Somatostatin-receptor Scintigraphy in Gastroenteropancreatic Tumors

An Overview of European Results

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INTRODUCTION

Somatostatin has been demonstrated in high concentrations in the hypothalamus, the cerebral cortex, the brain stem, the gastrointestinal tract, and the pancreas. In the central nervous system, it acts as a neurotransmitter, whereas its hormonal activities include the inhibition of the release of growth hormone, insulin, glucagon, and gastrin (for a review, see ref. 1). Also, antiproliferative effects have been reported, both *in vitro* on tumor cell lines, and *in vivo* on neuroendocrine human tumors.

High-affinity somatostatin receptors have been identified in the brain and on many cells of neuroendocrine origin, like the somatotroph cells of the anterior pituitary and the pancreatic islet cells.[2,3] Also, cells not known classically as neuroendocrine, such as lymphocytes, may possess these receptors.[4] Besides, somatostatin receptors have been demonstrated on a variety of human tumors by classical biochemical binding techniques, as well as by *in vitro* autoradiography. These tumors include those with APUD (amine precursor uptake and decarboxylation) characteristics (pituitary tumors, endocrine pancreatic tumors, carcinoids, paragangliomas, small cell lung cancers, medullary thyroid carcinomas, pheochromocytomas} as well as meningiomas, well-differentiated brain tumors (astrocytomas), neuroblastomas, and some human breast cancers.

Because of the short plasma half-life of somatostatin (2-4 min), analogues more suitable for medical treatment have been developed. The somatostatin analogue, octreotide, has been shown to bind to somatostatin receptors on both tumorous and nontumorous tissues.

An ^{111}In-labeled somatostatin analogue ([DTPA-D-Phe^1]-octreotide] was developed for its use in scintigraphy. [DTPA-D-Phe^1]-octreotide was shown to bind ^{111}In efficiently in a single-step labeling procedure. The binding as well as the biological

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activity of this new radionuclide was shown to be similar to that of octreotide, making it a good radiopharmaceutical for *in vivo* imaging of somatostatin receptor–positive tumors.[5] [^{111}In-DTPA-D-Phe^1]-octreotide is excreted mainly through the kidneys, 90% of the dose being present in the urine 24 h after injection.[6]

[^{111}In-DTPA-D-Phe^1]-octreotide (OctreoScan 111®), scintigraphy was performed in more than 1000 patients at the University Hospital Rotterdam (UHR), without any side effects being noticed.[7] To avoid a paradoxical hypoglycemia, the only precaution taken was a glucose-infusion in case of an insulinoma if the response to octreotide was unknown beforehand.

In this report, European data of octreotide scintigraphy of GEP tumors are reviewed. Because of the frequent localization of these (small) tumors in the upper abdomen where their presence (recognition) may be obscured by the physiologic accumulation of radioactivity, especially in kidneys, liver, and spleen, it seems that for this type of tumor the protocol of scintigraphy is of the utmost importance.

PROTOCOL OF [^{111}IN-DTPA-D-PHE^1]-OCTREOTIDE SCINTIGRAPHY AT UNIVERSITY HOSPITAL ROTTERDAM

The preferred dose of ^{111}In is about 200 MBq, coupled to 10 μg (DTPA-D-Phe^1]-octreotide. With such a dose, it is possible to perform single photon emission computerized tomography (SPECT), that is "CT in nuclear medicine," which may increase the sensitivity for detecting octreotide receptor–expressing tissues and which gives a better anatomical delineation than planar views. This is especially the case if the lesion(s) is (are) located in the skull or abdomen.

Planar and SPECT images are obtained with a large-field-of-view gamma camera, equipped with a medium-energy parallel-hole collimator. The pulse height–analyzer 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. The acquisition parameters are for planar images (anterior and posterior views necessary!): (1) 128 × 128 word matrix, (2) images of head/neck: 300,000 preset counts (or max. 15 min) at 24 h and 15 min present time (≈ 200,000 counts) at 48 h after injection, (3) the remainder of the body with separate images of the chest (including as little as possible of the liver and spleen (!) and, in case of suspicion of metastases in the armpits, projections of the shoulders with upraised arms), the upper abdomen (including liver/spleen and kidneys), and lower abdomen: 500,000 counts (or max. 15 min). For SPECT images, these parameters are (A) single-head camera, (1) 60 projections, (2) 64 × 64 word matrix, (3) at least 45–60 second acquisition time per projection; or (B) three-head camera, (1) 120 projections, (2) 64 × 64 word matrix, (3) at least 30 seconds acquisition time per step (45 seconds for SPECT of the head). In case the counting time to obtain these counts for the planar views is short, especially when tissues with relatively high accumulation (*e.g.* abdominal organs) are included in the field of view, additional images with a longer counting time (up to 15 min per planar view) are necessary in order to visualize also lesions with low somatostatin receptor density. The above-mentioned counting times per projection for planar imaging with a single-head camera also imply an appropriate (long) duration of whole body scintigraphy with a dual-head camera, for example, at least 30 min from head up to and including the pelvis. SPECT studies are inevitable, especially if (small) tumors are located in the abdomen and not visualized on planar images, because of overprojection by other tissues or organs. Examples are islet cell tumors in the head or tail of the pancreas and tumors in the (hilus of) the

liver. In special cases, after obtaining an initial negative SPECT study, for example, in which the tumor might be very small or express a low density of ligand receptors, another SPECT study with a longer counting time per step might be indicated in the same session or on another day, thus using the same administered radioligand. In general, the more counts that are being collected, the better are the results in detecting or localizing ligand receptor–expressing tissue(s). SPECT analysis is performed with a Wiener filter on original data. The filtered data are reconstructed with a Ramp filter.

Planar and SPECT 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 may also represent radioactive bowel content. Four-hour images of the abdomen are recommended by others because at that time radioactive bowel content is almost always absent. One should realize that the relative high background radioactivity at 4 h might obscure the localization of lesions with low-receptor density at this moment, however. These lesions may be visible at 24 h, because of a six times lower bloodpool radioactivity at 24 h after injection of the radioligand and a relatively long, effective half-life of the radiolabel in the tumor. This difference in results of 4 and 24 h images necessitates scanning after 48 h, inasmuch as 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 (also) the region of interest, the use of laxatives is highly recommended, starting from the moment of injection.

RESULTS

TABLE 1 illustrates the results of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in patients with gastroenteropancreatic (GEP) tumors and those of autoradiography with [^{125}I-Tyr^3]-octreotide. Scintigraphic investigations were carried out at fifteen

TABLE 1. Scintigraphy with [^{111}In-DTPA-D-Phe^1]-Octreotide in Gastroenteropancreatic Tumors[a]

	EMT	EUR	Combined	Autoradiography
Carcinoids	87% (182)	96% (72)	89%	88% (62)
Gastrinomas	73% (67)	100% (12)	77%	100% (6)
Insulinomas	46% (24)	61% (23)	53%	67% (27)
Motilinomas	1/1			
Nonsecreting tumors	82% (60)	89% (18)	83%	100% (4)
Glucagonomas	100% (5)	100% (3)	100%	100% (2)
VIPomas	88% (8)	1/2	80%	
Total	281/347 (81%)	115/130 (88%)	396/477 (83%)	
Pancreatic adenocarcinomas		0% (24)		0% (12)

[a]Results of the European Mallinckrodt Trial (EMT) (including 15 centers), the Erasmus University Rotterdam (EUR) (ref. 7), and the combined data of EMT and EUR. Autoradiographic ([^{125}I-Tyr^3]-octreotide) data (Dr. J. C. Reubi) are based on tumor samples from other patients than mentioned in the scintigraphic results. See also remarks in PROTOCOL and DISCUSSION.

centers in various countries in Europe (collected in the "European Mallinckrodt Trial") (EMT) and at the University Hospital Rotterdam (UHR), respectively.

The differences in results between the EMT and UHR are less than 10% for carcinoids, nonsecreting endocrine pancreatictumors, and glucagonomas, whereas gastrinomas and insulinomas show a larger difference in sensitivity. The a priori chance, based on *in vitro* autoradiography with radiolabeled octreotide, of obtaining a positive octreoscan in a patient with a gastrinoma is 100 percent (TABLE 1). Actually the a priori chance might be lower in a patient with a suspicion (*i.e.*, based on endocrine testing) of having a gastrinoma, because not every patient with this suspicion will have a gastrinoma. The distribution of the primary sites of pancreatic and duodenal gastrinomas, found by one or more of the applied imaging techniques in the EMT and at the EUR (n = 46), was as follows: pancreas 87%, and duodenum 13%, of which [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy was positive in 90% and 50%, respectively. In the EMT, conventional imaging modalities (CIM), mainly CT scanning, were able to localize tumor(s) in 50 out of 67 (75%) patients with a strong clinical suspicion of having a gastrinoma. Octreotide scintigraphy of the lesions found by CIM was positive in 42 out of 50 (84%) patients, while octreotide scintigraphy found additional lesions in about 40% of these patients. In the 8 patients with positive CIM and negative octreotide scintigrams, tumor localization, according to CIM was as follows: pancreas (3), duodenum (3), liver hilus, and liver. In 6 out of 8 (75%) of these patients 1. the dose of [^{111}In-DTPA-D-Phe^1]-octreotide was between 100 and 129 MBq and/or 2. no abdominal SPECT had been performed. In the CIM-negative patients, octreotide scintigraphy demonstrated (a) lesion(s) in 6 out of 17 (35%) patients. The combination of CIM and octreotide scintigraphy localized lesions in 56 out of 67 (84%) patients with a suspicion of having a gastrinoma.

The a priori chance, based on autoradiography with radiolabeled octreotide, of obtaining a positive octreoscan in a patient with an insulinoma is 67 percent (TABLE 1). In the EMT patients with a suspicion of having an insulinoma, 17 out of 24 (71%) had a lesion found by CIM, whereas 9 out of 17 (53%) had a positive octreotide scintigram. In 3 out of 8 (38%) negative octreoscan patients, the dose of [^{111}In-DTPA-D-Phe^1]-octreotide was between 103–123 MBq, and no abdominal SPECT had been performed. In the CIM-negative patients, octreotide scintigraphy found a lesion in 2 out of 7 (29%) patients. The combination of CIM and octreotide scintigraphy localized lesions in 19 out of 24 (79%) patients with a strong clinical suspicion of having an insulinoma.

TABLES 2 and 3 show the CIM and octreotide scintigraphy results of EMT and UHR in gastrinomas and insulinomas in comparison with a recent overview of results of imaging techniques reported in the literature.[8,9]

DISCUSSION

A comparison of the results obtained at the University Hospital Rotterdam (UHR) and another fifteen centers in Europe (collected in the European Mallinckrodt Trial) (EMT) shows a few remarkable similarities and differences. The overall sensitivity of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy for detecting the primary GEP tumor and its metastases is high, for example, 80–90 percent. The sensitivity of this scanning technique for tumors generally expressing a high density of octreotide receptors, for example, carcinoids, glucagonoma, and the so-called "nonsecreting" pancreatic endocrine tumors, is very high, and the difference in results in both groups of centers is less than ten percent. Apparently, the below-mentioned differ-

TABLE 2A. Primary Gastrinoma[a]

Procedure	Sensitivity Mean (percent)	Range (percent)	Specificity Mean (percent)	Range
US	23	21–28	92	92–92
CT scan	50	35–59	90	83–100
Angiography	68	35–68	89	84–94
IOUS	83			
MRI	21		33	
PVS	73		33	
Intraarterial Secretin test	78	55–100	100	
Transillumination of duodenum (only duodenal gastrinoma)	83		88	
Endoscopic US (only upper abdomen)	86			
CIM in EMT	75			
Octreoscan	77	73–100		

[a]Sensitivity and specificity of various imaging modalities to localize the primary and metastases of gastrinomas (modified from an overview in ref. 8, based on data reported in the literature; ref. 9; and this report (results of conventional imaging techniques (CIM), mainly based on CT scanning in the European Mallinckrodt Trial (EMT) and [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in EMT and EUR). See TABLE 1. US = ultrasound; IOUS = intraoperative US; PVS = selective gastrin sampling from portal venous tributaries.

ences in scanning procedure are not that relevant for the sensitivity of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy in these types of tumors. On the other hand, a difference of 15% and higher in sensitivity has been found for the insulinomas and gastrinomas, respectively. A closer look at the scanning procedure used at UHR and EMT, reveals a few remarkable differences, which might explain the contrasting findings in the insulinoma and gastrinoma patients, inasmuch as the presence of octreotide receptors in insulinomas is not 100%, as is the case in gastrinomas, but about sixty-five percent. Also, a bias of patient selection might be involved in the difference in sensitivity for the insulinomas. Probably, the same might hold for differences in the endocrine inclusion criteria applied for both the gastrinomas and insulinomas. The major differences in the scanning protocol were fourfold: In the

TABLE 2B. Metastases of Gastrinoma[a]

Procedure	Sensitivity Mean (percent)	Range (percent)	Specificity Mean (percent)	Range
US	14	14–63	100	
CT scan	54	35–72	99	98–100
Angiography	62	33–86	98	96–100
IOUS	NE		NE	
MRI	67		100	
PVS	NE		NE	

[a]See legend for TABLE 2A.

TABLE 3. Insulinomas[a]

Procedure	Sensitivity Mean (percent)	Range (percent)
US	33	0–66
CT scan	35	11–50
Dynamic CT scan	66	
Selective arteriography	63	17–100
All imaging studies	80	50–90
Transhepatic portal venous sampling	92	89–96
Operative US	83–90	
Endoscopic US (only upper abdomen)	81	
CIM in EMT	71	
Octreoscan	53	46–61

[a]Sensitivity and specificity of various imaging modalities to localize the primary of insulinomas (modified from an overview in ref. 8, which is based on data reported in the literature, including data from ref. 9 and this report). See legend for TABLE 2A.

EMT false-negative [^{111}In-DTPA-D-Phe^1]-octreotide, scintigrams have especially been obtained in patients who were (1) injected with a much lower dose of ^{111}In (-labeled ligand) and (2) not investigated with SPECT. (3) If SPECT was applied, the counting time per projection/view or step was much shorter than the time used at UHR. Furthermore most of our SPECT studies have been performed with a three-head gamma-camera, which has several advantages over the usual one-head gamma-camera, for example, a higher sensitivity. SPECT is absolutely necessary in cases in which tumor radioactivity on planar images is or might be obscured by overprojection of radioactivity originating from other organs or tissues (FIG. 1). Examples are the small endocrine tumors and/or octreotide receptor–expressing tumors with low-receptor density localized in the head and/or tail of the pancreas, duodenum, or hilus of the liver. In these cases the planar images of [^{111}In-DTPA-D-Phe^1]-octreotide scintigraphy may miss the abnormalities in contrast to the SPECT images, because of their view on the tumor from different angles. Also in these cases it is important to underline that the longer the counting time (both for planar and SPECT imaging), the more information is being collected and the higher is the chance to localize a tumor (FIG. 2). Therefore, peptide-receptor scintigraphy requires a learning process both for the technician and for the nuclear medicine physician. The above-mentioned protocol can serve as a guide in this process.

In contrast to the UHR patients with insulinomas and gastrinomas, a high proportion of such patients in the EMT might have been asked to undergo octreotide scintigraphy while they were already diagnosed, and their tumor(s) localized for a longer time. This might explain the high proportion of patients (with larger tumors than at the time of first referral?) localized with CIM, mainly by CT scanning. This is especially the case if the CIM sensitivities (70–75%) of the EMT are being compared with those of the literature[8,9] (TABLES 2 and 3). Of course this might also influence in a positive way the results of octreotide scintigraphy. Nevertheless octreotide scintigraphy was able to localize (1) additional metastases in about one third of the CIM-positive group of patients and (2) lesions in about one third of the CIM-negative group of patients with a strong clinical suspicion of having an insulinoma or gastrinoma.

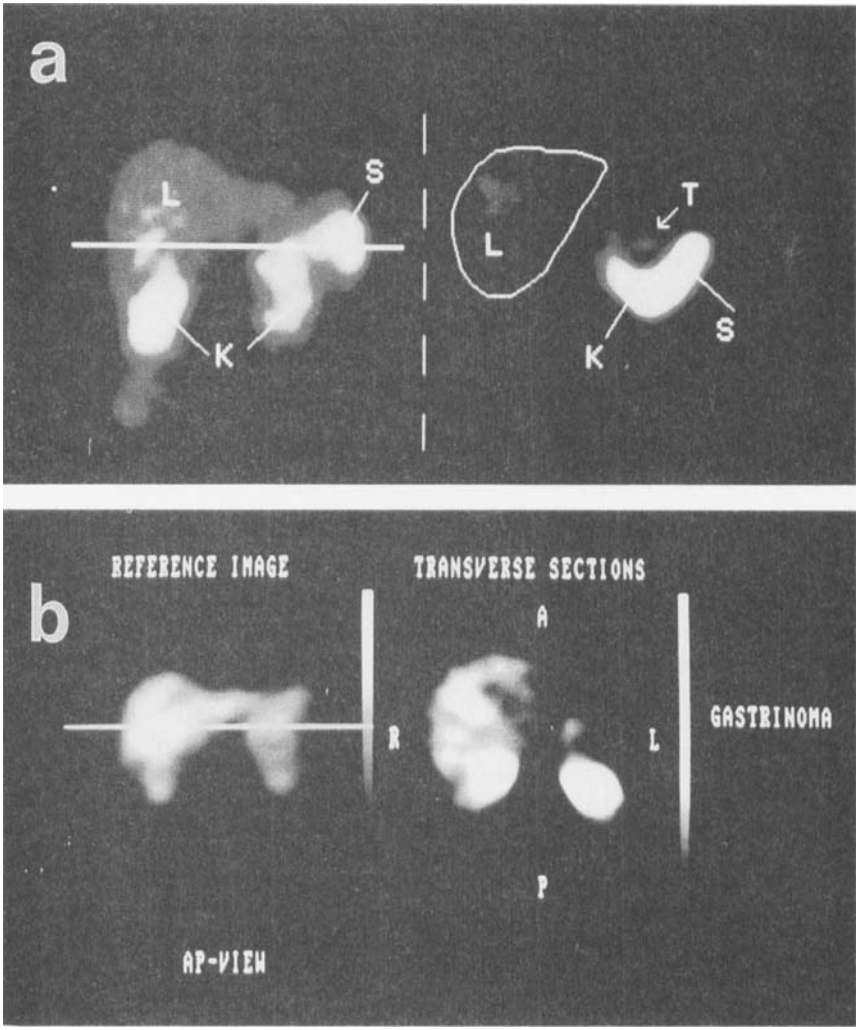

FIGURE 1. Two examples of octreotide scintigraphy in patients with an insulinoma (**a**) and a gastrinoma (**b**) of which the anterior and posterior planar abdominal images did not show a lesion (not shown). The SPECT images, that is, the right-sided images in **a** and **b**, illustrate the actual localization of the tumors. SPECT studies are inevitable, especially if (small) tumors are located in the abdomen and not visualized on planar images and because of overprojection by other tissues or organs. Examples are islet cell tumors in the head or tail of the pancreas and tumors in the (hilus of) the liver. In these cases, the planar images of [^{111}In-DTPA-D-PHE^{1}]-octreotide scintigraphy may miss the abnormalities in contrast to the SPECT images because of their view on the tumor from different angles. In **a**, L = liver, S = spleen, K = kidney, and **T** = tumor.

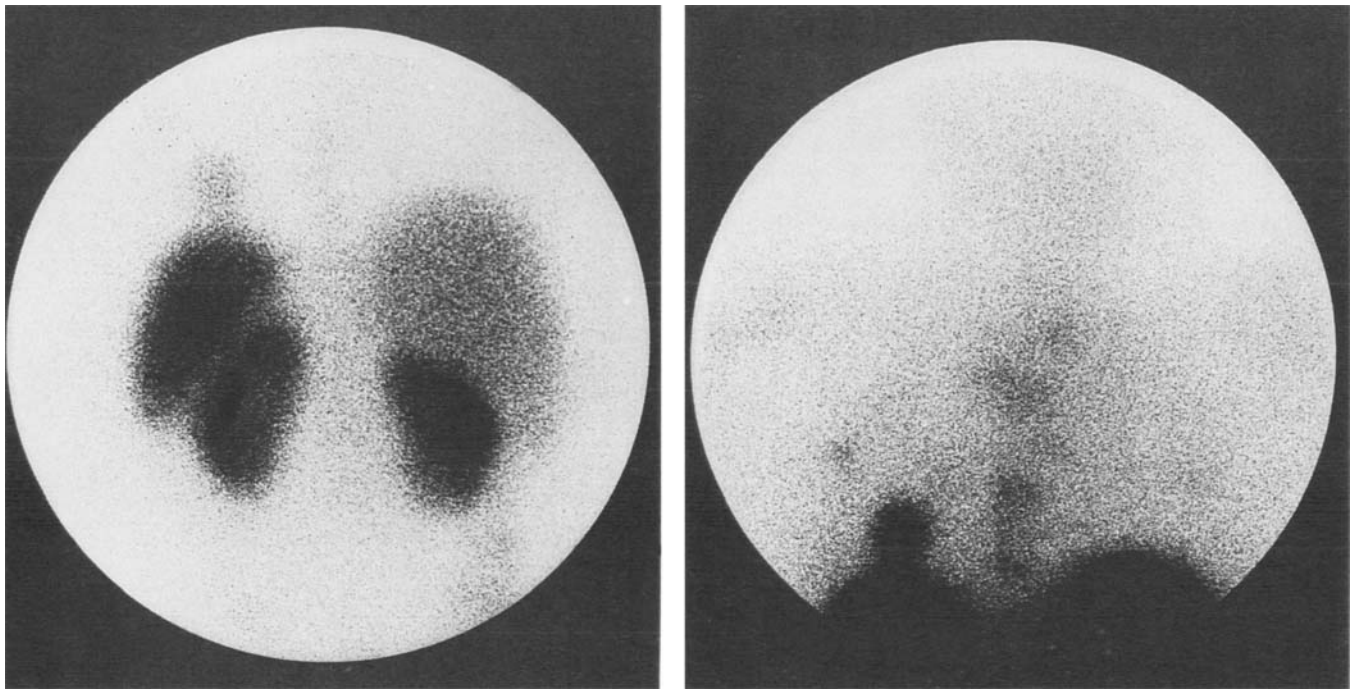

FIGURE 2. The longer the counting time (both for planar and SPECT imaging), the more information is being collected and the higher is the chance to localize a tumor with octreotide scintigraphy. The two planar octreotide scintigrams (posterior thoracic-abdominal views) have been obtained in a consecutive way from the same patient with a history of breast cancer. The left image (3 min counting time) only shows a hotspot just above the spleen, whereas the right image (15 min counting time) shows this hotspot not only more intense, but also several spots in the spinal column and the chest, representing proven metastases of somatostatin receptor–expressing breast cancer.

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