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Prospective Study of Somatostatin Receptor Scintigraphy and its Effect on Operative Outcome in Patients With Zollinger-Ellison Syndrome

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Objective

To determine the relative abilities of somatostatin receptor scintigraphy (SRS) and conventional imaging studies (computed tomography, magnetic resonance imaging, ultrasound, angiography) to localize gastrinomas before surgery in patients with Zollinger-Ellison syndrome (ZES) subsequently found at surgery, and to determine the effect of SRS on the disease-free rate.

Summary Background Data

Recent studies demonstrate that SRS is the most sensitive imaging modality for localizing neuroendocrine tumors such as gastrinomas. Because of conflicting results in small series, it is unclear in ZES whether SRS will alter the disease-free rate, which gastrinomas are not detected, what factors contribute to failure to detect a gastrinoma, or whether the SRS result should be used to determine operability in patients without hepatic metastases, as recently recommended by some investigators.

Methods

Thirty-five consecutive patients with ZES undergoing 37 exploratory laparotomies for possible cure were prospectively studied. All had SRS and conventional imaging studies before surgery. Imaging results were determined by an independent investigator depending on surgical findings. All patients underwent an identical surgical protocol (palpation after an extensive Kocher maneuver, ultrasound during surgery, duodenal transillumination, and 3 cm duodenotomy) and postoperative assessment of disease status (fasting gastrin, secretin test imaging within 2 weeks, at 3 to 6 months, and yearly), as used in pre-SRS studies previously.

Results

Gastrinomas were detected in all patients at each surgery. Seventy-four gastrinomas were found: 22 duodenal, 8 pancreatic, 3 primaries in other sites, and 41 lymph node metastases. The relative detection order on a per-patient or per-lesion basis was SRS > angiography, magnetic resonance imaging, computed tomography > ultrasound. On a per-lesion basis, SRS had greater sensitivity than all conventional studies combined. SRS missed one third of all lesions found at surgery. SRS detected 30% of gastrinomas ≤1.1 cm, 64% of those 1.1 to 2 cm, and 96% of those >2 cm and missed primarily small duodenal tumors. Tumor size correlated closely with SRS rate of detection. SRS did not increase the disease-free rate immediately after surgery or at 2 years mean follow-up.

Conclusions

SRS is the most sensitive preoperative imaging study for extrahepatic gastrinomas in patients with ZES and should replace conventional imaging studies as the preoperative study of choice. Negative results of SRS for localizing extrahepatic gastrinomas should not be used to decide operability, because a surgical procedure will detect 33% more gastrinomas than SRS. SRS does not increase the disease-free rate. In the future, more sensitive methods to detect small gastrinomas, especially in the duodenum and in periduodenal lymph nodes, or more extensive surgery will be needed to improve the postoperative disease-free rate in ZES.

Several studies have demonstrated that gastrinomas, similar to carcinoid tumors and other pancreatic endocrine tumors except insulinomas, have high densities of somatostatin receptors[1–3] and that these can be used to image these tumors using radiolabeled somatostatin analogues.[2–4] Recent studies indicate that somatostatin receptor scintigraphy (SRS) is more sensitive than conventional imaging studies (ultrasound [US], computed tomographic [CT] scan, magnetic resonance imaging [MRI], angiography) at identifying metastatic disease in the liver with these tumors.[2,4–7] It is also more sensitive in many[5,7–10] but not all studies[11,12] at identifying the primary neuroendocrine tumor and extrahepatic metastases.

The impact of SRS on the surgical outcome is unclear in such pancreatic endocrine tumor syndromes as Zollinger-Ellison syndrome (ZES). It is unclear whether the increased sensitivity of SRS will lead to an increased disease-free rate. Some have recommended[13] that surgical exploration should not be done if conventional imaging studies are negative because of the low possibility that exploration will result in cure in such cases. Whether this recommendation is even more applicable with a negative preoperative SRS, because of its increased sensitivity, is unclear. Lastly, in numerous studies of conventional imaging studies, both gastrinoma size and location were determined to be important factors affecting preoperative localization.[14–16] Whether similar influences will affect SRS is unclear because studies involving small numbers of patients provide conflicting messages. One recent study[17] including four duodenal gastrinomas reported that 75% were imaged by SRS as small as 0.4 cm, suggesting that SRS would be useful to localize even small duodenal gastrinomas that are missed currently in 50% to 100% of cases by conventional imaging studies.[8,17–22] However, another study[8] involving eight cases of isolated duodenal gastrinomas reported that 38% were localized; however, routine duodenotomy was not performed and therefore several duodenal tumors could have been missed.[18,23]

The present study was designed to address these issues by prospectively studying 35 consecutive patients with ZES who underwent exploratory laparotomy for possible cure. To address the question of the relative sensitivity of SRS, all patients underwent detailed imaging studies with conventional imaging studies, then SRS with [^{111}In-DTPA-D-Phe^{1}]octreotide with single-photon emission computed tomography (SPECT) imaging before operation. To address the effect of SRS on the disease-free rate, all patients underwent an identical surgical protocol used in our studies before SRS and an identical follow-up protocol to evaluate disease-free status.

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MATERIALS AND METHODS

Since June 1994, all patients with ZES undergoing SRS and considered for surgical resection were included in this protocol. Thirty-five consecutive patients were entered into this protocol. This protocol is part of the ongoing National Institutes of Health prospective study of patients with ZES, approved by the Clinical Research Committee of the National Institute of Diabetes and Digestive and Kidney Diseases. Twenty-seven of the patients had no previous gastrinoma resection. Ten surgical procedures were on 10 patients who had noncurative resections of gastrinomas 1 to 11.4 years (mean 5.5 ± 1.1 years) before the study.

ZES was diagnosed as described elsewhere.[24] Serum gastrin levels were determined by Bioscience Laboratories (New York, NY). The diagnostic criteria for multiple endocrine neoplasia type I (MEN I) in a patient with ZES have been described elsewhere.[25]

Basal acid output and maximal acid output were determined for each patient using methods described previously.[26] Doses of oral gastric antisecretory drug were determined by establishing the dose required to reduce gastric acid output to <10 mEq/hour before the next dose of medication and to <5 mEq/hour in patients who had had gastric acid-reducing surgery or who had advanced esophageal disease.[27]

Time from onset of the disease to exploration was determined for all patients as described previously[24,28] by determining the time of onset as the time of the beginning of continuous symptoms compatible with gastric acid hypersecretion, including peptic ulcer disease, abdominal pain, esophageal reflux disease, or diarrhea that responded to gastric antisecretory treatment.

Specific Protocol

The localization and the extent of gastrinomas were evaluated in all patients as described elsewhere[14,18] by using upper gastrointestinal endoscopy and conventional imaging studies (CT, MRI, transabdominal US,[29] selective abdominal angiography and bone scanning). With MRI, T_1-weighted spin-echo sequences and STIR (short inversion time inversion-recovery sequences) sequences were obtained with a repetition time of 400 to 600 mR (TR = 400 to 600 mR) and an echo time of 10 mR (TE = 10 mR), as described.[30,31] CT scans were performed,[14,31] with 5-mm-thick sections with an oral contrast agent (diatrizoate sodium, Winthrop-Breon, Rensselaer, NY) before and after the rapid (3 ml/sec) intravenous injection of 130 ml of a nonionic contrast agent (iopamidol 300, Winthrop-Breon). Selective abdominal angiography was performed with injection of the splenic, superior mesenteric, gastroduodenal, and hepatic arteries, as described elsewhere.[14,16] One radiologist evaluated the results of all conventional imaging studies (JLD).

SRS was performed as described previously.[5,7] Briefly, patients were hydrated before and after intravenous injection of [^{111}In-DTPA-D-Phe^{1}]octreotide and were routinely administered a laxative on the night of administration to avoid artifacts from radioactive accumulation in the intestine. Each patient was administered 6 mCi intravenously. The [^{111}In-DTPA-D-Phe^{1}]octreotide was obtained from Mallinkrodt Diagnostic Imaging Service Radiopharmacy (Beltsville, MD) and was prepared as a unit dose in an injectable form. Images were obtained at 4 and 24 hours after injection using a Trionix or ADAC dual-headed gamma camera (Research Laboratory Inc., Twinsburg, OH). At 4 hours, a 30-minute whole-body scan, 10-minute planar spot views of the abdomen, and 35-minute SPECT images of the abdomen were obtained. Additional SPECT images of the abdomen were obtained 24 hours after injection. Forty-second, 128 × 128 matrix SPECT images were acquired at 4° intervals. The images were reconstructed with the manufacturer's software using a standard filter back projection algorithm. A Hamming filter (Twinsburg, OH) was used. Images were shown as orthogonal (transverse, coronal, or sagittal) sections and as reprojected views.

All new patients ($n = 27$) and all patients ($n = 10$) who had undergone a previous exploratory laparotomy for possible gastrinoma resection who had extrahepatic gastrinoma localized and did not have diffuse liver metastases, MEN I, or a recent exploration (in the last 6 months) underwent surgical exploration.[32] Patients with MEN I underwent exploration if a tumor ≥3 cm was detected.[33,34] At exploration, an extensive search for the gastrinoma was performed.[18,35,36] Briefly, palpation was performed after an extended Kocher maneuver, endoscopic transillumination of the duodenum was performed,[37] US with a 10-MHz real-time transducer was performed,[18] and a 3-cm longitudinal duodenotomy was centered in the anterolateral surface of the descending (second) duodenum.[18] After surgery, all patients had fasting serum gastrin levels and a secretin provocative test performed before discharge.[24,35] Patients were re-evaluated 3 to 6 months after the resection with conventional imaging studies, including angiography, SRS, and functional studies to assess disease activity (fasting gastrin levels, secretin test, acid secretory tests)[24,35,38,39] and at yearly intervals thereafter. Patients were defined as being disease-free if fasting serum gastrin levels were normal, the secretin test was negative (<200 pg/ml increase postsecretin),[39] and imaging studies, including the SRS, were normal.[24]

The results of the preoperative imaging studies were evaluated by the location of tumors found at exploration and by the results of imaging studies after surgery. In four patients, endoscopic US was used to clarify the location of the lesions seen on SRS or conventional imaging studies. Endoscopic US was performed using an Olympus GF-EUM20 endoscope (Olympus America, Melville, NY). To evaluate the imaging study's sensitivity, both per-patient and per-lesion analyses were performed. There were 74 gastrinomas found at exploration; however, in the lesion-by-lesion analysis, results from two patients were not included in this analysis (two duodenal tumors and two lymph node metastases). Both patients had a duodenal and a lymph node gastrinoma with a single positive focus on the SRS and normal conventional imaging studies. It was not possible to determine which of the two lesions in each patient was positive for the SRS.

Statistics

Fisher's exact test, McNemar test, and Student's t test were used. Values differing by p values < 0.05 were considered significantly different. Correlation coefficients and best fit for tumor size compared to the SRS result were calculated using a least-squares analysis.

RESULTS

The patients in our study resemble those in most large series of patients with ZES in mean age, slight male preponderance, percentage with previous gastric surgery, and basal and maximal acid output (Table 1).[40–42] Only four patients (11%) had MEN I, a figure lower than the 20% to 25% usual occurrence rate in ZES[33,34,40,43–45] because patients with MEN I underwent exploratory laparotomy in our protocol only if lesions ≥3 cm were detected. The average time from onset of ZES until exploration was 9.7 ± 1.2 years (range 1.2 to 26). Five patients (14%) had undergone previous gastric acid-reducing surgery, and one patient had undergone total gastrectomy with no tumor resection (Table 2).

There were 37 surgical explorations for gastrinomas in the 35 patients, of which 27 patients underwent their first exploration for gastrinoma resection (see Table 2). Ten operations were performed in 10 patients who had a previous resection of a gastrinoma. In the previous exploration, four patients had duodenal tumors resected, five patients had lymph nodes containing gastrinoma only found, and one patient had a pancreatic gastrinoma resected; the surgeries were performed a mean of 5.5 ± 1.1 years (range 1.1 to 11) previously. At exploration, in 33 of the 37 patients, our routine gastrinoma procedure was performed,[18] consisting of palpation after an extensive Kocher procedure and mobilization of the distal pancreas, US, duodenal transillumination, and a 3-cm duodenotomy (see Table 2). In four patients who were undergoing a re-exploration, a duodenotomy was not performed because it had been done during the previous procedure. One younger patient (age 40), during a previous exploration elsewhere, was found to have two lymph nodes that were positive for metastatic gastrinoma on biopsy; this patient underwent a Whipple resection when a 1-cm duodenal gastrinoma and three positive lymph nodes were found (see Table 2). One patient with ZES and malignant hypercalcemia with diffuse liver metastases and a 6-cm pancreatic tail gastrinoma underwent distal pancrea-

Table 1. CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS STUDIED

Patient Characteristics	Number
Total number of patients	35
Age (yrs)	
Mean ± SEM	51 ± 1
(Range)	(35–71)
Female gender	14 (40%)
MEN-I present	4 (11%)
Previous gastric surgery*	5 (14%)
Time from onset to surgery (yrs)†	
Mean ± SEM	9.7 ± 1.2
(Range)	(1.2–26)
Fasting serum gastrin (pg/ml)‡	
Mean ± SEM	3692 ± 1114
Median	810
(Range)	(133–550,000)
Basal acid output (mEq/hr)§	
Mean ± SEM	42 ± 5
(Range)	(10–96)
Maximal acid output (mEq/hr)§	
Mean ± SEM	65 ± 6
(Range)	(12–117)

* Gastric surgery includes any previous gastric acid-reducing operation including a previous parietal cell vagotomy (n = 1), vagotomy and Billroth I resection (n = 2), vagotomy and Billroth II resection (n = 1), and total gastrectomy (n = 1).
† Time from onset to surgery was the time from onset of disease as determined as described previously to time of surgery (28).
‡ One patient with a fasting gastrin level of 550,000 pg/ml was not included in the mean.
§ Basal and maximal acid output of the 30 patients without previous gastric acid-reducing surgery are shown.
MEN-I = Multiple Endocrine Neoplasia-type 1.

tectomy and liver transplantation when no lymph node metastases were found (see Table 2).

Gastrinoma was found in all patients at each of the 37 surgeries. In 35 of the 37 surgeries (95%), a gastrinoma resection was performed. One patient had a primary lesion in the caudate lobe of the liver only; a sample was taken for biopsy but the lesion was not resected because it could not be removed by a wedge resection and had been stable in size before surgery for >1 year. One patient had a gastrinoma adherent to the superior mesenteric artery; a sample only was taken for biopsy.

A total of 74 gastrinomas were found: 33 primary tumors and 41 positive lymph nodes. In one patient with MEN I, four duodenal tumors, and three lymph nodes containing metastatic gastrinoma, an additional 15 to 25 small (<0.5 cm) duodenal gastrinomas involving the entire proximal duodenum were not resected. In 19 patients (54%), there were 22 duodenal gastrinomas found (see Table 2). In 6 patients, only duodenal gastrinomas were found, and in 13 patients, lymph node metastases were also present (see Table 2). Pancreatic gastrinomas were found in eight patients (22%); three patients also had a positive lymph node metastasis, and one patient had a pancreatic gastrinoma with metastases limited to the liver. Three patients had likely primary tumors in extrapancreatic, extraduodenal locations: one patient had a gastrinoma limited to the common bile duct, a second patient had an invasive tumor with positive lymph nodes originating from the biliary duct, and a third had a tumor localized to the caudate lobe only over a 5-year period. Eight patients (23%) had gastrinoma in lymph nodes only; however, two of these patients had a duodenal gastrinoma, and one had a pancreatic gastrinoma removed during a previous surgical resection.

Before each of the 37 explorations, conventional imaging studies (US, CT scan, MRI, selective angiography) and SRS were performed; the results are summarized in Table 3. On a per-patient analysis for each exploration, the relative order of sensitivities was SRS (78%), angiography (57%), MRI (57%) ($p < 0.02$), > CT scan (51%) > ($p < 0.01$), > US

Table 2. OPERATION PERFORMED, SURGICAL FINDINGS, AND SURGICAL RESULT

Parameter	Number (%)
Total number of patients	35
Total number of operations	37
Initial surgery for gastrinoma	27 (80)
Previous surgery for gastrinoma*	10 (20)
Operations done	
Duodenotomy†	33 (89)
Tumor resection	35 (95)
Whipple resection‡	1 (3)
Liver transplantation§	1 (3)
No resection‖	2 (5)
Tumor location/extent at surgery	
Duodenal only	6
Duodenal plus lymph node(s)	13
Pancreatic only	3
Pancreatic plus lymph node(s)	4
Other primary site¶	2
Other primary site plus lymph node(s)	1
Lymph node only	8
Disease-free immediately postoperation#	
Initial resection	16 (59)
All patients	21 (60)
Disease-free latest follow-up**	
Initial resection	11 (40)
All patients	15 (43)

* Ten patients previously had a noncurative resection of a gastrinoma.
† Four patients had a duodenotomy on a previous operation.
‡ One patient with duodenal gastrinoma and five positive lymph nodes underwent a Whipple resection.
§ One patient with Zollinger-Ellison Syndrome and malignant-hypercalcemia without bone metastases but with diffuse liver metastases and negative lymph nodes underwent distal pancreatectomy (6 cm tumor) and liver transplantation.
‖ Two patients described in methods section had primary tumors biopsied only.
¶ Other primary sites include two gastrinomas found in biliary ducts and one in the liver.
\# Disease-free immediately postoperation refers to patients with normal fasting gastrin levels and negative secretin tests within 2 weeks of the surgical resection.
** Disease-free latest follow-up refers to patients disease-free as defined in methods section at the last follow-up which was 2 ± 0.1 years postoperatively (range 1.5 mos–3.2 yrs).

Table 3. ABILITY OF VARIOUS IMAGING MODALITIES TO LOCALIZE GASTRINOMAS FOUND AT SURGERY

Imaging Modality	Tumor Imaged			
	Gastrinoma Location			
I. Per Patient*	Duodenum (n = 19) (%)	Pancreatic and Other Primary Sites† (n = 10) (%)	Lymph Node (n = 24) (%)	Total (n = 37) (%)
Ultrasound	0 (0)	2 (20)[f]	5 (21)[h]	6 (16)[i]
CT scan	1 (5)	5 (50)[c]	12 (50)[b,e]	18 (51)[f]
MRI	2 (10)	6 (60)[b]	12 (50)[b,e]	21 (57)[f]
Angiography	3 (15)	6 (60)[a]	12 (50)[a,g]	21 (57)[f]
Any conventional study‡	3 (15)	8 (80)[c]	15 (62)[b]	27 (73)
SRS	6 (32)	9 (90)[c]	20 (83)[c]	29 (78)
II. Per Lesion§	Duodenum (n = 20) (%)	Pancreatic and Other Primary Sites† (n = 11) (%)	Lymph Node (n = 39) (%)	Total (n = 70) (%)
Ultrasound	9 (0)[e]	2 (18)[e]	5 (13)[i]	7 (10)[i]
CT scan	1 (5)	6 (54)[b]	13 (33)[b,i]	20 (29)[i]
MRI	2 (10)	6 (54)[b]	14 (36)[a,h]	22 (31)[i]
Angiography	3 (15)	6 (54)[a]	12 (31)[i]	21 (30)[i]
Any conventional study‡	3 (15)	8 (72)[b]	19 (49)[b,g]	30 (43)[h]
SRS	6 (30)	10 (90)[b]	31 (80)[c]	47 (67)

* Per patient analysis is the results for each patient at each of the 37 exploratory laparotomies.
† Other primary sites refers to primary gastrinomas not found in the pancreas or duodenum and includes two tumors originating in the biliary tract and one in the liver.
‡ Any conventional imaging study refers to the combined results with transabdominal ultrasound, CT scanning, MRI and selective angiography.
§ Per lesion analysis is the ability of the indicated imaging modality to localize each lesion in the indicated location. Results from 33 patients undergoing 35 laparotomies are analyzed. Two patients with a duodenal tumor and a single lymph node metastasis with negative conventional imaging studies are excluded because it was not possible to identify which of the two lesions in each patient was the positive SRS.
a = $p < 0.05$, b = $p < 0.01$, c = $p < 0.001$, or d = $p < 0.0001$ compared to the results with duodenal gastrinomas with the indicated imaging modality; e = $p < 0.05$, f = $p < 0.02$, g = $p < 0.01$, h = $p < 0.001$, i = $p < 0.0001$ compared with result with SRS for the indicated gastrinoma location.
SAS = somatostatin receptor scintigraphy.

(16%) ($p < 0.0001$). SRS was as sensitive as the combination of all conventional studies when analyzed on a per-patient basis (78% *vs.* 70%). However, on a per-lesion basis, SRS was significantly more sensitive ($p < 0.0001$) than all conventional studies combined (69% *vs.* 43%). The addition of all conventional imaging results to SRS detected only three additional lesions (4%) in three different patients. A similar order of sensitivities was obtained when the ability of each imaging modality to localize each of the 70 lesions (duodenal 20, positive lymph nodes 39, pancreatic 8, other sites 3) found at exploration was determined (see Table 3, Figs. 1 and 2). Although the SRS was positive in 78% of patients for a lesion found at exploration, it localized only 67% of all lesions found (see Table 3).

Whether analyzed on a per-patient basis or a per-lesion basis, the sensitivities of the conventional imaging studies, either alone or together, and for SRS were significantly less for identifying duodenal tumors before surgery than for lymph node metastases, pancreatic gastrinomas, or gastrinomas in other primary sites (see Table 3). Examples of such a result are shown in Figure 1 for two patients. In one patient (right panel), conventional imaging studies and SRS demonstrated a single 4-cm lesion in the pancreatic head area. At exploration, the lesion seen on the conventional imaging studies and the SRS was a 4-cm peripancreatic lymph node containing metastatic gastrinoma. No preoperative imaging study identified the 1-cm gastrinoma resected from the second part of the duodenum. In the second patient (left panel), all conventional imaging studies were negative before surgery; however, the SRS demonstrated a lesion in the midpancreatic area that, by endoscopic US, was in the same position as an enlarged 2.5-cm lymph node. At surgery, a 2.2-cm lymph node containing metastatic gastrinoma was found in this area; however, all studies missed a 0.5-cm primary gastrinoma in the beginning of the fourth part of the duodenum.

To provide additional insight into the basis for the difference in imaging studies in identifying gastrinomas in different tissues, we compared the size of the gastrinoma in different tissues with the ability of SRS to localize it. Most duodenal gastrinomas (73%) were ≤1.1 cm in diameter, whereas most primary gastrinomas in other locations and in metastatic lymph nodes were >1.1 cm (Fig. 3A). The mean diameter of duodenal gastrinomas was 0.95 ± 0.11 cm, significantly less than the 2.1 ± 0.4 cm of pancreatic and other nonpancreatic, nonduodenal sites and the 2.6 ± 0.4 cm of metastatic lymph nodes (Fig. 3B). Similarly, SRS detected significantly fewer duodenal gastrinomas (30%)

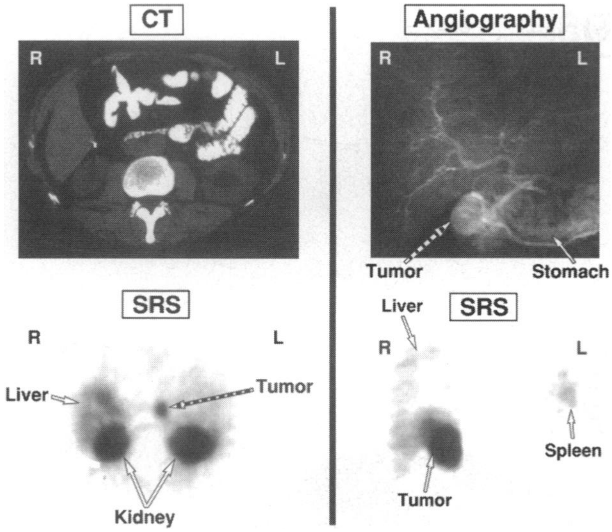

Figure 1. Ability of conventional imaging studies and SRS to localize gastrinomas before surgery in two patients with a duodenal gastrinoma and metastatic lymph node. In the left panel are shown results from a patient in whom the CT scan (top) was negative but the SRS demonstrated a lesion in the midpancreas. On endoscopic US, this represented a 2.5-cm peripancreatic lymph node. At surgery, a 2.2-cm peripancreatic lymph node was found at the lower border of the pancreas in the same area as the lesion on SRS. After a duodenotomy, a 0.5-cm duodenal gastrinoma was found in the beginning of the fourth part of the duodenum; this was not detected by tumor localization studies before surgery. In the right panel, in another patient a selective injection of the gastroduodenal artery demonstrated a 4-cm lesion in the pancreatic head area. SRS demonstrated a single tumor in the same location seen on angiography by SPECT imaging. At surgery, a 4-cm peripancreatic lymph node was found in the pancreatic head area in the same location as the lesion was seen before surgery. After a duodenotomy, a 1-cm gastrinoma was found in the second part of the duodenum. These two patients demonstrate the inability of conventional imaging studies or SRS to identify small duodenal gastrinomas, whereas one or both detected the larger lymph node metastasis.

than primary tumors in other sites (90%) or metastatic lymph nodes (80%) (see Fig. 3B). That this difference in detection rate is largely the result of tumor size, not the tissue *per se*, is suggested by the data in Figures 3C and 3D. When tumors were <1.1 cm, SRS detected only 30%, whereas for larger tumors it had a markedly increased sensitivity ($p < 0.02$), detecting 64% of tumors 1.1 to 1.9 cm. It had an even greater sensitivity ($p < 0.01$) of 96% for detecting tumors >2 cm (see Fig. 3C). Significantly fewer gastrinomas were detected, the smaller the size for both the lymph node metastases and primary tumors (see Fig. 3D). In fact, when the gastrinoma's median size was correlated with the ability of SRS to detect the gastrinoma, there was a highly significant positive correlation ($r = 0.97$, $p = 0.01$) between the two variables, with the regression equation best fitted by the equation $y = 37x + 11$ (Fig. 4).

An example of the sensitivity of SRS for detecting gastrinomas >1.1 cm in diameter is shown in Figure 2. This patient had a biochemical relapse 4 years after a resection of a 4-cm pancreatic tail gastrinoma with four positive lymph nodes, and SRS demonstrated six lesions extending from the pancreatic head across to the pancreatic tail, two of which were seen on conventional imaging studies to be 1.5- and 2-cm lymph nodes. At surgery, all lesions were found to be metastatic disease in lymph nodes, and each was >1.1 cm in diameter (see Fig. 2).

To determine whether the use of SRS might be altering the ability to render patients disease-free, we determined the disease-free rate for all patients and for the 27 patients who had gastrinoma resections for the first time and underwent an identical surgical protocol to that which we reported previously[35] in 80 patients before the availability of SRS. For all patients, 60% were disease-free in the immediate postoperative period, and 43% were disease-free with a mean follow-up of 2 ± 0.1 years (range 1.5 months to 3.2 years) (see Table 2, Fig. 5). For the 27 patients undergoing their initial gastrinoma resection, the immediate postoperative disease-free rate was 59%; at 2.1 ± 0.1 years after resection, the disease-free rate was 41% (see Fig. 5).

DISCUSSION

Numerous recent studies have demonstrated that in patients with ZES, similar to patients with carcinoid tumors and other pancreatic endocrine tumors except insulinomas, SRS is the most sensitive imaging modality for detecting either the primary tumor or hepatic metastases.[2–7,9,17,20] It remains unknown whether this increased sensitivity will result in an increased disease-free rate after resection. Further, several aspects of SRS remain unclear in relation to surgical exploration in patients with ZES. If the recommended complete surgical exploration is performed routinely (extensive Kocher maneuver with careful palpation, US, duodenal transillumination, and duodenotomy), the percentage and location of gastrinomas that might be missed by SRS remain unclear.[18,35,46] Further, some have recommended[13] that routine surgical exploration should not be performed in patients with ZES unless a clearly definable lesion is seen on imaging studies. To determine whether this recommendation is justified, it is important to establish the results of exploration in patients who have had a preoperative SRS to determine what type of lesion it misses. Lastly, it remains unclear, for gastrinomas in various locations not detected by SRS, whether lesion size or location is the important determinant. With conventional imaging studies and with methods such as surgical US, both tumor size and location are important factors in determining whether gastrinomas are detected before surgery.[14–16,29,30,47]

These uncertainties in the utility of SRS exist because, in various series of its use in patients with gastrointestinal neuroendocrine tumors,[5,8,9,17,48] not all patients underwent exploration, and relatively few patients with gastrinoma were included; therefore, there were not sufficient patients to allow comparison of tumor size, location, and SRS detection rate. Further, detailed exploration with duodenotomy was not always performed, so a true assessment of the detection of small duodenal tumors was not available.

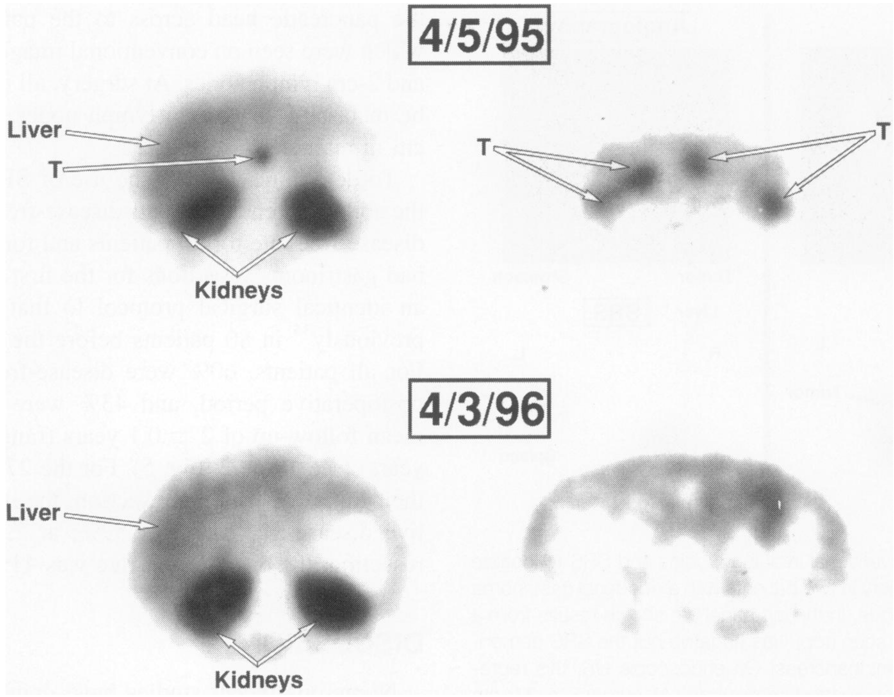

Figure 2. SRS in a patient with recurrent gastrinoma. This patient had a 4-cm pancreatic tail gastrinoma with four metastatic lymph nodes resected 4 years before the present study. Increasing fasting gastrin levels documented a recurrence, and conventional imaging studies (US, CT, MRI, angiography) demonstrated two enlarged peripancreatic lymph nodes of 1.5 and 2.5 cm. SRS showed six lesions, one in the pancreatic head area and five in the mid and distal peripancreatic area. Five of these are shown in the two top SRS transverse sections. At surgery, six lymph nodes (1.2, 2.1, 1.5, 1.3, 1.5 cm) in the indicated locations were found and excised. The two lower SRS sections are the same projections after surgery, when the fasting gastrin and secretin tests were negative, as was the SRS. This case illustrates that SRS has greater sensitivity for metastatic gastrinoma in lymph nodes >1 cm in diameter, even in a widely separate area, than conventional imaging studies.

Lastly, the same type of surgical protocol was not carried out in any of the studies before and after the introduction of SRS to allow the effect of SRS on the disease-free rate to be established unequivocally.

The present study was designed to address each of these issues. Specifically, we had two primary aims: first, to determine the sensitivity of SRS for detecting gastrinomas in different locations and whether gastrinoma location or tumor size was an important variable for detection by SRS, and second, to determine whether the use of SRS altered the percentage of patients with gastrinoma rendered disease-free.

In regard to the first aim of evaluating the results of SRS after a standardized surgical exploration, we found that SRS detected 67% of all the gastrinomas found at exploration, including 52% of primary gastrinomas found and 80% of lymph nodes containing metastatic gastrinoma. Therefore, SRS missed approximately one third of all extrahepatic gastrinomas that were found at exploration in our study. Similar to several other studies,[2,4,5,8,9,17,20] we found that SRS was significantly more sensitive than conventional imaging studies and on a lesion-by-lesion basis was even more sensitive than all conventional imaging studies combined (US, CT scan, MRI, selective angiography) (67% *vs.* 43%, $p < 0.001$). The addition of all conventional studies to SRS detected only three (4%) additional lesions found at exploration in three patients. These results address the question recently raised[5,17] as to whether SRS will complement or replace conventional imaging studies before surgery in patients with ZES, suggesting that SRS can largely replace conventional localization studies. In the present study, SRS detected only 30% of duodenal gastrinomas; however, it detected 90% of pancreatic gastrinomas or primary gastrinomas in other locations. These results are similar to a recent study[8] in which SRS detected only 38% (3 of 8) duodenal gastrinomas; however, this differs from another study[17] in which 75% of the duodenal gastrinomas (3 of 4) were detected. In this latter study, gastrinoma size did not appear to be a factor in SRS detection because in contrast to conventional imaging, which failed to detect any gastrinoma <1 cm, SRS detected 57% (4 of 7 tumors) of gastrinomas <1 cm, including one 0.4-cm duodenal tumor.

Several results in our study support the conclusion that the ability of SRS to detect a gastrinoma is primarily related to the size of the tumor, not to the site of the gastrinoma. First, duodenal gastrinomas had an average size approximately half that of either primary gastrinomas in other locations or lymph node metastases and were detected sig-

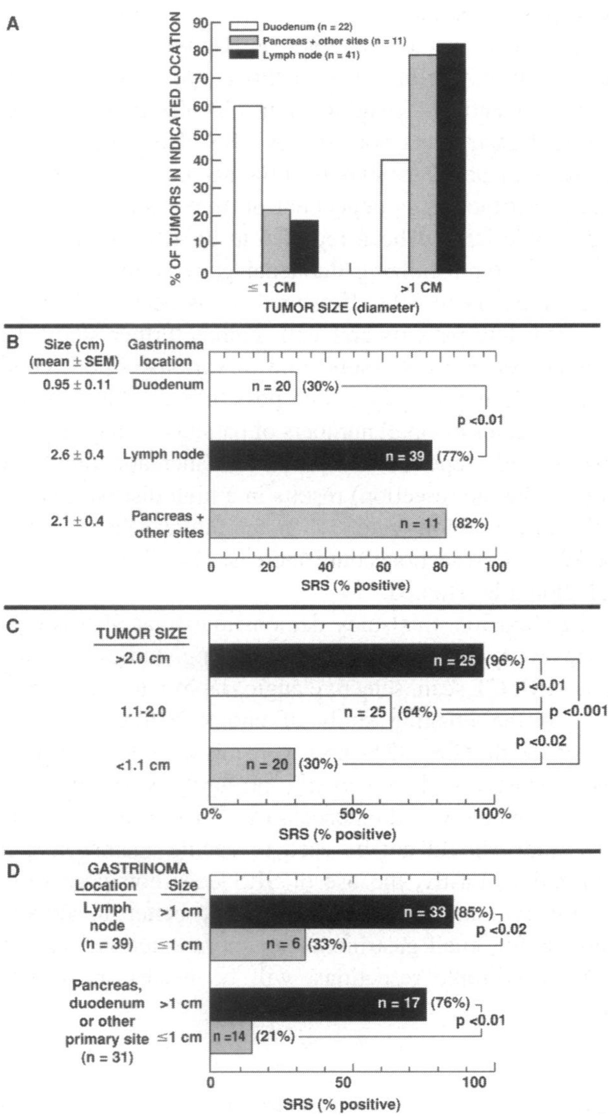

Figure 3. Location and size of gastrinomas and ability of SRS to image tumors of different size and location. (A) Location and size of the 74 gastrinomas. Shown is the percentage of the 22 duodenal and 8 pancreatic as well as 3 primary gastrinomas in nonduodenal pancreatic sites and 41 lymph nodes positive for metastatic tumor that measured >1 cm and ≤1 cm. Results are expressed as the percentage of the gastrinomas at the indicated locations that were >1 cm or ≤1 cm. (B) Comparison of the mean size and ability of SRS to localize gastrinomas in different locations. Shown are the mean sizes of 20 duodenal, 8 pancreatic, and 3 primary gastrinomas in nonduodenal pancreatic sites and 39 lymph nodes positive for metastatic tumor. The percentage of each of the gastrinomas in the indicated locations that were localized before surgery by SRS is shown. Duodenal gastrinomas were significantly smaller than pancreatic gastrinomas or primary tumors in other locations or metastatic lymph nodes. Similarly, SRS had significantly lower sensitivity for detecting duodenal gastrinomas. (C) Ability of SRS to detect gastrinomas of different sizes. The 70 gastrinomas found at surgery were divided into three different groups by tumor diameter and the percentage of each group identified before surgery by SRS. (D) Ability of SRS to detect gastrinomas of different sizes in different locations. The 70 gastrinomas found at surgery were divided into groups depending on the tissue diameter and tumor location. The numbers within the column refer to the number of tumors in each group. The percentage is the percentage of tumors detected in each group correctly identified by SRS before surgery. SRS detected 28 of 33 lymph nodes >1 cm in diameter and 15 of 17 primary gastrinomas of this size, whereas for gastrinomas <1 cm it detected 2 of 6 lymph nodes and 3 of 14 primary tumors.

nificantly less often by SRS than the gastrinomas in other locations. Second, the ability of SRS to detect lesions in any tissue correlated directly ($r = 0.97$) and significantly ($p = 0.01$) with the size of the tumor. Lastly, SRS detected small lymph node metastases (<1 cm) as poorly as it detected small primary gastrinomas and conversely detected large lymph node metastases as well as it detected large primary gastrinomas. These latter results argue strongly that the size of the gastrinoma is an important determinant.

The mechanism of the size effect was not examined in the present study; however, it could be that the number or the density of somatostatin receptors present that can bind radiolabeled octreotide, the amount of radioactivity that needs to be internalized by the tumor to allow detection, the resolution of the radionuclide detector, or possibly the subtype of somatostatin receptor present could change as the tumor increases in size. The resolution of the radionuclide detector may be an important factor in many duodenal tumors because they are frequently in close proximity to larger peripancreatic metastatic lymph nodes, whose image could obscure that of the primary gastrinoma. An observation suggesting tumor size *per se* is an important variable is the fact that small gastrinomas in other sites were detected with the same low frequency as duodenal gastrinomas. Further, only 33% (2 of 6) of the small isolated duodenal gastrinomas were detected; this figure did not differ significantly from the 25% (4 of 16) detected by SRS when a peripancreatic node was present. Similar results[49,50] have been reported using different radionuclides to image parathyroid adenomas and have been shown to be related to the size of the adenoma, suggesting that the amount of radioactivity that needs to be internalized to provide adequate resolution may be an important variable.

The low 30% detection rate for duodenal gastrinomas in our study is compatible with the fact that the SRS has a limited ability to detect small gastrinomas (≤1 cm), and that 60% of duodenal gastrinomas were ≤1 cm in our study. In a recent large study[28] in which 48 duodenal gastrinomas were analyzed, 92% of all the duodenal gastrinomas were ≤1 cm. These results suggest that the addition of SRS will be of limited use for the preoperative localization of duodenal gastrinomas. Because duodenal gastrinomas represent 50% to 90% of all the primary gastrinomas found in patients with ZES in recent series,[8,28,40] these results suggest that additional localization methods will need to be evaluated if duodenal gastrinomas are to be localized before surgery. This point is discussed further below.

The second aim of our study was to determine whether the use of SRS increased the percentage of patients rendered

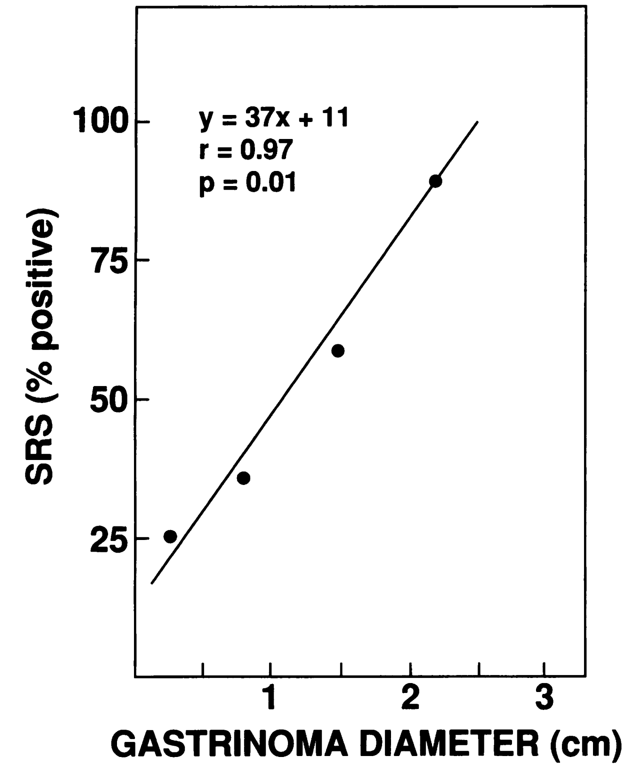

Figure 4. Correlation of gastrinoma size with SRS result. Gastrinomas were grouped into four sizes of <0.5 cm, 0.5 to 1.1 cm, 1.2 to 1.5 cm, and 1.6 to 2.5 cm in diameter, containing 4, 17, 19, and 16 gastrinomas, respectively. The median size of each group was plotted against the percentage of each group detected by SRS. The correlation coefficient (r) and best fit was determined by least-squares analysis.

disease-free. Sixty percent of our patients were disease-free immediately after surgery; 43% were disease-free at 2 years of mean follow-up.[24,35] To compare this disease-free rate to the disease-free rate in our previous series involving patients before SRS was available, it is important to consider whether the operation was the initial resection of a gastrinoma or was performed for recurrence. Our previous studies show that the disease-free rate was much lower in patients who underwent surgery for recurrence than after the initial exploration (30% *vs.* 59% immediately after surgery).[24,32,35] In the present study, 20% of the patients were undergoing exploration for a recurrence and were not undergoing their initial exploration. The disease-free rate in the 27 patients undergoing their initial exploration was compared to results from an identical surgical protocol used in 81 patients that we reported in two pre-SRS surgical studies.[24,35] Neither immediately after surgery (disease-free status 50% to 59%) nor at 2 years of mean follow-up (38% to 45%) was there a difference in the disease-free rate between the two pre-SRS studies and the present post-SRS study. These results demonstrate that although SRS is much more sensitive than the previously used conventional localization methods, it is not sufficiently more sensitive to improve the disease-free rate.

This result has important implications for the future if the long-term disease-free rate is to be improved further. Tumor localization methods other than SRS must be developed to localize small occult gastrinomas. Conventional imaging studies will not be of value for this purpose. In the present study, conventional imaging studies localized only a single duodenal gastrinoma not seen by SRS. This figure is consistent with previous studies showing that their ability to image gastrinomas is dependent on tumor size.[14,16,17,29,51] Endoscopic US has been reported to be a sensitive modality[8,21,52,53] for localizing duodenal gastrinomas and to be complementary to SRS. However, it has been evaluated in relatively few patients and will require further study. Besides endoscopic US, application of various radiodetection methods during surgery is one possibility.[54] Alternatively, several studies of small numbers of patients with gastrinoma have recently reported that proximal pancreaticoduodenectomy (Whipple resection) results in a high disease-free rate with a low morbidity rate.[55–58] In the future, selective use of the Whipple resection could increase the disease-free rate and should be studied.

In conclusion, this study demonstrates that SRS is equal in sensitivity to all conventional imaging studies combined (US, MRI, CT scan, selective angiography) and can replace them as the imaging study of choice before surgery in patients with ZES. SRS, however, missed one third of the gastrinomas found at surgery, primarily small duodenal tumors found by a duodenectomy. Therefore, a negative SRS study should not be used to decide against surgical exploration. Lastly, the use of SRS does not increase the disease-free rate; to accomplish this, better localization methods for small gastrinomas or more extensive surgery, such as Whipple resections, will be needed in selected cases.

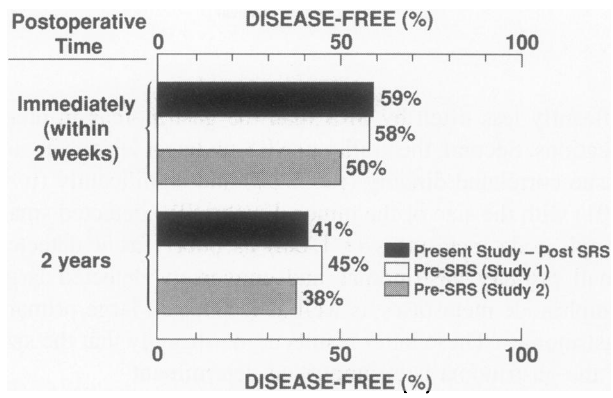

Figure 5. Comparison of disease-free rates in studies before and after SRS in patients with ZES. Disease-free was defined as a negative secretin test, normal fasting gastrin levels, and negative tumor localization studies after resection.[24] Results were calculated immediately after surgery (within 2 weeks of resection) and at a mean follow-up of 2 years. The post-SRS results are from this study for the 27 patients who underwent a first-time resection using an identical protocol to that used in the other two studies.[24,35] The first pre-SRS study, by Norton et al,[35] included 73 patients and the shortest follow-up was 3 months. The second study[24] included these 73 patients plus 8 additional patients (81 patients total).

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