Surgical Management of Zollinger-Ellison Syndrome; State of the Art

Ellen H. Morrow, MD, Jeffrey A. Norton, MD*

Zollinger-Ellison Syndrome (ZES) was originally described in 1955. It is a syndrome of acid hypersecretion caused by a gastrin-producing tumor (gastrinoma). Since the recognition of this disease entity, diagnosis and treatment strategies have changed greatly. The purpose of this review is to describe the current standard in diagnosis and surgical management of ZES and to outline some controversies that have arisen recently.

EPIDEMIOLOGY

The incidence of ZES in the United States is one to three new cases per million per year, making it a rare condition. Eighty percent of gastrinomas occur sporadically, while 20% are associated with Multiple Endocrine Neoplasia Type 1 (MEN-1). ZES causes 0.1% to 1% of peptic ulcer disease. Men are slightly more likely to develop ZES. The mean age at which symptoms begin is 41 years. Patients with MEN-1-associated ZES are likely to present at a younger age; in the third decade of life. ZES occurs in approximately 25% of patients with MEN-1.

PRESENTATION

The presenting signs and symptoms of ZES have also changed with earlier recognition and diagnosis. Initially, it was described as gastric acid hypersecretion, ulcers in unusual locations (jejunum), recurrent ulcers, and nonbeta islet cell tumors of the pancreas. Subsequent studies of large numbers of patients with ZES have demonstrated that common presenting symptoms include abdominal pain, diarrhea, heartburn, nausea, and weight loss. Diarrhea is a common problem as approximately 80% of patients...
with ZES have this symptom. Given the nonspecific nature of these symptoms, and the rarity of ZES as compared with more common disorders, such as gastroesophageal reflux disease or routine peptic ulcer disease, there is commonly a significant delay in the diagnosis of ZES. The most common initial diagnosis for patients with ZES is idiopathic peptic ulcer disease. The mean time from onset of symptoms to diagnosis of ZES is 5.9 years. Although the time to diagnosis has remained constant over the past 30 years, there is some evidence that it may prove even more challenging with the widespread use of proton pump inhibitors (PPI). PPI provide very effective acid suppression, which may defer the diagnosis even further.

The presentation of ZES in MEN-1 may differ somewhat from patients with sporadic ZES. A recent NIH study demonstrated a higher incidence of severe esophageal disease including Barrett’s esophagus in patients with MEN-ZES. Despite the high frequency of ZES in MEN-1, the diagnosis is still usually delayed. Only 5% of patients with MEN-1 are initially diagnosed correctly, compared with 2% of patients with sporadic ZES.

Given the continued delay in diagnosis of ZES, recommendations have been made regarding factors which should increase a clinician’s suspicion for the syndrome. Patients who present with the triad of abdominal pain, diarrhea and weight loss, patients who have recurrent or refractory ulcers, patients with prominent gastric rugal folds on endoscopy, or patients with MEN-1 and gastrointestinal symptoms should be tested for ZES. In addition, symptoms of acid hypersecretion associated with diarrhea should indicate the possibility of ZES.

At the time of diagnosis, some patients will have minimal or nonimageable tumor while others may have advanced disease (ie, greater than 40% have lymph node metastases). The duodenum is the most common site of a primary gastrinoma, while the pancreas is the second most common site. Lymph node metastases do not affect survival, while liver metastases do. Hepatic metastases occur more commonly with pancreatic gastrinomas than duodenal. They may occur in up to 60% of pancreatic cases and less than 10% of duodenal cases.

**DIAGNOSIS**

Suspicion for the diagnosis of ZES should be aroused when any of the above factors are present. Once the clinician suspects ZES, diagnostic workup should begin with

![Fig. 1. A large duodenal gastrinoma which is visible on CT.](image)
a fasting serum gastrin level and ascertainment of the presence of gastric acid hyper-
secretion. All patients with ZES will have a fasting gastrin greater than 100 pg/mL.\textsuperscript{7} A
greater than tenfold increase in serum gastrin is more characteristic, and can be diag-
nostic of ZES with gastric pH less than 2.1.\textsuperscript{5} Patients should have PPI held for one
week before this test, as acid suppression with PPI will artificially elevate the gastrin
level.\textsuperscript{2,12,15} H2 blockers should be held for 2 days.\textsuperscript{5} Table 1 outlines other conditions
which can cause elevated serum gastrin, including renal failure, short bowel
syndrome, antral G cell hyperplasia, atrophic gastritis and retained gastric antrum.\textsuperscript{2,3}

Demonstration of acid hypersecretion (in the presence of elevated gastrin) is also
critical to make the diagnosis of ZES. Therefore, gastric pH or basal acid output
must be measured off medications that inhibit acid secretion, such as PPI, and so
forth. Basal acid output greater than 15 mEq/hr is diagnostic as is pH less than 2.3

The secretin stimulation test is also confirmatory and can be used to establish the
diagnosis in patients with otherwise equivocal results (ie, gastrin between 100 and
500 pg/mL, and gastric pH <2.1).\textsuperscript{5} However, it is positive in only 85% of patients
with ZES.\textsuperscript{3} This is a provocative test in which a 2U/kg bolus of secretin is given intra-
venously (IV), and serum gastrin is subsequently measured at certain time points. A
rise in serum gastrin of 200 pg/mL is consistent with ZES. The secretin test can also
be used for patients who cannot have their PPI withheld.\textsuperscript{8} However, in our experience

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<td>Differential diagnosis of biochemical abnormalities seen in Zollinger-Ellison syndrome</td>
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<tr>
<td>Zollinger-Ellison syndrome</td>
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<tr>
<td>Gastric outlet obstruction</td>
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<tr>
<td>Retained gastric antrum</td>
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<td>G-cell hyperplasia</td>
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\textit{Data from} Peterson DA, Dolan JP, Norton JA. Neuroendocrine tumors of the pancreas and gastro-
all patients with ZES can have the PPI held despite grave concerns by referring doctors.

**PREOPERATIVE IMAGING**

Once the biochemical diagnosis of ZES is established, imaging should be undertaken in an attempt to localize the tumor. Tables 2 and 3 outline the sensitivities of the various imaging modalities. Somatostatin receptor scintigraphy (SRS) is the study of choice (Fig. 3). SRS uses radiolabelled octreotide and single photon emission computed tomography (SPECT) to image the gastrinoma. The sensitivity of SRS has been shown to equal that of all other imaging modalities combined.\(^{16,17}\) Its sensitivity is estimated between 58% and 78% and it can image tumors in ectopic locations.\(^{16,18,19}\) The sensitivity of SRS is dependent on tumor size. It detects 96% of tumors larger than 2 cm, but in one study SRS missed 33% of gastrinomas identified at surgery.\(^{16}\) These tumors were generally small (ie, <1 cm) tumors located within the duodenum. SRS is the best study for localizing primary and metastatic gastrinoma.\(^{17}\) The use of SRS affects management plans in 19% to 53% of cases.\(^{18,20}\)

Endoscopic ultrasound (EUS) may be the most sensitive study for pancreatic gastrinomas.\(^{21}\) However, EUS is not generally helpful for duodenal tumors or liver metastases. EUS may be most useful, therefore, in patients with MEN-1 who are likely to have multiple small pancreatic tumors.

CT provides more anatomic information than SRS, but has lower sensitivity (see Table 2). It is critical to exclude large tumors within the pancreas and liver metastases. Gastrinomas are vascular tumors so they are best imaged on the arterial phase of CT (Fig. 4). It is an important study, and should be used as one of the two initial imaging modalities. MRI can be used to provide anatomic information if, for some reason, CT is not preferred in a given case.

**SURGICAL MANAGEMENT: STANDARD OF CARE**

There are two main goals in the treatment of ZES: control of acid production and its sequelae, and treatment of a potentially malignant tumor. Surgical treatment is currently focused on treatment of the tumor, as very effective medical therapy for acid hypersecretion has existed since the development of proton pump inhibitors, such as omeprazole. The typical dose to control acid hypersecretion is 40 mg omeprazole twice a day. Intravenous PPI, such as protonix, are used during surgery and the usual dose in ZES is 80 mg IV every 12 hours. Gastric pH should be measured to be certain acid hypersecretion is controlled. Historically, total gastrectomy was used to treat patients with ZES, but this has not been necessary since the development of PPI, which are much more powerful than H2-receptor antagonists.\(^{22,23}\)

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**Table 2**

Results of preoperative imaging studies for primary gastrinoma

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<tr>
<th>Imaging Modality</th>
<th>Sensitivity</th>
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<tr>
<td>SRS</td>
<td>85%</td>
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<tr>
<td>CT</td>
<td>54%–56%</td>
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<tr>
<td>MRI</td>
<td>25%–30%</td>
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<tr>
<td>EUS</td>
<td>67%</td>
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<tr>
<td>Arterial Angiography</td>
<td>28%–59%</td>
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Gastrinomas are most frequently located in the duodenum (60%) especially in patients with negative imaging studies. The gastrinoma triangle is an area defined by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially. Approximately 80% of gastrinomas are found in the gastrinoma triangle, and tumors to the left of the superior mesenteric artery are more malignant than those in the triangle. It is controversial, but there is evidence for the existence of lymph node primary gastrinomas. One study suggests that approximately 15% of patients with ZES may have lymph node-primary gastrinomas. This has been proven by cure of ZES with long-term follow-up following removal of only lymph nodes in the gastrinoma triangle. Others suggest, however, that the primary tumor, probably within the duodenum, was missed and that these patients will recur.

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<th>Imaging Modality</th>
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<tr>
<td>SRS</td>
<td>92%</td>
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<tr>
<td>CT</td>
<td>42%–56%</td>
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<tr>
<td>MRI</td>
<td>71%–83%</td>
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<tr>
<td>Arterial Angiography</td>
<td>61%–62%</td>
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Fig. 3. Fused SRS and CT images demonstrating multiple neuroendocrine tumors.
It is estimated that 60% to 90% of gastrinomas are malignant.\textsuperscript{5} Tumor progression and metastases are the chief determinants of survival in patients with ZES whose acid production is controlled medically.\textsuperscript{24,26,27} The chief goal of surgery, then, is to cure or control the tumor, and prevent metastases. These goals vary somewhat depending on whether gastrinoma occurs sporadically, or in the setting of MEN-1.

In sporadic ZES, the goal of surgery is to cure the disease. All patients with a biochemical diagnosis of sporadic ZES should undergo surgical exploration. This is recommended because high-cure rates have been demonstrated in patients with sporadic ZES. A series of 123 patients showed an immediate postoperative cure rate of 60\%, a 5-year cure rate of 40\%, and a 10-year cure rate of 34\%.\textsuperscript{28} Given that up to 30\% of gastrinomas can be missed by preoperative imaging studies, surgical exploration is warranted in all patients with biochemical diagnosis of sporadic ZES regardless of imaging results.

The recommended surgical approach is exploratory laparotomy with extended Kocher maneuver and careful palpation of the pancreas and duodenum for nodules. Intraoperative ultrasound (IOUS) should be used for identification of small pancreatic lesions. IOUS may have higher sensitivity than preoperative imaging methods because it can localize tumors with resolution to 5 mm in the pancreas.\textsuperscript{29,30} Enucleation of pancreatic head tumors should be performed, or distal pancreatectomy for tail lesions, and duodenotomy and regional lymphadenectomy.\textsuperscript{19} Some also recommend intraoperative gastrin measurements to confirm surgical cure before closure.\textsuperscript{31} This is not standard in all centers, however, and may not be necessary since a high-cure rate has been demonstrated with standard surgical procedure including duodenotomy (\textbf{Fig. 5}).\textsuperscript{32}

Duodenotomy is indicated in all patients undergoing surgery for ZES. Duodenotomy is the most effective method of identifying duodenal gastrinomas, which represent 60\% of gastrinomas.\textsuperscript{33} Making duodenotomy a standard part of operations for ZES doubled the cure rate from 30\% to 60\%.\textsuperscript{34,35} Lymph node sampling is also an important part of surgery for ZES. In addition to the existence of primary lymph node gastrinomas, there is a high rate of lymph node metastases. Removal of all regional lymph nodes is recommended.\textsuperscript{3}
In patients with MEN-1, the management of gastrinomas is somewhat controversial and more complicated. Patients with MEN-1 are unlikely to be cured of ZES with surgery. Some studies have demonstrated cures, but they did not do a full biochemical assessment postoperatively, including negative secretin test and measurement of serial levels of fasting gastrin. A large NIH study demonstrated a 0% cure rate in patients with ZES and MEN-1. This may be secondary to the fact that their tumors tend to be multiple, small, and located in the duodenum. There have been cures in patients with MEN-1 treated with Whipple pancreaticoduodenectomy; however, most suggest that the low-grade malignancy rate of duodenal gastrinoma does not warrant this potentially morbid surgery.

Despite the evidence against surgical cure in patients with ZES and MEN-1, there is still significant benefit to surgery in many of these patients. The goal of surgery for patients with ZES and MEN-1 is largely prevention of metastatic disease. The extent of liver metastases is the main determinant of survival. Surgical resection of the primary pancreatic gastrinoma has been shown to prevent the development of liver metastases. The risk of developing liver metastases increases with the size of the primary pancreatic gastrinoma. Patients with gastrinomas less than 1 cm have a 4% rate of liver metastases compared with 28% with gastrinomas that are 1 to 3 cm and a 61% rate of liver metastases with tumors greater than 3 cm. For this reason, it is recommended that patients with ZES and MEN-1 undergo surgery to remove any pancreatic gastrinoma greater than 2 cm.

Another aspect of the treatment of patients with ZES in MEN-1 is the sequencing of procedures. The majority of patients with MEN-1 have primary hyperparathyroidism secondary to multigland hyperplasia. Surgical treatment of the parathyroid hyperplasia can reduce the effects of excess gastrin secretion on acid hypersecretion. For this reason, patients with hyperparathyroidism and ZES in the setting of MEN-1 should have their parathyroid surgery first. The recommended procedure is a three and one-half gland parathyroidectomy.

**Surgical Management; Controversies**

Although the above guidelines have been established over the past 50 years of research and treatment of ZES, some controversial aspects of treatment remain and some new controversies are arising.

Control of acid hypersecretion is no longer the primary focus of surgical management; however, the question remains as to whether acid-reducing procedures should...
be performed at the time of laparotomy for tumor resection in ZES. Vagotomy is not a standard part of surgical procedures for ZES at this time, but including parietal cell vagotomy does appear to reduce the long-term need for acid-inhibitory pharmacotherapy in patients who have persistent or recurrent disease. This may be important since there are likely to be some adverse sequelae of long-term acid-inhibition therapy. Achlorhydria occurs frequently in patients using PPI, and may lead to B12 and iron deficiency. Further, in patients with MEN-1 and ZES, long-term use of PPI have led to the development of malignant gastric carcinoid tumors. For these reasons, vagotomy may be considered when laparotomy is performed for gastrinoma.

The use of pancreaticoduodenectomy in ZES is also debated. Given the good prognosis of patients with even metastatic gastrinoma, there is hesitation about using a procedure with high morbidity and mortality. Patients with distant metastases still have a 15-year survival of 52% according to some authors. In addition, performing a Whipple makes it more difficult to come back in the future to remove recurrent tumor (Fig. 6), or to treat future liver metastases with interventional methods because of the altered anatomy.

There are studies that have demonstrated the possibility of cure in patients with MEN1 using pancreaticoduodenectomy. These small studies did not, however, use a full biochemical assessment serially to rule out recurrent disease. A more recent study demonstrated a cure rate of 77% in patients with MEN1-ZES, but mean follow-up was less than one year. Some also estimate a higher rate of duodenal gastrinomas in patients with MEN, up to 90%, making pancreaticoduodenectomy potentially a more definitive procedure for prevention of recurrence. For these reasons, some authors currently recommend that Whipple be the first line procedure for patients with MEN1-ZES who have their source of gastrin localized to the pancreatic head by selective arterial secretin injection.

Our current recommendation is that Whipple procedure be reserved for young patients with large pancreatic head tumors that are not amenable to enucleation. It is possible that Whipple resection can result in increased cure rates, especially in patients with MEN-1 who are not often cured with more conservative surgical procedures. Further studies need to be done to compare long-term survival and quality of life.

Relative consensus does seem to exist in the surgical management of metastatic disease, although controlled clinical trials do not exist. There is evidence that resection of liver metastases improves survival, although it is difficult to conclude for certain that the demonstrated differences in survival are dependent on surgical treatment, and not
the extent of disease itself.\textsuperscript{36,55} A significant percentage of patients with metastatic gastrinoma can undergo liver resections that result in removal of all known disease with 5-year survival up to 85\%.\textsuperscript{56} In addition to possible survival benefit and surgical cure of metastatic disease, there may be benefit of cytoreductive surgery in ameliorating the functional endocrine tumor syndrome.\textsuperscript{57} The current recommendation is to attempt to perform liver resection when at least 90\% of the tumor appears to be able to be removed on preoperative imaging studies.

Laparoscopy is increasingly used for complex abdominal procedures, and in particular, the laparoscopic experience with pancreatic resections is growing. There are several reports of laparoscopic resections of pancreatic neuroendocrine tumors especially insulinoma.\textsuperscript{58,59} Laparoscopic distal pancreatectomy is a promising procedure with a complication (fistula) rate equal to or less than open procedures.\textsuperscript{59} Enucleation also appears to be feasible laparoscopically. Laparoscopic treatment of gastrinoma, however, presents some significant challenges. More than half of gastrinomas occur in the duodenum, or other extra-pancreatic locations. Gastrinomas tend to be larger than other neuroendocrine tumors, and they are more often metastatic. These factors make gastrinomas less amenable to minimally invasive techniques, as evidenced by a higher conversion rate in reported series.\textsuperscript{58}

Since many gastrinomas are located in the duodenum, there has been some discussion of the possibility of endoscopic removal. There have been reports using snare polypectomy or band ligation. Some of these cases have reported cure of ZES, but there has also been at least one perforation.\textsuperscript{60} Lee and colleagues\textsuperscript{61} reported treatment of ZES with endoscopic band ligation. In this case, the patient had refused surgery. The serum gastrin level dropped from 647 to 100 pg/mL, and a postoperative biopsy near the banding site was negative for tumor.

This is an interesting report, but there are several factors that would seem to prevent endoscopic treatment from being equal to surgery in patients who are eligible for surgery. First, gastrinomas occur in a submucosal location, which makes them somewhat less amenable and safe for endoscopic resection. In addition, they are often invasive beyond the submucosa. Secondly, banding does not allow removal of the lesion, but rather causes it to slough. This makes pathologic examination less complete. It is therefore difficult to assess margins. Thirdly, in previous studies endoscopy was inferior to duodenotomy for detection of gastrinomas.\textsuperscript{33} It is probable that gastrinomas would be missed if they were detected by endoscopy only. Finally, up to 60\% of gastrinomas are associated with lymph node metastases at the time of diagnosis, making endoscopic treatment of the duodenal gastrinoma an incomplete oncologic procedure.\textsuperscript{62}

**SURVEILLANCE**

Gastrin levels and secretin tests are the most sensitive methods for detecting recurrence of gastrinoma.\textsuperscript{19,63} SRS should also be used for restaging periodically.

**OUTCOMES**

Surgery results in cure of ZES for 60\% of patients with sporadic disease. The cure rate at 5 years is 40\%.\textsuperscript{26} Patients with MEN-1 are rarely cured. Surgery also impacts the rate of progression to liver metastases, and the rate of disease-related death. In a large series, 15 year disease-related survival was 98\% for operated patients and 74\% for unoperated patients.\textsuperscript{35} The existence and extent of liver metastases are the main determinants of survival.\textsuperscript{45}
SUMMARY

Much has been learned about the diagnosis and treatment of ZES, and certain questions require further investigation. Delay in diagnosis of ZES is still a significant problem, and clinical suspicion should be elevated. The single best imaging modality for localization and staging of ZES is somatostatin receptor scintigraphy. Goals of surgical treatment for ZES differ between sporadic and MEN-1–related cases. All sporadic cases of ZES should be surgically explored, including duodenotomy, even with negative imaging results, because of the high likelihood of finding and removing a tumor for potential cure. Surgery for MEN-1–related cases should be focused on prevention of metastatic disease, with surgery being recommended when pancreatic tumors are greater than 2 cm. The role of Whipple procedure, especially for MEN-1 cases, should be explored further. Laparoscopic and endoscopic treatments are more experimental, but may have a role.

REFERENCES


