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# Aggressive Resection of Metastatic Disease in Selected Patients with Malignant Gastrinoma

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Fifteen patients with Zollinger-Ellison syndrome followed at the National Institutes of Health with extensive metastatic disease had an actuarial 5-year survival of 20%. Therefore, in 1982 a prospective study to examine the effect and feasibility of removing all gross tumor in selected patients with extensive metastatic disease was instituted. Five patients with extensive metastatic gastrinoma confined to the abdomen in whom imaging studies suggested the possibility of complete surgical resection were entered into this study and underwent attempted complete surgical resection and chemotherapy with streptozotocin, doxorubicin, and 5-fluorouracil. Median follow-up was 24 months. Surgical resection of all gastrinoma was possible in 4/5 patients attempted. In one patient in whom all gross disease could not be resected, the residual tumor progressed and the patient died 19 months after operation. All four patients with all disease resected appeared to benefit since all of them had a significant reduction in antisecretory medications and are enjoying normal activity and work. Three patients have had no detectable tumor on follow-up, and two of these patients are clinically and biochemically "cured" with normal fasting gastrin levels and negative provocative gastrin tests at 14 and 32 months. Therefore, aggressive resection of metastatic disease in selected patients with malignant gastrinoma is recommended.

**O**F PATIENTS with Zollinger-Ellison syndrome, 25–40% have metastatic disease.<sup>1</sup> In Zollinger's experience, 60% of gastrinomas are malignant.<sup>2,3</sup> Fifty per cent of patients treated with total gastrectomy or medical antisecretory therapy will eventually die of their tumors.

The best treatment for metastatic gastrinoma is not known. Total gastrectomy has been reported to result in a reduction in size of metastatic deposits in a rare patient<sup>4</sup>; in the premedical antisecretory era, it was suggested that total gastrectomy improved survival rate of patients with

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metastatic disease.<sup>5</sup> However, in subsequent studies, it was shown that total gastrectomy furnished neither predictable nor permanent protection from subsequent tumor growth and metastases.<sup>6</sup> Chemotherapy is partially effective against metastatic gastrinoma; however, no complete responses or cures have been documented.<sup>7</sup> Another complicating factor in treating patients with metastatic gastrinoma is the variable clinical course. Some patients can be followed more than 20 years with stable or slowly progressive metastatic disease, whereas in others the tumor progresses rapidly and causes the patient's death.<sup>8</sup>

In the studies of Zollinger et al., patients with metastatic gastrinoma had a 5-year survival rate of 42% and a 10-year survival rate of 30%.<sup>3</sup> In these early studies, good imaging techniques were not available. The extent of disease was generally established at surgery, and thus the true extent of metastatic disease was difficult to establish. Since January 1975, we have performed detailed imaging studies on all patients with Zollinger-Ellison syndrome and found that in 15 patients with extensive metastatic disease, the actuarial 5-year survival was 20% (Fig. 1).

Zollinger et al.<sup>3</sup> have noted that in patients with gastrinomas complete tumor resection prolonged average survival from 3 years to 9 years. These observations have been interpreted by Zollinger<sup>3</sup> and other authorities to support an aggressive surgical attempt to resect metastatic gastrinoma, including major hepatic lobectomy.<sup>9</sup> However, in those reports, patients with advanced disease were included with other patients who had minimal disease.<sup>9</sup>

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In 1982, we instituted a prospective study to attempt to resect all gross tumor in any patient with extensive gastrinoma in whom we thought it might be possible to do so with a 20% operative mortality or less. We combined this aggressive surgical approach with a chemotherapy regimen that gave a 60% response rate.<sup>7</sup> The present paper reports five patients who underwent this regimen. Two patients treated with surgery and chemotherapy have a complete biochemical and radiographic arrest of Zollinger-Ellison syndrome with follow-up of 14 and 32 months, respectively.

### Methods

During the period from January 1975 to August 1985, 87 patients were seen at the National Institutes of Health (NIH) with Zollinger-Ellison syndrome. Each patient was evaluated initially for the extent of gastrinoma by ultrasound, abdominal computed tomography (CT) with intravenous contrast, and abdominal angiography. Twenty patients (23%) of 87 had extensive metastatic gastrinoma confined to the abdomen. Since January 1982, we have evaluated aggressive surgical removal of all gross disease to determine if it is feasible and helpful in such patients. Ten of the 20 patients with extensive metastatic disease confined to the abdomen presented after January 1982. The imaging studies in these 10 patients suggested that in five the full extent of tumor might be surgically resectable, and these patients were selected for the current study. Four of the five patients were given chemotherapy after and one before operation as monthly cycles consisting of<sup>7</sup> streptozotocin 3.0 g/m<sup>2</sup> body surface area, doxorubicin 40 mg/m<sup>2</sup>, and 5-fluorouracil 1200 mg/m<sup>2</sup>.

Each of the five patients was admitted within 2 months of surgery and underwent the following evaluations: measurement of fasting serum gastrin; secretin provocative testing using 2 units/kg of GIH secretin<sup>10</sup>; calcium provocative testing using 5 mg/kg body weight per hour for 3 hours<sup>11,12</sup>; determination of basal and pentagastrin stimulated maximal acid output after discontinuation of all antisecretory medications<sup>7</sup>; determination of the intravenous dose of cimetidine that reduced gastric acid secretion to less than 10 mEq/hr; and determination of the effect of a single dose of oral ranitidine or cimetidine on basal acid secretion.<sup>13</sup>

To further define the extent of the tumor, the following studies were performed on each of the five patients before surgery: chest roentgenograms, full lung tomograms, bone scan, bone survey, liver-spleen scan, upper gastrointestinal endoscopy and x-ray including hypotonic duodenography, CT of the abdomen with intravenous contrast, ultrasound, and arteriography (celiac, superior mesenteric, hepatic, splenic, gastroduodenal, and additional vessels as dictated by other imaging studies). If metastatic gastrinoma to the

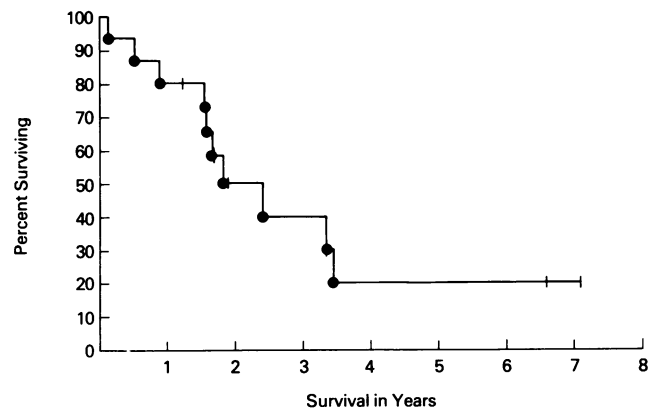


FIG. 1. Actuarial survival of 15 patients with metastatic gastrinoma. Ten of 15 patients were dead with a median follow-up of 24 months.

liver was suggested by the imaging studies, particular attention was given to the distribution of metastases to determine whether the metastases were limited to one lobe. If selective arteriography and CT scans gave differing results, CT of the liver with lipid soluble contrast material (EOE-13) was performed.<sup>14</sup> In patients considered for partial hepatic resection or in whom tumor might involve the vena cava, an inferior vena cavagram was performed.

Serum gastrin determinations were performed by Bioscience Laboratories (New York, NY) using Walsh gastrin antibody No. 1611 (lot 4A). All serum gastrin samples were diluted to give levels in the middle of the gastrin standard curve. On the evening prior to surgery, oral antisecretory medication was stopped and intravenous cimetidine was begun at a rate determined to maintain gastric acid secretion to less than 10 mEq/hour. This was continued through the operative and postoperative period until the patient was able to take oral antisecretory medications.

The goal of surgery was to remove all tumor identified on preoperative studies as well as any additional tumor identified at operation. At laparotomy, the pancreas, stomach, liver, mesenteric, and retroperitoneal areas as well as areas suggested to be involved by the preoperative studies were carefully explored. In each of the three patients who underwent liver resections, the abdominal incision was extended into the right chest to facilitate exposure of the right lobe of the liver. Bulk tumor in the liver was removed by formal right hepatic lobectomy in two and trisegmentectomy in one patient. The Cavitron Ultrasonic Dissector (Cooper Medical, Stamford, CT) was used to divide the liver parenchyma. All visible tumor was excised including enucleating tumor from the contralateral liver lobe in the one patient with the trisegmentectomy. Subtotal pancreatic resections with splenectomies were performed in three patients, the cut surface of the pancreas was divided with the thoracoabdominal 55

TABLE 1. Clinical Characteristics of Patients

Patient Number	Age/Sex	Duration from Onset Symptoms (yrs)	Duration from Diagnosis (yrs)	Previous Surgery	Antisecretory Medications*
1	43/M	4.5	1	1—Splenectomy; gastrinoma resection	Cimetidine 900 mg Q6 hr
2	53/M	4.5	1.5	1—Exploratory laparotomy 2—Splenectomy; ligation; bleeding varies	Ranitidine 600 mg Q4 hr
3	50/M	3.5	2	1—Exploratory laparotomy	Ranitidine 750 mg Q6 hr
4	67/F	2.5	1.5	1—Highly selective vagotomy	Ranitidine 600 mg Q6 hr
5	56/M	1.6	0.5	1—Vagotomy + pyloroplasty 2—Two explorations for liver hemorrhage	Ranitidine 2100 mg Q6 hr

\* Antisecretory medication dose was that dose which reduced basal gastric acid secretion to  $\leq 10$  mEq/hr, determined as outlined previously.<sup>7</sup>

stapler and 4.8 mm staples (U.S. Surgical, Norwalk, CT). Complete tumor removal required subtotal gastric resection in two patients. The left kidney capsule was opened in one patient and intracapsular tumor was enucleated. Porta-hepatis, celiac, mesenteric, and retroperitoneal lymphadenopathy was excised.

After surgery, all patients underwent fasting serum gastrin determinations, secretin-provocative tests and were discharged, taking their antisecretory medications in the same dosage as before operation. Patients were readmitted 1–3 months later and a complete re-evaluation, as outlined above, was performed. Subsequently, patients underwent a similar evaluation every 6 to 12 months. All patients were treated with postoperative chemotherapy for 1 year, except patient 2 who had received chemotherapy before operation. Chemotherapy was given as outlined above.

### Results

Four of the five patients were males and the mean age was 54 years. All patients had the sporadic form of Zollinger-Ellison syndrome. No patient had multiple endo-

crine neoplasia type I. The mean duration from diagnosis of Zollinger-Ellison syndrome to arrival at NIH was 1.3 years (Table 1). All patients had at least one prior upper abdominal operation related to Zollinger-Ellison syndrome. All patients required high levels of antisecretory medications to control gastric acid output and symptoms (Table 1).

Preoperative serum gastrin concentrations were markedly elevated in all patients, except in patient 2 who had a good response to chemotherapy lowering his gastrin level to 125 pg/ml (Table 2). A positive secretin test (increase 200 pg/ml) or positive calcium test or both were present in four patients. Basal acid output was markedly elevated in all patients, and basal acid output/maximum acid output ratio was above 0.6 in all patients (Table 2).

The preoperative radiologic evaluation was usually accurate in demonstrating the extent of disease (Table 3). Patient 1 had tumor inside the capsule of his left kidney and in retrocaval lymph nodes, which was well seen on CT and arteriography (Fig. 2). Three patients (patients 3, 4, 5; Table 3, Fig. 3) had extensive hepatic metastases with either no involvement or minimal involvement of the left lobe predicted before and confirmed at operation (Fig. 3, Table 3). In patient 2, the preoperative work-up showed that the tumor was localized to the pancreatic tail and the surrounding retroperitoneum. Gastrinoma present in the inferior vena cava had completely disappeared on chemotherapy (Fig. 4). However, at surgery there was a positive margin at the transected pancreas, and tumor was left in the pancreatic head as well as around the left kidney. In patient 4, preoperative endoscopic antral biopsy gave a diagnosis of gastrinoma. This biopsy led us to perform a subtotal gastrectomy, but on careful pathological analysis of the stomach no tumor was found. Finally, in patient 5 positive porta-hepatis lymph nodes were found at operation but not imaged before operation (Table 3). In addition, selective arteriogram showing a gastrinoma in the pancreatic tail led us to perform a subtotal pan-

TABLE 2. Laboratory Characteristics of Gastrinoma (Preoperative)

Patient Number	Serum Gastrin Concentration (pg/ml)			BAO/MAO (mEq/hr)
	Fasting	Secretin	Calcium	
1	500	69	460	94/95
2	125	130	56	28/44
3	2,061	2,469	ND	40/49
4	160,000	30,000	4,800	33/38
5	1,220	386	0	40/42

ND = not determined.

BAO and MAO refer to basal and maximal acid output determined as described in "Methods."

Secretin and Calcium refer to the maximal change in serum gastrin concentrations with the intravenous administration of either secretin (2 units/kg—bolus) or calcium (5 mg/kg/hour for 3 hours) as outlined in "Methods."

TABLE 3. Preoperative Tumor Assessment, Operative Findings, and Operative Course

Patient Number	Preoperative Assessment* Location/Extent of Tumor	Indication for Surgery	Operative Findings	Operation	Complications
1	3 × 4 cm mass above left kidney; numerous retroperitoneal lymph nodes	Increase in tumor size	3 (2 × 3 cm) nodes in retroperitoneum along diaphragm; 3 × 4 cm tumor mass in left kidney	Resection gastrinoma from retroperitoneal nodes and within left kidney (bivalve left kidney and enucleate tumor)	None
2	7 cm retroperitoneal mass (distal pancreas)	Increase in tumor size	7 cm mass tail of pancreas; positive margin on resected pancreas	Subtotal pancreatectomy	None
3	Liver metastases; two superficial mets in left lobe only; abscess in right hepatic lobe; 6 cm tumor in pancreatic tail	Increase in tumor size	7 cm tumor abscess right lobe with 2 other mets left lobe; 6 cm tumor tail of pancreas invading into stomach.	Trisegmentectomy; subtotal pancreatectomy, splenectomy, partial gastrectomy	Subhepatic abscess (reoperation)
4	7 × 9 cm tumor in right lobe liver; left lobe spared	Increase in tumor size, liver abscess	6 × 6 × 3 cm right lobe lesion lymph nodes and stomach negative	Right hepatic lobectomy; subtotal gastrectomy	Biloma drained percutaneously
5	Diffuse hepatic metastases; left lobe spared; pancreatic tail tumor by angiography	Recurrent right pleural effusions; hepatic hemorrhages	Coagulum; pleural fluid positive; common duct lymph nodes positive; Right Lobe Liver 5 × 7 cm in diameter, mass invading into diaphragm; pancreas negative	Right hepatic lobectomy; subtotal pancreatectomy, splenectomy.	None

\* Preoperative assessment of tumor size was by CT scan, selective angiography, and EOE scan as described in "Methods."

atectomy. The pancreas felt firm and indurated at exploration, and no definite tumor could be palpated. Pathological analysis of the specimen showed no tumor in the pancreas. Following surgical exploration, all patients had all gross tumor removed, except patient 2 who clearly had tumor left in the pancreatic head. The decision was made not to perform a Whipple pancreaticoduodenectomy in any patient.

All the operative procedures were lengthy. Two patients suffered postoperative complications that prolonged their hospitalizations (Table 3). Patient 3 had a large *Escherichia coli* right hepatic gastrinoma abscess at the time of surgery that had developed when his liver metastases were embolized at another institution. He required re-exploration for drainage of an *E. coli* subhepatic abscess. Patient 4 had a right subdiaphragmatic bile collection that was

drained percutaneously. No patient died in the postoperative period.

Median postoperative follow-up was 24 months. Patient 2, who had unresected gross disease, had documented tumor progression by 3-months follow-up. It was not possible to reduce his dose of antisecretory medication after operation; in fact, his basal acid output and acid secretion after 300 mg of ranitidine was greater at 3-months follow-up than before operation (Fig. 5). He died 19 months after operation of metastatic tumor. All other patients demonstrated definite improvement following surgery. Fasting gastrin concentrations and basal acid output both fell dramatically from preoperative levels in patients 1, 3, 4, and 5 (Table 4). In addition in these four patients, the same dose of antisecretory medication inhibited gastric acid secretion more effectively than before operation (Fig.

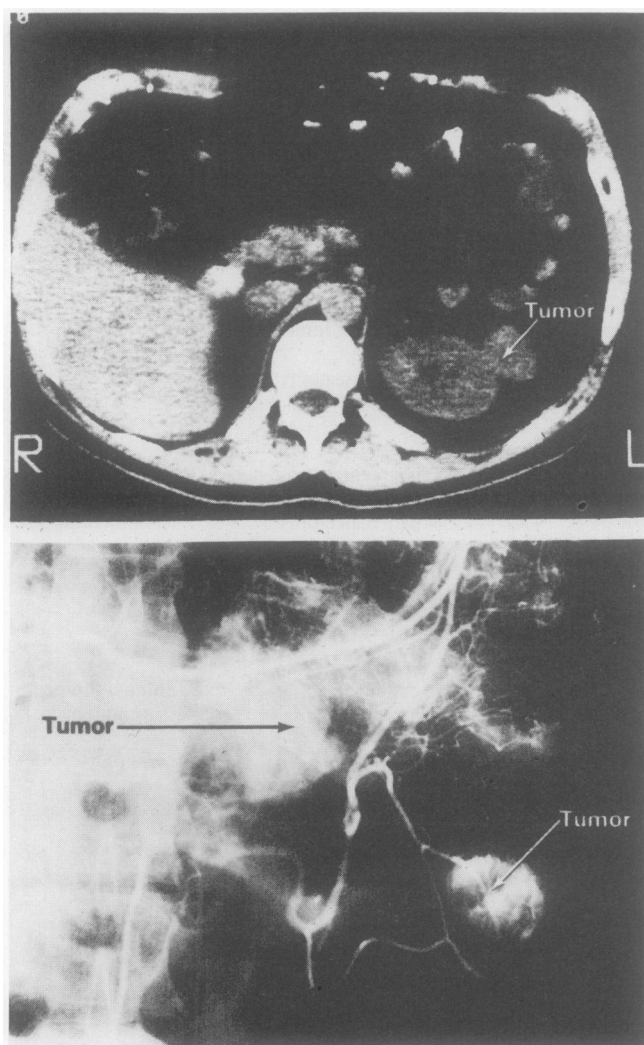


FIG. 2. Computerized tomography (*top*) of patient 1 shows metastatic gastrinoma inside capsule of left kidney. Selective arteriogram (*bottom*) shows metastatic gastrinoma in retrocrural lymph nodes. These lesions were all found at subsequent surgical exploration.

5). None of the three patients with extensive hepatic metastases (patients 3, 4, and 5; Table 4) had evidence of hepatic tumor on infusion CT after operation (Table 4, Fig. 3); but on selective angiographic studies, one patient (patient 4) had evidence of three small hepatic lesions, less than 0.5 cm in size.

Three of the 5 patients (patients 1, 4, and 5) have no evidence of tumor radiologically with follow-up of 14, 22, and 32 months (Table 4). Patient 1 (Fig. 6, Table 4) and patient 5 (Table 4) not only have no radiographic evidence of tumor, but also have no biochemical evidence of residual tumor. In both patients, fasting serum gastrin concentrations and secretin and/or calcium provocative tests have remained in the normal range. Radiologic studies and biochemical assessment of the gastrinoma for the pa-

tient followed for the longest period of time (patient 1, 32 months) are shown in Figure 6. Concomitant with a return to the normal range of the fasting gastrin concentration and a negative calcium provocative test, the basal and maximal acid output decreased 87% and 65%, respectively, and remained decreased for 32 months (Fig. 6). Patients 3 and 4 had evidence of progression at 1-year follow-up; patient 3 had increased number of liver metastases on arteriogram, and patient 4 had no radiographic evidence of disease but had an increase in fasting gastrin concentration (Table 4). In patient 4, however, with subsequent chemotherapy, fasting gastrin concentrations have decreased to only slightly above the normal range; on follow-up at 18 months, no radiographic evidence of tumor was found (Table 4), and the secretin and calcium-provocative tests remained negative.

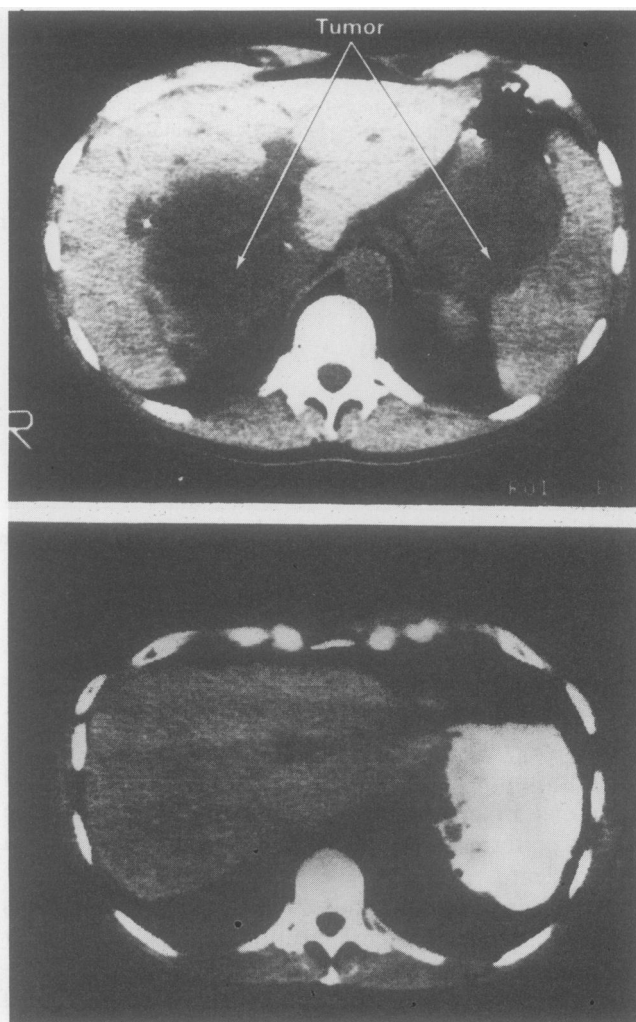


FIG. 3. Preoperative (*top*) and postoperative (*bottom*) computerized tomography of patient 3. Preoperative study shows large tumor mass in the right hepatic lobe and pancreatic tail. Postoperative study shows that both have been removed.

## Discussion

The management of patients with Zollinger-Ellison syndrome is evolving. The introduction of cimetidine,<sup>15</sup> ranitidine,<sup>13</sup> famotidine,<sup>16</sup> and subsequently omeprazole<sup>17</sup> has changed the role of surgery in the management of these patients.<sup>18-20</sup> Classically, total gastrectomy has been the procedure of choice to control the gastric acid output, but potent antisecretory medications are eliminating the need for this procedure. Of the patients with metastatic gastrinoma who survived total gastrectomy and subsequently died, 50-70% of the deaths were due to tumor progression.<sup>1,2</sup> Zollinger and Ellison have documented that the 12-year survival of patients with liver metastases and lymph node metastases is 30% (personal communication). Although these results suggest that many patients with metastatic disease may have a prolonged survival, in that group with extensive metastatic disease, which comprises 20% of all our patient population, the 5-year survival was only 20%. These patients may develop not only distant metastases to bone and die in a short time but also life-threatening complications of their disease. Patient 2 had a 35 unit hemorrhage from gastric varices secondary to splenic vein obstruction by tumor that necessitated his first operation. Patient 3 had a liver abscess and presented to a local emergency room in septic shock following embolization of a large gastrinoma metastasis in the right lobe. Finally, patient 5 had two operations at another hospital to control life-threatening hemorrhage from the right lobe of his liver following minor trauma. We believe that this hemorrhage was from a large gastrinoma metastasis within the right lobe.

Aggressive surgical resection of metastatic disease in a variety of cancers is currently being achieved in selected patients with acceptable mortality and morbidity and clear therapeutic gains. Patients with solitary liver metastases from colorectal cancer have enjoyed 24% 5-year survival following surgical resection of metastatic lesions.<sup>21</sup> Patients with pulmonary metastases from sarcomas have improved survival following resection of metastatic nodules.<sup>22</sup>

The rarity of gastrinomas and their indolent course compared to other cancers make controlled, randomized trials at a single institution nearly impossible. The goal of this study was to evaluate a cohort of patients with extensive metastatic disease to see if surgery is feasible and helpful in these patients. Zollinger had reported that resection of all tumor prolonged survival in patients with Zollinger-Ellison syndrome,<sup>3</sup> but he had not extended surgery to the extent described here.

Our experience corroborates the recommendations of Zollinger<sup>3</sup> and others.<sup>5,9</sup> Four of five patients clearly benefited from metastatic tumor resection. One patient had gross tumor left after exploration, and that patient progressed and died of disease. The other patients with all

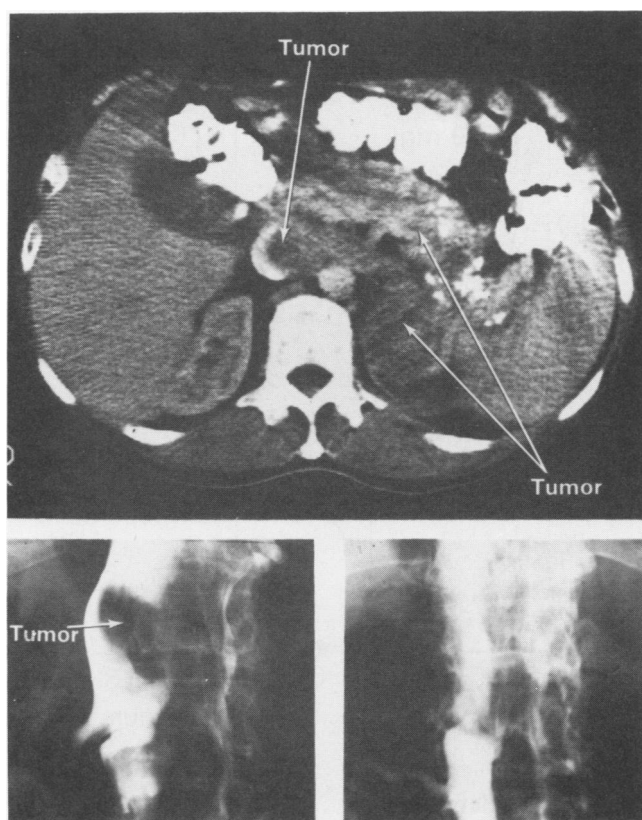


FIG. 4. Initial computerized tomography (patient 2) of upper abdomen (*top*) showing tumor in head of pancreas and tumor in tail of pancreas invading left kidney. Venogram (*bottom, left*) shows tumor mass from pancreatic head invading inferior vena cava. Preoperative chemotherapy markedly reduced mass in pancreatic head resulting in normal inferior vena cavagram (*bottom, right*), and normal fasting serum gastrin level (125 pg/ml). However, at surgical exploration, there was a positive margin in the transected pancreas at the head.

tumor resected had a significant reduction in antisecretory medications. The patients remained asymptomatic, and all were enjoying normal activity and work. The results in patients 1 and 5 appeared most impressive because each had no radiological or biochemical evidence of residual tumor. This result was unexpected in patient 1 because he had a large pancreatic tail primary with metastases to retrocrural lymph nodes and the left kidney. Patient 5 had equally extensive disease with multiple metastases in the liver, involvement of the diaphragm, and a positive bile duct lymph node. Postoperative follow-up in patient 1 is almost 3 years and in patient 5 more than 1 year, and each has no evidence of Zollinger-Ellison syndrome. Each have normal gastrin levels, normal provocative testing, minimally elevated basal acid output, and no radiographic evidence of recurrent disease.

These results do not establish that survival is improved by aggressive resection of metastatic gastrinoma. In our study, there are only a small number of patients and the

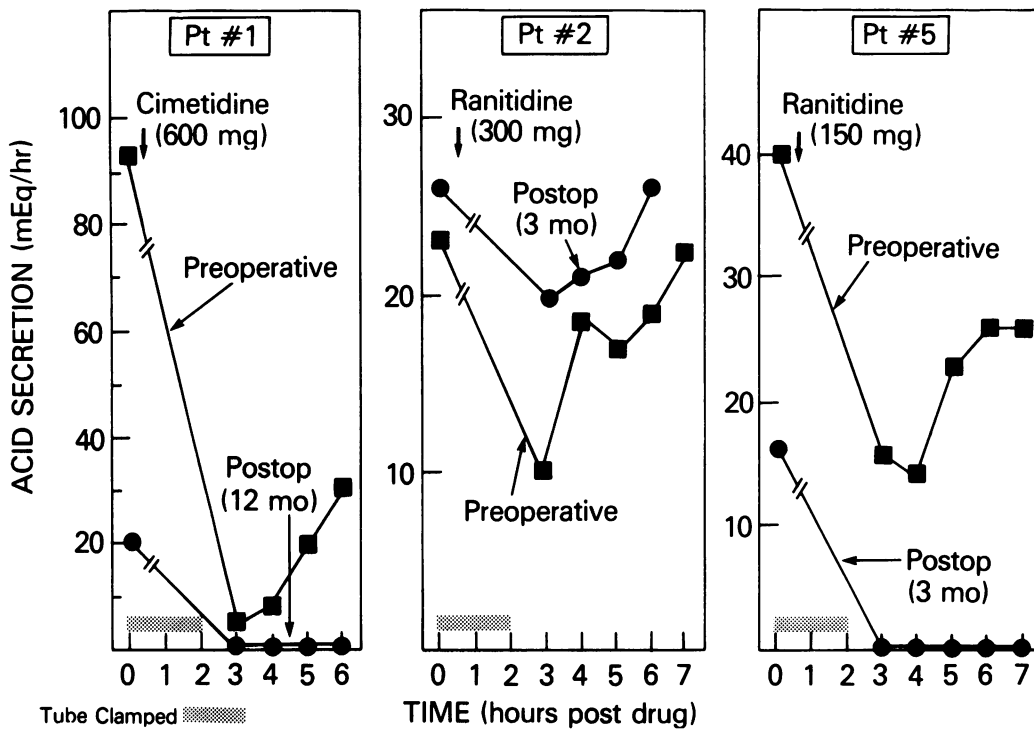


FIG. 5. Acid secretion (mEq/h) both basal (time 0) and following a single dose of antisecretory drug before and after operation for three separate patients (1, 2, and 5). Patient 2 had a higher basal acid output after operation and less control with the same dose of ranitidine as before operation. However, both other patients (1 and 5) had a reduction in basal acid output and improved control with the same dose of medication as before operation.

follow-up is relatively short. To establish that survival is actually improved by aggressive resection of metastatic disease is difficult, because patients with extensive metastatic gastrinoma that is potentially resectable are not common and the clinical course of patients who do not

undergo extensive surgery is highly variable. Therefore, a control group is essential. Because no one institution sees sufficient numbers of such patients, this study could only be done as a cooperative trial. Nevertheless, because of the generally poor results with chemotherapy, because our

TABLE 4. Postoperative Course of Patients

Patient Number	Time after Operation												Current Status
	3 Months			12 Months			18 Months			30 Months			
	Tumor Extent	Fast Gastrin (pg/ml)	BAO	Tumor Extent	Fast Gastrin (pg/ml)	BAO	Tumor Extent	Fast Gastrin (pg/ml)	BAO	Tumor Extent	Fast Gastrin (pg/ml)	BAO	
1	Negative	25	15	Negative	27	12				Negative	22	15	Working full time, asymptomatic
2	Pancreatic tail mass	400	26	Left perirenal mass	1600	10	Left perirenal mass; inferior vena cava mass; liver metastases	700	ND				Died 19 months, metastatic
3	3 small lesions in liver	100	8	6 small lesions in liver	160	21	No change in size or number of liver lesions	130	19				Working full time, asymptomatic
4	Negative	300	3	Negative	1310	33	Negative	174	ND				Asymptomatic
5	Negative	89	16	Negative	60	ND							Asymptomatic

ND = not determined; BAO = basal acid output; Fast Gastrin = fasting gastrin concentration.

Tumor status determined by selective angiography or CT scanning as outlined in "Methods."



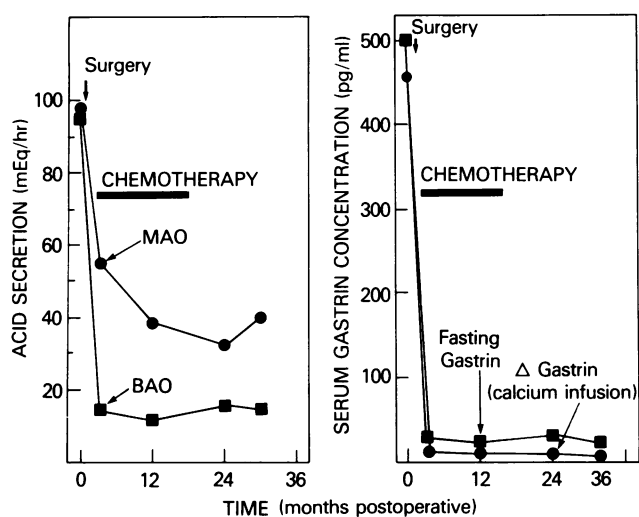


FIG. 6. Acid secretion (*left*) and serum gastrin concentration (*right*) in patient 1 as time from surgery and chemotherapy progress. BAO (basal acid output) decreased from nearly 100 mEq/h before operation to 15 mEq/h after operation, and his BAO/MAO (maximal acid output) ratio dropped from nearly 1 before operation to  $<0.4$ . In addition, his fasting serum gastrin dropped from 500 pg/ml before operation to 25 pg/ml after operation with no increment with calcium infusion. These results are consistent with a "biochemical cure" of Zollinger-Ellison syndrome.

results demonstrate that in patients with extensive metastatic disease the 5-year survival is less than 20%, and because with the increased ability to control gastric acid secretion the course of the malignancy is becoming an increasingly important determinant of survival, a study of the effect of aggressive surgery in patients with advanced disease seems increasingly important.

Our experience with the five patients reported in this study supports Zollinger's original observations and leads us to recommend an aggressive surgical approach for *total* gross tumor resection in selected patients with extensive metastatic disease. If all gross tumor cannot be removed, we believe that surgical exploration and partial resection is not helpful.

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