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The Use of Somatostatin Receptor Scintigraphy in the Differential Diagnosis of Pancreatic Duct Cancers and Islet Cell Tumors

Casper H. J. van Eijck, M.D., Ph.D.,* Steven W. J. Lamberts, M.D., Ph.D.,†
Luciene C. J. M. Lemaire, M.D.,* Hans Jeekel, M.D., Ph.D.,* Fre T. Bosman, M.D., Ph.D.,‡
Jean-Claude Reubi, M.D.,Ph.D.,§ Hajo A. Bruining, M.D., Ph.D.,*
and Eric P. Krenning, M.D., Ph.D.‖

From the Departments of Surgery, Internal Medicine III,† Pathology,‡ and Nuclear Medicine,‖ University Hospital, Rotterdam, The Netherlands; and the Department of Pathology,§ University of Berne, Berne, Switzerland*

Objective
In the present study, the diagnostic value of somatostatin receptor scintigraphy (SRS) was evaluated in the preoperative workup in patients with pancreatic duct cancers and islet cell tumors, as well as in the follow-up of these patients.

Methods
Twenty-six patients with suspected primary pancreatic duct cancers and 48 patients with islet cell tumors were studied. The SRS was performed using the radionuclide-labeled somatostatin analogue ^{111}In-octreotide. Another group of 12 patients who were still alive more than 3 years after pancreaticoduodenectomy for pancreatic duct adenocarcinomas also underwent SRS.

Results
In 31 (65%) of 48 patients, the primary pancreatic islet cell tumor as well as its often previously not yet recognized metastases could be visualized. In contrast, none of the 26 pancreatic adenocarcinomas or their metastases could be seen. In 5 of 12 patients who were alive more than 3 years after pancreaticoduodenectomy for pancreatic duct adenocarcinomas, metastatic lesions were visualized at SRS. In retrospect, these patients were not operated on for adenocarcinomas but for "nonfunctioning" islet cell tumors.

Conclusions
The present study supports the concept that SRS has a place in the preoperative differential diagnosis of islet cell tumors and pancreatic duct cancers as well as in the follow-up, especially in those cases in which no tumor histologic analysis was obtained, or the pathologic examination of the tumor tissue had not included special staining procedures for neuroendocrine characteristics. Our results also indicate that the evaluation of the results of investigations on the role of surgery or radiation therapy and chemotherapy or both in pancreatic duct cancer have to be interpreted with caution, if no histologic analysis and staining for neuroendocrine characteristics was performed.

Somatostatin receptors (SS-Rs) have been found on a variety of neuroendocrine tumors like carcinoids, paragangliomas, as well as on brain tumors, such as meningiomas.[1-3] The SS-Rs also are present on most pancreatic islet cell tumors,[4,5] whereas previous *in vitro* studies indicate the absence of these receptors on pancreatic duct cancers.[6]

Endocrine pancreatic tumors or islet cell tumors constitute a small, but important, group of pancreatic tumors. The annual incidence of islet cell tumors was found to be 0.4 per 100.000 population.[7] Most of these tumors produce multiple hormones, but usually excessive secretion of one hormone predominates, causing specific clinical symptomatology.[8,9] However, approximately 15% to 40% of islet cell tumors do not give rise to hormone-related symptoms and are therefore called "nonfunctioning."[10,11] The reasons why they are clinically silent include the absence of the release hormones, the production of biologically inactive prohormones, the production of hormones that do not cause clinical symptoms (*e.g.*, pancreatic polypeptide, chromogranin A), and downregulation of hormone receptors or the production of inhibitory hormones, such as somatostatin, or both.[12] Most patients with nonfunctioning islet cell tumors have rather uncharacteristic symptoms at presentation. The correct diagnosis is therefore made at a late stage when extensive tumor growth has occurred.[7,13,14] In general, islet cell tumors grow slowly, but the significantly shorter survival of patients with nonfunctioning islet cell tumors compared with those that cause signs and symptoms of hormonal secretion indicates a more malignant behavior of this subtype.[7] However, this also might be because these tumors are diagnosed later. In 70% to 80% of the cases, liver metastases are present at the time of diagnosis in patients with nonfunctioning islet cell tumors.

Preoperative differentiation between pancreatic duct carcinomas and islet cell tumors is of importance, because palliative surgery in patients with islet cell tumors is not only of value to relieve clinical symptoms but also to decrease the tumor burden, which might enhance the effect of medical treatment.[15]

Recently we introduced a new nuclear medical technique in which SS-R-positive tumors could be visualized *in vivo* after the administration of a radionuclide-labeled somatostatin analogue followed by gamma-camera scintigraphy.[16-20] In the present study, we investigated the diagnostic value of this technique in the workup of patients with pancreatic endocrine and exocrine tumors. The results of this *in vivo* technique were correlated with the results of *in vitro* receptor autoradiographic studies in tumor specimen.

Address reprint requests to Casper H. J. van Eijck, M.D., Ph.D., Department of Surgical Oncology, University Hospital Dijkzigt, Dr. Molewaterplein 40, 3015 GD, Rotterdam, The Netherlands.
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PATIENTS AND METHODS

Patients Selection

Twenty-six patients with primary pancreatic duct cancers (mean age, 64 years; range, 42–81) were studied. After clinical and laboratory investigations searching for a primary tumor in the pancreas, all patients underwent ultrasonography, computed tomography (CT) scanning, and endoscopic retrograde cholangiopancreatography. Whenever possible, cytologic analysis of the tumor was obtained. After informed consent was obtained from the patient to participate in this study, somatostatin receptor scintigraphy (SRS) was performed after bowel preparation on an outpatient basis. Without surgeons' taking into consideration the scintigraphic results, 22 patients were subsequently operated on for suspected pancreatic duct carcinoma. Four patients were not operated on because of cytologically proven metastatic disease.

Tumor tissue specimens from these 22 patients who were operated on were stained with hematoxylin and eosin and examined for homogeneous cell structure and characteristic growth patterns of exocrine and endocrine tumors. The Grimelius silver staining technique was used, as well as immunocytochemical staining with antisera against neuron-specific enolase and chromogranin A to confirm a possible endocrine nature of the tumor. In addition, immunocytochemical staining with antisera against insulin, gastrin, pancreatic polypeptide, vasoactive intestinal polypeptide, somatostatin, glucagon, and neurotensin was performed. Tumors were histologically classified by one pathologist, who was not informed about the SRS results. Whenever enough tumor tissue was available, the presence of SS-Rs was studied by *in vitro* autoradiographic analysis on cryostat sections, as has been described previously.[4]

Another group of 12 patients who were still alive more than 3 years after subtotal (n = 10) or total (n = 2) pancreaticoduodenectomy performed for pancreatic duct adenocarcinomas also underwent an SRS. Five of these patients were known to have metastatic disease when SRS was performed. Revision of the tumor blocks of these patients that had been previously reviewed by other pathologists took place as described above. No more autoradiographic analysis could be done on these tumor specimens.

The results of the scintigraphy of the patients described above where compared with the results obtained in 48 patients with endocrine pancreatic tumors. Part of the results obtained in 25 individuals have been described previously.[21]

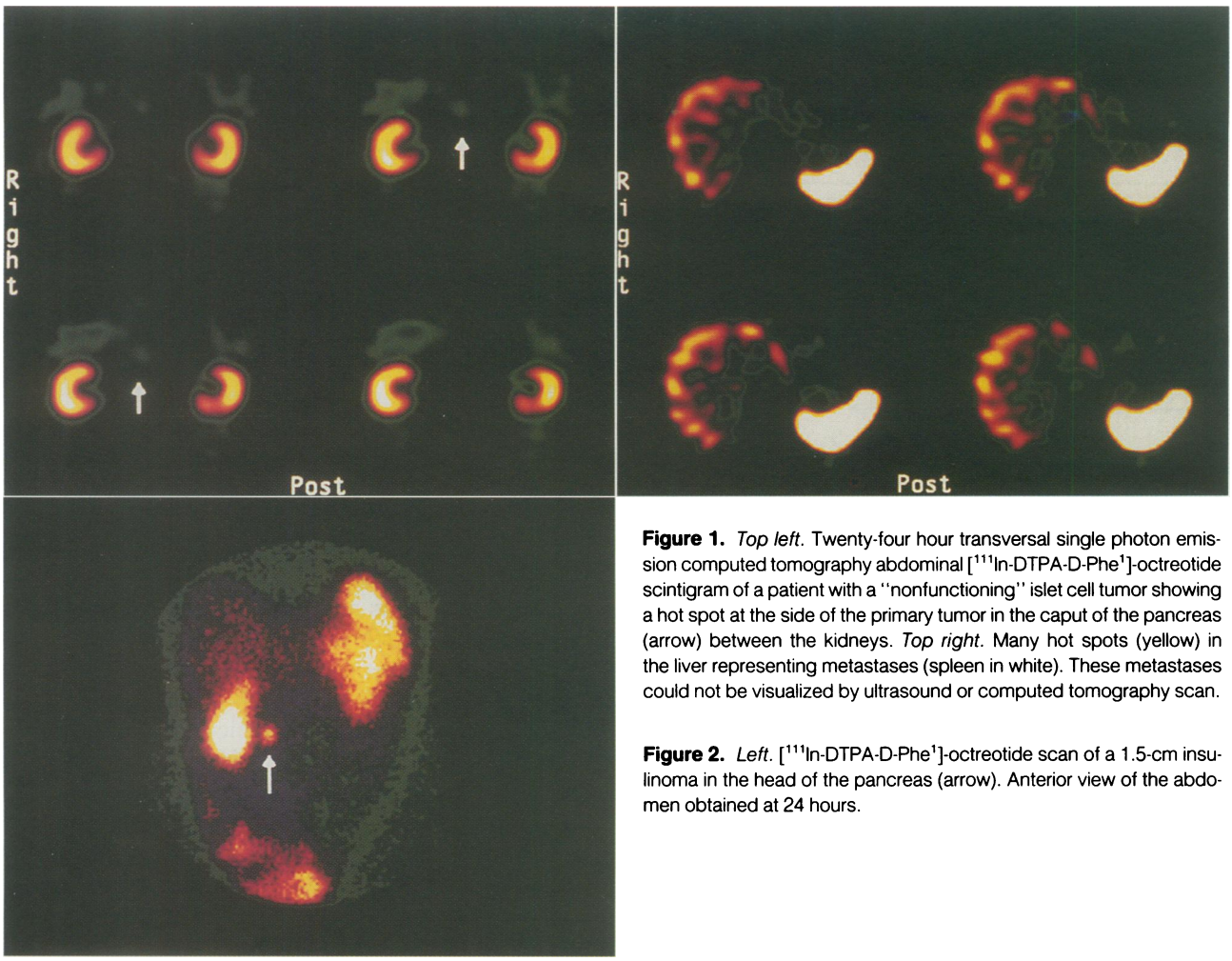

Figure 1. *Top left.* Twenty-four hour transversal single photon emission computed tomography abdominal [^{111}In-DTPA-D-Phe^{1}]-octreotide scintigram of a patient with a "nonfunctioning" islet cell tumor showing a hot spot at the side of the primary tumor in the caput of the pancreas (arrow) between the kidneys. *Top right.* Many hot spots (yellow) in the liver representing metastases (spleen in white). These metastases could not be visualized by ultrasound or computed tomography scan.

Figure 2. *Left.* [^{111}In-DTPA-D-Phe^{1}]-octreotide scan of a 1.5-cm insulinoma in the head of the pancreas (arrow). Anterior view of the abdomen obtained at 24 hours.

Material

The somatostatin analogue [DTPA-D-Phe^{1}]-octreotide (Mallinckrodt Medical BV, Petten, The Netherlands) was labeled with "ultra-pure" Indium 111 ([^{111}In], Mallinckrodt Medical BV, Petten, The Netherlands). The labeling procedure has been described elsewhere.[22] Doses ranged from 222 MBq to 272 MBq [^{111}In-DTPA-D-Phe^{1}]-octreotide.

Scintigraphy

After bowel preparation (2 L polyethyleneglycol), planar and, in most patients, also single photon emission computed tomography images were obtained as described previously.[20,23]

RESULTS

[^{111}In-DTPA-Phe^{1}]-octreotide scintigraphy (SRS) was carried out before operation in 26 patients with suspected pancreatic duct carcinomas. None of these tumors or their metastases could be visualized. Twelve patients were subsequently treated by a Whipple procedure, 2 by total pancreatectomy, 2 patients by a palliative procedure (gastroenterostomy or choledochoduodenostomy or both) after transduodenal biopsy was performed, and 6 patients had a biopsy only. Four patients were not operated on because cytologic analysis of suspected lesions in the liver showed adenocarcinoma. Pancreatic duct carcinoma was found in 18 patients who were operated on. None of these tumors showed neuroendocrine characteristics. In 16 of these tumors, autoradiographic studies of the surgically removed tumor tissue could be done and no SS-Rs were present. In two patients, the tumor was so extensive that no resection could be done. Transduodenal biopsies in these two patients, however, showed atypia without any evidence of infiltrating tumor cells, which must be considered a sampling error. The other two patients underwent a Whipple procedure for chronic pancreatitis. In these patients also, no abnormalities were detected at SRS. No autoradiographic analysis was done on the tissue of these patients.

Table 1. INCIDENCE OF SOMATOSTATIN RECEPTORS ON ENDOCRINE PANCREATIC TUMORS *IN VIVO* AND *IN VITRO* AS DEMONSTRATED BY SCINTIGRAPHY AND AUTORADIOGRAPHY

	In Vivo	*In Vitro*
Vipomas	1/1	1/1
Gastrinomas	13/14	10/11
Glucagonomas	1/1	1/1
Insulinomas	13/28	8/11
"Nonfunctioning" islet cell tumors	2/2	2/2
Somatostinomas	1/2	—

Because long-term survival of patients with pancreatic duct carcinoma is rare, we looked in retrospect at our group of long-term survivors after surgery for pancreatic duct carcinomas. Long-term survivors were defined as patients who lived more than 3 years after the primary operation. Of 62 patients who had been operated on between 1985 and 1990, 12 patients were found to be alive for 3 or more years. Five of these 12 patients were known to have metastases. These 12 patients underwent SRS. In seven patients, no abnormalities were seen, whereas other investigations also suggested that these patients were tumor free at that moment. However, in five "survivors" in whom the presence of metastases was known, all metastatic lesions as well as a number of additional tumor sites were visualized at SRS. Examples of the scintigram obtained in one of these patients are shown in Figure 1.

Revision of the original tumor blocks, including the additional staining procedures mentioned above, showed that these five patients in retrospect were operated on primarily for nonfunctioning islet cell tumors. In the group of seven patients without known metastases and without abnormalities at SRS, revision of the pathologic analysis confirmed that these patients indeed had been cured from pancreatic duct cancer.

Table 1 lists the results of *in vivo* scintigraphy of a group of 48 patients with different islet cell tumors. Twenty-one of the tumors have been investigated both *in vitro* and *in vivo*. In all cases, the results *in vitro* and *in vivo* investigations were parallel.

The application of SS-R imaging proved to be highly successful. The primary endocrine pancreatic tumors as well as their often previously not yet recognized metastases could be visualized in 31 (65%) of these 48 patients. Metastases were actually scintigraphically evident in 13 patients. Twenty-six of these patients subsequently were operated on in our hospital, allowing surgical evaluation of the scintigraphic results. In one patient with gastrinoma, no lymph node metastasis on the aortic arch was found at operation, despite it being suggested at CT scanning. In another patient with gastrinoma who had familial multiple endocrine adenomatosis type I, the scintigraphically detected tumor was indeed found in the tail of the pancreas, but during operation, an additional islet cell tumor was found in the corpus of the pancreas. This tumor had not been seen on SRS. Unfortunately, no somatostatin autoradiographic analysis of this tumor was done.

The visualization of insulinomas with this technique proved to be more difficult. We localized the tumors with SRS in only 13 of 28 patients investigated to date. *In vitro* autoradiographic analysis showed that all insulinomas contained receptors for somatostatin-14 and somatostatin-28, but that octreotide receptors were absent on the tumors, which could not be visualized *in vivo*. An example of the gamma picture obtained in one patient with an insulinoma is shown in Figure 2.

DISCUSSION

After Schönbrunn and Tashjian first measured SS-Rs in 1978 using the clonal pituitary cell line GH4C,[24] SS-Rs have been shown on a variety of human tumors, using various iodinated SS analogues in homogenate ligand-binding assays or autoradiographic analysis on tissue sections.[25,26] Large numbers of binding sites with high affinity for SS were found on most tumors with amine precursor uptake and decarboxylation (APUD) characteristics, as well as on meningiomas, well-differentiated brain tumors (astrocytomas), neuroblastomas, and human breast tumors.[27–43] Examples of tumors with amine precursor uptake and decarboxylation characteristics that are often SS-R-positive are growth-hormone-producing pituitary adenomas, endocrine pancreatic tumors, carcinoids, paragangliomas, small cell lung cancers, medullary thyroid carcinomas, and pheochromocytomas. Recently, at least five different human SS-R subtypes have been cloned.[44–48] Octreotide binds with high affinity to subtype 2 ($SSTR_2$), whereas this analogue has a relatively low affinity to $SSTR_3$ and $SSTR_5$ and shows no binding to subtypes 1 and 4 ($SSTR_1$ and $SSTR_4$). The majority of the receptor-positive human tumors expressed the SS-R_2 subtype, whereas only a minority of tumors had exclusively other SS-R subtypes.[47]

For the visualization of SS-R-positive tumors, we used a radionuclide-labeled somatostatin analogue, [^{111}In-DTPA-D-Phe^1]-octreotide, because there are several arguments that octreotide scintigraphy represents SS-R imaging. Pretreatment with high doses of unlabeled octreotide prevents tumor uptake of [^{111}In-DTPA-D-Phe^1]-octreotide in rats bearing SS-R-positive tumors.[22] Autoradiographically, it also was found that only the anterior lobe of the rat pituitary, which is the only part of this organ with SS-Rs, showed specific binding of the radioligand after its injection.[49] As has been found in our study as well, a close relation exists between the presence

of SS-Rs, showed with *in vitro* autoradiographic analysis, and the visualization of tumors and diseases by *in vivo* octreotide scintigraphy.

There are many promising reports on the potential benefit of radiolabeled monoclonal antibodies for *in vivo* tumor detection. However, their widespread application has been hampered for several reasons. The low tumor-to-background ratios achieved with this technique is because of the large molecules often used, which lead to a high background radioactivity. Because of the rapid clearance of the small-sized [^{111}In-DTPA-D-Phe^1]-octreotide by the kidneys, a much higher tumor-to-background ratio can be obtained. Antibody formation, which often can be found after administration of monoclonal antibodies, is extremely rare in patients treated with octreotide. Therefore, the SS-R imaging can be repeated easily without any risk of an anaphylactic reaction.

Generally, patients with pancreatic islet cell tumors have a better prognosis than those with exocrine, mostly ductal adenocarcinomas.[50] However, despite improvements in diagnostic methods, the median delay between the appearance of the first symptoms and the diagnosis has not been reduced, and most patients are encountered when the tumor has reached an advanced stage.[8,13,14] As pointed out by Eriksson et al.,[7] there is a need for optimalization of screening patients with uncharacteristic abdominal symptoms for the presence of islet cell tumors. In addition to the measurements of plasma levels of chromogranin A and pancreatic hormones, SS-R scintigraphy can be used to show the presence of such tumors.

In this study, the sensitivity of the SS-R scintigraphy in localizing islet cell tumors was high, except in the case of insulinomas. The presence of other subtypes of SS-Rs in this tumor is well known. Only approximately 60% of the insulinomas express the $SSTR_2$ subtype, and this necessitates the development of other radionuclide-labeled somatostatin analogues that recognize other subtypes of the SS-R. Other factors that generally may interfere with the visualization of neuroendocrine tumors include the presence of unlabeled somatostatin (*e.g.*, by autocrine, paracrine, or endocrine production of somatostatin or somatostatin analogue administration). In both cases, this may result in receptor blockade or "down" regulation of the receptor.

Finally, the difference in SS-R expression between islet cell tumors and pancreatic duct cancers seems to offer the possibility to differentiate between these tumors before operation. This is important, because palliative surgery in patients with islet cell tumors is not only of value to relieve clinical symptoms but also to decrease tumor burden, which might enhance the effect of medical treatment, resulting in a better clinical condition and a longer survival.[15] The use of SS-R scintigraphy as a diagnostic technique for suspected islet cell tumors is favored because of its harmless, noninvasive nature. In islet cell tumors, ultrasound and CT are usually limited to the pancreas and liver region, thereby missing possible extra-abdominal metastases. Further studies comparing intraoperative ultrasound, surgical palpation, and guided surgery using a hand-held radionuclide-detecting probe after the administration of [^{111}In-DTPA-D-Phe^1]-octreotide are necessary to determine the best method to localize the endocrine tumor before operation. Therefore, the SS-R scintigraphy should be performed to see if the tumor contains SS-Rs, to support diagnosis of an islet cell tumor, and to stage the patient directly.

The present study supports the concept that SRS may have a place in the preoperative differential diagnosis of endocrine pancreatic tumors, especially nonfunctioning islet cell tumors, and pancreatic ductal cancers, as well as in the follow-up, especially in those cases in which the pathologic examination of the tumor tissue had not included special staining procedures for neuroendocrine characteristics. Our results also indicate that the evaluation of the investigative results on the role of surgery or radiation therapy and chemotherapy or both in pancreatic duct cancer have to be interpreted with caution, if no histologic analysis and staining for neuroendocrine characteristics were performed.

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