Somatostatin Receptor Imaging with Indium-111-Pentetreotide in Gastroenteropancreatic Neuroendocrine Tumors: Safety, Efficacy and Impact on Patient Management

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Indium-111-pentetreotide, a radiolabeled somatostatin analog, has been proposed for imaging tumors bearing somatostatin receptors. This study evaluates the safety, efficacy and impact on patient management of this scintigraphic agent in patients with gastroenteropancreatic (GEP) neuroendocrine tumors. **Methods:** We studied 47 consecutive patients with a proven or clinically suspected GEP neuroendocrine tumor who were imaged 4 and 24 hr after injection of ^{111}In-pentetreotide. The patients were monitored for adverse reactions and changes in vital signs or clinical chemistry over 24 hr. The scintigraphic findings were compared with results from conventional imaging methods. The patients were followed over a minimal 6-mo period during which further localization procedures were performed to confirm or refute the additional tumor sites found at scintigraphy. **Results:** No adverse reactions or clinically relevant changes in clinical chemistry were noted after injection of the radiopharmaceutical. The final diagnosis of a GEP neuroendocrine tumor was retained in 38 patients. Somatostatin receptor-positive lesions were found in 33 of these patients, whereas conventional methods were positive in 31 patients. Of the 54 sites seen by conventional procedures, 50 sites were also detected scintigraphically. **Conclusion:** Indium-111-pentetreotide is a safe, sensitive imaging agent in the detection of GEP neuroendocrine tumor sites. Indium-111-pentetreotide also provides information on the somatostatin receptor status of the tumor and may therefore aid in therapeutic decisions.

Key Words: gastroenteropancreatic neuroendocrine tumors; somatostatin receptor imaging; indium-111-pentetreotide

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G astroenteropancreatic (GEP) neuroendocrine tumors are generally slow-growing and may remain indolent for many years. A distinguishing feature of these tumors is their production of peptides that may cause symptoms characteristic of excessive hormonal production. Since many GEP neuroendocrine tumors are malignant, the initial clinical presentation may be dominated by symptoms associated with the tumor bulk or the metastatic localizations. Complete surgical excision is the treatment of choice but in many patients such treatment is not possible (1-6). Palliative treatments such as surgical debulking, chemotherapy, interferon and hepatic artery embolization have resulted in symptomatic improvement and in partial tumor regression (6-9). Somatostatin analogs offer an alternative therapeutic modality. In addition to inhibiting properties on hormonal secretion, the use of these analogs may have a beneficial effect on tumor growth (10-12).

The optimal management of patients with GEP neuroendocrine tumors requires the judicious choice of treatment options that consider the severity of endocrine symptoms and the presence or absence of metastases. Therefore, it is essential to undertake studies to establish accurate staging of the disease. Noninvasive imaging modalities such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI) may yield valuable information regarding tumor localization and the presence of metastases (13). Recently, a new scintigraphic imaging approach was introduced by Krenning et al. (13). On the basis of in vitro studies showing the presence of a high number of somatostatin binding sites on neuroendocrine tumors in comparison with normal tissue, Krenning et al. developed a radioiodinated somatostatin analog, ^{123}I-Tyr3-octreotide, suitable for in vivo somatostatin receptor imaging (14-16). The method has been successfully used to image patients with somatostatin receptor-bearing tumors, including GEP neuroendocrine tumors (17,18). An ^{111}In-labeled analog, pentetreotide, has been developed (19-21) and has a longer half-life and lower hepatic clearance, resulting in higher quality images, particularly over the abdomen.

The purpose of this study was to prospectively evaluate

the safety and the efficacy of ^{111}In-pentetreotide in the localization of primary and metastatic GEP endocrine tumor sites. The scintigraphic findings were compared with results obtained from conventional imaging modalities. We also investigated the impact of the scintigraphic findings on patient management.

MATERIAL AND METHODS

Study Design

This prospective open study was designed to evaluate the safety and the efficacy of ^{111}In-pentetreotide scintigraphy for the detection and localization of GEP neuroendocrine tumors. The study was approved by the local Ethics Committee and all patients gave written informed consent before inclusion into the study. Over a 16-mo period, all patients referred with a known or suspicion of GEP endocrine tumor were considered for entry into the study according to the following inclusion criteria: (1) demonstration or high suspicion of GEP endocrine tumor on the basis of histology and/or abnormal hormone levels and (2) a complete clinical status, including relevant clinical chemistry and extensive evaluation of tumor localization by conventional imaging methods had to be available. After completion of the scintigraphy the patients were followed over a minimal 6-mo period, during which further localization procedures were performed to evaluate additional tumor sites found during scintigraphy. The clinicians in charge of patient care were informed of the scintigraphic results and allowed to use this information for patient management. The impact of the scintigraphic findings on the patient management was reported by the clinician at the end of the follow-up period.

Patients

Forty-seven consecutive patients (22 males and 25 females, mean age: 53 ± 16 yr) were enrolled in the study. Nine patients were subsequently taken off the study: two patients had no follow-up and seven patients were subsequently found to have no GEP endocrine tumor, including two nonendocrine pancreatic adenocarcinomas. In the 38 remaining patients, the diagnosis of GEP endocrine tumor was based on histology in 28 patients and on abnormal hormone levels in 10 patients. These 38 patients included 19 carcinoids, 10 gastrinomas, 5 nonfunctioning islet cell carcinomas, 2 insulinomas and 2 multiple endocrine neoplasia type I syndromes (MEN-I) with increased pancreatic polypeptide levels and 1 case of moderate increase in glucagon. Thirteen patients who previously underwent surgical resection of a primary localization had residual or recurrent disease at the time of the study. In 15 patients treated with octreotide, the drug was discontinued 12 hr to 10 days before injection of the radiopharmaceutical.

Somatostatin Receptor Imaging

Pentetreotide (Mallinckrodt Medical, Petten, The Netherlands) was labeled with ~210 MBq [111]InCl₃ according to the manufacturer's recommendations. The labeling efficiency, assessed by reverse-phase chomatography (C18 SEP-PAK® cartridges; Waters, Millipore Corporation, Milford, MA), was higher than 97% in all but four cases. Patients received an intravenous injection of 207 ± 40 MBq of ^{111}In-pentetreotide. The scintigraphic procedure included 4-hr and 24-hr planar anterior and posterior images (matrix size 128 × 128) of the chest, upper and lower abdomen and anterior views of the head and proximal lower legs. At least 500 kc were recorded over the chest and abdomen and 50 to 200 kc were obtained for the head and neck and lower leg views. SPECT of the

abdomen was performed 24 hr after injection. Sixty-four 40-sec views (matrix size: 64 × 64) were acquired through a 360° arc. Planar and SPECT images were acquired using a large field of view gamma camera equipped with a medium-energy, general-purpose collimator. In order to reduce bowel activity, laxatives (bisacodyl 7.5 mg) were given 8 hr postinjection. In four patients, laxatives were repeated at 24 hr and additional abdominal views were acquired at 48 hr. The scintigraphic images were reviewed by two observers blinded to the results of other imaging procedures. The sites of abnormal uptake were described with reference to an anatomical area, such as the liver, extrahepatic abdomen, mediastinum, lungs, bones and peripheral nodes. When multiple hot spots were seen in one anatomical area, they were considered as a single lesion. Unless stated, the results of somatostatin receptor imaging (SRI) include the findings obtained from 4-hr and 24-hr planar and SPECT acquisitions.

Safety Evaluation

Blood pressure, heart and respiratory rates were recorded before the test, and 5 and 30 min after the injection of ^{111}In-pentetreotide. The patients were monitored for adverse reactions during the initial 30-min period and were further asked to report any adverse reaction that might have occurred at the end of the test. Blood and urine samples were collected before and 24-hr after injection to evaluate potential changes in hematological and biochemical parameters: hemogram, electrolytes, urea, creatinine, uric acid, bilirubin, liver enzymes, microscopic urine analysis and proteinuria.

Efficacy Evaluation

The scintigraphic results were compared with those previously obtained by conventional imaging modalities, including conventional x-rays, contrast-enhanced CT (performed in all patients), US, MRI and, in a limited number of cases, angiography and endoscopic US of the pancreas. The mean interval between CT and scintigraphy was 7.8 ± 13.5 days (median: 3 days). Each patient was classified either SRI-positive when at least one lesion was seen during scintigraphy, or SRI-negative when no lesion could be detected during scintigraphy. The tumor localizations detected by conventional imaging modalities (CIM) prior to SRI were used as reference. When discordant results were observed between the tumor sites shown by CIM obtained prior to SRI and by scintigraphy, the real significance of these lesions was further evaluated using all information available at the end of the study, including CIM, histology and surgical data obtained during the follow-up period. Finally, available histologic results, for 27 lesions (in 21 patients) at the time of SRI was used as a gold standard to compare the sensitivity of CIM and SRI.

Evaluation of Impact on Patient Management

On the basis of the data available prior to SRI, double analysis was performed using independent criteria. First, the patients were considered as potential candidates for surgery when at least one lesion had been detected by CIM. Second, they were considered as potential candidates for octreotide treatment when they were not under octreotide therapy at the time SRI was performed. At the end of the follow-up period, the impact of ^{111}In-pentetreotide on patient management was assessed by reviewing the therapeutic decision made by the referring clinician on the basis of SRI results and classified as follows: no influence, octreotide discontinued, started or dosage changed, surgery planned, performed or rejected.

Statistical Analysis

All results were expressed as mean ± standard deviation unless otherwise stated. The difference between the safety data collected prior to and after ^{111}In-pentetreotide injection was evaluated by paired Student's t-test. The sensitivity of SRI and CIM were compared using the McNemar test for paired data. Probability values lower than 0.05 were considered significant.

RESULTS

Safety

Following administration of ^{111}In-pentetreotide, vital signs remained unchanged and no side effects were observed. Compared with the initial values, minor biochemical changes were found 24 hr after tracer injection: hemoglobin from 2.08 ± 0.32 mM (baseline) to 2.04 ± 0.31 mM (24 hr; p < 0.01), calcium from 2.44 ± 0.18 mM to 2.40 ± 0.19 mM (p < 0.01), alkaline phosphatase from 87 ± 76 IU/liter to 82 ± 65 IU/liter (p < 0.05) and gamma-glutamyl-transpeptidase from 78 ± 91 IU/liter to 74 ± 82 IU/liter (p < 0.05).

Efficacy

Patients. Tumor sites were detected by conventional imaging methods in 31 of the 38 patients with proven GEP endocrine tumors. Of these 31 CIM-positive patients, 30 were positive on scintigraphy. Among these, one was positive only on 24-hr planar images and two only on the SPECT images. One pancreatic insulinoma detected by US and subsequently proven by surgery showed no abnormal tracer uptake (Table 1). Three of the seven CIM-negative patients were positive on SRI. One of these patients increased plasma gastrin following cephalic pancreatectomy for gastrinoma and SRI demonstrated recurrence in the pancreatic bed and liver metastases that were later confirmed by CT.

The second patient (Fig. 1) presented with recurrent carcinoid syndrome 11 yr after resection of a carcinoid tumor of the terminal ileum and 6 yr after splenopancreatectomy for pancreatic recurrence. SRI disclosed abnormal uptake in the pancreatic bed and in the liver while concomitant CIM was negative. CT and MRI repeated within 6 mo following SRI confirmed the presence of liver metastases.

In the third patient, studied 3 yr after resection of an ileal carcinoid tumor, SRI showed hot spots over the lower abdominal area histologically proven to be peritoneal implants (Fig. 2). CIM and SRI were concordantly negative in four patients: one with a carcinoid syndrome, one with recurrent ectopic secretion of adrenocorticotropic hormone (ACTH) after removal of a lung carcinoid tumor, one with recurrent hypergastrinemia after resection of a gastrinoma and one MEN-I patient with increased pancreatic polypeptide levels.

Lesions. Fifty-four tumor sites were visualized with conventional imaging methods performed prior to the scintigraphy (Table 2). Of these 54 CIM localizations, 50 were also found with SRI: 41 were detected on the 4-hr images and confirmed at 24-hr, two were detected by 24-hr planar imaging and seven using only SPECT. The four SRI-neg-

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TABLE 1
Results of SRI and CIM in 38 Patients with Proven GEP Endocrine Tumor

Tumor type	No. of Patients	CIM	SRI
Carcinoid	19	15 (79%)	17 (89%)
Gastrinoma	10	8 (80%)	9 (90%)
Nonfunctioning ICC	5	5 (100%)	5 (100%)
Insulinoma	2	2 (100%)	1 (50%)
MEN-I	2	1 (50%)	1 (50%)
Total	38	31 (82%)	33 (87%)

*Percentage of positive patients.
ICC = islet-cell carcinoma; MEN-I = multiple endocrine neoplasia type.

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ative lesions were observed in four different patients. Three of these patients underwent surgery: one pancreatic insulinoma detected by US was confirmed, one splenic lesion suspected by CT was not confirmed by surgical palpation and one hepatic lesion suspected on CT was found to correspond to nonspecific inflammatory tissue at histology. Taking into account these surgical findings, SRI was positive in 96% of the lesions detected with CIM. The detection rate of 4-hr planar imaging and 24-hr imaging, excluding SPECT, was 79% and 83%, respectively. In addition, SRI revealed 29 unsuspected lesions mainly localized outside the liver (Table 2). Six of these lesions were detected on 24-hr images only and one by SPECT only. Six localizations were further confirmed by histology, 14 were corroborated by additional imaging procedures performed during the follow-up period, and nine lesions remained unconfirmed. Considering only the true-positive lesions of CIM and SRI, the scintigraphy disclosed significantly more tumor sites than CIM (p < 0.001). Of the 27 lesions proven by histology, 18 were detected by CIM and 25 by SRI, indicating a higher sensitivity of SRI (93%) compared to CIM (67%; p < 0.05).

Impact on Patient Management. On the basis of their clinical status prior to scintigraphy, 16 patients with a single known lesion (n = 9) or without a known lesion (n = 7) were considered as potential candidates for curative surgery (Table 3). Two of these patients with a single lesion and three with no known lesion were found to have multiple tumor sites at scintigraphy and were no longer considered for curative surgery. Conversely, one patient with an islet cell carcinoma was initially excluded from surgery on basis of CIM findings highly suggestive of liver metastases. However, SRI showed a single pancreatic lesion without tumoral spread and the patient underwent a surgical exploration with biopsies that revealed no liver involvement and thereby authorized cephalic pancreatectomy. Thus, SRI modified patient selection for surgery in six cases and had no influence in five cases (no tumor localized). In addition, in six patients with a single suspected lesion, SRI showed no additional tumor site and confirmed the feasibility of
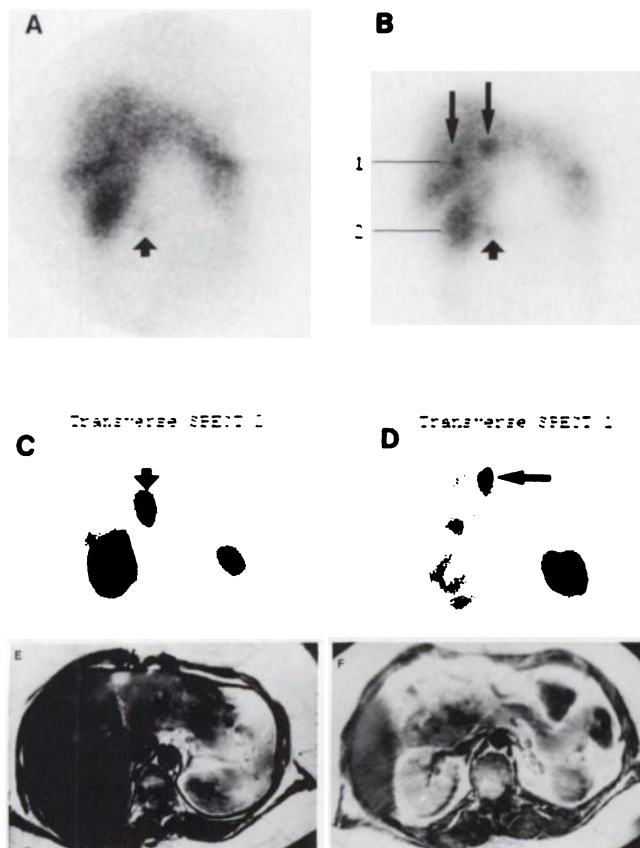
FIGURE 1. Indium-111-pentetreotide scintigraphy in a patient with recurrent carcinoid disease 10 yr after resection of a primary ileal carcinoid and 6 yr after a splenopancreatectomy for recurrent disease. Conventional imaging studies performed prior to scintigraphy showed no tumor site. An area of increased uptake is visualized along the right kidney (↑) on 4-hr (A) and 2-hr (B) planar abdominal views. Two hepatic hot spots (↑) are also seen on the 24-hr planar image. Transverse SPECT slices obtained at 24 hr localized the extra-hepatic spot over the pancreatic area (C, ↑) and confirms the presence of liver metastases (D, ↑). MRI performed during the follow-up period confirms the existence of liver metastases (E, ↑). Although the area of the pancreatic head appears heterogeneous, no tumor is clearly identified (F, ↑).

FIGURE 2. Indium-111-pentetreotide scintigraphy in a patient with elevated urinary excretion of 5-HIAA 3 yr after resection of a primary ileal carcinoid. Conventional imaging techniques showed no recurrent lesions. The anterior views of the lower abdomen obtained 4 hr (A), 24 hr (B) and 48 hr (C) after injection show abnormal accumulation of radioactivity above the bladder (↑). Notice the progressive decrease of bladder activity (↑), resulting in better visualization of these abdominal lesions subsequently found to correspond to peritoneal carcinoid implants.

curative surgery. Surgery was performed in four patients. Two asymptomatic patients refused surgery (Table 3, Patients 9 and 10) and one patient with a severe liver dysfunction was rejected by the surgeon and subsequently treated with octreotide (Patient 13). One 80-yr-old patient with an insulinoma (Patient 12) was submitted for therapeutic challenge with octreotide that dramatically decreased insulin production and improved her symptoms. Thus, chronic octreotide treatment was preferred to surgical resection.

The 23 patients not treated with octreotide before the study included 11 patients with known metastatic disease, 4 without any demonstrated lesion and 8 with a single lesion potentially curable by surgery. Twenty of these patients had positive somatostatin receptor scintigraphy and were therefore susceptible to benefit from octreotide therapy (Table 4). Following these scintigraphic findings, oc-
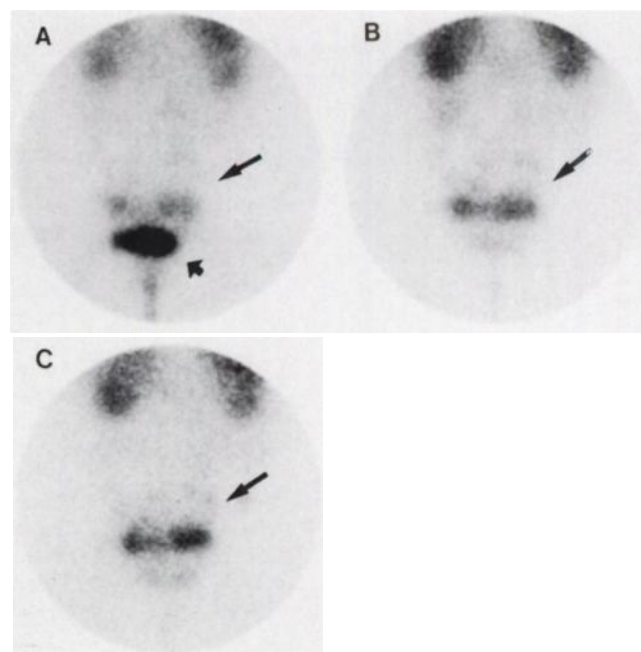
treotide treatment was effectively started in 13 patients and was proposed but refused by two patients. In five cases, the clinician did not consider octreotide therapy: three patients were treated by surgery (palliative in one case) and two by chemoembolization of liver metastases. In addition, in patients responding poorly to standard-dose octreotide treatment, the evidence of an intense tumor uptake led to

TABLE 2
Distribution of the Lesions Detected by CIM and SRI According to the Anatomical Site

	Number of sites		
Anatomical site	CIM+ and SRI+	CIM+ and SRI−	CIM− and SRI+
Liver	19	2 (1)*	2 (2)†
Abdomen (extra-hepatic)	25	2 (1)	13 (11)
Mediastinum	—	—	7 (3)
Lungs	1	—	2 (1)
Bones	2	—	2 (0)
Peripheral nodes	3	—	3 (3)
Total	50	4 (2)	29 (20)

*Numbers in parentheses are CIM lesions further confirmed as false-positive.

†Numbers in parentheses are SRI lesions further confirmed as true-positive.

TABLE 3
Impact of SRI on the Surgical Decision in 16 Patients with No Lesion or a Single Lesion Detected by CIM Prior to SRI

Patient no.	Primary	CIM Lesions	SRI Lesions	SRI Impact on surgery	Therapeutic decision
1	Gastrinoma (R)	No lesion	Pancreas, liver	Surgery rejected	Octreotide increased
2	Gastrinoma (R)	No lesion	No lesion	—	No treatment
3	MEN-I	No lesion	No lesion	—	No treatment
4	Carcinoid (R)	No lesion	No lesion	—	Octreotide discontinued
5	Carcinoid (R)	No lesion	Pancreas, liver	Surgery rejected	Octreotide started
6	Carcinoid (R)	No lesion	Peritoneum	Surgery rejected	Octreotide started
7	Carcinoid	No lesion	No lesion	—	No treatment
8	Insulinoma	Pancreas	No lesion	—	Surgery
9	Carcinoid (R)	Mesenteric node	Mesenteric node	Surgery confirmed	Surgery
10	MEN-I	Pancreas	Pancreas	Surgery confirmed	Surgery
11	Gastrinoma	Pancreas	Pancreas, mesentery, stomach	Surgery rejected	Octreotide
12	Insulinoma	Pancreas	Pancreas	Surgery confirmed	Octreotide started*
13	Nonfunctioning ICC	Pancreas	Pancreas	Surgery confirmed	Octreotide started*
14	Nonfunctioning ICC	Duodenum	Duodenum	Surgery confirmed	Surgery
15	Carcinoid	Ileum	Ileum	Surgery confirmed	Surgery
16	Carcinoid (R)	Liver	Liver, mesentery	Surgery rejected	Octreotide started

*Contra-indication for surgery due to poor medical condition.
ICC = islet-cell carcinoma; MEN-I = multiple endocrine neoplasia, type I; R = primary tumor resected at the time of SRI.

increase the dosage of the drug in four cases whereas the absence of tumor uptake led to the withdrawal of the drug in one case.

Thus, considering the impact of SRI on octreotide and surgical treatment, the information provided by the scintigraphy guided the therapeutic decision in 20 of 38 patients (53%).

DISCUSSION

The principal findings of this study are that somatostatin receptor scintigraphy using ^{111}In-pentetreotide is a safe and effective method for the evaluation of patients with endocrine GEP tumors and that the scintigraphic information can influence patient management.

TABLE 4
Clinical Impact of SRI on Octreotide Therapy

Treatment prior to SRI	Number	Lesion status	Number	Therapeutic decision	Number
No octreotide	23	SRI+	20	Octreotide	15*
				Surgery	3
				Liver chemoembolization	2
		SRI−	3	Surgery	1
				No treatment	2
Octreotide	15	SRI+	13	Octreotide continued	9
				Octreotide increased	4
		SRI−	2	Octreotide continued	1
				Octreotide discontinued	1

*Includes two asymptomatic patients who refused octreotide therapy.

Injection of ^{111}In-pentetreotide did not expose the patients to adverse reactions and the minor biochemical changes observed 24 hr after injection were without clinical relevance. In a limited number of patients, the interruption of octreotide therapy during the test reinduced clinical symptoms, i.e., cutaneous flushing or diarrhea, related to the temporary absence of hormone secretion inhibitor. However, these symptoms were transient and rapidly controlled when octreotide therapy was resumed. The recommendation to withdraw somatostatin analogs before administration of the radiolabeled compound is based on the observation that the tumor somatostatin binding sites are saturable. In a rat tumor model, pretreatment with 1 mg of octreotide resulted in a significant reduction of ^{111}In-pentetreotide uptake by the tumor and prevented clear imaging of the lesion (20). The need to discontinue octreotide therapy is questionable since it has been shown that continuous treatment with octreotide during scintigraphy in patients with neuroendocrine tumors might enhance tracer accumulation in carcinoid tumors, whereas physiological uptake was reduced (22).

SRI was positive in 33 of 38 patients, indicating an overall detection rate of 87% which was slightly higher than that obtained with a combination of conventional imaging methods (82%). With the exception of one insulinoma, all CIM-positive patients showed positive scintigraphic results. Conversely, in three patients without known lesions, SRI disclosed metastatic disease that was further confirmed by histology or by CIM performed during follow-up.

The sensitivity of SRI found in the present study is comparable to the 82%–92% of sensitivity reported by other investigators using ^{111}In-pentetreotide (17,23–26).

The high rate of positivity obtained with in vivo SRI is not surprising since high-affinity somatostatin binding sites have been found in vitro on most GEP endocrine tumors (14,27,28). The majority of these tumors contain high numbers of receptors homogeneously distributed throughout the tumor and expressed on both the primary and the metastatic sites (27). In a series of 62 carcinoid patients, Reubi et al. detected somatostatin receptors in 54 tumors examined in vitro (87%) (27). A similar detection rate was found in vivo in our group of carcinoid patients (89%). The two SRI-negative carcinoid patients who were also CIM-negative could belong to the group of atypical carcinoids. One of these negative patients presented cutaneous flushing with an increase in serotonin levels but normal urinary excretion of 5-HIAA. The second patient, who previously underwent surgical removal of a bronchial ACTH-producing carcinoid tumor, presented a recurrent Cushing syndrome with increased ACTH levels. The patient did not improve with octreotide treatment, suggesting that the ectopic ACTH-secreting tumor was not bearing somatostatin receptors. The majority of bronchial carcinoids including some ACTH-producing tumors were reported somatostatin receptor negative on in vitro examination and are often less differentiated tumors (27,28).

Islet cell carcinomas are known to bear somatostatin receptors in 88%–100% of all cases, in contrast to exocrine human pancreatic adenocarcinomas that never are somatostatin receptor positive (17,27,29). In our series, the two nonendocrine pancreatic carcinomas were SRI-negative whereas 16 of the 17 patients with islet cell carcinoma were SRI-positive. It is noteworthy that the five nonfunctioning tumors were all SRI-positive. In this type of tumor, somatostatin imaging provides a unique noninvasive method to assess the somatostatin receptor status of the tumor since these patients cannot be evaluated using an acute in vivo octreotide test. The only SRI-negative islet cell carcinoma was an insulinoma with proven pancreatic tumor localization, which is in accordance with the lack of sensitivity obtained by other investigators in insulinomas (26,30). The low detection rate for insulinomas may be related to the presence on insulinoma cells of somatostatin receptors with a lower affinity for the radioligand used for in vivo imaging. Whereas most GEP endocrine tumors express a somatostatin receptor having a similar affinity for native somatostatin and octreotide, a high percentage of insulinomas have been found to express only receptors with high affinity for somatostatin-14 or somatostatin-28 (14,17). There is now good evidence that this receptor corresponds to the somatostatin receptor subtype III which has a lower affinity for octreotide (26,31).

In two patients with Zollinger-Ellison syndrome, SRI showed gastric uptake that corresponded to diffuse gastric carcinoid tumors. The hyperplasia of enterochomaffin and enterochomaffin-like cells observed in these patients was a complication of chronic hypergastrinemia and should therefore be considered as a secondary tumor in patients with Zollinger- Ellison syndrome (32).

Indium-111-pentetreotide detected 96% of the tumor sites previously recognized by CIM. The rate of detection was independent of lesion localization since hepatic and extrahepatic sites were visualized with a similar sensitivity. Most of the previously published studies investigated the rate of positivity of ^{111}In-pentetreotide scintigraphy but did not prospectively compare the sensitivity of the method in tumor localization with the results obtained by conventional localization procedures. In a retrospective study of 24 GEP endocrine patients with 45 lesions, King et al. found 9 CT-positive lesions that were missed by scintigraphy and concluded CT to be more sensitive (93%) than scintigraphy (73%) (30). In a review of 52 carcinoid patients, Kwekkeboom et al. reported a 50% detection rate with SRI in patients with known liver metastases (25). These results were obtained with either ^{111}In-pentetreotide or ^{123}I-Tyr3-octreotide. The latter compound has a preferential hepatobiliary excretion that may hamper the interpretation of planar and SPECT abdominal images. Also, the lower success rate reported by these groups, particularly for hepatic localizations, could be related to the fact that abdominal SPECT was not systematically performed. In our study, SPECT demonstrated the presence of eight additional lesions that were not visible on planar views due to the superimposition of activity from normal organs.

Somatostatin receptor imaging revealed 29 previously unrecognized abdominal and extra-abdominal localizations 15 patients. Twenty of these 29 SRI additional sites were subsequently confirmed, whereas nine were not further explored since they were found in patients with proven metastatic lesions that were all somatostatin receptor positive. Multiple lesions were detected by SRI in 5 of 16 patients suspected of having one tumor localization. The information provided by SRI for these patients was clinically relevant since surgical outcome strongly depends on disease extent.

Comparing the overall results obtained with CIM and scintigraphy in the detection of the 72 proven tumor sites, SRI was significantly more sensitive (97%) than conventional localization techniques (70%). A major advantage of scintigraphy is that this high success rate was achieved using a single whole-body procedure, whereas assessment by conventional methods necessitated a minimum of two to three different imaging procedures (80 CIM versus 38 SRI). This represents a significant advantage in terms of working days lost and patient discomfort.

More tumor sites were observed at 24 hr than at 4 hr due to enhanced contrast (26), especially over the liver and outside the abdomen. In our experience, however, the combination of 4-hr and 24-hr images appeared to be a satisfactory protocol. Indeed, despite the systematic use of laxatives, some bowel activity was observed at 24 hr, especially in the colon. Therefore, the interpretation of 24-hr images was facilitated by comparison with the 4-hr images on which intestinal activity was seldom visualized.

The treatment of carcinoids and islet cell carcinomas requires careful evaluation of each patient and the thera-

peutic approach should be appropriate to the clinical situation. The ideal therapy to prevent tumor progression and to suppress hormone hypersecretion is complete surgical excision of tumoral tissue (1-6). Therefore, preoperative imaging studies have become increasingly important to establish tumor localization and extent. Although methods such as US, CT or MRI provide valuable information, as the success rate of these methods seldom exceeds 70% (3,4,33-35), more invasive techniques such as selective angiography, percutaneous transhepatic venous sampling and selective intra-arterial secretin or calcium injection tests may further increase tumor detection rates (13,33,36-39).

More recently, endoscopic ultrasonography has been reported to be the most sensitive imaging method, detecting 80% of islet cell carcinomas not detected by CT or US (40). Despite the increasing success of these imaging techniques, tumor detection remains difficult, particularly when localized outside the pancreas and the liver regions. Therefore, a preoperative imaging test that would accurately localize the tumor and its potential metastases in the whole body would assist the clinician in selecting those patients who could benefit from surgery.

In patients with metastatic disease, palliative treatments have been proposed, including surgical tumor debulking, hepatic artery embolization, chemotherapy, interferon, as well as a more conventional medical regimen to control the endocrine syndrome (6-9,41). Octreotide has been successfully used to control the carcinoid syndrome and the symptoms related to excessive hormone release in islet cell carcinomas (10-12). Besides a beneficial effect on symptoms, there is some evidence that octreotide may also play an antiproliferative role (42-45). In carcinoids, octreotide was shown to prolong patient survival and to induce tumor regression in 17% of the patients (6,10). Recently, a multicenter trial investigated the antiproliferative effect of long-term octreotide treatment in 96 patients with GEP endocrine tumors (46). Even though no significant tumor shrinkage was observed, octreotide prevented tumor growth in 40% of the patients with previously progressive disease.

In light of these therapeutic considerations, somatostatin receptor scintigraphy may have potential implications in patient management. In our series, surgery had been rejected in five cases following scintigraphic evidence of metastatic disease. In addition, in a patient with suspected metastatic disease, surgical exploration was performed based on scintigraphic findings of localized disease. Due to its high sensitivity, SRI could be proposed as a first-line method in patients with laboratory data consistent with secreting GEP neuroendocrine disease. When SRI shows a single lesion, further evaluation is required to obtain more precise information on the regional extension in view of curative surgery. Conversely, when SRI shows multiple lesions, thereby ruling out potential curative surgery, there is no need for further accurate localization procedures. Apart from its use for tumor localization and staging, the

method may also provide valuable information regarding tumor receptor status and help in the selection of patients likely to benefit from octreotide therapy.

In our series, scintigraphic findings led to a change in medical treatment, including initiation of therapy with octreotide in 13 patients, an increase in dose in four and withdrawal of the drug in one. There is some evidence that only well differentiated carcinoids retain the ability to express somatostatin receptors. A negative somatostatin receptor scan could therefore be suggestive of poorly differentiated or even anaplastic carcinoids which are known to respond to combined chemotherapy using etoposide and cisplatin (27,47). The cost-benefit implications of SRI have not been directly addressed in this study. It is clear, however, that by reducing the number of diagnostic procedures needed and by guiding the choice of the most appropriate therapy, SRI may have a significant impact on financial and social costs, including patient discomfort, morbidity and hospital stay.

In summary, ^{111}In-pentetreotide scintigraphy appeared to be a safe, sensitive in vivo procedure for imaging GEP neuroendocrine tumors. Due to its high sensitivity, the method can be proposed for tumor detection and staging. Future therapeutic implications for SRI could be quantification of somatostatin receptor density subtypes susceptible of binding radiolabeled somatostatin analogs to predict the potential benefit of metabolic radiotherapy using a radiolabeled somatostatin analog.

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