Ability of Somatostatin Receptor Scintigraphy to Identify Patients with Gastric Carcinoids: A Prospective Study

Fathia Gibril, James C. Reynolds, Irina A. Lubensky, Praveen K. Roy, Paolo L. Peghini, John L. Doppman, and Robert T. Jensen

Digestive Diseases Branch, National Institute of Diabetes and Digestive Kidney Diseases; Nuclear Medicine and Diagnostic Radiology Departments, Warren Grant Magnuson Clinical Center; and Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Gastric carcinoids are of increasing clinical concern because they may develop in hypergastrinemic states, especially with the increased chronic use of potent acid suppressants that can cause hypergastrinemia. However, gastric carcinoids are difficult to diagnose. Somatostatin receptor scintigraphy (SRS) has a high sensitivity and specificity for localizing carcinoids in other locations. The purpose of this study was to determine whether SRS could localize gastric carcinoids. **Methods:** Two groups of patients with Zollinger-Ellison syndrome (ZES) with hypergastrinemia, each having a different increased risk of developing gastric carcinoids, were studied. One hundred sixty-two consecutive patients with ZES were studied prospectively, with 39 having multiple endocrine neoplasia, type 1 (MEN-1) (high increased risk), and 123 not having MEN-1 (low increased risk). Patients were admitted to the hospital initially and then yearly, undergoing SRS with SPECT, upper gastrointestinal endoscopy, and Jumbo Cup biopsies of any gastric abnormalities, as well as random biopsies of the gastric body. Tumor localization studies were also performed. Both the results of the routine SRS interpretation and the results of a masked review, with particular attention to the stomach of high risk MEN-1 patients, were correlated with the gastric biopsy results. **Results:** Gastric SRS localization was positive in 19 (12%) of 162 patients. Sixteen patients had a gastric carcinoid, and 12 of these patients had SRS localization. The sensitivity of SRS in localizing a gastric carcinoid was 75%, with a specificity of 95%. Positive and negative predictive values were 63% and 97%, respectively. **Conclusion:** SRS is a noninvasive method that can identify patients with gastric carcinoids with a reasonable sensitivity and a high specificity. SRS should prove useful in the treatment of patients with hypergastrinemic states that have an increased incidence of gastric carcinoids. In patients with MEN-1, one must realize that localization in the upper abdomen on SRS may be caused by a gastric carcinoid and not a pancreatic endocrine tumor.

Key Words: somatostatin receptor scintigraphy; Zollinger-Ellison syndrome; carcinoid; gastric carcinoid; neuroendocrine tumor

J Nucl Med 2000; 41:1646–1656

Received Sep. 13, 1999; revision accepted Mar. 2, 2000.

For correspondence or reprints contact: Robert T. Jensen, MD, NIH/NIDDK/DDB, Bldg. 10, Rm. 9C-103, 10 Center Dr., MSC 1804, Bethesda, MD 20892-1804.

Gastric carcinoids are of increasing clinical importance. Whereas in older studies gastric carcinoids composed only 2%–3.8% of all carcinoids (*1*,*2*), more recently investigators have suggested that the incidence may be significantly higher—11%–30% of all carcinoids (*3*,*4*). In addition to the increased frequency of gastric carcinoids, they are receiving more attention because of a recognition that they occur not only sporadically (type III) but with increased frequency in chronic hypergastrinemic states (atrophic gastritis, type I; and Zollinger-Ellison syndrome [ZES], type II) (*5*,*6*). Recognition of gastric carcinoids is important because each type can, on occasion, become malignant and metastasize to lymph nodes or the liver (type I, 5%; type II, 30%; and type III, 71%) (*5*,*6*). Furthermore, gastric carcinoids can produce the carcinoid syndrome, and they are likely to receive even more attention because of the recent increased long-term use of proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) for the treatment of moderate to severe gastroesophageal reflux disease (*7*). Studies have shown that hypergastrinemia develops in 80%–100% of patients with reflux disease (*8*,*9*), and long-term studies of animals have shown that hypergastrinemia can result in gastric carcinoids, some of which are malignant (*10*). No increased rate of gastric carcinoids has been shown in humans treated chronically with proton pump inhibitors; however, the potential for gastric carcinoids certainly exists with longer treatment than that used in the animal studies.

Because of the increased clinical importance of gastric carcinoids and the difficulty in diagnosing them, the need for noninvasive diagnostic methods is growing. Currently, the only reliable method is upper gastrointestinal endoscopy with biopsy. Some have suggested that serum chromogranin levels (*11*) and histamine breakdown products, such as *N*-methyl imidazole acetic acid (*12*), excreted in urine reflect a mass of enterochromaffin-like (ECL) cells, from which gastric carcinoids originate in patients with hypergastrinemic states. However, the clinical usefulness of these cells in diagnosing gastric carcinoids is unproven.

Gastric carcinoids, similar to other carcinoids, have a high

density of somatostatin receptors (*13–15*). With recent studies showing that [^{111}In-diethylenetriaminepentaacetic acid (DTPA),D-Phe^{1}]octreotide and somatostatin receptor scintigraphy (SRS) are highly sensitive and specific in localizing carcinoids in other locations (*13,14,16,17*), the possibility exists that SRS can be used to localize gastric carcinoids in patients with hypergastrinemic states. To assess this possibility, we prospectively studied the ability of SRS to identify gastric carcinoids in 2 groups of patients who had hypergastrinemia caused by a gastrinoma and who were at increased risk of gastric carcinoids (*18*). One group of patients had the sporadic form of ZES, which has an increased but relatively low risk (1%) of causing gastric carcinoids (*19,20*). The second group of patients had ZES as part of the multiple endocrine neoplasia, type 1 (MEN-1), syndrome, in which the risk of gastric carcinoids is high (29%–34%) (*19,20*). All patients underwent upper gastrointestinal endoscopy with multiple biopsies to assess the SRS results and to determine whether gastric carcinoids were present.

MATERIALS AND METHODS

Patients and General Methods

One hundred sixty-two consecutive patients with ZES were considered for this study. Thirty-nine patients had ZES with MEN-1, and the remaining 123 patients had sporadic ZES.

The diagnosis of ZES was established as described previously (*18,21*) by determining fasting serum gastrin levels and basal and maximal acid output and by performing secretin and calcium provocative tests (*22*). Serum gastrin levels were determined by Bioscience Laboratories (New York, NY) and Mayo Clinic Laboratories (Rochester, MN) (*21*). The diagnostic criteria for the presence of MEN-1 in a patient with ZES have been described (*23*) and included biochemical evidence of either primary hyperparathyroidism or pituitary disease or a family history compatible with MEN-1 syndrome.

ZES was determined to have begun when continuous symptoms compatible with gastric acid hypersecretion started (*24*). For analysis, the duration of disease was calculated from onset until the death of the patient or July 23, 1998, when recruitment for this study ended. The diagnosis of gastric carcinoid was considered to have occurred when the carcinoid was first histologically confirmed.

All patients included in this study were enrolled in an ongoing prospective study of the ability to diagnose and treat patients with ZES at our institution. This study was approved by our institutional review board, and all patients gave written informed consent.

Specific Protocol

Enrollment in the study required that the patients have ZES, consent to undergo SRS at the National Institutes of Health (NIH), and have an upper gastrointestinal endoscopy with biopsies to assess for a gastric carcinoid. All 162 patients with ZES eligible for the study were enrolled. One hundred sixteen patients had been admitted to the NIH previously, and 46 patients were newly referred (Table 1). All previously admitted patients had undergone conventional imaging (sonography, CT, MRI, or selective abdominal angiography) and upper gastrointestinal endoscopy with biopsies during their initial visit. Also, these patients had been reassessed annually with upper gastrointestinal endoscopy and biopsies, conventional imaging studies, fasting serum gastrin measurements, and provocative tests of gastrin release (*21*). SRS had not been performed previously. These patients underwent repeated conventional imaging studies (sonography, CT, or MRI) and, if the results were equivocal, selective abdominal angiography, SRS, and upper gastrointestinal endoscopy with biopsies and assessment of disease activity (studies of fasting gastrin levels or acid secretion). Newly referred patients underwent studies to establish the diagnosis (gastrin provocative testing, serum gastrin determinations, acid secretory studies) and studies to establish the presence or absence of MEN-1. SRS was performed as described previously (*25*). Briefly, 222 MBq (6 mCi) [^{111}In-DTPA,D-Phe^{1}]octreotide (Mallinckrodt Diagnostic Imaging Service Radiopharmacy, Beltsville, MD) were injected intravenously. Four hours after injection, a 30-min whole-body scan and 10-min spot views of the abdomen were obtained, and SPECT of the abdomen was

TABLE 1
Characteristics of ZES Patients

Characteristic	No. of patients
Total no. of patients	162
Age (y)	
Mean ± SEM	54 ± 1
Range	19–80
No. of men	92 (57)
MEN-1 present	39 (24)
Other endocrine tumors present (besides gastrinomas)	
Parathyroid only	19 (49)
Pituitary only	1 (3)
Parathyroid and pituitary	12 (31)
Parathyroid and thymic carcinoid	3 (8)
Parathyroid, pituitary, and bronchial carcinoid	4 (10)
Fasting gastrin level (pg/mL)	
Mean ± SEM	6,100 ± 2,648
Range	21–380,000
Basal acid output (mEq/h)*	
Mean ± SEM	30 ± 2
Range	0–144
Maximal acid output (mEq/h)*	
Mean ± SEM	55 ± 3
Range	1–155
Evaluation status†	
Initial	46 (28)
Follow-up	116 (72)
Disease duration (y)‡	
Mean ± SEM	14 ± 1
Range	0.33–42

*Basal and maximal acid outputs are most recent values.

†Evaluation status refers to whether patient was undergoing initial evaluation of gastrinoma location and extent or had undergone previous initial evaluation and was now being evaluated during follow-up visit.

‡Disease duration was time from onset of disease to time of this study.

Normal value for fasting serum gastrin level is <200 pg/mL. Upper limit of normal for basal and maximal acid output in men is <10.5 and 48 mEq/h, respectively; in women, <5.6 and 30 mEq/h, respectively (*40*). Values in parentheses are percentages.

performed. Twenty-four hours after injection, SPECT was repeated for most patients. For SPECT, 3 different cameras were used: a dual-head BIAD (Trionix, Twinsburg, OH), a triple-head XLT (Trionix), and a dual-head Vertex (ADAC Laboratories; Milpitas, CA). With camera 1, 60 images of 30 s each were acquired at 3° intervals. The images were reconstructed with the manufacturer's backprojection algorithm and a Hanning filter using a high-frequency cutoff of 0.75 cycles per centimeter. With camera 2, 40 images of 40 s each were acquired at 3° intervals and were processed as for camera 1. With camera 3, 60 images of 30 s each were acquired at 3° intervals and were reconstructed with a Hanning filter using a high-frequency cutoff of 0.55 cycles per centimeter. A step-and-shoot mode was used in all cases. The images were displayed for review as reprojected or orthogonal (transverse, coronal, or sagittal) views.

After the initial evaluation in this study, all patients underwent yearly evaluations including SRS, conventional imaging, assessment of disease-free status, and upper gastrointestinal endoscopy with biopsies. Gastric acid hypersecretion was controlled with antisecretory drugs to ≤10 mEq/h for the hour before the next drug dose (≤5 mEq/h if gastric acid–reducing surgery had been performed) (*21*,*22*). Patients with disease metastatic to the liver underwent such an evaluation every 3–6 mo (*24*).

Three groups of patients underwent detailed surgical exploration. The first was new patients who had sporadic ZES but no diffuse liver metastases (*18*). The second was all patients who had sporadic ZES and had undergone surgical exploration previously for gastrinoma resection, who now had extrahepatic gastrinoma localized by conventional imaging, but no diffuse liver metastases were present. The third group was patients who had ZES with MEN-1 and findings positive for an extrahepatic tumor 3 cm or more in diameter (n = 55) (*26*). Total gastrectomy was performed on 2 patients with ZES with MEN-1 in whom invasive gastric carcinoids were found at the time of exploratory laparotomy. Postoperatively, all patients were evaluated at 3–6 mo with conventional imaging (sonography, CT, MRI, or selective abdominal angiography) as well as SRS and biochemical studies to assess surgical outcome (*21*,*26*). Patients for whom a gastrinoma had been resected during a prior admission and during this study (n = 115) were reevaluated yearly. Fifty-five of those patients were not rendered free of disease, and 53 were (postoperative evaluation for 7 patients is not yet available). A disease-free status was defined by normalization of the fasting serum gastrin level, negative findings from a gastrin stimulation test with secretin (increase < 200 pg/mL) or with calcium (increase < 395 pg/mL), and no evidence of tumor recurrence on any imaging study (*21*,*26*). If patients were suspected, on the basis of imaging studies, of having metastases to the liver, the diagnosis was confirmed by either CT- or sonography-guided percutaneous biopsy, by laparoscopy, or by minilaparotomy (n = 25). The results of conventional imaging studies were determined by a single radiologist.

Detailed upper gastrointestinal endoscopy was performed on all patients using a videoscope GIF 100 endoscope (Olympus America, Inc., Melville, NY) with a 3.7-mm biopsy channel. Particular attention was directed to the body of the stomach and to a search for any mucosal abnormalities or nodules. All mucosal abnormalities observed at endoscopy were biopsied with Jumbo Cup biopsy forceps (Pauldrach, Pensacola, FL), with a pin before August 30, 1996, and without a pin since August 31, 1996. In addition, at least 2 random Jumbo Cup biopsies were taken from the greater curvature of the body of the stomach of every patient, and Grimelius-stained sections were examined histologically for gastric carcinoids. Gastric mucosal biopsy samples were fixed in 10% neutral buffered formalin and embedded in paraffin, and 5-μm consecutive histologic sections were cut for evaluation. Three sections from each biopsy sample were stained with hematoxylin-eosin, and one was stained with Grimelius' silver stain to identify argyrophil ECL cells. For the Grimelius-stained sections, the number and arrangement of ECL cells were evaluated under the light microscope at medium (×20) and high (×40) powers, and changes in ECL cells were assessed using the classification of Solcia et al. (*27*).

Because the aim of this study was to evaluate the frequency of gastric SRS localization and its clinical usefulness, we first analyzed the SRS report to determine how often gastric SRS localization was recognized without prior knowledge of the presence of a gastric carcinoid. We then correlated the SRS findings with the presence or absence of a carcinoid. Because of the increased occurrence of gastric carcinoid in patients with ZES with MEN-1 and the possibility that the carcinoid could be confused with a pancreatic neuroendocrine tumor (*6*,*18–20*), all SRS studies of these patients (n = 39) were reviewed for gastric SRS localization by 1 nuclear medicine physician, who was unaware of the endoscopic or pathologic findings for the stomach. In the 2 patients without MEN-1 with known gastric carcinoid, the SRS findings were reviewed similarly. This review included a cine display of the reprojected images and a concordant display of orthogonal (coronal, transverse, and sagittal) images. Particular attention was directed to the gastric area for isotope uptake. If uptake was present, the SRS pattern was classified as diffuse, focal, or a combination of both. The diffuse pattern showed uniformly homogeneous uptake of isotope without discrete foci in the gastric wall. The focal pattern showed areas of discrete foci of uptake in the gastric wall.

Statistics

Differences with a significance level of less than 0.05 were considered significant. Values were expressed as mean ± 1 SEM. The χ^2, Fisher exact, and Student *t* tests were used. Sensitivity, specificity, positive predictive value, and negative predictive value were determined.

RESULTS

The clinical and laboratory characteristics of the enrolled patients are shown in Table 1. These patients resemble patients with ZES in other large series (*18*) with regard to sex, age, percentage with MEN-1, basal acid output, maximal acid output, serum fasting gastrin level, and disease duration. All but 1 of the 39 patients with ZES with MEN-1 had hyperparathyroidism. Forty-four percent of the patients with MEN-1 had a pituitary adenoma, 8% had a thymic carcinoid, and 10% had a pituitary adenoma and a bronchial carcinoid. Forty-six patients (28%) were undergoing an initial evaluation, and 116 patients were being followed up (Table 1).

Most patients (70%) underwent gastrinoma resection during follow-up, including 2 patients with MEN-1 with advanced disease who subsequently required cytoreductive surgery and total gastrectomy for invasive gastric carcinoids after the SRS study (Table 2). Of the 70% of patients who

TABLE 2
Extent of Disease

Extent of disease	No. of patients
Total no. of patients	162
Gastrinoma resected*	114 (70)
Disease-free after resectioning†	53 (33)
Not disease-free after resectioning	54 (34)
Postoperative evaluations not available‡	7 (4)
Gastrinoma not resected§	48 (30)
Liver metastases‖	25 (15)
Liver metastases only	16 (10)
Liver and bone metastases¶	9 (5)

*Two patients with advanced disease underwent cytoreductive surgery as well as total gastrectomy for invasive gastric carcinoid tumors.

†Disease-free was defined as normal fasting gastrin level, negative findings from secretin provocative testing, and negative imaging findings (*21*).

‡Seven patients had not yet returned for their postoperative evaluations.

§No resection was performed because 4 patients had negative laparotomy findings and remaining 44 patients did not fit surgery protocol (13 patients had MEN-1, 6 had coexistent medical conditions, and 25 had liver metastases).

‖Liver metastases were histologically proven in all patients.

¶Bone metastases were diagnosed by histology in 2 patients and by bone scanning, MRI, or SRS in 7 patients.

Values in parentheses are percentages.

underwent exploratory laparotomy (n = 114), 33% were rendered free of disease, 34% were not, and the remaining 4% (7 patients) had not yet undergone postoperative evaluation (Table 2). Forty-eight patients did not undergo gastrinoma resection. In 25 of these, diffuse liver metastases were present; in 23, either no gastrinoma was found at surgery (n = 4) or the patient did not meet the criteria for surgical exploration (n = 19). Of the 25 patients with diffuse liver metastases, 9 also had bone metastases (Table 2).

Of the 162 patients, gastric SRS localization was reported for 9 on the initial report: as a diffuse pattern in 67% and as a diffuse and focal pattern in 33% (Table 3). Most of these initially reported patients (6/9) had ZES with MEN-1. Because SRS has been reported to be sensitive in detecting gastrinomas, other pancreatic endocrine tumors, and carcinoids (*13,25*), we first needed to establish whether a true gastric SRS localization had originally been interpreted as gastric and as a gastrinoma or another pancreatic endocrine tumor. This information was determined by reanalyzing all SRS studies in patients with ZES with MEN-1. This group was selected because it is reported to have a greater than 30-fold increased occurrence of gastric carcinoids compared with patients with sporadic disease, and almost all members of the group have other pancreatic endocrine tumors and gastrinomas by the time gastric carcinoids develop (*19,20*). With reanalysis, 10 additional patients with ZES with MEN-1 were found to have gastric localization (Table 3) on the SRS who were originally reported as not having gastric localization. Most unreported gastric localizations (9/10) showed a diffuse pattern, and the remaining patient had a diffuse and focal pattern. The gastric localization in the initial reports had been mistaken for gastrinomas or pancreatic endocrine tumors. A gastric carcinoid was present in all but 2 of the patients with initially unreported localizations (Table 3). In fact, 1 patient with an initially unreported localization with a diffuse and focal pattern had invasive gastric carcinoids necessitating total gastrectomy during exploratory laparotomy for cytoreductive surgery for metastatic tumor. The gastric carcinoids in this patient were mistaken for gastrinomas on the initial preoperative SRS study.

The relationship between gastric SRS localization and the presence or absence of a gastric carcinoid in patients with sporadic ZES or with ZES with MEN-1 is shown in Table 4. A proven gastric carcinoid was present in 16 of 162 patients (10%). A gastric nodule was seen on upper gastrointestinal endoscopy in 10 of 16 patients with a proven gastric carcinoid and was absent in the remaining 6 patients at the time of diagnostic upper gastrointestinal endoscopy (Table 4). In 2 patients with a gastric carcinoid associated with gastric nodules, an invasive gastric carcinoid was confirmed by total gastrectomy. Overall, gastric SRS localization was found in 12% (19/162) of patients, including the 10 patients initially not reported to have gastric localization on SRS (Tables 3 and 4). Eighty-eight percent (143/162) of patients did not have gastric SRS localization. Of the 19 patients with gastric SRS localization, a gastric carcinoid was found in 63% (12/19). This finding was highly, significantly different ($P < 0.00001$) from that for the 143 patients without SRS localization, of whom only 3% (4/143) had a gastric carcinoid (Table 4). The pattern of gastric SRS localization was diffuse in 15 of 19 patients (79%), whereas a diffuse and focal pattern was seen in 4 of 19 patients (21%) with positive

TABLE 3
Initially Reported and Unreported Positive Gastric SRS Localization in ZES Patients

Characteristic	Positive gastric SRS localization: Initially reported* (n = 9)	Positive gastric SRS localization: Unreported† (n = 10)	Total (n = 19)
MEN-1 present	6 (67)	10 (100)	16 (84)
MEN-1 absent	3 (33)	Not done	3 (16)
Diffuse pattern	6 (67)	9 (90)	15 (79)
Focal and diffuse pattern	3 (33)	1 (10)	4 (21)
Gastric carcinoid present	4 (44)	8 (80)	12 (63)
Gastric carcinoid absent	5 (56)	2 (20)	7 (37)

*Initially reported refers to SRS results originally reported for all patients before any review.

†Unreported refers to MEN-1 patients who were originally reported as not having gastric localization but in whom gastric localization was found on reanalysis.

Data are numbers of patients, with percentages in parentheses.

TABLE 4
Gastric SRS Localization Findings in ZES Patients

Characteristic	Gastric SRS localization finding			
	Positive (n = 19)			
	Diffuse pattern*	Diffuse and focal pattern†	Total positive	Negative (n = 143)
Total no. of patients (n = 162)	15 (79)	4 (21)	19 (100)	143 (100)
MEN-1 present (n = 39)	12 (63)	4 (21)	16 (84)‡	23 (16)
MEN-1 absent (n = 123)	3 (16)	0 (0)	3 (16)	120 (84)
Gastric carcinoid present (n = 16)	8 (42)	4 (21)	12 (63)‡	4 (2)
MEN-1 present (n = 14)	8 (42)	4 (21)	12 (63)	2 (1)
MEN-1 absent (n = 2)	0 (0)	0 (0)	0 (0)	2 (1)
Gastric carcinoid absent (n = 146)	7 (37)	0 (0)	7 (37)‡	139 (97)
MEN-1 present (n = 25)	4 (21)	0 (0)	4 (21)	21 (15)
MEN-1 absent (n = 121)	3 (16)	0 (0)	4 (21)	118 (82)
Gastric nodule present with gastric carcinoid (n = 10)§	5 (26)	3 (16)	8 (42)	2 (1)
MEN-1 present (n = 9)	5 (26)	3 (16)	8 (42)	1 (0.5)
MEN-1 absent (n = 1)	0 (0)	0 (0)	0 (0)	1 (0.5)
Gastric nodule absent with gastric carcinoid (n = 6)§	3 (15)	1 (5)	4 (21)	2 (1)
MEN-1 present (n = 5)	3 (15)	1 (5)	4 (21)	1 (0.5)
MEN-1 absent (n = 1)	0 (0)	0 (0)	0 (0)	1 (0.5)

*Gastric SRS localization was initially reported for 6 of 15 patients with diffuse pattern and detected only on detailed review in 9 patients. Each initially unreported patient had MEN, with 8 patients having gastric carcinoid and 2 patients not having gastric carcinoid.

†Gastric SRS localization was initially unreported for 1 of 4 patients who had MEN with diffuse and focal pattern and detected only on detailed review. This patient had MEN-1 with advanced gastrinoma and invasive carcinoid tumors necessitating total gastrectomy.

‡$P < 0.00001$ compared with patients with negative SRS (n = 146).

§Gastric nodule present or absent refers to endoscopic findings in stomach at time diagnosis of gastric carcinoid tumor was made histologically.

Values in parentheses are percentages of patients with either positive or negative SRS localization with indicated SRS pattern and characteristic.

findings for gastric SRS (Table 3). Gastric localization with a diffuse pattern was associated with the presence of gastric carcinoid in 8 of 15 patients (53%), whereas all 4 patients with a diffuse and focal pattern had a gastric carcinoid ($P = 0.13$) (Table 4). Eight of the 54 patients undergoing exploratory laparotomy during this study had gastric SRS localization as well as localization of gastrinoma before surgery. Five of the 8 patients had a gastric carcinoid, including the 2 patients who underwent total gastrectomy for an invasive gastric carcinoid, whereas the remaining 3 of 8 patients did not have a gastric carcinoid. Seven of the 8 patients had a postoperative follow-up SRS study, and the remaining patient did not. The postoperative SRS study remained unchanged for gastric localization in all except the 2 patients who underwent total gastrectomy (Fig. 1).

The relative frequency of gastric SRS localization and gastric carcinoid in patients with ZES with MEN-1 (n = 39) and with sporadic ZES (n = 123) was compared (Table 4). Of the 19 patients with gastric SRS localization, 16 (84%) had ZES with MEN-1. This value was significantly higher ($P < 0.00001$) than the only 16% (23/143) of patients having ZES with MEN-1 with negative findings for gastric SRS (Table 4). Furthermore, gastric localization as a diffuse and focal pattern was seen exclusively in patients with ZES with MEN-1 (n = 4) (Table 4). Gastric carcinoid was present more frequently in patients with ZES with MEN-1 than in patients with sporadic ZES (14/39 [36%] versus 2/123 [1.6%], respectively; $P < 0.00001$). The rate of positive gastric SRS localization in the presence of a proven gastric carcinoid was 75% (12/16) overall (Table 5) and was almost significantly greater ($P = 0.05$) in the 12 patients with ZES with MEN-1 and gastric carcinoids (86% [12/14]) than in the 2 patients with sporadic ZES with gastric carcinoids (0% [0/2]) (Table 4). Furthermore, the rate of negative findings for gastric SRS localization in the absence of gastric carcinoid was significantly less ($P < 0.005$) in patients with ZES with MEN-1 (21/25 [84%]) than in patients with sporadic ZES (118/121 [98%]) (Table 6).

To evaluate further the potential clinical usefulness of gastric SRS localization in a typical setting, we determined the specificity and sensitivity of gastric SRS localization in patients with a gastric carcinoid. The overall rate of a positive finding for gastric SRS localization in the presence of a gastric carcinoid was significantly higher ($P < 0.00001$) than the overall rate of a positive finding for gastric localization in the absence of a gastric carcinoid (12/16 [75%] versus 7/146 [5%]) (Table 4). Gastric SRS localization had a sensitivity of 75% for occurring in patients with a proven gastric carcinoid, a positive predictive value of 63%, a specificity of 95%, and a negative predictive value of 97% (Table 5).

The clinical and laboratory characteristics of patients with or without a gastric carcinoid in the presence or absence MEN-1 were compared (Table 6). Patients with a gastric carcinoid with ZES with MEN-1 did not differ in age, sex, or disease duration from patients with a gastric carcinoid with sporadic ZES. These 2 groups of patients did not differ in the time from disease onset to the diagnosis of gastric carcinoid, the presence or absence of a gastric nodule on upper gastrointestinal endoscopy, or the fasting serum gastrin

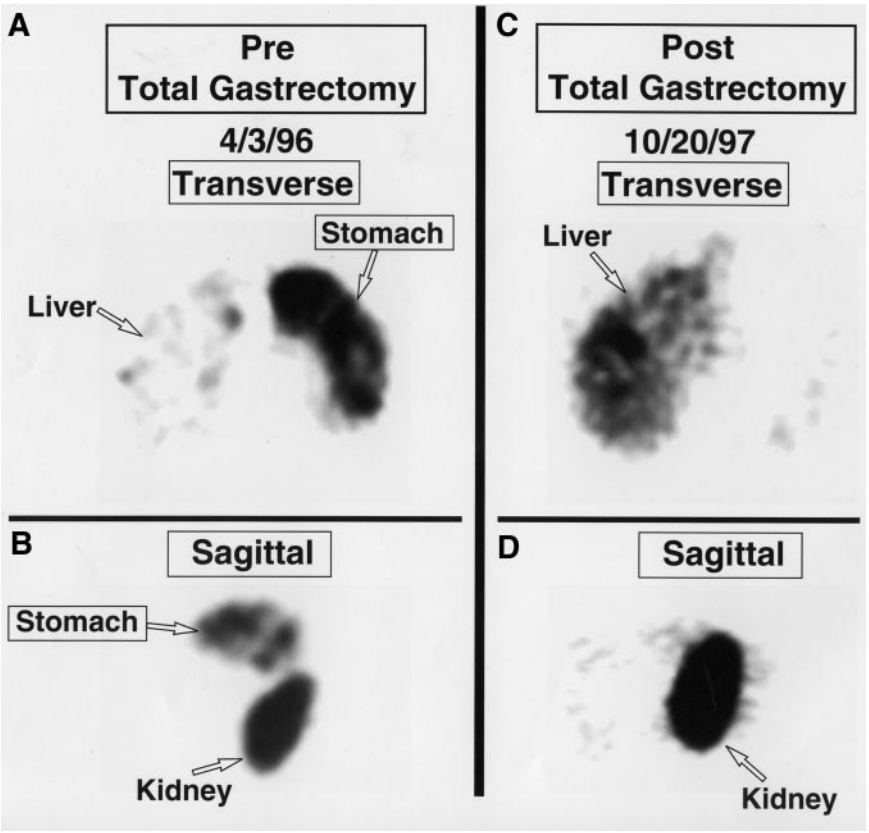

FIGURE 1. Example of focal and diffuse gastric localization on SRS in patient with ZES, MEN-1, and multiple gastric carcinoids with carcinoid syndrome. Before total gastrectomy, transverse view (A) and sagittal view (B) showed diffuse and focal uptake in stomach. After total gastrectomy, gastric localization was no longer seen on SRS on either transverse view (C) or sagittal view (D). This patient had ZES of 16 y duration, and gastric carcinoid was diagnosed 10 y after disease onset. Upper gastrointestinal endoscopy before total gastrectomy showed multiple large gastric mucosal nodules. Histologic examination after gastrectomy showed numerous carcinoids in stomach and severe linear and micronodular hyperplasia of gastric ECL cells with dysplastic changes. Mean fasting serum gastrin level was 49,000 pg/mL (normal value is <200 pg/mL).

level. However, the frequency of gastric SRS localization was borderline significant ($P = 0.05$) in patients with a gastric carcinoid with ZES with MEN-1 compared with patients with a gastric carcinoid with sporadic ZES (12/14 [86%] versus 0/2 [0%]) (Table 6). On the other hand, patients with or without a gastric carcinoid or with or without MEN-1 did not differ in age, sex, or disease duration, but the serum gastrin level was significantly higher ($P < 0.05$) in patients with gastric carcinoids than in patients without gastric carcinoids (Table 6). In patients with ZES with MEN-1, the rate of occurrence of other endocrinopathies did not differ between those who did and those who did not have a gastric carcinoid (Table 6).

TABLE 5
Indices of Gastric SRS Localization in Patients with Gastric Carcinoids with ZES

Index	Positive gastric SRS localization (gastric carcinoid) (%)
Sensitivity	75
Positive predictive value	63
Specificity	95
Negative predictive value	97

Sensitivity, specificity, and negative predictive values were calculated on basis of results of 162 SRS studies. Of 162 studies, 19 were positive for gastric localization. In 162 patients studied, 16 had gastric carcinoid tumor and 12 of these 16 had positive gastric SRS localization.

Examples of gastric SRS localization are shown in Figures 1–5. Figures 1, 3, and 5 are examples of gastric SRS localization in patients with a gastric carcinoid and with ZES with MEN-1. In Figure 1, the SRS before total gastrectomy showed a diffuse and focal SRS pattern in the stomach. The diagnosis of gastric carcinoid was confirmed, and gastric localization on SRS subsequently disappeared after total gastrectomy. Figures 3 and 5 show gastric SRS localization with a diffuse SRS pattern in patients with proven gastric carcinoids. Figures 2 and 4 are examples of gastric SRS localization with diffuse SRS patterns in patients without a gastric carcinoid and with sporadic ZES. In the patient whose SRS is shown in Figure 2, 2 random biopsies of the gastric body showed linear and diffuse hyperplasia of ECL cells. In the patient whose SRS is shown in Figure 4, 2 random biopsies of the gastric body showed moderate hyperplasia of ECL cells.

DISCUSSION

Numerous studies show that more than 85% of carcinoids in several locations possess somatostatin receptors and that SRS is a sensitive method to localize these tumors (*13,14*). Recent studies show that gastric carcinoids also possess somatostatin receptors, and case reports have shown that SRS can occasionally localize gastric carcinoids (*15,28–30*). In older studies, gastric carcinoids made up 3.2% of all

TABLE 6
Characteristics of Patients Regarding Gastric Carcinoids

Characteristic	Gastric carcinoid present		Gastric carcinoid absent	
	MEN-1 present (n = 14)	MEN-1 absent (n = 2)	MEN-1 present (n = 25)	MEN-1 absent (n = 121)
Age (y)				
Mean ± SEM	50 ± 3	61 ± 8	48 ± 2	56 ± 1
Range	34–69	52–70	26–75	19–80
No. of men	8 (67)	2 (100)	11 (41)	71 (58)
Disease duration (y)*				
Mean ± SEM	17 ± 2	16 ± 3	12 ± 2	15 ± 1
Range	8–31	13–19	2–29	1–42
Time from disease onset to gastric carcinoid (y)†				
Mean ± SEM	11 ± 1	10 ± 1	NA	NA
Range	6–17	9–12		
Endoscopic findings in patients with a carcinoid‡				
Gastric nodule present	9 (64)	1 (50)	NA	NA
Gastric nodule absent	3 (21)	1 (50)	NA	NA
Positive gastric SRS localization	12 (86)	0 (0)	4 (16)	3 (2)
Diffuse pattern	8 (57)	0 (0)	3 (12)	3 (2)
Diffuse and focal pattern	4 (29)	0 (0)	0 (0)	0 (0)
Negative gastric SRS localization	2 (14)	2 (100)	21 (84)	118 (98)
Fasting gastrin level (pg/mL)				
Mean ± SEM	23,900 ± 11,000	19,460 ± 18,500	1,000 ± 430	5,200 ± 3,200
Range	190–123,000	920–38,000	57–10,000	21–380,000
Associated endocrine tumors present (besides gastrinomas)				
Parathyroid only	6 (50)	NA	13 (50)	NA
Pituitary only	0 (0)	NA	1 (4)	NA
Parathyroid and pituitary	3 (25)	NA	9 (35)	NA
Parathyroid and thymic carcinoid	2 (17)	NA	1 (4)	NA
Parathyroid, pituitary, and bronchial carcinoid	1 (8)	NA	3 (12)	NA

*Disease duration was time from onset of disease to time of this study.

†Time from ZES onset to diagnosis of gastric carcinoid was calculated from time of disease onset until diagnosis of gastric carcinoid was first made histologically.

‡Gastric nodule present or absent refers to endoscopic findings in stomach at time diagnosis of gastric carcinoid tumor was made histologically.

NA = not applicable.

Values in parentheses are percentages.

carcinoids and 5.6% of all gastrointestinal carcinoids (*3*,*31*,*32*); however, recognition of gastric carcinoids is increasingly important for several reasons. First, some studies have shown that gastric carcinoids are increasing as a percentage of the total carcinoids detected (*3*,*31*). Whether this increase is a true increase in frequency or just an increase in detection rate is unclear. Second, the sporadic form of gastric carcinoid (type III carcinoid), which is not

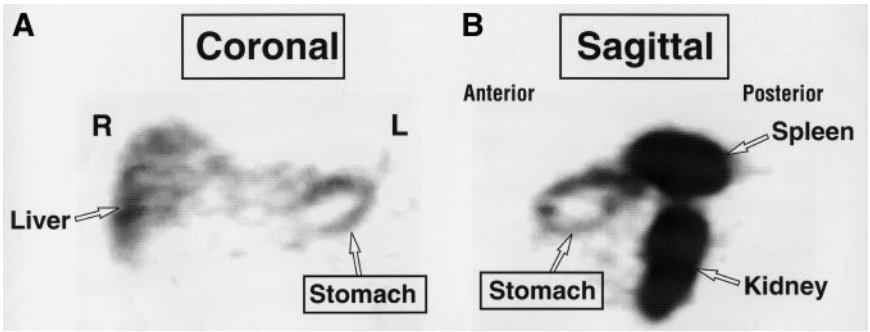

FIGURE 2. Example of diffuse gastric localization on SRS in patient with ZES without MEN-1 or gastric carcinoid. Coronal view (A) and sagittal view (B) of SRS show diffuse uptake in stomach. This patient had ZES of 15 y duration. Upper gastrointestinal endoscopic findings were unremarkable except for hypertrophic gastric folds. Histopathology of 2 random Jumbo Cup biopsy (Pauldrach) samples from greater curvature showed linear and diffuse hyperplasia of gastric ECL cells. Mean fasting serum gastrin level was 250 pg/mL (normal level is <200 pg/mL).

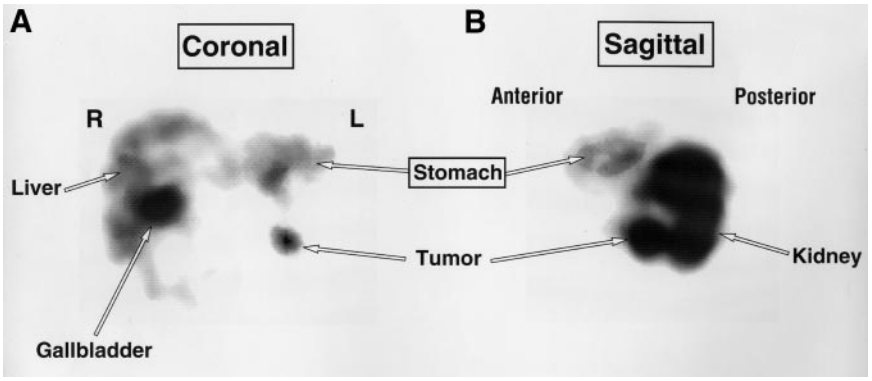

FIGURE 3. Example of diffuse gastric localization on SRS in patient with ZES with MEN-1 and multiple gastric carcinoids. Coronal view (A) and sagittal view (B) of SRS showed diffuse uptake in stomach. This patient had ZES of 15 y duration. Gastric carcinoid was diagnosed 7 y after disease onset. Upper gastrointestinal endoscopy showed multiple gastric mucosal nodules. Histology of 1 gastric nodule showed carcinoid and diffuse, linear hyperplasia of gastric ECL cells. Patient did not have carcinoid syndrome. Mean fasting serum gastrin level was 1500 pg/mL (normal level is <200 pg/mL).

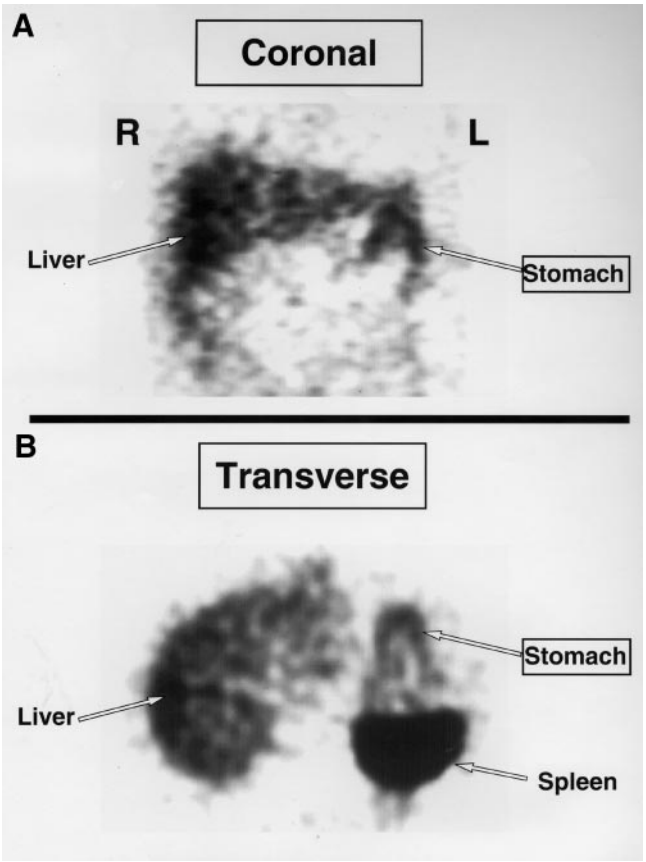

FIGURE 4. Example of diffuse gastric localization on SRS in patient with ZES without MEN-1 or gastric carcinoid. Coronal view (A) and transverse view (B) of SRS showed diffuse uptake in stomach. This patient had ZES of 11 y duration, and mean fasting serum gastrin level was 2900 pg/mL (normal level is <200 pg/mL). Upper gastrointestinal endoscopic findings were unremarkable except for prominent gastric folds. Histology of 2 random Jumbo Cup biopsy (Pauldrach) samples from gastric body on greater curvature showed moderate linear hyperplasia of ECL cells with dysplastic changes.

associated with hypergastrinemic states, has a high rate of metastasis (71%) and is usually recognized only late in its course (*6,32*). Third, hypergastrinemic states such as atrophic gastritis (type I carcinoid) and ZES, particularly as part of MEN-1 syndrome (type II carcinoid), are associated with a markedly increased incidence of gastric carcinoids (*6,32*). For example, in some studies, 2%–9% of patients with atrophic gastritis and 18%–30% of patients with ZES with MEN-1 have been reported to have gastric carcinoids (*6,19,32*). In patients with type I and II carcinoids, 10%–20% of the carcinoids can be malignant (*6,32*). Gastric carcinoids in hypergastrinemic states are receiving increasing attention because chronic treatment of gastroesophageal reflux disease, which is common, with proton pump inhibitors (omeprazole, lansoprazole, and pantoprazole) causes hypergastrinemia in 90%–100% of patients (*8,33*). In animals, such long-term treatment has caused gastric carcinoids, some of which are malignant (*18,32,34*). Fourth, in the MEN-1 syndrome, in which multiple endocrine tumors develop (parathyroid > pancreas > pituitary > stomach > lung) (*35*), it is essential the gastric carcinoids be distinguished from pancreatic endocrine tumors. This distinction has an important clinical relevance because the pancreatic endocrine tumors are frequently malignant and are treated surgically, whereas most gastric carcinoids are small, pursue an indolent course, and are not treated surgically (*35,36*).

At present, gastric carcinoids can be diagnosed only by invasive methods such as upper gastrointestinal endoscopy with either cytology or biopsy. Whether SRS is generally useful for this localization is unknown, because no systematic studies have been done. This study was designed to address this question. The population included groups of patients with different risks of developing gastric carcinoids. One group comprised patients with ZES without MEN-1 (sporadic ZES), who have only a slightly increased risk of developing gastric carcinoids, resemble patients treated long term with proton pump inhibitors for idiopathic gastroesophageal reflux disease, and develop hypergastrinemia (*20,32*).

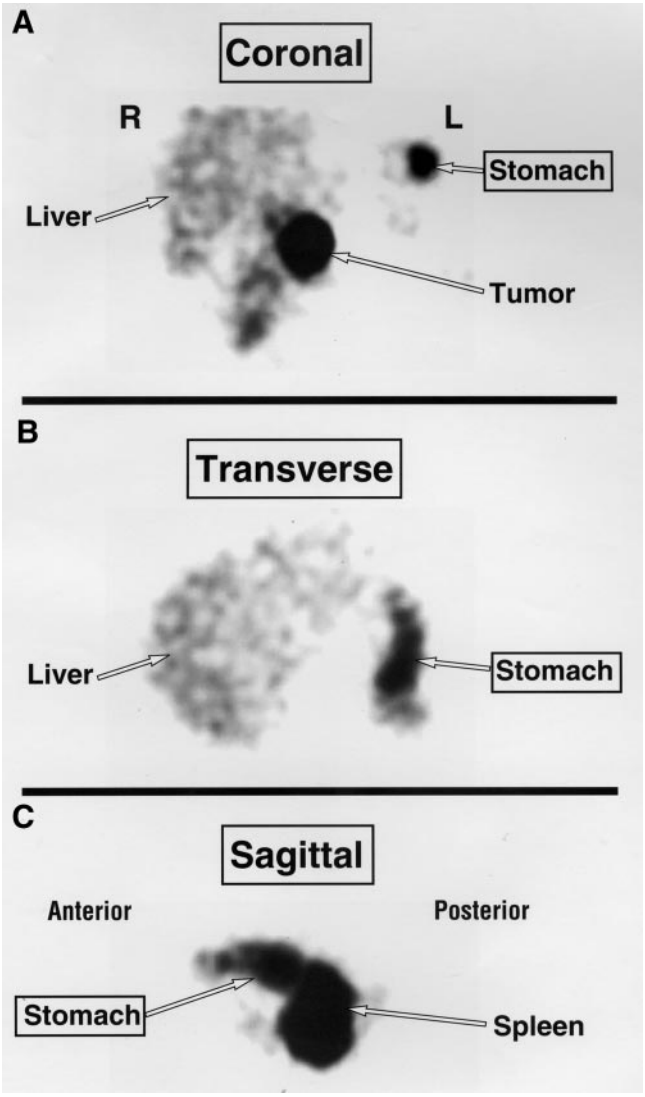

FIGURE 5. Example of diffuse gastric localization on SRS in patient with ZES with MEN-1 and gastric carcinoid. Coronal view (A), transverse view (B), and sagittal view (C) of SRS showed diffuse uptake in stomach. This patient had ZES of 20 y duration as part of MEN-1 syndrome, and gastric carcinoid was diagnosed 17 y after onset of disease. Gastric carcinoid was diagnosed by biopsy of gastric nodule. Patient did not have carcinoid syndrome. Mean fasting serum gastrin level was 3862 pg/mL (normal level is <200 pg/mL).

The second group included patients with ZES with MEN-1, who have a more than 30-fold increased incidence of developing gastric carcinoids (*19,20*).

In this study, all patients underwent a detailed gastroscopic examination with biopsies, 90% underwent more than 2 such studies, and 2 patients underwent total gastrectomy. Furthermore, to evaluate the maximal potential of SRS for gastric localization, a single nuclear medicine physician carefully reviewed the SRS findings for patients with ZES with MEN-1, with particular attention to the gastric area, after the initial reading.

The results of this study provide several important insights into the potential value of SRS in identifying patients with a gastric carcinoid. First, gastric carcinoids were present in 16 of 162 patients (10%), and SRS had a 75% sensitivity in identifying patients with gastric carcinoids and a positive predictive value of 63%. These values are comparable with the sensitivity of SRS for localizing primary pancreatic endocrine tumors (*13,14,25*) and primary carcinoids in other locations (*13,14*). However, this degree of sensitivity was obtained only when the SRS findings were carefully reviewed by a nuclear medicine physician who specifically assessed whether the stomach was involved. On the routine reading of the SRS, its sensitivity was reduced by approximately 40%. Therefore, especially in patients with ZES with MEN-1, who more frequently have gastric carcinoids, if careful attention had not been paid to the possibility of a gastric carcinoid, the lesions seen on SRS would frequently have been falsely attributed to a pancreatic endocrine tumor, which is present in 80%–100% of these patients (*18,35–37*).

Second, SRS had a high specificity (95%) and a high negative predictive value (97%). Therefore, SRS rarely gave a false-positive location for gastric carcinoid lesions if this possibility was carefully assessed. This result contrasts with that of a recent study that showed SRS to have a false-positive rate of 12% for localization of pancreatic endocrine tumors (*17*). In our study, 7 patients had SRS gastric localization but no carcinoid. Of these 7, 4 had ZES with MEN-1. The basis for this false positivity remains unclear. A small gastric carcinoid may have been missed by the gastric biopsies, and the findings for these patients may actually not be false-positive. Also, the localization may have been caused by a markedly increased ECL proliferation without a gastric carcinoid. This possibility is supported by the fact that somatostatin receptors are found on gastric ECL cells (*30,38*) and that more advanced forms of ECL cell hyperplasia are present in most patients with ZES with MEN-1 (*18,19*). Furthermore, studies of hypergastrinemia in animals have suggested that ECL proliferative changes can be classified in a progression from hyperplasia to dysplasia to carcinoid (*27*). In fact, in all patients with type I (atrophic gastritis) or type II (ZES) carcinoids and gastric carcinoids, ECL proliferative changes were present, with most (>65%) having advanced changes. That the SRS may be identifying this ECL hyperplasia is supported by the finding that in most patients (79%) the SRS localization pattern was a diffuse uptake. Because in most patients multiple gastric carcinoids were not detected on gastric biopsies, this finding raises the possibility that advanced proliferative changes in ECL cells, rather than multiple gastric carcinoids, are being detected. However, this possibility is only speculation. We did not attempt to establish that ECL changes are more advanced or diffuse in patients with positive SRS results, because the variability of ECL changes from biopsy to biopsy has not been studied and the number of biopsies needed to represent the overall extent of gastric ECL change is unclear. Further-

more, how best endoscopically to localize cell gastric carcinoids is unknown. Therefore, the possibility that they may exist in the false-positive SRS localizations cannot be excluded.

Lastly, a false-positive gastric localization may represent a gastric gastrinoma, because almost all these tumors possess high densities of somatostatin receptors and are frequently seen with SRS (*13*,*25*,*39*). This possibility is, however, unlikely because gastrinomas are rarely located in the gastric body (<0.5%) and in the only case seen in our 250 patients at the NIH, the tumor was not occult and could be detected by upper gastrointestinal endoscopy.

CONCLUSION

Although gastric carcinoids in hypergastrinemic states generally pursue an indolent course, a study has shown that up to 30% can pursue an aggressive course that includes lymph node metastases (*6*). Furthermore, the natural history of these tumors is still largely unknown. Therefore, in patients at increased risk for their development, especially patients with ZES with MEN-1 or with atrophic gastritis and pernicious anemia, surveillance for gastric carcinoids is indicated. The potential value of SRS in identifying patients with gastric carcinoids is supported by our analysis of the value of clinical and laboratory characteristics in identifying such patients. Except for the presence of MEN-1, no characteristic was helpful in identifying which patients might have gastric carcinoids. Furthermore, in patients with atrophic gastritis and pernicious anemia, no clinical or laboratory characteristic has been found to reveal those with gastric carcinoids. Therefore, the availability of SRS—the first noninvasive method found to identify gastric carcinoids—should prove useful in the treatment of patients with hypergastrinemic states or other diseases (e.g., MEN-1) with an increased incidence of gastric carcinoids. Additional studies are needed to define the role of repeated endoscopy with biopsies or SRS in identifying which patients harbor gastric carcinoids.

REFERENCES

1. Godwin JD II. Carcinoid tumors: an analysis of 2,837 cases. *Cancer*. 1975;36:560–569.
2. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer.* 1997;79:813–829.
3. Gilligan CJ, Phil M, Lawton GP, et al. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. *Am J Gastroenterol*. 1995;90:338–352.
4. Sjoblom SM. Clinical presentation and prognosis of gastrointestinal carcinoid tumours. *Scand J Gastroenterol*. 1988;23:779–787.
5. Rindi G, Azzoni C, La Rosa S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: prognostic evaluation by pathological analysis. *Gastroenterology*. 1999;116:532–542.
6. Rindi G, Bordi C, Rappel S, La Rosa S, Stolte M, Solcia E. Gastric carcinoids and neuroendocrine carcinomas: pathogenesis, pathology, and behavior. *World J Surg.* 1996;20:168–172.
7. Kahrilas PJ, Hogan WJ. Gastroesophageal reflux disease. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease*. 5th ed. Philadelphia, PA: WB Saunders; 1993:378–401.
8. Jansen JB, Klinkenberg-Knol EC, Meuwissen SG, et al. Effect of long-term treatment with omeprazole on serum gastrin and serum group A and C pepsinogens in patients with reflux esophagitis. *Gastroenterology*. 1990;99:621–628.
9. Lamberts R, Creutzfeldt W, Struber HG, Brunner G, Solcia E. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis. *Gastroenterology*. 1993;104:1356–1370.
10. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. *Scand J Gastroenterol.* 1985(suppl 108);20:53–69.
11. Borch K, Stridsberg M, Burman P, Rehfeld JF. Basal chromogranin A and gastrin concentrations in circulation correlate to endocrine cell proliferation in type-A gastritis. *Scand J Gastroenterol*. 1997;32:198–202.
12. Kolby L, Wangberg B, Ahlman H, et al. Histidine decarboxylase expression and histamine metabolism in gastric oxyntic mucosa during hypergastrinemia and carcinoid tumor formation. *Endocrinology*. 1996;137:4435–4442.
13. Krenning EP, Kwekkeboom DJ, Bakker WH, et al. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med*. 1993;20:716–731.
14. Jensen RT. Peptide therapy: recent advances in the use of somatostatin and other peptide receptor agonists and antagonists. In: Lewis JH, Dubois A, eds. *Current Clinical Topics in Gastrointestinal Pharmacology*. Malden, MA: Blackwell Science; 1997:144–223.
15. Nilsson O, Kolby L, Wangberg B, et al. Comparative studies on the expression of somatostatin receptor subtypes, outcome of octreotide scintigraphy and response to octreotide treatment in patients with carcinoid tumours. *Br J Cancer*. 1998;77:632–637.
16. Jensen RT. Presence of somatostatin receptors on gastro-enteropancreatic endocrine tumors (GEP's): impact on clinical management with somatostatin receptor imaging and other uses of somatostatin analysis. In: Lamberts SWJ, ed. *Octreotide: The Next Decade*. Bristol, UK: Bioscientific Ltd.; 1999:149–178.
17. Gibril F, Reynolds JC, Chen CC, et al. Specificity of somatostatin receptor scintigraphy: a prospective study and the effects of false positive localizations on management in patients with gastrinomas. *J Nucl Med*. 1999;40:539–553.
18. Jensen RT, Gardner JD. Gastrinoma. In: Go VLW, DiMagno EP, Gardner JD, Lebenthal E, Reber HA, Scheele GA, eds. *The Pancreas: Biology, Pathobiology and Disease*. 2nd ed. New York, NY: Raven Press; 1993:931–978.
19. Lehy T, Cadiot G, Mignon M, Ruszniewski P, Bonfils S. Influence of multiple endocrine neoplasia type 1 on gastric endocrine cells in patients with the Zollinger-Ellison syndrome. *Gut*. 1992;33:1275–1279.
20. Jensen RT. Gastrinoma as a model for prolonged hypergastrinemia in man. In: Walsh JH, ed. *Gastrin*. New York, NY: Raven Press; 1993:373–393.
21. Fishbeyn VA, Norton JA, Benya RV, et al. Assessment and prediction of long-term cure in patients with Zollinger-Ellison syndrome: the best approach. *Ann Intern Med*. 1993;119:199–206.
22. Metz DC, Pisegna JR, Fishbeyn VA, Benya RV, Jensen RT. Control of gastric acid hypersecretion in the management of patients with Zollinger-Ellison syndrome. *World J Surg.* 1993;17:468–480.
23. Benya RV, Metz DC, Venzon DJ, et al. Zollinger-Ellison syndrome can be the initial endocrine manifestation in patients with multiple endocrine neoplasia-type 1. *Am J Med.* 1994;97:436–444.
24. Weber HC, Venzon DJ, Lin JT, et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: a prospective long-term study. *Gastroenterology*. 1995;108:1637–1649.
25. Gibril F, Reynolds JC, Doppman JL, et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas—a prospective study. *Ann Intern Med*. 1996;125:26–34.
26. Norton JA, Fraker DL, Alexander HR, et al. Surgery to cure the Zollinger-Ellison syndrome. *N Engl J Med*. 1999;341:635–644.
27. Solcia E, Bordi C, Creutzfeldt W, et al. Histopathological classification of nonantral gastric endocrine growths in man. *Digestion*. 1988;41:185–200.
28. Kolby L, Wangberg B, Ahlman H, et al. Gastric carcinoid with histamine production, histamine transporter and expression of somatostatin receptors. *Digestion*. 1998;59:160–166.
29. Wangberg B, Forssell-Aronsson E, Tisell LE, Nilsson O, Fjalling M, Ahlman H. Intraoperative detection of somatostatin-receptor-positive neuroendocrine tumours using indium-111-labelled DTPA-D-Phe1-octreotide. *Br J Cancer.* 1996;73:770–775.
30. Tang LH, Modlin IM. Somatostatin receptor regulation of gastric carcinoid tumours. *Digestion*. 1996;57:11–14.
31. Modlin IM, Sandor A, Tang LH, Kidd M, Zelterman D. A 40-year analysis of 265 gastric carcinoids. *Am J Gastroenterol.* 1997;92:633–638.
32. Jensen RT, Norton JA. Carcinoid tumors and the carcinoid syndrome. In: DeVita

VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott-Raven; 1997:1704–1723.
33. Lamberts R, Creutzfeldt W, Stockmann F, Jacubaschke U, Maas S, Brunner G. Long term omeprazole treatment in man: effects on gastric endocrine cell populations. *Digestion*. 1988;39:126–135.
34. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. *Digestion*. 1986(suppl 1);35:42–55.
35. Metz DC, Jensen RT, Bale AE, et al. Multiple endocrine neoplasia type 1: clinical features and management. In: Bilezekian JP, Levine MA, Marcus R, eds. *The Parathyroids*. New York, NY: Raven Press; 1994:591–646.
36. Norton JA, Jensen RT. Multiple endocrine neoplasia. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. 5th ed. Philadelphia, PA: Lippincott-Raven; 1997:1723–1729.
37. Thompson NW, Lloyd RV, Nishiyama RH, et al. MEN I pancreas: a histological and immunohistochemical study. *World J Surg.* 1984;8:561–574.
38. Modlin IM, Tang LH. The gastric enterochromaffin-like cell: an enigmatic cellular link. *Gastroenterology*. 1996;111:783–810.
39. Wulbrand U, Wied M, Zofel P, Goke B, Arnold R, Fehmann H. Growth factor receptor expression in human gastroenteropancreatic neuroendocrine tumours. *Eur J Clin Invest*. 1998;28:1038–1049.
40. Feldman M. Gastric secretion. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease*. 3rd ed. Philadelphia, PA: WB Saunders; 1999:541–558.