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Zollinger-Ellison syndrome: Recent advances and controversies

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Abstract

Purpose of review—To review the recent advances and current controversies in patients with Zollinger-Ellison syndrome (ZES)

Recent findings—Recent advances in the management of ZES include: (i) improved understanding of the pathogenesis of gastrinoma and pancreatic neuroendocrine tumors (pNETs), (ii) new prognostic classification systems, (iii) new diagnostic algorithms, (iv) more sensitive localization studies, (v) new treatment strategies including improved control of gastric acid secretion and role for surgery, and (vi) new approaches to patients with advanced disease. Controversies include: (i) the best approach to a patient with hypergastrinemia suspected of possibly having ZES, (ii) the appropriate gastrin assay to use, (iii) the role of surgery in patients with ZES, especially those with multiple endocrine neoplasia type 1 (MEN1), and (iv)the precise order of therapeutic modalities in the treatment of patients with advanced disease.

Summary—This review updates clinicians regarding important advances and controversies required to optimally diagnose and manage patients with ZES.

Keywords

Gastrinoma; Zollinger-Ellison syndrome; gastrin; pancreatic endocrine tumor syndrome; neuroendocrine tumor

INTRODUCTION

In the last few years there are a number of advances regarding the pathogenesis, management, and specific treatment of gastrinomas causing the Zollinger-Ellison-syndrome(ZES), as well as other pancreatic neuroendocrine tumors(pNETs), and number of areas of controversy. In this article we will review these, concentrating on articles within the 2–3 years. [1●,2,3●,4,5●,6●●,7–11]. In general, topics that deal specifically with gastrinomas will be dealt with because a number of recent articles/reviews deal with general aspects of all pNETs including: clinical features, pathophysiology/diagnosis[1●]; surgery[2,3●]; localization[4,5●] and treatment of advanced disease[cytoreduction, liver-

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CONFLICTS OF INTEREST: None:

directed treatments(embolization, chemoembolization, radioembolization), biotherapies(somatostatin-analogues, interferon), peptide-radio-receptor-therapy [PRRT], chemotherapy and molecular-targeted medical therapies with mTor-inhibitors(everolimus) and tyrosine-kinase inhibitors(sunitinib), liver-transplantation][6●●,7–11]. Furthermore, a number of consensus guidelines covering all aspects of management of pNETs, including gastrinomas, have recently been published[8,9,12,13●●]

CLINICAL PRESENTATION

Symptoms of ZES are characteristically due to acid hypersecretion caused by the presence of a neuroendocrine tumor(NET) ectopically-secreting gastrin(gastrinoma), most frequently duodenal, less frequently pancreatic, in location[14–17]. In the past, most patients presented with refractory peptic-ulcer disease(PUD) or complications of acid hypersecretion such as perforation, penetration, bleeding, and esophageal stricture [16–18]. In the current era of effective antisecretory medications (PPIs and histamine H2 receptor antagonists) this form of presentation has markedly decreased [14,16,19●,20], however, a number of recent reports still describe cases presenting with these complications[21–23]. This should not be too surprising, because the delay in diagnosis of ZES remains 6–9 years and hasn't changed, despite >3600 articles on ZES and the widespread availability of gastrin-radioimmunoassays[16,20]. At present, most ZES patients present with pain due to a typical duodenal ulcer or gastroesophageal reflux(GERD), but up to 75% manifest diarrhea and this may be the sole presenting symptom in 3–10%[16,24●], as well illustrated in a recent case-record in the New England J Medicine[24●].

In 20–25% of ZES patients, concomitant Multiple-Endocrine-Neoplasia-type 1(MEN1) is present[9,14,25,26]. MEN1 is an autosomal-dominant syndrome due to defects in the MEN1-gene(chromosome-11q13), resulting in alterations of a 610-amino acid nuclear-protein, menin[27]. These patients characteristically develop hyperparathyroidism(90–99%), pNETs(80–100%) and pituitary adenomas(50–65%), with the most common, functional pNET-syndromes being ZES(mean-54%, range 20–61%) and insulinoma(7–31%)[27]. Although most patients initially present with hyperparathyroidism, a proportion can present with ZES and the hyperparathyroidism can be mild and difficult to detect[25–28]. Two recent papers[21,23] report these patients can also present with PUD complications(bleeding, perforation). Although this is now a less common form of presentation with the availability of antisecretory drugs, nevertheless it is not uncommon or surprising because the delay in diagnosis in MEN1 patients, in whom ZES should be potentially suspected in all, is still 5 years[25,27]. Recent studies show that ZES presents 10 years earlier in MEN1 patients(mean-33.2 yrs), and that the hyperparathyroidism can effect the activity of the ZES, and can even mask the ZES's presence if adequately controlled[16,25,29,30], therefore it is important all patients with MEN1 be assessed for ZES.

Although ZES occurs in most cases as a separate distinct syndrome, it is important to remember that it is one of the pNET-syndromes most frequently reported in association with other functional pNETs syndromes[16,25] such as Cushing's syndrome, carcinoid syndrome, insulinoma, and parathyroid hormone-related protein secreting tumors. In recent

papers these include: Cushing's syndrome, especially in patients with advanced metastatic gastrinoma(ectopic-Cushing's) or in patients with MEN1(pituitary-Cushings)[25,27,31–33] [25,34];insulinomas(especially in MEN1 patients)[25,35];or PTH-RPomas[36].

Pathology, classification, and molecular pathogenesis

In the original description of ZES[37] and in most early studies, it was thought that the gastrinoma was pancreatic in location(non-β-cell-tumor)[18,37], however recent surgical series[14,38–41] show 40–90% of gastrinomas are duodenal, in both patients with/without MEN1. This change is due to the fact that duodenal gastrinomas are frequently small(<1-cm), not seen on imaging and thus were easily missed in the early studies, and are still missed at surgery, if a routine duodenotomy isn't performed[14,38,39,42,43]. Primary gastrinomas are uncommonly located in other intra-abdominal locations including:lymph nodes(controversial), stomach, mesentery, renal capsule, splenic hilum, omentum, ovary and in the liver/biliary tract[41,44,45,46●,47–49]. Rarely (<0.3%) primary gastrinomas may occur in extra-abdominal locations such as the heart and lung[41].

In early studies, 60–90% of gastrinomas were associated with metastases[14,39,41]. Surgical studies demonstrate that 30–70% of patients with duodenal or pancreatic gastrinomas have lymph nodes metastases. Liver metastases, however, are much more frequent in patients with pancreatic gastrinomas[41,50]. At present, the molecular basis for this difference is unknown.

Recently, it has been proposed that gastrinomas, as well as all pNETs and carcinoid tumors should be classified as neuroendocrine tumors (NETs)[51●●,52]. A number of different classification systems have been proposed including the WHO classification, European-Neuroendocrine-Tumor-Network classification (ENETs), and an American classification system by UJCC/IUCC[51●●,52]. WHO classifies NETs in different sites into poorly-differentiated or well-differentiated endocrine tumors or carcinomas with the well-differentiated further divided into classes with different behavior depending on size, functionality, location, invasiveness, and proliferative indices[51●●,52]. Both a grading system and a TNM classification have been proposed[51●●,52]. Proper classification of gastrinomas is essential, because they have prognostic value and in some cases affect treatments recommended[51●●,52,53]. Most gastrinomas are classified as well-differentiated pNETs-Grade 1.

The origin/pathogenesis of gastrinomas remains enigmatic. In contrast to GI adenocarcinomas, mutations in common tumor suppressor genes are uncommon (p53, retinoblastoma, etc) and alterations in common oncogenes(Ras, myc, etc) are uncommon[15,54●,55●,56]. However, recent studies report overexpression of interacting proteins may lead to inactivation of both the retinoblastoma protein cascade and p53 tumor suppression genes in pNETs[57,58]. Alterations in the MEN1 gene occur in 44% of sporadic gastrinomas and other pNETs and of p16/MTs1 in 50–92%[54●,55●,56]. Also reported are frequent alterations in the mTor pathway as well as the importance of tyrosine-kinase-receptors for tumor growth[54●,55●,56]. The exact cell of origin of gastrinomas, remains a subject of controversy with some suggesting that pancreatic gastrinomas may originate from islet and/or duct cells[59,60]. In the case of duodenal gastrinomas in patients with MEN1,

but not with sporadic duodenal gastrinomas, studies suggest their pathogenesis involves increasing degrees of proliferation of duodenal G-cells concomitant with loss-of-heterozygosity at the MEN1-locus(11q13) in the G-cell[59,61].

DIAGNOSIS/DIFFERENTIAL DIAGNOSIS OF ZES

The diagnosis of ZES is not straight-forward and is becoming both controversial as well as more difficult. It is becoming more controversial because of the difficult of diagnosing ZES with the widespread use of PPIs and the contrasting approaches proposed in different papers/guidelines recently[12,13●●,62●●,63●●,64–66]. It is becoming more difficult because of the widespread use of PPIs which can mask/delay the diagnosis, and can cause hypergastrinemia themselves which can confuse the diagnosis[64●●,65–69]. Furthermore, it is reported that many of the gastrin assays used worldwide give erroneous results, either underestimating or overestimating the fasting-gastrin concentrations level[62●●,70●●]. Each of these issues will be briefly discussed below.

The first study usually performed when ZES is suspected is a fasting-serum gastrin concentration[62●●,69], because in >99% of ZES patients, fasting-hypergastrinemia is present, except in uncommon, special circumstances(previous gastrinoma resection, MEN1/ZES post-parathyroidectomy)[29,62●●,71,72]. Alarmingly, a recent study[70●●] reported that seven of 12 commercial gastrin assay kits inaccurately measured fasting-serum/plasma gastrin concentrations either over- or under-estimating the true value, because these assays used antibodies with inappropriate specificity, that were insufficiently validated. These assays could result in ZES being unduly suspected or result in the diagnosis being missed[62●●,70●●]. Furthermore, secretin(or glucagon in countries where secretin is not available)[73], and to a lesser extent, calcium gastrin-provocative tests are needed in a subset of patients with ZES, to firmly establish the diagnosis[62●●,74] and a positive response(>120 pg/ml increase=secretin, ≥395 pg/ml=calcium) can only be determined using an accurate gastrin-assay[74]. Therefore, without a reliable gastrin-assay it is not possible to be certain ZES is present or not. To circumvent these problems it is recommended that either one of the 5 reliable gastrin-assays listed in this paper be used or a group well-versed in diagnosing ZES in your area be contacted to ascertain which gastrin-assay in your area is reliable.

Hypergastrinemia can either be physiological(due to hypo-/achlorhydria) or inappropriate due to a disease process such as ZES, resulting in the inappropriate release of gastrin, despite the presence of gastric acidity[69,75]. Physiological-hypergastrinemia is the most common cause of fasting hypergastrinemia and frequently observed in patients with chronic atrophic gastritis/pernicious anemia (hypochlorhydria), chronic helicobacter infection of the oxyntic mucosa (hypochlorhydria), PPI use (hypochlorhydria), and renal failure (decreased excretion of gastrin)[62●●,65,66,69,75]. This group of patients is much more frequent than ZES and therefore must be distinguished from patients with ZES[62●●,65,66,69]. Unfortunately, in patients with chronic atrophic gastritis/pernicious anemia, there is no level of hypergastrinemia alone that can separate these patients from patients with ZES In most recent reviews as well as all recent guidelines[1●,12,13●●,62●●,63●●,66,69] it is proposed that the only certain approach to identify most patients with hypergastrinemia as

possibly having ZES, is to assess the gastric-pH. In a review of 1219 patients with ZES[76], it is reported that 100% of patients, without previous gastric acid-reducing surgery and off antisecretory medications, had a gastric pH <2. This approach, however, is somewhat controversial because this approach is not without potential risk, because ZES patients can quickly develop acid-peptic complications when taken off PPIs for the recommended one week[62●●,64●●,69]. Furthermore, because PPIs have a long duration of action(up to 1 week), to be certain uninhibited gastric acidity returns, it is recommended the PPIs be stopped for at least one week[1●,12,13●●,62●●,63●●,66,69]. A recent study[64] reports two patients with suspected ZES(later proven) who developed severe complications of PUD when the PPIs were stopped(esophageal stricture, intestinal perforation), and it is proposed that PPI treatment be maintained and the diagnosis of ZES established while the patient continues to take PPIs or a reduced dose of PPIs. Unfortunately, as pointed out in two recent commentaries[62●●,63●●], this is not possible in most cases, because many patients with ZES continue to have profound acid-inhibition with low doses of PPIs; there is no clinical feature that unequivocally establishes the diagnosis of ZES; there is no absolute level of gastrin or any tumor marker(chromogranin A, etc) that distinguishes ZES; pNETs are frequently not seen on imaging studies, and even the establishment of a pNET containing-gastrin does not unequivocally establish the diagnosis of ZES[62●●,63●●]. Lastly, a positive secretin-provocative test(≥120-pg/ml increase) which is frequently used to establish the diagnosis of ZES in questionable cases and has a sensitivity of 94% and specificity of 100%[74], may not give reliable results while patients are taking PPIs, because PPI's use can lead to a false-positive secretin test[77]. Because of these potential difficulties in making the diagnosis of ZES and withdrawing PPIs, it is recommended that the best approach is to consider referring the patient to a group well-versed in establishing the diagnosis of ZES[12,13●●,15,62●●,63●●]. If this is not possible it is recommended that, after establishing no active PUD is present, the patient be treated with high doses of a histamine H2-receptor antagonist(ranitidine-450–600 every 4–6 hour), while the PPI is withdrawn for 3–7 days, and then stopping the ranitidine for 24 hours and assessing the gastric acidity and fasting gastrin[1●,12,13●●,62●●,63●●,66,69]. A diagnosis of ZES is established if the patient has a (i) fasting-gastrin >10 -fold normal with a gastric-pH<2(40%-patients) or(ii) fasting gastrin <10-fold, if the gastric pH<2, and there is presence of a positive secretin-stimulation test or gastric hypersecretion[1●,12,13●●,62●●,63●●, 66,69]. The later studies are needed in patients with <10-fold elevation of ZES(60%-patients), because a number of diseases can also give hyperchlorhydria/hypergastrinemia in this range besides ZES, including H. pylori infections, renal failure, antral hyperplasia/ hyperfunction, retained antrum syndrome and large small bowel resections[8,14,15,62●●]. Because of the potential pitfalls in securing the diagnosis of ZES and withdrawing PPIs, the best approach may be to refer the patient to a group well-versed in establishing the diagnosis of ZES[12,13●●,15,62●●,63●●].

CONTROL OF ACID HYPERSECRETION

Acid hypersecretion can now be controlled medically in almost all patients with ZES, except for a small percentage(<0.2%) who can't or won't take oral antisecretory drugs[12–15,17,19●,20,69]. PPIs(omeprazole, esomeprazole, rabeprazole, pantoprazole,

lansoprazole) are the drugs-of-choice because of their potency/long-durations of action, allowing once- or twice-a-day dosing[12–15,17,19●,20,69]. H2RAs are also effective, however high, frequent doses are required, and at least one dose-change per year is needed[14,15,19●,69]. Furthermore, in situations where oral dosing can not be used(during or after surgical procedures, vomiting, gastric obstruction, severe esophageal stricture, etc), intravenous(IV) PPIs are the drugs-of-choice[19●,78]. Studies show IV-pantoprazole can control acid hypersecretion when given intermittently with 2- or 3-times-a-day dosing[19●, 78], whereas IV-H2RAs must be given in high doses by continuous infusion[19●,69]. Patients with complicated ZES (severe GERD, Billroth 2 resections, and MEN1 with untreated hyperparathyroidism) are more difficult to treat and require usually twice-a-day PPI dosing often at higher doses (i.e.>20–40 mg/day-omeprazole)[14,15,19●]. Until recently, there was little data on the treatment of pregnant females with ZES[79] but recent data suggests that oral H2RAs or PPIs are effective and safe during pregnancy [19●,80,81].

PPIs and H2RAs have the ability to control the acid hypersecretion of ZES patients for >10 years. Dose increases are usually required yearly with H2RAs but not usually required with PPIs, demonstrating these drugs remain effective and tachyphlaxis is not a problem[13,14,19●,69]. Long-term PPI treatment in ZES has proven safe with very few side effects (<0.1%) causing treatment to be stopped[19●] [83–87]. The long-term effects of PPI-induced hypo-/achlorhydria include a potential concern related to possible nutrient malabsorption[vitamin B12(VB12), calcium, iron], and the possible effect of enhanced hypergastrinemia, resulting in the possible development of gastric carcinoids or other neoplasms[19●,82–84]. Low VB12 levels, but not body iron stores, are not infrequent in ZES and low VB12 levels occur more frequently in ZES patients treated with PPIs[19●,85]. Recent epidemiologic studies[83,84,86] demonstrate prolonged PPI use may result in an increased incidence of bone fractures, but there are no specific studies in ZES[19]. There are a number of reports of PPI induced nephritis, pneumonias, hypomagnesemia, enteric infections and lansoprazole including colitis, but none of these are reported in ZES patients[19●,83,84,87].

Prolonged hypergastrinemia in animals and humans man causes proliferation of gastric mucosal enterochromaffin-like (ECL) which rarely progresses to carcinoid tumors in humans cells(ECL-cells), and in numerous animal models of chronic hypergastrinemia, with time, gastric carcinoids(ECLomas) can develop, some of which are malignant[82,88,89]. It has been proposed the gastric carcinoids develop through a sequence involving increasing degrees of ECL-cell hyperplasia(diffuse, linear, micronodular, dysplasia) [19●,82]. PPIs increase the incidence of gastric carcinoids in animals, but not in man[90]. However, hypergastrinemia alone in man appears to rarely cause a gastric carcinoid, at least up to 10-years, because they rarely occur in patients with sporadic ZES(nonMEN1)[19●,82,88]. In contrast, gastric carcinoids develop in 23% of patients with ZES/MEN1[89] and are not infrequent in chronic atrophic gastritis/pernicious anemia[90] suggesting an accompanying defect may be needed in man, such as loss of the MEN1 gene or the presence of chronic atrophic gastritis, at least for the short term development of gastric carcinoids(<10 years) [19●,82,88,89]. There is no evidence PPIs in patients with ZES increases the rate of development of gastric carcinoids[19●,82,91]. Some studies propose that hypergastrinemia

is associated with the development of colon cancers, but there is no evidence they occur at increased rate in ZES or that PPIs increase their development[19●,82].

LOCALIZATION OF GASTRINOMA

Tumor localization and assessment of tumor extent is essential for the management of ZES[4,5●,6●●,12,13–15,92]. Numerous imaging modalities are used for preoperative assessment or serial assessment of tumor location/extent including: cross-sectional imaging studies(CT scanning, MRI, ultrasound);selective-angiography; somatostatin-receptor-scintigraphy(SRS) using ^{111}Indium-labeleled-somatostatin analogues or ^{68}Gallium-labeled-somatostatin analogues with positron emission tomographic imaging(PET-scanning);endoscopic ultrasound(EUS) and assessment of gastrin hormonal-gradients either assessed trans-hepatically in portal venous drainage or in hepatic veins after selective intra-arterial secretin-stimulation [5●,12,14,15,93–95]. At the time of surgical exploration the use of intraoperative ultrasound(IOUS), transillumination of the duodenum, and performance of a duodenotomy to localize small duodenal primaries is recommended[14,96,97].

Cross-sectional imaging with CT or MRI with contrast enhancement (CT, MRI) remains the most widely used initial imaging-study in ZES patients, because of its widespread availability, however their detection rate is size-dependent missing many lesions <1cm[5●, 15,43,92,98,99]. SRS is the most sensitive modality for assessing the extent of the disease and is valuable in ZES, as in other pNETs, for detecting liver/distant metastases, as well as the primary tumor[15,99–101,102●]. In the US, SRS is performed using ^{111}Indium-labeleled-somatostatin analogues with SPECT imaging. Studies in Europe, and in a few center in the US, demonstrate that ^{68}Gallium-labeled-somatostatin analogues with positron-emission-tomographic scanning (PET)-scanning, is more sensitive, and likely will become the procedure-of-choice in the future[5●,101,102●]. Cross-sectional imaging will detects 30–50% of primary gastrinomas<1–2 cm whereas, SRS with ^{111}Indium-labeleled-somatostatin analogues with SPECT imaging detects 60–70%. For hepatic metastases, cross-sectional imaging will detects hepatic metastases in a patient with proven hepatic metastases in 70–80%. whereas SRS will detects them in 85–95%[15,99,100,103]. EUS is useful for localizing pancreatic gastrinomas, but misses ~50% of duodenal gastrinomas and thus is of limited value in ZES [104]. Assessment of gastrin gradients is now rarely used in ZES patients.

SURGICAL TREATMENT OF Localized GASTRINOMA

Recent guidelines and other studies agree that in patients with sporadic ZES(without MEN1/ZES), surgery for cure should be attempted if there is not an accompanying illness limiting life expectancy or increasing surgical risk[3,12–15]. The immediate postoperative cure-rate in the NIH prospective studies is 50–60% and the long-term cure rate is 35–40%[38,97,105]. Surgical resection in ZES patients decreases the rate of development of hepatic metastases and increases survival[32,50,106,107]. Even in ZES patients with negative imaging, a recent study reports an experienced surgeon will find a gastrinoma in 98% and 50% will be cured[108●●]. In this study[108●●] the patients with negative imaging had a mean delay of 8.9 years from onset of ZES to surgery which was significantly longer than patients with

positive imaging, and 7% had liver metastases at the time of surgery, raising the possibility the long delay to the development of liver metastases. While it is well-established the presence/development of liver metastases is an important prognostic factor in patients with ZES, the routine resection of lymph nodes is controversial, not only because of the controversy over whether lymph-node primary gastrinomas exist[109–111], but also because the importance of identifying lymph node metastases is controversial, with some studies showing they have prognostic significance and others not [32,50,112●,113●]. Recently the importance of lymph node metastases in gastrinomas[112●,113●,114,115] and all pNETs[112,114] has been investigated. Lymph-node metastases occurred in 43–82% of patients with gastrinomas[[112●,113●,114,115], and in recent studies the postoperative survival rate in pNET patients or patients with gastrinomas with positive lymph nodes [112●,113●] was significantly lower. In one study[112●] the time to the development of liver metastases was significantly reduced in patients with lymph node metastases, and in a large subgroup of patients with gastrinomas with longer followup, the presence of lymph-node metastases was associated with decreased disease-related survival and the decrease was a function of the number of lymph nodes involved. Each of these studies concluded that lymphadenectomy should be routinely performed in patients with gastrinomas and other pNETs and that this not only has prognostic value, it may prolong recurrences and increase survival[112●,113●,114,115].

Another area of increasing surgical controversy is the role for laparoscopic surgery in patients with ZES. Laparoscopic resection is increasingly being used in patients with pNETs, especially in patients with insulinomas or in some cases with nonfunctional pNETs, which are localized by imaging[116,117]. A small number of patients with ZES have undergone laparoscopic resection[116–118] with favorable outcomes. Because of the need for (i) complete exploration of the abdomen, especially of the gastrinoma triangle area [duodenum/pancreatic head-area], (ii) routine lymphadenectomy, and (iii) routine duodenotomy combined with a Kocher-maneuver, it has been recommended that the standard operation in ZES patients not be performed laparoscopically. However, there may be a place for laparoscopic surgery in selected cases such as patients with localized distal pancreatic gastrinoma. The timing, type of operation and place of routine surgical exploration in patients with MEN1/ZES remains controversial. This occurred because numerous studies demonstrate these patients usually(>85%) have duodenal gastrinomas, in additional to pancreatic pNETs which are primarily nonfunctional pNETs(<15% gastrinomas) and the duodenal gastrinomas are invariably multiple, often small(<0.5cm), and in 40–60% of cases associated with lymph-node metastases[14,40,105,119]. Consequently, enucleation or local resection rarely leads to long-term cure. Some authors suggest that cure can only be achieved by performing a pancreaticoduodenectomy(Whipple/or related-operation)[14,27,40,119]. MEN1/ZES patients with small(<1.5–2 cm) pancreatic pNETs have excellent prognoses(survival up to 90–100%–15 years without surgery), as well as MEN1/ZES patients with small duodenal gastrinomas. Some propose all patients with MEN1/ZES undergo surgical exploration and resection/enucleation of any pNET; others that only selected patients with pNETs>2 cm undergo exploration and still others that that aggressive resection with pancreaticoduodenotomy, if needed, be considered[14,27,104,120,121]. Still others

recommend routine pancreaticoduodenectomy in an attempt at cure. Each approach has its advocates but there are no prospective studies to provide guidance. This confusion partially exists because the current natural history of patients with MEN1/ZES or MEN1/pNETs is unclear[9]. Recent ENETs/NANETs guidelines[12,13●●] recommend that routine surgery for possible cure not be undertaken routinely but be reserved for ZES patients with >2cm lesions and pancreaticoduodenectomy generally not be performed.

TREATMENT OF GASTRINOMA PATIENTS WITH ADVANCED METASTATIC DISEASE

It should be kept in mind that most gastrinomas (60–90%) are malignant and most are not cured by surgery. Treatment directed at the metastatic gastrinoma in patients with advanced disease, as with other advanced pNETs, is becoming increasingly important, now that the hormone excess-state can be effectively managed in most cases[6●●,122●●]. [6●●, 122●●] [14]. Only 40% of sporadic ZES patients are cured and almost none with MEN1. The presence of liver metastases is one of the most important prognostic factors for survival in patients with ZES, with survival decreasing with increasing extent of hepatic metastases[15,32,50]. The 10-year survival in patients with diffuse metastatic gastrinoma in the liver is 15–25%[6●●,32,50]. There are only a limited number of studies specifically addressing the treatment of ZES patients with advanced disease, and most data comes from series with patients with all the different pNETs, gastrinomas included. This occurs because most centers have limited numbers of these patients and more importantly, became the antitumor treatments of advanced pNETs are similar for all the different pNETs, with differences occurring primarily in the treatment of the different hormone excess-states. Recently, a number of guidelines became available covering antitumor treatment in patients with advanced, metastatic disease due to pNETs[6●●,12,13,122●●,123,124], as well as a number of recent reviews that cover all aspects of these treatments. These include reviews of use of cytoreductive surgery[6●●,122●●,125–127], chemotherapy[6,10,122●●,128,129], liver-directed therapies(embolization, chemoembolization, radioembolization, radio-frequency ablation)[6●●,122●●,125–127,130,131●], biotherapies(somatostatin analogues/interferon)[6●●,125,132●,133], liver transplantation[6●●,125,134], targeted-molecular therapies(mTOR(everolimus)/tyrosine-kinase receptors(sunitinib)[6●●, 10,125,135●●,136●●,137], and peptide-radioreceptor-therapy(PRRT) using radiolabeled-somatostatin-analogues[6●●,138●]. Because this area is well covered in recent reviews and the findings/approaches are not specific for ZES, but used for all pNETs, this area will be only be briefly discussed.

Cytoreductive surgery is recommended for the <15% of ZES patients in which at least 90% of visible metastatic tumor is considered resectable[6●●,122●●,125, 126], however only 5–15% of patients with metastatic ZES fall into this category. It has been used in small numbers of patients with gastrinomas[14,139]. Whether this approach prolongs survival, however, is not known because no controlled-studies exist. A recent study [140] in patients with ZES/pNETs demonstrates that many patients with advanced disease with vascular abutment/invasion on preoperative imaging studies may benefit from surgery, because in

contrast to those with adenocarcinoma, the pNETs can still be resected, with vascular reconstruction needed only in a small subset.

Chemotherapy(streptozotocin in combination with 5-fluorouracil and/or doxorubicin) remains an important treatment in patients with metastatic gastrinomas [14,129,141]. It produces a response rate of 20–45%, but no long-term cures, and the drugs have considerable side-effects, especially nephrotoxicity. Recently, in 30 patients with different metastatic pNETs, the combination of temozolomide/capecitabine had a partial response rate of 70%, with a median progression-free survival of 92%[142]. Whether this high response rate will be corroborated by other studies and also seen in patients with metastatic gastrinomas is unclear at present.

Liver-directed therapies(embolization, chemoembolization, radioembolization, radio-frequency-ablation) are used in patients with hepatic predominant disease, but are used less frequently in ZES than in other metastatic pNETs, because in ZES, the hormone excess-state can be well-controlled medically, whereas in other functional pNETs, refractory states to drugs may develop, necessitating this approach[6●●,122,130]. In various studies 50–100% of patients with metastatic pNETs have a symptomatic response,25–86% an objective tumor-response, and the mean duration of response is 6–45 mos[6●●,122,130]. Radioembolization with ^{90}Yttrium-microspheres is a relatively new treatment with an objective response-rate of 55%(12 studies) with stable disease in 32%[6●●,122,127,130]. Radiofrequency-ablation can be used alone or at the time of surgical exploration and involves the use of thermal energy to ablate local metastatic deposits[6●●,127,130,131]. The response rates are 80–95%, lasting up to 3 years[6●●,126,130]. Whether any of these liver-directed therapies prolong life or whether one is better than the other is now known, which is the preferred one or when exactly should they be used, has not been addressed in any prospective study.

Biotherapy with somatostatin analogues and/or interferon for their antiproliferative effects in patients with advanced metastatic gastrinomas has been used[143,144], as is the case with other advanced pNETs[6●●,112,122●●]. These agents have primarily a tumoristatic effect causing tumor stabilization in 40–80%, and a decrease in tumor size in regression following chemotherapy, and should be considered first-line in only selected cases. In contrast, in the US NCCN guidelines recommend the use of everolimus/sunitinib as a possible first-line treatment for unresectable well-differentiated pNETs[6●●,150].

Peptide-radioreceptor-therapy(PRRT) using radiolabeled-somatostatin analogues is based on the finding that most pNETs(60–100%) overexpress somatostatin receptors, and this allows targeting of cytotoxic-radiolabeled compounds[6●●,138●,151]. Either of two different radiolabels has generally been used: ^{90}Yttrium-labeled- or ^{177}Lutetium-labeled-somatostatin analogues, coupled by various linkers. With ^{177}Lu-labeled-octreotate in 510 patients with various malignant NETs(40%-pNETs)[6●●,138●,151,152] complete-tumor regression was seen in 2%, partial-regression in 28%, minor-regression in 16%, stabilization in 35%. In 310 patients followed[152], the median duration of objective-responses was 46 mos and median disease-related-survival was not reached(>48 mos). PRRT using either ^{90}Yttrium-labeled- or ^{177}Lutetium-labeled-somatostatin analogues has been used in a number of patients with

ZES with advanced tumors, with partial tumor-response occurring >40% and in fact, the response rate is one of the highest of all patients treated with metastatic NETs, however the recurrence-rate is also high [152,153]. Severe side-effects are uncommon with hematological toxicity in 15% with 0.8% developing a myelodysplastic disorder, liver toxicity occurring in 0.6%, and renal toxicity is uncommon with ^{177}Lu-analogues, and more frequent with ^{90}Y-analogs[6●●,138●,151,152]. This treatment is not approved for routine use in the US or Europe, however this approach appears promising and is now undergoing, in both the US and Europe, a double-blind, prospective study in patients with advanced GI-ileal carcinoids, to prospectively evaluate its efficacy/toxicity.

CONCLUSIONS

There have been recently numerous advances in the management/treatment/understanding of ZES as well as a number of areas of controversy, each of which are reviewed here.

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Key Points

- There are new advances, as well as controversies, in the diagnosis and management of patients with Zollinger-Ellison syndrome (ZES).
- The widespread use of PPIs, which itself induces hypergastrinemia, is making the diagnosis of ZES more difficult to accomplish.
- Although the diagnosis of ZES requires the measurement of fasting serum gastrin, new data suggests that many current commercial gastrin assays are not reliable.
- The surgical treatment of patients with ZES and MEN1 remains controversial.
- Novel modalities to treat advanced ZES include cytoreductive surgery, liver-directed therapies (embolization, chemoembolization, radioembolization), chemotherapy, biotherapy (somatostatin analogous, interferon), molecular-directed therapies (everolimus, sunitinib), liver transplantation and peptide-radioreceptor therapy, a number of which have recently been evaluated by prospective, phase 3 double-blind studies in patients with advanced neuroendocrine tumors .