking of receptor binding of iodinated octreotide with excess unlabelled octreotide in in vitro autoradiography.

5. Positive scans predict the suppressive effect of octreotide on hormone secretion from endocrine active tumours [23, 24].

As mentioned under point 1, high-dose octreotide pretreatment in rats prevents the in vivo visualization of somatostatin receptor-positive tumours. Yet, in our experience and that of others, neuroendocrine tumours may remain visible during treatment with octreotide, though the tumour uptake of [^{111}In-DTPA-D-Phe^1]-octreotide is less (up to 50%) than without octreotide treatment. In this respect it should be taken into account that many of these tumours contain high numbers of somatostatin receptors and that even high doses of octreotide (1500 μg/day or more subcutaneously) may not result in complete occupancy of the somatostatin receptors. It should also be considered that the expression of receptors on a tumour is not a steady state, but a process in which recycling of receptors occurs.

Summarizing, we think that there is sufficient evidence to conclude that [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy indeed represents somatostatin receptor imaging in vivo.

Tumours with low-affinity binding of octreotide

The majority of the numerous human tumours investigated up to now with [^{125}I-Tyr^3]-octreotide autoradiogra-

Table 4. Comparison of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy (OC) and ^{123}I-MIBG scintigraphy (MIBG) performed in the same (27) patients[a, b]

Tumour type (number)	Number of lesions visualized		
	OC>MIBG	Equal	MIBG>OC
Phaeochromocytoma (8)	2	4	2
Neuroblastoma (5)	0	4	1
Paraganglioma (4)	3	1	0
Carcinoid (1)	0	1	0
Unclassified APUDoma (1)	1	0	0
Medullary thyroid carcinoma (1)	1	0	0
Adenocarcinoma (primary unknown) (1)	1	0	0

[a] No uptake in either investigation: carcinoid (1), non-Hodgkin's lymphoma (2), adrenal haematoma (1), liposarcoma (1), plasma cell granuloma of lung (1)
[b] In all patients histological proof of the tumour was obtained

phy expressed a somatostatin receptor with a high affinity for octreotide. However, a restricted number of somatostatin receptor-containing tumours expressed a somatostatin receptor subtype with an at least two orders of magnitude lower affinity for octreotide than SS-14. This receptor subtype has been observed in a small percentage (<10%) of pituitary adenomas, carcinoids, glial tumours, meningiomas and breast cancers and in a higher percentage of insulinomas. These insulinomas were not visualized with [^{123}I-Tyr^{3}]-octreotide scintigraphy [23]. Approximately 50% of the medullary thyroid carcinomas also had this low-affinity somatostatin receptor, as did all somatostatin receptor-positive ovarian tumours. These findings [13] are in agreement with the presence of the cloned somatostatin receptor subtype III (see "Somatostatin and somatostatin receptors"). It is clear that for scintigraphic and radiotherapeutic purposes other types of radiolabelled somatostatin analogues with a high affinity for this receptor subtype will have to be developed.

Comparison of octreotide and MIBG scintigraphy

MIBG scintigraphy is a very sensitive imaging technique for phaeochromocytomas and neuroblastomas. It is also used to visualize various other tumours that are derived from neuroendocrine cells. In Table 4 a comparison of the results of octreotide scintigraphy and MIBG scintigraphy, performed in our hospital in the same patients within a period of 2 months, is given. In 8 of 13 patients with phaeochromocytoma or neuroblastoma, the results of octreotide scintigraphy and MIBG scintigraphy were comparable, whereas in two patients octreotide scintigraphy demonstrated more tumour sites than MIBG scintigraphy and in three patients the reverse was true. Interestingly, octreotide scintigraphy was superior to MIBG scintigraphy in five of seven patients with other neuroendocrine tumours, four of whom had paragangliomas. Examples of the two imaging techniques in the same patients are given in Figs. 6–8.

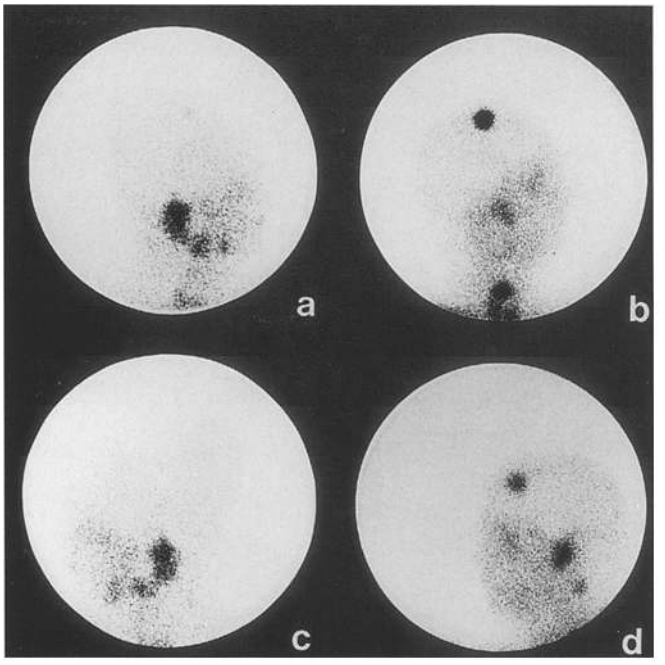

Fig. 6A–D. A comparison between MIBG and octreotide scintigraphy in a patient with multiple paragangliomas. Right (**A**, **B**) and left (**C**, **D**) lateral image of the head and neck. **A**, **C** After ^{123}I-MIBG; **B**, **D** after [^{111}In-DTPA-D-Phe^{1}]-octreotide. On the right lateral image abnormal uptake of labelled octreotide is seen in the parietal region and above the thyroid, as well as the contralateral temporal paraganglioma (**B**). With ^{123}I-MIBG only the parietal lesion is faintly visualized (**A**). On the left lateral image increased uptake of labelled octreotide is present in a temporal and vagal paraganglioma, while the contralateral parietal metastasis of the paraganglioma is also seen (**D**). On the MIBG scintigram only the parotid and submandibular salivary glands are visualized (**C**). Note that uptake of ^{123}I-MIBG in the parotid and submandibular salivary glands can hamper the recognition of paragangliomas

A comparison between our results with octreotide scintigraphy and results of MIBG scintigraphy as reported in the literature is given in Table 5 [63, 64]. As is clear from these data, the two imaging techniques are

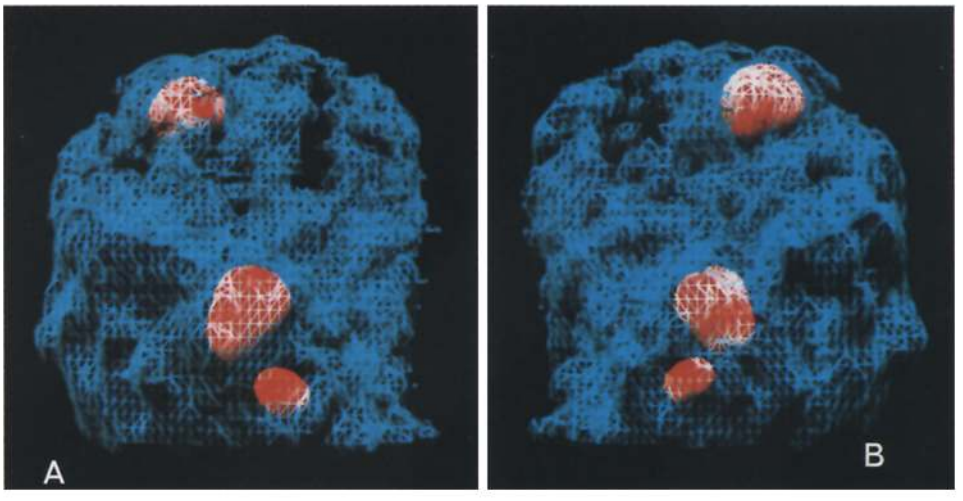

Fig. 7A,B. Three-dimensional reconstruction from a three-head camera of the head of the same patient as in Fig. 6. **A** Left lateral image; **B** right lateral image

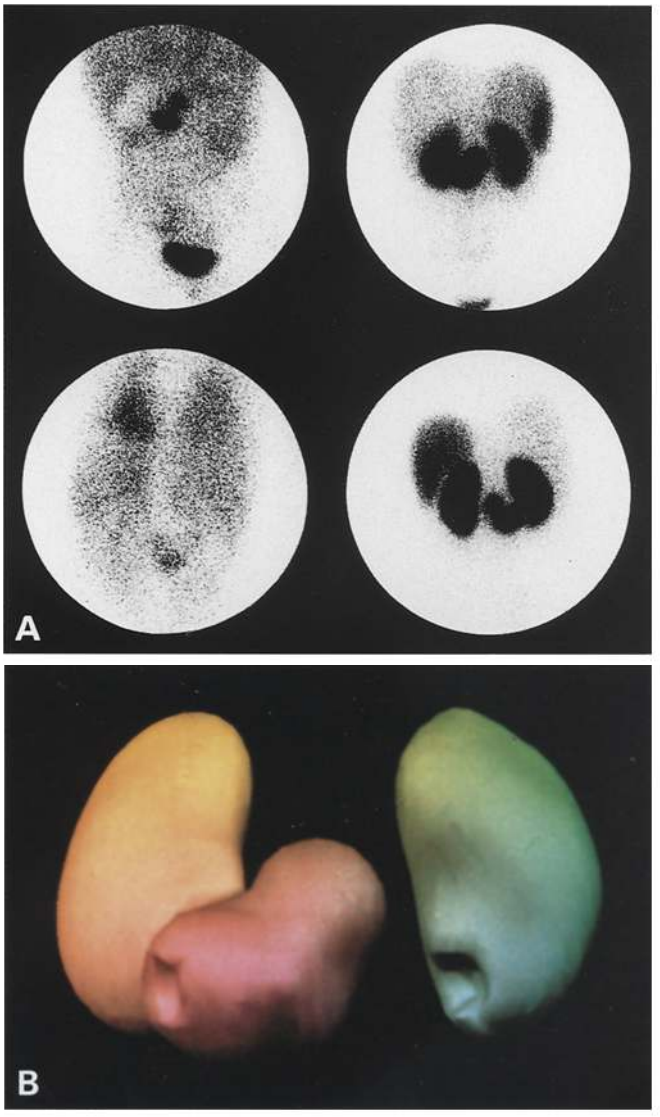

Fig. 8. a A comparison between MIBG and octreotide scintigraphy in a patient with a carcinoid of the duodenal papilla. Anterior (upper panels) and posterior (lower panels) images of the abdomen. Left panels: After ^{123}I-MIBG; Right panels: after [^{111}In-DTPA-D-Phe^1]-octreotide. There is pathological uptake of both radiotracers in two spots in the upper abdomen. Note the visualization of the kidneys on the octreotide scintigrams and the higher resolution on the posterior images with octreotide scintigraphy. **b** Three-dimensional reconstruction from a three-head camera of the upper abdomen of the same patient as in **a**. Both kidneys are visualized and in between them, in purple, is the carcinoid of the duodenal papilla

about equally sensitive for phaeochromocytomas and neuroblastomas. In neuroendocrine tumours other than phaeochromocytomas, however, the results of octreotide scintigraphy are superior to those obtained with MIBG. However, in tumours which show sufficient uptake, an advantage of MIBG over octreotide scintigraphy may be that positive diagnostic scanning can be followed by radiotherapy, whereas therapy with β-emitting radionuclide-coupled somatostatin analogues is at present still not possible.

Table 5. Comparison of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy (OC) and ^{123}I-MIBG scintigraphy (MIBG) in different patients with comparable tumours. The data on ^{123}I-MIBG scintigraphy are based on the literature [63, 64]

Tumour type	Percentage of scans positive (number)	
	OC	MIBG
Phaeochromocytoma	86% (14)	88% (>1000)
Neuroblastoma	89% (9)	91% (841)
Paraganglioma	100% (33)	52% (25)
Medullary thyroid carcinoma	71% (28)	35% (178)
Carcinoid	96% (72)	70% (237)
Endocrine pancreatic tumour	80% (56)	25% (4)

Comparison of octreotide and monoclonal antibody scintigraphy

Over the past decade, the use of radiolabelled monoclonal antibodies or fragments thereof for tumour imaging has received much interest. However, despite the many promising reports on the potential benefit of radiolabelled monoclonal antibodies for in vivo tumour detection, their widespread application has been hampered by low tumour to background ratios (because the large molecules – Fab 50 kDa, IgG 150 kDa and IgM 900 kDa – lead to a high background radioactivity) (Fig. 2) [65], lack of specificity and human anti-mouse antibodies formation. Because of the rapid clearance of the small sized [^{111}In-DTPA-D-Phe^1]-octreotide by the kidneys (see "Metabolism in man"), much higher tumour to background ratios can be obtained when labelled octreotide is used instead of labelled monoclonal antibodies. Also, there are indeed many convincing arguments to support the view that octreotide scintigraphy is receptor imaging (see above). Lastly, antibody formation in patients treated with the somatostatin analogue octreotide is extremely rare, having until now been described in only four cases [66–68] although hundreds of patients with pituitary acromegaly or gastrointestinal neuroendocrine tumours have been treated for several years.

Conclusions

[^{111}In-DTPA-D-Phe^1]-octreotide is a new radiopharmaceutical with great potential for the visualization of various somatostatin receptor-positive (neuroendocrine) tumours, granulomas and (autoimmune) diseases in which activated leucocytes play a role. Thus far a lot of experience with the first group of patients has been obtained by various investigators. The sensitivity of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in localizing neuroendocrine tumours is high, except in the case

of insulinomas. The presence in this tumour of more than one subtype of somatostatin receptor with different affinities for octreotide necessitates the development of other somatostatin analogues which, in contrast to octreotide, also bind with high affinity. Injection of a "cocktail" of these analogues, possibly labelled with different radionuclides, should increase the sensitivity of the technique for this type of tumour. The use of [^{111}In-DTPA-D-Phe^1]-octreotide whole-body scintigraphy as a first localization technique, e.g. for neuroendocrine tumours, is strongly favoured both by its harmless, non-invasive nature and by the easy interpretation. In, for instance, endocrine pancreatic tumours, ultrasonography and CT are usually limited to the pancreas and liver region [69], thereby missing possible metastases, e.g. in the chest, especially in the left supraclavicular region. Inconclusive results with ultrasonography and CT, particularly with tumours less than 2 cm in diameter, are usually followed sequentially by invasive localization methods, e.g. transhepatic selective portal venous sampling and selective visceral arteriography. These usual methods may fail to localize the tumour in 40%–60% of patients [69]. However, intra-operative ultrasound is probably also a powerful alternative to these invasive techniques.

The value of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in other tumours, like breast cancer and malignant lymphomas and in the above-mentioned diseases, has still to be established. The same holds for the use of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy as a predictive tool in discriminating those patients with diseases not classically known as neuroendocrine who might benefit from octreotide treatment.

Future radiotherapy with radiolabelled chelated somatostatin analogues would be a logical development, since it is known that these radioligands bind with high affinity to somatostatin receptor positive tumours. The rapid decrease in blood radioactivity and the predominantly renal clearance are advantageous, although the amount of renal accumulation and the relatively long renal effective half-life limit the maximally applicable radiation dose. Studies are needed to investigate how to lower the renal radioactivity, e.g. by co-administration of certain drugs and/or amino acids.

Another application of radiolabelled somatostatin analogues is in the use of a hand-held radionuclide probe [70] which could help the surgeon as an intra-abdominal an/or intrathoracic scanner in the search for the primary tumour and its metastases and as a guide for complete resection of the tumour. Also one could think about its external use to try to increase the sensitivity of localization of axillary metastases, e.g. in breast cancer and malignant lymphomas. Of course, for this technique a high tumour to background ratio and a relatively long effective half-life in the tumour would be essential, indicating the need for an appropriate interval between injection of the radioligand and use of the probe.

The basis of somatostatin receptor scintigraphy and its reported possibilities, especially in nuclear oncology, should encourage many to explore the usefulness of other labelled peptides in oncology and immunology.

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