ANNALS OF SURGERY
Vol. 220, No. 3, 320–330

Surgery in Zollinger-Ellison Syndrome Alters the Natural History of Gastrinoma

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Objective
The authors assessed the impact of gastrinoma resection on the subsequent development of hepatic metastases in Zollinger-Ellison syndrome.

Summary Background Data
The symptoms of acid hypersecretion can be controlled medically in Zollinger-Ellison syndrome with high-dose pharmacologic therapy. The current role of surgery is curative excision of the gastrinoma. Because biochemical cure is obtained only in a portion of the patients and the neoplastic disease may be indolent in this syndrome, the ability of surgical resection of gastrinoma to alter or improve the subsequent development of hepatic metastases and mortality has not been defined.

Methods
One hundred twenty-four patients with the biochemical diagnosis of Zollinger-Ellison syndrome and no hepatic metastases on initial imaging studies were evaluated. Ninety-eight patients underwent surgical exploration for curative gastrinoma resections while 26 patients were managed medically. Long-term follow-up regarding development of hepatic metastases and survival were evaluated.

Results
Surgical exploration with gastrinoma excision resulted in a significantly decreased incidence of hepatic metastases 3% (3/98) compared with patients managed medically 23% (6/26) with comparable follow-up ($p < 0.003$). Two deaths due to metastatic gastrinoma occurred in the nonoperative group compared with no disease-specific deaths in the surgical group ($p = 0.085$).

Conclusions
For the patient with Zollinger-Ellison syndrome without metastatic disease, surgical exploration with attempted curative gastrinoma resection is recommended because it may alter the natural history of this syndrome.

The role of surgery as treatment for Zollinger-Ellison syndrome has evolved since the description of this disease in 1955.[1] The initial standard surgical therapy was total gastrectomy to eliminate the target organ from excessive levels of gastrin.[2] Advances in the pharmacologic control of acid hypersecretion during the past two decades has eliminated the need for surgical acid reduction procedures. The development and use of high doses of H_2-blocking agents and more recently, H^+-K^+-ATPase pump inhibitors can control symptoms in virtually all patients with Zollinger-Ellison syndrome.[3] With the increased ability to control the gastric acid secretion, the natural history of the gastrinoma increasingly becomes the determinant of long-term survival.

Despite these developments, as recently as the early 1980s,[4] it was recommended that surgical exploration for possible curative excision of the gastrinoma not be done routinely. Although at present, most investigators recommend routine surgical attempts at cure, many physicians still remain unsure of the value of surgery.[5] This continued uncertainty of the possible value of surgery has occurred primarily because no study has demonstrated surgical exploration for gastrinoma resection extends life or decreases the incidence of metastases, although it is assumed that it would. However, this study was not done because of the rarity of this disease or because most physicians have already decided the appropriate therapy—i.e., within each institution patients are either explored surgically for gastrinoma excision or managed medically.

Because of a unique set of circumstances, there have existed two groups of patients that were observed for long-term follow-up at our institution that could partially answer this question. At the National Institutes of Health (NIH), a group of patients continued to be observed for long-term follow-up who did not undergo surgical exploration for a number of reasons; in addition, a large group underwent surgical exploration for gastrinoma excision. The analysis of these two groups allows an assessment of the possible effects of routine surgical exploration on the natural history Zollinger-Ellison syndrome.

METHODS

Since 1975, close to 200 consecutive patients have been referred to the NIH with a diagnosis of the Zollinger-Ellison syndrome for evaluation and treatment on an approved institutional protocol. As described previously, the diagnosis of Zollinger-Ellison syndrome was confirmed by preoperative testing.[6,7] All patients were evaluated with fasting serum gastrin concentrations, acid secretory studies, and stimulation tests with intravenous secretin (2 units/kg) or intravenous calcium infusions (5 mg/kg/hr calcium × 3 hr). Both basal and pentagastrin-stimulated maximal acid output were measured. The diagnosis of Zollinger-Ellison syndrome was made if at least two of the following three criteria were met: 1) elevated fasting serum gastrin > 100 pg/mL; 2) basal acid output > 15 mEq/hr if the patient has had no previous acid reduction surgery or >5 mEq/hr if the patient had had prior acid reduction surgery; and 3) an incremental increase in serum gastrin in stimulation tests > 200 pg/mL after secretin or >395 pg/mL after calcium.

All patients were evaluated at presentation with radiologic studies to identify the location and extent of the gastrinoma. All patients underwent abdominal ultrasound, abdominal computed tomography, and selective hepatic, gastroduodenal, splenic, and superior mesenteric angiography. Since 1987, all patients underwent magnetic resonance imaging of the abdomen. Any patient with radiographic evidence of metastatic gastrinoma to the liver on initial evaluation was eliminated from analysis in the present study.

Surgical exploration for gastrinoma extirpation was performed in 98 patients. The operative approach has been well described[8] and will be reviewed briefly. All patients underwent complete exposure and exploration of the pancreas, including intraoperative ultrasound, to identify intrapancreatic lesions. All patients had evaluation of peripancreatic, porta hepatis, and celiac lymph nodes. All patients had a complete abdominal exploration, including evaluation of the liver. Since 1987, all patients have had an extensive exploration of the duodenum, including intraoperative endoscopy, transillumination,[9] and exploratory duodenotomy.[7] Postoperatively, patients are evaluated with serial biochemical testing and repeat radiographic studies as recently described.[10] Biochemical cure after surgery with excision of the gastrinoma is defined as normalization of fasting gastrin levels, normalization of the secretin stimulation test, and negative imaging studies.[7] Patients are evaluated by serial abdominal imaging studies every 6 to 12 months, including computed tomography scans, magnetic resonance imaging scans, and abdominal ultrasound.

A second group of 26 patients, who were documented biochemically to have Zollinger-Ellison syndrome, were managed medically without surgical exploration. These patients had the same extensive evaluation as the surgical patients, including selective angiography to determine tumor location and extent. These patients did not undergo operative exploration because of patient refusal of

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Accepted for publication April 1, 1994.

Table 1. THE REASON FOR NO SURGICAL EXPLORATION IN THE PATIENTS TREATED MEDICALLY AND THE DEVELOPMENT AND DEATH DUE TO GASTRINOMA METASTASES TO THE LIVER IN THIS GROUP

Reason	No. of Patients	No. with Liver Metastases	Deaths
Refused operation	12	3	2
MEN-1 known or suspected	10	3	0
Co-morbid medical diseases	3	0	0
Unable to give informed consent	1	0	0

surgery (n = 12), known or suspected multiple endocrine neoplasia-1 (MEN-1; n = 10), severe concomitant medical problems (n = 3), and inability to give informed consent (n = 1) (Table 1). These patients were treated with oral antisecretory drug titrated to suppress acid output.[3] They were observed for follow-up every 6 to 12 months with serial radiologic imaging studies including abdominal ultrasound, computed tomography scans, and more recently, abdominal magnetic resonance imaging scans. Patients underwent selective angiography every 4 to 6 years to screen for the development of hepatic metastases, which would affect medical therapy because of the need to initiate chemotherapeutic treatment.

The incidence of hepatic metastases was analyzed by the Fisher Exact Test. The disease-specific survival was graphed by the Kaplan-Meier method and analyzed for significant differences by the Breslow modification of the Kruskal-Wallis test.

RESULTS

The demographic characteristics, the initial biochemical testing, and the acid output measurements for patients managed medically and those explored for gastrinoma resection are shown in Table 2. The mean age and age range is similar in both groups, indicating that age of presentation was not a factor that influenced surgical *versus* nonsurgical management. One difference in these two populations is a greater incidence in patients with MEN-1 disease in the group that was managed medically (35%) compared with the group undergoing surgical exploration (15%). This difference is expected because the presence of MEN-1 places patients in the "no operation" group because the optimal role of surgery in this patient population is not well defined. Specifically, on the current NIH protocol, patients with MEN-1 and Zollinger-Ellison syndrome undergo surgical exploration for tumor excision only if a primary tumor > 3 cm in size is identified on preoperative imaging studies. However, almost two thirds of the patients in the nonoperative group had sporadic Zollinger-Ellison syndrome, not MEN-1.

The initial measurements of acid output, and fasting gastrins were quite similar in these two patient populations (Table 2). The peak increment in gastrin after secretin stimulation was higher in the nonoperative group, but this value shows a large degree of variation between patients, as indicated by the high standard error, and was not significantly different.

Length of Follow-Up

In evaluating and comparing two patient populations in regards to natural history of a disease, a key component is the time period in which the patients were studied. Specifically, the overall duration of follow-up and a comparable period of evaluation between the two patient groups is needed. The duration of follow-up data since the initial symptoms of Zollinger-Ellison syndrome, the initial biochemical diagnosis, and the initial NIH evaluation for patients managed medically and those who were surgically explored is shown in Table 3. Initial symptoms are defined as the time point at which patients have clinical events related to acid excess—consisting of either peptic ulcer disease or severe diarrhea—that were constant in nature. The time to biochemical diagnosis is considerably shorter than the time from initial symptoms, highlighting the delay in recognition and diagnosis of this syndrome. The mean length of follow-up for both times since symptoms and since diagnosis is very com-

Table 2. DEMOGRAPHIC AND DIAGNOSTIC FEATURES IN ZOLLINGER-ELLISON SYNDROME PATIENTS MANAGED MEDICALLY OR SURGICALLY

Feature	No Operation	Surgical Exploration
n	26	98
Age (mean; range)	56 (23–76)	53 (16–76)
Male:female	13:13	68:30
No. MEN-1 (%)	9 (35%)	15 (15%)
BAO (mEq/hr)*	54 ± 5	41 ± 2
MAO (mEq/hr)*	69 ± 7	62 ± 3
Fasting gastrin (pg/mL)*	1640 ± 547	1590 ± 436
Peak gastrin increase with secretion stimulation (pg/mL)*†	5502 ± 2769	2904 ± 614

* Data shown as mean ± SEM.

† Secretin stimulation is 2 U/kg iv secretin with serial measurement of serum gastrin.

BAO = Basal acid output; MAO = Maximal acid output.

Table 3. LENGTH OF TIME OF FOLLOW-UP SINCE INITIAL SYMPTOMS, DIAGNOSIS, AND INITIAL NIH EVALUATION IN ZOLLINGER-ELLISON SYNDROME PATIENTS MANAGED MEDICALLY OR SURGICALLY

	No Operations	Surgery for Cure
Time since initial symptoms of ZES	15.4 ± 1.5 (2.7–30.9)	14.0 ± 0.8 (1.6–38.6)
Time since biochemical diagnosis of ZES	9.4 ± 0.9 (1.5–19.1)	7.7 ± 0.4 (1.1–21.7)
Time since initial NIH evaluation	8.7 ± 0.9 (1.5–19.0)	6.3 ± 0.3 (0.7–16.8)

All data shown in years as mean ± SEM, (range).

parable between the nonoperative group and the group undergoing surgical exploration. The length of follow-up in this patient population also is considerable, with the mean follow-up since diagnosis of 9.4 years in the medical management and 7.7 years in the patients undergoing operation with maximal follow-up intervals of approximately 20 years in both groups (Table 3).

A third data point relating to follow-up is time from initial NIH evaluation. This time point is important because, for most patients, this represents the initial radiologic evaluation to identify primary gastrinomas and potentially hepatic metastases. Again, the time since initial evaluation is similar, with a tendency toward longer follow-up in the medically managed group. One reason the overall follow-up times are slightly longer in the medically managed group is because of the higher incidence of MEN-1 patients. Multiple endocrine neoplasia-1 patients generally have an earlier diagnosis because of the history and earlier referral to our institution, with several patients having follow-up of more than than 15 years.

Preoperative Localization Studies

All patients in both groups were evaluated by abdominal ultrasound, computed tomography scans, and angiography to identify the location and size of primary tumors at initial evaluation (Fig. 1). The most sensitive study is angiography, which detects hypervascular lesions in the pancreas, duodenum, or surrounding lymph nodes, and the angiogram was initially positive in approximately one third of patients in both groups—medially managed and surgically explored.[11,12] Computed tomography scans and ultrasound were less sensitive, but identified tumors in 10 to 15% of patients in both groups. Combining all initial imaging tests, including magnetic resonance imaging scans, which were done consistently since 1987 (data not shown in Fig. 1), the group undergoing surgical exploration had tumors identified in 52% of patients compared with 39% of patients for the group treated medically. The identification of lesions on these preoperative studies did not influence the decision to recommend surgical exploration, except for the question of the size of lesion in patients with MEN-1, as discussed previously.

Operative Findings

Gastrinoma was identified and resected in 83 of the 98 patients undergoing operative exploration (85%) (Fig. 2). In approximately one half of the patients in which tumor was found, the primary gastrinoma was located in the wall of duodenum (40%), and half of these duodenal lesions were associated with histologically positive lymph node metastases. Primary gastrinomas were found in the pancreas in 19 patients (23% of all patients in which tumors were found), and a larger number of patients had tumors in lymph nodes only (26% of all patients in which tumors were found). At the most recent evaluation, 48 patients are considered biochemically cured with normal fasting gastrins, negative secretin stimulation tests, and no tumors on imaging studies. This disease-free population represents 58% of the patients in which tumors were found and 49% of the overall patient population undergoing surgical exploration.

For all 98 patients treated surgically, there were no operative deaths. The surgical morbidity in this patient population has been described recently,[7] and significant complications occur in approximately 10% of this group.

Incidence of Hepatic Metastases

The incidence of the development of hepatic metastases is 23% in the patients who did not undergo surgical exploration (6 of 26 patients) and 3% in the patients who were operated on for gastrinoma resection (3 of 98 patients) (Fig. 3). Each patient scored as having hepatic metastatic disease had clear changes with new lesions appearing on serial radiologic examination. Each of these nine patients has had histologic confirmation of metastatic gastrinoma by percutaneous biopsy or surgical resection of the new lesion, confirming metastatic neuroendocrine tumor. This eightfold difference in the incidence of hepatic metastases is statistically significant at the $p < 0.003$ level by the Fisher exact test.

Two deaths have occurred in the nonoperative group of patients because of metastatic gastrinomas, compared with no deaths due to gastrinoma in the group treated surgically. Figure 4 shows the Kaplan-Meier plot of disease-specific survival for these two populations ($p =$

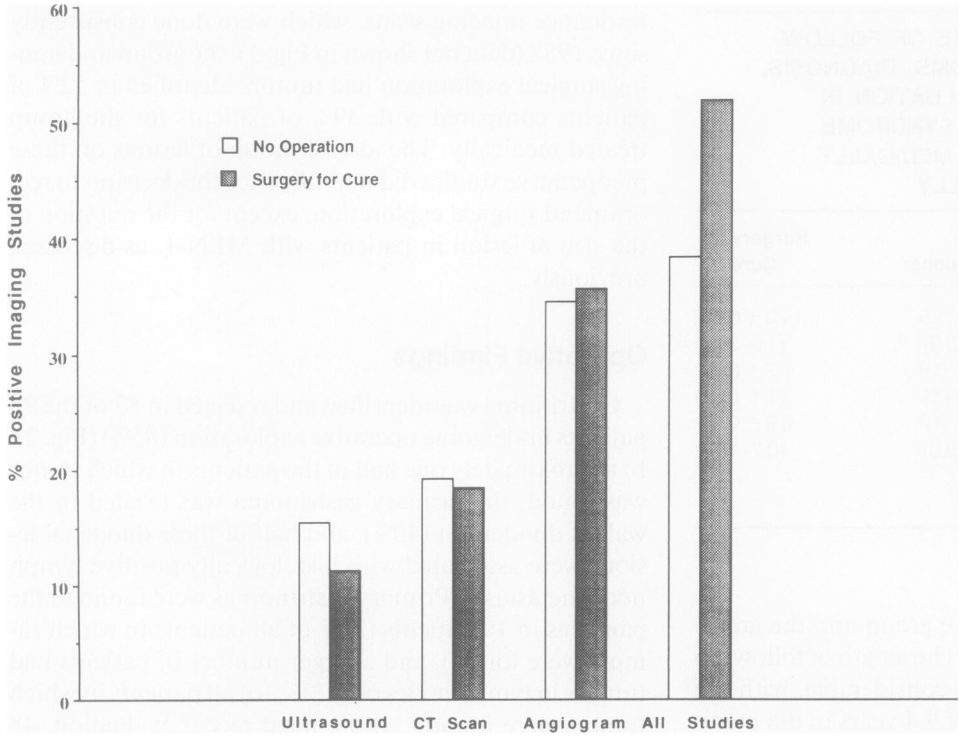

Figure 1. Per cent positive imaging studies in identifying primary gastrinomas at the initial NIH evaluation for patients managed medically and for the group undergoing surgical exploration for gastrinoma excision. All patients in both groups underwent abdominal ultrasound, abdominal computed tomography scans, and selective celiac and mesenteric angiography. The all studies column identifies the patients with positively imaged tumor considering the results of all imaging studies.

0.085). Death due to other causes was censured in this analysis. In the group of patients who were managed medically and went on to develop metastases in the liver, three patients initially refused exploration, and three patients were not operated on because they had MEN-1 disease (Table 1). Both deaths occurred in patients who refused surgical exploration.

A detailed analysis of the patients who developed metastatic disease during the follow-up interval are shown in Tables 4 and 5. No clear difference in terms of the age or sex exists between patients who develop hepatic metastases and those who do not (Table 4). One might expect that the group of patients who develop hepatic metastases would have longer duration of disease, but this was not the case. Specifically, the mean time since initial symptoms and since biochemical diagnosis either is similar or shorter in the subgroup of patients who develop liver metastases compared with those patients who do not (Table 4). The mean time to the development of hepatic metastases is similar in the six patients who did not undergo operation (5.0 years) compared with the three patients who did (3.9 years) (Table 5). The patients who developed metastatic disease with MEN-1 disease had a slightly longer interval from the time of diagnosis to the

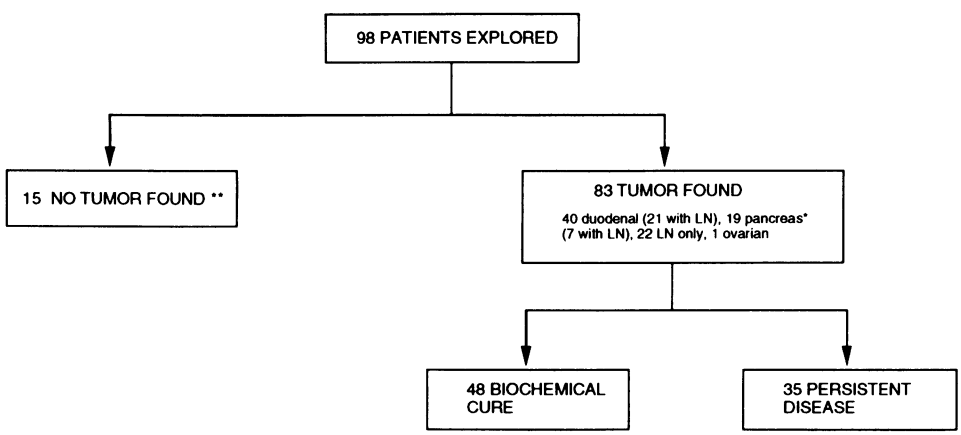

Figure 2. Flow diagram for the findings at initial exploratory laparotomy to excise gastrinoma in the group of patients who underwent operations. In the 83 patients in whom tumors were found, the location of the primary gastrinoma is indicated. Biochemical cure is defined as normal fasting gastrin and negative secretin stimulation test at the most recent follow-up, with no evidence of gastrinoma on imaging studies. Persistent disease indicates either elevated fasting gastrins, positive secretin test stimuli, or positive imaging studies. *Patients who subsequently developed liver metastases (LN = lymph node).

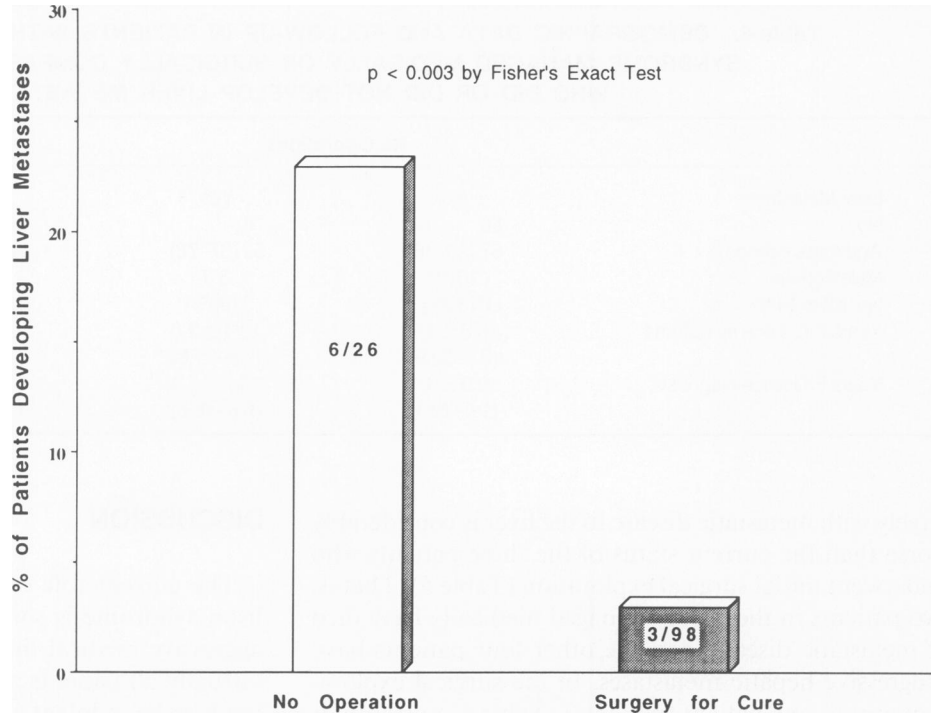

Figure 3. Per cent of patients in the medically managed and the surgically treated groups who went on to develop hepatic metastases from gastrinomas.

time of appearance of liver metastases (Table 5). The time interval from diagnosis to liver metastases is virtually identical for the patients with sporadic gastrinomas in the group that underwent surgical resection and those three patients who did not have MEN-1 who were treated medically (Table 5).

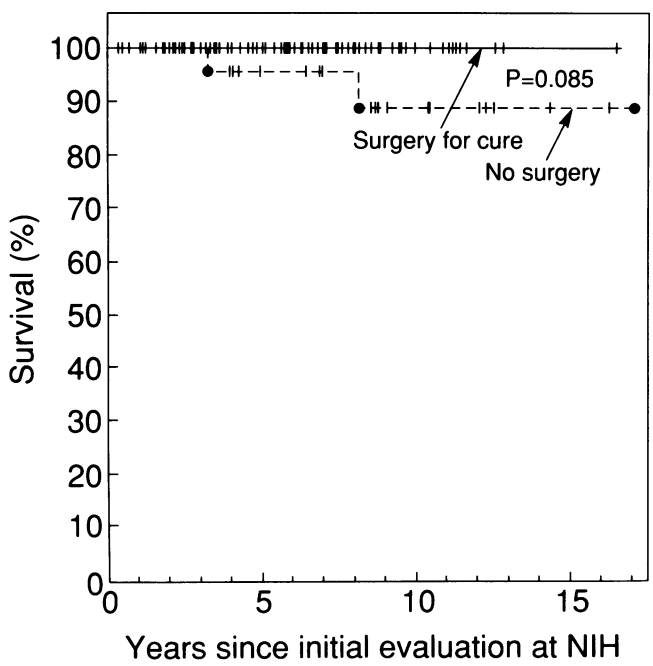

Figure 4. Disease-specific survival for patients in the medically managed group and those who underwent operations for excision of gastrinoma. Deaths due to causes unrelated to Zollinger-Ellison syndrome have been censored in this analysis. Statistical analysis is by the Breslow modification of the Kruskal-Wallis test.

For the seven patients who developed hepatic metastases, in which the site of the primary gastrinoma is known either by imaging studies or by surgical exploration, all seven have primary tumors within the pancreas, despite the fact that at least half of the gastrinomas appear to originate in the duodenum (Fig. 2). Four of these pancreas lesions were located in the head, and three were in the body-tail region. In the six patients treated nonoperatively, the primary tumor site is based on serial imaging studies. In the patients who underwent surgical explorations for gastrinoma excisions, gastrinomas were identified and removed at the junction of the body and tail of the pancreas by distal pancreatectomies (patient 9, Table 5). Two other patients (patients 7 and 8, Table 5) have unclear sites of primary gastrinomas. Both of these patients had negative exploratory laparotomies at the initial operation to resect gastrinoma. One patient developed a single lesion in the left lobe of the liver that was removed via left hepatic lobectomy, resulting in biochemical cure at 3-month follow-up since this procedure. Another patient underwent a right hepatic wedge resection of a single nodule with no other source of primary gastrinoma found on a repeat evaluation of the pancreas and duodenum. This patient had normalization of fasting gastrin but persistent abnormal secretin stimulation test.

The current status of the six patients treated nonoper-

Table 4. DEMOGRAPHIC DATA AND FOLLOW-UP IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME MANAGED MEDICALLY OR SURGICALLY COMPARING PATIENTS WHO DID OR DID NOT DEVELOP LIVER METASTASES

	No Operations		Surgery for Cure	
Liver Metastases	No	Yes	No	Yes
No.	20	6	95	3
Age (mean; range)	57 (23–76)	52 (37–72)	53 (16–76)	50 (37–57)
Male:Female	10:10	3:3	67:28	1:2
No. MEN-1 (%)	6 (30%)	3 (50%)	15 (16%)	0 (0%)
Years F/U since symptoms	16.0 ± 1.9 (2.7–30.9)	13.4 ± 2.0 (7.8–21.8)	14.0 ± 0.8 (1.6–38.6)	8.5 ± 2.2 (4.2–11.7)
Years F/U since diagnosis	9.0 ± 1.1 (1.5–19.1)	10.7 ± 1.4 (6.6–16.6)	7.7 ± 0.4 (1.1–21.7)	7.1 ± 2.0 (3.2–9.3)

atively with metastatic disease to the liver is considerably worse than the current status of the three patients who underwent initial surgical exploration (Table 5). That is, two patients in the group managed medically have died of metastatic disease, and the other four patients have progressive hepatic metastases. In the surgical exploration group, one patient (patient 7, Table 5) currently is biochemically and radiographically free of disease, and another patient (patient 8, Table 5) is radiographically free of disease at the present time.

DISCUSSION

The current role of surgical therapy in Zollinger-Ellison syndrome is somewhat controversial.[4,5,7] Because aggressive medical therapy can eliminate symptoms in virtually all patients and because the neoplastic disease tends to be indolent and difficult to cure biochemically, some investigators argue that the risks and complications of gastrinoma excision outweigh any real benefits from this procedure.[5] This review of our current data of pa-

Table 5. LOCATION OF PRIMARY GASTRINOMA, TIME TO METASTASES AND CURRENT STATUS IN PATIENTS WHO DEVELOP METASTATIC GASTRINOMA TO THE LIVER

Patient	MEN-1	Location of Primary Gastrinoma	Initial Operative Findings	Time From Diagnosis to Liver Metastases	Current Status
No operation					
1	No	Pancreas head	NA	3.7 years	Dead from gastrinoma
2	No	Pancreas head	NA	7.2 years	Dead from gastrinoma
3	No	Pancreas head	NA	1.0 years	Failed chemotx; alive with slowly progressive liver and pancreas disease
4	Yes	Pancreas body	NA	5.0 years	Alive with slowly progressive liver and pancreas disease
5	Yes	Pancreas body/tail plus duodenal nodule	NA	7.2 years	Alive with slowly progressive liver and pancreas disease
6	Yes	Pancreas head	NA	6.2 years	Failed chemotx; alive with progressive liver and pancreas disease
Surgery for gastrinoma resection					
7	No	? Hepatic primary	Negative	2.2 yrs	Left hepatic lobectomy; biochemically cured
8	No	Unknown	Negative	6.1 yrs	Right hepatic wedge resection; elevated gastrins; current imaging negative
9	No	Pancreas body/tail	Distal pancreatectomy	3.3 yrs	Treated with chemotherapy with response

NA = not applicable.

tients undergoing surgical exploration to excise gastrinoma shows a highly significant benefit in terms of prevention of hepatic metastases as opposed to a group managed medically.

One key issue in making the conclusion that surgical exploration with gastrinoma resection can alter the natural history of Zollinger-Ellison syndrome is to be certain that the two patients populations are comparable at the outset. The defining characteristics of the patients managed medically at initial evaluation were similar to the patients who underwent surgical exploration. The age, acid output, gastrin levels, and initial radiologic imaging studies to identify a primary gastrinoma are essentially identical (Table 1, Fig. 1).

A second component that validates the conclusions drawn from this study is the duration and completeness of follow-up for both groups. The mean time since initial symptoms is approximately 15 years for both groups, and the mean time since the biochemical diagnosis of Zollinger-Ellison syndrome is between 7.5 and 9.5 years. The follow-up times in the group managed medically is consistently longer to a slight degree compared with the surgical group. This longer follow-up time is primarily due to the greater proportion of MEN-1 patients in this group who generally have been diagnosed earlier and observed in follow-up longer. This small difference ranging between 10 and 15% for the various follow-up time intervals does not detract from the eightfold decrease in the incidence of hepatic metastases between these two patient populations. The mean time to development of metastases in the nine patients ranged between 4 and 5 years (Table 4). It does not appear that simply observing patients for a longer follow-up time in the group managed surgically will make up the dramatic difference between the incidence of hepatic metastases.

One notable difference between the two patient populations is the greater percentage of MEN-1 disease in the group managed medically; three of these patients eventually developed hepatic metastases. One defining characteristic that places patients in the nonoperative group is suspicion or documentation of having MEN-1. Ten patients were known or suspected to have this syndrome and, with further follow-up, it became clear that nine of these patients definitively could be categorized as patients with MEN-1. The role of surgery to treat gastrinoma in MEN-1 disease is controversial.[13–15] Obtaining biochemical cure of Zollinger-Ellison syndrome postoperatively in this patient population is difficult because of the multicentric nature of the disease. Furthermore, the incidence and degree of nonfunctional neuroendocrine tumors make it difficult to identify which lesion is responsible for the elevated gastrins. Although it recently has been claimed[16] that most of the gastrinomas in patients with MEN-1 and Zollinger-Ellison syndrome are duodenal in location, the tumors frequently are multiple, and it is not clear if they can be resected fully without a Whipple procedure.[17] Therefore, our current protocol is to perform abdominal exploration with tumor excision only when a clear mass consistent with a neuroendocrine tumor greater than 3 cm in size is identified on imaging studies because natural history data indicates that larger lesions are more likely to metastasize.[13,18] Weighting the surgical treatment group with patients with MEN-1 who have large pancreatic tumors tends to increase the incidence of subsequent hepatic metastases. There is no evidence that patients with MEN-1 with Zollinger-Ellison syndrome have a more malignant course; in fact, in two[19,20] of the six series in which this was examined, patients with MEN-1 had a better survival rate, suggesting that the tumor pursued a more benign course; in the other four, there was no difference.[21–24] This difference tends to make the inclusion of these patients in the nonsurgical group have a less malignant course, if anything. Furthermore, simply because the patients with MEN-1 are placed in the group that is managed medically—because of protocol criteria as opposed to refusal of surgery—does not detract from the observation that three of these patients who were observed for long-term follow-up developed new hepatic lesions (Table 5). Finally, statistical analysis of the difference in incidence of hepatic metastases in the patients with sporadic Zollinger-Ellison syndrome (non-MEN-1) managed medically (18%), compared with those surgically treated (4%), still is significantly different ($p < 0.05$).

The difference in the incidence of hepatic metastases of 23% and 3% between these two groups somewhat understates the true difference in the clinical status of these patients with metastatic disease because of two peculiar cases in the group who underwent surgical exploration. Although one might expect that patients with identifiable larger primary tumors would be most likely to have subsequent hepatic metastases, two of the three patients in the group undergoing surgery in this category had initial negative exploratory laparotomies. Both of these patients, on follow-up imaging studies, developed single hepatic lesions that were resected and shown to be neuroendocrine tumors. One patient achieved a biochemical cure after hepatic resection (patient 7, Table 5), whereas a second patient had a normal fasting gastrin and negative imaging studies after hepatic resection, but still had an abnormal secretin stimulation test. The results of these two patients raise the question of whether primary hepatic gastrinomas exist,[25] and if either of these patients were in that unusual category, they are identified incorrectly as having metastatic disease to the liver. Nevertheless, these two patients currently are clinically free of disease, whereas the group of six patients in the medically managed population had two deaths and four patients

with persistent disease. These four patients with hepatic metastases also have progressive disease of the pancreas, revealed by imaging studies, and have only medical treatment options available.

Another feature of this patient population is that all patients who developed liver metastases with clearly identified primary tumors have gastrinomas arising from the pancreas. The biology of pancreatic gastrinomas may predispose to the development of hepatic metastases, whereas the more common duodenal gastrinomas appear to metastasize much less frequently to the liver.[26,27] In contrast, both sites of primary tumors appear to metastasize equally to lymph nodes. Therefore, these two sites of primary gastrinomas appear to differ fundamentally in biologic behavior. Whether this is a function of size or the biology per se of the tumors remains to be determined.

The most important conclusion from the analysis of our current natural history data is that patients with Zollinger-Ellison syndrome should be advised to undergo abdominal exploration with aggressive resection of primary and regional gastrinomas. This procedure can be performed with minimal morbidity and results in a highly significant decrease in the subsequent development of hepatic metastases, which can lead to patient death. Because the mean age of presentation for this disease is relatively young, this decrease in the incidence of hepatic metastases ultimately may translate into a clear survival difference. Currently, the difference in disease-specific mortality shows a p value of 0.085 and already is borderline statistically significant (Fig. 4). Further follow-up of these patient populations, particularly in light of the current status of the patients managed medically, may result in the conclusion that initial exploration to resect gastrinomas ultimately leads to an improved overall survival.

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Discussion

DR. STANLEY R. FRIESEN (Prairie Village, Kansas): I was happy to see that this abstract was on the program because it's