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Gastrinomas: Medical or Surgical Treatment

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Synopsis

This article reviews the role of surgical and medical management in patients with Zollinger-Ellison syndrome (ZES) due to a gastrin-secreting neuroendocrine tumor (gastrinoma). It concentrates on the status at present but also briefly reviews the changes over time in treatment approaches. Generally, surgical and medical therapy are complementary today; however, in some cases such as patients with ZES and Multiple Endocrine Neoplasia type 1 the treatment approach remains controversial.

Keywords

Zollinger-Ellison syndrome; gastrinoma; neuroendocrine tumor; acid secretion; proton pump inhibitors; Multiple Endocrine Neoplasia-type 1

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, while at other times both are available and used to different extents by different groups and 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 where the exact role of surgery or medical treatment remains unclear and contentious. In this article, these aspects will be discussed showing changes over time, but generally concentrating on the role of each in the current management of ZES.

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I. General/Definitions

ZES was first described in 1955 in two patients by two surgeons at Ohio State University, RM Zollinger and EH Ellison, and 6 additional cases were described by other surgeons in the discussion of this article[1]. A later review of the literature prior to 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 endocrine 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(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, and in most it is not fully processed to biologically active gastrin-17–34; however, 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 NETs (F-panNETs) secreting biologically-active peptides causing a functional syndrome (insulinomas, VIPomas, glucagonomas, etc.) differ from other more common neoplasms (colon, pancreatic adenocarcinomas, etc) in presenting to the clinician two different treatment problems [8–11]. In each syndrome, the hormone excess-state needs to be controlled (i.e. gastric acid hypersecretion in gastrinomas) and the tumor itself dealt with, because in all cases except insulinomas, F-panNETs are malignant in >50% of cases (i.e. 60–90% for gastrinomas)(Figure 1A) [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 <50% of all ZES patients in most series [4, 14–16]. Thus, both treatment of the gastric acid hypersecretion and the tumor *per se* have remained separate treatment problems in most ZES patients, and surgical and medical approaches have played variably important roles in the treatment of each over the years [4, 17, 18].

II. Roles of medical and surgical treatment in control of gastric acid hypersecretion in ZES patients: Past vs present

II.A. 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], it the morbidity of the devastating effects of uncontrolled acid hypersecretion in ZES patients has become clear. This occurs because ZES patients have on the average a basal acid output (BAO) 4–6-fold elevated and in some patients up to >10 fold increased, combined with an increased maximal ability to secrete acid (MAO) (Figure 1B) due to the stimulatory and trophic effects of chronic hypergastrinemia on the parietal cells, gastric enterochromaffin-like (ECL cells) 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 the acid hypersecretion, with pain due to peptic ulcer disease (73–98%), heartburn (52–56%-recent series), diarrhea (60–75% recent series), weight loss (7–53%) and symptoms due to the complications of the acid hypersecretion (bleeding, strictures, perforation, penetration) [6]. These early studies as well as later studies have taught clinicians that ZES patients require control of the gastric acid hypersecretion at all times, both acutely when first seen and long-term [9, 16, 24–27].

II.B. Past-control of acid hypersecretion: medical vs surgical

Initially, medical therapy had no role in the control of acid hypersecretion in ZES patients, with anticholinergic drugs, radiation, and other drugs, being ineffective [9, 28]. Surgery, ultimately only total gastrectomy (i.e., removal of the primary target for gastrin) proved to be the only effective treatment in most patients, because it was not possible to surgically cure the patients in most cases by removing the gastrinoma resulting in long-term cure [4, 9, 25, 29, 30]. Thus, a surgical approach was the only effective treatment for the gastric acid hypersecretion until the development of histamine H2-receptor antagonists in the 1970's [9, 31, 32].

The histamine H_2 receptor antagonists (metiamide, cimetidine, ranitidine, nizatidine, famotidine, etc.) were all effective in different series at reducing the acid hypersecretion, but results in different series reported a 0–60% failure rate [18, 26, 31–33], which was primarily due to a failure to use established criteria for acid control and to titrate the dose in different patients [18, 24]. The NIH studies demonstrated that if sufficient drug was used to control the acid hypersecretion to <10mEq/hr prior to the next drug dose (<5mEq/hr if patient had previous gastric acid-reducing surgery), then in 100% of the patients acid secretion could be controlled, and peptic lesions both healed and the development of new ones prevented [18, 26, 27, 31, 33]. Unfortunately, in many patients this took high, frequent doses of the histamine H_2 receptor antagonists, and it was true for all members of this class with the dosing only varying by their potency [18, 26, 27, 31, 33]. Similarly, during times of surgery and when patients could not take oral medications, parenteral administration of histamine H_2 receptor antagonists required relatively high doses given by continuous intravenous administration [18]. Furthermore, patients treated long-term with histamine H_2 receptor antagonists required yearly reassessment of acid control and on the average required one dosing change (usually an increase) once per year [18, 33, 34]. Because of the requirement for dose titration in all patients coupled with the decreasing availability of gastric acid analysis in the US and in other countries until the development and availability of proton pump inhibitors (PPIs) in the 1980s[35], both histamine H_2 receptor antagonists and the continued use of total gastrectomy and other surgical products such as parietal cell vagotomy coupled with the use of histamine H_2 receptor antagonists were used by different groups to control acid hypersecretion in ZES patients from 1970s to 1990s[18, 24, 26, 33, 36].

II.C. Present-control of acid hypersecretion-medical vs surgical

At present the pendulum has swung almost 180 degrees from the initial use of only surgical treatments to control the acid hypersecretion in ZES patients to the almost exclusive use of medical therapy. Currently, except for the rare patient (<1%) who cannot or will not reliably take oral medications, PPIs have become the drugs of choice [8, 18, 22, 35, 37]. This has

occurred because PPIs have a long duration of action allowing once or twice a day dosing in most patients, little tachyphylaxis is seen with <1 dosing change per year, and in most patients acid hypersecretion is adequately controlled without requiring dose titration with measurement of gastric acid secretory rates on the drug [17, 18, 22, 31]. All PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rebeprazole) have been shown to be efficacious in ZES for controlling the acid hypersecretion, and PPIs have proven safe and effective for >10 years of treatment and except for low vitamin B_{12} levels in some patients, no side-effects have limited their use [17, 18, 21, 31, 38, 39]. From epidemiological studies on patients without ZES taking long-term PPIs (GERD, idiopathic peptic ulcer disease, etc.) a number of side-effects of PPI have been proposed including bone fractures, dementia, hypomagnesemia, decrease nutrient absorption (vitamin B_{12}, iron, calcium, etc.), interstitial renal disease, various bacterial overgrowths in the gut (clostridia, etc.) and interference with metabolism or absorption of a number of drugs [40, 41]. There are no specific reports of these occurring with increased frequency in ZES patients or limiting further PPI treatment.

In cases where patients cannot take oral medications (i.e., during surgery, surgical recovery, etc) parenteral PPIs have also become the agents of choice because of their potency and long duration of action[18, 42]. They can be given by intermittent intravenous injections which are more convenient than prolonged continuous infusion of histamine H_2 receptor antagonists [18, 42].

Histamine H_2 receptor antagonists remain effective and can be used in the rare patient who cannot take PPIs; however, they are rarely used today because of the need for high doses, frequent dosing, assessment of acid control to determine proper dosing and for continuous infusion with parenteral administration [8, 18].

Although surgery is not the primary method for acute or long-term control acid hypersecretion in ZES patients, it nevertheless plays a long-term role in its effect on gastric hypersecretion post-curative resection of the gastrinoma. As mentioned earlier, cure is generally not possible in >50% of all patients (Figure 2) (discussed in detail in a later section); nevertheless, a significant proportion of patients can be rendered disease-free post-gastrinoma resection [8, 14, 15, 43–47]. There are relatively few studies of the effect of the curative resection on the acid secretory rates, but in a number of reports a proportion of disease-free patients are able to stop or significantly decrease all antisecretory drugs [8, 14, 15, 43–46, 48]. Four detailed prospective studies [42, 48–50] of the effect of curative resection of the gastrinoma on disease-free status have been reported and provided some important findings. First, post-curative gastrinoma resection, the mean BAO decreased by 75%, the MAO by 50%, and remained at similar levels for up to 4 years. Second, even though the BAO and MAO markedly decreased post-curative resection, 67% of patients continued to show mild hypersecretion for up to 4 years even though the patients remained disease free (normal fasting serum gastrin levels, negative imaging, negative secretin tests)(Figure 3A). Third, post-curative resection the ranitidine daily dose could be reduce by 66%, and 40% of patients could be removed from all antisecretory drugs. These results demonstrate that curative resection of the gastrinoma has a profound effect on the acid secretory rates, although some patients continue to show mild-moderate hypersecretion and require low doses of antisecretory drugs by an unknown mechanism at present, even though cured.

III. Roles of medical and surgical treatment in treatment of sporadic gastrinoma: Past vs present

III.A. General points: treatment directed at gastrinoma

Most patients with ZES have a sporadic, non-inherited form (75–80%), whereas the remainder (20–25%) have it as part of the Multiple Endocrine Neoplasia type 1 syndrome (MEN1/ZES), an autosomal dominant disorder [51, 52]. This distinction is important for many aspects of the treatment, both directed at the acid hypersecretion and the gastrinoma itself [51–53]. In this section, treatment directed at the gastrinoma in sporadic cases will be discussed, and in a later section the special aspects in the use of surgical or medical approaches for the treatment of MEN1/ZES will be considered, a number of which are contentious [16, 53–56].

Initially, it was thought that almost all sporadic gastrinomas occurred in the pancreas, similar to insulinomas; however, it is now established that most (60–95%) occur in the duodenum and in recent series they are 3–9-fold more frequent than pancreatic gastrinomas [15, 45]. Duodenal and pancreatic gastrinomas differ in their biological behavior in that both are associated with frequent lymph node metastases (30–70%) [16, 57, 58] ; however, the pancreatic tumors have a much higher rate of liver metastases[57, 58], which is one of the primary determinants of long-term survival (Figure 1A), with the result that patients with pancreatic gastrinomas have a worse prognosis [57–59]. Sporadic gastrinomas as a group are malignant in 60–90% of cases, and approximately 13–53% (mean-34%) of patients have liver metastases at presentation, with the majority being diffuse liver involvement [57–60].

III.B. Past-treatment directed at sporadic gastrinoma: nonsurgical vs surgical approach

With the increased ability to medically control acid hypersecretion in sporadic ZES patients, since the 1980's attention has shifted increasingly to the possible role of surgery for curative resection. Initially, a number of authorities recommended a non-operative approach in sporadic ZES patients with either small or no tumors imaged [61, 62]. This was based on the fact that patients at that time were rarely cured, and in 30–60% of patients no gastrinoma was found at surgery [9, 61, 62] and because these patients generally did very well with long-term acid suppression alone [61, 62]. This situation occurred primarily because it was not yet clear that most of the sporadic gastrinomas were in the duodenum, and that only with a careful search for these could they be found (mobilization of duodenum, duodenotomy, transillumination of duodenum) [45, 63–66], because they were often <1 cm in diameter [45, 57, 67](Figure 4A.). Furthermore, it was not appreciated in MEN1/ZES patients the gastrinomas were also in the duodenum, the imaged pancreatic tumors were usually NF-panNETs, and that these patients could rarely be cured because of the multiplicity of the duodenal gastrinomas (Figure 2) without aggressive resections such as a Whipple resection, which was not routinely recommended [8, 14, 15, 53, 56, 68].

III.C. Present-treatment directed at sporadic gastrinoma: nonsurgical vs surgical approach

In direct contrast to the treatment of the gastric acid hypersecretion in sporadic ZES which has changed from surgical to largely medical, the approach to the tumor has changed in most

centers, and became increasingly surgical, with decreasing numbers of patients with potentially resectable sporadic disease followed medically with control of acid hypersecretion only. All existing guidelines including ENETs, NANETs, ESMO's and the NCCN [8, 12, 13, 69, 70] recommend that in sporadic ZES surgical resection should be carried out, if possible complete tumor removal can be performed, and there are no accompanying medical conditions limiting life expectancy or increasing surgical risks to unacceptable levels.

This change in approach to the sporadic gastrinoma to an increasing surgical option, whenever possible, has occurred for a number of reasons. First, acid hypersecretion can now be well-controlled throughout the surgical period, whereas in the past, the lack of effective medical therapies for this, resulted in mortalities as high as 30% [9, 25, 30]. Second, tumor imaging modalities (discussed below), have markedly improved in sensitivity making it possible to better localize the primary and stage the disease, preventing unnecessary surgery [8, 54, 71]. Third, more recent surgical studies have demonstrated increasing disease-free rates approaching 40–63% of patients operated on without Whipple resections [44–47, 58](Figure 2), and higher in patients with Whipple resections [15, 72]. Fourth, importantly, two studies [73, 74] have provided evidence that surgical resection in sporadic ZES leads to a decreased rate of the development of liver metastases, which are the most important determinate of long-term survival [57–59] (Figure 1A), while also one study [74] demonstrated increased disease-related survival with surgery. Fifth, the surgical approach to find duodenal gastrinomas has been studied and demonstrated that specific techniques are needed to find this tumor (duodenotomy, mobilization of duodenum, intra-operative transillumination of duodenum in some cases) [45, 63–66](Figure 4A). Sixth, a recent study demonstrates that even in patients with sporadic ZES with negative preoperative imaging studies, an experienced surgeon will find gastrinoma in 98% of the patients with 50% rendered disease-free, which is not different from the results in patients with positive imaging preoperatively [44] (Figure 4B). Seventh, the importance of routine lymphadenectomy in sporadic ZES has been emphasized in number of studies and is now routinely recommended. The presence of 'lymph node primary gastrinomas' is controversial, even though a number of studies have reported long-term (up to 20 years) with disease free survival post resection of only a lymph node [75–78]. Studies have reported increased disease-free survival when lymph nodes are routinely resected in sporadic ZES patients [47]. Furthermore, in two studies[14, 77] the recurrence or relapse rate after achieving disease-free status post-resection of a primary lymph node gastrinoma was lower than that after resection of a duodenal or pancreatic primary. Therefore, routine removal of lymph nodes can not only increase the disease-free survival rate, but the number of positive lymph nodes or the lymph node ratio has important prognostic significance in gastrinomas and other panNETs[12, 79–83].

III.D. Present-surgical treatment directed at sporadic gastrinoma-controversies

Despite the general recommendation that patients with sporadic ZES should undergo surgical resection if possible, there are a number of specific areas in the surgical management that are controversial. In addition to the question of primary lymph node gastrinomas, which were discussed in the previous paragraph, other areas of controversy include: the role of Whipple resection (cephalic pancreaticoduodenectomy); the role of

laparoscopic surgery in patients with sporadic gastrinomas; the role of surgical resections in patients with advanced disease or disease possibly involve mesenteric blood vessels; and the extent/timing of imaging in patients without tumors on cross-sectional imaging pre- or post-surgical procedures.

Currently, in the different guidelines the preferred approach if possible is enucleation, local resection for pancreatic head lesions or distal pancreatectomy when necessary for distal pancreatic lesions [8, 12, 13, 69, 70]. Whipple resections are generally reserved for large pancreatic head or duodenal lesions which are unable to be adequately removed with enucleation [8, 12, 13, 15, 69, 70]. One of the main problems with rendering patients disease-free is that lymph node metastases are found in 30–70% of cases and are therefore often missed without more extensive surgery such as a Whipple resection. Studies support an increased disease-free rate with Whipple resection [15, 72], but because of possible long-term complications, coupled with the excellent prognosis of patients who are not cured but with small residual disease, more aggressive general use of Whipple resections is currently not generally recommended [8, 12, 13, 69, 70].

Laparoscopic surgery is increasingly being used in patients with panNETs, especially those with localized insulinomas, NF-panNETs and in MEN1 patients with panNETs [84–89]. In contrast to these other panNETs, only a small number of patients with gastrinomas have been treated with laparoscopic surgery [16, 84, 87, 90–92]. This is in large part due to the need for an extensive exploration with a Kocher maneuver, duodenotomy (Figure 4A), routine lymphadenectomy, exploration of the gastrinoma triangle and liver as well as biliary system, required in patients with ZES [16, 55].

Similar to other advanced NETs, the role of surgical resection in ZES patients with advanced metastatic disease or even with extensive invasive localized disease is not well-defined. Unfortunately, most patients presenting with hepatic metastases with gastrinomas have metastases in both hepatic lobes, with only 5–15% have localized hepatic metastases [57, 58, 60]. If imaging studies support the resectability of the metastases, then surgical resection is generally recommende, if the patient is an operative candidate without other medical conditions precluding surgery [8, 12, 43]. Similarly, if most or all imaginable disease is thought surgically resectable, surgery is generally recommended [8, 12, 43]. Patients with gastrinomas as well as other malignant panNETs/NETs not uncommonly present with local invasion and/or vessel encasement or possible involvement, which has led them to frequently not being considered surgical candidates [93]. A few recent studies have challenged this thinking[93–95]. One recent study [93] demonstrated 17% of all gastrinomas fall into this category demonstrating possible major vascular involvement (Figure 5), and in 42 patients a panNETs could be resected with only 9 patients requiring vascular reconstruction, 30% showed long term disease-free status and post-resection the patients had a 10-year survival of 60%. This result [93] led the authors to conclude that surgical resection of panNETs with vascular abutment/invasion is indicated and generally successful without requiring vascular reconstruction, and thus should not be a contraindication to surgery.

Originally, cross-sectional imaging studies (CT, MRI, ultrasound) were primarily used to attempt to localize the primary tumor and establish the extent of the tumor involvement in

ZES patients. Even with dramatic improvements in sensitivity, most small gastrinomas (<1–1.5cm) were missed[10, 60, 96, 97] and other approaches were increasingly used such as functional studies assessing gastrin gradients either after selective portal venous sampling or hepatic venous sampling after selective intra-arterial secretin injection [60, 98, 99] which had sensitivities of 71–86%. The development of somatostatin receptor imaging (SRI) utilizing the fact that gastrinomas, similar to most NETs, overexpress somatostatin receptors (primarily sst 2), has largely replaced functional imaging studies such as gastrin sampling [8, 16]. Initially, ^{111}In-penetreotide was used with SPECT/CT imaging and shown to be more sensitive that any cross-sectional imaging study to allow whole body scans at one time and to be the most sensitive modality for localizing distant metastases in patients with advanced ZES [12, 16, 100–102]. Recently, this is being replaced by ^{68}Ga-DOTA-somatostain peptide PET/CT which has even greater sensitivity and is now approved for use in both the US and Europe [71, 96, 103, 104]. Endoscopic ultrasound (EUS) is the most sensitivity modality for detecting intra-pancreatic lesion, but its utility is limited in patients with sporadic ZES because the majority of the gastrinomas are duodenal and these are missed on EUS [8, 15]. In general, almost all patients with sporadic ZES undergo a conventional imaging study and it is recommended that they also should have SRI, preferably with ^{68}Ga-DOTA-somatostain peptide PET/CT, especially if a surgical procedure is considered.[12, 16, 71, 96]. At present, the best timing of imaging tests post-surgically is not established or whether they will be more sensitive than functional studies (i.e., assessing serum gastrin, secretin testing) in detecting recurrences postoperatively in ZES patients.

IV. Roles of medical and surgical treatment in treatment of MEN1/ZES: Past vs present

IV.A. General points: Treatment of MEN1/ZES

The 20–25% of patients with ZES due to MEN1(MEN1/ZES) have a number of specific problems due to the presence of the MEN1 that affect the medical and surgical treatments[51–53, 55]. MEN1 patients characteristically develop hyperplasia/tumors of multiple endocrine organs with 98–100% developing multiple parathyroid adenomas with hyperparathyroidism, 80–100% developing panNETs and 50–60% pituitary adenomas [51–53, 55]. For the panNETs, 80–100% develop microscopic NF-panNETs (0–13%-symptomatic), and 54% develop MEN1/ZES (range 20–61%), while insulinomas occur in 18%(range 7–31%) with the other F-panNET syndromes occurring <3% [51–53, 55]. These patients also developed tumors in other organs to a lesser extent including adrenal adenomas/carcinomas (27–36%), carcinoid tumors [bronchial/lung (0–8%), gastric (7–35%), thymic (0–8%%)], nonendocrine tumors of the skin [angiofibromas/collagenomas (60–90%)], central nervous system tumors [meningiomas, schwannomas, ependymonas](0–8%), and smooth muscle tumors (1–7%-leiomyomas/leiomyosarcomas) [51, 55, 105]. Characteristically, these patients present with hyperparathyroidism; however, in some recent series up to 33% present with F-panNETS [52, 106, 107].

The specific features of MEN1 create a number of unique problems in the medical and/or surgical management of the ZES in these patients. First, the hyperparathyroidism can affect the activity of the hormone excess state of the F-panNET such as gastrin/acid secretion and

the control of the acid hypersecretion in MEN1/ZES [18, 108–110](Figure 3B). Second, microscopic NF-panNETs are present in all MEN1 patients and in up to 80% larger sizes, and thus not only may require treatment but their presence, complicates the localization of the gastrinoma [51, 53, 54, 111]. In 85–100% of MEN1/ZES patients in different series the gastrinomas occur in the duodenum; however, in a minority of patients (0–15%) they are reported in the pancreas [51, 53, 112–114]. Third, in MEN1/ZES patients the duodenal gastrinomas are almost always multiple, frequently small (<0.5cm), and associated with lymph node metastases in 40–60% [53, 113, 115]. The result of this is MEN1/ZES patients cannot be cured of all their NF-pNETs or gastrinomas (Figure 2) without aggressive resections such as Whipple resection [51, 53, 54]. In contrast, other F-panNETs in MEN1 patients (insulinomas, glucagonomas,etc) are generally curable [51, 53, 116]. Fourth, the natural history of MEN1 patients is changing; however, it is at present largely unknown although the mean age at death is still shortened at 55–60 years old in a number of studies [53, 105, 117]. MEN1 patients are now rarely dying of acid hypersecretion due to MEN1/ZES, which was a major cause of death in early series [52, 53, 105, 117]. However, other tumors such as thymic carcinoids are now increasingly described in MEN1 patients, especially males, and are aggressive and an increasing cause of death [53, 105, 117]. The lack of the long term natural history is particularly important for NF-panNETs and gastrinomas, because in many cases these patients are treated without surgery, as discussed below.

IV.B. Present-specific aspects of control of acid hypersecretion in MEN1/ZES-medical vs surgical

In general, the management of acid secretion in MEN1/ZES patients follows the patterns discussed in paragraphs II.A-II.C above in patients with sporadic ZES, with initially only a surgical approach with total gastrectomy being effective, to later, where an increasing medical approach has been used, with first histamine H_2 receptor antagonists and still later PPIs were increasingly used. At present, as for sporadic ZES, the drugs of choice both for control of the acid hypersecretion in MEN1/ZES patients are PPIs [8, 11, 13, 18].

However, surgery still can play an important role in facilitating control of the acid hypersecretion in MEN1/ZES patients. In contrast to the situation in patients with sporadic ZES where acid hypersecretion could be markedly altered by curing a significant number of patients, cure is rare in MEN1/ZES without aggressive resections, which are not routinely recommended in any current guidelines (ENETs, NANATES) [12, 51, 69]. Surgery can play a role in facilitating the control of acid hypersecretion in MEN1/ZES patients by correcting the hyperparathyroidism by an appropriate parathyroidectomy (i.e. 3.5 gland or 4-gland removal with a parathyroid implant) [51, 52, 108, 110](Figure 2B). From acid secretory studies in patients with MEN1/ZES with hyperparathyroidism, increased relative resistance to the effects of antisecretory drugs have been reported, and higher drug doses than in sporadic ZES patients are frequently required [118]. Calcium is a potent stimulating of gastrin release from gastrinomas [119], and number of studies report that in patients with MEN1/ZES with hypercalcemia due to the hyperparathyroidism, when the hyperparathyroidism is corrected they have a decreased magnitude of hypergastrinemia (sometimes gastrin levels return to normal), a decrease in secretin-stimulated gastrin release, and an increase in sensitivity to anti-secretion drugs (Figure 2B) [108, 112, 120].

IV.D. Present-treatment directed at MEN1/panNET/gastrinoma: nonsurgical vs surgical approach

At present this is an area of considerable disagreement between a surgical and nonsurgical approach. Whereas all agree that patients with F-panNETs with MEN1, excluding gastrinomas, should undergo routinely surgical exploration because of their high (>90–100%) cure rate, this is not the case with patients with gastrinomas or with NF-panNETs [12, 13, 51, 53, 116]. As stated above, gastrinomas/NF-PanNETs are almost always multiple and often small in size (<0.5 cm) and thus they are rarely curable unless aggressive resections are performed, such as Whipple resections or even total pancreatectomy with NF-panNETs [15, 51, 53, 121, 122]. This fact, coupled with increasing evidence that patients with PanNETs or with MEN1/ZES with small tumors (<1.5–2cm) have an excellent long-term prognosis without surgery [8, 51, 53, 54, 121, 123, 124](Figure 6), has led to the current controversy on their treatment. Additional points that contribute to this controversy is that these patients frequently present at younger ages than seen with sporadic forms of these tumors, and are often asymptomatic in the case of NF-panNETs. Not only are these resections associated with morbidity/mortality, long-term complications can occur. Also, recent studies report patients with MEN1 have an increased incidence of diabetes/glucose intolerance which are not uncommon after pancreatic resections, reported in 24–86% of MEN1 patients post-resection and 17–25% after pancreaticoduodenectomy[53].

Current recommendations from a number of societies including ENET, NANETs and the Endocrine Society [8, 12, 13, 125] recommend that small panNETs (<1.5–2m) in patients with NF-pNETs or MEN1/ZES be treated conservatively. All agree that if patients with these small panNETs are treated conservatively it is important that they be closely monitored. How to best monitor these small pancreatic NETs in MEN1 patients is also an area of contention [54]. Cross-sectional imaging studies will miss >50% of lesions <1.5 cm; however, SRI has greater sensitivity, but it is not established to be reliable for assessing serial changes in tumor size, and the issue of repeated radiation exposure can be a factor in these patients [53, 54]. Numerous studies show that for intrapancreatic NETs such as NF-panNETs, EUS is the most sensitive modality for their detection, and allows accurate assessment of changes in NET size on repeated examinations [54, 89, 126–128]. Serial studies show that most panNETs in MEN1 patients <2 cm are relatively stable and uncommonly increase rapidly in size [54, 127, 129–131]. In MEN1/ZES with imaged NETs <2cm the role of EUS is much more limited because these NETs are not intrapancreatic and often missed by EUS, and thus they are usually followed by repeated cross-sectional imaging studies [54]. Although recent studies demonstrate that ^{68}GaDOTATOC-PET/CT is much more sensitive for detecting lesions in MEN1 patients than cross-sectional imaging, at present its exact role initially and in follow-up is unclear and controversial in MEN1 patients [54, 132–135].

One of the most pressing problems is to identify predictors for which patients with NF-panNETs or gastrinomas will pursue an aggressive course in MEN1 patients [53, 105, 136]. Although numerous factors (both clinical and tumoral features) have been reported to have prognostic value in MEN1 patients for the development of a panNETs or their aggressive behavior, similar to patients with sporadic panNETs, in general they are not particularly helpful in a given patient [51, 59, 105, 136–139]. In sporadic panNETs, the WHO grading has

been shown to have important prognostic value[12, 140, 141]. Preliminary studies in MEN1 patients suggest that the histological grade of the tumors has predictive value; however, the majority (>80%) are G1 and some of these can also pursue an aggressive course [142]. Recently, the predictive value of using ^{18}F-FDG-PET/CT has been proposed for patients with MEN1 with panNETs [143]. Numerous studies demonstrate that in most well differentiated NETs (G1, G2) the ^{18}F-FDG PET/CT is negative, but in a proportion it is positive and this correlates with aggressive behavior [71]. In the above recent study[143] in 49 patients with MEN1 undergoing ^{18}F-FDG PET, 6/8 patients (75%) with FDG-avid panNETs harbored aggressive or metastatic NETs, compared to only 1/41(2.4%) without FDG avidity for a sensitivity of 86%, specificity of 95% for identify aggressive panNETs. Although a few genotype-phenotype correlations with prognostic value have been reported in patients with MEN1 with panNETs including: mutations in JunD, CHES1, truncation mutations in the N- or C-terminal of the MEN1 gene, missense mutations in the MEN1 gene) and the *CDNK1B* V109G polymorphism, they have not well studied prospectively and are not widely used at present[131, 139, 144–148].

A laparoscopic approach is being increasingly used in MEN1 patients with insulinomas, other localized nongastrinoma panNETs and NF-panNETs, but is not generally used in patients with MEN1/ZES, except the occasional patient with a gastrinoma limited to the pancreatic tail [86, 89, 149]. In a meta-analysis [150] i of pancreatic distal resection for all indications, the laparoscopic approach resulted in a lower complication rate, less blood loss, and shorter hospital stays; however, the rate of development of postoperative fistulas was similar. Whereas the results in MEN1 patients are more limited, the available results support the conclusions that minimally-invasive approaches in MEN1 patients with the panNETs listed above is safe and feasible [86, 89].

V. Roles of medical and surgical treatment in treatment of MEN1/ZES patients with advanced disease

As discussed in section IV above, unfortunately most patients with advanced metastatic disease with MEN1/ZES present with diffuse hepatic metastases and in only a minority (<15%) is surgical resection (i.e., generally, removal of least 90% of the disease) possible and recommended [13, 57, 75, 124, 151]. The patients with advanced metastatic disease that is nonresectable and that is progressive have a decreased survival (Figure 1, Figure 6) and thus require treatment which involves a number of possible anti-tumor nonsurgical approaches. These include: medical therapy (everolimus, or tyrosine kinase inhibitors such as sunitinib), peptide radioreceptor therapy (PRRT) with ^{177}Lu-labeled somatostatin analogues (which will likely be approved by the FDA this coming year based on a recent successful phase 3 trial in GI midgut NETs[152]), chemotherapy or liver-directed therapies (embolization, chemoembolization, radioembolization). These treatments are similar to that in other advanced NETs and are not specific for MEN1/ZES and have been recently reviewed in other publications [153–157], so will not be dealt with further in this article.

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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 two management problems which must both be dealt with: control of the acid hypersecretion which causes refractory peptic disease, and control of the gastrinoma which is malignant in 60–90% of cases.
- 20–25% of patients with ZES have it as part of the MEN1 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.

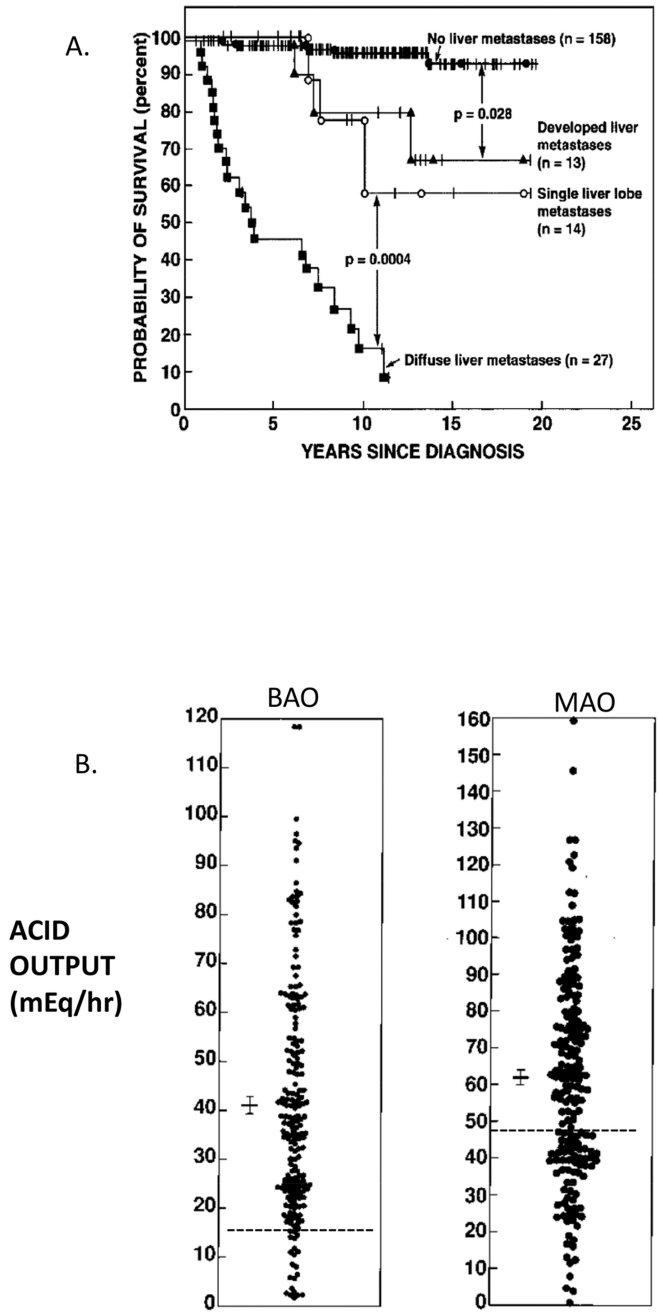
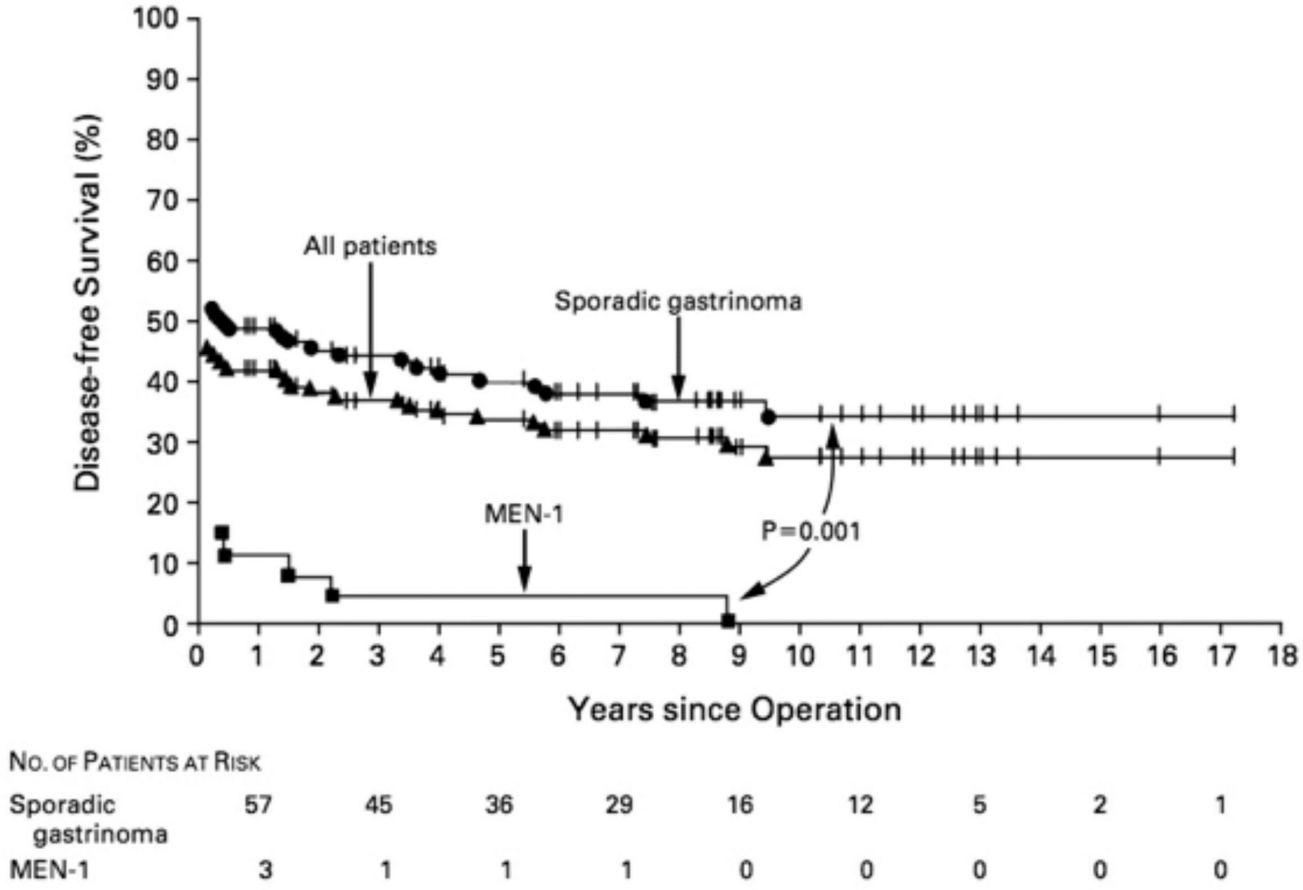


Figure 1.

Extent of disease effect on survival and acid hypersecretion in ZES patients. Panel A. Shown are results from 212 ZES patients prospectively followed.. Panel B. Results are from 205 ZES patients without previous gastric acid recuing surgery. Each point represents data from one patient. The dotted line is the upper limit of normal. The mean ± SEM is shown for each.

Data from Refs 3, 15 and 58.



No. of Patients at Risk									
Sporadic gastrinoma	57	45	36	29	16	12	5	2	1
MEN-1	3	1	1	1	0	0	0	0	0

Figure 2.

Disease free survival post-surgery (enucleation, resection) in patients with ZES with or without MEN1. Data are from 123 patients with sporadic ZES and 28 patients with MEN1/ZES. Patents were treated by a fixed protocol involving enucleation of tumor, local tumor resection, and distal pancreatectomy where indicated, but without Whipple resections. *Adapted from* Norton JA, Fraker DL, Alexander HR et al. Surgery to cure the Zollinger-Ellison syndrome. N Engl J Med 1999;341:635–644; with permission.

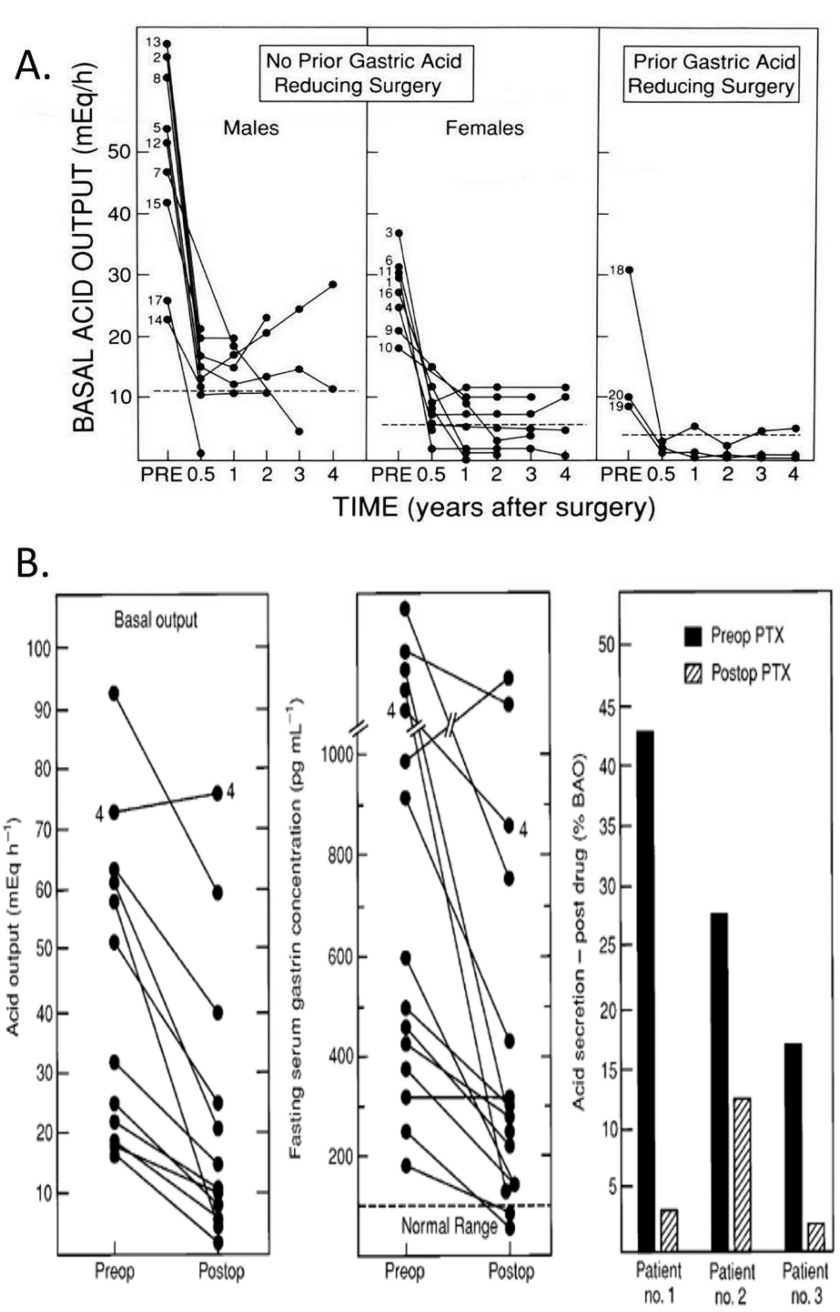


Figure 3.

Effect of curative gastrinoma resection on basal acid hypersecretion(BAO) (Panel A) and effect of parathroidectomy (Panel B) on basal acid hypersecretion, fasting serum gastrin levels and responsiveness to antisecretory drugs in MEN1/ZES patients with hyperparathyroidism.

Panel A. Shown are results from 20 patients surgically rendered disease-free. Mean preoperative BAO was 39 mEq/hr, and the mean serum fasting gastrin 1020 pg/ml (nl<100). By 3–6 mos. postoperatively BAO had decreased 75% and remained unchanged. Dotted lines show upper limit of normal in these studies.

*Adapted from Pis*egna JR, Norton JA, Slimak G, et al. Effects of curative resection on gastric secretory function and antisecretory drug requirement in the Zollinger-Ellison syndrome. Gastroenterology 1992;102:767–778; with permission.

Panel B. Shown are results from 10 consecutive MEN1/ZES patients with hyperparathyroidism with basal acid output, fasting serum gastrin levels(FSG), and sensitivity to antisecretory drugs (Histamine H2 receptor antagonists [], determined before and a different times post parathyroidectomy. All patients except patient 4 became normocalcemic post parathyroidectomy. Post parathyroidectomy 9/10 (90%) had a decrease in BAO, and 7/10 showed a decrease in FSG including to normal levels in 2 patients. Acid responsiveness was expressed as the percent of the BAO at a given time after taking the same dose of histamine H_2 receptor antagonist. In each of the three patients studied the given dose of histamine H_2 receptor antagonist caused greater acid suppression post parathyroidectomy.

Adapted from Norton JA, Cornelius MJ, Doppman JL et al. Effect of parathyroidectomy in patients with hyperparathyroidism, Zollinger-Ellison syndrome and multiple endocrine neoplasia Type I: A prospective study. Surgery 1987;102:958–966; with permission.

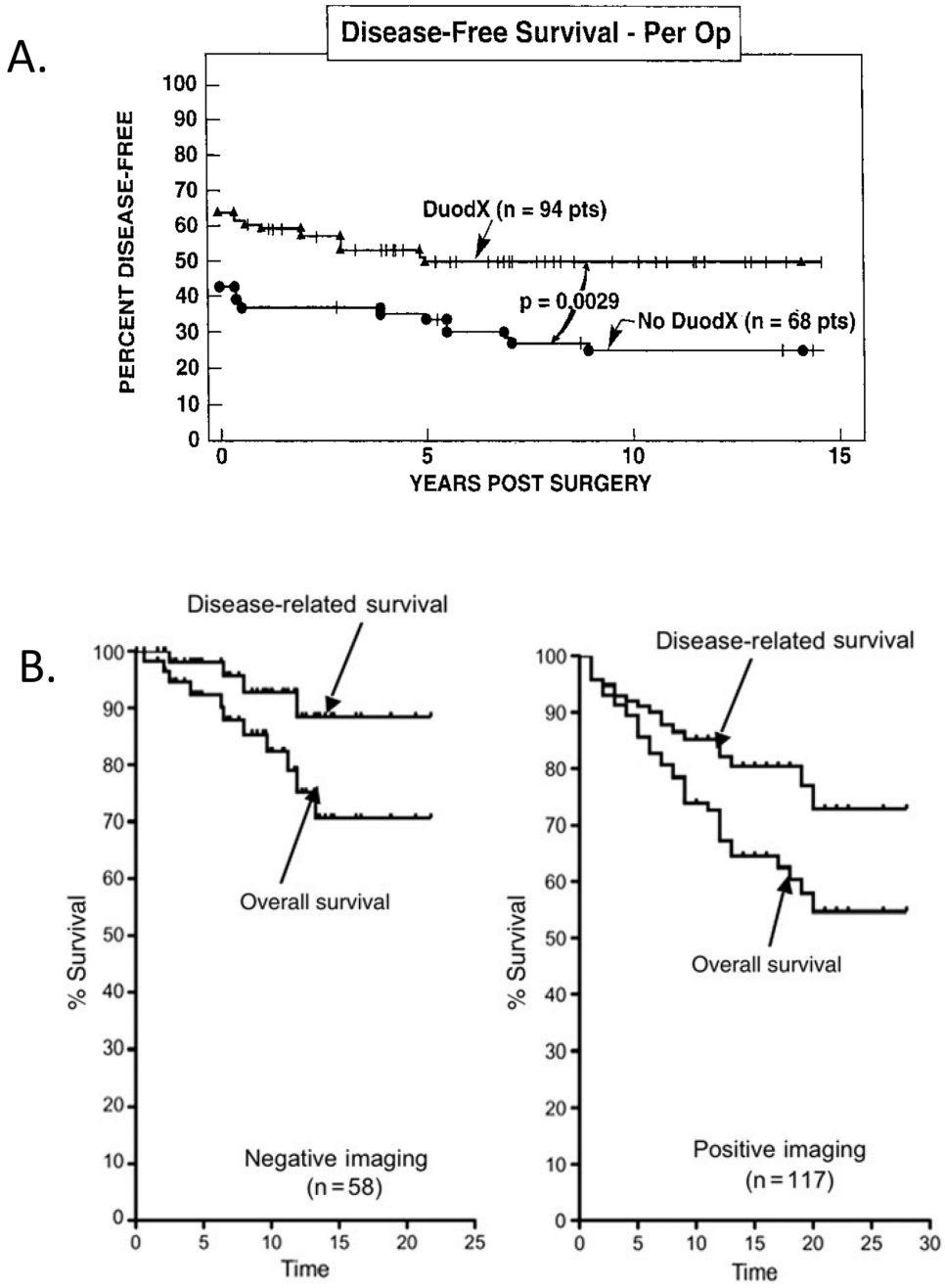


Figure 4.

Results of performing a duodenotomy (Panel A) on disease-free status and results of surgical exploration for possible cure in ZES patients with or without positive pre-operative imaging studies (Panel B). Panel A. Effect of duodenotomy(DUODX) on disease free-status in 142 patients with ZES without MEN1. With DUODX, gastrinomas were found in 98%, duodenal gastrinomas in 62%, and the cure rate postoperatively was 65% compared with patients without DUODX ($p<0.01$) in whom gastrinomas were found in 76%, 18% had duodenal gastrinomas found and 44% were cured post resection. Modified and drawn from data in [45]. Panel B. Surgical results from 117 patients with sporadic ZES with positive imaging are

compared to results in 58 patients with sporadic ZES with negative preoperative imaging. Postoperatively 63% of the patients with negative imaging were disease free postoperatively, whereas it was seen in 54% with positive imaging and at a 20-yr follow-up, the negative imaging patients had a better survival (71% vs 58%), and better disease related survival (88% vs 73%, [p=0.15]).

Adapted from Norton JA, Fraker DL, Alexander HR et al. Value of surgery in patients with negative imaging and sporadic zollinger-ellison syndrome. Ann Surg 2012;256:509–517; with permission.

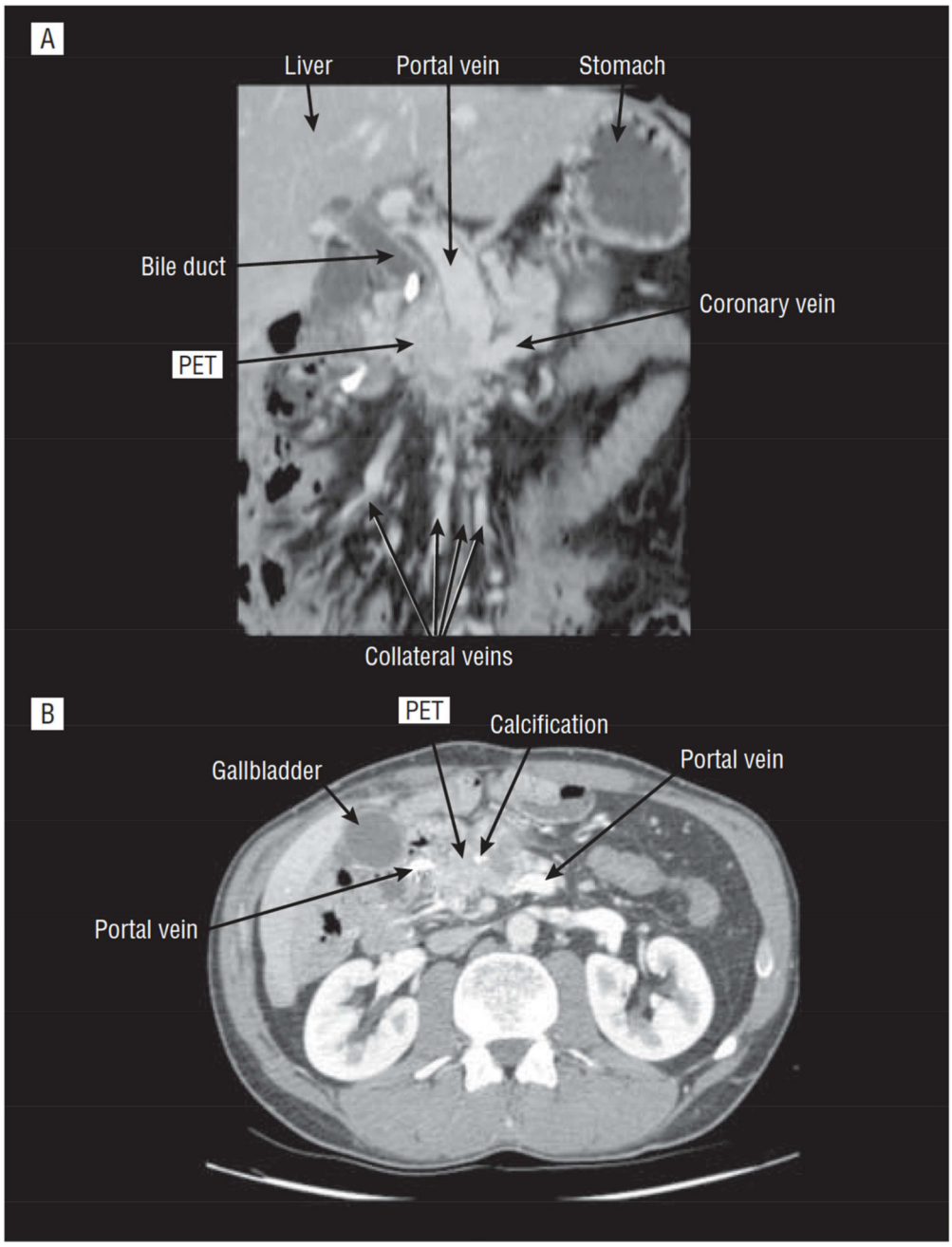


Figure 5.

Imaging results in a patient with a panNET obstructing the proximal portal vein. Panel A shows a coronal planar view and Panel B shows a transverse view of the CT scan. The label PET shows the location of a panNET obstructing the proximal portal vein and with the development of extensive collateral veins. This patient had the tumor and a portion if the portal vein resected with venous reconstruction. This patient is representative af a subgroup of gastrinomas and other PanNET that are thought by many to be unresectable because of the vascular involvement, however a recent study[93] shows most are resectable.

Adapted from Norton JA, Harris EJ, Chen Y et al. Pancreatic endocrine tumors with major vascular abutment, involvement, or encasement and indication for resection. Arch Surg 2011;146:724–732; with permission.

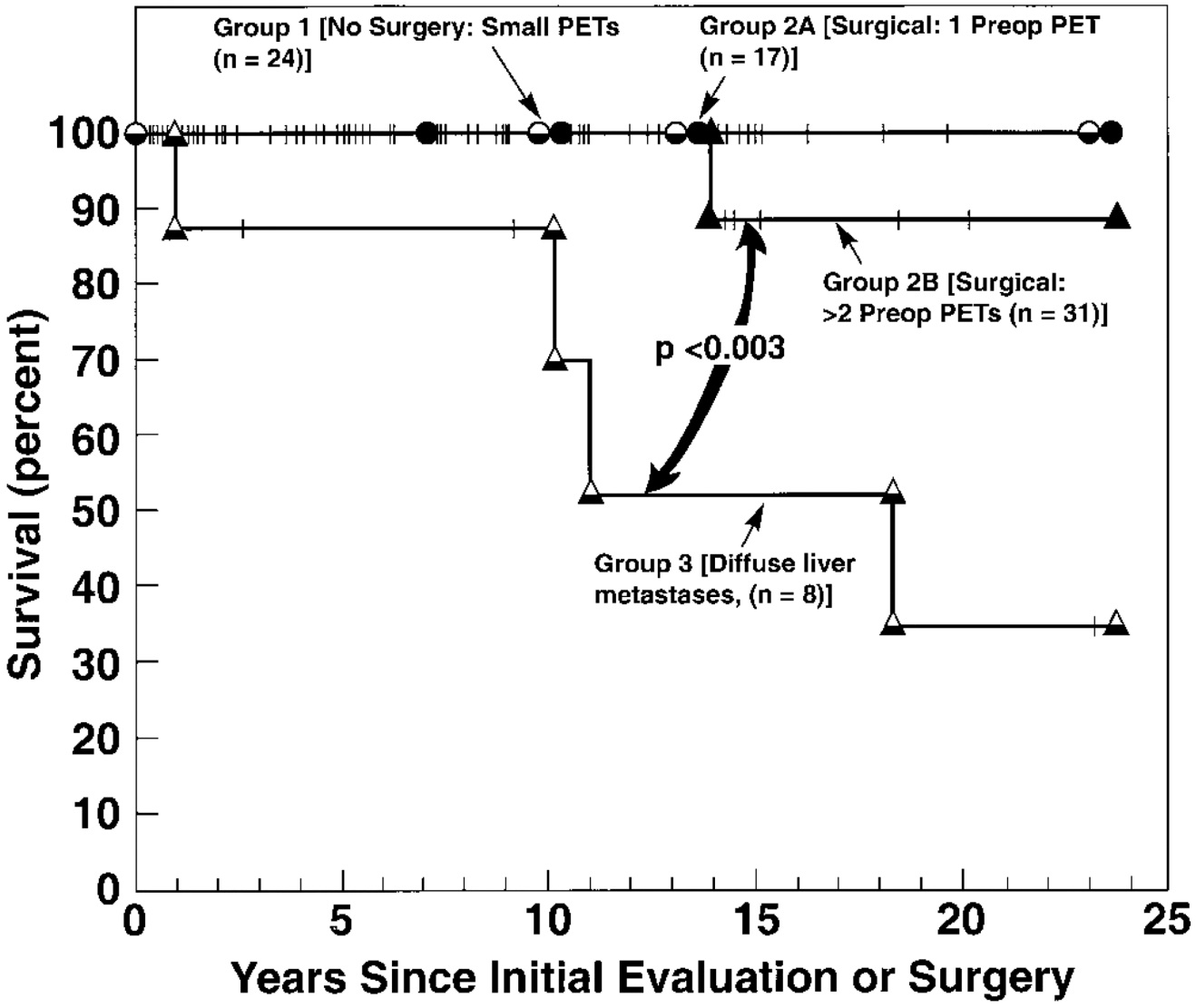


Figure 6.

Survival of different groups of MEN1/ZES patients. Data are for 81 MEN1/ZES patients of which 17 were in group 1(all panNETs imaged preoperative <2.5 cm diameter-no surgery); and Group 3 (n=8) with diffuse liver metastases and no surgical resection. Group 2 consisted of 17 patients in Group 2A with a single panNET (2.5–6 cm in diameter) and Group 2B (n=31) with two or more lesions >2.5 cm, who underwent laparotomy. Group 1, 2A and 2B had similar 15-year survival rates of 89–100%, which was better than patients with diffuse liver metastases in Group 3 (52%). This study concluded that patients with small panNETs<2.5cm with MEN1/ZES can be followed without surgery (15-yr survival=100%) and that patients with larger lesions should have them resected if possible [124].

Adapted from Norton JA, Alexander HR, Fraker DL et al. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 2001;234:495–506; with permission.