Resolved and Unresolved Controversies in the Surgical Management of Patients With Zollinger-Ellison Syndrome

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Objective: Highlight unresolved controversies in the management of Zollinger-Ellison syndrome (ZES).

Summary Background Data: Recent studies have resolved some of the previous controversies including the surgical cure rate in patients with and without Multiple Endocrine Neoplasia-type1 (MEN1), the biological behavior of duodenal and pancreatic gastrinomas, role of imaging studies to localize tumor, and gastrectomy to manage acid output.

Methods: Review of the literature based on computer searches in Index Medicus, Pubmed and Ovid.

Results: Current controversies as identified in the literature include the role of endoscopic ultrasound (EUS), surgery in ZES patients with MEN1, pancreaticoduodenectomy (Whipple procedure), lymph node primary gastrinoma, parietal cell vagotomy, reoperation and surgery for metastatic tumor, and the use of minimally invasive surgical techniques to localize and remove gastrinoma.

Conclusions: It is hoped that future studies will focus on these issues to improve the surgical management of ZES patients.

(*Ann Surg* 2004;240: 757–773)

In 1991,[1] we identified unresolved surgical issues in the management of patients with ZES. Since 1991, there have been studies that have resolved some of these controversies. However, a number still exist. Resolved controversies[1] include determination of percentages with and without MEN1 that are surgically cured (without Whipple resection) (Controversy 1 and 2, 1991),[1] definition of the biologic behavior of duodenal versus pancreatic gastrinomas (Controversy 3, 1991),[1] development of new imaging modalities (Controversy 4, 1991),[1] and defining the role of gastric surgery (Controversy 5, 1991).[1] However, controversies still exist in the role of surgery in both MEN1 (20% to 30%)[2] and sporadic ZES (70% to 80%).[2] Eight issues will be considered: lymph node primary gastrinoma; the role of endoscopic ultrasound (EUS); routine surgery in patients with ZES and MEN1; pancreaticoduodenectomy; routine lymphectomy; parietal cell vagotomy; reoperation; surgery in advanced, aggressive disease; and finally, laparoscopic or endoscopic resection of gastrinomas.

Recently Resolved or Partially Resolved Controversies

Surgical Cure Rate in Patients With ZES and MEN1 (Table 1)

Before 1990, it was not appreciated that the majority of gastrinomas in patients with MEN1 and ZES were located in the duodenum.[1,3,4] This contributed to the low cure rate[1,5–10] and the controversy about routine surgical exploration for cure.[1] Since 1990, our study published in 1999[11] and other studies (Table 1) have demonstrated that the surgical cure rate in these patients is very low (0% to 10%)[11–15] without pancreaticoduodenectomy.

Some[3,16,17] (Table 1) have reported cures; however, they did not include a negative secretin test and normal fasting gastrin levels measured postoperatively. Further, in most of these studies the follow-up was short. Patients develop late recurrences[18,19] and the secretin test and gastrin levels are the most sensitive method to detect recurrence.[18] Further, the role of pancreaticoduodenectomy for cure or improved survival is unclear.

Surgical Cure Rate in Patients With Sporadic ZES (No MEN1)

In patients with sporadic ZES, there was a disagreement on the disease-free rate in patients' postresection.[1] This occurred because most studies had small numbers of patients and follow-up was short and incomplete.[1,20] In 1999, our study was published,[11] which involved 123 patients with a mean follow-up of 8 ± 4 years. In 93% of patients, gastrinomas were found, including each of the last 81. The postoperative cure rate was 60%, 40% at 5 years, and 34% at 10

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TABLE 1. Surgical Cure in Series Since 1990 of Patients With MEN1 and ZES (Nonpancreaticoduodenectomy Results)

Author (Year)	Ref. No.	No. of Patients	% Cured (F/U Time)
Pipeleers-Marichal (1990)	3	4	50% (Immediate; FSG only, no Sec)
Cherner (1992)	240	1	100% (30 y)
Farley (1992)	174	15	0%
Grama (1992)	142	12	67% (Immediately postop) 0% (at 5 y)
Melvin (1993)	241	19	5% (Mean 10 y)
Mignon (1995)	242	36	61% (Immediately postop) 3% (up to 8 y)
Thompson (1997, 1998)	17,130	27	66% (Basal FSG normal) 33% (negative Sec)
Kisker (1998)	78	2	0% (Immediately postop)
Jordan (1999)	23	3	0%
Norton (1999)	11	28	16% (Immediately postop) 6% (at 5 y)
Bartsch (2000)	146	7	42% (0.1–14 y)
Kato (2000)	164	2	100%
Norton (2001)	137	48	19% (Immediately postop) 0% (at 5 y)
Thodiyl (2001)	243	1	0%
Gauger and Thompson (2001)	131	37	62% (Basal FSG only) 33% (neg. Sec)

F/U, follow-up; FSG, fasting serum gastrin levels; Sec, secretin provocative test for ZES[239]; postop, postoperative.

years.[11] These results, coupled with no mortality and low morbidity (<15%) with surgery,[12] strongly supported routine surgical exploration because it was both safe and produced long-term cures in some patients.[21]

Biologic Behavior of Duodenal and Pancreatic Gastrinomas (Table 2)

Studies have provided information on the biologic behavior of pancreatic and duodenal gastrinomas. Studies have shown that both locations are equally malignant (40% to 70% metastases), and the postoperative disease-free rate is similar.[11,22,23] However, duodenal tumors are smaller, less likely to metastasize to liver, and have a better prognosis than pancreatic tumors.[22–29]

Recent studies[22,24] support the hypothesis[27] that there is an aggressive and nonaggressive form of gastrinoma. The aggressive form comprises 24% of patients. It is more common in woman and those without MEN1. It has a short disease duration, higher serum gastrin levels, large pancreatic tumors, liver metastases, and a long-term survival rate of 30% compared with 96% for the nonaggressive form[22,24] (Table 2). This also applies to liver metastases.[30–33] Of 19 liver gastrinomas, 26% demonstrated no growth, 32% had slow growth, and 42% had rapid growth. In patients with rapid growth, 62% died, whereas no other died.[30]

Studies have shown a number of clinical, laboratory, tumoral, flow cytometric, and molecular-biologic features which are predictors of aggressive growth (Table 2) The further definition of these features will likely have a significant impact on the surgical management of NET as additional studies are

performed. Unfortunately, the molecular pathogenesis of gastrinomas is largely unknown.[34–38] Recent studies demonstrate that alterations in 2 tumor suppressor genes, the *MEN1* gene and $p16^{INK4a}$, are frequent in PETs but do not predict aggressive behavior.[34,39–41] Unfortunately at present, none of the abnormalities are sufficiently predictive to allow operative strategy to be affected.

Development of Additional Imaging Modalities That Might Increase Surgical Cure Rate

Although there have been improvements in MRI and CT scanning since 1991, these have not resulted in enhanced detection of small gastrinomas.[42–47] Major advances have been in the use of somatostatin receptor scintigraphy (SRS) and, perhaps, EUS. Whereas the role of SRS is clear,[14,44,47–49] that of EUS is controversial.[45] Gastrinomas express somatostatin receptor that binds octreotide and images tumor.[47,48,50–53] SPECT imaging is necessary for high sensitivity.[50,54–57] SRS allows total body imaging and detection of distant metastases and primary gastrinomas in unusual intra-abdominal locations.[58–62] It is more sensitive than all conventional imaging studies combined.[43,47,50,51] It is also the most sensitive modality for detecting bony metastases.[63,64] The addition of SRS identifies additional tumor that affects management.[47,56,65–67] Unfortunately, SRS misses 50% of small duodenal gastrinomas.[22,26,46,58,68,69] It gives no information on tumor size and exact location of tumor,[46] knowledge of which alters surgical approach. Therefore, a CT or MRI[42,70] is performed with SRS. In the patient seen in Figure 1, CT and MRI are negative, whereas SRS detected tumor in the left hepatic lobe.

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TABLE 2. Characteristics of Aggressive Gastrinomas and PETs

I. Aggressive gastrinomas*
  A. Clinical features
    Occurs in 24% of all patients[22,24]
    Liver metastases present initially (19% all pts), or develop (5% all pts)[22]
    Female gender predominantly (6% vs. 32%, $P < 0.00001$)[22]
    Short disease history at ZES diagnosis (mean, 2.7 vs. 5.9 y, $P < 0.00001$)[22]
    Markedly elevated fasting gastrin (mean, 5157 vs. 1711 pg/mL, $P < 0.00001$)[22]
    Large tumor (>3 cm)[22,24]
    Primarily pancreatic, nonduodenal (92% vs. 34%, $P < 0.00001$)
    Poor survival (10-y survival, 30% vs. 96%, $P < 0.00001$)[22]
  B. Tumor flow cytometric features[244]
    Low % nontetraploid aneuploid
    Multiple stem-line aneuploid frequent (25%) $P = 0.00022$
  C. Molecular biological features (comparing aggressive/nonaggressive)
    High *HER2*/neu expression ($P = 0.032$)[245]
    High 1q LOH (83% vs. 13%, $P = 0.0004$)[246–248]
    Increased EGF receptor expression (43% vs. 6%, $P = 0.034$)[249]
    Equal *MEN1* gene mutation rate ($P = 0.22$)[40]
    p16[INK4a] gene abnormality not predictive[39]
II. All PETs including gastrinomas[31,197,250,251] (prognostic factors for aggressive disease)
  A. Clinical tumoral features
    A.1. Univariate analysis[†]
      Liver metastases ($P = 0.0001$)
      Liver metastases progression ($P = 0.0001$)
      Lymph node metastases ($P = 0.0001$)
      Extranodal/extrahepatic metastases ($P = 0.0001$)
      Local invasion by primary PET ($P = 0.0001$)
      Primary tumor size ≥3 cm ($P = 0.0011$)
      Nonfunctional PET ($P = 0.009$)
      Poor tumoral differentiation ($P = 0.0001$)
      Incomplete tumor resection ($P = 0.0002$)
    A.2. Multivariate analysis[†]
      Liver metastases ($P < 0.00001$)
      Poor tumoral differentiation ($P = 0.0001$)
      Incomplete tumor resection ($P = 0.0007$)
  B. Histological poor prognostic factors[31,197,250,251]
    B.1. All PETs[‡]
      Flow cytometric DNA results (high index of aneuploidy)
      Ag NOR percentage >5%
      Ha-*Ras* oncogene overexpression
      Lack of progesterone receptor immunoreactivity
      Presence of α-HCG immunoreactivity

High expression of proliferating cell nuclear antigen (PCNA)
      Hi Ki 67 index
      p53 Overexpression
    B.2. Nonfunctional PETs[§]
      Tumor size (diameter ≥4 cm) ($P = 0.02$)
      Vascular invasion ($P < 0.001$)
      Perineural invasion ($P < 0.001$)
      Mitosis (≥2) ($P = 0.036$)
      Capsular penetration ($P < 0.001$)
      Ki 67 (>2%) ($P < 0.001$)
      Nuclear atypia ($P < 0.044$)
      Progesterone receptors ($P = 0.007$)
  C. Molecular biologic features[34]
    MEN1 (11q13) LOH presence (21–62%) in 1 study,[252] not 4 others[34,248,253,254]
    p53 Overexpression[34]
    Aberrant hypermethylation (87%) [RASSF1A (75%) > INK4a/p16 (40%)]
    > O[6]–M GMT
    CGH studies/genomic wide allelotyping[‖]/LOH studies
Losses
  1p LOH (34%)[248,256]
  3p LOH (8%-47%)[34,248,253,254]
  3q LOH (8%-41%)[34,257]
  6q LOH (18%-68%)[34,253,254,257]
  22q LOH (96%)[258]
Gains
  7q (16%-68%)[34]
  17q (10%-55%)[34,257]
  17p (10%-50%)[34,257]
  20q (13%-58%)[34,257]

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 *Statistics are in regard to the indicated feature in aggressive versus nonaggressive gastrinomas or PETs.
  [†]Results from Madeira et al,[197] which included 44 nonfunctional PETs, 23 gastrinomas, 7 secreting calcitonin, 4 glucagonomas, 3 insulinomas, 1 somatostatinoma.
  [‡]Results primarily from La Rosa et al[250] and Bordi and Viale.[251]
  [§]Results primarily from La Rosa et al.[250]
  [‖]Results from 9 comparative genomic hybridization studies/genomic wide allelotyping[34,247,253,257,259–263] involving 220 PETs (30 gastrinomas).

At surgery in addition to the liver tumor, a small (0.3 cm) duodenal gastrinoma and an adjacent positive lymph node were found, which were missed by SRS. Despite the value of SRS, it does not increase surgical cure rate. In 37 consecutive patients, the disease-free rate with SRS did not differ from that seen without SRS.[18,46,71] What effect SRS has on surgical approach and results in patients with advanced gastrinomas is also unclear.

Recent studies have reported that helical CT scanning with contrast can detect small PETs and duodenal tu-

mors.[72–76] In one study,[73] it was more sensitive than SRS and localized 4 of 4 duodenal gastrinomas. In our experience and that of others,[68] similar results have not been found.[46]

In terms of intraoperative localization techniques, the major advance since 1990 is the establishment of routine duodenotomy as an essential part of the surgical approach.[14,29] Duodenal gastrinomas are 3 to 10 times more common than pancreatic gastrinomas, small (<1.0 cm in diameter), may be multiple, and have (40% to 70%) lymph node metastases but rarely (5%) hepatic metastases.[11–13,22,23,46,58,68,69,77–80] Numerous studies demonstrate that these small duodenal tumors are best detected by routine duodenotomy and that endoscopic transillumination of the duodenum can be helpful.[12,13,29,58,77,79,81] Although it has been established that significantly more duodenal tumors are found using duodenotomy,[14,25,82] it has not been clearly established that its use increases the surgical cure rate.

Role of Gastric Surgery in Management of ZES

In 1991, this was considered an unresolved issue (Controversy 7).[1] Gastric surgery included the role of total gastrectomy for acid control, total or partial gastrectomy to treat gastric carcinoids which develop in hypergastrinemic states,[83–86] and parietal cell vagotomy. Acid hypersecretion can be controlled in all patients with ZES with proton pump inhibitors.[58,87–90] In one review of 116 patients[88] with ZES, each had acid hypersecretion controlled by omeprazole for long periods. Numerous other studies have similar results with PPIs.[58,89–91] A parenteral PPI, intravenous pantroprazole, is effective[89,92,93] similar to parenteral omeprazole.[94,95] Therefore, total gastrectomy for acid hypersecretory control is not indicated.

Hypergastrinemic states are associated with an increased risk of gastric carcinoids, some of which (10% to 20%) may be malignant.[96,97] In most cases, these gastric carcinoids are small and can be treated endoscopically.[96,98–100] However, some are large, multiple, and invasive and need surgery.[96,98–100] In patients with sporadic ZES, the risk of gastric carcinoids is low (<2%).[86,101–103] In one recent study[86] involving 106 patients with sporadic ZES, none had a gastric carcinoid tumor. Even though gastric carcinoids have been reported in patients with sporadic ZES,[96,103–105] this study[86] concluded that they are rare. In contrast, gastric carcinoids develop in 13% to 37% of patients with ZES with MEN1.[101–103] Although most of these (80% to 90%) are not invasive,[96,97] aggressive cases can occur and require a total gastrectomy.[106] The true frequency of aggressive gastric carcinoids in patients with MEN1/ZES is likely low (<10%).[100] Nevertheless, total gastrectomy may be required in some and this may increase as patients age.[100]
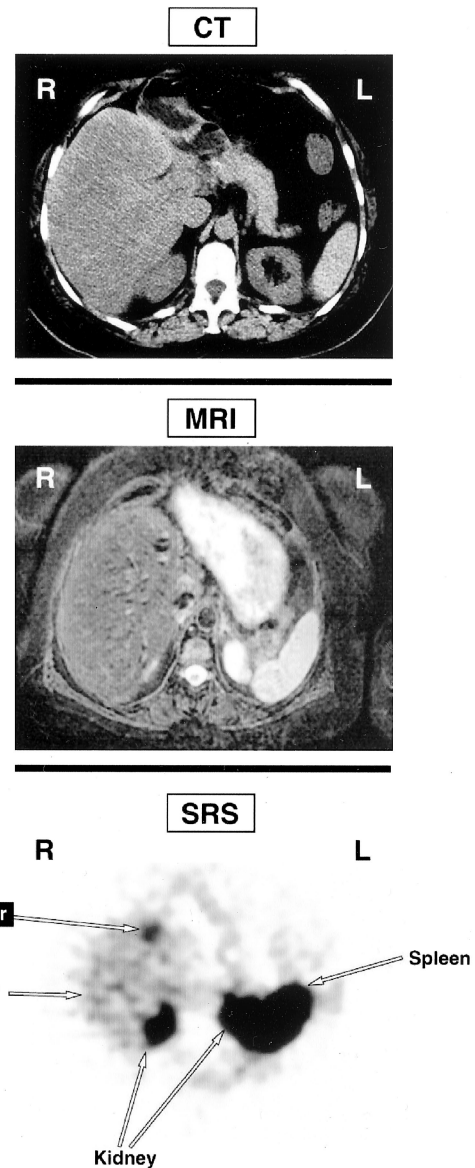
FIGURE 1. Comparison of CT scan, MRI scan, and SRS in a patient with ZES. Neither the CT scan (top) nor MRI (middle) localizes a gastrinoma. SRS however, showed a focus in the left lobe of the liver. At surgery the patient had two 1 cm left lobe liver metastases and a small duodenal (0.3 cm gastrinoma plus an adjacent lymph node. This result demonstrates the enhanced sensitivity of SRS but also shows that it frequently misses small tumors[46,68]

Current Controversies

Need for EUS as a Routine Preoperative Tumor Localization Study

EUS is recommended for preoperative tumor localization and staging in ZES.[44,45,68,107–116] Figure 2 demonstrates the ability of SRS to give regional and EUS specific local-

ization. EUS has high sensitivity (Table 3) and the ability to perform cytologic confirmation of tumor but is operator-dependent, and false positives can occur.[44,45,107–109,113,117] Further, cytologic confirmation for PET may not be needed because the diagnosis is made by hormonal and functional studies,[118,119] and it does not provide information on distant metastases.

An important issue in assessing EUS in gastrinomas is its sensitivity in different locations. Most studies suggest that EUS has a high sensitivity for detecting neuroendocrine tumors within the pancreas (Table 3). However, 2 recent series[116,120] reported low sensitivities for pancreatic insulinoma (Table 3). Whether the differences in sensitivities are due to operator-dependence, patient populations, or instrumentation is unclear. In contrast to pancreatic PETs, the sensitivity of EUS is more variable in ZES with gastrinomas in different locations (Table 3). Whereas the sensitivity[108,111,113,115,121,122] was 85% for detection of pancreatic gastrinomas, it was only 43%[68,108,113,115,116,123,124] for detection of duodenal gastrinomas. Because gastrinomas are found 3 to 10 times more frequently in the duodenum than in the pancreas,[11,58,68] this lack of sensitivity in localizing duodenal gastrinomas is a significant limitation. Furthermore, in an EUS study in patients with ZES,[68] 57% of duodenal gastrinomas localized by EUS were seen only on endoscopy, not by ultrasound. No other preoperative imaging study, including SRS, reliably localizes many duodenal gastrinomas,[46] and therefore, it was hoped that EUS could do this. However, EUS adds little in this regard. Another important point is that pancreatic gastrinomas are generally larger than duodenal gastrinomas,[22,24] and since the sensitivity for tumor detection by imaging modalities, including SRS, is dependent on tumor size,[42,46,70,125–127] pancreatic gastrinomas are frequently detected by conventional imaging studies or SRS.[45] Last, a recent study[117] reports pancreatic nodules in 1% of all patients examined by EUS that can be easily mistaken for a PET. The benefit of EUS specifically in this context has not been well evaluated. Because of the factors reviewed above, in the case of ZES we would not recommend the use of EUS as a routine preoperative imaging study, especially in the 75% to 82% of patients with sporadic ZES. We would recommend SRS and CT scan with contrast as the routine initial studies, which will identify distant disease and most primaries. In patients with negative results from both of these tumor localization studies, either angiography with secretin stimulation or EUS should be considered as an additional preoperative study. Secretin stimulation with hepatic vein gastrin sampling during angiography has an advantage in that a positive response does not depend on tumor size[128] and it has been shown to be a sensitive modality for localizing duodenal gastrinomas.[128,129] However, it has the disadvantage that it only provides regional localization within an area,
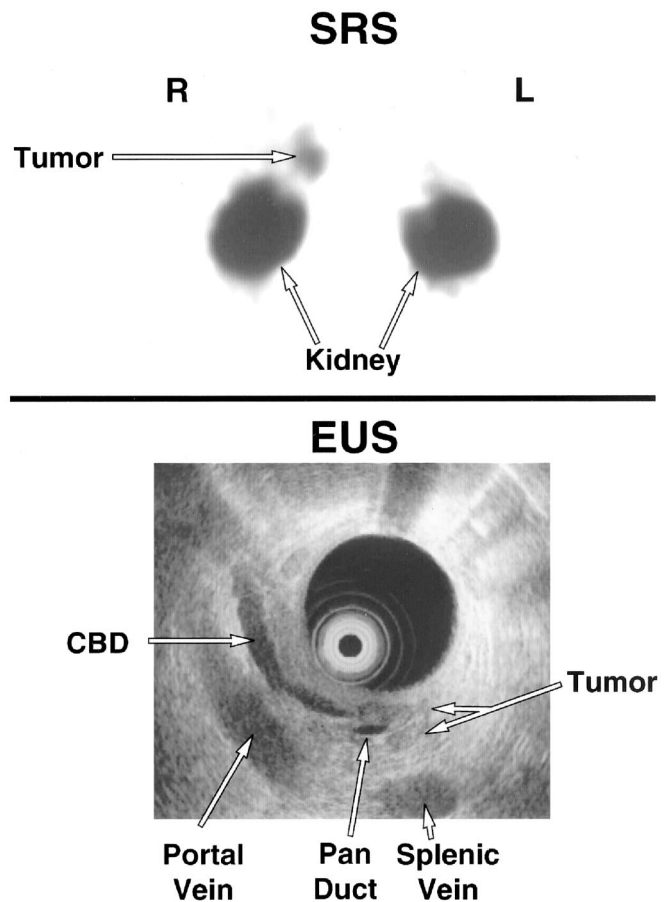
FIGURE 2. Results of SRS (top) and endoscopic ultrasound (EUS) localization of a gastrinoma. SRS localized a gastrinoma to the duodenum/pancreatic head area (arrow-labeled tumor). EUS localized a gastrinoma in the pancreatic head (labeled tumor) situated between the pancreatic duct (Pan duct) and common bile duct (CBD).

and the area it localizes to is the gastrinoma triangle, the location of most occult gastrinomas.[128,129]

In patients with MEN1 and ZES, it also has been proposed that EUS should be a routine preoperative study.[130–132] Recent studies demonstrate that the majority (60% to 100%) of these patients have duodenal gastrinomas,[3,11,130,131] but in addition, they usually possess pancreatic microadenomas or larger tumors detected on conventional imaging studies or SRS.[101,133–135] In up to 30% of the patients, these larger pancreatic tumors are not gastrinoma.[11,68,79,107,136] While EUS will frequently miss the small duodenal gastrinomas in MEN1 patients similar to sporadic cases, it will help define the exact location of additional pancreatic NETs as well as metastatic lymph nodes that frequently occur.[11,68,132,137] Therefore, EUS may be particularly useful preoperatively in patients with MEN1 and ZES, especially patients who have had previous abdominal sur-

TABLE 3. Endoscopic Ultrasound for the Localization of Gastrinomas in Various Studies

Author (Year)	Ref. No.	No. of Patients	% EUS Localization
I. Gastrinomas (duodenal/pancreatic/lymph nodes)			
Lightdale (1991)	264	3	66%
Glover (1992)	265	2	0%
Palazzo (1992)	266	15	60%
Rosch (1992)	267	7	86%
Ruszniewski (1995)	108,121	22	28% DUO; 75% PAN; 62% LN
Cadiot (1996)	68	21	57% DUO; [33% EUS/24% ENDO]
Zimmer (1996)	115	12	63% DUO; 89% PAN
Proye (1998)	113	15	28% DUO; 85% (PAN + LN)
De Angelis (1999)	124	8 (DUO)	38% DUO; 80% LN
Anderson (2000)	111	18	100% PAN
Gines (2001)	268	3	100%
Mirallie (2002)	116	26	46% DUO; 75% PAN; 57% LN
II. All PETs (primarily pancreatic/insulinomas)			
Glover (1992)	265	19	68% [78% INS (n=14)]
Palozzo (1992)	266	24	88%
Rosch (1992)	267	37	82% [81% INS (n=31)]
Zimmer (1994)	114	25	88%
Ruszniewski (1995)	108	19 (INS)	89%, all INS
Pitre (1996)	269	11 (INS)	90% INS
Schumacher (1996)	120	14 (INS)	57%, all INS
De Angelis (1999)	124	23 (all PAN)	87% PAN; 92% INS
Anderson (2000)	111	54 (all PAN)	92% PAN
Mirallie (2002)	116	29 (INS)	47%, all INS
Nesje (2002)	270	7 (INS)	71%, all INS

DUO, duodenal; PAN, pancreatic; ENDO, endoscopic result; LN, lymph node; INS, insulinoma; EUS, endoscopic ultrasound.

gery, which can increase the difficulty of exploration during surgery.

Routine Surgical Exploration in Patients With ZES and MEN1

Recent studies report that cure of ZES in patients with MEN1 rarely occurs. Whether routine surgical exploration should be performed in a patient with ZES and MEN1 to possibly reduce the malignant spread and eventually increase survival still remains controversial.[11,17,101,137–144] A number of groups recommend routine surgical exploration to decrease the probability of malignant spread.[17,140,142,143,145] The operation includes distal pancreatectomy, intraoperative ultrasound and enucleation of tumors in the pancreatic head, duodenotomy, and removal of lymph nodes along the celiac trunk and hepatic ligament.[17,143,144] In contrast, other groups recommend that surgical exploration only be performed when a tumor of 2 to 3 cm is imaged.[11,101,138] There is not only disagreement about when surgical exploration should be performed but also what

operation, with differences primarily over whether distal pancreatectomy should be done.[101,130,137,140,146]

This controversy has occurred for 3 principal reasons. First, no group has followed sufficient numbers of these patients for a long enough time in a controlled study. Second, these patients, even with metastatic disease, have a 15-year survival of 52%.[137] Therefore, very long-term studies are needed to resolve treatment strategies. Finally, the natural history of patients with MEN1/ZES in the current era with satisfactory treatment of the parathyroid and pituitary disease is largely unknown.[147] Even in patients dying of metastatic neuroendocrine tumors,[101,148–150] it is unknown whether it is due to metastatic gastrinoma, another PET, development of a thymic carcinoid,[151] or a gastric carcinoid.[106,147,152] However, results over the last decade suggest that progression of the gastrinoma and/or other PETs is becoming one of the most important determinants of long-term survival.[138,148,153,154] These findings support the role for surgery in selected patients. Second, a recent prospective study demon-

strated that 23% of the PETs in MEN-1 patients had aggressive growth and hepatic metastases.[155] Further, 38% of the patients with aggressive tumors died of tumor, which was significantly different from patients with nonaggressive PETs. These findings also support the role for surgery in selected patients. Third, when these patients were explored with imageable tumors of 2 to 3 cm, the majority (50% to 70%) had lymph node involvement; however, metastases to the liver were rare.[11,140,145] This observation has led some to propose earlier exploration.[11,140] Fourth, in a recent study involving 81 patients[137] with MEN1/ZES, the 15-year survival was 100% in 25 patients with no surgical exploration with PETs <2.5 cm, 100% in 17 patients with a single PET <6 cm (with surgical exploration), and 89% in 31 patients with ≥2 tumors or >6 cm tumor (with surgery). In this study,[137] these excellent survival rates were achieved without performing routine distal pancreatectomy, suggesting that it is not essential.

At present there are no reliable clinical, laboratory, or tumoral markers that allow prediction in an individual patient with ZES and MEN1 of the aggressiveness of the PET. The most important predictor of survival in patients with gastrinomas is the development of liver metastases, not lymph node metastases.[22,138] Numerous studies have demonstrated that in gastrinomas, PETs, and carcinoids, primary tumor size is highly predictive of liver metastases.[22,24,27,31,138,156] Therefore, at present, because patients with ZES/MEN1 are not cured, those with tumors ≤2 cm have a 100% 15-year survival, and those with larger tumors have an increased probability of developing liver metastases, we continue to recommend surgical exploration only for MEN1/ZES patients with an imageable tumor ≥2 cm and not to perform a routine distal pancreatectomy. Additional studies are needed to clearly define whether a more aggressive approach is indicated.

Should Pancreaticoduodenectomy Be More Frequently Used in ZES?

Most centers with considerable experience in management of patients with ZES do not recommend pancreaticoduodenectomy.[11–13,15,17,19,101,137,143,157,158] However, a number of small series have reported the use of Whipple resection in patients with ZES with or without MEN1 (Table 4). In a high proportion of these cases, Whipple resection has resulted in cure in patients with ZES both with and without MEN1 (Table 4). This has resulted in the hypothesis that Whipple resection may provide a better chance of cure and increased survival, especially in patients with MEN1, where long-term cure with the standard operation is rarely achieved.[19,146,159–161] In the largest series[159] involving 12 patients with ZES, of whom 3 had MEN1, 92% of the patients were cured post-Whipple resection. Even though normal fasting gastrin levels persisted during a median follow-up of

6 years, suggesting cure, serial secretin tests were not done such that early recurrences may have not been detected.[18] Further, Whipple resection may make reoperation more difficult, which is important in patients with ZES and MEN1 because they frequently develop additional large PETs. The development of hepatic metastases occurring after a Whipple resection cannot be treated with liver embolization[118,162,163] because of the risk of ascending infection. Nevertheless, because of these results (Table 4) it has been recommended by a number of authorities that Whipple resection be performed in patients with a large pancreatic head or duodenal tumor that cannot be enucleated, with multiple duodenal tumors, with multiple lymph nodes with a duodenal or pancreatic head tumor, or if the patient is not cured after removal of a duodenal or pancreatic head gastrinoma with or without lymph node metastases by the standard operation (as assessed by intraoperative secretin or other methods).[19,146,159–161,164]

At present, before more frequent use of Whipple resection can be recommended, a number of important issues need to be clarified. First, it should be established by a systematic study that Whipple resection in both sporadic ZES and patients with ZES with MEN1 leads to increased long-term cure, established by complete biochemical assessment (fasting gastrin levels and secretin test). Second, the long-term side effects of Whipple resection and their frequency need to be carefully assessed. This is an important point because this is largely unknown, and if significant, it could be a major determining factor against its use because these patients currently have an excellent quality and duration of life. Furthermore, the presence of lymph node metastases is not a justification for Whipple resection because they have not been shown to decrease survival.[22,138] Third, ultimately it will need to be established that a Whipple resection extends survival in patients with ZES with and without MEN1. This will be difficult because for sporadic ZES the 10-year survival is 95%[11] and in ZES/MEN1 it is 86%.[11] Furthermore, it has not been established that these patients' survival is determined by gastrinoma and not some other tumor such as thymic carcinoid,[151] another PET, or some other tumor.[151]

Do Lymph Node Primary Gastrinomas Occur and Should Routine Removal of Duodenal/Pancreatic Head Lymph Nodes Be Part of the Standard Surgical Exploration?

The possible presence of lymph node primary gastrinomas in patients with ZES remains a controversial subject.[13,23,165–173] There are numerous reports in the literature of patients with ZES (almost all with sporadic ZES) who had a lymph node(s) only resected and were cured by biochemical testing and imaging studies both short term and long term.[10,13,23,27,68,165–171,174–185]

Recently, our experience with 176 patients with ZES with or without MEN1 who underwent surgical exploration

TABLE 4. Pancreaticoduodenotomy in Patients With Zollinger-Ellison Syndrome

Author (Year)	Ref. No.	Total No. of ZES Patients (# MEN1)	No. Disease Free (%)	Median Follow-up (y) [Range]
Waddell (1968)	271	4 (1)	4 (100)	1.0 [0.25–4.8]
Oberhelman (1972)	272	4	4 (100)	5.8 [0.1–11]
Bonfils (1981)	273	4	0	ND
Roche (1982)	274	1	100	0.1
Cavina (1986)	276	1	1 (100)	1.5
Stamm (1986)	276	2	2 (100)	1
Vogel (1987)	180	1	1 (100)	2
Olbe (1989)	277	4 (1)	3 (75)	10 [1–27]
Pipeleers-Marchial (1990)	3	2 (2)	2 (100)	ND
Rosato (1990)	278	1	1 (100)	ND
Delcore (1992)	160	5 (2)	3 (60)	8.5 [5–12]
Farley (1992)	174	4	4 (100)	ND
Udelsman (1993)	279	1	ND	2
Stadil (1995)	159	12 (3)	11 (92)	6 [0.5–14]
Schroder (1996)	280	2 (1)	2 (100)	1.6 [0.25–2.9]
Phan (1997)	281	6	6 (100)	2.5 [0.1–3.4]
Jordan (1999)	23	8 (1)	1 (12)	1 [0–6]
Partensky (1999)	282	2	2 (100)	11.5 [7–16]
Bartsch (2000)	146	3 (3)	3 (100)	2 [1–3]
Kato (2000)	164	4 (2)	4 (100)	8 [2–11]
Lairmore (2000)	283	5 (5)	ND	ND
Siech (2000)	284	2	1 (50)	4
Norton (2001)	137	2 (2)	0 (0)	4.3 [1.7–6.9]
Thodiyil (2001)	243	6	6 (100)	5.2 [1–6]
Sarmiento (2002)	285	2 (1)	ND	ND

MEN1, multiple endocrine neoplasia-type 1.

for the occurrence of a possible lymph node primary was analyzed (Fig. 3).[165] Twenty-six patients (15%) followed for a mean of 10 years fulfilled all the criteria for a lymph primary.[165] Of the 138 sporadic ZES patients, 36 patients (26%) had only lymph nodes removed and 22 patients (16%) were disease-free immediately postresection and thus, had a possible lymph node primary (Fig. 3). During follow-up, 16 patients (12%) remained cured and, therefore, fit the diagnosis for a lymph node primary (Fig. 3). During this follow-up period, 6 patients relapsed and 2 had small duodenal primaries that were missed at the original exploration. These long-term cure results strongly support the conclusion that lymph node primary tumors exist.[165] This possibility is further supported by 2 recent pathology studies[172,173] that report neuroendocrine cells can be found in abdominal lymph nodes. Unfortunately, no clinical, laboratory or operative feature of the lymph node predicted which lymph node was a primary or a metastasis. This presents a potential problem for the surgeon. First, these findings do not determine whether a primary tumor is likely missed and whether a more aggressive resection like Whipple is indicated.

Second, it provides an additional reason to support removal of peripancreatic lymph nodes and lymph nodes along the celiac trunk and hepatic ligament as part of the surgical exploration.[17,69,144,165,166] In addition to recognizing possible lymph node primaries, the routine removal of lymph nodes may increase surgical cure rate in patients where an accompanying primary tumor is found, although at present this is unproven.

Role of Parietal Cell Vagotomy

Although at present parietal cell vagotomy is not frequently performed, some have advocated its routine use[186,187] or its use in selected patients.[188,189] Hence, its exact role remains controversial. In a study by Richardson et al,[186] parietal cell vagotomy resulted in a 75% decrease in basal acid output. However, only 9% of the patients were able to stop all antisecretory drugs. Furthermore, parietal cell vagotomy[188] increased the sensitivity to the antisecretory action of other drugs such as histamine H_2-receptor antagonists. Richardson[188] recommends it be routinely performed. However, the availability and effectiveness of PPIs led to them as the
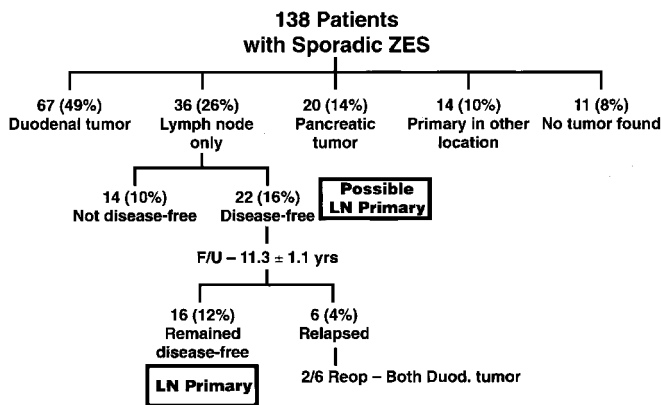
FIGURE 3. Algorithm showing patients with sporadic ZES based on the primary location and likely lymph node primary gastrinoma. Of the 138 patients, 36 had a lymph node only removed and 22 (16% of total) were disease free, suggesting a possible lymph node primary tumor. Subsequently, the patients were reevaluated with a yearly assessment for cure over a mean of 11.1 ± 1.3 years, 16 patients (12% of total) remained disease-free and are considered to have lymph node primary gastrinomas.[165,166] Of the 6 patients who relapsed, 2 had duodenal primaries.
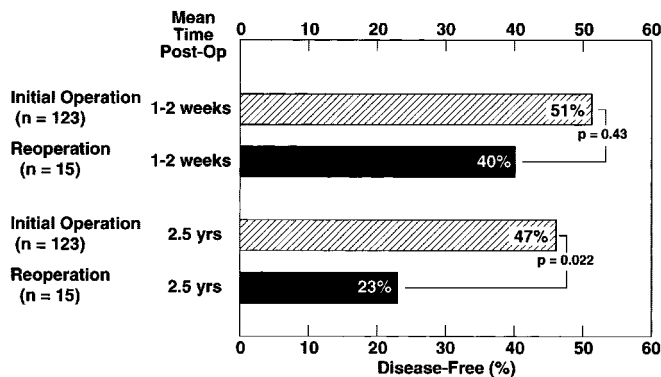
FIGURE 4. Comparison of the disease-free rate after initial surgical exploration and after reoperation for recurrent tumor. Plotted are the disease-free rates within 1 to 2 weeks of surgery and at a follow-up of at least 2.5 years. Results are plotted from data[11] for initial surgery in 123 patients, and for reoperation[195] in 15 patients

preferred treatment.[87,90] In 1996, McArthur et al[187] reported results from an 11-year follow-up study of Richardson's patients. This study[187] demonstrated that parietal cell vagotomy continued to reduce acid secretion by 80% from preoperative values and that 32% of the patients required no drugs up to 16 years after the operation. An accompanying editorial[188] pointed out that (1) 60% to 70% of patients with ZES are not cured long term and will need gastric antisecretory drugs[11,188,190]; and (2) the expense of medication is a significant deterrent in long-term compliance. The mean cost of

omeprazole is $3276/y.[188] There is increasing concern about the consequences of achlorhydria, which occurs in 35% of patients on omeprazole[188,191] It may lead to vitamin B12 and iron malabsorption.[191–194] Finally, some patients with ZES who are cured postresection[189] continue to require gastric acid antisecretory drugs long term. The performance of routine parietal cell vagotomy may allow more than one third to stop PPIs[187] or switch to histamine H_2-antagonists, which are less expensive and potent. For these reasons, parietal cell vagotomy should be considered as a routine adjunct at the time of surgical exploration for cure. However, surgical exploration should not be performed solely to do a parietal cell vagotomy.

Place of Surgical Reexploration in Patients With ZES

Long-term studies show that most patients with sporadic[11,190] and MEN1 ZES[11,19,137,141] are not cured. Further, some will harbor aggressive tumors and may benefit from reexploration. At present, the indications for surgical reexploration, the type of operation such as a Whipple procedure, are largely undefined and controversial. Reoperations will be more important as ZES patients are living longer and localization methods such as SRS are improving. Only 1 study[195] has dealt with this problem (Fig. 4). In this study[195] of 120 patients with ZES undergoing surgical exploration (14% had MEN1/ZES), 78 patients (65%) had persistent disease postoperatively, and 17 patients undergoing 18 reoperations were analyzed. The indication used for reexploration[195] was identification of imageable disease during follow-up. SRS was not used,[195] which is an important factor in considering the applicability of this study to the present. Tumor was removed in all 17 patients at reexploration. The results of reexploration in the 15 patients with sporadic ZES are compared with initial exploration. There was no significant difference immediately postoperatively in the disease-free rate between the initial or second operation (51% versus 40%, Fig. 4, top); however, at 2.5 years postresection[195] 47% of the initial patients remained disease free, while only 23% following reoperations (Fig. 4, bottom). These results demonstrate the long-term cure rate was lower with reoperation. However, reoperation was thought to be indicated because some patients were still able to be rendered disease free.

This study's applicability to current management is unclear for a number of reasons. First, SRS is now available, widely used, and may identify recurrent disease earlier. Second, the 15-year survival rate postoperatively of these patients, even if not cured, is 95%[11] and with ZES/MEN1 is 93%.[137] Therefore, survival may not be altered by reexploration. Other variables such as tumor growth or molecular findings in the tumor (Table 2) may be used to identify a subset who may benefit from reexploration Last, should Whipple resection be considered in a subset of these patients

at reexploration? How should this subset be selected? Will either secretin angiography or EUS be useful in selecting these patients? At present, all of these questions are unanswered and require study.

Role of Surgery in Treatment of Aggressive, Advanced Disease

The most important predictor of survival in patients with ZES and other gastrointestinal neuroendocrine tumors is hepatic metatases.[22,24,31,118,138,156,196,197] Furthermore, the extent of the liver metastases is also important.[24] Figure 5 shows survival data from 212 patients with ZES. Patients without any liver metastases had a 95% 20-year survival from diagnosis, whereas patients with diffuse metastases had a 10-year survival of only 15% (Fig. 5). Patients who had a single liver lobe metastasis or less than 5 discrete metastases in both liver lobes also had a decreased survival (60% at 15 years); however, it was significantly better than patients with diffuse metastases. Therefore, in ZES,[14,137,198–200] and other malignant NETs,[201–207] possible resection and cryoablation of hepatic metastases has been recommended. Only 5% to 15% of patients have metastases limited to 1 lobe or a discrete limited number (<5) in 2 lobes that would be fully resectable.[24,137,196,198,200,201,206,208] Therefore, surgery for cure is only possible in a fraction of these patients. In various studies, this surgery in patients with advanced NETs is reported to occasionally result in cure,[106,129,198,207] to have 5-year survival rates of 71% to 85%,[106,129,198,201,202,207] and to result in increased survival.[129,201,205] However, these results are difficult to evaluate for a number of reasons. First, there are no controlled trials where the groups are appropriately matched to control groups without cytoreductive surgery. Therefore, patients with resectable disease are not comparable to those with unresectable disease and differences in survival may be independent of surgery. Second, patients with functional NETs are often considered together with nonfunctional NETs in evaluating the value of cytoreductive surgery. Patients with advanced functional NETs in whom the symptoms of the hormone-excess state are not well controlled medically may benefit from enhanced symptom control postresection, whereas in patients with nonfunctional NETs or gastrinomas who are usually asymptomatic, the value of surgery is almost entirely assessed by its effect on survival. Third, because of the relatively slow growth of these malignant NETs compared with common malignancies such as adenocarcinomas, these studies need to be long term to demonstrate differences in survival with significant numbers of patients, which is difficult because of the rarity of ZES and other GI neuroendocrine tumors.

Because of these reservations, at present there are insufficient data to unequivocally determine in whom, if any patient, cytoreductive surgery or aggressive resection with advanced disease with ZES should be performed. Most of the
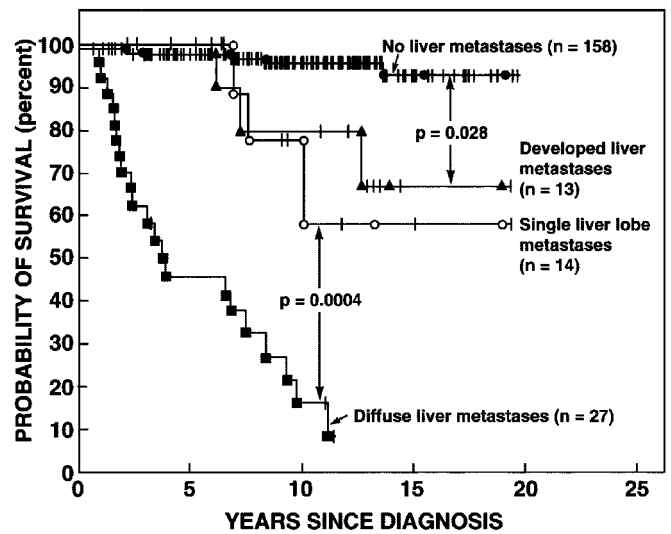
FIGURE 5. Effect of the extent of liver tumor on the survival of 212 patients. Disease-related survival is shown plotted in the form of Kaplan and Meier. Numbers in parenthesis refer to the number of patients in each group. Figure is drawn from the data in Yu et al.[24]

surgical studies demonstrate these resections can be performed with acceptable morbidity, low mortality, and suggest they may prolong life. Because the medical treatment of advanced disease in patients with ZES, as well as most NETs,[118,156] is generally unsatisfactory, our approach at present is to attempt surgical resection in any patient with advanced disease where all or at least 90% of the gross tumor is thought to be resectable based on imaging studies. This approach is used, recognizing that additional studies are needed to clearly establish its value in both patients with ZES and those with other advanced neuroendocrine tumors.

Role of Laparoscopic Surgery or Endoscopic Resection of Duodenal Gastrinomas in Patients With ZES

Recently endoscopic removal of duodenal gastrinomas has been reported,[209–214] as well as use of the laparoscope to attempt to surgically resect primary gastrinomas[215] or other PETs (especially insulinomas),[215–223] as well as laparoscopic treatments of advanced disease in patients with metastatic PETs including gastrinomas.[224,225]

Endoscopic removal of duodenal gastrinomas or other duodenal neuroendocrine tumors is described using snare polypectomy with or without submucosal saline injection,[209–213,226] or using endoscopic-assisted band ligation.[227] EUS may be useful because it has been shown[226] to allow assessment of the depth of invasion of the duodenal NET, determining whether it is confined to the submucosal layer and can be safely removed. In a few cases, endoscopic removal of a

duodenal gastrinoma has resulted in cure.[210,211,228] Nevertheless, in at least 1 case[211] a duodenal perforation occurred. Our results from studies of duodenal tumors would suggest a number of important reservations in regard to this endoscopic approach. First, more than half of the duodenal gastrinomas are associated with adjacent metastatic lymph nodes,[11,22,28,77] and endoscopic removal of the primary will not allow lymph node removal, which may contribute to cure. Second, almost half of duodenal gastrinomas are locally invasive beyond the submucosa[28] and may not be easily removed by endoscopic means. Furthermore, aggressive endoscopic removal of these invasive tumors will likely lead to a significantly increased complication rate. Third, in patients with MEN1 the duodenal gastrinomas are invariably multiple, making their removal endoscopically difficult. Furthermore, no removal of the pancreatic macroadenomas that are frequently present can be carried out. For these reasons, we recommend against attempted endoscopic removal of duodenal gastrinomas.

Laparoscopic resection of pancreatic PETs, especially insulinomas, is being increasingly used.[216–223,229–233] With insulinomas, especially in the distal pancreatic body or pancreatic tail, the laparoscopic approach using either enucleation or distal pancreatectomy has had a high success rate.[219,220,223,232,234] At present, the experience with gastrinomas is very limited.[215] In both of the patients with gastrinoma in one study,[215] laparoscopic resection had to be converted to a laparotomy because of the extent of disease. The role for laparoscopic surgery for gastrinoma resection appears to be much more limited than its potential utility for insulinoma for a number of reasons. First, gastrinomas are 3 to 10 times more common in the duodenum than the pancreas. Furthermore, in the duodenum the gastrinomas are frequently small (<1.0 cm). Although there are reports of resection of duodenal carcinoids laparoscopically,[235,236] the experience is very limited and it is unclear whether laparoscopy can successfully find and resect small duodenal gastrinomas. Second, laparoscopic resection of pancreatic PETs (primarily insulinomas) has generally been successful when the tumor was found on preoperative imaging and less successful if not seen on preoperative imaging.[232] Many gastrinomas are not localized preoperatively, especially duodenal gastrinomas, and this will likely decrease the success rate. Third, many gastrinomas (>50% to 70%) are associated with adjacent lymph node metastases and are not solitary primaries, as in the case of insulinomas. This will make a laparoscopic approach more difficult, prolong its duration, and may limit its success. Fourth, laparoscopic resection of pancreatic body/tail PETs is generally successful; however, laparoscopic resection of PETs in the pancreatic head region has been more difficult because of the adjacent important structures.[232] Greater than 75% of gastrinomas are in the pancreatic head region in the so-called gastrinoma triangle,[9,14,58] complicating the laparoscopic approach. For the reasons outlined above, we

recommend against a laparoscopic approach in patients with ZES and support the continued use of open surgery.

A laparoscopic approach is also being used to identify and treat patients with advanced malignant PETs including gastrinomas.[224,225,237] Laparoscopic radiofrequency ablation of liver metastases of malignant PETs is reported to have low morbidity[224,225] and to result in a decrease in tumor markers in 65% of patients with metastatic GI neuroendocrine tumors.[224] While this may be a useful approach in patients with functional GI neuroendocrine tumors with poor medical control of the hormone-excess state, this is not the case with ZES where excellent treatment exists for the acid hypersecretion. Therefore, in the case of ZES, as with nonfunctional PETs, this approach will not be widely adopted if it is not shown to extend survival. A laparoscopic approach has been shown to be useful in staging the extent of malignant PETs and preventing unnecessary surgery.[237] With the recent widespread use of SRS, which is highly sensitive for identifying hepatic metastases[43,56,65,66,238] as well as helical CT,[72–74,76] it is unclear whether the use of preoperative laparoscopy is warranted for this indication. At present, we do not recommend its routine preoperative use for staging gastrinomas or PETs.

CONCLUSIONS

Whereas a number of controversies involved in the surgical treatment of Zollinger-Ellison syndrome[1] have been resolved over the last decade, a number of areas are identified in this article and discussed, where controversies remain unresolved. It is hoped by pointing out these specific areas and discussing them that surgeons who treat these patients will focus on some of these issues. Only by their systematic study will additional advances be made and these existing controversies resolved.

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