

Zollinger-Ellison Syndrome: Classical Considerations and Current Controversies

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Key Words. Gastrinoma • Peptic ulcer • Multiple endocrine neoplasia type 1 • Gastric acid

Learning Objectives

Compare the approaches to management of sporadic and MEN-1 associated Zollinger-Ellison syndrome variants.

Discuss the controversies in surgical and medical management of Zollinger-Ellison syndrome.

ABSTRACT

Zollinger-Ellison syndrome (ZES) is an endocrinopathy characterized by gastrin-secreting tumors, responsible for causing the formation of multiple, refractory, and recurrent peptic ulcers in the distal duodenum and proximal jejunum. Two main variants have been described, sporadic and those found in association with parathyroid and pituitary tumors, a genetic disorder known as multiple endocrine neoplasia-1 (MEN-1). Biochemical serum evaluation for elevated gastrin, followed by radiological or nuclear localization of the primary lesion, is mandated for establishing diagnosis. The mainstays of treatment include management of hypersecretory state with medical suppression of gastric acid production and surgical resection of primary

tumor for the prevention of malignant transformation and metastatic complications. Medical therapy with proton pump inhibitors has virtually eliminated the need for acid-reducing surgical procedures. Surgical approach to sporadic and MEN-1-associated ZES varies based on our understanding of the natural history of the condition and the probability of cure; however, resection to a negative microscopic margin is indicated in both cases. Postoperative surveillance involves measurement of gastrin level, followed by imaging if elevation is detected. Re-excision of recurrent or resection of metastatic disease is a subject of controversy; however, at the present time aggressive cytoreductive approach is favored. *The Oncologist* 2014;19:44–50

Implications for Practice: Surgery plays a key role in the treatment of Zollinger-Ellison syndrome, an endocrinopathy characterized by gastrin-secreting tumors responsible for causing multiple recurrent and often refractory ulcers in the GI tract. Although medical therapy with proton pump inhibitors has virtually eliminated the need for acid-reducing surgical procedures in patients with this condition, resection of the primary lesion is still indicated in most cases. However, the extent of resection, timing of intervention, and reoperation for recurrent disease are topics of controversy. The historical considerations as well as evidence-based recommendations for management are summarized in this article.

INTRODUCTION

In April 1956, at the annual meeting of the American Surgical Association in Philadelphia, Dr. Robert M. Zollinger and Dr. Edwin H. Ellison described two cases of a condition whereby patients developed severe, recurrent, multifocal ulcerative lesions of the proximal gastrointestinal tract. These lesions appeared to be refractory to any attempt at surgical resection and were curiously associated with tumors located in the adjacent pancreas. The manuscript, titled “Primary Peptic Ulcerations of the Jejunum Associated with Islet Cell Tumor of the Pancreas,” proposed a diagnostic triad for the clinical syndrome they had identified. This included mucosal ulcerations in unusual locations such as distal duodenum or

proximal jejunum, gastric acid hypersecretion, and presence of non- β -cell pancreatic tumors [1]. Based on clinical observations, Zollinger and Ellison hypothesized a presence of a previously unknown pancreatic cell tumor capable of secreting a humoral factor effecting excitability of gastric acid-producing cells. Although the elaboration of the epidemiology, pathogenesis, clinical manifestations, and physiological sequelae of this entity was to follow in the upcoming decades, this was the first formal discussion at a scientific forum of what eventually became known as Zollinger-Ellison syndrome (ZES).

In the 1960s, gastrin was discovered as the key hormone in the pathogenesis of the gastric hypersecretion [2]. With

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further advances in biochemical detection techniques, as well as improved understanding of the gastrointestinal hormone interactions, specifically the identification of the role of secretin stimulation on the serum gastrin levels [3], the diagnosis of ZES could now be conclusively established. It was observed that some cases of ZES were decidedly sporadic, whereas others occurred in constellation with other clinical features that comprised what we now understand to be a genetic syndrome that later became known as MEN-1 [4]. Advances in radiological imaging, angiography, and endoscopic techniques allowed for more precise tumor localization. Finally, understanding the natural history of the tumors responsible for ZES has allowed us to make evidence-based recommendations about their ultimate management.

It is the purpose of the current review to present a historically based overview of the diagnosis and treatment of Zollinger-Ellison syndrome and to discuss some of the controversies that exist today with regard to its management.

EPIDEMIOLOGY AND PATHOGENESIS

The early estimates of ZES incidence were most likely falsely low given large degree of overlap with peptic ulcer disease [5]. Whereas the true incidence remains unknown, there is general consensus that approximately 0.1–3 persons per million develop gastrinoma each year in most geographical areas [6, 7]. This rate has largely remained constant since ZES was originally described. Females have a slightly greater preponderance for developing the disease, and cases have been reported in both the very young and the very old, although gastrinoma is most frequently diagnosed between the ages of 20 and 50 [5, 7–9].

Approximately 80% of the time, the primary causative lesion is thought to arise sporadically; in the remainder of recorded cases, this entity exists as part of MEN-1, an autosomal dominant disorder characterized by tumors of the pituitary, the parathyroid, and the pancreas [4].

Gastrinomas are derived from the enteroendocrine cells that arise from the embryologic endoderm, and form tumors mainly in the pancreas, but also in the proximal small intestine. Because of their origin, these are generally classified under the larger umbrella term of neuroendocrine tumors (NETs) [10]. The World Health Organization classifies NETs into two broad categories, well differentiated and poorly differentiated, and most gastrinomas are considered well-differentiated NETs on the basis of histopathological analysis [11]. It has been observed that most gastrinomas arise in the duodenum, with tumors located in the pancreas carrying greater malignant potential [12].

The pathophysiology of ZES is related to the trophic action of gastrin on parietal cells of the gastric antrum and the resulting hypersecretory acid milieu [3]. An overwhelming majority of patients with this disease consequently develop peptic ulcers, often large and multiple, frequently in distal duodenum and even proximal jejunum (an uncommon location for ulcers resulting from *Helicobacter pylori* or the use of nonsteroidal anti-inflammatory drugs).

DETECTION AND DIAGNOSIS

Most patients experience severe refractory heartburn and epigastric pain, often accompanied by profound diarrhea, which is a result of the combination of osmotic load of high

Table 1. Differential diagnosis of hypergastrinemia

Gastrinoma
Gastric outlet obstruction
Retained antrum syndrome
Previous vagotomy
Antral G cell hyperplasia/hyperfunction
Pernicious anemia
Atrophic gastritis
Short gut syndrome
Renal failure

gastric acid secretion as well as a malabsorptive component from inactivation of pancreatic digestive enzymes by the acid [13, 14]. In addition, high serum gastrin concentration may inhibit sodium and water reabsorption by the intestinal brush border, thus proving a secretory component as well. Severe diarrhea may be a sole presentation of ZES in as many as 20% of the patients [15]. Other common complaints at presentation include abdominal pain, weight loss, or history of renal colic/nephrolithiasis in patients with MEN-1.

Only a small proportion of patients with peptic ulcer disease (PUD) are ultimately diagnosed with ZES. A high index of suspicion should exist in cases of refractory gastric hyperacidemia, in cases of ulcers that recur in spite of maximal medical management, and in the presence of ulcers that are large, multiple, or located in uncommon areas (distal to the first portion of the duodenum). Biochemical analysis of the serum in patients with suspected ZES includes first measuring fasting gastrin levels, 72 hours off proton pump inhibitors (PPIs). A value greater than 1,000 pg/mL is diagnostic, and a value greater than 100 pg/mL is suggestive of this diagnosis, when identified in the presence of gastric acid. Measurement of gastric pH is required to exclude secondary hypergastrinemia (such as that associated with chronic achlorhydria) [5] (Table 1).

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Falsely low gastrin levels, despite the presence of gastrinoma, have been reported; this occurs because the tumor secretes bioactive gastrin precursor molecules, only one subtype of which is detected by the commercially available assay [16]. Therefore, in situations in which gastrin level testing is nondiagnostic, or is low but the suspicion for a tumor remains, additional testing is recommended to identify and localize the lesion. The simplest, and most sensitive and reliable, confirmatory test in this setting is the provocative secretin test, which consists of intravenous administration of 2 µg/kg secretin. An increase of greater than 100 pg/mL in serum gastrin levels is considered positive, whereas a rise of 200 pmg/mL above baseline is virtually diagnostic [3, 10, 17]. This test is also the most sensitive indicator of recurrent or

Table 2. Diagnostic accuracy of imaging for localization of gastrinoma

Modality	Sensitivity (%)	Comments
CT	50	Tumors enhance on early arterial phase because of high vascularity; sensitivity decreases for tumors <2 cm
MRI	25–50	Low T1 and high T2 signal intensity
SRS	80	Additional ability to detect extra-abdominal metastatic lesions; enhanced sensitivity when combined with single photon emission computed tomography (SPECT)
EUS	70	Much higher sensitivity for pancreatic compared with duodenal lesions; can guide needle biopsy to obtain tissue diagnosis
Angiography/arterial stimulation	40–60	Contrast administered into GDA and inferior pancreaticoduodenal artery; may be performed intraoperatively

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; GDA, gastroduodenal artery; MRI, magnetic resonance imaging; SRS, somatostatin receptor scintigraphy.

persistent disease in patients who have undergone attempted surgical resection. Positivity necessitates further radiological investigation for the presence of another lesion [18].

Any patient diagnosed with ZES should also be screened for MEN-1, which includes evaluating levels of prolactin, calcium, PTH, and pancreatic polypeptide. Interestingly, in patients with MEN-1, hyperparathyroidism is diagnosed after establishing ZES in approximately 50% of the patients [19].

Finally, an endoscopic gastroduodenoscopy should be performed to rule out secondary complications in patients with long-standing acid hypersecretion. Nearly all patients will develop ulcers at some point in the course of their disease, and more than half will exhibit endoscopic evidence of mucosal injury, such as erosive inflammation, stricturization, and perforation; these esophageal complications can develop even in the presence of antisecretory medications [20].

Radiologic imaging is recommended before undergoing any surgical exploration to localize the lesion and identify or rule out metastatic disease [21, 22]. Computer tomography (CT) and magnetic resonance imaging (MRI) both have good diagnostic accuracy for detecting lesions >3 cm; however, both frequently miss tumors smaller than 2 cm [22–25]. Somatostatin receptor scintigraphy has a higher sensitivity than conventional imaging (i.e., CT or MRI) and higher specificity than all combined for detection of extrahepatic gastrinoma, and is the imaging study of choice for identifying primary tumors and metastatic lesions in ZES [26, 27]. In recent years, endoscopic ultrasound has also become an important tool for localization of endocrine tumors located in the pancreas, as it allows good visualization of subcentimeter tumors (Table 2) [28–30].

In select situations in which biochemical and radiological investigative testing fails to identify a discrete lesion in a patient with suspected ZES, a selective arterial secretin test can be used to ascertain the presence of a tumor. Using this method, a selective cannulation of splenic, hepatic, gastroduodenal artery and superior mesenteric artery is performed, and small amount of secretin is infused locally; serial gastrin measurements are then taken from the right hepatic vein, thus establishing the relative site of the lesion [31].

Even with all the sophisticated diagnostic testing available today, a primary lesion has not been identified in approximately 30% of the patients with ZES [32, 33]; in this situation,

a surgical exploration with extensive and thorough examination of the pancreas and duodenum is warranted. The technique and rationale for this will be discussed later in this review.

MEDICAL MANAGEMENT

In the era before the discovery and widespread introduction of histamine-2 receptor blockers and PPIs, acid-reducing surgical procedures were the mainstay of treatment for patients with ZES. The relative morbidity of surgical interventions, which often involved total gastrectomy, was thought to be far outweighed by the potential complications of chronic hypersecretory state. Today, as PPIs are highly effective antisecretory agents that are well tolerated and have few long-term negative side effects even with chronic use at high doses, these medications have become the first-line therapy for patients with hypergastrinemia [34, 35]. PPIs bind $H^+K^+ATPase$ at the luminal aspect of the gastric parietal cell, thus interfering with both basal and stimulated gastric acid secretion. Most patients require doses that are slightly higher than those necessary for patients with idiopathic PUD; however, many can achieve acceptable outcomes with daily dosing because of the long duration of action of these drugs. A small percentage needs twice to multiple times the dose to maintain subphysiologic gastric acid levels [34]. Interestingly, mucosal healing is not correlated with symptom relief, and so endoscopic surveillance at regular intervals is recommended. There has been some concern about chronic hypergastrinemia and achlorhydria associated with long-term PPI use—several investigators have raised concerns about the development of gastric carcinoid tumors in this setting [36]. However, this has not been borne out in human clinical trials, and PPIs remain the recommended first-line agents for control of acid secretion in patients with ZES [34].

SURGICAL MANAGEMENT

With the advent of inexpensive, easy to administer, and well-tolerated pharmacologic options, acid-reducing surgical procedures largely fell by the wayside, instead replaced by the highly effective medical therapy. The role of surgical management of ZES has instead shifted to eradication of primary tumor and control/prevention of metastatic spread [21, 22].

Surgical approach to gastrinoma differs in sporadic ZES and ZES associated with MEN-1. As already mentioned, even

Table 3. Sporadic and MEN-1-associated ZES

	Sporadic ZES	MEN-1 ZES
Prevalence	80%	20%
Family history	No	Yes
Other endocrinopathies	No	Yes
Gastrinoma size	>2 cm	<2 cm
Number of tumors	Single	Multiple
Most common tumor location	Pancreas	Duodenum
Lymph node primary	10%	No
Surgical cure rate	60%	Rare
Malignant potential	High	Low

although many gastrinomas are well-differentiated, over half do carry malignant potential and mortality results from metastatic disease (Table 3) [27, 37–42]. It has been observed that even though for the most part gastrinomas are slow-growing tumors, and their metastatic propensity is low if the lesion is less than 2 cm in size, presence of metastatic disease dramatically worsens prognosis and decreases survival. Because of this, a case has been made for early surgical exploration and excision of primary lesions in patients with ZES to prevent distant spread. Unfortunately, complete surgical resection is possible in less than half of patients with sporadic ZES and not at all in patients who also have MEN-1.

In sporadic ZES, as many as 40%–70% of patients already have lymph node metastases at surgery, and 20%–40% present with unresectable liver metastases [27, 43, 44]. In patients with MEN-1, gastrinomas are frequently small (and thus undetectable by localization imaging), multiple, and have a very high metastatic propensity. This makes it virtually impossible to achieve cure without an aggressive surgical resection such as a pancreaticoduodenectomy [27, 39, 41–48]. Despite this, surgical excision is advocated for patients with solitary gastrinomas who do not have other contraindications to surgery. Surgical excision is also advocated for patients whose metastatic disease is amenable to resection.

The general approach to surgical exploration of the region should first involve identification of any metastatic lesions in the liver and the peritoneum. This should be followed by exposure and mobilization of the entire duodenum and pancreas, allowing for the examination of the gastrinoma triangle. In the late 1980s, Dr. Bruce Stabile and Dr. Ed Passaro noted that more than two thirds of all primary gastrinoma lesions are located in this region, roughly defined by the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially, both dorsally and ventrally (Fig. 1) [49, 50]. Mandating a thorough surgical exploration of this area resulted in nearly doubling the detection rate and removal of primary gastrinoma lesions.

The pancreas should be examined in its entirety, including intraoperative ultrasound, whether the lesion of interest is palpable or not. Small tumors may be enucleated, with care taken not to disrupt the pancreatic duct. Larger tumors may necessitate more extensive resections, such as a distal or a proximal pancreatectomy. In select situations, a central pancreatectomy may be considered for tumors located in

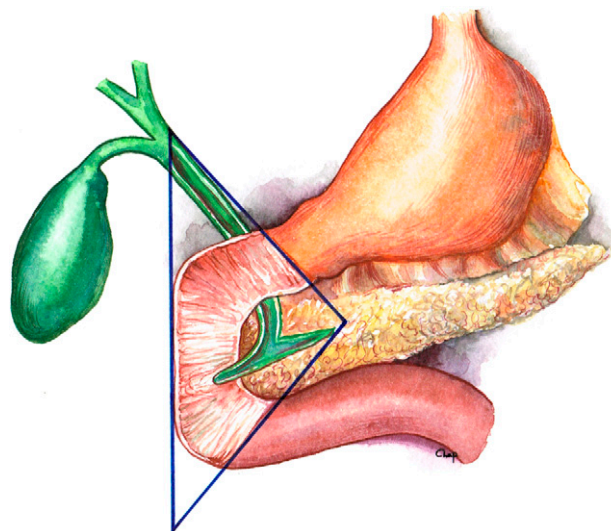


Figure 1. Gastrinoma triangle. Borders are defined by confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially, both dorsally and ventrally.

the body of the gland to maximally preserve endocrine function [51].

Examination of the duodenum is also an obligatory step of this procedure. A lateral duodenotomy must be made, and the duodenum can be evaluated using manual palpation, taking special care to assess the second and third portions. The duodenotomy can then be closed in a single layer longitudinally without appreciably narrowing the lumen. The extent of exploration and resection in patients with MEN-1 is a subject of controversy, as these patients are almost never cured of their disease by removing the primary tumor.

For patients who have metastatic disease to the liver at presentation, surgical options do include resection of both the primary and the metastatic tumor, provided there is no extrahepatic disease and that sufficient size and function of the remnant liver can be ensured. Other therapies exist, such as administration of octreotide, hepatic artery embolization, chemo- and radiotherapy, and molecular targeted therapies, and all have been investigated, but no level 1 data exist regarding their efficacy [34, 52–55]. Additionally, patients with recurrent disease may be considered for re-excision, as some reports have demonstrated adequate disease-free survival at relatively long term follow-up with this strategy [56–58].

OUTCOMES AND SURVEILLANCE

Surgical cure rates for ZES are a debated topic in current literature. Some groups have published complete surgical cures in sporadic gastrinoma; however, it should be noted that many of these studies have follow-up that is short and incomplete. Additionally, many of these define recurrence based on identification of radiologically detectable tumors rather than biochemical serum testing, even though the latter is a more sensitive and specific modality for detection of recurrent disease [44, 59, 60]. A more accurate estimate of approximately 40% at 10 years comes from several groups that present prospective data on patients with sporadic tumors who underwent resection [21, 42, 44, 61].

It is virtually impossible to achieve surgical cure in patients with MEN-1 ZES, with evidence of biochemical relapse present in more than 95% of patients within 3 years of surgery. However, resection of biologically active and radiologically/intraoperatively identifiable lesions remains the current recommendation because of improved survival thought to be secondary to prevention of distant metastatic spread.

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For all comers, data collected over the last 50 years suggest that, after a R0/R1 resection, most patients should enjoy a greater than 10-year survival, even if the disease recurs. Lymph node status and achieving eugastrinemia are not associated with a survival benefit; instead, the presence of metastatic disease is the marker most profoundly associated with poor long-term prognosis [37, 61, 62].

It is recommended that fasting gastrin level be checked annually and that subsequent imaging/localization investigations be performed based on the presence of symptoms and elevated gastrin levels in those who undergo successful surgical resection [63].

CONTROVERSIES IN CURRENT MANAGEMENT

As laparoscopic techniques become more widely adopted in the surgical community, there has been increasing interest in using minimally invasive methods for the management of gastrinomas. Endoscopic resections of duodenal tumors, as well as laparoscopic enucleations or distal parenchymal resections of pancreatic lesions, have been described [64–67]. However, manual palpation still remains an essential component of surgical exploration for gastrinoma, as approximately 30% of the tumors are not detected with standard radiological localization techniques preoperatively. Specialized training and skill in advanced laparoscopic techniques are required of any surgeon undertaking resection of a lesion in this anatomic region. In addition, when dealing with larger tumors, it is sometimes difficult to assess the extent of disease and lymph node involvement, as well as to perform the required extent of resection, with minimally invasive approach only. Thus, role of laparoscopy remains limited in the definitive surgical management of gastrinoma.

The extent of surgical resection, in particular for patients with MEN-1, remains subject of debate as well. Tumors in MEN-1/ZES tend to be smaller, multifocal in location, and poorly defined with preoperative localization methods, compared with sporadic ZES. Because of this, there is a nearly universal recurrence of disease in this group of patients. Several small series have reported high cure rates with aggressive resection, favoring pancreaticoduodenectomy (Whipple procedure); however, this approach, although intuitively reasonable, suffers

from a number of issues [41, 68–73]. First, no randomized controlled prospective data exist that support higher and more durable cure rates using Whipple procedures compared with less extensive resections. Second, in cases of local recurrence, reoperation is far more difficult and wrought with complications if a pancreaticoduodenectomy had already been performed. Third, if a metastatic lesion in the liver develops after the primary resection, the patient who has undergone a Whipple procedure would not be a candidate for local control therapies such as hepatic artery embolization due to concern for ascending infection. Thus, the recommendation to perform pancreaticoduodenectomy in patients with gastrinomas exists only for those with large lesions in head of pancreas not amenable to enucleation, bulky proximal disease, multiple duodenal lesions, and clinically involved regional lymph nodes.

The role of parietal cell vagotomy simultaneous with resection of the primary lesion is controversial. With use of PPIs as well as in the absence of primary gastrin-secreting tumor, acid-reducing surgical procedures have fallen out of favor. However, the long-term effects of chronic PPI therapy have not been well-elaborated, and the financial burden of approximately \$3,300 per year is not inconsequential [44]. In response to this, several groups have continued to perform vagotomy at the time of primary tumor resection, and have observed that postoperatively, close to one third of the patients were able to stop antisecretory medications completely [74]. Therefore, selective vagotomy should be considered for patients undergoing surgical exploration for ZES.

Metastectomy, re-excision of locally recurrent lesions, and cytoreductive resections in patients who present with multifocal metastatic disease have all been performed with adequate outcomes. Although no long-term prospective data exist, based on results of smaller scale retrospective studies, at present, it is believed that long-term benefits of aggressive surgical management sufficiently outweigh the potential risks of complications related to this approach, provided the patient is thought to be physiologically capable of tolerating the procedure [44, 71, 75, 76].

CONCLUSION

Zollinger-Ellison syndrome remains a challenging condition more than 50 years after its discovery. Diagnosis should be prompted by high index of suspicion based on clinical presentation, and confirmatory biochemical testing should be performed. Sporadic and MEN-1-associated variants should be distinguished. All patients without contraindication to surgery should undergo surgical exploration following radiological and nuclear localization studies. The optimal approach, open versus minimally invasive, remains the subject of debate; however, it is clear that gastrinoma triangle should be carefully and meticulously explored at the time of surgery, with inclusion of intraluminal duodenal evaluation. Extent of surgical resection, vis-à-vis prophylactic pancreaticoduodenectomy, is controversial; however, current recommendation remains to aim for R0/R1 outcome. Postoperative surveillance should center on biochemical serum testing, and cases of recurrence should be carefully considered for possible reoperation. Further studies with longer follow-up are necessary to conclusively

describe the natural history of this condition, identify factors predictive of recurrence and survival, and make categorical recommendations regarding treatment.

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