Curative Resection in Zollinger–Ellison Syndrome

Results of a 10-Year Prospective Study

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Since 1980, 73 patients with Zollinger–Ellison syndrome (ZES) without radiographic evidence of liver metastases were studied on a prospective protocol including medical management of gastric acid hypersecretion, extensive radiographic tumor localization, and exploratory surgery to find and resect gastrinoma for potential cure. Each patient had gastric acid hypersecretion effectively controlled with either H_2-blockers or omeprazole. Patients were divided prospectively into two groups, with all patients undergoing the same preoperative localization studies and extensive laparotomy. In contrast to group 1 (1980–1986) (36 patients), group 2 (1987–Oct. 1990) (37 patients) also underwent additional procedures (transillumination and duodenotomy) at surgery to find duodenal gastrinomas. Preoperative imaging studies localized tumor in 38 (52%) patients, and portal venous sampling for gastrin determinations was positive in 49 (67%) patients. Gastrinomas were found and resected in 57 (78%) patients. Significantly more gastrinomas (92% of patients) were found in group 2 than in group 1 patients (64%) ($p < 0.01$). This increase was due to increased numbers of duodenal gastrinomas in group 2 than in group 1 patients (43% *versus* 11%; $p < 0.01$). The increased ability to find duodenal gastrinomas did not significantly improve the immediate disease-free rate, which was 58% for all patients. Duodenal primary gastrinomas were found to have a significantly greater incidence of metastases (55%) and a significantly shorter disease-free interval (12 months) than pancreatic gastrinomas (22% and 84 months, respectively) suggesting that duodenal gastrinomas may be more malignant and not more frequently curable than pancreatic gastrinomas. Operations were performed with no deaths and 11% morbidity rate. Long-term follow-up showed that 50% of patients initially rendered disease free would develop recurrent disease by 5 years. Survival was excellent for all patients, and none died of malignant spread of the tumor or uncontrolled peptic ulcer disease, with a mean follow-up of 5 years. This finding is in contrast to patients who presented with metastatic disease on imaging studies and had a 20% 5-year survival rate. This study suggests that all patients with localized sporadic ZES can have the gastric acid hypersecretion managed medically, that overall survival of these patients is excellent, most (78%) can have all gastrinoma found and resected, and some (30%) will be cured (long-term disease-free survival).

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THE ZOLLINGER–ELLISON SYNDROME as originally described was clinically characterized by severe peptic ulcer disease associated with profound gastric acid hypersecretion in the presence of a non-beta islet cell tumor of the pancreas,[1] which now is known to be secondary to ectopic release of gastrin by the tumor. Since its original description, it has been apparent that all patients have two fundamental aspects of their disease that must be managed: the profound gastric acid hypersecretion and the malignant nature of the gastrinoma.[2–11]

Initially, attention was primarily directed at controlling the life-threatening gastric acid hypersecretion, which, if left improperly treated, led to perforation and hemorrhage.[1,3,4] For many years, total gastrectomy was the only effective treatment for the gastric acid hypersecretion because resection of the gastrinoma was almost always not successful.[1,3,4,8] In the last few years, however, with the availability of progressively more potent gastric antisecretory agents, medical control of gastric hypersecretion has become increasingly more effective.[5,11–17] With the recent availability of H^+-K^+-ATPase inhibitors such as omeprazole, gastric hypersecretion can now be controlled in all patients, and it is recommended that total gastrectomy currently be used only in the rare patient who can not or will not take oral antisecretory drugs.[5,11,15–18]

In contrast to the control of the gastric acid hypersecretion, where great progress has been made and there is general agreement in the treatment approach, the ap-

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proach to the gastrinoma remains unclear and controversial.[9,10,18] Because gastrinomas, unlike insulinomas, but similar to glucagonomas, VIPomas, somatostatinomas, PPomas, or GRFomas, are malignant in 60% to 90% of patients in older studies,[3,4,11,19,20] most authorities agree that effective surgical treatment needs to be developed.[6,7,9,11,21,22] This view is reinforced by the fact that 60% of all patients in long-term studies in which acid hypersecretion is controlled died of the malignant nature of the disease,[2,3,23] demonstrating that it will become the main determinant of long-term survival. Many physicians still have reservations about sending these patients for routine surgical exploration, however, because of varied surgical results. Authorities have varied from recommending routine surgical exploration to recommending that routine surgical exploration not be done.[5,9,10,18,22,24–30] The primary reason for this difference of opinion in approach to the gastrinoma is that surgical cure rates have varied from 5% to 35% in different series[2,5,6,7–11,22,24–28,30,31] and even up to 82% in a recent study,[29] and the results have been limited in various studies because of a number of features. First, even in recent series because of the uncommonness of the disease the number of patients in the series is small and the studies often are not prospective in nature. Second, the follow-up is often short, and provocative tests are not routinely done to assess true long-term disease-free survival. Third, often the most advanced imaging studies as well as other, newer localization studies are not performed, so that it is not apparent whether a better cure rate could have been obtained with state-of-the-art localization studies. Fourth, in almost all older series, a significant percentage of patients had total gastrectomy, in contrast to the present, where it is now rarely needed. Because gastrinomas in some recent studies in up to 40% of cases are duodenal in location[11,21,29,32] and would frequently be removed by chance with the resected gastroduodenal segment, the true cure rate without such blind resection, which is not done today, is not established.

The aim of the present study was to address each of the inconsistencies reviewed above and to attempt to define the ability to localize gastrinomas and surgically cure patients with Zollinger–Ellison syndrome. This was accomplished by a 10-year prospective study examining the ability to surgically cure 73 consecutive patients with Zollinger–Ellison syndrome who had no evidence of the multiple endocrine neoplasia type 1 syndrome or metastatic disease by imaging studies.

Materials and Methods

Since 1980, 121 consecutive patients were referred to our institution with a diagnosis of Zollinger–Ellison syndrome and studied according to an approved protocol. The diagnosis of Zollinger–Ellison syndrome was initially confirmed in each patient by measuring fasting serum gastrin concentration, the increment in serum gastrin level in response to 2 U/kg of a bolus injection of intravenous (I.V.) secretin and an I.V. calcium infusion (5 mg/kg/hour calcium × 3 hours) and the basal and pentagastrin-stimulated maximal acid output as previously described.[11,32–35]

The diagnosis of Zollinger–Ellison syndrome was confirmed if at least two of the following three criteria were present: elevated fasting serum gastrin level > 100 pg/mL, basal acid output greater than 15 mEq/hour if the patient had had no previous gastric surgery, or greater than 5 mEq/hour if the patient had had prior gastric surgery, and an increase in serum gastrin level of 200 pg/mL after the I.V administration of secretin, or 395 pg/mL after an I.V. calcium infusion.[11,32–35]

The oral antisecretory drug dosage requirement was determined for each patient, as described previously,[11,35,36] and was defined as the amount of antisecretory drug required to suppress acid output < 10 mEq/hour in the final hour before the next scheduled dose of medication. If the patient had had prior gastric surgery, then a dose of medication to reduce acid output to <5 mEq/hour was determined.[5,11,35–37] A parenteral antisecretory drug dose to control gastric acid output at the time of surgery was determined as described previously in all patients.[38–40]

All patients (n = 121) underwent upper gastrointestinal series, upper gastrointestinal endoscopy, computed tomography, ultrasound, and selective hepatic, gastroduodenal, splenic, and superior mesenteric arteriography.[32,41–44] Since 1987, patients also underwent magnetic resonance imaging (MRI) of the abdomen and liver.[45]

Patients with evidence of liver metastases on imaging studies that could have biopsies done percutaneously or laparoscopically (n = 18) were excluded from this study and placed on protocols for advanced disease.[46,47] Patients with evidence of multiple endocrine neoplasia type I (n = 22), in whom routine surgical exploration is not generally recommended,[5,11,18] were excluded from this study and placed in a separate protocol.[48,49] Patients with severe concomitant medical problems (n = 8) (severe cardiac disease [n = 2], chronic obstructive lung disease [n = 1] or advanced liver disease [n = 5]) that precluded surgery were excluded. All remaining patients (n = 73) underwent percutaneous transhepatic venous sampling of the portal vein and its tributaries for gastrin levels before surgery,[50] and 18 patients since 1988 underwent secretin injections of selective arteries and measurement of gastrin levels in hepatic venous or other venous samples to localize the gastrinoma during arteriography, as described recently.[51]

The results of the radiographic imaging and localizing studies were available to the operating surgeon. Surgery

was performed in the last 67 cases by one surgeon (JAN) and in the first six cases by another surgeon (JWH).[33] On the basis of the type of exploration done, patients were prospectively divided into two groups, and the results from each group were analyzed separately. Group 1 consisted of patients from 1980 through 1986 (36 patients) who underwent the standard extensive laparotomy briefly outlined below. Patients in group 2 underwent exploration from 1987 through October 1990 (37 patients), and these patients underwent an identical standard extensive laparotomy to patients in group 1, but in addition, an enhanced search for duodenal gastrinomas using transduodenal endoscopic illumination[52] and duodenotomy. Briefly, in the standard extensive laparotomy,[32] the liver, pelvis, small intestine, pancreas, stomach, duodenum, mesenteric, and retroperitoneal regions in the upper abdomen were explored. The pancreatic head and duodenum were exposed and mobilized by performing an extended Kocher's maneuver that included mobilizing the ascending colon and hepatic flexure. The pancreatic body and tail were inspected and palpated by opening the gastrocolic ligament and exposing the lesser sac. The splenic flexure of the colon was also mobilized to facilitate inspection and palpation of the pancreatic tail, and all women had careful palpation of the ovaries. After complete operative exposure and careful palpation, since 1982 each patient (n = 62) underwent intraoperative ultrasound using a 10-MH_z real-time transducer as previously described.[53] Patients in group 2, in addition, underwent intraoperative endoscopic transillumination of the duodenum, performed as described previously,[52] with or without duodenotomy[21] to more carefully examine the duodenum for any evidence of small duodenal gastrinomas not detected by the other methods. Briefly, intraoperative endoscopic transillumination was performed by passing an upper gastrointestinal endoscope orally at the time of surgery and carefully transilluminating the duodenum. Biopsies were performed on all abnormalities seen by the endoscopist or that failed to transilluminate.[52] A 3-cm duodenotomy was performed along the antimesenteric aspect of the duodenum centered on the second portion of the duodenum with the option to extend in either direction. The duodenal wall was carefully palpated with the index finger inside the duodenum and the thumb on the outside, and the distal third and fourth parts of the duodenum were examined similarly by everting them into the incision. Any suspicious pancreatic, gastric, liver, duodenal, bowel, or peripancreatic nodule or lymph node that was identified by any method (palpation, intraoperative ultrasound, transillumination) was removed for pathologic analysis. In the bowel or stomach wall, a suspected tumor was excised with a full-thickness rim of normal gut around the tumor. In the pancreatic head or adjacent lymph node areas, suspected tumors were excised. In the distal pancreas, suspected tumors were resected along with the surrounding pancreas and spleen. In one patient, an ovarian cystadenocarcinoma was identified, and this patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. If a gastrinoma was not found, no gastric or pancreatic resection was performed.

After surgery, before discharge, each patient underwent determination of fasting serum gastrin level and the change in serum gastrin level after secretin provocation performed as described previously.[32] Each patient was discharged on the same dose of antisecretory drug as preoperatively. Patients then were re-evaluated at 3 to 6 months postoperatively and then yearly for evidence of tumor recurrence and control of gastric hypersecretion.[29,32] At the 3- to 6-month follow-up, tumor recurrence was assessed by noninvasive imaging studies (ultrasound, MRI scan, computed tomography [CT] scan), selective abdominal angiogram, and functional studies (fasting gastrin concentration, secretin and calcium provocative studies, basal acid output).[29] The criteria for disease-free survival of patients with Zollinger–Ellison syndrome were: (1) normal fasting serum gastrin concentration (<100 pg/mL), (2) a negative secretin- (<200 pg/mL increase) and calcium-provocative test (<395 pg/mL increase),[34] and (3) no evidence of tumor on follow-up imaging studies

Disease-free survival and survival were graphed by the Kaplan-Meier method and analyzed for significant differences by the Breslow modification of the Kruskal-Wallis test. Proportions were compared by the Fisher's exact test. Differences with $p < 0.05$ were considered significant.

Results

Patient Characteristics, Medications, and Localization Studies

Seventy-three patients were entered prospectively into this study. Fifty patients were men, and 23 patients were women (Table 1). The mean age of all patients was 49 years. Twenty-six patients (36%) had had prior upper abdominal surgery, including either partial gastrectomy or vagotomy in most these patients. There was a mean time of 8 years between the onset of symptoms and the diagnosis of Zollinger–Ellison syndrome, and one patient had symptoms of peptic ulcer disease for 35 years before the diagnosis of Zollinger–Ellison syndrome.

The basal acid output was markedly elevated in all but five patients who had had prior subtotal gastrectomy and vagotomy, and the mean basal acid output for all patients was 58 mEq/hour (Table 1). In most patients, the serum gastrin level was markedly elevated, with a mean fasting serum gastrin concentration of 909 pg/mL. All but five patients had an abnormal serum gastrin response to se-

cretin or calcium provocation, with a mean increment of 1669 pg/mL and 424 pg/mL, respectively.

Each patient preoperatively had the gastric acid output successfully controlled by oral antisecretory medication (Table 1). As the study progressed, we have employed more potent medications, making the control of the acid output progressively easier. As the potency of the antisecretory medication increased,[5,11,36] as is evidenced from Table 1, the dose of antisecretory medication decreased, with a mean cimetidine dose of 6.0 g/day (n = 11); ranitidine, 2.2 g/day (n = 39); famotidine, 0.3 g/day (n = 9); and omeprazole, 84 mg/day (n = 14) (Table 1). Currently, most patients are managed with one daily dose of omeprazole, requiring approximately 60 to 120 mg/day (Table 1).

In 52% of patients preoperative imaging studies demonstrated a gastrinoma. In 67% of patients, a positive gastrin gradient (> 50% increase over simultaneous peripheral sample[50]) on portal venous sampling for gastrin was found. All but two of these gastrin gradients were present in the superior or inferior pancreaticoduodenal vein, suggesting that the gastrinoma was present within either the pancreatic head or duodenum[50] (Table 1). A similar proportion of patients had marked increments in hepatic vein gastrin levels after the injection of secretin into the gastroduodenal artery, suggesting similar localization (data not shown).[51]

TABLE 1. *Preoperative Characteristics, Antisecretory Medication Dose, and Localization Results of Patients With Zollinger-Ellison Syndrome*

n	Sex M:F	Mean Age (yr) (range)	No. With Previous Upper Abdominal Surgery	Mean Time From Symptoms to Surgery (yr) (range)	Mean Basal Acid Output (mEq/hr) (range)	Mean Fasting Gastrin (pg/mL) (range)	Delta Secretin Gastrin (pg/mL) (range)	Antisecretory Drug Requirement								Tumor Localization Studies	
								Cimetidine		Ranitidine		Famotidine		Omeprazole		Δ Imaging* Positive	Δ PVS Positive
								n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)	n	Mean Dose (mg/day) (range)		
73	50:23	49 (29–66)	26 (36%)	8 (1–35)	58† (4–159)	909 (133–7000)	1669‡ (67–21700)	11 (15%)	6050 (2400–12000)	39 (53%)	2260 (300–5400)	9 (12%)	308 (80–800)	14 (19%)	84 (60–120)	38 (52%)	49 (67%)

* Imaging includes ultrasound, computerized tomography scan, magnetic resonance imaging scan, and selective arteriogram.

† Five patients had basal acid output <15 mEq/hr, and each had had prior acid reduction surgery, including previous vagotomy and antrectomy.

‡ Seven patients had a less than 200 pg/mL increment in serum gastrin level after the administration of 2 U/kg of secretin IV (negative secretin test result).

PVS, selective transhepatic sampling of the protal vein and its tributaries for serum gastrin determination with a positive gradient equal to or greater than a 50% increase over simultaneous peripheral value as defined in Methods.

Ability to Find Gastrinoma

Gastrinomas were found and resected in 57 of 73 patients (78%) (Table 2). The addition of procedures to more carefully examine for duodenal gastrinomas (group 2) significantly improved the ability to find and resect gastrinomas (Table 2). Specifically, before these procedures, 64% of patients (23 of 36) had gastrinomas removed (group 1, Table 2), whereas subsequently 92% of patients (34 of 37) had gastrinomas excised ($p < 0.01$) (group 2, Table 2). The increase in gastrinomas found in group 2 was entirely due to an increased proportion of duodenal wall gastrinomas excised and not to an increased ability to find gastrinomas in the area of the duodenum, within the pancreas, or in adjacent duodenal lymph nodes (Table 3). Specifically, in the initial 36 patients in group 1, only four duodenal wall gastrinomas were excised. In contrast, in group 2, in which an extensive search of the duodenum was added, 16 of the 37 patients had duodenal wall gastrinomas excised (43%) (Table 3). This difference was significant ($p < 0.01$), and it implied that duodenal wall gastrinomas were likely being missed in the 37% of patients in whom no gastrinomas were found in group 1 (Table 2). The average size of the duodenal gastrinoma in group 2 was 6 mm, with 38% between 1 and 5 mm, and the remainder between 6 and 10 mm, whereas the

TABLE 2. *Ability to Find Gastrinoma as a Function of Intensive Operative Focus on the Duodenum*

Result of Surgery	Surgical Group* I (n = 36)†‡	II (n = 37)‡	Total (n = 73)
Gastrinoma found (n)	23 (64%)†‡	34 (92%)‡	57 (78%)
Gastrinoma not found (n)	13 (36%)†‡	3 (8%)‡	16 (22%)

* Group 1 (1980–1986) and group 2 (1987–October 1990) differed in that patients in group 2 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† Numbers are the number of patients in the indicated surgical group with the indicated surgical result. Numbers in parentheses are the percentage of patients in the indicated group with the indicated surgical result.

‡ Significant differences betwen group 1 and group 2 by Fisher's exact test ($p < 0.01$).

four duodenal gastrinomas in group 1 had a mean size of 6 mm (range, 4 to 10 mm), with only 1 tumor < 5 mm, suggesting that small duodenal gastrinomas may have been missed in group 1. In group 1, the proportion of patients with pancreatic gastrinomas (33%) was significantly higher than those with duodenal gastrinomas (11%, $p < 0.05$), whereas in group 2, duodenal wall gastrinomas were found in 43% of patients, and the occurrence of these tumors was as common as pancreatic tumors (30%) ($p > 0.1$) (Table 3).

Ability to Cure

Of the 73 total patients explored, 42 patients (58%) at 3 to 6 months had a normal fasting serum gastrin concentration, negative gastrin provocative tests, and negative imaging, and thus were defined as disease free, as outlined in Methods. At the 3- to 6-month follow-up after operation in group 1, 19 of 36 patients (52%) were disease free, which was not significantly different from group 2, with 23 of 37 (62%) patients disease free ($p = 0.5$). Therefore, although the use of extensive duodenal evaluation significantly improved the ability to find and resect gastrinoma (Table 3), it did not significantly improve the ability to render patients disease-free. To further investigate this finding, the ability to render patients disease free was considered as a function of tumor location (Table 4). The 3- to 6-month disease-free rate was similar in patients in groups 1 and 2 for pancreatic gastrinomas (92% *vs.* 73%, $p = 0.5$) and gastrinomas within lymph nodes (83% *vs.* 71%, $p = 1.0$). In addition, the percentage disease free for duodenal gastrinomas was not significantly different in group 2 (62%) and group 1 (50%, $p = 1.0$, Table 4). These results suggest that the failure of the disease-free rate to increase in patients in group 2 (although more tumors were found) was likely not due to a failure to render more patients with duodenal gastrinomas disease-free even though more duodenal gastrinomas were found in group 2 than in group 1 (Table 3). To investigate the basis for this further, the malignant potential (as defined by the presence of pathologically proven lymph node or liver metastases) of duodenal and pancreatic primary gastrinomas was compared. A greater proportion of patients with duodenal gastrinomas had evidence of metastases, 55% *versus* 22%, $p = 0.05$ (Table 5). The higher presence of metastatic disease in patients with duodenal primaries may explain the inability to significantly increase the short-term cure rate in group 2 patients, even though additional gastrinomas were found in this group.

Long-term Follow-up and Survival

To assess long-term disease-free survival, each patient was evaluated yearly. The median follow-up of all patients was 45 months (range, 3 to 120 months). Of the 42 patients who were resected and appeared to be disease free at initial postoperative evaluation, 10 patients have developed evidence of recurrence (Fig. 1, top panel). There appear to be 2 peak periods for the detection of recurrence, one at less than 1 year and the second at 5 years (Fig. 1, top panel). Recurrent Zollinger–Ellison syndrome was manifested by elevated fasting serum levels of gastrin and/or abnormal gastrin provocative testing results only in 6 patients and elevated serum gastrin levels and/or gastrin provocative test abnormalities plus recurrent tumor on imaging studies in 4 patients. The four patients with recurrent gastrinoma on imaging studies were re-resected at 8, 5, 2 and 1 year following the initial procedure and one was again able to be rendered disease-free. These reoperations included excision of gastrinoma from perinephric nodes, liver, duodenum, and adjacent duodenal

TABLE 3. *Location of Primary Gastrinoma in Various Surgical Groups*

Surgical Group*	Location of Primary Gastrinomas Resected† Duodenum‡‖¶	Pancreatic	Lymph Nodes Only
Group 1 (n = 36)	4 (11%)	12¶ (33%)	6 (17%)
Group 2 (n = 37)	16‖ (43%)	11 (30%)	7 (20%)
Both (n = 73)	20 (27%)	23 (32%)	13 (18%)

* Group 1 (1980–1986) and group 2 (1987–October 1990) differed in that patients in group 1 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† One patient had an ovarian gastrinoma, and 13 patients had no tumor found.

‡ Numbers refer to the number of patients in each group with a gastrinoma found in the indicated location. Numbers in parentheses are the percentage of the total patients in the indicated surgical group with gastrinomas in this location.

‖ Proportion of duodenal gastrinomas found was significantly greater in group 2 *vs.* group 1 patients ($p < 0.01$).

¶ Proportion of pancreatic gastrinomas found in group 1 was greater than that of duodenal gastrinomas found in group 1 ($p < 0.05$)

TABLE 4. *Ability to Initially Surgically Cure Patients With Zolliner-Ellison Syndrome as a Function of Primary Tumor Location*

	Location of Resected Primary Gastrinoma											
	Duodenum			Pancreas			Lymph Nodes			Total		
Group*	No. With Tumor Found	No. Cured†	% Cured‡	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured	No. With Tumor Found	No. Cured	% Cured
I	4	2	50	12	11	92	6	5	83	22§	18§	82
II	16	10	62	11	8	73	7	5	71	34	23	67
Both	20	12	60	23	19	83	13	10	77	56§	41§	37

* Group 1 (1980–1986) (n = 36) and group 2 (1987–October 1990) (n = 37) differed in that patients in group 2 underwent additional procedures to search for duodenal gastrinomas as described in Methods.

† Cure defined as a normal fasting gastrin concentration, negative imaging studies, and negative secretin and calcium provocative tests as described in Methods at a follow-up evaluation 3 to 6 months after operation.

‡ Cure refers to the percentage of patients with a gastrinoma found who were cured.

§ One patient had a primary ovarian gastrinoma and was cured. She is excluded from this analyusis.

nodes. The initial determination at 3 to 6 months postoperatively of no evidence of disease by normal serum gastrin level, negative imaging studies, and normal response to provocative testing did not predict that an individual patient will remain free of disease (Fig. 1, top panel). Long-term follow-up suggests that 50% of patients in this category will develop evidence of recurrent disease at 5 years (Fig. 1, top panel). Furthermore, the tumor recurrence rate long-term did not differ significantly for patients with primary tumors successfully resected from the pancreas or lymph nodes (Fig. 1, bottom panel). Patients with duodenal gastrinomas had a significantly shorter median disease-free interval (12 months) than did patients with pancreatic primary tumors (84 months, $p < 0.01$) but not those with lymph node gastrinomas (60 months, $p = 0.1$). Specifically, for patients who were initially found to be disease free with duodenal tumors, the 5-year disease-free rate was only 40%, whereas for patients with pancreatic tumors who were disease free at 3 to 6 months, the 5-year disease-free rate was 70%; similarly, for lymph node gastrinomas it was 60% (Fig. 1, bottom panel).

Of the 16 patients in whom no gastrinoma was found at operation, each patient retained functional evidence of Zollinger–Ellison syndrome, but only one patient has subsequently developed gastrinoma on imaging studies 6 years later. That patient was re-explored and gastrinoma was excised from the pancreas, and the patient is currently disease free. Two patients in this group have died on long-term follow-up (7-year follow-up), but in both cases the death was not related to Zollinger–Ellison syndrome (one death due to metastatic colon cancer, and the other to liver failure) (Fig. 2). Of the 15 patients who had tumor found and resected but were not rendered disease free on functional studies, only one has developed recurrent tumor on imaging study. This patient initially had a pancreatic body gastrinoma, and 3 years later developed a mesenteric lymph node near the ligament of Treitz that was excised, but his serum levels of gastrin remain elevated. Long-term survival (7 years) in this group is excellent (100%) (Fig. 2). Long-term survival of patients disease free at the 3- to 6-month postoperative follow-up was also excellent. In follow-up up to 9 years, only one patient has died of causes unrelated to the Zollinger–Ellison syndrome (cancer of the oropharynx). There are no apparent differences in survival in any surgical group (Fig. 2).

In contrast to the 73 patients in the current study undergoing surgical exploration with no evidence of metastatic disease on the initial evaluation who had excellent long-term survival (mean survival, 90% at 5 years) (Fig. 2), the 5-year survival in all patients with sporadic disease who did not enter the study because of metastatic gastrinoma was less than 20% ($p < 0.001$) (Fig. 2).

TABLE 5. *Presence of Metastatic Disease* With Duodenal and Pancreatic Primary Lesions*

Location of Primary Gastrinoma	n	No. With Metastases (%)
Pancreas	23	5 (22)
Duodenum	20	11 (55)†

* Metastatic disease was defined as the percentage of tumor in an adjacent lymph node (n = 12) or the liver (n = 4) in patients with a primary gastrinoma at the indicated site in group 1 and group 2.

† A significantly greater proportion of patients with duodenal primary lesions had metastases ($p = 0.05$).

Complications

Of 79 operations to excise gastrinoma from 73 patients (6 patients were operated on for recurrent or metastatic gastrinoma) with Zollinger–Ellison syndrome, there were no operative deaths, and nine operations (11%) produced complications. Complications included hemorrhage (n = 1), colon injury (n = 1), abscess (n = 2), wound infection

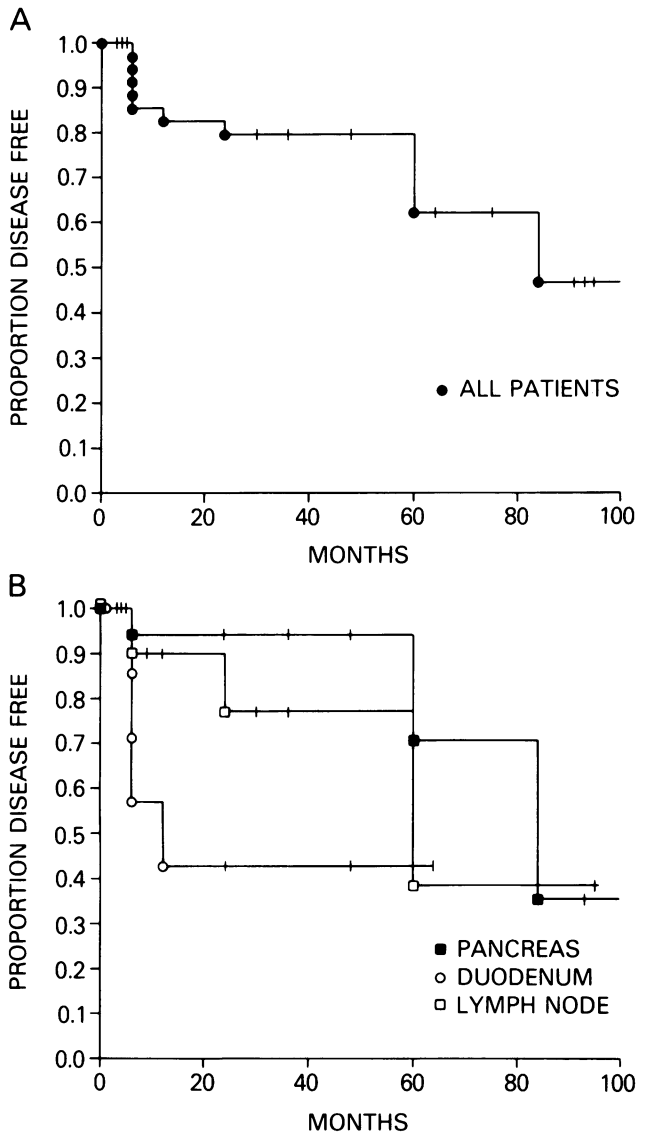

FIG. 1. Time to recurrence of Zollinger–Ellison syndrome in patients initially disease free by surgery. (Top) The Kaplan–Meier plot of the time to recurrence for all patients (n = 42) who were disease free of Zollinger–Ellison syndrome at the initial (either 3- or 6-mo) postoperative follow-up. Disease free is defined as no evidence of gastrinoma on imaging studies, normal fasting gastrin concentration, and negative secretin and calcium provocative tests as outlined in Methods. Recurrent disease has developed in few patients. (Bottom) Kaplan–Meier plot of the time to recurrence of Zollinger–Ellison syndrome of patients who were rendered disease free of Zollinger–Ellison syndrome at the initial postoperative follow-up divided by primary disease site: duodenum (n = 12), pancreas (n = 19), and lymph node (n = 10). One patient with the primary ovarian gastrinoma is excluded. Patients with primary duodenal gastrinomas had a significantly shorter disease-free interval than patients with pancreatic gastrinomas ($p < 0.01$). The differences between patients with duodenal gastrinomas and those with lymph node-only gastrinomas were not significant ($p = 0.1$). The median disease-free survival for patients with duodenal, pancreatic, or lymph node primary gastrinomas was 12, 84, and 60 months, respectively.

(n = 2), pulmonary embolus (n = 1), septic thrombophlebitis (n = 1), duodenal leak (n = 1), and small bowel obstruction (n = 1). One patient had two complications: wound infection and a small bowel obstruction. Of the complications that occurred, six required a repeat surgical procedure. Follow-up suggests long-term sequelae of only one complication, hearing loss and dizziness secondary to the prolonged use of gentamicin to treat an abdominal abscess.

Discussion

When this study was initiated in 1980, a number of advances had occurred that suggested that a prospective study to localize and resect gastrinomas for cure in a large number of consecutive patients would provide results that would clarify the management of the tumor in these patients. With the widespread use of the gastrin radioimmunoassay and secretin provocative testing, the ability to diagnose Zollinger–Ellison syndrome in patients with peptic ulcer disease was greatly facilitated[54,55] and might lead to the early detection of smaller, more curable gastrinomas. Radiographic methods to localize islet cell tumors also were improving dramatically, including improved CT scanning,[56,57] subtraction angiographic methods, and improved ultrasound devices. Reports suggested that selective pancreatic arteriography could accurately localize 90% of insulinomas and other islet cell tumors such as gastrinomas, as well as identify metastatic dis-

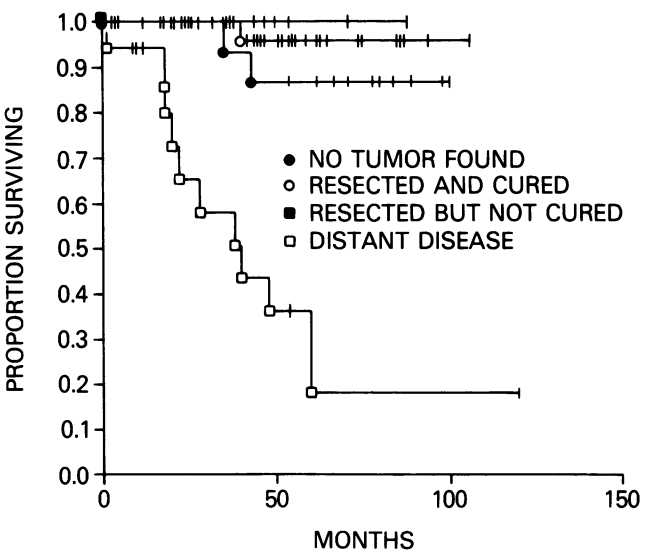

FIG. 2. Survival of patients with Zollinger–Ellison syndrome from the day of diagnosis. Patients were divided into four groups based on preoperative evaluation, operative findings, and initial postoperative evaluation: patients who had biopsy confirmation of bulky metastatic gastrinoma on initial evaluation (n = 18, open squares), patients who had no tumor found during surgery (n = 16, closed circles), patients who had all tumor resected and were functionally disease free (cured) at initial postoperative evaluation (n = 42, open circles), and patients who had all tumor resected but were functionally not disease free (cured) (n = 15, closed squares). There were no significant differences seen among the three groups who did not have metastatic gastrinoma. However, the group with distant disease survived for a significantly shorter time than all other patient groups ($p < 0.001$).

ease.[58–60] Studies suggested that transhepatic venous gastrin sampling from the portal vein and its tributaries could greatly improve localization of gastrinomas.[61,62] Furthermore, with the increased ability to control gastric acid hypersecretion medically in all patients, obviating the need for routine total gastrectomy,[12] it was possible to have time to both perform detailed imaging studies preoperatively and to concentrate on localizing and removing the gastrinoma at surgery. The detailed imaging studies allowed identification of patients without metastatic disease who would possibly benefit from surgery as well as more precise information about the location of the primary gastrinoma.[56,57,59,60] The control of gastric acid hypersecretion preoperatively allowed the effects of long-term gastric acid hypersecretion such as metabolic and nutritional abnormalities to be corrected to reduce the risks of extensive surgery, and allowed detailed surgical exploration directed at the tumor to be carried out without the risks of gastric acid hypersecretion at operation and postoperatively. Earlier attempts to operatively localize and resect gastrinomas were limited[4] because of the lack of good preoperative localization methods that could identify patients who might benefit from surgery and because surgeons had to remove the stomach, a procedure that required a major proportion of the operating time, removing time and energy needed to extensively explore and find gastrinoma. The present study was designed to incorporate new state-of-the-art preoperative localization procedures as they became available. For example, in the mid-1980s, a number of studies reported increasing numbers of gastrinomas being found in extrapancreatic sites, primarily within the duodenum.[6,7,22,24,63,64] These gastrinomas were frequently small, missed by preoperative imaging studies, and could only be found by extensive search of the duodenum. Furthermore, one study in the mid-1980s reported that — in contrast to the original studies of Zollinger and Ellison, in which gastrinomas occurred at a rate of 20% in the duodenum and in a pancreatic distribution of 4:1: 4 in the pancreatic head, body, and tail — 90% of gastrinomas were in the pancreatic head area, thus suggesting that many of the gastrinomas not being found in up to 50% of patients in some series might be in this area.[22] To address these issues, beginning in 1987 we added procedures (patients in group 2) to more intensively explore the duodenum, including intraoperative endoscopy with transillumination of the duodenum, the secretin angiogram with hepatic venous gastrin sampling to functionally localize gastrinomas,[52] and duodenotomy to those procedures that had been done before 1987 (Group 1). Regardless of the localizing test results in either group of patients, the current protocol required that a standardized surgical exploration be carried out in all patients with sporadic Zollinger–Ellison syndrome without evidence of liver metastases. Routine surgical exploration was carried out to find and remove gastrinomas for accurate staging and prognosis information, for control of the malignant potential of the tumor, and for potential cure of Zollinger–Ellison syndrome.

The results of the ability of surgery to cure a large number of patients with Zollinger–Ellison syndrome provide important information for physicians who are trying to manage these patients. First, the overall immediate disease-free rate as documented by a 3- to 6-month postoperative evaluation with normal serum gastrin levels, negative secretin and calcium provocative tests, and no evidence of tumor on imaging studies was 42 of 73 patients or 58% (Table 2). These results are better than every other modern prospective series except one recent study[29] involving small numbers of cases, which reported an immediate postoperative cure rate of 82%, in which patients were treated in similar fashion to patients in group 2 in the present study. The findings of the present study in combination with this other study[29] suggest that the short-term cure rate is significantly higher than that previously reported.[3,4,7,8,27,30] Second, the ability to find gastrinoma during the current study significantly improved as the study focused on the duodenum. Specifically, in the initial 6 years (1980 to 1986, group 1), gastrinomas were found in 64% of patients, whereas when additional procedures to localize duodenal gastrinomas were employed (group 2, 1987 to present), gastrinomas were found in 92% of patients. The increase was entirely due to localizing more duodenal gastrinomas, frequently of small size (< 6 mm). Because the preoperative imaging studies rarely localized these tumors, these results demonstrate that negative imaging studies, even when performed by the best experts available, will not reliably predict whether an experienced surgeon will find a tumor at surgery. Third, the increased ability to find and resect duodenal gastrinomas did not, as yet, result in a statistically significant improvement in cure rate (Table 2). However, there appears to be an upward trend (62% in group 2 *vs.* 52% in group 1, $p = 0.5$). Previous studies had suggested that extrapancreatic gastrinomas were more likely curable.[63–65] Our findings do not support this conclusion. In the present study, the ability to cure patients with duodenal gastrinomas was not greater than that for gastrinomas arising in other sites. In fact, the long-term disease-free rate for duodenal gastrinomas was lower. These results suggest that as increasingly more patients with duodenal gastrinomas are found that would have been missed without detailed duodenal exploration, the disease-free rate may increase, but not disproportionally to that seen in the patients with pancreatic gastrinomas. Fourth, the surgical procedure was done with a 11% morbidity rate and no deaths. Long-term morbidity rate was very low (1%). Fifth, the ability of gastrinoma excision to render disease-free patients with Zollinger–Ellison syndrome is maximum immediately after operation and decreases with length of follow-up. The long-term disease-free rate, in other words 5 years, is half the

initial figure, or approximately 30% of all patients sustain long-term cure (Fig. 1, lower panel). This percentage is significantly higher than that suggested in older studies.[3,4,7,8,10,24,25,27,30] When this study was started, the reported long-term cure rate was less than 10%.[3,6–8,27,30] The current results in a large number of patients as well as data from other recent studies[26,29] suggest that the long-term cure rate may even be greater than 30%. The present study demonstrates that studies that suggest high cure rate with minimal follow-up[26,29,33,66] are likely to be significantly overestimating the true long-term cure rate. Furthermore, studies suggesting cure in which long-term repetitive gastrin provocative testing is not done are almost certainly overestimating the true long-term cure rate. In the present study of the 10 patients who developed evidence of recurrent Zollinger–Ellison syndrome, in six there was only functional data suggesting the recurrence (positive provocative testing with or without an elevated fasting gastrin concentrations), and in the remaining four, functional evidence as well as a gastrinoma on imaging studies. The results suggest that postoperatively all disease-free patients should have at least yearly evaluations with imaging studies and functional studies (basal acid output, fasting gastrin concentration, and gastrin provocative tests) to evaluate for continued cure.

The long-term disease-free rate in the present study also provides important information on which further treatment strategies can be based. Despite finding gastrinomas in 78% of all patients and in 92% of patients in group 2 in which specific additional procedures were added to localize duodenal gastrinomas, the disease-free rate fell off to 30% for all patients by 5 years. These results suggest it will be important to identify factors contributing to the development of recurrent disease and predicting which patients have a high risk of recurrence. The present results demonstrate that the location of the primary gastrinoma is one factor that is an important determinant of recurrence. In the present study the median disease-free interval was 5 times longer for patients cured after lymph node gastrinomas were removed (median, 60 months) and 7 times longer after resection of pancreatic gastrinomas (median, 84 months), than after resection of duodenal gastrinomas (median, 12 months). This finding is unexpected, and the basis for this finding is unclear. Numerous previous studies suggested that extrapancreatic gastrinomas are not only more likely to be curable than pancreatic tumors, but that duodenal gastrinomas have a lower malignant rate than do pancreatic gastrinomas.[63,65,67,68] This was proposed because pancreatic tumors were ectopic in nature, because the normal adult pancreas does not have G cells, whereas duodenal tumors were entopic, arising from G cells that are distributed in the adult duodenum.[67,68] In the present study, however, 55% of duodenal gastrinomas and 22% of pancreatic gastrinomas were associated with metastatic disease. These observations combined with the high recurrence rates with duodenal gastrinomas suggest that duodenal gastrinomas are more often malignant and are clearly not more likely to be curable, as proposed previously. It is likely in previous studies that small duodenal gastrinomas were frequently missed and that the detection of only lymph nodes led to an underestimation of the true malignant rate and curability. In the future, additional management steps directed at improving long-term cure rate in these patients will need to be identified.

Despite the malignant nature of gastrinoma as documented by recurrent disease and, in some patients, lymph node or liver metastases, antisecretory medications and surgery provide near perfect long-term survival of patients with sporadic Zollinger–Ellison syndrome who present without evidence of liver metastases (Fig. 2). These long-term survival results provide information that has a significant bearing on current management strategies. First, in the present study as well as in previous studies,[7,9,24,69] patients in whom no gastrinomas were found had survival rates of 80% to 100%, which was not significantly different from that for cured patients. The current results suggest that these missed tumors may most likely be small duodenal microgastrinomas. This excellent long-term prognosis contradicts recent studies[64,70,71] suggesting the use of Whipple pancreaticoduodenotomy after selective venous gastrin gradients that localize tumors to the pancreatic head area when no tumor can be located at surgery. At present, it is not clear that the morbidity rate and potential mortality rate of this procedure do not significantly outweigh its potential to increase cure and survival rate. Secondly, it may be argued, because the 5-year survival is >90% and is not significantly different in patients without a gastrinoma found than in patients with a gastrinoma resected but not cured, or in patients cured, that surgery is not indicated. There are, however, that there are a number of points that argue against this approach. It is unknown what percentage of the resected patients would have developed metastatic liver disease during follow-up if no surgery was done. We have observed other patients before this study who did not undergo surgical exploration who developed metastatic gastrinoma in the liver during follow-up. With the limited information available, the rate of such change is unknown and which patients will develop metastatic disease is unclear. Studies from carcinoid tumors that histologically resemble gastrinomas[11] demonstrate that the rate of developing metastatic disease is proportional to the size of the primary tumor. In patients with primary tumors < 1 cm in diameter, between 0% and 15% develop metastases, and in patients with >2-cm tumors, as many as 50% develop metastases.[19] Imaging studies rarely localize gastrinomas < 1 cm in diameter, 50% of gastrinomas 1 to 3 cm, and 70% > 3 cm[43–45]; there-

fore, with the use of radiographic imaging alone, gastrinomas < 3 cm are frequently missed and may only be found at surgery. If such patients had not undergone resection and developed metastatic disease, the prognosis would be generally poor, as shown in the present study for patients with metastatic disease. In contrast, the risk of laparotomy is low. Furthermore, in the patients who are disease free (up to 30%) the surgical procedure has long-term benefit. In these patients, antisecretory drugs can be stopped or markedly decreased, and the long-term potential risk of chronic hypergastrinemia or taking lifelong antisecretory agents can be avoided. In patients treated for up to 5 years with histamine H_2-receptor antagonists or omeprazole, there have been no drug-related side effects. All patients need to take these agents at least daily, however, and few patients have been maintained on these drugs longer than 5 years. Lastly, chronic hypergastrinemia can cause gastric carcinoid tumors in both humans and animals, some of which are malignant[17,72–74] and the long-term, lifetime risk of chronic hypergastrinemia has not been clearly defined. Therefore, for the 30% of patients disease free, long-term surgical removal may have significant long-term benefit.

In conclusion, this study of laparotomy and gastrinoma resection in patients with sporadic Zollinger–Ellison syndrome and no evidence of liver metastases suggests that tumors can be found in a higher proportion of patients than previously thought possible. In the last 37 consecutive patients, gastrinomas were found and excised in 34. This result was different from the findings in the initial 36 patients, and it became evident that the use of techniques to find duodenal gastrinomas accounted for the observed difference. The short-term disease-free rate was 58%. Careful long-term follow-up indicated that 50% of patients initially disease free developed recurrent disease by 5 years. Patients who developed evidence of recurrent disease by radiographic imaging studies still were able to have all recurrent tumor removed for control. Surgery was performed with acceptable morbidity and mortality rates. This strategy of medical management of gastric acid hypersecretion and surgical resection of gastrinoma resulted in no deaths from Zollinger–Ellison syndrome or treatment during the current follow-up period (>4 years). This study suggests that patients with Zollinger–Ellison syndrome can be effectively and safely managed by antisecretory medications to control gastric acid hypersecretion and surgery to control malignant potential of tumor in nearly all patients and to cure 30% of patients.

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