Gastrinomas
Medical or Surgical Treatment

Jeffrey A. Norton, MD[a], Deshka S. Foster, MD[a], Tetsuhide Ito, MD, PhD[b], Robert T. Jensen, MD[c,*]

KEYWORDS

• Zollinger-Ellison syndrome • Gastrinoma • Neuroendocrine tumor • Acid secretion • Proton pump inhibitors • Multiple endocrine neoplasia type 1

KEY POINTS

- Zollinger-Ellison syndrome (ZES) is caused by a gastrin-secreting neuroendocrine tumor that results in marked acid hypersecretion.
- All patients with ZES have 2 management problems that must both be dealt with: control of the acid hypersecretion, which causes refractory peptic disease, and control of the gastrinoma, which is malignant in 60% to 90% of cases.
- Twenty percent to 25% of patients with ZES have it as part of the multiple endocrine neoplasia type 1 syndrome that needs to be recognized, as its management differs from sporadic cases (75%–80%).
- Over the years, surgical and medical approaches have played varying roles in the treatment of each aspect of ZES.
- Presently, the roles of medical and surgical approaches are generally complementary; however, in several areas the selective use of one over the other is controversial.

The relationship between surgical treatments and medical treatments in the various management aspects of the Zollinger-Ellison syndrome (ZES) has taken many forms. In some aspects of ZES at different times, only one of these approaches has been used, whereas at other times both are available and used to different extents by different groups; thus, they have had a somewhat adversarial relationship, whereas in other cases they are complementary. The latter is the situation at present in most instances; however, there remain management aspects whereby the exact role of surgery or medical treatment remains unclear and contentious. In this article, these

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[a] Department of Surgery, Stanford University School of Medicine, 291 campus Drive, Stanford, CA 94305-5101, USA; [b] Neuroendocrine Tumor Centra, Fukuoka Sanno Hospital, International University of Health and Welfare, 3-6-45 Momochihama, Sawara-Ku, Fukuoka 814-0001, Japan; [c] Digestive Diseases Branch, NIDDK, National Institutes of Health, Building 10, Room 9C-103, Bethesda, MD 20892-1804, USA
* Corresponding author.
E-mail address: robertj@bdg10.niddk.nih.gov

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aspects are discussed showing changes over time but generally concentrating on the role of each in the current management of ZES.

GENERAL/DEFINITIONS

ZES was first described in 1955 in 2 patients by 2 surgeons at the Ohio State University, RM Zollinger and EH Ellison; 6 additional cases were described by other surgeons in the discussion of this article.[1] A later review of the literature before this time concluded at least 4 cases of probable gastrinomas had been described previously,[2] but it was Zollinger/Ellison who made the critical hypothesis that the gastric acid hypersecretion was due to secretion of the pancreatic neuroendocrine tumor (panNET).[1,2] At present, it is known that ZES is due to the ectopic secretion of gastrin by a neuroendocrine tumor (NET) (gastrinoma) resulting in gastric acid hypersecretion,[3–5] which characteristically causes advanced gastroesophageal reflux disease (GERD) and/or peptic ulcer disease, often refractory in nature.[1,6] The terms *gastrinoma* and *ZES* are frequently used synonymously; however, historically gastrinoma referred to the NET secreting gastrin and ZES to the clinical manifestations of the disease. Numerous tumors, including non-NET neoplasms, synthesize gastrin; in most it is not fully processed to biologically active gastrin-17 to 34; consequently, these do not cause ZES because they do not secrete sufficient amounts of fully processed gastrin and, thus, are generally not called gastrinomas by most clinicians and in most classifications of panNETs.[7,8]

Gastrinomas, like all other functional panNETs (F-panNETs) secreting biologically active peptides causing a functional syndrome (insulinomas, VIPomas, glucagonomas, and so forth), differ from other more common neoplasms (colon, pancreatic adenocarcinomas, and so forth) in presenting to the clinician 2 different treatment problems.[8–11] In each syndrome, the hormone excess state needs to be controlled (ie, gastric acid hypersecretion in gastrinomas) and the tumor itself dealt with, because in all cases except insulinomas, F-panNETs are malignant in greater than 50% of cases (ie, 60%–90% for gastrinomas) (**Fig. 1**A).[8–11] Whereas complete surgical resection would treat both of these problems with one approach, as is the usual case with patients with insulinomas,[10,12,13] unfortunately surgical cure in ZES, even today, is seen in less than 50% of all patients with ZES in most series.[4,14–16] Thus, both treatment of gastric acid hypersecretion and the tumor per se have remained separate treatment problems in most patients with ZES; surgical and medical approaches have played variably important roles in the treatment of each over the years.[4,17,18]

ROLES OF MEDICAL AND SURGICAL TREATMENT IN CONTROL OF GASTRIC ACID HYPERSECRETION IN PATIENTS WITH ZOLLINGER-ELLISON SYNDROME: PAST VERSUS PRESENT

General Points: Acid Hypersecretion

Since the first description of patients with ZES and detailed reports from the original ZES registry and various early series,[1,9,19,20] the morbidity of the devastating effects of uncontrolled acid hypersecretion in patients with ZES has become clear. This result occurs because patients with ZES have on average a basal acid output (BAO) that is elevated 4- to 6-fold and in some patients increased up to greater than 10-fold, combined with an increased maximal ability to secrete acid (MAO) (**Fig. 1**B) due to the stimulatory and trophic effects of chronic hypergastrinemia on the parietal cells, gastric enterochromaffin-like cells, and other gastric mucosal cells.[3,9,21–23] In almost all cases the initial clinical symptoms of patients with ZES are due to the effects of acid hypersecretion, with pain due to peptic ulcer disease (73%–98%), heartburn