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Preoperative Localization of Gastrointestinal Endocrine Tumors Using Somatostatin-Receptor Scintigraphy

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Objective

The purpose of this study was to determine the value of somatostatin-receptor scintigraphy (SRS) in the preoperative localization of gastrointestinal endocrine tumors. The authors report their preliminary experiences with this new technique as compared to conventional imaging studies like computed tomography (CT) and ultrasonography (US).

Summary Background Data

Most endocrine tumors possess high-affinity somatostatin-receptors. Using the stable, ^{111}Indium labelled somatostatin analogue pentatreotid, which binds to these receptors, it is possible to detect somatostatin-receptor–positive tumors scintigraphically.

Methods

In nine patients with various gastrointestinal endocrine tumors, SRS, CT, and US were performed before surgical exploration. The preoperative imaging studies and intraoperative ultrasound (IOUS) were then compared to findings on surgical exploration.

Results

Twelve primary tumors were found in 8 patients at surgical exploration. These primary tumors were correctly identified with SRS in five patients, with US in four patients, and with CT in three patients. In one patient with the Zollinger-Ellison syndrome, scintigraphy suggested a tumor in the area of the hepatoduodenal ligament, while CT and US had negative results. The underlying gastrinoma could not be identified despite extensive surgical exploration. Scintigraphy, CT, and US showed comparable results in the detection of metastases in four patients.

Conclusions

The data from this small series suggest that SRS is helpful in the preoperative localization of gastrointestinal endocrine tumors.

Table 1. ENDOCRINE GASTROINTESTINAL TUMORS: DIAGNOSIS AND THERAPY

Patient No.	Age (yr)	Sex	Diagnosis (Based on Preoperative and Intraoperative Findings)	Surgical Therapy
1	49	M	2 metastases of a functionally inactive endocrine pancreatic tumor removed 5 years ago	Extirpation of the 2 metastases located at the right colonic flexure and at the minor curvature of the stomach
2	50	F	ZES with a solitary gastrinoma in the pancreatic head (tumor diameter, 14 mm)	Enucleation of the tumor
3	77	M	Carcinoid tumor of the terminal ileum with incomplete small bowel obstruction and multiple liver metastases	Ileocoecal resection
4	55	M	Functionally inactive carcinoid tumor in the upper paraduodenal position with 2 local metastases (tumor diameters, 7–12 mm)	Extirpation of the 3 tumors
5	42	F	Carcinoid tumor of the ascending colon with local metastases and multiple small liver metastases	Right hemicolectomy
6	51	M	ZES, tumor not found after extensive surgical exploration including IOUS, pancreatic exploration, duodenal transillumination, and duodenotomy	Extensive surgical exploration without identification of the tumor
7	42	M	ZES with a solitary duodenal wall gastrinoma (tumor diameter, 3 mm)	Extirpation of the tumor that was localized by duodenal transillumination
8	39	F	Insulinoma in the pancreatic head (tumor diameter, 13 mm)	Enucleation of the tumor
9	34	M	MEN I syndrome with 5 functionally inactive pancreatic tumors (1 pancreatic head, 4 body of the pancreas; diameters, 2–15 mm)	Enucleation of a solitary tumor from the pancreatic head, resection of the pancreatic body

ZES: Zollinger-Ellison syndrome; IOUS: intraoperative ultrasound; MEN I: multiple endocrine neoplasia, type I.

Regarding localization, biologic behavior, clinical presentation, and prognosis, gastrointestinal endocrine tumors are a heterogeneous group. A common characteristic, compared to other gastrointestinal neoplasias, is the difficulty in localizing endocrine tumors preoperatively. This is true for insulinomas, the tumors most often encountered. They can be visualized preoperatively in only 40% to 70% of patients.[1] Fortunately, experienced surgeons will identify insulinomas at surgical exploration in more than 95% of all cases, especially if intraoperative ultrasonography (IOUS) is used.[2] Thus, preoperative imaging procedures may be of little use once the diagnosis is established. Other common endocrine tumors (such as gastrinomas and carcinoids) are often small, multiple, and may not be confined to the boundaries of parenchymal organs. This reduces the value of conventional imaging techniques, such as computed tomography (CT) or ultrasonography (US), as well as more invasive techniques such as angiography or selective blood sampling. Gastrinomas can be identified preoperatively with US in 20% to 30% of cases, with CT in 20% of cases, with magnetic resonance tomography in 20% of cases, and with selective angiography in 20% to 70% of cases.[3–5] Slightly better results have been reported for the preoperative localization of intestinal carcinoids.[6]

Especially for tumors that are often malignant (*e.g.*, gastrinomas or carcinoids), or multiple (*e.g.*, multiple endocrine neoplasia type I syndrome [MEN I]), or of small size and growing outside parenchymal organs (*e.g.*, gastrinomas), accurate preoperative localization would be desirable for the planning of appropriate surgical therapy.

The new method of somatostatin-receptor scintigraphy (SRS) may be a helpful tool to increase the yield of successful preoperative localization of gastrointestinal endocrine tumors.

Somatostatin is known to inhibit a variety of secretory processes within the hypothalamus, pancreas, and gastrointestinal tract.[7,8] It binds to specific, high-affinity receptors on target cells within the central nervous system, hypothalamus, adrenals, pancreas, and gastrointestinal tract.[9] A high density of somatostatin-receptors is expressed on many endocrine tumors. Furthermore, somatostatin-receptors have been reported in meningiomas, small cell lung cancer, and cancer of the prostate and breast.[10–13]

The pharmacologic application of native somatostatin, due to its short biological half-life, is limited. With the development of long-acting somatostatin analogues, somatostatin is now used to treat symptoms of endocrine tumors and to prevent pancreatic fistula after pancreatic

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Table 2. RESULTS OF DIFFERENT METHODS IN THE PREOPERATIVE AND INTRAOPERATIVE LOCALIZATION OF ENDOCRINE GASTROINTESTINAL TUMORS

Patient No.	Diagnosis	Localization of Primary Tumor					Localization of Metastases				
		SRS	CT	US	IOUS	Surgical Exploration	SRS	CT	US	IOUS	Surgical Exploration
1	2 metastases of a functionally inactive endocrine pancreatic tumor						+	(+)	(+)	ND	+
2	Solitary pancreatic gastrinoma	+	–	–	+	+					
3	Carcinoid tumor in terminal ileum with liver metastases	+	+	+	ND	+	+	+	+	+	+
4	Paraduodenal carcinoid tumor with 2 local metastases	+	+	+	ND	+	+	+	+	ND	+
5	Carcinoid tumor in ascending colon with small liver metastases and local metastases	+	+	+	ND	+	(+)	+	(+)	ND	+
6	ZES, gastrinoma not identified at surgical exploration	–	–	–	–	–					
7	Gastrinoma in duodenal wall	–	–	–	–	+					
8	Insulinoma	–	–	+	+	+					
9	MEN I, 5 functionally inactive tumors	+	(+)	(+)	(+)	+					

–: tumor not localized; (+): some, but not all tumors localized; +: all tumors localized; ND: procedure not done; SRS: somatostatin scintigraphy; CT: computed tomography; US: percutaneous ultrasound; IOUS: intraoperative ultrasound; ZES: Zollinger-Ellison syndrome; MEN I: multiple endocrine neoplasia, type I.

surgery.[14,15] It may also have an antiproliferative effect on certain tumors.[16–18] Somatostatin analogues are known to bind to somatostatin-receptors in a great number of endocrine tumors. Therefore, these analogues were labelled radioactively and then applied intravenously; scintigraphy was used to detect their distribution.[19] With this technique, somatostatin-receptor–positive tumors were reliably identified in animal experiments.[20] Further investigations in humans showed that somatostatin-receptor–positive primary tumors and metastases from carcinoids, endocrine pancreatic tumors, paragangliomas, meningiomas, pituitary adenomas, neuroblastomas, and medullary thyroid carcinomas could be regularly identified with SRS.[21]

We have used SRS for clinical evaluation since 1991. In nine patients with proven gastrointestinal endocrine tumors, SRS was applied preoperatively in addition to conventional imaging procedures. We report our preliminary experiences with this new technique in the preoperative localization of gastrointestinal endocrine tumors.

PATIENTS AND METHODS

In 1991, at the University Hospital Marburg, 51 patients with various endocrine tumors underwent SRS during a prospective clinical trial. This trial was approved by the hospital's ethics committee. In 42 patients SRS was performed during regular follow-up after previous surgical or medical treatment. If these patients had metastatic disease or evidence of tumor recurrence and were not considered to be candidates for surgery, they were entered into a trial of somatostatin treatment. This trial was conducted to evaluate a long-acting somatostatin analogue (Sandostatin, Sandoz, Nürnberg, Germany) in the treatment of various endocrine tumors.[18] However, in nine patients the diagnosis of gastrointestinal endocrine tumors was established recently and the patients were candidates for surgery. SRS was used preoperatively for localization (Table 1). Besides SRS, all nine patients underwent CT of the abdomen plus preoperative and IOUS. We then compared the results of these four imaging procedures with our findings on surgical exploration. The imaging studies were considered to have positive results when these results could be confirmed at surgical exploration.

SRS

The somatostatin analogue pentatreotid (Octreo-scan, Mallinckrodt, Petten, The Netherlands) is labelled with ^{111}Indium. A dose of 122 to 244 milibecquerel of ^{111}In-pentatreotid (10 to 20 μg of pentatreotid) was given intravenously. Planar whole-body scans were done 4 hours and 21 to 24 hours after the injection using a gamma camera (Body-scan, Siemens, München, Germany). Detailed planar scans of the abdomen, thorax, and the head were done with an emission computed tomography (ECT) compatible gamma camera (Gammadiagnost,

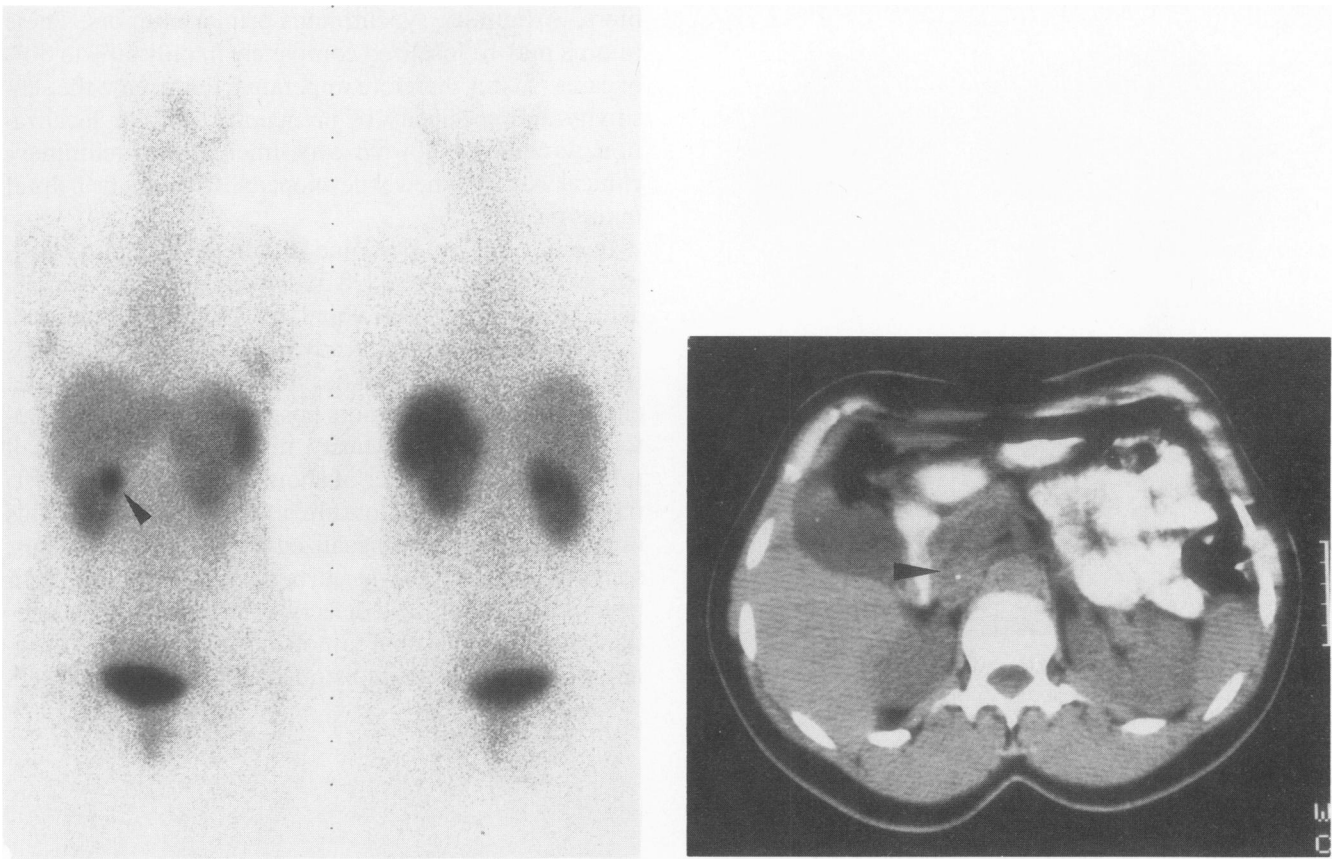

Figure 1. (Left) Whole-body SRS in a patient with the Zollinger-Ellison syndrome (patient 2). Left ventral view, right dorsal view. Nonspecific enhancement to the liver, spleen, kidneys, and bladder. The gastrinoma (diameter, 14 mm) localized within the pancreatic head is shown at the left, near the upper pole of the right kidney (arrowhead). (Right) Corresponding CT scan of the pancreatic head showing the area where the gastrinoma was found at surgery (arrowhead). No suspicious lesions in the area of the pancreatic head could be identified on CT scan.

Philips, Hamburg, Germany). For single photon emission computed tomography (SPECT) investigations of the abdomen, liver, and thorax, the gamma camera did a whole circle around the patient and delivered 64 scans. After filtration of the raw data (Metz-Filter Philips, Hamburg, Germany), the transverse, sagittal, and frontal sections were constructed. This allowed the spatial attachment of tumors so we could compare these results with CT and US.

RESULTS

In 8 patients (patients 2 through 9), 12 primary tumors were identified (Table 2 and Figs. 1, 2, and 3). SRS correctly localized the primary tumors in five patients . Tumors were identified by US in four patients and by CT scan in three patients. In one patient (patient 9) with the MEN I syndrome, five primary tumors in the pancreas were found. SRS identified one solitary tumor in the head of the pancreas. Four tumors in the body of the pancreas (diameter range, 2 to 15 mm) could not be discriminated separately with SRS, but rather showed a diffuse enhancement of this area in scintigraphy. One patient with the Zollinger-Ellison syndrome had an intense enhancement in the area of the duodenum and the hepatoduodenal ligament in SRS, while neither US nor CT showed a tumor. The patient later underwent surgery. But even after extensive surgical exploration, which after exploration of the pancreas routinely included duodenal transillumination, duodenotomy, and IOUS, the underlying gastrinoma could not be identified. Thus, the result of SRS cannot be considered positive in this patient, although the enhancement seen at scintigraphy might be caused by a small gastrinoma that was not detected at surgery.

Metastases were present in four patients. In two patients the extent of metastatic tumor growth was established preoperatively with SRS, CT, and US. In one patient two extraparenchymal metastases were identified by SRS, while CT and US only identified one tumor

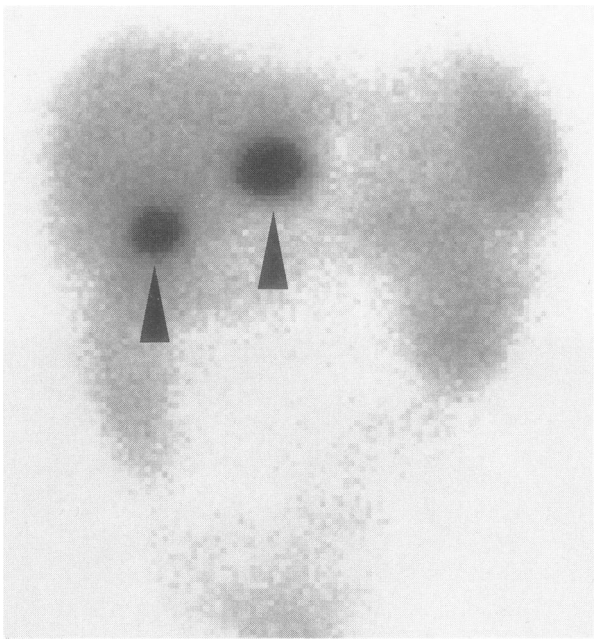

Figure 2. Abdominal SRS in a patient with two metastases of a functionally inactive endocrine pancreatic tumor (patient 1). Ventral view. Nonspecific enhancement to the liver, spleen, and kidneys. Enrichment of the radiopharmaceutical is seen in projection to the right colonic flexure and below the left lobe of the liver. This enhancement is due to two metastases localized in the mesentery of the right colonic flexure and behind the lesser curve of the stomach (arrowheads).

each. In one patient, small hepatic metastases of a carcinoid (diameter, < 1 cm) were only identified with CT and not with SRS or US.

SRS, CT, and US could be compared regarding their ability to localize gastrointestinal endocrine tumors, taking the results of surgical exploration as a reference in eight patients. False-negative results in the localization of primary tumors were obtained with SRS in two patients, with CT in four patients, and with US in three patients. Taking all three methods together, a false-negative result was obtained in only one patient (patient 7). Regarding the localization of metastases, the three methods were comparable.

DISCUSSION

Currently, no single imaging procedure successfully localizes gastrointestinal endocrine tumors preoperatively with a high enough sensitivity and specificity to render other imaging procedures unnecessary.[22,1] Only the use of the combined imaging procedures, followed by thorough surgical exploration, can lead to the identification of tumors in most patients.[23] These combined efforts provide for the identification of insulinomas in more than 95% of cases.[2] However, results are unsatisfactory with gastrinomas, other malignant endocrine tumors, or multiple synchronous primary tumors. These tumors may be localized completely in only 40% to 80% of cases.[23,1] It is therefore imperative to increase the sensitivity and specificity of preoperative tumor localization. As could be shown in experimental and preliminary clinical work, the newly developed SRS might be helpful in this regard.[21,24]

In our small group of nine patients, preoperative SRS was superior to CT and US in detecting primary tumors. The three methods were equal in detecting metastases.

SRS has some obvious advantages. The technique is simple, noninvasive, and has no potentially serious side effects. If endocrine tumors possess somatostatin-receptors in a high enough density, it can localize even small tumors up to a diameter of about 1 cm.[21] Due to a first-pass effect of the somatostatin analogue in the liver, this organ can regularly be visualized scintigraphically. Thus, somatostatin-receptor–negative tumors in the liver can be visualized as storage defects. Using whole-body scintigraphy, extraintestinal tumors or metastases of intestinal tumors can be demonstrated. CT scanning and US

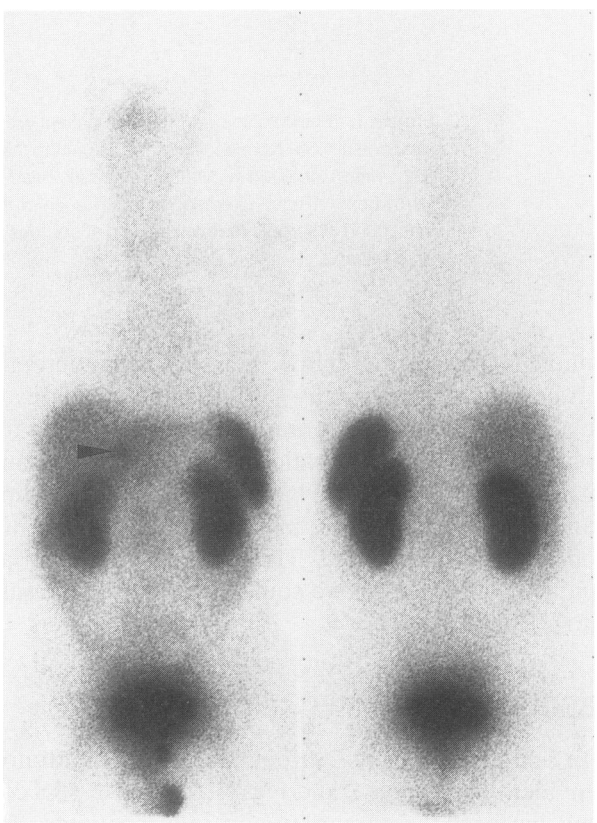

Figure 3. Whole-body SRS in a patient with the Zollinger-Ellison syndrome (patient 6). Left ventral view, right dorsal view. Nonspecific enhancement to the liver, spleen, kidneys, and bladder. ^{111}In-pentatreotid enrichment in the area of the hepatoduodenal ligament (arrowhead). Despite extensive surgical exploration, no gastrinoma could be identified in this area.

are of limited value in localizing lesions in the area of tissue borders, isodense lesions within parenchymal organs, or recurrent tumors in the scarred tissue after surgery. In contrast, these technical limits do not apply to SRS.

However, SRS has some disadvantages. It may not be able to regularly detect tumors with a diameter smaller than 1 cm.[21,24] To identify a tumor outside the liver, the tumor has to be somatostatin-receptor positive. Unfortunately, between 10% (carcinoids) and 40% (insulinomas) of gastrointestinal endocrine tumors are somatostatin-receptor–negative and thus may not be identified using scintigraphy.[10,13] Due to a first pass-effect in the liver, a physiologic enhancement in the spleen, and renal excretion, these organs show a high background activity in scintigraphy. It is not possible to accurately predict tumor size with scintigraphy because the size of the enhancement seen on scintigraphic scans primarily depends on the density of somatostatin receptors on the tumor cells.

Despite these obvious disadvantages, our preliminary results show that SRS is helpful in the preoperative localization of gastrointestinal endocrine tumors. In the past, excellent data for sensitivity or specificity of most new localization procedures in endocrine surgery published in preliminary studies could not be repeated after investigation of a larger number of patients. Therefore, we would like to comment on our results quite reluctantly. We suggest that SRS is unlikely to reach a sensitivity and specificity high enough to replace the conventional imaging procedures. Rather, the method will complement conventional procedures. Our results obtained with nine patients are too preliminary to recommend the use of SRS in certain tumors and discourage it in others. Whether SRS is superior to CT or US under certain conditions or in special tumors (*e.g.*, those that are most likely to express somatostatin receptors) needs to be further established in clinical studies.

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