Gastrinoma Excision for Cure

A Prospective Analysis

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The role of surgery in the treatment of gastrinoma is unclear. The purpose of this study was to determine prospectively the surgical cure rate using a controlled clinical trial. Eleven patients who fit the entry criteria underwent abdominal exploration and attempted tumor resection for cure. A historical control group was used for comparison. Cure was defined as: (1) normal serum gastrin level, (2) no response to intravenous secretin, (3) no symptoms when antisecretory medications are stopped, and (4) no tumor recurrence on follow-up examination. Tumors found in both groups tended to be small (1.5 cm *vs.* 2.2 cm), multiple (71% *vs.* 40%), and in lymph nodes (70% *vs.* 70%). All tumors identified were located anatomically within the gastrinoma triangle. Tumors were found in 10 of 11 patients (91%) in the study group, and significantly more patients had their tumors excised for cure as compared to controls (82% *vs.* 27%, $p < 0.05$). The current prospective cure rate for gastrinoma is higher than previously appreciated and tumors within lymph nodes do not preclude curative resection.

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THE ROLE OF SURGERY in the treatment of gastrinoma remains unclear.[1-5] Optimal therapy would be complete surgical excision of the tumor to alleviate gastric acid hypersecretion, as well as to prevent tumor progression. Historically it was believed that tumor excision for cure was possible in only 2% to 5% of patients.[4] Therefore therapy was directed primarily at controlling gastric acid hypersecretion with H_2-antagonists or total gastrectomy. Recently, however, a number of scientific advances have improved our ability to successfully remove gastrinoma for cure. They are the gastrin radioimmunoassay (RIA),[6] perioperative acid control,[7] improved patient selection,[8] knowledge of tumor location,[9] and information on the clinical course of patients with tumors within lymph nodes.[10]

As a result of the gastrin RIA, patients are now seen earlier with resectable tumors.[11] Perioperative control of gastric acid hypersecretion with H_2-receptor antagonists has allowed safer explorations and more aggressive attempts at tumor resection.[12] Intraoperative identification of small or occult tumors has been facilitated by the recognition that most gastrinomas are located in a specific anatomic area called the gastrinoma triangle.[9] Now that a number of investigators have reported long-term cures resulting from the excision of these tumors, patients with tumors in lymph nodes are potential candidates for cure.[8,10,13-16] In contrast patients with hepatic metastases or multiple endocrine neoplasia type I syndrome (MEN I) are unlikely to have complete tumor excision and are therefore not candidates for cure.[17]

Collectively these advances have profoundly influenced the ability to successfully resect gastrinomas for cure. Clinical data to support this assertion is found in the results of several recently reported series in which the collective cure rate was 32%.[8,18,19] To investigate the surgical cure rate prospectively, we began a controlled clinical trial in 1982 in which appropriate candidates had abdominal exploration solely to identify intraoperative tumors and excise for cure.

Patients and Methods

From August 1982 to October 1988, 15 consecutive patients were evaluated for excision of gastrinoma for cure. There were nine men and six women, with a mean age of 49 years (range, 32 to 72 years). The diagnosis of gastrinoma was made in all 15 patients based on clinical evidence of severe peptic ulcer disease, fasting serum hypergastrinemia (> 200 pg/mL), and increased serum gastrin (> 200 pg/mL) when secretin was administered intravenously.

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The criteria used for candidate selection was (1) sporadic gastrinoma without associated MEN I syndrome, (2) no preoperative evidence of hepatic metastases, and (3) acceptable surgical risk for abdominal exploration. Screening for MEN I syndrome was performed by obtaining a thorough family history and measurement of serum calcium, phosphate, and parathyroid hormone levels. In any uncertain case, a serum prolactin assay was also performed. All patients were screened before operation for evidence of hepatic metastases by abdominal CT scan.

Using the above criteria, of the 15 patients seen, two had MEN I syndrome and two had hepatic metastases, which left 11 patients for study. After informed consent, all patients underwent laparotomy, abdominal exploration, and tumor excision as previously described.[9] An extensive and diligent search for tumors was performed, concentrating the dissection in the area of the gastrinoma triangle. Whether a primary tumor in the pancreas or duodenum was found, all lymph nodes identified within the gastrinoma triangle were excised and submitted for histologic examination. This was done to identify occult lymph node disease. If tumors were identified only within lymph nodes, with no evidence of primary disease after exhaustive exploration, patients were closed and continued on H2-antagonists until the results of serum gastrin and secretin tests were known. No major pancreatic or gastric resection was performed. Surgical cure was defined as (1) normal serum gastrin level, (2) no responsive to intravenous secretin, (3) no symptoms when antisecretory medications were stopped, and (4) no tumor recurrence on follow-up examination.

The current analysis is based on follow-up observations through November 1, 1988. Each patient had a postoperative secretin test within 2 months of discharge. If the results were negative, antisecretory medications were stopped and the patients were followed. Eight of 11 have been continuously followed at 6-to-12 month intervals for periods of 2 to 72 months with physical exams, serum gastrin determination, and secretin tests at approximately 6-month intervals.

For comparison, an external historical control group consisting of consecutive patients seen by the authors between 1974 and 1981 was used. Each patient seen during this time period was evaluated for entry into this study using the same criteria that was applied to the prospective group described above. Consecutive patients were evaluated to minimize selection bias. The years 1974 to 1981 were used because these patients were seen in the period immediately before the initiation of this study and after the introduction of the gastrin RIA.

Nineteen patients were seen during this time period; five patients with MEN I syndrome and three patients with hepatic metastases, which left 11 patients in the control group for analysis. All patients had laparotomies and tumor resection was attempted. During this time period, 10 patients also had a total gastrectomy in addition to attempted tumor removal. Postoperative follow-up was similar to that described for the study group above. In all, seven patients have been followed continuously for 84 to 168 months, two patients died after 12 and 32 months of follow-up, and two patients were lost to follow-up after 48 and 24 months.

Statistical analysis was performed using the chi square, two-sided Fischer's exact test, or the unpaired Student's t test. Significance was defined as $p < 0.05$.

Results

Patient characteristics between the control group and the study group are given in Table 1. The patients in the two groups were similar in age, sex, and average duration of symptoms before diagnosis. Complications due to peptic ulcer disease (upper GI bleeding greater than two units, perforation, or obstruction/stricture) were common in both groups before operation for attempted tumor removal (100% *vs.* 73%). The types of complications seen were similar in both groups with upper GI bleeding occurring most often.

The two groups differ significantly in the timing of their complications in relation to diagnosis. All of the complications in the control group (11 of 11 subjects) occurred before the diagnosis of gastrinoma was made. In this group the presence of a severe ulcer complication usually prompted the initial evaluation of the Zollinger–Ellison syndrome. In the study group, however, five of the seven complications (four bleeding, one obstruction) occurred after the diagnosis of gastrinoma was made. In addition, at the time of their complication, all five patients were taking a H_2-receptorantagonist.

TABLE 1. *Clinical Characteristics of the Control and Study Groups*

Characteristic	Historic Control 1974–1981 (N = 11)	Study Group 1982–1988 (N = 11)	p value
Age, mean + SD (yrs.)	49 ± 11	50 ± 11	NS†
Sex			
Male	9 (82)‡	7 (64)	NS
Symptom duration (yrs.)	7 ± 4	6 ± 5	NS
Previous operations	6 (55)	3 (27)	NS
Ulcer complications	11 (100)	8 (73)	
Bleeding	9	7	NS
Obstruction	1	1	NS
Perforation	1	0	NS
Before Tx.§	11	2	*p < 0.01
After Tx.	0	6	*p < 0.02

* Two-sided Fischer's exact test.
† NS, not significant.
‡ Percentages shown in parentheses.
§ Tx., treatment.

The major indication for surgical referral in nine of ten patients in the study group was endoscopic evidence of persistent duodenal ulceration (seven patients), esophageal inflammation (one patient), or esophageal stricture (one patient), despite treatment with a variety of H_2-receptor antagonists. Objective evidence of persistent ulceration/and or inflammation was present in five of these patients, despite a subjective improvement in symptoms.

Tumors were located at laparotomy in 91% (10 of 11) of patients in the study group. In contrast tumors were found in only 64% (7 of 11) of patients in the control group. All 24 tumors found in both groups of patients were within the anatomic boundaries of the gastrinoma triangle. The location of tumors removed from patients in the study group are depicted in Figure 1.

The characteristics of the tumors found in both groups were similar (Table 2). The mean tumor size ([control] 1.5 cm + 1.3 cm, *vs.* [study] 2.2 cm + 1.7 cm), incidence of multiple tumors (45% *vs.* 40%), occurrence of tumors in extrapancreatic/extraintestinal sites (14% *vs.* 36%), and occurrence of tumors within lymph nodes (71% *vs.* 70%) were not different for the groups. Primary nodal tumors (*i.e.*, without detection of a corresponding primary tumor) were found and excised in one patient in the control group and in four patients in the treatment group (Table 3).

The surgical cure rate was significantly higher for patients in the study group (27% *vs.* 82%, $p < 0.05$). Interestingly the excision of primary nodal tumors resulted in the cure of one patient in the control group (follow-up, 84 months), and in three of four patients in the prospective treatment group (median follow-up, 12 months). The median follow-up was significantly longer for the control group when compared to the study group (120 months *vs.* 9 months, $p < 0.01$).

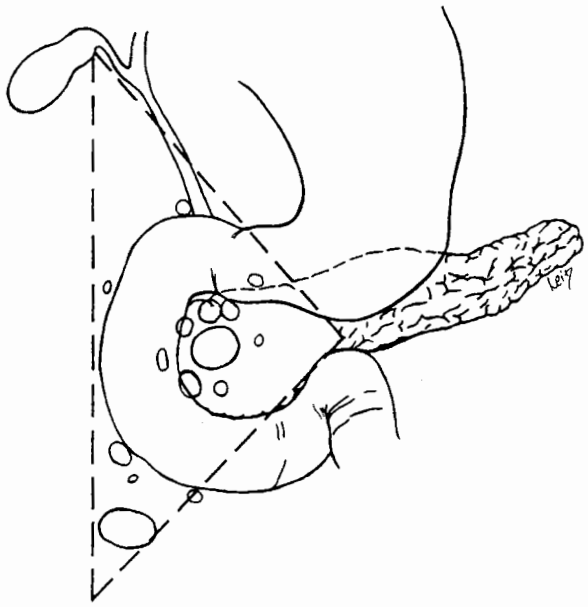

FIG. 1. Intra-abdominal location of 16 tumors found in ten patients in the study group.

TABLE 2. *Tumors Found in Patients Explored for Gastrinoma*

	Historic Control 1974–1981 (N = 11)	Study Group 1982–1988 (N = 11)
Patients with + exploration	7 (64)†	10 (91)
Pancreatic	4	3
Duodenal	2	3
Extra/extra*	1	4
Patients with multiple tumors	5 (71)	4 (40)
Total tumors found	13	16
Mean size of tumors (cm ± SEM)	1.5 ± 1.3	2.2 ± 1.7

* Extra/extra, extrapancreatic/extraintestinal tumors.
Percentages shown in parentheses.

Because a total gastrectomy was performed in 10 of 11 patients in the control group, morbidity and mortality rates could not be compared directly. It is for this reason that operative complications were evaluated for the study group only. Three related complications occurred in one patient in the study group, resulting in an overall morbidity rate of 10%. There were no reoperations or perioperative deaths. Complications occurred in a 71-year-old man and included a perioperative subendocardial myocardial infarction, renal insufficiency, and a prolonged postoperative ileus. All complications responded to conservative management and recovery was complete.

Discussion

Surgical cure rates reported for gastrinoma excision have gradually improved.[17] Conventional teaching was that surgical cure rates were in the range of 2% to 5%,[4] and cure was believed to be theoretically impossible in 80% of patients.[20] As a result of this perception, medical treatment with H_2-receptor antagonists has been advocated as the initial form of therapy until either medical treatment fails or the patient develops a life-threatening complication. The ideal treatment of gastrinoma is still surgical excision of the tumor if this can be accomplished

TABLE 3. *Characteristics of Lymph-Node Tumors Found in Patients with Gastrinoma*

Characteristic	Historic Control 1974–1981 (n = 11)	Study Group 1982–1988 (n = 11)
Patients with lymph-node tumor	5 (45)*	7 (64)
Solitary	1	4
Occult	3	2
Multiple	1	1
Total lymph-node tumors	6	9

* Percentages shown in parentheses.

with a high probability of success and low risks of morbidity and mortality.

In this study we reported on 11 patients who we considered candidates for surgical cure. These patients were matched with 11 patients derived from the authors' own series who were seen from 1974 to 1981. The limitations of comparison between these two groups is well recognized.[21] Nevertheless, considering the rarity of this tumor, the limited experience accrued by any one practitioner, and the methodologic problems in multi-institutional clinical study, a prospective randomized trial seems unlikely. We believe such a comparison seems reasonable and, for now, is the best alternative available.

In terms of the therapeutic philosophy prevalent in the two different time periods studied, it is interesting to note that in contrast to the control group, all peptic ulcer complications in the study group occurred after the diagnosis of gastrinoma had been made. In fact 75% of these complications occurred while the patients were on histamine H_2-receptor antagonists. Although the authors were not following the patients at this time, the available information indicates that all six patients were compliant, took their medication as prescribed, and were asymptomatic at the time the complication occurred (Table 4). Therapy was ongoing for 11 to 60 months before their complications. It has been well documented that merely assessing subjective symptoms is unreliable in predicting the efficacy of H_2-receptor antagonists therapy in this group of patients.[21] Because of this fact, four of the six patients (67%) were followed at 3-to-6 month intervals by routine endoscopy. In all four of these patients persistent ulceration and inflammation was found. Doses of medication were increased in three of the four patients and bethanecol was added to the regimen of the fourth. Despite these adjustments, complications still occurred. Clearly the main criticism of this finding is that the dosages of medications given to these patients were inadequate to control the gastric hypersecretion in patients with gastrinoma. While the dosages given in this study are large in comparison to patients with peptic ulcer disease, they were considerably lower than the mean dose of cimetidine (4.6 g/day) or its equivalent given at the National Institutes of Health (NIH).[2] Therefore, based on this data, no definitive conclusions can be drawn with regard to the overall efficacy of histamine H_2-receptor antagonists in the treatment of gastrinoma. It can be stated, however, that the dosages given in this series were inadequate to control the peptic ulcer complications in this group of patients, and routine endoscopy does not preclude therapeutic failure.

TABLE 4. *Patients in Study Group Who Had Complications While on H_2-Receptor Antagonist Therapy*

Patient	Medication	Dosage (g/day)	Complication	Length of Tx.* (months)
1	Cimetidine	2.4	Bleeding	36
2	Cimetidine	1.2	Bleeding	11
5	Ranitidine	.9	Esophageal stricture	12
6	Cimetidine	2.4	Bleeding	60
8	Cimetidine	1.2	Bleeding	12
9	Famotidine	.12	Obstruction	12

* Tx., treatment.

One of the differences found between the control and study groups is the success of identifying tumors at laparotomy. In the control group, 64% of patients had tumors identified and resected. This value compares favorably with the 41% to 70% rate reported in recent surgical series.[8,18,19,22,23] In contrast 91% of patients in the study group had tumors identified and excised. Although these values are not statistically different, this increased rate of tumor identification is a major factor contributing to the improved surgical cure rate. Possible reasons for this increase in tumor identification include better preoperative imaging, changes in operative technique, or increased experience by the operating surgeon (learning curve).

Although preoperative localization (CT scan) was not available in the control group, its impact on tumor identification in the study group was minimal. In this study preoperative CT scanning had a 30% sensitivity (3 of 10 patients) and 100% specificity. These results are comparable to the early reports on CT localization in the literature but they are much lower than the recently reported series in which a sensitivity rate of 59% to 78% was found.[24–26] There are several variables in our CT data that may explain this discrepancy. Although all patients who underwent CT scanning in our study had both oral and intravenous contrast, we do not routinely give the bolus intravenous contrast infusion technique as described by Stark et al.[26] This may decrease our sensitivity in tumor localization by diminishing the vascular blush seen with tumors in their series. In addition, in contrast to the studies previously mentioned, the CT scans in our series were interpreted by different staff radiologists at several UCLA-affiliated hospitals in which the patients were seen. Consequently we did not have the benefit of a single radiologist who interpreted all the scans. Perhaps the most important variable, however, is the size and location of tumors found in our study. It has been shown that the ability of CT to identify tumors is directly related to the tumor size (0% at a size of less than 1 cm *vs.* 83% to 95% at a size of more than 3 cm) and tumor location (pancreatic 80% *vs.* extrapancreatic 35%).[25] Three patients in this study had tumors measuring 1 cm or less in diameter and seven patients had tumors in extrapancreatic locations. Viewed in this context, our sensitivity for CT scanning is consistent with that reported in the literature.

It should be noted, however, that of the three patients with positive CT scans, two patients had multiple tumors

TABLE 5. *Patients in Study Group Who Underwent Attempted Excision of Gastrinoma for Surgical Cure*

Patient	Age	Sex	Tumor Location	Preop. Gastrin (pg/mL)	Postop. Gastrin (pg/mL)	Postop. Secretin Test	Follow-up (months)
1	33	M	Triangle*	3858	84	−	72
2	54	M	Triangle	176	74	−	37
3	49	F	Triangle	1100	99	−	15
4	40	M	Triangle	196	55	−	12
5	59	F	Triangle	1568	88	−	11
6	59	M	Triangle	190	46	−	9
7	49	M	Triangle	3131	434	+	7
8	65	F	Triangle	2605	95	−	7
9	71	M	Triangle	1428	74	−	6
10	56	F	Triangle	5494	63	−	2
11	55	M	Not found	1100	875	+	1

* Within the gastrinoma triangle.

(four tumors in total), of which only one was identified on CT scan before operation. All of these tumors were occult within lymph nodes and could only be identified by frozen section histology. Furthermore resection of a tumor visualized on CT without careful intraoperative exploration would have resulted in a number of occult tumors being missed. Therefore, although CT scans are useful in the preoperative evaluation of hepatic metastases and may provide evidence of tumor location in up to 78% of patients, its role seems limited in actual tumor identification.

When analyzing the types of tumors present in this series, of particular interest is the small average size, incidence of extrapancreatic tumors, and the number of tumors within lymph nodes found in both groups of patients.

The average tumor size is comparable between groups and is consistent with the average sizes recently reported in the literature.[8,19] Extrapancreatic and duodenal gastrinomas are believed to be a subgroup of patients with gastrinoma that have a favorable cure rate.[14–16] In addition some studies have suggested that because of the introduction of the gastrin RIA, the incidence of this type of gastrinoma is increasing.[11,18,23] In this study 43% of the control group and 70% of the study group had tumors in this location. The increased incidence of these tumors in the study group, although again not statistically different, is another factor that contributes to the observed differences in cure rate. Although early surgical series reported a low incidence of these tumors,[27,28] recent reports confirm our finding that a larger percentage of tumors are now found in these locations.[8,19] If this observation is correct, it suggests that gastrinomas may now be more amenable to cure. Some investigators have cited the gastrin radioimmunoassay and earlier diagnosis as the reason for this apparent shift in location, although the data is unclear.[11,23]

Extrapancreatic/extraintestinal tumors were found in one patient in the control group (14%) and in four patients (40%) in the study group. Of these five patients, all had primary nodal tumors located in the peripancreatic region. There was no associated pancreatic or duodenal tumors found in these patients. Of these five patients, four are surgical cures with a median follow-up of 14 months (range, 2 to 84 months). This high incidence of isolated lymph node involvement in any one series is unusual; however a number of authors have reported similar success in excising primary nodal gastrinomas for cure.[8,10,14–16] In the majority of previous reports, however, most patients also had a concomitant total gastrectomy. One of the criticisms of these early reports is that a small undetected primary tumor in the surgical specimen could not be ruled out entirely. Three out of the four patients in this series who were surgical cures had no other resection performed besides lymph-node removal. This experience supports the existence of isolated aberrant primary gastrinoma within lymph nodes.[10]

Operative technique and the surgeon's experience are both uncontrolled factors in this study in terms of the ability to locate tumors at laparotomy. From a technical standpoint, the major differences between the two patient populations and time periods studied were the thorough dissection and extensive tissue sampling carried out in the area of the gastrinoma triangle in patients in the study group. The gastrinoma triangle is defined as the junction of the cystic duct and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the junction between the neck and body of the pancreas medially.[9] As pointed out before, many of these tumors were small, multiple, and occult within lymph nodes. Although difficult to quantitate experimentally, we believe that careful dissection, palpation, and lymph node sampling in this area has improved our ability to localize tumors during operation and resect them for cure.

The surgical cure rate for the study group was 82% and that in the control group was 27% ($p < 0.05$). Contributing factors, as mentioned previously, include improved tumor identification, increased surgical experience, and a increased percentage of extrapancreatic tumors. All patients in this series who are considered cures are followed clinically off antisecretory medications and with periodic serum gastrin levels and secretin tests (Table 5). In the analysis of this data, the relatively short follow-up (9 months, range 2 to 74 months) in the treatment group is an area of contention. Some series report a failure rate as high as 42% within the first 6 months.[8] In our experience we have yet to see a patient with sporadic gastrinoma after successful resection and a negative postoperative secretin test develop other tumors. Unlike other malignancies, gastrinoma has a very sensitive and specific serum marker, namely the stimulation with secretin to detect primary and recurrent tumors.[29] Imaging studies, *i.e.*, ultrasound, CT scan, or angiogram, are not cost-effective for routine postoperative surveillance for recurrent tumors unless the patient has biochemical evidence of disease, *i.e.*, elevated serum gastrin or positive secretin test. Therefore, even with a relatively short follow-up (median, 9 months), based on the biochemical profiles of our patients, we believe this data is meaningful.

The clinical expression of gastrinoma has changed markedly since the early reports on surgical experience with this tumor. In selected patients a meticulous abdominal exploration and lymph node sampling in a specific anatomic area will result in an excellent rate of intraoperative tumor identification. When tumors are identified and excised, even if present as isolated tumors within lymph nodes, the surgical cure rate can be as high as 82% at a median follow-up of 9 months. These results can be accomplished without major pancreatic or gastric resection, and with an acceptable morbidity rate (10%) and no surgical deaths. The current prospective surgical cure rate for gastrinoma is higher than previously appreciated. Abdominal exploration and surgical excision of gastrinoma for cure is the optimal treatment for this group of patients.

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