

## SURGERY TO CURE THE ZOLLINGER-ELLISON SYNDROME

JEFFREY A. NORTON, M.D., DOUGLAS L. FRAKER, M.D., H. RICHARD ALEXANDER, M.D., DAVID J. VENZON, PH.D., JOHN L. DOPPMAN, M.D., JOSE SERRANO, M.D., PH.D., STEPHAN U. GOEBEL, M.D., PAOLO L. PEGHINI, M.D., PRAVEEN K. ROY, M.D., FATHIA GIBRIL, M.D., AND ROBERT T. JENSEN, M.D.

**ABSTRACT**

**Background and Methods** The role of surgery in patients with the Zollinger–Ellison syndrome is controversial. To determine the efficacy of surgery in patients with this syndrome, we followed 151 consecutive patients who underwent laparotomy between 1981 and 1998. Of these patients, 123 had sporadic gastrinomas and 28 had multiple endocrine neoplasia type 1 with an imaged tumor of at least 3 cm in diameter. Tumor-localization studies and functional localization studies were performed routinely. All patients underwent surgery according to a similar operative protocol, and all patients who had surgery after 1986 underwent duodenotomy.

**Results** The 151 patients underwent 180 exploratory operations. The mean ( $\pm$ SD) follow-up after the first operation was  $8\pm 4$  years. Gastrinomas were found in 140 of the patients (93 percent), including all of the last 81 patients to undergo surgery. The tumors were located in the duodenum in 74 patients (49 percent) and in the pancreas in 36 patients (24 percent); however, primary tumors were found in lymph nodes in 17 patients (11 percent) and in another location in 13 patients (9 percent). The primary location was unknown in 24 patients (16 percent). Among the patients with sporadic gastrinomas, 34 percent were free of disease at 10 years, as compared with none of the patients with multiple endocrine neoplasia type 1. The overall 10-year survival rate was 94 percent.

**Conclusions** All patients with the Zollinger–Ellison syndrome who do not have multiple endocrine neoplasia type 1 or metastatic disease should be offered surgical exploration for possible cure. (N Engl J Med 1999;341:635-44.)

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**T**HE Zollinger–Ellison syndrome is characterized by severe peptic ulcer disease that results from gastrin-secreting tumors (gastrinomas) of the gastrointestinal tract.<sup>1,2</sup> In about 75 percent of patients the tumors are sporadic, and 25 percent of patients have multiple endocrine neoplasia type 1 (MEN-1).<sup>1,3</sup> Patients with the Zollinger–Ellison syndrome have two problems that require treatment<sup>4</sup> — the hypersecretion of gastric acid and the gastrinoma itself.<sup>1,2</sup> Although most gastrinomas grow slowly, 60 to 90 percent are malignant and 25 percent show rapid growth.<sup>2,5,6</sup>

The hypersecretion of acid can now be controlled in almost every patient by the administration of inhibitors of gastric H<sup>+</sup>/K<sup>+</sup>-ATPase.<sup>1,7</sup> Therefore, the

natural history of the gastrinoma is becoming the main determinant of long-term survival.<sup>1,5,8</sup> Surgical excision is the logical treatment; however, the role of surgery in patients with sporadic gastrinomas<sup>1,9,10</sup> and in patients with MEN-1<sup>10-13</sup> is controversial. Because the tumors are uncommon, few studies have involved enough patients to permit analysis of the variables that could affect surgical outcome. In studies undertaken before effective medical treatment was available, many patients died from acid-related complications, so the effects of resection of the gastrinoma were often not clear. As a result, there is no agreement on whether no,<sup>9,10</sup> some,<sup>9,10,14</sup> or all<sup>15</sup> patients with the Zollinger–Ellison syndrome should undergo surgical exploration. To address these issues, in 1981 the National Institutes of Health began a prospective study of the results of surgical resection according to a fixed protocol in consecutive patients with the Zollinger–Ellison syndrome. The study was designed to allow the incorporation of any advances in preoperative or operative localization of tumors into the study so that the results would reflect the best available surgical treatment.

**METHODS**

All patients with a diagnosis of the Zollinger–Ellison syndrome who were referred to the National Institutes of Health starting in 1981 were considered for the surgical protocol. Previous reports have described the methods used (including the standard operative approach, duodenotomy, preoperative tumor localization, and postoperative assessment of cure), the immediate postoperative and 3-to-6-month cure rate in 32 patients, the results of adding routine duodenotomy to the protocol and the 45-month cure rate in 73 patients with sporadic gastrinomas, and the immediate postoperative cure rate in 10 patients with MEN-1.<sup>16-19</sup> The study was approved by the Clinical Research Committee of the National Institute of Diabetes and Digestive and Kidney Diseases, and all patients gave written informed consent.

The diagnosis of MEN-1 in study patients with the Zollinger–Ellison syndrome was based on studies of acid secretion, measurements of fasting serum gastrin, the results of secretin and calcium tests of gastrin secretion, the presence of a family history compat-

From the Department of Surgery, University of California, San Francisco, and the San Francisco Veterans Affairs Medical Center, San Francisco (J.A.N.); the Surgical Metabolism Section, Surgery Branch, National Cancer Institute, Bethesda, Md. (D.L.F., H.R.A.); the Biostatistics and Data Management Section, National Cancer Institute, Bethesda, Md. (D.J.V.); the Diagnostic Radiology Department, Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, Md. (J.L.D.); and the Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Md. (J.S., S.U.G., P.L.P., P.K.R., E.G., R.T.J.). Address reprint requests to Dr. Jensen at NIH/NIDDK/DDB, Bldg. 10, Rm. 9C-103, 10 Center Dr., MSC 1804, Bethesda, MD 20892-1804, or at robertj@bdg10.niddk.nih.gov.

ible with the diagnosis of MEN-1, and the presence of associated endocrinopathies that occur in patients with MEN-1.<sup>20</sup>

### Surgical Protocol for the Cure of Gastrinoma

We evaluated the location of the primary tumor (or in some patients, of the multiple primary tumors) and the location of metastatic gastrinomas in all patients, using conventional imaging studies (computed tomography, magnetic resonance imaging, transabdominal ultrasonography, and selective abdominal angiography).<sup>18,21,22</sup> Starting in June 1994, all patients also underwent somatostatin-receptor scintigraphy.<sup>22</sup> Functional localization of the gastrinoma was performed with the use of either transhepatic portal venous sampling (January 1980 to April 1992) or hepatic venous sampling after the selective intraarterial injection of secretin to obtain blood samples for measurements of serum gastrin (January 1988 to the present).<sup>23,24</sup>

We enrolled patients in the surgical protocol for possible cure, on the basis of criteria described previously,<sup>16-19,25</sup> if they had not undergone previous resection of the gastrinoma or if they had undergone an unsuccessful laparotomy and were later found on imaging studies to have a localized extrahepatic gastrinoma and if they did not have MEN-1. Patients with MEN-1 underwent exploration if a tumor of 3 cm or larger was detected by imaging.<sup>19</sup> Patients with liver metastases thought to be completely resectable were included. We used two surgical protocols.<sup>17</sup> Before 1987, an extensive search for the gastrinoma was performed through palpation, intraoperative ultrasonography,<sup>18</sup> and an extended Kocher maneuver,<sup>16,17</sup> which involves elevating the duodenum and pancreatic head by dividing the ligamentous attachments to the retroperitoneum. In 1987, additional procedures were added for localizing duodenal gastrinomas.<sup>17,18</sup> These included endoscopic transillumination of the duodenum at surgery and a longitudinal incision of 3 cm in the descending duodenum.<sup>18</sup>

Tumors in the head of the pancreas were enucleated. Tumors in the body and tail of the pancreas were enucleated if possible; otherwise, they were resected. Before the patients were discharged from the hospital, serum gastrin was measured before and after the administration of secretin.<sup>17,26</sup> The patients were reevaluated with imaging studies and the same serum gastrin measurements three to six months after resection and at yearly intervals thereafter.<sup>17,26,27</sup> Patients were considered to be free of disease if fasting serum gastrin concentrations were normal, the secretin test was negative,<sup>27</sup> and imaging studies were negative.<sup>26</sup> A gastrinoma of the lymph node was termed a primary tumor if it occurred in a patient who was free of disease after resection of a gastrinoma that was only in a lymph node. For the secretin test, 2 units of secretin (Ferring Laboratories, Suffern, N.Y.) per kilogram of body weight were given by intravenous bolus injection after temporary discontinuation of antisecretory-drug therapy, and serum gastrin was measured 2, 5, 10, and 20 minutes later. A normal response was defined as an increase in the serum gastrin concentration of less than 200 pg per milliliter (95.4 pmol per liter) above the preinjection value; a greater increase was interpreted as indicating a gastrinoma.

Preoperative hypersecretion of gastric acid was controlled medically in all patients.<sup>28</sup> Control of acid secretion was reevaluated three to six months after surgery, and antisecretory-drug therapy was then discontinued or the dose decreased if possible.<sup>29</sup>

### Statistical Analysis

We used Fisher's exact test or the chi-square test to compare categorical variables and the Mann-Whitney U test to compare continuous variables. The probabilities of survival and disease-free survival were calculated and plotted according to the method of Kaplan and Meier.<sup>30</sup> We compared the probabilities of survival at predetermined times using Greenwood's formula for the standard error of the survival estimates and the standard large-sample formula for the difference between two independent proportions. The disease-free rate was calculated as the percentage of patients who were free of disease during a specific follow-up period. The

disease-free rates are estimates of the frequency of recurrence among patients who had long-term follow-up; these rates differ from the disease-free survival rates calculated from the Kaplan-Meier estimates of the survival probabilities in the entire cohort.

## RESULTS

Between December 1981 and August 1998, we enrolled 151 patients with the Zollinger-Ellison syndrome, of whom 123 had sporadic gastrinomas and 28 had gastrinomas with MEN-1 (Table 1). The patients with MEN-1 were younger and had higher preoperative serum gastrin concentrations while fasting than the patients with sporadic gastrinomas, but the groups were otherwise similar.

Before the surgery, conventional imaging studies were positive in 24 to 48 percent of the patients with sporadic gastrinomas (Fig. 1). Somatostatin-receptor scintigraphy was positive in 79 percent of the 54 patients with sporadic gastrinomas who underwent testing and was equal in sensitivity to the results with all conventional imaging studies combined ( $P=0.07$ ) (Fig. 1). In patients with sporadic gastrinomas, functional localization by measurement of gradients in serum gastrin concentrations had greater sensitivity than any conventional imaging study ( $P<0.001$ ), but the sensitivity was not greater than that of somatostatin-receptor scintigraphy (Fig. 1). More patients with MEN-1 than with sporadic gastrinomas had positive results on conventional imaging studies, as a result of the admission criterion of an imaged mass of 3 cm or greater.

### Operative Findings

The 151 patients underwent 180 operations; 23 patients had 2 operations, and 2 had 3 or more operations (Table 2). Gastrinomas were found in 88 percent of the initial surgical explorations and 100 percent of subsequent explorations, with no significant differences between patients with sporadic gastrinomas and patients with MEN-1. Gastrinomas were found during subsequent operations in seven patients who had negative results on the initial operations. Gastrinomas were found in 96 percent of all surgical explorations performed beginning in 1987, when additional procedures were included to localize duodenal gastrinomas at surgery. Before these procedures were used, gastrinomas were found in only 68 percent of operations. This difference was due almost entirely to the difference in results for patients with sporadic gastrinomas. Starting in March 1991, gastrinomas were found in 81 consecutive patients who underwent 87 operations.

A primary tumor was found in 93 percent of all patients — 93 percent of the patients with sporadic gastrinomas and 96 percent of the patients with MEN-1 (Table 2). In the patients with sporadic gastrinomas, the primary tumor was the gastrinoma, but not all of the tumors in patients with MEN-1 were gastrinomas. Two of the 5 tumors (40 percent)

**TABLE 1.** CHARACTERISTICS OF THE 151 PATIENTS WITH THE ZOLLINGER-ELLISON SYNDROME BEFORE INITIAL SURGICAL EXPLORATION.\*

CHARACTERISTIC	SPORADIC GASTRINOMAS (N=123)	MEN-1 (N=28)	TOTAL (N=151)
Age — yr	49±10	43±14†	48±10
Male sex — no. (%)	80 (65)	14 (50)	94 (62)
Duration of symptoms before surgery — yr‡	7±4	11±8	8±7
Time from surgery to last follow-up or death — yr	8±4	7±5	8±5
Preoperative basal acid secretion — mmol/hr§	45±26	43±28	45±26
Preoperative serum gastrin during fasting — pg/ml¶			
Mean	1908	26,800	6529
Range	113–36,000	225–550,000	113–550,000
Previously attempted resection of gastrinoma — no. (%)	1 (1)	2 (7)	3 (2)
Previously abdominal surgery — no. (%)**			
None	100 (81)	21 (75)	121 (80)
Any	23 (19)	7 (25)	30 (20)
Preoperative therapy with gastric antisecretory drugs — no. (%)			
H <sup>+</sup> /K <sup>+</sup> -ATPase inhibitor	66 (54)	15 (54)	81 (54)
Histamine H <sub>2</sub> -receptor antagonist	57 (46)	11 (39)	68 (45)
None	0	2 (7)	2 (1)

\*Plus-minus values are means ±SD. MEN-1 denotes multiple endocrine neoplasia type 1.

†P=0.007 for the comparison with the patients with sporadic gastrinomas.

‡The duration of symptoms before surgery was the time from the onset of symptoms of peptic ulcer disease until surgery at the National Institutes of Health.

§Preoperative basal (unstimulated) acid secretion was measured in 111 patients with sporadic gastrinomas and 19 patients with MEN-1 who had not had a previous operation to reduce gastric acid or a previous total gastrectomy.

¶To convert values for gastrin to picomoles per liter, multiply by 0.477.

||P=0.003 for the comparison with the patients with sporadic gastrinomas.

\*\*Previous abdominal surgery included surgery to reduce gastric acid in 16 patients, attempted resection of gastrinomas in 3 patients, oversew of perforated peptic ulcer in 8 patients, cholecystectomy in 3 patients, repair of hiatal hernia in 1 patient, and resection of a colon tumor in 1 patient.

resected in patients with MEN-1 before 1987 were gastrinomas; thereafter, 17 of the 26 tumors resected in patients with MEN-1 after 1986 were gastrinomas.

The most frequent location of the gastrinoma was the duodenum (Table 2). In patients with sporadic gastrinomas, duodenal gastrinomas were 3.4 times as common as pancreatic gastrinomas (47 percent of patients vs. 14 percent of patients), and in patients with MEN-1, duodenal gastrinomas were 2.7 times as common as pancreatic gastrinomas (including only tumors that stained positive for gastrin; 16 of 28 patients vs. 6 of 28 patients) (Table 2). Eleven percent of all patients, primarily the patients with sporadic gastrinomas, had gastrinomas classified as primary lymph-node gastrinomas,<sup>31,32</sup> and 9 percent had primary gastrinomas in sites other than the duodenum, pancreas, or lymph nodes. A larger percentage of patients with MEN-1 had pancreatic tumors (68 percent, vs. 14 percent among patients with sporadic gastrinomas; P=0.002); however, when only patients who had positive staining for gastrin were consid-

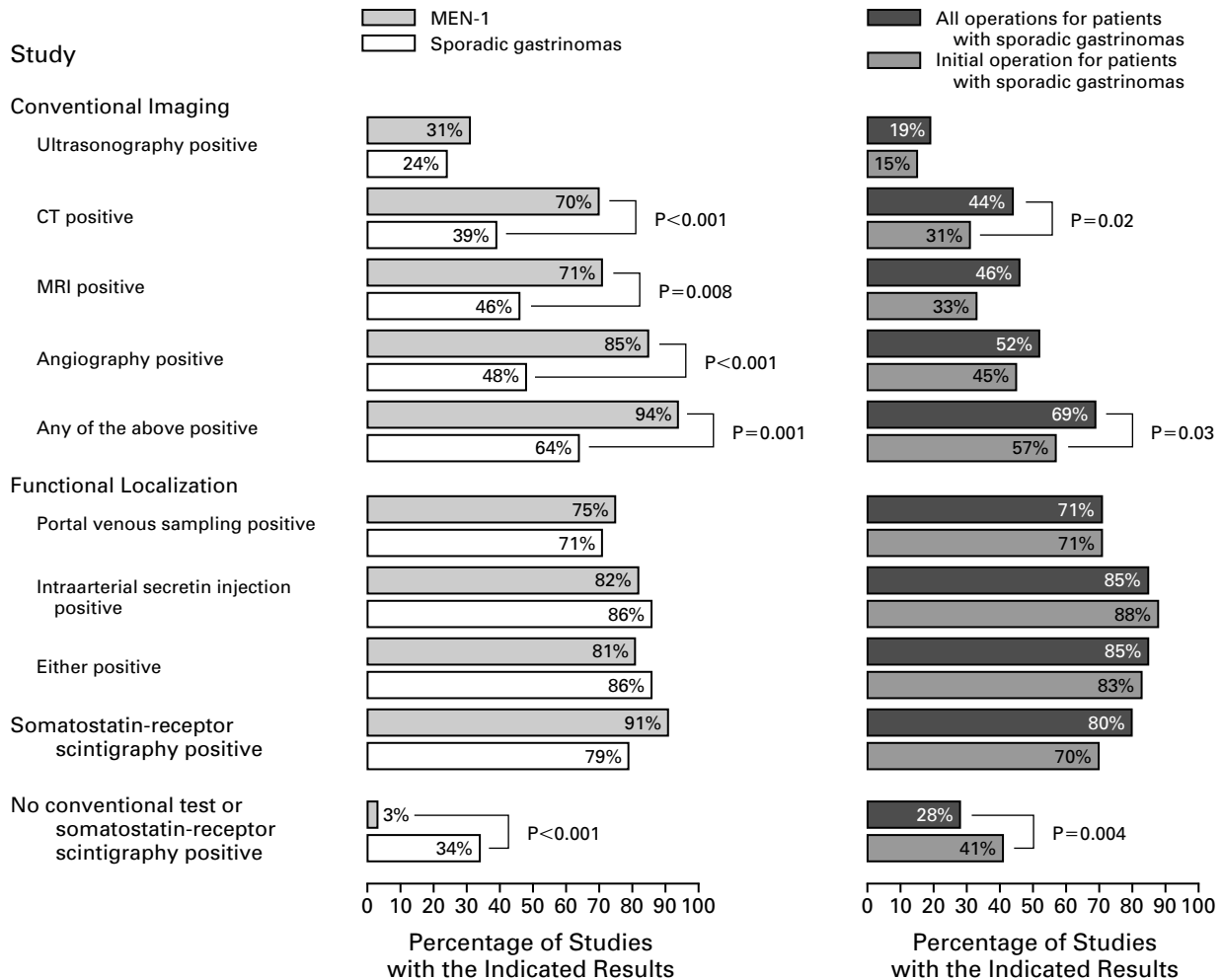
ered, only one third of the pancreatic tumors in the patients with MEN-1 were gastrinomas.

In terms of the extent of the tumor, only a primary tumor was found in 48 percent of the 151 patients, mainly in patients with sporadic gastrinomas. For all patients, metastases occurred most commonly to lymph nodes, and duodenal gastrinomas were more frequently associated with lymph-node metastases than were primary tumors in other sites.

The gastrinomas were resectable in almost all patients; only a biopsy was performed in 2 percent of the surgical explorations (Table 2). Tumor resection or enucleation was possible in 76 percent of the patients. A distal pancreatectomy was required in 14 percent of the patients, and a hepatic resection in 8 percent.

**Follow-up**

Forty-five percent of the patients were free of disease immediately after the resection of their gastrinomas, mostly patients with sporadic gastrinomas (Table 3 and Fig. 2). Of the patients with MEN-1,



**Figure 1.** A Comparison of the Results of Preoperative Imaging Studies in All Patients with the Zollinger–Ellison Syndrome (Left-Hand Panel) and a Comparison of the Results of Preoperative Imaging Studies Performed before Initial and Subsequent Operations and before Only the Initial Operation in Patients with Sporadic Gastrinomas (Right-Hand Panel).

The results are expressed as the percentage of operations performed in patients for whom the indicated localization study was performed preoperatively. In the left-hand panel, the 28 patients with multiple endocrine neoplasia type 1 (MEN-1) had a total of 32 operations, and the 123 patients with sporadic gastrinomas had a total of 148 operations. Somatostatin-receptor scintigraphy was performed before the last 54 surgical explorations (43 in patients with sporadic gastrinomas and 11 in patients with MEN-1), of which 27 were initial explorations. Portal venous sampling for measurement of serum gastrin was performed before 97 operations, 85 of which were in patients with sporadic gastrinomas. Intraarterial secretin injection with measurement of serum gastrin in hepatic venous blood was performed before 103 operations, 92 of which were in patients with sporadic gastrinomas. In the right-hand panel, there were a total of 148 operations (in 123 patients), of which 123 were initial operations (in 123 patients). The P values for all comparisons other than those shown were >0.05. CT denotes computed tomography, and MRI magnetic resonance imaging.

all but one patient relapsed by 3 years, and all had relapsed by 10 years, whereas of the patients with sporadic gastrinomas, 45 percent and 34 percent of the patients remained free of disease at 3 and 10 years, respectively (Fig. 2A).

In patients with sporadic gastrinomas, the disease-free rate at five years was not influenced by the results of preoperative localization studies, the presence of limited liver metastases, or the location of the primary gastrinoma (Table 3). Among patients who

were followed for an average of seven years, 17 of the 74 patients with sporadic gastrinomas who were free of disease immediately after surgery relapsed (23 percent), as compared with 5 of 5 patients with MEN-1 (100 percent) (Table 3).

The rate of disease-free survival among patients with sporadic gastrinomas was 40 percent at 5 years and 34 percent at 10 years (Fig. 2A). In contrast, in patients with MEN-1, the rate of disease-free survival was 4 percent at 5 years and 0 percent at 10 years

**TABLE 2.** LOCATION OF PRIMARY TUMOR, EXTENT AND SIZE OF TUMOR, AND TYPE OF OPERATION IN 151 PATIENTS WITH THE ZOLLINGER-ELLISON SYNDROME.\*

CHARACTERISTIC	SPORADIC GASTRINOMAS	MEN-1	TOTAL
No. of patients	123	28	151
No. of abdominal surgical explorations	148	32	180
No. of operations with tumors found/total no. (%)	131/148 (89)	31/32 (97)	162/180 (90)
No. of patients with tumors found/total no. (%)	113/123 (92)	27/28 (96)†	140/151 (93)
No. of patients with tumors found on initial operation/total no. (%)	106/123 (86)	27/28 (96)	133/151 (88)
No. of patients with tumors found on subsequent operations/total no. (%)‡			
All patients	25/25 (100)	4/4 (100)	29/29 (100)
Patients with negative results on initial operation	7/7 (100)	0	7/7 (100)
No. of operations with tumors found/total no. (%)			
1981-1986	23/35 (66)§	5/6 (83)	28/41 (68)§
1987-1998¶	108/113 (96)	26/26 (100)	134/139 (96)
Location of primary tumors — no. with tumor/total no. (%)			
Duodenum	58/123 (47)	16/28 (57)	74/151 (49)
Pancreas	17/123 (14)	19/28 (68)**	36/151 (24)
Lymph node††	16/123 (13)	1/28 (4)	17/151 (11)
Other‡‡	13/123 (11)	0/28	13/151 (9)
Unknown§§	22/123 (18)	2/28 (7)	24/151 (16)
Size of tumor — no. of operations/total no. (%)			
≤1 cm	63/131 (48)	16/31 (52)	79/162 (49)
>1 cm	68/131 (52)	15/31 (48)	83/162 (51)
Extent of tumor — no. of patients/total no. (%)			
Primary tumors only	64/123 (52)¶¶	9/28 (32)	73/151 (48)
Primary tumors plus lymph-node involvement	37/123 (30)	17/28 (61)	54/151 (36)
Duodenum plus lymph node	32/123 (26)	12/28 (43)	44/151 (29)
Pancreas plus lymph node	4/123 (3)	10/28 (36)	14/151 (9)
Other plus lymph node	0/123	0/28	0/151
Lymph node only	27/123 (22)	2/28 (7)	29/151 (19)
Liver metastases	8/123 (7)	4/28 (14)	12/151 (8)
Type of surgery — no. of operations/total no. (%)			
Exploration with no duodenotomy	68/148 (46)	16/32 (50)	84/180 (47)
Exploration and duodenotomy	78/148 (53)	16/32 (50)	94/180 (52)
Biopsy only***	3/148 (2)	1/32 (3)	4/180 (2)
Distal pancreatectomy	13/148 (9)	12/32 (38)	25/180 (14)
Tumor resection or enucleation	115/148 (78)	22/32 (69)	137/180 (76)
Proximal pancreatoduodenectomy	1/148 (1)	1/32 (3)	2/180 (1)
Hepatic resection	13/148 (9)	2/32 (6)	15/180 (8)

\*MEN-1 denotes multiple endocrine neoplasia type 1.

†Before receiving a diagnosis of MEN-1, one patient had negative results on surgical exploration after negative localization studies.

‡After the initial surgical exploration, 27 patients had one more operation, 1 patient had two more, and 1 patient had four more.

§P<0.001 for the comparison with the operations that took place after 1986.

¶In 1987, routine comprehensive exploration of the duodenum was begun (through transillumination and duodenotomy).

||P=0.002 for the comparison with patients with MEN-1.

\*\*Of the 19 patients with MEN-1 who had pancreatic tumors, 6 had positive staining for gastrin.

††Gastrinoma of the lymph node was termed a primary tumor if it occurred in a patient who was free of disease after resection of a lymph-node gastrinoma.

‡‡Other primary sites included the ovary (one patient), liver (six), heart (one), pylorus (two), omentum (one), common bile duct (one), and jejunum (one).

§§Unknown location refers to patients in whom no primary tumor was found (11 patients) or patients in whom only metastatic lymph nodes (12 patients) or liver metastases (1 patient) were found.

¶¶P=0.01 for the comparison with patients with MEN-1.

|||P<0.001 for the comparison with patients with MEN-1.

\*\*\*Biopsy only was performed in two patients with diffuse liver metastases, one patient with an unresectable duodenal lesion, and one patient with a gastrinoma of the caudate lobe of the liver.

**TABLE 3. RESULTS OF SURGERY IN PATIENTS WITH THE ZOLLINGER–ELLISON SYNDROME.\***

RESULTS	SPORADIC GASTRINOMAS		MEN-1	TOTAL
	no. of patients/no. of operations (%)			
Free of disease				
Immediately after surgery	74/144	(51)†	5/32 (16)‡	79/176 (45)
At 5 yr	45/91	(49)	1/18 (6)‡	46/109 (42)
Free of disease at 5 yr				
Surgery between 1981 and 1986§	14/33	(42)	1/6 (17)	15/39 (38)
Surgery between 1987 and 1998	31/58	(53)	0/12‡	31/70 (44)
Results of preoperative imaging studies in patients free of disease at 5 yr¶				
Conventional imaging				
Positive	28/49	(57)	1/17 (6)‡	29/66 (44)
Negative	17/42	(40)	0/1	17/43 (40)
Functional localization				
Positive	38/74	(51)	1/13 (8)	39/87 (45)
Negative	5/13	(38)	0/3	5/16 (31)
Either type of study positive	44/86	(51)	1/17 (6)‡	45/103 (44)
Both types of study negative	1/5	(20)	0/1	1/6 (17)
Preoperative liver involvement in patients free of disease at 5 yr				
Yes	4/9	(44)	0/1	4/10 (40)
No	41/82	(50)	1/17 (6)‡	42/99 (42)
Location of primary tumors in patients free of disease at 5 yr				
Duodenum	19/34	(56)	0/8**	19/42 (45)
Pancreas	9/12	(75)	0/11‡	9/23 (39)
Lymph node	12/15	(80)	1/1 (100)	13/16 (81)
Other	5/7	(71)	0/0	5/7 (71)
Operation undergone in patients free of disease at 5 yr				
Initial	42/84	(50)	1/16 (6)††	43/100 (43)
Subsequent	3/7	(43)	0/2	3/9 (33)
All relapses‡‡	17/74	(23)	5/5 (100)	22/79 (28)

\*A patient was considered free of disease if the fasting serum gastrin concentration was normal, the secretin test was negative, and the imaging studies were negative. Results were calculated for each operation, and the values were calculated as the percentages of patients who underwent surgery, were followed for the period indicated, and were free of disease at the indicated follow-up time. For the 16 patients with more than one surgical exploration, only results from the first two operations were included. MEN-1 denotes multiple endocrine neoplasia type 1.

†In 4 of 148 operations, disease-free status was not assessed immediately after surgery.

‡P<0.001 for the comparison with the patients with sporadic gastrinomas.

§In 1987, routine surgical exploration of the duodenum was begun (through transillumination and duodenotomy).

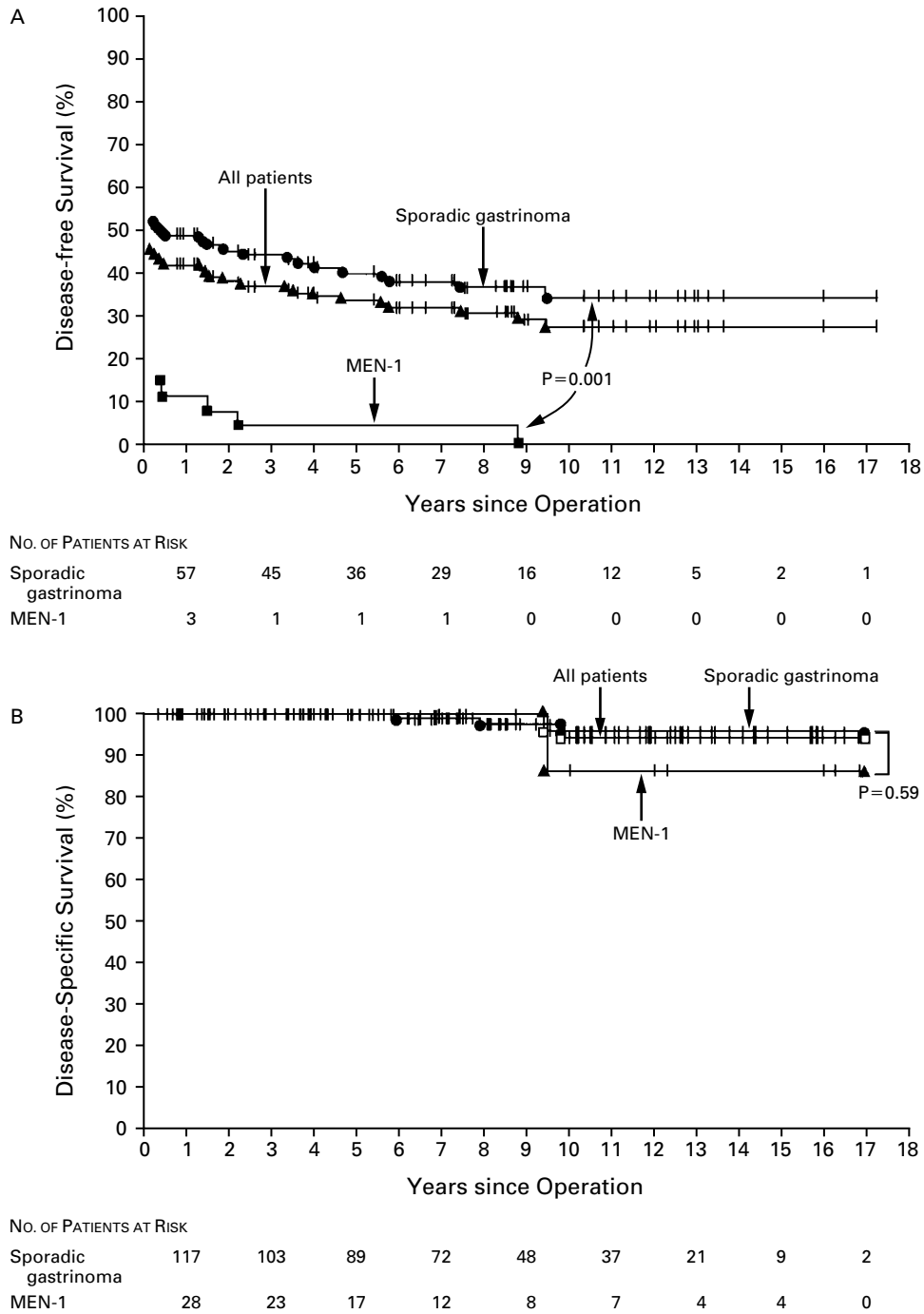
¶The conventional imaging studies performed were ultrasonography, computed tomography, magnetic resonance imaging, and selective angiography. Functional localization studies performed were portal venous sampling for the measurement of serum gastrin or intraarterial secretin injection with hepatic venous sampling for the measurements of serum gastrin.<sup>23,24</sup> Two patients who were free of disease at five years did not undergo functional localization testing.

||P=0.03 for the comparison with the patients with sporadic gastrinomas.

\*\*P=0.004 for the comparison with the patients with sporadic gastrinomas.

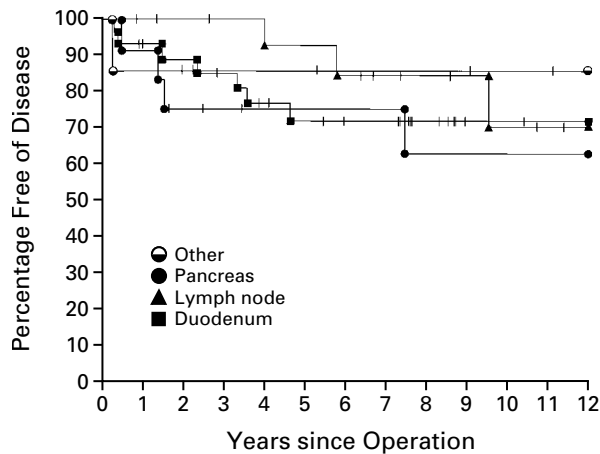
††P=0.001 for the comparison with the patients with sporadic gastrinomas.

‡‡Relapse was considered to have occurred in a patient who was free of disease immediately after surgery and then had a recurrent tumor on a subsequent evaluation. Shown is the total number of patients during any follow-up interval who had a relapse divided by the total number of disease-free patients in each category immediately after surgery.



**Figure 2.** Disease-free Survival (Panel A) and Disease-Specific Survival (Panel B) among Patients with the Zollinger-Ellison Syndrome.

Panel A shows a Kaplan-Meier plot of disease-free survival. The data on disease-free survival are presented as percentages plotted as a function of the number of operations rather than the number of patients. Five of the 28 patients with multiple endocrine neoplasia type 1 (MEN-1) who underwent 32 surgical explorations of the abdomen and 74 of the 123 patients with sporadic gastrinomas who underwent 144 surgical explorations were free of disease immediately after surgery. The results are expressed as the percentage of the total number of surgical patients in each group who were free of disease at the indicated postoperative time. Panel B shows a Kaplan-Meier plot of survival with respect to the Zollinger-Ellison syndrome. There were four deaths from the Zollinger-Ellison syndrome: three from progressive metastatic disease and one from a paradoxical cerebral embolus through a patent foramen ovale. The results reflect only deaths that resulted from manifestations of the Zollinger-Ellison syndrome or malignant gastrinomas. Tick marks indicate the end of follow-up in individual patients.



NO. OF PATIENTS AT RISK

Duodenum	25	21	15	13	3	2
Pancreas	12	8	7	7	6	6
Lymph node	16	14	12	9	7	3
Other	7	5	5	4	4	2

**Figure 3.** Kaplan–Meier Plot of Disease-free Survival According to Location of the Primary Tumor in Patients with Sporadic Gastrinomas.

The results are expressed as the percentage of patients with a primary tumor in the indicated location who were free of disease immediately after resection who were still free of disease at the indicated postoperative times. Tick marks indicate the end of follow-up in individual patients. The numbers below the figure show the numbers of patients with a primary tumor in each location who remained in the analysis.

(Fig. 2A). The rates of disease-free survival at 5 and 10 years were not significantly different for patients with primary tumors in different locations (Fig. 3).

When only deaths due to manifestations of the Zollinger–Ellison syndrome or malignant gastrinoma were included, the 5- and 10-year rates of survival among the patients with sporadic gastrinomas were 100 percent and 95 percent (Fig. 2B). The corresponding rates among the patients with MEN-1 were 100 percent and 86 percent (Fig. 2B). Only 4 of the 151 patients (3 percent) died from a cause related to the Zollinger–Ellison syndrome, and none of these deaths were related to gastric acid hypersecretion. Overall, 21 patients (14 percent) died from any cause, and the rate did not differ significantly between the two groups.

**DISCUSSION**

The value of surgical exploration as a means of cure in patients with the Zollinger–Ellison syndrome is even more controversial today than when this study was started in 1981.<sup>9,10,13</sup> The reasons for the controversy include the slow growth of many gastrinomas, the variable rate of cure, and the lack of in-

formation on the long-term results of potentially curative resections. Until recently, many patients died from complications of gastric acid hypersecretion, surgical series included relatively few patients, follow-up after resection was often short, and there was no standard operative approach that incorporated methods that improve intraoperative detection of gastrinomas. In the current study, a large number of patients were enrolled, advances in the preoperative and intraoperative detection of tumors were incorporated into the protocol, follow-up was long, and all patients received drugs to control gastric-acid hypersecretion.

Our results support the conclusion that exploratory laparotomy should be performed routinely in patients with sporadic gastrinomas if diffuse hepatic metastases are not present. Gastrinomas were found in 93 percent of the patients in our study. In approximately one third of patients with sporadic gastrinomas, the results of imaging studies are negative. Surgical exploration almost always detects gastrinomas in patients whose imaging studies are negative, however, so negative results should not be a reason for not performing laparotomy.<sup>9,10</sup> In our study, the disease-free rate immediately after resection was 51 percent, and it was sustained in the majority of patients during follow-up. These results demonstrate that a substantial proportion of patients with sporadic gastrinomas have long-term disease-free survival.

If routine surgery is to be advocated for patients with sporadic gastrinomas, careful preoperative imaging is essential, so as to exclude patients with more extensive disease who might not benefit from surgery and to identify the primary tumor. Somatostatin-receptor scintigraphy, which images the entire body at one time, is more sensitive for detecting gastrinomas than any conventional imaging study.<sup>22</sup> Since this test became available, all liver metastases detected at exploration have been detected by the test.

Most gastrinomas are found in the pancreas, duodenum, or lymph nodes near the head of the pancreas, but they have also been found in the heart, liver, bile ducts, ovary, kidney, mesentery, and other sites.<sup>1,33-35</sup> They were found in such sites in 9 percent of our patients, a finding that highlights the importance of whole-body imaging by procedures such as somatostatin-receptor scintigraphy. Extensive exploration of the head of the pancreas and especially the duodenum must be carried out at surgery if gastrinomas are to be found. In earlier studies, duodenal gastrinomas were less common than pancreatic gastrinomas,<sup>1</sup> whereas in the present study, duodenal tumors were more common, undoubtedly as a result of the institution in 1987 of surgical procedures to detect duodenal gastrinomas. These procedures are essential if duodenal tumors are to be detected, because most duodenal tumors are not identified by any imaging study.<sup>17,18</sup> Whether endoscopic ultraso-

nography will make possible the preoperative identification of these small duodenal gastrinomas was not addressed in our study and is not yet clear.

Lymph nodes in the region of the head of the pancreas and duodenum should be routinely removed at surgery even if they appear normal, because they may contain microscopic gastrinoma.<sup>17</sup> The existence of primary lymph-node gastrinomas is controversial.<sup>31</sup> The present study suggests that they may exist. Of the 15 patients with sporadic gastrinomas in whom only a resected lymph node contained a tumor and who were free of disease after resection and were followed for at least five years, only 3 patients relapsed. Aggressive resections, including pancreatoduodenectomies, are being recommended increasingly for patients with gastrinomas.<sup>1,12</sup> However, in the present study, in which few patients underwent aggressive surgery, the 10-year disease-specific rate of survival was 94 percent.

The question of whether surgery can be curative in patients with MEN-1 is also controversial.<sup>1,11,13,19,36</sup> Many, but not all, gastrinomas in patients with MEN-1 occur in the duodenum; in this study, 57 percent of such patients had gastrinomas located in the duodenum. However, even with the institution of procedures to identify duodenal gastrinomas, only 16 percent of these patients were free of disease immediately after surgery, and only 6 percent at five years. Proximal pancreatoduodenectomy has been found to result in cure in some patients with MEN-1<sup>12</sup>; however, few patients have been treated with this procedure. Larger gastrinomas are more likely to metastasize,<sup>5,37</sup> but it is not known whether earlier surgery — when the tumors are smaller than 3 cm — would result in an increased rate of cure.

Almost half of our patients with sporadic gastrinomas were not free of disease after surgery. Somatostatin-receptor scintigraphy is not likely to improve this rate.<sup>38</sup> Therefore, more sensitive methods for intraoperative tumor localization, such as intraoperative scintigraphy,<sup>39</sup> will have to be developed, or more aggressive surgery, such as proximal pancreatoduodenectomy, will need to be performed. More aggressive surgery might be justified in some patients through the use of intraoperative measurements of serum gastrin to determine whether the gastrinoma has been completely resected<sup>40</sup> or through the identification (by methods not yet described) of subgroups of patients with a poor prognosis.

In conclusion, we found that half of our patients with sporadic gastrinomas were free of disease immediately after surgery and that long-term cure was possible in the majority of these patients. These results support the recommendation that patients with sporadic gastrinomas should undergo routine surgical exploration for possible curative resection. Conversely, patients with MEN-1 rarely become free of disease, even after extensive duodenal exploration;

therefore, surgical exploration for cure of the gastrinoma is not routinely recommended in these patients.

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