Localization and Resection of Gastrinomas in Zollinger-Ellison Syndrome

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From 1971–1986, 24 patients were diagnosed as having Zollinger-Ellison syndrome (ZES) and 22 patients had laparotomy. Of this group, gross tumor was identified in 15 of 22 patients. Ten of 15 patients had resection of their gastrinomas with the specific aim of curing the disease. This group had responded favorably to either cimetidine or ranitidine before operation. Preoperative transhepatic portal venous sampling (PVS) with gastrin determinations was performed in six patients; three patients had this procedure twice. The tumor was correctly localized by PVS in five of six patients. In four of six patients, the tumor was easily found at surgery. In two of six patients (33%) PVS was vital to intraoperative decisions. Criteria for biochemical cure are normal periodic fasting gastrin and secretin infusion tests. Of the 10 patients who had resection for potential cure, two patients failed within 48 hours of surgery on the basis of an elevated fasting serum gastrin level in one patient and a positive secretin infusion test in the other patient. Eight patients were considered cured with follow-up from 6 months through 15 years. Of the eight cured patients, the tumors were located as follows: four were extraintestinal and extrapancreatic, four were in the duodenal wall, one patient had a tumor located in the uncinate process of the pancreas, and one tumor was located in a lymph node along the lesser curve of the stomach. Two patients had mobilization of the pancreas and duodenum for a "blind" pancreatoduodenectomy based on preoperative PVS (2 procedures each patient). In one patient a 3-mm gastrinoma was enucleated from the posterior uncinate process. The second patient had pancreatoduodenectomy with findings of two duodenal wall gastrinomas. Both patients remained cured of ZES beyond 2 years. It is concluded that PVS does indeed locate some tumors before operation, even those not easily found at surgery. ZES can be cured by an aggressive approach combining preoperative tumor localization and tumor resection. Of the eight patients biochemically and perhaps biologically cured, follow-up was greater than four years in five patients, greater than two years in two patients, and beyond six months in one patient.

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RECENT REVIEWS HAVE BOTH DOCUMENTED AND DISCUSSED the changing trends in the treatment of Zollinger-Ellison syndrome (ZES). Therapeutic options have ranged from the early palliation or "cure" of the physiologic gastric hypersecretory state by total gastrectomy to the more recent attempts at cure of a potentially malignant (50% 10-year survival rate) disease by aggressive surgical resection.[1–6] The excellent success of drugs such as cimetidine, ranitidine, famotidine, and omeperazole in treating the gastric hypersecretion of ZES[7–10] and decreasing the threat of postoperative hemorrhage and perforation have now allowed a more aggressive approach to resection of gastrinomas without total gastrectomy at the initial operation.

In an attempt to localize gastrin-secreting tissue before operation, transhepatic portal vein catheterization and venous sampling with gastrin determinations has been advocated to better locate tumor tissue, especially gastrinomas that are not easily identified at surgery. Although the ultimate efficacy and cost-effectiveness of this procedure remains to be established, portal venous sampling (PVS) does indeed locate tumors and may help the difficult intraoperative decisions as to the magnitude of resection of gastrinomas and their metastases.[11,12]

We have previously documented the presence of extrapancreatic and extraintestinal gastrinomas and their ultimate resection for cure.[6] Since our initial experience supported the concept that ZES can be cured, we have continued the trend of adequate documentation of the disease, evaluation of the response to medical therapy, preoperative localization of gastrinomas, and an aggressive surgical approach to resection of gastrinomas.

TABLE 1. *Gastrinoma Resection*

Patient #	Year	Location	Gastrin (pg/mL)	Therapy	Cure
1	1971	Liver-left lobe	1500	Resection, TG	Yes
2	1977	Lesser curve	760	Resection, TG	Yes
3	1978	Below mid-pancreas	310	Resection, TG	Yes
4	1981	Splenic hilum	275	Resection	Yes
5	1982	Duodenum	710	Resection	Yes
6	1984	Pancreas	450	Enucleation	Yes
7	1984	Duodenal wall (2)	740	Whipple procedure	Yes
8	1984	Duodenum + node	9000	Resection	No
9	1985	Duodenum + node	3000	Resection	Yes
10	1986	Lesser curve (node)	850	Resection	No

TG = total gastrectomy.

This review evaluates our total experience with ZES and a subgroup of patients who had laparotomy with a specific goal of curing the potentially malignant disease without resorting to total gastrectomy.

Materials and Methods

Twenty-four patients with documented ZES were evaluated at the University of Florida College of Medicine from 1971–1986. The diagnosis of ZES was initially confirmed in all patients with measurements of fasting serum gastrin levels, and basal and maximal gastric acid secretion. Serum gastrin response to secretin infusion was evaluated in most patients. Criteria for the diagnosis of ZES were a fasting serum gastrin determination greater than 150 pg/mL, a secretin infusion response of 200 pg/mL above baseline levels, and basal acid secretion of greater than 15 mEq/h. Methods for serum gastrin evaluation and secretin infusion testing have previously been reported.[13]

All patients have undergone at least one barium upper gastrointestinal examination, upper gastrointestinal endoscopy, and in the years since the medications were available, aggressive initial medical therapy with either cimetidine or ranitidine to evaluate the degree of acid secretory suppression.

In recent years, all patients had abdominal ultrasound examination, computed tomography and, in many patients, celiac and superior mesenteric arteriography. Six patients recently had percutaneous transhepatic venous sampling of the portal vein and its tributaries for gastin analysis before anticipated surgery. Three patients had this procedure twice. Transhepatic PVS was performed using the Hawkins needle guide technique in which the 22 gauge needle guide itself was used to locate the portal vein.[14] A small 3 or 4 French catheter was subsequently used to obtain samples from the main portal, splenic, and superior mesenteric trunks and their tributaries. Criterion for a positive test was a very demonstrable gastrin gradient.

Twenty-two of 24 patients eventually had exploratory laparotomy with gross biopsy-proven tumor identified in 15 patients. Ten of these 15 patients had resection of their gastrinomas with the aim of curing the disease. The remainder of the patients had total gastrectomy both with and without tumor resection.

All patients had fasting serum gastrin determinations and secretin infusion tests in the early postoperative period. Without long-term follow-up on all patients, it is difficult to define the criteria for curing ZES. Our criteria were fasting serum gastrin determinations below 100 pg/mL and biochemical response to secretin infusion of less than 200 pg/mL during the follow-up period.

Results

Since 1971, 24 patients were evaluated and diagnosed as having ZES. Twenty-two patients had exploratory laparotomy with tumor identified in 15 patients. Of this group, 10 patients had resection for potential cure. The remaining five patients had total gastrectomy with and without resection of gross tumor. In the patients in whom no tumor was found, all had total gastrectomy. There were no postoperative deaths from total gastrectomy and/or tumor resection.

Table 1 lists the 10 patients who had resection for cure. Patients 1–4 have previously been reported and represented four extraintestinal and extrapancreatic lesions.[11] As noted, patients 1–3 had resection of the tumor and total gastrectomy. All patients in this group are cured with a minimum follow-up of 5 years. Of the remaining six patients operated on since 1981, four gastrinomas were located in the duodenum (patient 7, 2 gastrinomas), one pancreatic lesion was located in the uncinate process, and one tumor was found within a lymph node located along the lesser curve of the stomach. Figure 1 demonstrates the location of gastrinomas in this group of 10 patients. The gastrinoma found in patient 4 appeared to be an accessory spleen at initial observation. Gastrinoma was

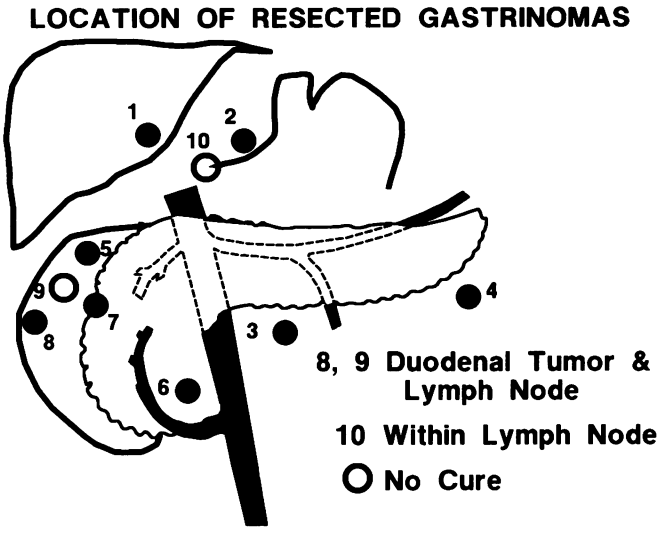

FIG. 1. The location of 10 gastrinomas in patients who had tumor resection for "cure." Open circle denotes the two patients who failed within 48 hours based on serum gastrin determinations. The black circles indicate the eight patients who have remained "cured" of their disease.

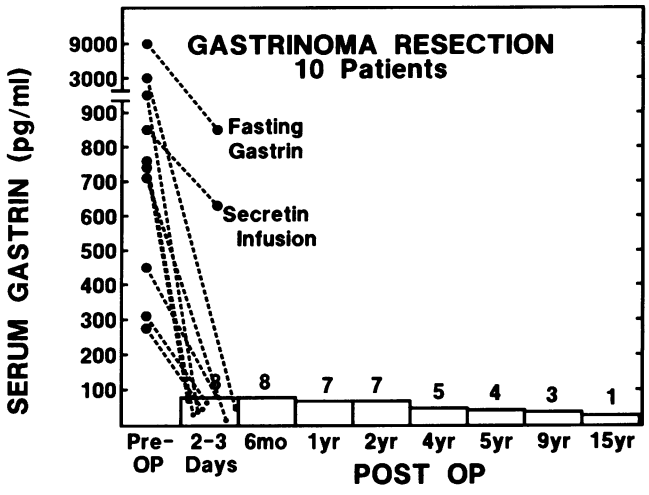

FIG. 3. Preoperative and postoperative serum gastrin determinations in 10 patients who had gastrinoma resection for "cure." Two patients failed within 48 hours and eight patients remained "cured" with a follow-up of 6 months to 15 years.

confirmed on frozen section. Two of the duodenal lesions (patients 8 and 9) also had tumor in adjacent lymph nodes. Both were resected with their nodes for potential cure. Although resected for cure, patients 9 and 10 represented early failures on the basis of postoperative gastrin determinations. The serum gastrin response in patient 9 was greatly decreased but still abnormal. Patient 10 had a postoperative normal fasting serum gastrin determination but a positive secretin infusion test. After operation, the lesion in patient 10 was noted to be within a rim of lymph node tissue. Patient 9 had a duodenal wall gastrinoma with a positive adjacent lymph node. A similar condition, that of a duodenal wall gastrinoma with a positive adjacent node, was found in patient 8, but the postoperative serum gastrin determinations and secretin infusion tests have remained normal since surgery.

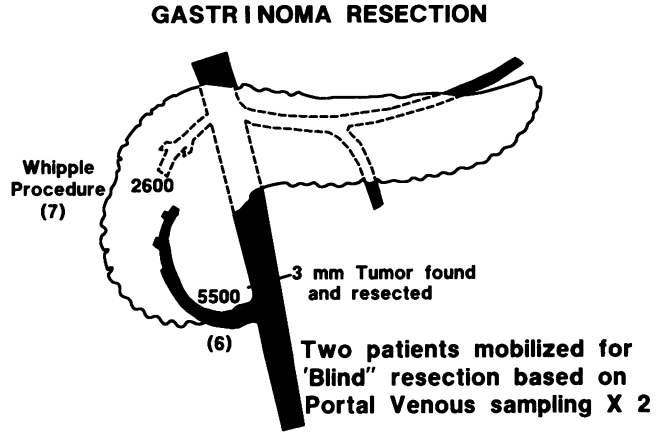

FIG. 2. The peak gastrin determination after PVS in two patients (6 and 7) who had mobilization for a "blind" pancreatic duodenectomy. In one patient (6) a small tumor was found and enucleated before major resection.

At laparotomy and after extensive search for tumor tissue, two patients (6 and 7) had mobilization of the duodenum and pancreas in preparation for a "blind" pancreatoduodenectomy based on preoperative portal venous sampling (Fig. 2). Immediately before transection of the head of the pancreas, a small 3-mm nodule was palpated deep in the posterior portion of the uncinate process. This tumor mass was enucleated and a frozen section was consistent with the primary gastrinoma. Serum gastrin determinations and response to secretin infusion have remained normal since surgery (2 years). Patient 7 had a pancreatoduodenectomy with two duodenal wall gastrinomas identified by the pathologist.

Overall, 8 of 15 patients in whom gross tumor was found or 8 of 10 patients who had resection of their gastrinomas for cure were believed to represent a cure of ZES. Figure 3 demonstrates follow-up serum gastrin determinations in all eight patients. With the exception of two patients who biochemically failed within 2 days of surgery, all remaining patients demonstrated serum gastrin determinations below 100 pg/mL throughout their years of follow-up. Secretin infusion tests have remained normal after operation in all patients in this group since 1978. There have been no deaths throughout the postoperative period and no evidence of metastatic disease. The two patients with abnormal gastrin determinations after operation remain asymptomatic on medical therapy with ranitidine. No decision has been made yet as to sec-

ond attempts at portal venous sampling or possible second-look surgery.

Transhepatic venous sampling of the portal vein with serum gastrin determinations was performed in six patients. Three patients had the procedure twice. The location of the tumors in these patients are noted in Figure 4. The results in one patient were considered false-positive. The gastrin gradient in this patient demonstrated high levels near the takeoff of the superior mesenteric vein. The tumor, however, was found in the wall of the duodenum with no evidence of tumor in or around the pancreas. Postoperative serum gastrin determinations after resection of this duodenal tumor have remained normal. The results in five patients were considered to be true-positives with gradients coinciding with the areas where tumor was found. In one patient, however, the lesion in the body of the pancreas was found to be both metastatic and unresectable due to local invasion and distant spread. Total gastrectomy was performed. In two of six patients (6 and 7) the tumor was not easily identified at surgery. As described, both patients had the pancreas and duodenum mobililized for a major resection, but a small gastrinoma was palpated and enucleated in patient 6. Patient 7 had a Whipple procedure with two separate gastrinomas located in the wall of the duodenum (Fig. 5). These were not palpated at surgery even with the duodenum opened. Figure 6 demonstrates the PVS gastrin gradient in patient 6 in which the 3-mm gastrinoma was found in the uncinate process. Of the entire group of six patients who had PVS, gastrinoma tissue was easily identified in four patients. In only two of six patients, therefore, PVS was considered essential in locating the gastrinoma and vital in considering major resection in patient 7.

A total of eight patients of the entire group of 24 patients were considered cured of their disease. This represented 36% of the 22 patients who had laparotomy and 53% (8/15) in whom tumor was found at surgery. The overall follow-up period was 8, 9, and 15 years in three patients, 4 and 5 years in two patients, 2 years in two patients, and beyond 6 months in one patient.

Discussion

The early treatment of ZES by total gastrectomy has evolved in several stages. These have included intensive medical therapy for most if not all patients, preoperative localization of tumors using various modalities, and, finally, an aggressive approach to resection of the primary tumor, metastases, and even blind pancreatoduodenal resection based on the results of PVS.

The evolving trends were made possible by the success of cimetidine, ranitidine, and newer drugs in controlling the gastric hypersecretion of ZES.[9,10] After this stage, the

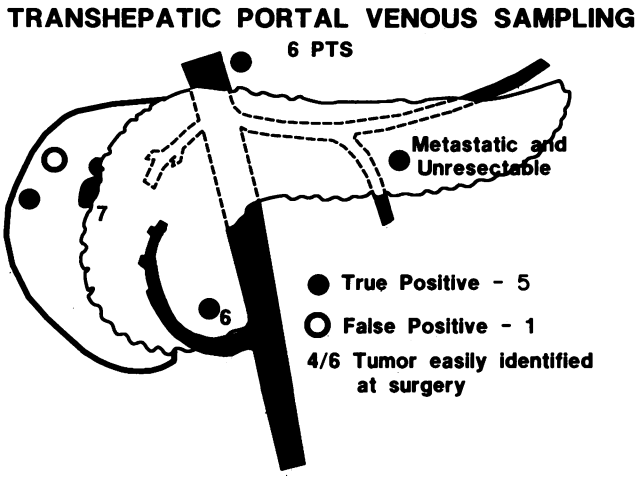

FIG. 4. Location of tumor in six patients who had preoperative transhepatic PVS. Tumor was resected in five of six patients.

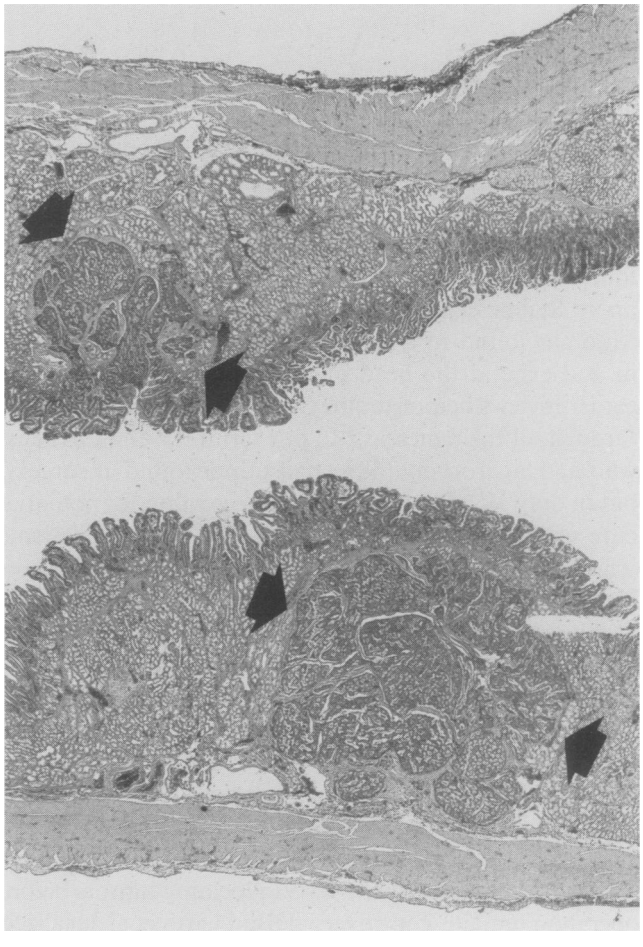

FIG. 5. Photomicrograph demonstrating the two duodenal wall gastrinomas identified and resected in patient 7.

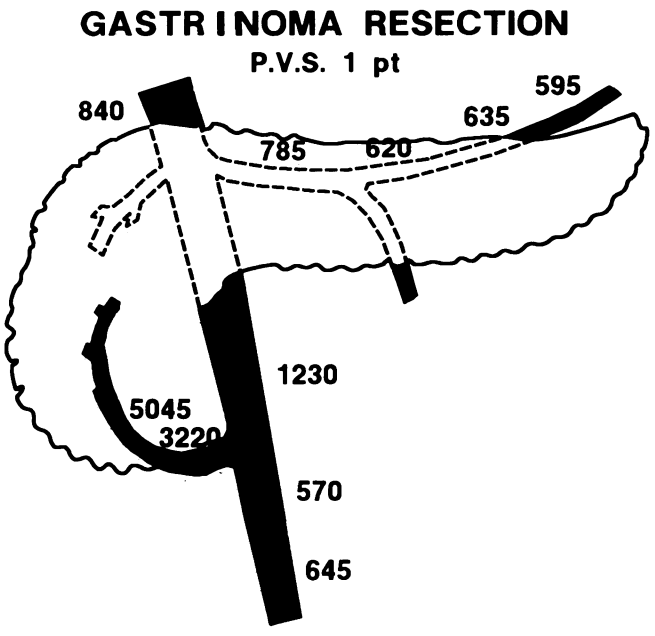

FIG. 6. Transhepatic PVS and gastrin determinations in pg/mL in patient 6. A 3-mm gastrinoma was resected from the posterior uncinate process.

emphasis changed to localization of the tumor before and during operation.

In recent reviews, and in up to 40% of patients in whom ZES was well documented, gastrinomas were not found during laparotomy.[15,16] Norton et al., however, reported that 73% of documented ZES patients had gastrinomas found either by preoperative imaging studies or laparotomy.[1] Stabile et al. documented greater than 80% of gastrinomas found in a "Triangle" encompassing the area in and around the head of the pancreas as opposed to earlier reviews demonstrating a more widespread location throughout the pancreas.[3] In our series, 15 of 22 patients who had laparotomy (68%) had tumor found at surgery, but in only 10 of 22 patients (45%) resection for potential cure was attempted and performed. Of the 10 patients who had resection for cure, at least six or seven tumors were located within the anatomic triangle reported by Stabile et al.[3] This included one of four extrapancreatic, extraintestinal tumors with the remaining three outside the reported area. Since 1981, however, all of the resected lesions appear to be within this triangle. Whether this represents a trend to earlier diagnosis of curable lesions as discussed by Thompson et al. is unclear as yet.[17] They reported finding only 26% of patients with metastatic disease over a 12-year period.

The role of transhepatic PVS in locating tumors before operation remains controversial. Burcharth et al. localized gastrinomas in 10 of 12 patients with ZES with five of six patients who were operated on undergoing pancreatoduodenal resection. They considered four resections probably curative.[11] The review by Roche et al. was quite interesting, provocative, and controversial in terms of "blind" pancreatoduodenal resections based on preoperative PVS.[12] Although gastrinomas were not found at laparotomy by the surgeon, even with positive preoperative gastrin gradients, they were, however, demonstrated by the pathologist after blind pancreatoduodenal resections. In our small series of six patients, tumor was easily identified at surgery in four patients, retrospectively suggesting that PVS was not cost effective. In two patients, however, tumor was not easily identified, and both patients had mobilization of the pancreas and duodenum for "blind" resection. One small tumor was eventually found, and only one patient had a Whipple procedure. Blind resection is quite controversial and, although we accept the concept, we would agree with Norton et al. that the 37% mortality reported by Roche et al. is too high to accept even when resecting for potential cure.[2]

Ten of 22 patients had resection for cure of the potentially malignant syndrome. In eight of 22 patients (36%) or eight of 10 patients who had attempted resection we believe that, at the very least, biochemical cure was achieved and, at the most, permanent cure in the patients followed for more than 4 years. Resection was attempted in two patients with duodenal tumors who had adjacent positive lymph nodes. One patient failed in the early postoperative period, but one patient remains cured. This is similar to the review by Friesen who reported "probable cure" in four of 10 patients with tumor in the lymph nodes.[5] On the basis of his experience and others in reporting "primary" gastrinomas in lymph nodes, our tenth patient had extensive resection of a lesser curve lymph node mass. Unfortunately, although postoperative serum gastrin determinations returned to normal, the patient demonstrated a positive secretin infusion response. We plan on restudying this patient in approximately 6 months to 1 year with both computed tomography (CT) and PVS. The second of our failures will similarly be restudied with CT and PVS. This patient had resection of a duodenal wall tumor and adjacent positive lymph node. No other tumor was palpable at surgery and the patient is now asymptomatic on a regimen of ranitidine therapy 1 year after laparotomy.

Our experience with CT scanning has been somewhat poor compared with the excellent results reported by Norton et al.[2] None of the 10 patients who had resection for cure had demonstrable lesions on CT scan. It is certainly possible that we are finding patients with ZES at an earlier stage with smaller tumors in the head of the pancreas or the anatomic triangle previously described. We may, however, be identifying fewer patients in recent years with ZES than we did a decade ago. As discussed by Wolfe et al. there has been a gradual decrease in the number of requests for serum gastrin determinations in

commercial laboratories.[18] They postulated that this decline was coincidental with the increasing availability of histamine H_2 antagonists and that many patients with peptic ulcer disease symptoms but underlying ZES may be adequately treated by empirical cimetidine or ranitidine therapy. We would suggest that most, if not all, patients with documented peptic ulcer disease should have at least one serum gastrin determination, even though their disease responds well to medical therapy.

Of the eight patients reported in this series whom we consider potentially cured, five patients have follow-up beyond 4 years. Although long-term follow-up beyond 10 years is necessary to consider the patients biologically cured, we believe that, in the seven patients beyond 2 years, normal serum gastrin determinations and normal responses to secretin infusion suggest both a biochemical and biological cure. Malagelada et al. recently reported what they considered permanent cure in seven of 18 patients in whom resection for cure was performed (39%).[4] Norton et al. reported a biochemical cure in 12 of 28 patients who had resection. Within 6 months, however, the "cure" rate fell to 30% (7 of 23 patients). They believed that this group might represent permanent cures and recommended an aggressive approach to tumor resection when possible.[2]

In conclusion, we believe that the data presented support the concept that ZES can be cured (33%) even with tumor in nodes or when tumor is not easily identified at surgery. Although controversial and not necessarily cost effective, we believe that PVS does, indeed, identify some tumors, even those that are not easily found at surgery. Similarly controversial is the role of "blind" pancreatoduodenal resection. If this procedure can be performed with low morbidity and mortality, then it indeed removes tumors that were not identified at initial laparotomy. Based on these data and other recent reviews, we support an aggressive approach to tumor resection involving initial evaluation of the response to medical therapy, preoperative localization of the tumor, laparotomy, and, finally, resection of tumors with metastases when present. It is likely that with the newer, more powerful drugs available, and perhaps with future gastric secretory suppressants, there may be little or no need to consider either total gastrectomy or highly selective vagotomy at initial exploration for ZES.

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Discussion

DR. JAMES C. THOMPSON (Galveston, Texas): I would like to congratulate Dr. Woodward, Dr. Vogel and their colleagues on this very good study.

As far as I can tell, their experience with transhepatic selective pancreatic vein catheterization is the best yet reported in the world since the original report from Flemming Stadel's group in "Gastroenterology" in 1979. I do not believe anyone has approached this degree of accuracy and certainly we have not.

We have studied 10 of our 36 patients with Zollinger-Ellison syndrome by this technique, and the examination was truly helpful in only one patient. We had three false-positives, three false-negatives, and in three patients the localization of the tumor was obvious at operation and we did not need the technique.

We have certainly had a much more difficult time finding the single isolated tumor than most seem to.

We have, like everyone else, lost many of our patients to the growth of metastatic tumors. I believe that we need to be very selective in talking about these. We have never been able to render a patient eugastrinemic,