GASTRINOMA

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ABSTRACT

Gastrinomas are neuroendocrine neoplasms (NENs), that occur primarily in the duodenum and pancreas, which ectopically secrete gastrin, resulting in the Zollinger-Ellison syndrome (ZES), which is due to marked hypersecretion of gastric acid causing severe gastro-esophageal peptic disease. ZES patients have two management problems that must be dealt with: control of the acid hypersecretion and control of the gastrinoma, which is malignant in 60-90% of cases. Most gastrinomas are sporadic, but 20-25% of patients have it as part of the Multiple Endocrine Neoplasia-type 1 syndrome (MEN1), an autosomal dominant disorder characterized by endocrine tumors/hyperplasia of multiple endocrine organs (parathyroid> pancreatic islets>pituitary>adrenal). It is important to identify those with ZES/MEN1 as their management differs from those with sporadic disease. Acid hypersecretion is now controlled medically both acutely and long term, with proton pump inhibitors (PPI) the drugs of choice. In patients with sporadic ZES, after detailed imaging with cross-sectional imaging and somatostatin receptor imaging (SRI), resection of the gastrinomas should be considered whenever possible, with cures reported in 20-45% of patients. The role of surgical resection of the gastrinomas in MEN1/ZES is controversial and it is generally recommended it be reserved for patients with tumors>1.5/2 cm because of the multiplicity of small gastrinomas resulting in very low cure rates. The diagnosis of ZES requires demonstrating fasting hypergastrinemia in the presence of inappropriate acid secretion (pH<2), however, because of the widespread use of PPIs and the lack of gastric acid testing, the diagnosis of ZES is becoming more difficult and referral to a specialty group is frequently required. Patients with advanced metastatic disease are treated as other patients with advanced NENs including with somatostatin analogues, chemotherapy, everolimus, sunitinib, liver directed therapies, and peptide radio-receptor therapy (PRRT) with radiolabeled somatostatin analogues.

GENERAL/DEFINITIONS

ZES was first described in 1955 by two surgeons, RM Zollinger and EH Ellison, in two patients with intractable peptic ulcer disease (1). Although previous cases had been described (2,3), including one well described case by Roar Strom in 1952 (3-5), in Zollinger/Ellison's two patients the authors were the first to propose the important association between the gastric hypersecretion and the presence of a pancreatic neuroendocrine neoplasm (PNEN) (1-3,6). Presently, the term gastrinoma and ZES are often used synonymous, however, in the past the term gastrinoma was also used to refer to a neoplasm synthesizing gastrin and ZES to the clinical manifestations (7). Numerous NENs and non-NENs can synthesize gastrin precursors which are not processed to the biologically active gastrin-17 or

gastrin-34 as in ZES, and thus are generally not called gastrinomas by clinicians or in most current classification systems of pNEN (7-9). In addition to being well-described in humans, Zollinger-Ellison syndrome due to a gastrinoma have also been reported in dogs (10-17), cats (10,18-22), and a Mexican gray wolf (23).

Like most other functional pNEN syndromes (F-pNEN) (insulinomas, glucagonomas, VIPomas, etc.), in ZES the functional syndrome due to the ectopic hormone secretion requires immediate treatment because it was the most frequent cause of morbidity/death prior to effective treatments (24-38). In addition, treatment must be directed at the gastrinomas itself, because similar to all other pNEN, except insulinomas, the majority (60-90%) are malignant (9,26,27,39-42). Whereas effective surgical resection would cure both problems, in <50% of ZES patients is curative resection possible because of advanced disease or the patients have MEN1/ZES, which can only be cured with Whipple resections, which are not generally recommended (discussed below) (6,9,43-49). Therefore, treatment of patients with ZES requires management of two different treatment problems: the acid hypersecretion and the malignant nature of the gastrinoma.

This chapter will review important aspects of the management of patients with ZES and important treatment issues at present, including the most recent studies up to 2023. It will concentrate on the most current important aspects and not cover comprehensively all areas of ZES or numerous areas in depth. For more in depth considerations the reader is referred to recent papers/reviews which cover ZES generally (6,33,38,40,46,49-54); its diagnosis (29,51,55-61), clinical features (24,25,41,62-69); acid hypersecretion (24,50,70-72); gastrin provocative testing and the diagnosis of hypergastrinemia (36,50,51,55,57,73-86); MEN1/ZES (30,44,47,57,64,85-96,96-102); medical treatment of acid hypersecretion (50,51,69,72,78,80,103-108);clinical course and prognosis (41,65,87,93,109-117); surgical treatment of the gastrinoma (6,44,50-52,80,92,95,96,99,100,102,103,118-128); imaging and tumor localization (37,50,90,112,124,125,129-141); treatment of advanced disease in ZES and other NENs (42,48,50,51,58,135,142-156); diagnosis and treatment of all/functional pNEN (24-26,34-36,36,48,48-50,54,58,148,156-165) and pathology, pathogenesis and classification of gastrinomas/NENs (9,50,58,86,96,117,158,166-174).

Before considering the diagnosis and management of ZES in more detail it is important to realize that there are a number of misconceptions about ZES, often because of comparison with other pNEN and these need to be kept in mind. They are listed in the Table 1 below and briefly discussed in the following sections.

Table 1. Widely Held Misconceptions About ZES
1) Gastrinomas, similar to a number of other pNEN (insulinomas, gastrinomas, PPomas), primarily occur in the pancreas. FACT: In recent studies, 60-100% of gastrinomas in both sporadic ZES and MEN1/ZES occur in the duodenum, with only 0-15% in the pancreas (6,43,50,95,102,127,175-179) (Table 2).
2) MEN1 is uncommon in ZES, similar to other pNEN such as insulinomas (3-5%), glucagonomas (<5%), PPomas/nonfunctional pNEN (<3%). FACT: MEN1 is found in the highest frequency of all pNEN syndromes in ZES patients occurring in 20-25% and is important to diagnose because of its different treatment aspects (30,50,64,72,87,89,95,102).
3) With the increased awareness of ZES and widespread availability of gastrin assays and sensitive imaging modalities, similar to some other pNEN, gastrinomas are being diagnosed earlier. FACT: The time of onset of symptoms to diagnosis of ZES remains 4-7 years (24,26,48,60,62,89,134) and a number of factors are contributing to make the diagnosis even more difficult (See point #4 below).
4) As recommended in all guidelines (9,72,80,152,157,180-182), similar to other functional pNEN syndromes (F-pNENs), ZES is currently diagnosed by demonstrating excess hormone production (fasting hypergastrinemia) in the presence of an unphysiological effect of the hormone hypersecretion (i.e., inappropriate acid hypersecretion (elevated basal acid output>15 mEq/hr., pH<2)) (9,50,51,55,56,59,70,72,73,79,181,183,184). FACT: In contrast to, for example, insulinomas, which are uniformly diagnosed by demonstrating fasting hyperinsulinemia with accompanying hypoglycemia (frequently during a fasting study) (29,50,185-188), in a recent review of the last 20 cases of ZES reported in the literature in 2018 (55), 95% of the diagnoses were reported without performing a gastric analysis or gastric pH assessment (55) and thus not using classical established criteria. This approach has complicated the diagnosis of ZES and the factors leading to this confusion will be discussed below in detail in the ZES diagnosis section.
5) In MEN1 patients, similar to other MEN1 patients with F-pNEN such as insulinomas and glucagonomas, most gastrinomas can be cured by nonaggressive surgical resections in MEN1/ZES patients. FACT: In contrast to other F-pNEN (29,157,189), the 5-year surgical cure rate of MEN1/ZES is <5% (6,30,43,44,88,190) without aggressive surgical resections such as Whipple resection, which are not recommended (6,9,88,92,93,118,123,157,180,182). However, without these resections, most patients with small tumors and adequate acid secretory control have an excellent prognosis, which has led to controversy in their treatment, and will be discussed in the surgical section later (30,43,47,92,93,95,102,118,157,180,182,191).

The misconceptions listed in Table 1 above as well as the factors specific to ZES that led to these misconceptions have led to controversies that are complicating numerous aspects of the management of ZES patients. These extend particularly to the current diagnosis of ZES, the management of both gastrinomas and nonfunctional pNENs in MEN1/ZES patients, and various aspects of the surgical management of these patients. Each of these will be discussed in more detail in the specific later sections in this chapter.

EPIDEMIOLOGY: ZES

PNEN account in different series for 1-10% of all pancreatic tumors with a prevalence of 1/100,000 and annual incidence of 1-4/million, which is increasing in frequency (192-194). In older series, insulinomas, gastrinomas, and NF-pNEN were reported with similar frequencies, however, in recent series of pNEN patients NF-pNEN make up 60-80% of all cases (24,48). Currently, for F-pNENs, insulinomas and gastrinomas are the most frequent, with incidences of 0.5-3/million in different series (26,50). Generally, insulinomas/gastrinomas are 8-10-fold more frequent than VIPomas, 17-fold more than glucagonomas, and >20 fold more the other F-pNENs (GRFomas, pancreatic ACTHomas, etc.) (26,50). Gastrinomas are the most frequent malignant F-pNEN, because 60-90% are malignant, like the other less common F-PNEN, in contrast to insulinomas, which are malignant in only 5-10% in most series (26,50,158,188).

Gastrinoma, as well as other pNENs, can occur both sporadically or as part of an inherited syndrome (30,158,195-197). Gastrinomas occur more frequently with an associated inherited pNEN syndrome than other F-pNEN, particularly in the case of MEN1, where 20-25% of all ZES patients have MEN1/ZES, compared to <3-5% of other F-pNEN syndromes (30,50,65,86,87,89). ZES is also rarely reported in other inherited syndromes associated with pNEN including the autosomal dominant syndromes, von Hippel –Lindau Disease (30,196,198,199), tuberous sclerosis (30,200), and neurofibromatosis type 1 and type 2 (30,199,201-204).

PATHOPHYSIOLOGY: CLINICAL FEATURES

In the majority of patients with ZES (>90%), the presenting symptoms are due to the marked gastric acid hypersecretion (24,28,62,64,70,205,206). Generally, only in patients with advanced disease late in the disease course are the prominent symptoms due to the tumor per se (abdominal pain, weight loss, anorexia, etc.) (24,28,40,62,205,206). The acid dependency of the above symptoms is shown by numerous studies reporting in a typical ZES patient, all of the presenting symptoms (including the PUD, pain, diarrhea, GERD symptoms, weight loss) disappear if the gastric acid hypersecretion is adequately controlled by any means (surgical, medical, acid aspiration) (7,27,28,40,103,106,207).

The ectopic release of gastrin by the gastrinoma is the direct cause of the gastric hypersecretion (49,170,208). In a typical ZES patient the fasting hypergastrinemia results in a markedly increased basal acid output (BAO) of approximately 4-fold (42-mEq/hr.) (70) and in some patients the BAO is increased more than >10-fold (27,28,70,206,209-212). Chronic hypergastrinemia also has trophic effects on the gastric mucosa, stimulating an increase in number of parietal cells and gastric enterochromaffin-like cells (ECL cells) (7,76,213-217) with the result the parietal cell mass is increased up to 4-6-times normal (27,76,218,219). This contributes to both the elevated BAO and increased maximal capacity to secrete acid, as shown by ZES patients having increased maximal acid outputs (MAOs) (27,70,76,212,219-221). Diarrhea which is seen in >70% of ZES patients (Table 3) in recent prospective studies is due to the effects of the gastric acid hypersecretion by causing structural damage to the small intestine, it interferes with fat transport; inactivates pancreatic lipase; can precipitate bile acids; and if prolonged, leads to steatorrhea (27,158,222).

Long-standing hypergastrinemia stimulates proliferation of the gastric enterochromaffin-like cells (ECL cells), which show such a response in ZES-patients (223). Gastric ECL cells are increased a mean of twofold in ZES (76,212,223-225). ZES patients can develop advanced ECL-proliferative responses, similar to the findings in animal studies of

chronic hypergastrinemia induced by various methods, and which, in some cases, results in neoplastic changes (7,76,213,217,226,227). It has been proposed that with chronic hypergastrinemia, the ECL cells undergo a progressive hyperplasia-neoplasia sequence of events beginning with simple hyperplasia, followed by linear hyperplasia, micronodular hyperplasia, adenomatoid hyperplasia, dysplasia (pre-carcinoid) and finally the development of carcinoids (7,76,217,226,228). In the prospective NIH studies greater than 98% of ZES patients demonstrated ECL hyperplasia (217,227), with 50% having advanced changes with sporadic ZES (7% dysplasia) (217) and 53% with MEN1/ZES (2%-dysplasia) (227). In ZES, there is a close correlation between the degree of ECL hyperplasia and the fasting serum gastrin level (76,217,227). Even though advanced ECL proliferative changes are seen in both sporadic and MEN1/ZES-patients, they have a marked difference in the rate of occurrence of gastric carcinoids. Gastric carcinoids occur in 0-33% of MEN1/ZES-patients (76,227), and in the one perspective NIH study were found in 23% (87,224,227,229-231). However, gastric carcinoids rarely occur (<1%) in sporadic-ZES patients (212,217,232-234), and it has been estimated they occur at least with 70-fold greater frequency in MEN1/ZES-patients (227). An important finding of the prospective NIH studies of ZES patients is there was no threshold effect of fasting gastrin on ECL growth, as had been previously proposed, with any increase in FSG being associated with increased ECL proliferation (76,217,227).

PATHOLOGY AND TUMOR CLASSFICATION

In the past, gastrinomas were frequently reported as nonbeta islet cell tumors (1), because they were originally thought to originate in the pancreas from the islets and to generally be pancreatic in location, similar to insulinomas (1,51,185,205,235,236). They were reported to occur in the pancreas with a distribution of pancreatic head: body: tail of 4:1:4 (27,40,63,205,237,238). Later studies described a small percentage of duodenal gastrinomas (239,240). Currently, duodenal gastrinomas are found 2-10 times more frequently than pancreatic (Table 2) (43,64,95,102,175-177,241-245). Therefore, prior to the mid-1980s, 80-95% of gastrinomas were reported in the pancreas, whereas now 45-100% are duodenal, and 0-45% pancreatic (40,175-177,236,241-244). Even as late as 1998, in Soga's review of 359 cases of ZES, only 11% of the patients had a duodenal gastrinoma (7,27,43,63,235).This likely occurred because of the analogies to insulinomas which are almost always in the pancreas, as well as the fact that duodenal tumors were being missed on preoperative localization studies or with a standard laparotomy because of their small size (Table 2) (27,43,175-177,241) and in many series no gastrinoma was found in a significant percentage of patients (7,27,28,40,63,235). Furthermore, a number of the early cases were patients with MEN1/ZES, and intra-pancreatic tumors were found (which were generally NF-pNEN) and these were attributed to be the source of the gastrin, with the true source being in a duodenal gastrinoma, which was not explored for or detected. Recent studies show that when careful attention is paid to the duodenum at surgery (duodenotomy, intraduodenal palpation, transillumination on occasion), more duodenal tumors were found (6,45,95,102,175,176,241-244,246-248). Primary gastrinomas are rarely found in other intra-abdominal sites: (particularly the ovary and liver/bile duct, as well as very uncommonly in the pylorus, spleen, mesentery, stomach, kidney) and in a few cases(<5 total) (<0.5%) in extra-abdominal locations, including the cardiac intraventricular spectrum and due to nonsmall cell lung cancer (Table 2) (40,45,109,110,121,126,176,236,249-265). A number of studies provide strong evidence that gastrinomas can arise in lymph nodes as the primary site, however, this is not universally accepted and some have proposed that they represent metastases

from occult primaries (27,40,43,258,259,266-274). The possibility that a lymph node primary tumor may occur is supported by studies demonstrating long-term cure after resection of only a lymph node gastrinoma (40,258,259,267). Furthermore, in 3-25% of patients without pNEN, chromogranin-positive rests occur in abdominal lymph-nodes (266,275). In the NIH prospective series, 11% of patients are classified as having primary lymph node gastrinomas (Table 2).

At surgery, it has been recently emphasized that 60-90% of gastrinomas occur within the "gastrinoma-triangle", which is an area formed by the junction of the cystic/common bile ducts posteriorly, the junction of the second/third parts of the duodenum inferiorly, and the junction of the pancreatic neck/body medially (40,176,177,244,276). This occurs primarily because of the high frequency of duodenal gastrinomas which are now found that fall into this area. Duodenal gastrinomas do not occur in equal proportion in all parts of the duodenum, but instead demonstrate a decreasing occurrence distally, with almost 90% of duodenal gastrinomas occurring in the $1^{st}/2^{nd}$ part of the duodenum (Table 2) (175,277,278).

In early studies, 60-90% of gastrinomas were associated with metastases (primarily lymph-node/liver) and therefore they should all be considered potentially malignant (9,39,205,236,257,279). The presence of metastases or gross invasion of normal tissue remains the only generally accepted criterion for the diagnosis of malignancy (27,40,280). Gastrinomas metastasize initially primarily to regional lymph nodes and the liver (27,109,236). Duodenal gastrinomas are characteristically small in size (Table 2), frequently <1 cm in diameter; however, they are associated with lymph node metastases in 47% of the cases in the NIH prospective studies (20-80%-literature), which is a similar percentage seen with the larger pancreatic gastrinomas (mean size 3.8 cm) (Table 2). From this data it has been proposed that gastrinomas in these two sites are equally malignant (109,110,175,281). However, from the NIH prospective studies it is also proposed that duodenal and pancreatic gastrinomas are not equally aggressive, because liver metastases occur in 52% of the NIH patients with a pancreatic gastrinoma (15-45%-literature) (Table 2), whereas liver metastases occur in only 5% of duodenal gastrinomas (10%-literature) (Table 2) (109,110,281). This is a similar rate to a recent collective series of 24 ZES cases with a duodenal gastrinoma in which 4 of the patients (16%) had liver metastases but 75% had lymph node metastases (282).Similarly in a recent review of 52 ZES patients(33-sporadic/19-MEN1/ZES) the rate of liver metastases was significantly lower in those with MEN1/ZES (21% vs 51%, p=0.031) (64). At presence the basis for this difference in aggressive behavior of pancreatic and duodenal gastrinomas is unclear. A genomic analysis (172) identified a number of molecular similarities and differences between duodenal gastrinomas and pNENs. In a comparison of RNA-seq data, duodenal gastrinomas and pancreatic pNENs shared 1233 common co-expressed transcripts, however duodenal gastrinomas expressed 909 distinct transcripts not seen in either normal duodenum or pancreatic pNENs and pancreatic pNENs had 588 unique transcripts not shared in normal pancreas or duodenal gastrinomas (172).The duodenal gastrinomas strongly expressed two inflammatory mediators (IL-17 and TGF-alpha), enrichment of mesenchymal, cytoskeletal, neuroactive-ligand receptor interaction, and calcium signaling pathway genes (64). In both duodenal and pancreatic neuroendocrine tumors alterations in expression of genes were found that were involved in cellular signaling cascades as well as in associated immune cells, and presence of proinflammatory cytokines, however it is unclear how these are related to the differences in biologic behavior of these two groups of NENs.

Duodenal gastrinomas in sporadic cases (75-80%) differ from those in MEN1/ZES patients in that they are usually solitary tumors, whereas in MEN1/ZES they

are multicentric, smaller and multiple (64,178,283,284).

Duodenal gastrinomas account for 44-66% of all duodenal NENs (285,286), however only 58 % are associated with the development of ZES (286). In a recent study (286) the characteristics of sporadic duodenal gastrinomas associated with ZES (n=24) or not associated with ZES (n=17) were compared. The duodenal gastrinomas associated with ZES had a higher mean Ki-67(1.74 vs 0.85, p=0.012), more frequently had associated lymph node metastases (75 vs 6%, p=0.012), more frequently were associated with liver metastases and presented more frequently with TNM stage ≥III (75 vs 6%, p<0.0010). In a recent collective study of 108 sporadic ZES patients (127) in which 68 had duodenal gastrinomas and 19 pancreatic tumors, the overall 5-yr survival was 94% and not affected by gastrinoma location. However, pancreatic location was associated with higher recurrence rate (p=0.0001) (127).

In the past literature, approximately one-third of ZES patients presented with metastatic liver disease, approximately one-third with no tumor found and one-third with localized disease (Table 2) (27,40). Some recent studies suggest an increasing proportion are being seen with earlier disease stages, without advanced disease (40) (Table 2). For example, in the last 221 patients seen at the NIH, the majority (65%) at presentation had localized disease, and in the remaining 35% of the patients, they were divided between those with hepatic metastases and those with no primary tumor found (40,109,110) (Table 2). This distribution of gastrinoma extent differs from that reported in various surgical series, because not all ZES patients are included in these series with exclusion of all non-operated patients including those with patients with diffuse liver metastases, most with MEN1/ZES and those with contra-indications to surgery (9,43,181,287,288). In the last 155 patients undergoing surgical exploration at NIH, 85% had limited disease and the remaining 15% either had limited hepatic metastases (8%) or no tumor was found (7%) (40). In older studies, up to 50% of patients had no tumor found (Table 2), whereas at present, gastrinomas are more frequently found, as evidenced by the recent NIH data in which in the last 81 patients explored for possible cure at NIH, a gastrinoma was found in all (43). As pointed out above this difference is almost entirely due to the careful exploration of the duodenal area with a Kocher maneuver, duodenotomy, intraluminal palpation, and transillumination, (43,63,175,176,244,247,289). It is likely the detection rate of primary gastrinomas will increase even further with the recent development and widespread use of somatostatin receptor imaging (SRI), which has superior sensitivity to conventional cross-sectional imaging (129,133,134,136,137,139,153). SRI was initially performed with ^{111}Indium (diethylenediamine penta-acetic-D-phenylalanine-1) octreotide with single photon emission CT (SPECT) detection, but has now been replaced by ^{68}Gallium DOTA (9,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid) labeled somatostatin analogues (generally ^{68}Ga-DOTATOC PET/CT) with positron-emission tomography detection because of its even greater sensitivity (129,134-137,139,153,290-293).

Distant, extrahepatic, metastases can occur with advanced gastrinomas (112,294-299). Metastases to bone are reported in 31% of ZES patients with advanced disease which occur primarily in the axial skeleton initially, however, they are uncommonly seen in ZES patients that do not have liver metastases (112,294,297,300). Their identification is important, because their detection frequently alters management (109,112,294,296,298,299).

Histologically, gastrinomas show the typical features of NENs, with cubical cells generally with few mitoses and having a granular, eosinophilic cytoplasm (236,280). They can demonstrate trabecular, gyriform

or glandular morphology; however, no specific pattern is predictive of biologic behavior (27,235,280). Duodenal gastrinomas occur in the submucosa, frequently infiltrate the mucosa and in the case of tumors >1 cm, the muscular layer (236). Duodenal gastrinomas usually have proliferative rates <10%, whereas pancreatic gastrinomas frequently have higher proliferative rates (236,286). Both duodenal and pancreatic gastrinomas may demonstrate blood vessel invasion (236,280). Gastrinomas are usually identified as a NEN by their histological appearance and positivity with immunohistochemistry for the NEN markers (chromogranin A, synaptophysin) (27,236,280,301). Gastrin immunoreactivity (Gastrin-IR) can be detected in most gastrinomas (27,236,302,303) and approximately one-half produce multiple hormones (27,236,302,303).

Recently, it has been proposed that gastrinomas, as well as all pNEN/GI-NENs (carcinoid tumors), should have a common classification as NENs (166,168,304-306). Several classification systems (International Union for Cancer Control/American Joint Cancer Committee (UICC/AJCC), World Health Organization (WHO), European Neuroendocrine tumor Society (ENENs)) for both staging and grading NENs have been proposed recently, validated for pNEN, GI-NENs (carcinoids) and NENs (carcinoids) in other locations and recently updated (158,166,168,306-308). The use of these classification systems is essential to the management of NEN patients because they not only have overall prognostic significance, they also have predictive value for different treatment approaches and thus can dictate the treatment approach in some cases (115,115,116,116,158,166,167,306,308). These classification systems use primarily tumor size, extent, differentiation of the tumor and invasion for determination of stage (306). The grade of the tumor is determined by evaluating proliferative indices (Ki-67 and mitotic index (MI)) and the degree of differentiation of the tumor (well vs poor). NENs are divided into three grades based on the proliferative indices with Grade 1(G1) or low grade, having a Ki67<3%(MI <2 mitoses/10-HPF; Grade 2(G2) or intermediate grade having a Ki67>3-20%(MI-2-20/10 HPF), and high grade or Grade 3(G3) having a Ki67>20%(MI>20 mitosis/10 HPF) (115,116,158,166,167,306-309). Recently (WHO2017, 2019) Grade 3 was divided into two different groups depending on tumor differentiation with G3NEN having well differentiated tumor cells, and G3NEC (neuroendocrine cancer) having poorly differentiated tumor cells (115,116,158,166,167,306,308,310). Recent studies show G3NENs and G3NECs not only vary markedly in survival, but they also vary in their molecular pathogenesis and their treatment approaches (115,116,158,166,167,306,310,311). Proper classification of gastrinomas is essential, because recent studies demonstrate it has prognostic value and may affect the type of treatment recommended (115,116,304-306,312). Most gastrinomas are well-differentiated, pNEN Grade 1 or grade 2 (38,64,236,286). In one recent retrospective cohort study (64) (n=52), the grades of gastrinomas in patients with MEN1/ZES differed from those with sporadic ZES in having lower grade (G1: 83 % vs 39%; G2 (11% vs 54%) G3: (5.6% vs 6.1%), as well as being smaller in size (1.7 cm vs 3.1 cm). A review of 171 gastrinomas in various papers published up to 10/2020 in which tumor grade was reported, shows that 74% of the gastrinomas were grade 1, 22% were Grade 2 and only 4% were Grade 3(313). There is limited data on the correlation of tumor grade in ZES patients with survival. In one study (65) on univariate analysis in MEN1/ZES and sporadic ZES patients(n=37) the presence of grade 3 gastrinomas correlated with decreased survival (p=0.008), however not on multivariate analysis. In a recent review (127) of 108 patients with sporadic ZES, no predictive factors for survival, including tumor grade, were identified, however, for recurrence post- surgical resection, only tumor size (p=0.005) and tumor grade (p=0.01) were independent predictors of tumor

recurrence. Two recent analyses (115,116) of prognostic factors in patients with any pNEN demonstrate that grade of the tumor was the most frequent significant prognostic factor cited in the studies analyzed both for overall survival and for disease free survival post-surgery (116) and in treatment of advanced resistant disease (115). These data would strongly suggest that the tumor grade of the gastrinoma in ZES patients will likely be a very important prognostic factor for assessing various aspects of long-term tumor behavior (survival/recurrence/aggressive growth).

Table 2. Characteristics of Gastrinomas (NIH Prospective Studies and Literature)

Characteristic	NIH Data (n=221) Mean (range) Percent	Literature Mean (range) Percent
Primary Location		
Pancreas	24	42 (0 – 70%)
Duodenum	49	15 (0 – 100%)
Lymph node	11	<1%
Other [(1)]	9	2 (0 – 18%)
Unknown	16	30 (7 – 48%)
Duodenal Location		
D-1	57	ND
D-2	32	ND
D-3	6	ND
D-4	3	ND
Percent Extent of Disease		
No tumor found	13	30 (7 – 50%)
Localized disease	70	36 (23 – 52%)
Metastatic disease to liver	17	34 (13 – 54%)
Extent Metastases		
Primary only	36	32 (23 – 50%)
Primary + lymph nodes	29	23 (8 – 61%)
Primary + liver metastases	23	32 (15 – 40%)
Liver metastases only	3	10 (4 – 15%)
Lymph node metastases only	16	11 (4 – 24)
Gastrinoma Size (cm)		
Mean (largest)	2 ± 0.2(0.1-4.8)	(1-6)
Duodenal	0.9 ±0.1(0.1-5)	(0.2-5.5)
Pancreatic	4 ± 0.3 (0.5-7)	(0.5-10)

Metastases: Duo vs Pancreatic		
Lymph node Metastases (%)		
Duodenal	47	(20-80%)
Pancreas	48	(up to 48% of patients had no primary 0-60%)
Liver Metastases (%)		
Duodenal	5	10
Pancreas	52	(15-45%)

Abbreviations: Duo-duodenal; D1-4-duodenal regions, 1,2,3,4;
Data are from (2,109,110,175,177,178,243,244,246,281,314-317).
(1) Other tumor locations include additional intra-abdominal sites (liver, bile duct, spleen pylorus, mesentery, ovary, lymph nodes) and very rarely extra-abdominal sites (heart, nonsmall cell lung cancer.

Tumors in a given patient in multiple locations can be monoclonal or polyclonal. In MEN1, multiple gastrinomas were reported to arise by independent clonal events in one study (318). A more recent study (114) which include 137 microscopic and macroscopic duodeno-pancreatic NENs and 36 matched metastases in 10 patients with MEN1 assessed tumoral ARX, PDX1, Ki67, gastrin expression and alternative lengthening of telomere. Most metastases (91%) originated from a single NET of origin, however, a few patients had likely multiple, metastatic primary NETS. In 6 patients with hypergastrinemia with MEN1, periduodeno-pancreatic lymph node metastases expressed gastrin and clustered with minute duodenal gastrinomas, not with larger pNEN. The pNEN frequently clustered with high grade or alternative lengthening of telomere positive primary tumors. It was concluded that in MEN-1 patients with ZES and pNEN a duodenal origin of the periduodeno-pancreatic lymph node metastases is likely even if preoperative localization studies do not reveal a duodenal tumor (114). Clonality (319) was analyzed in 20 sporadic gastrinomas from eight patients in whom the tumor was present in at least two separate sites. A combination of methods was used to assess clonality, including MEN1 gene mutation analysis, loss of heterozygosity analysis of the MEN1 locus, and analysis of X-chromosome inactivation at the human androgen receptor locus (human androgen receptor analysis). In three patients, a somatic MEN1 gene mutation was detected in the tumor. Identical mutations were found in other tumors at different sites within the same patients. Human androgen receptor analysis in three informative patients and loss of heterozygosity analysis in five patients revealed identical clonal patterns in the tumors from multiple sites in each patient. This study (319) concluded that sporadic gastrinomas at multiple sites are monoclonal and that MEN1 gene alterations in gastrinomas occur before the development of tumor metastases.

TUMOR BIOLOGY

Similar to other NENs, gastrinomas frequently synthesize (pancreatic polypeptide, insulin, glucagon, somatostatin) and also secrete multiple, gastrointestinal peptides as well as chromogranins, alpha-subunits of the glycoprotein hormones, and neuron-specific enolase (27,280,303,320-322). In one study (303) plasma levels of hormones other than gastrin are elevated in 62% of ZES-patients, with one additional hormone elevated in 44% and two in 18%. Motilin is the most common plasma hormone also elevated (30%), followed by human pancreatic

polypeptide (27%), neurotensin (20%) and gastrin-releasing peptide (10%) (303). The occurrence of a second F-pNEN syndrome does occur in ZES patients (27,303,323,324) with cases of concomitant ZES and insulinoma (87,303,324-331),GRFomas (326,332,333), ectopic Cushing's syndrome (66-68,113,325,334-345), glucagonomas (87,324,328,342,343,346-348), VIPoma (324,325), somatostatinomas (339,349), carcinoid syndrome (87,325,327,343,350) and PTHrPomas (351) all described. Even though secondary F-pNEN syndromes have been described in ZES, in general they are relatively infrequent, except for the development of Cushing's syndrome in patients with advanced metastatic gastrinomas (66,68,109,113,325,336). In a prospective study from NIH of 45 ZES patients with a mean follow-up of 146 mos. from ZES, only one patient (2%) developed a second F-pNEN syndrome onset for a rate of 0.16%/yr (1% of patients every 6 yrs. of follow-up). This rate was considerably less than that reported in another study (352) of 353 patients with all pNEN(169=gastrinomas) in which 6.8% of all patients developed a secondary pNEN syndrome over a 19-mo. mean follow-up(rate=4.3%/yr.). Ectopic Cushing's syndrome has been more frequently reported in patients with ZES (27,113,334,336,345,353) as well as other pancreatic endocrine tumors (353-356). In a prospective study from the NIH (109) ectopic Cushing's syndrome developed in 4% of all patients with ZES studied (9/212), 17% (9/54) with liver metastases, 21% (7/33) dying of ZES-related causes and 25% (5/20) with bone metastases. It was an independent predictor of poor survival ($p < 0.005$) with patients having a 10-year survival of 0%. Ectopic Cushing's syndrome only developed in patients with metastatic liver disease. Similar to bone metastases, development of ectopic Cushing's syndrome was a strong predictor of poor prognosis with patients only surviving a mean of 1.7 ± 0.4 years after its onset (109).

The gastrin-gene covers a 4 kilobase area and consists of 3 exons and 2 introns, with the coding region translating into a 101-amino acid peptide, pre-progastrin (7,7,8,170,357,358). In normal antral G-cells, pre-progastrin undergoes a number of post-translational processing steps including dibasic cleavages, removal of the glycine extended COOH-terminal amino acids and sulfation, leading to the formation of progastrin, then COOH-terminal glycine-extended forms and finally the biologically active forms consisting of 2 COOH-amidated gastrins, gastrin-17 (G-17) and gastrin-34 (G-34), existing in sulfated and non-sulfated forms (7,8,170,357,358). Normally, >90% of antral gastrin is G-17, while in the duodenum only 40-50% is G-17(7,8,357,358). In the circulation, normal G34 is the predominant form (>60%) and sulfated/non-sulfated forms occur equally (7,8,357,358). In contrast, in patients with gastrinomas the relative concentrations of G-17 are higher (74-80%), and increased concentrations of partially processed forms are found (progastrin, NH_2- and COOH- terminal fragments, COOH-glycine extended fragments, incompletely amidated fragments) (7,8,27,357-360). Alterations in post-translational processing have been correlated with the presence of metastatic disease (7,8,27,359,360); however, no prospective studies have established their usefulness in an individual case (7) and they are currently rarely measured.

Chromogranin A (CgA) is a 48-kilodalton protein stored in secretory granules of neuroendocrine cells and is widely used as an immunocytochemical marker to identify tumors as NENs (27,236,280,301,322,361-364). CgA is released simultaneously with the release of polypeptides and thus can be used as a general plasma tumor marker for NENs (322,361-363,365-368). Plasma CgA levels are elevated in 80-100% of ZES patients, as is the case in patients with other pNEN/GI-NENs (carcinoids) (322,365-370). Changes in plasma CgA levels are reported to be useful for assessing changes in tumor mass in some studies;

however, in other studies, including in patients with gastrinomas, it has been found to be a relatively insensitive marker for tumor progression and/or NEN identification (115,116,364-369,371-375). One major problem with using plasma CgA as a tumor marker in ZES patients is that the chronic hypergastrinemia causes gastric ECL cell proliferation which increases plasma CgA (24,362-364,368,376). Thus, in ZES, elevated plasma CgA can come from the gastrinoma or from hyperplastic ECL cells (24,377-379). Unfortunately, plasma CgA is also increased by inflammatory disorders, other endocrine diseases, the use of proton pump inhibitors, gastrointestinal disorders, cardiovascular disorders and altered renal function, and therefore minimally or moderately elevated plasma CgA levels in the range frequently seen with small gastrinomas/pNEN overlap with values found in these other disorders (361-364,368).

In patients with gastrinoma, a number of agents stimulate the release of gastrin including secretin (61,74,75,84,380-384), glucagon (385-387), bombesin/GRP (380,388), muscarinic cholinergic agonists (380), beta-adrenergic agonists(389), calcium (74,75,380,383,384,390) and a standard meal (74,384,391,392); in addition, native and synthetic somatostatin analogues (octreotide, lanreotide) can decrease serum gastrin (7,103,393-396). Studies demonstrate that gastrinomas possess secretin receptors, somatostatin receptors, bombesin/GRP receptors, and calcium-sensing receptors (380,388,397-401). These findings have been used clinically for ZES diagnosis with the development of secretin, calcium, glucagon and standard meal provocative tests and the use of somatostatin analogues to control acid hypersecretion (7,56,74,75,103,391,394). The clinical aspects of gastrin provocative testing will be discussed in a later section on ZES diagnosis. Currently, somatostatin analogues are uncommonly used to control acid hypersecretion in ZES patient, because they must be given parenterally, whereas effective long-acting, oral antisecretory agents such as PPIs are available and are the drugs of choice (29,103,142,151,181,182,396). Somatostatin analogues are used for their anti-growth effects or to control ectopic secretion of other hormones in gastrinoma patients, as in other F-pNEN (25,58,142,148,152,155,402,403), and this will be discussed in later sections. Furthermore, the presence of somatostatin receptors on gastrinomas, as well as on other pNEN/NENs, is used for tumor localization, as well as to deliver cytotoxic radiotherapy to patients with advanced tumors (51,129,133,134,136,137,139,142,185,404), both of which will be discussed later in the treatment sections.

The exact mechanisms by which secretin, calcium, glucagon, or a meal stimulate an increase, and somatostatin analogues a decrease, in serum gastrin in ZES patients is not completely clear (27,74,397). The most likely explanation is a direct effect on gastrin release from the gastrinoma through activation of specific receptors which are known to be present on these cells, although others have proposed (in the case of the secretin-test) that it is an exaggerated physiological response (397,405,406). The evidence for a direct effect is that presence of receptors for these agents which have been shown on gastrinomas. Furthermore, in dispersed/cultured gastrinoma cells, calcium and secretin stimulate gastrin release, and secretin activates adenylate-cyclase in these cells which stimulates gastrin release (380,393,397,399,407-409). whereas somatostatin causes inhibition (393,409). Also, a direct relationship has been shown between the magnitude of expression of secretin receptors on gastrinomas and the magnitude of the secretin-stimulated response in ZES patients (397).

The exact pathogenesis or cell-of-origin of pancreatic or duodenal gastrinomas remains unclear. As mentioned above, gastrinomas and other pNEN were frequently called islet cell tumors, however it is still

controversial that those arising in the pancreas actually originate from pancreatic islets (410,411). Numerous older studies have reported that gastrin is found only in the fetal/developing pancreas in islet cells so if pancreatic gastrinomas arose from islets, the possible cell of origin was unclear (8,27,412-414). Passaro and colleagues proposed two different subpopulations of gastrinomas existed (414-416). One group occurred in the gastrinoma triangle (duodenum, pancreatic head, peri-duodenal lymph nodes), which were to the right of the superior mesenteric artery, which originated form the ventral pancreatic bud and were relatively more benign with frequent positive lymph nodes, low rate of liver metastases and high cure rate (414-417). In contrast, the second group occurred outside the gastrinoma triangle, were entirely within the pancreas, were to the left of the superior mesenteric artery, arose from the dorsal pancreatic bud, and were more aggressive with lower cure rates and liver frequency of liver metastases (414-417). Numerous studies support the conclusion that duodenal and pancreatic gastrinomas differ in biologic behavior (109,110,127,170,172,281,415,418-420). Furthermore, in numerous studies gastrin-producing G cells were found in the adult duodenum, but not in the adult pancreas; therefore, supporting the proposal that different cells-of-origin were likely for duodenal and pancreatic gastrinomas (27,40,412,413,418,419). This proposal is further supported by a study (420) which demonstrates that all 15 duodenal gastrinomas show sonic hedgehog expression with none showing expression of pancreatic-duodenal homeobox 1, whereas the reverse pattern was seen in 11 pancreatic gastrinomas. It has been suggested that gastrinomas in the gastrinoma triangle area originate from stem cells in the ventral pancreatic bud, and that these cells become dispersed in lymphoid and duodenal tissue and give rise to the gastrinomas in this area (414) Others have proposed that gastrinomas originate from multi-potential, endocrine- programmed stem cells that undergo inappropriate and incomplete differentiation toward the G-cell in the islets/pancreas (27,413,418). Although some recent studies propose that cancer stem cells, which have been described in a number of solid tumors, could also be important in the pathogenesis of pNEN or GI-NENs, at present they have not been convincingly identified and isolated in GEP-NEN pathologic samples (421). A recent detailed lineage tracing study of gastrin expressing cells in pancreas provides some of the strongest evidence that pancreatic gastrinomas in sporadic ZES cases may originate from the islets (412). In this study (412) during fetal stages up to postnatal day 7 gastrin expressing cells were abundant, whereas a small population of gastrin expressing cells existed in adult islets which co-expressed glucagon or insulin and the pancreatic gastrin positive cells were found to originate from PTF1a+ and neurogenin 3 expressing progenitors that were a subpopulation of alpha and beta cells. Furthermore, disruption of the MEN1 gene in the progenitor cells, resulted in the development of pancreatic gastrin-expressing tumors, but no animals developed ZES (412). Recent studies provide evidence that gastrinomas in MEN1/ZES may have different pathogenesis than sporadic gastrinomas and also the development of the duodenal gastrinomas and pancreatic tumors differ in these patients. In MEN1/ZES patients, it has been proposed that the duodenal gastrinomas arise from the G cells by a process of hyperplasia similar to proposed for the response of ECL cells to gastrin in the stomach (422,423). In MEN1/ZES patients, it is proposed that the pivotal event in the development of the multifocal gastrin neoplasms is the allelic deletion of the second MEN1 allele (422,424). However, this sequence was not seen in sporadic duodenal gastrinomas (422,424). Previous studies (424) have reported that in MEN1 gastrinomas only 46% of the tumors exhibited LOH at the MEN1 locus with the remaining 55% not exhibiting allelic loss of the MEN1 gene locus, despite having precursor lesions such as hyperplastic G cells in the crypt base or in Brunner's glands, suggesting that mechanisms besides loss of the wild type MEN1 allele may be involved in the transition from G-cell

hyperplasia to duodenal gastrinoma (425). Recent studies (170,173,174,426,427) using mice with targeted MEN1 deletion bred onto a somatostatin null background and treated with omeprazole to induce hypergastrinemia developed gastric carcinoids as well as hyperplastic gastrin-expressing cells in the lamina propria of the proximal duodenum expressing markers for enteric glial cells such as glial fibrillary acidic protein. Because in these experiments, the MEN1gene had been deleted from the epithelial cells, this suggested a possible non-cell autonomous mechanism was involved. This conclusion was supported by a study (427) reporting duodenal gastrinomas as well as their metastatic lymph nodes showed immunohistochemical staining for enteric glial cell markers, whereas it was not seen in pancreatic gastrinomas (170,174,427). From these findings the authors (170,174) proposed that duodenal gastrinomas in these patients may arise from a neural crest-derived cell and /or an endodermally derived epithelial cell.

For pancreatic pNEN in MEN1 patients, two studies have come to different conclusions, with one concluding that PETs arise from duct cells (411) and the other concluding that they arise from islet cells (422,428).

Important insights into the natural history and prognosis of the gastrinoma per se have been provide by a number of long-term studies of patients with or without MEN1 (64,87,89,93,109-111,258,314,315,429-434). In ZES patients without MEN1(sporadic ZES), 25% of their gastrinomas show aggressive growth behavior (109,110). Aggressive growth is associated with a decreased ten-year survival (30%) compared to the excellent survival in those with nonaggressive disease (10 yr.-survival=96%) (110). A similar aggressive growth pattern has been described in patients with MEN1/ZES; however, the percentages are different, with only 14% demonstrating aggressive growth (111). In the sporadic ZES patients, those with aggressive growth are characterized by more frequently having liver metastases, a pancreatic primary, a large primary (>3 cm), a short disease history, higher gastrin levels, female gender, and sporadic ZES (109,110). In general, patients with MEN1/ZES have a better prognosis than patients with sporadic ZES (110). Finally, long-term studies demonstrate that even in patients with liver metastases, their rate of tumor growth may markedly vary with 42% demonstrating rapid growth, 26% having no tumor growth and 32% demonstrating a slow growth over a three-year period (429). Deaths only occurred in the subgroup with rapid tumor growth (62% died during follow-up) (429). This result has important implications for treatment in gastrinomas as well as other NENs with a number of studies demonstrating the rate of tumor growth prior to treatment is an important prognostic predictor of patient's survival, outcome and even response to different therapies (402,429,435-440).

MOLECULAR PATHOGENESIS

The molecular pathogenesis of gastrinomas, similar to other pNEN /NENs, differs from more common adenocarcinomas, but has remained largely unknown until recently (29,170,172,174,427,441-443,443-448). In contrast to many adenocarcinomas, mutations of common tumor suppressor genes (p53, retinoblastoma, etc.) and oncogenes (Ras, myc, jun, Src, etc.), are infrequent in gastrinomas and other pNEN (29,158,308,310,311,441,443,443,446,448-453). This is not the case with G3NECs, which are uncommon in gastrinomas (<5%), which have a higher mutation rate for p53, Rb and p16(158,310). Whereas mutations of common oncogenes or tumor suppressor genes are uncommon in pNEN, recent studies provide evidence that both the p53 pathway and the retinoblastoma (RB) pathway are frequently altered in pNEN (454-457). The Rb pathway is inactivated in most pNEN (including gastrinomas) (455) by amplification of genes encoding the cyclin-dependent

kinases Cdk4/Cdk6. A second study (454) found a low rate of p53 mutations in pNEN (<3%); however, the p53 pathway was altered in 70% of pNEN through aberrant activation of its negative regulators- MDM2 (22%), MDDM4 (320%), and WIPI (15%). A third study found the p53 target gene PHLDA3 is frequently inactivated in pNEN and this correlates with tumor progression and poor prognosis (456,457)

As discussed above, gastrinomas, as well as other pNEN not only occur sporadically (75%-gastrinomas), but can also occur as part of various inherited syndromes (30,114,158,195,197,458,458-462), including MEN1, tuberous sclerosis, neurofibromatosis, von Recklinghausen's disease and von Hippel-Lindau disease (VHL), and investigations of the altered genes in these diseases have provided insights into the molecular pathogenesis of pNEN (30,195,196,442,449). Approximately 20-25% of patients (Table 3) (27,30,87,89,463) with ZES have Multiple Endocrine Neoplasia type 1 syndrome (Wermer's syndrome) (MEN1/ZES). MEN1 is an autosomal dominant disorder due to mutations in the MEN1 gene on the long arm of chromosome 11 (11q13). The MEN1 gene has 10-exons encoding for a 610 amino acid protein, MENIN (30,87,97,317,448,464). A recent sequencing study (446) showed in sporadic pNEN, MENIN is also important with 44% having an inactivating mutations of the Multiple Endocrine Neoplasia-type 1(MEN1) gene. Mutations in the MEN1 gene occur in one-third of sporadic gastrinomas (30,441,449,450,465). Furthermore, 5-95% of patients with sporadic pNEN have loss of heterozygosity (LOH) at the MEN1 locus(11q13) including in 44% of sporadic gastrinomas (30,318,463). These results strongly suggest alterations in MENIN are important in the pathogenesis of sporadic gastrinomas and in the inherited syndrome, MEN1. The exact molecular alteration that occurs with MENIN mutations that results in pNEN, including gastrinomas, is not clear. However, it is known that MENIN is a nuclear protein that interacts with a large number of proteins (30,98,463,464,466,467). MENIN interacts with SMAD3; RPA2(a DNA-processing-factor); the AP1-transcription factor, JunD; nuclear factor-□B(NF-□B), Pem, FANCD2 (a DNA-repair-factor), nucleoside diphosphate kinase, NM23 cytoskeletal-associated proteins and various histone-modifying enzymes (30,463,464,466,467). A recent large WGS study (443) of pNENs found an MEN1 mutation in 41% of the pNENs and altered copy number in 70% and concluded that MEN1 played a central core pathway role in pNENs molecular pathogenesis interacting with each of the key cascades found to be altered in these tumors. This included MEN1(443) interacting with altered key genes involved in DNA damage repair (MLH1-4, MSH5, etc.), chromatin modification (SETD2, MLL3, etc.), altered telomere length (DAXX, ATRX, etc.), mTOR signaling (PTEN, TSC1-2,etc), homologous recombination and double break repair(CHEK2, BRAC1,TP53, etc.) and cell cycle regulation(CDK2C, JNK, etc.).

In recent sequence studies(446) of pNENs was carried out, and it was found that in addition to alterations in the MEN1 gene in 21-100%% (443,446,448), mutations were found in frequently in genes encoding for two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain associated-protein) (25-40%) and ATRX (alpha-thalassemia/mental retardation syndrome X-linked) (18-35%), followed by mutations in mTor pathway genes (15-54%) (443,446,448). MEN1/DAXX/ATRX are important in the epigenetic landscape including DNA methylation, histone modifications, posttranscriptional regulation, and are thought to play important roles in the pathogenesis of pNEN (308,443,446,448,452). Recent studies provide evidence that pNEN are heterogeneous (308,447,452,468,469). The presence of the MEN1/DAXX/ATRX mutant phenotype, which is present in 60% of pNEN, has been reported to

correlate with a worse prognosis (448,452,470-474). The MEN1/DAXX/ATRX mutant profile of pNEN is associated with an islet alpha-cell lineage pattern (high ARX, low PDX1, high HNF1A expression) and has a much worse recurrence free survival (470). Numerous recent studies in pNENs (114,444,445,475,476) including gastrinomas support the importance of the cell lineage (alpha cell, beta cell, intermediate pattern), as well as alterations in DAXX, ATRX, alternative lengthening of telomeres and MEN1 mutations as determinants and prognostic factors for identify patients with pNENs showing aggressive growth and cohorts associated with decreased survival.

The VHL locus occurs at 3p25, and chromosome 3 alterations are reported in 21-50% of sporadic pNEN (449,477). However, these chromosome 3 alterations are rarely associated with a mutation at the VHL locus, suggesting that it is not involved in pNEN development; however, a locus telomeric to the VHL locus may be involved. Recent studies provide evidence for the importance in pNEN/gastrinomas of alterations in the DPC4/SMAD gene (20% in pNEN), the p16/MTS1 tumor suppressor gene (50-90%), mTor/Akt/PI3K pathway, amplification of the HER-2/neu proto-oncogene, as well as increased expression of a number of growth factors and/or their receptors (platelet-derived growth factor, hepatocyte growth-factor, epidermal growth factor, insulin-like growth-factor 1) (441,442,449,450,478,479). Numerous recent studies provide evidence that the mTor/Akt/PI3K pathway is particularly important for mediating the growth of pNEN (478,479). This evidence includes the success of the mTOR inhibitor, everolimus, in extending disease-free survival in patients with advanced pNEN (480), but also studies showing the mTor/Akt/PI3K/ signaling cascade plays a central role in pNEN cell growth and proliferation (442,478,479,481). Additional evidence for the importance of the mTor/Akt/PI3K pathway comes from a study showing mutations in mTor pathway genes (15%) in sporadic pNEN (443,446) as well as from a study (482) reporting the effects of a single nucleotide polymorphism. Replacing arginine by glycine in codon 388 (R388)) of the fibroblast growth factor receptor 4 (FGF4) (482) diminishes the responsiveness to mTor inhibitors in pNEN, and its presence in pNEN is associated with advanced tumor stage and liver metastases.

Numerous chromosomal alterations have been identified in sporadic pNEN and accumulate with advancing stage and tumor progression (158,308,452). Comparative genomic hybridization (CGH) and genomic-wide allelotyping studies report that chromosomal gains/losses occur frequently in pNEN, including in gastrinomas, and that the distribution of these changes differs between GI-NENs (carcinoids) and pNEN, supporting the conclusion that they have a different pathogenesis (29,48,449-451). In pNEN, allelic losses occur most frequently at chromosomal locus 1p (25-75%), 1q (20-90%), 3p (40-95%), 11p (30-50%), 11q (30-70%) and 22q (40-95%) (441,449,450,478). With pNEN, chromosomal gains occur most frequently at 17q (10-55%), 7q (15-70%), and 4 q (33%) (441,449,450,478). A number of these alterations are associated with malignant behavior including deletions at chromosome 1, 3p, 6, 11q, 17p and 22p, and gains on chromosome 4, 7, 14q, Xp (441,449,450,478). Deletions are more frequently seen in the primary tumor and gains in the metastases (452). The commonly mutated genes in pancreatic cancer such as KRAS, TP53, p16/cdk2A and SMAD4 and not commonly mutated in pNEN (446,469).

Results have been reported from a number of studies in which pNEN were studied using microarrays to perform gene expression profiling (449,450,478,483-485). Results from 8 studies in pNEN have been summarized (478) and they demonstrate a wide variation in the number of genes up-regulated (45-668) or down-regulated (25-323). These studies and others (483,484,486) describe a number of gene

alterations that correlate with prognosis, survival, and relapse, but it is not clear presently which gene changes are of most important in the molecular pathogenesis of the pNEN.

CLINICAL FEATURES AND PRESENTATION: ZES

ZES most frequently occurs between the ages of 35-65 with a mean age of 41 yrs. (range-41-53) (7,27,62,235) but is reported in both children (487,488,488-491) and the elderly (27,62,63,235). There is a slight male predominance and in most series 20-35% of cases occur as part of the MEN1 syndrome (Table 3) (30,62,87,88). The main presenting symptoms are summarized in Table 3. Abdominal pain remains the most prominent symptom (>70%), and it is most frequently due to the presence of a duodenal ulcer, with a lesser subset presenting with pain due to gastro-esophageal reflux disease (GERD 20-44%%) (62). Whereas, in the older literature the ulcer was frequently described as occurring in abnormal locations outside the duodenum or as multiple ulcers, at present, most ZES patients present with a typical duodenal ulcer that is indistinguishable form that seen in idiopathic peptic ulcer disease (27,28,62). Similarly, the pain at presentation is similar to that seen in patients with idiopathic gastro-esophageal peptic disease (28,62). Diarrhea was uncommonly reported in older series, however in more recent series it is present in more than one-half the patients, and in 9-20% of patients it is the principal or a prominent presenting feature (Table 3) (51,55,60,62,87,490,492-495). The diarrhea differs from that seen with VIPomas in that it is characteristically not large volume (<1 L/day) and is more characterized by increased frequency and mild steatorrhea, if it is present (28,62,222). The presence of the diarrhea is an important clinical clue that when associated with peptic ulcer disease, should suggest the diagnosis of ZES (9,24,28,51,55,59,62,181), and this will be discussed in more detail in a later section on diagnosis of ZES.

Table 3. Clinical Features of Patients with ZES

Feature	NIH data (n= 261)	Literature data (range)
INITIAL SYMPTOM (percentage)		
Abdominal pain	75	26–98
Diarrhea	73	17–89
Heartburn	44	0–56
Nausea	30	8–37
Vomiting	25	26–51
Bleeding	24	8–75
Pain and bleeding	19	19–44
Pain and diarrhea	55	28–56
FINDINGS AT PRESENTATION		
Prominent gastric folds	94%	(10-30%)
OTHER CLINICAL FEATURES		
Gender (percentage male)	56	44–70
Mean age onset (years)	41	41–53
MEN1 present (percentage)	22	10–48

PAST CLINICAL FEATURES		
History-confirmed peptic ulcer (percentage)	71	71–93
History of Esophageal stricture (percentage)	4	4–6
History of Abdominal perforation (percentage)	5	5–18

Note. NIH data are from 261 patients with ZES prospectively studied (62). Literature data are from 11 series (50,64). Abbreviations: ZES-Zollinger-Ellison syndrome, MEN1-Multiple Endocrine Neoplasia type 1, ND-no data

In the past before effective nonsurgical methods to control acid hypersecretion was available, many ZES patients with ZES developed severe complications of the gastric acid hypersecretion (1,28,205,235). These included severe peptic ulcer disease (with perforation or penetration, with or without fistula formation), bleeding (22-45%), strictures leading to gastric outlet obstruction) (up to 20%) or GERD complications (esophageal ulcers, strictures, ulcers, bleeding, Barrett's, rarely perforation) (up to 20) (1,28,62,205,235,496,497). At present, because of the widespread off label antisecretory drug use, it is uncommon to have patients present with symptoms due to complications from advanced peptic ulcer disease /GERD (62,498-501). In the NIH prospective study (62), only 4% of the 261 ZES patients had a perforation due to a peptic ulcer disease and 5% had esophageal strictures, although 10% had duodenal scarring due to chronic peptic ulcer disease (Table 3). At present, while a duodenal ulcer is usually present at diagnosis, it is not advanced, with 18-65% having no ulcer present (27,62,205), although up to 91% have a history of peptic ulcer disease (Table 3).

The diarrhea is a consequence of the acid hypersecretion and not due directly to the hypergastrinemia per se, as shown in numerous studies which report any method that controls the acid hypersecretion (nasogastric section, medications, surgery), without changing the level of hypergastrinemia, all lead to a decrease or cessation of the diarrhea (9,28,55,62,222,502).

In early studies of ZES patients, gastroesophageal reflux disease (GERD) symptoms (i.e., heartburn, pain) were either uncommon or not reported, so that 7 early series of ZES patients reported before 1986, the GERD symptoms were reported to occur in only at 0-2% of all patients (62). More recent GERD symptoms are increasingly reported in series of ZES patients, with 44% of 261 ZES patients having GERD symptoms at presentation in the prospective NIH series (62), and 49-61% in other series in the recent literature (Table 3) (62,498,503). Other gastrointestinal symptoms such as nausea (30%) and vomiting (25%) as well as weight loss (17%) are not infrequent in ZES patients at presentation (Table 3). The cause of the weight loss can be multifactorial, including from effect of the gastric acid hypersecretion on intestinal absorption causing malabsorption, decreased appetite, or from advanced metastatic disease resulting in anorexia, pain or other symptoms (62). In most patients early in their disease course or without widespread metastatic disease, the weight loss is due to maldigestion and malabsorption (28,62,222).

Approximately 20-25% of patients (Table 3) (27,30,87,89,190,463) with ZES have Multiple Endocrine Neoplasia type 1 syndrome (Wermer's syndrome) (MEN1/ZES) and these patients have a

number of important differences including clinical presentation and disease course from patients with ZES without MEN1(sporadic ZES) (27,30,64,87,89,190,463). These aspects will be discussed in the next section.

MEN1/ZES-GENERAL AND CLINCIAL FEATURES

MEN1/ZES-General

As discussed above, MEN1 is an autosomal dominant disorder resulting from mutations in the MEN1 gene located on the long arm of chromosome 11 (11q13) (30,87,317,464). The MEN1 gene has 10-exons with 9-exons encoding for a 610 amino acid protein, MENIN (30,87,317,464). The exact molecular alteration that occurs with MENIN mutations that results in pNEN, including gastrinomas, is not clear.

MEN1 causes NENs and hyperplasia in multiple endocrine organs (Table 4) that classically includes: hyperparathyroidism due to multi-gland parathyroid hyperplasia; pancreatic NENs (nonfunctional pNEN>gastrinoma> insulinoma>>other) (Table 4); and pituitary adenomas (prolactinomas>ACTH-secreting>growth hormone-secreting) (Table 4) (30,87,463,504,505). Each may be associated with a functional syndrome. The most frequent pNEN is a nonfunctional pNEN (NF-pNEN) with 80-100% developing microscopic NF-pNEN; however, NF-pNEN cause symptoms in only 0-13% (30,87). Gastrinomas are the most frequent functional pNEN (mean 54%, range 20-61%) (62,87,463,505,506) (Table 3). In addition, classically, adrenal tumors (rarely functional) and thyroid disease can occur in <50%, and these patients have an increased incidence of carcinoid (stomach, lung, thymus) (Table 4). Recently it has become recognized that these patients can develop a number of other tumors including smooth muscle tumors (leiomyomas, leiomyosarcomas), CNS tumors (meningiomas, schwannomas, ependymomas); and skin tumors (angiofibromas> collagenomas >lipomas >melanoma) (Table 4).

As will be discussed in the separate sections below the presence of MEN1 in ZES patients is important to recognize because it affects all aspects of the disease including: the pathogenesis, the pathologic findings; the clinical presentation; the treatment approaches; the prognosis and the role of surgery; and the need for genetic counseling (9,30,64,87-89,93,181,190,463,505,507-509).

Table 4. Clinical Features of Multiple Endocrine Neoplasia - Type I (MEN1)

	Average Frequency (range) % of all patients
Hyperparathyroidism	97 (78-100)
Pancreatic Endocrine Tumors	
Pancreatic endocrine tumors (panNENs)	81-100
Nonfunctional or PPomas	80-100 (microscopic) 0-13 (symptomatic)
Gastrinomas	54 (20-60)
Insulinomas	18 (7-30)
Glucagonomas	3 (1-8)
VIPomas	1 (1-15)

Somatostatinomas	0-1
GRFoma	<1
Pituitary Tumors	54-65 (15-100)
Prolactin-secreting	15-45
Growth-hormone secreting	6-20
Cushing's syndrome	16
Adrenal Tumors Cortical adenomas Hyperplasia, carcinoma (uncommon)	27-36 (symptoms<2%)
Thyroid Tumors- adenomas	0-10 (0-30) (<1% symptomatic)
Carcinoid Tumors	
Gastric (ECLoma)	7-35 (symptomatic<5%)
Lung	0-8
Thymic	0-8
Skin Tumors	40-100
Angiofibromas> collagenomas> café-au-lai> macules> lipomas	88%>72>38>34(symptomatic<1%)
Smooth muscle tumors- Leiomyomas, leiomyosarcomas	1-8% (symptomatic<1%)
CNS tumors- Meningiomas>ependymomas, schwanomas	0-8%>0-1% (symptomatic<1%)

Data from references (27,30,87,89,257,463,505).

MEN1/ZES-Clinical Features

For the 20-25% of patients (Tables 4 and 5) (27,30,87,89,463) with ZES with the Multiple Endocrine Neoplasia type 1 syndrome (MEN1/ZES), the presentation of mild hyperparathyroidism is best detected by an assessment of plasma ionized calcium levels, combined with assessment of plasma parathormone levels using a more sensitive assay such as intact PTH-IRMA assays (87,510). In general, the clinical manifestations of ZES are largely similar to those of patients with sporadic and MEN1/ZES, although patients with MEN1/ZES tend to have diarrhea less frequently as one of the presenting symptoms (26% vs 53%) (511). A carefully taken clinical, personal, and family history of endocrinopathies can be particularly important in suspecting MEN1/ZES, because up to 75% have a family history of MEN1 (Table 4) and 24-42% have a personal history compatible with renal colic (30,87,89). The presence of the MEN1 can affect the manifestations of ZES and aspects of its presentation, which will be discussed in a later section dealing with the diagnosis of ZES. In one study (64) the delay in diagnosis of ZES was greater in MEN1/ZES patients than in sporadic cases (7.4 ± 4.9 yrs. vs 3.9 ± 0.2 yrs, p=0.022).

Table 5. Features of Patients with MEN1/ ZES		
Feature	**NIH Data (n=106) Mean (range)**	**Literature (range)**
I. MEN1 Tumor/hyperplasia		
Hyperparathyroidism	100 (94%)	88% (78-100%)
Pituitary disease	60%	31% (28-60%)
Adrenal abnormality	45%	13% (13-35%)
Other functional pNEN)	6%	15.7%
Smooth muscle tumor	7%	0.2%
Thyroid disease	6%	5% (3-25%)
CNS tumor (meningioma, etc.)	8%	<1%
Carcinoid Gastric Bronchial Thymic	30% 20% 8% 6%	6% 4% 2% 2%
Skin tumor Lipoma Melanoma Collagenoma Angiofibroma	 5% 2% 72% 88%	 3% <1% <1% <1%
II. Age/duration		
Age (yrs. Age at study Age at onset ZES Age onset MEN1	 51.2 ± 1.2 (23.8 – 80) 29.8 ± 1.1 (10.2 – 61) 34.7 ± 1.0 (12.1 – 61)	 43.5 ± 0.5 (43-51) 36.6 ± 0.6 34.1 ± 0.5
Duration (yrs.) Of ZES Of MEN1	 16.6 ± 0.9 (1.4 – 43) 21.5 ± 1.1 (1.4 – 58)	 ND ND
III. Other MEN1 feature		
Family History of MEN1	70%	76%
First MEN1 symptom Asymptomatic (screening) HPT ZES Pituitary other	 5% 38% 45% 8% 2%	 1.3% 38% 41% 12% 8%

Abbreviations: MEN1 = multiple endocrine neoplasia type-1; ZES = Zollinger-Ellison syndrome; HPT = hyperparathyroidism; NIH = National Institutes of Health; ND=no data
NIH data are from (27,62,87,227,512-514)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Differential Diagnosis: When Should You Suspect ZES

Despite many articles on the diagnosis of ZES, the diagnosis is continuing to be delayed by 4-7 years from disease onset with no shortening occurring over the last few years (27,29,56,59,62,184,511), and in fact, numerous studies support the conclusion the diagnosis is becoming more difficult and may be delayed even further in the future (24,51,55,56,59,77,78,515-517). The diagnosis of ZES has historically been frequently missed and delayed, because ZES is an uncommon cause of PUD (1-3 new cases/million population/year), whereas idiopathic PUD is 1000-fold more frequent (2300 cases/ year /million) and their initial clinical manifestations can closely resemble each other (27,40,55,56,511,515). In the past when there was ineffective gastric antisecretory medications, ZES would often present with advanced, refractory peptic disease suggesting the diagnosis, however, at present, most patients present with a typical appearing duodenal ulcer, without complicated disease, as seen in patients with idiopathic PUD (28,40,511). This is occurring primarily because of the widespread available of potent gastric acid suppressant drugs (i.e., PPIs), which in conventional doses used to treat idiopathic GERD/PUD, also generally control the acid hypersecretion occurring in most ZES patients (70,105,518,519). The result of this change and others, are making the diagnosis more difficult primarily for two reasons: first, the widespread use of PPIs can both lead to a false negative diagnosis of ZES because the symptoms and acid secretion are well controlled on the PPI, as well as lead to a false-positive diagnosis of ZES because it can induce fasting hypergastrinemia (24,51,55,56,76-78,515,517). Secondly, there is an increasing unreliability of serum gastrin assays which are essential for the diagnosis of ZES (55,56,516,520-522). Each of these points will be discussed in detail later in this section.

A number of clinical/laboratory findings should suggest the diagnosis of ZES, and these are summarized in Table 6.

The presence of diarrhea with PUD is a particularly important clue to the possible presence of ZES, because in recent series when a history for diarrhea is careful sought it is present in >60% of ZES patients (Table 3,4,6). Conversely, in patients with idiopathic PUD/GERD, the occurrence of diarrhea is now uncommon, because the use of high doses of Mg containing antacids is now rare, which were a frequent cause of diarrhea in the past in patients with PUD/GERD (523,524).

Table 6. Findings That Should Suggest Possible Diagnosis of ZES
I. Symptoms
A. Peptic ulcer disease or gastro-esophageal reflux disease (GERD) with:
diarrhea (>60%)
without H. pylori or use of NSAIDs (PUD) (10-50%)
with a long history of persistent or severe symptoms (i.e., >3 yrs.) (>50%)
with refractoriness to treatment
with a PUD complication (bleeding, perforation, penetration) (10-15%)
with a GERD complication (esophageal stricture, perforation, ulcer) (<5%)
with weight loss (15-20%)
with family history of PUD or GERD
with family history of endocrinopathy (esp. renal lithiasis, hyperparathyroidism)
B. Persistent diarrhea (50-80%) which is:
responsive to gastric acid antisecretory drug treatment (H_2-R, PPIs)
secretory
associated with abdominal pain (50-70%)
associated with malabsorption that is unexplained
unexplained
with esophageal disease/symptoms (40-70%)
not responding to specific treatments of diarrheal diseases
with weight loss (15%)
with history of endocrinopathies or peptic ulcer disease (25%)
with family history of endocrinopathies (esp. renal lithiasis, hyperparathyroidism)
II. Signs
Multiple peptic ulcers in unusual locations (<10%)
GASTRIC OUTLET OBSTRUCTION DUE TO PEPTIC ULCER DISEASE (PUD) (3-10%)
Esophageal stricture due to peptic ulcer disease (3-5%)
PUD/GERD with findings of endocrinopathy or with MEN1-related tumors
Prominent gastric folds on UGI endoscopy/Imaging (94%)
III. Laboratory/Radiology findings
PUD/GERD/unexplained diarrhea with: Hypergastrinemia Hypercalcemia Positive somatostatin receptor imaging Positive pancreatic mass

Numbers in parenthesis refer to percentage of ZES patients with these features. Table prepared from data in ref. (56,62,73,87,89,133,512,525).

Furthermore, in any patient with chronic diarrhea without an evident cause, especially if it is fasting in nature, ZES should be suspected (Tables 3,4,6) (60,62,63,87,183,222,490,492-494,498).

In idiopathic PUD, H. pylori infection (>80%) or the widespread use of NSAID/aspirin are a frequent contributing factor, whereas they are frequently not present in ZES patients with a duodenal ulcer (approximately 50%), thus the lack of their presence should raise the possibility of ZES (60,80,526-531). Although less common than in the past, any patient with severe PUD/GERD or with a PUD/GERD complication (stricture, obstruction, perforation, bleeding, penetration), ZES should be suspected (Tables 3,5,6). Because of the frequent occurrence of MEN1 in ZES patients (20-25%) (Table 5), any patient with PUD/GERD/unexplained diarrhea with a personal or family history of an endocrinopathy or a laboratory finding suggesting an endocrinopathy (especially hyperparathyroidism, renal stones, pituitary disease) should lead to suspicion of ZES (Tables 4,5,6). An unappreciated finding that was not emphasized in the past, but which recent studies show is present in up to 94% of ZES patients is the presence of prominent gastric folds on upper gastrointestinal endoscopy or imaging studies (Table 3) (62).

Establishing ZES Diagnosis

If ZES is suspected, a fasting serum gastrin level (FSG) is generally the initial study performed (9,29,55,56,59,182,184). FSG levels are elevated in almost all patients with ZES (>99%), except in some unusual circumstances, such as post-parathyroidectomy in MEN1/ZES or post-noncurative gastrinoma resection (73,74,190,498,508,509,511,532-534). Because of its high sensitivity, the assessment of FSG is an excellent screening test (40,56,498). However, an elevation of FSG alone has a low specificity for establishing the diagnosis of ZES, and no matter how high the FSG level, is not sufficient for a ZES diagnosis (29,40,51,55,56,59,184,498). Many physicians assume that a very high level of FSG (>10-100-fold elevated) is indicative of ZES; however, similar magnitudes of elevation in FSG levels can occur in patients with chronic atrophic gastritis/pernicious anemia, renal failure or those taking PPIs (55,56). For example, FSG levels 10-20-fold elevated are not uncommon in patients with chronic atrophic gastritis (367,535-537). Furthermore, in patients without ZES taking PPIs, although hypergastrinemia is frequent seen (see next paragraph) (80-100%), the FSG is usually increased<3-fold, although in some patients it is increased >10-fold (55,56,59,76,78,376,515,538-543).

Hypergastrinemia can either be physiological which develops as a physiological response to anything causing chronic hypo-/achlorhydria or it may be pathological or inappropriate which occurs in the presence of normal or even elevated gastric acid secretion, which would physiologically suppress gastrin release (Table 7). In humans the disorders causing physiological hypergastrinemia are due to CAG/pernicious anemia, use of PPIs, or H. pylori infections, which are much more frequent than ZES, and thus need to be excluded as a cause of the hypergastrinemia to establish a firm diagnosis of ZES.

Table 7. Causes of Chronic Hypergastrinemia
A. Associated with gastric acid hyposecretion/achlorhydria
Chronic atrophic gastritis (CAG)
Pernicious anemia
Treatment with potent gastric acid antisecretory agents (especially PPIs/uncommonly-H_2-R)
H. pylori infections
Chronic renal failure
Post acid-reducing surgery/vagotomy
Inherited inactivating mutations in H^+K^+ATPase (1)
B. Associated with gastric acid hypersecretion
H. pylori infections
Antral G cell hyperfunction/hyperplasia
Gastric outlet obstruction
Chronic renal failure
Short bowel syndrome (rare)
Retained gastric antrum syndrome (rare)
ZES

1)-includes ATP4R mutations encoding for the alpha subunit of H^+K^+ATPase (544-547)

Therefore, historically, the next study generally recommended in a patient in whom fasting hypergastrinemia was detected and the possibility of ZES was being considered, was an assessment of gastric pH or fasting basal gastric secretory output (9,27,29,55,56,59,72,76,181,182,185,548). Gastric secretory rates are now rarely measured (55,70,72,105) and are available in only a few specialty centers and thus will be discussed briefly below for completeness. If the patient has fasting hypergastrinemia with a gastric pH≤2, ZES should be strongly suspected (55,59,70,73), as summarized in Table 8, because an NIH ZES study found that all ZES patients off of any antisecretory drug had a fasting gastric pH≤2 (70). As shown in Table 8 the diagnosis is established in the group with FSG increased>10-fold combined with gastric pH≤2. However, in the 60% of patients with FSG<10 fold elevated, the diagnosis is strongly suspected but not proven, because there are a number of other diseases (majority=rare) which can also cause these findings that are not ZES which are listed in Table 7 (51,55,56,59,73,74,76).

Table 8. Established and Recently Proposed (untested) Criteria for the Diagnosis of ZES
I. Established Criteria for diagnosis of ZES Required all: Fasting serum hypergastrinemia (FSG) and gastric fluid pH≤2. 1. If FSG> 10 times elevated (over ULN) and gastric pH≤2, the diagnosis of ZES is established (exclude retained antrum almost always by history) (40% of ZES patients) 2. If FSG is <10 fold elevated and gastric pH≤2, need to perform additional testing to exclude other causes of FSG/ hyperchlorhydria) (60%) a. Secretin test positive (≥120 pg/ml increase) b. Elevated basal acid output (>15 mEq/Hr)
II. Possible new criteria for diagnosing ZES in patients with Fasting Hypergastrinemia in the absence of PPI therapy (gastric pH data not available) (Proposed; not evaluated or/and should not be routinely used) A. Strongly supportive of ZES diagnosis 1. Active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with: a. a positive somatostatin receptor scintigraphy imaging (SRI) with either 68Ga-DOTATATE PET/CT or 111In-DTPA-octreotide with SPECT/CT imaging. b. a positive biopsy or cytology for a neuroendocrine tumor (NEN) (stronger support if a gastrinoma is found) c. a positive secretin test. d. known or strongly suspected MEN1 syndrome (i.e., a positive family history, hyperparathyroidism, or pituitary disease) 2. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism, or pituitary disease) with a positive gastrinoma by cytology/biopsy B. Moderately supportive of ZES diagnosis (consider this a tentative diagnosis) 1. Positive somatostatin receptor scintigraphy imaging (SRI) with either 68Ga-DOTATATE PET/CT or 111In-DTPA-octreotide with SPECT/CT imaging (sporadic disease only) or positive cytology or biopsy for a NEN, ideally a gastrinoma, (sporadic disease or MEN1 syndrome present) with a biopsy-proven absence of atrophic gastritis and negative autoimmune markers. (1,2) C. Weakly supportive of ZES diagnosis (insufficient alone for even a tentative diagnosis) 1. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism, or pituitary disease) with positive imaging or an SRI (1) 2. MEN1 syndrome absent but positive SRI or imaging for possible tumor (3).
III. Possible new criteria supporting the diagnosis of ZES in patients with Fasting Hypergastrinemia taking PPIs (4) (gastric pH data not available) (Proposed; not evaluated or and should not be routinely used) A. Moderately supportive of ZES diagnosis (ZES is likely)

1. In a patient with or without MEN1 with active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with a positive biopsy or cytology for a neuroendocrine tumor (NEN) (stronger support if a gastrinoma is found.
2. In a patient without MEN1 with active peptic ulcer disease (PUD) or a history compatible with recent PUD or improvement in diarrhea with PPIs combined with
a positive somatostatin receptor scintigraphy imaging (SRI) with either 68Ga-DOTATATE PET/CT or 111In-DTPA-octreotide with SPECT/CT imaging. (5)

B. Weakly supportive of ZES diagnosis (consider this a tentative diagnosis)
1. In a patient without active PUD or history of diarrhea responding to PPIs without MEN1 with a biopsy-proven absence of atrophic gastritis and negative autoimmune markers with a positive SRI (6,7)
2. In a patient without active PUD or history of diarrhea responding to PPIs with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism, or pituitary disease) with a biopsy-proven absence of atrophic gastritis. (6) and negative autoimmune markers. (7)

C. Minimally supportive of ZES diagnosis (consider this a possible diagnosis only)
1. In a patient without active PUD or history of diarrhea responding to PPIs without MEN1 with a positive SRI
2. A patient with known MEN1 or strongly suspected MEN1 (i.e., a positive family history, hyperparathyroidism, or pituitary disease) without active PUD or history of diarrhea responding to PPIs with prominent gastric folds (8).

Part II and part III are from (55), Part I data from (55,73,74)

(1) Under such conditions a NEN is confirmed but since MEN1 patients develop multiple NENs in various locations NEN(s) identified on SRI may not be a gastrinoma(s) (30,89,90,549).

(2) Five biopsies (2-antrum, 2-corpus,1- incisura angularis) of the stomach are recommended to diagnose atrophic gastritis) (550,551).

(3) SRI can be positive in nonngastrinoma NENs, numerous other tumors and both physiological and pharmacologic processes, so alone is not specific for gastrinoma (134,401,552).

(4) The potential for a false-positive secretin test in patients with hypo-/achlorhydria limits the usefulness of the secretin test in patients taking PPIs unless the gastric pH≤2.

(5) Under these conditions a NEN is likely but since MEN1 patients develop multiple NENs in various locations NEN(s) a positive SRI or biopsy may not be a gastrinoma(s) (30,89,90,549)

(6) Five biopsies (2-antrum, 2-corpus,1- incisura angularis) of the stomach are recommended to diagnose atrophic gastritis) (550,551).

(7) Biopsy and autoimmune markers can both be negative in confirmed autoimmune gastropathy (550,551).

(8) Prominent gastric folds are present in 94% of ZES patients when initially seen, however they are not specific for ZES (62)

Abbreviations: ULN-upper limit of normal; FSG-fasting serum gastrin level; CAG-chronic atrophic gastritis, PPI-proton pump inhibitor; PUD-peptic ulcer disease; SRI-somatostatin imaging

The increased widespread use of PPIs has made the diagnosis of ZES more difficult (51,55,56,59,78,185). PPIs are potent gastric acid suppressants and because of their long durations of action (up to one week) (40,55,553-556) they induce hypergastrinemia in 80-100% of normal (55,56,59,78,184,376,515,538-543). The hypergastrinemia with PPIs develops rapidly (within 5 days); is a common finding among patients even without gastroesophageal disease since these agents are widely prescribed; are now available as over-the-counter medications; and are one of the most over-prescribed medications (185). The degree of hypergastrinemia is variable among PPI users, however in >20% of those taking PPIs in some studies the FSG increased >4-fold, and FSG levels>5-fold are not infrequent, with FSG levels even exceeding >10-fold increased have been reported (55,56,59,78,376,515,538-543). Furthermore, in contrast to H_2R antagonists (cimetidine, ranitidine, nizatidine, famotidine), PPIs control symptoms in most ZES patients at conventional doses used in the treatment of idiopathic PUD/GERD (103,518,519,557-559), whereas with H_2R antagonists, higher doses and/or more frequent dosing are usually needed than used to treat the typical patient with idiopathic GERD/PUD (40,72,103-106,559-562). In the past, ZES patients treated with conventional doses of H_2R antagonists continued to have symptoms suggesting the diagnosis, whereas this is not the case with PPIs (56,56,59,515). Therefore, PPIs both mask and delay the diagnosis of ZES because of their effective symptom control at conventional doses and they also complicate the diagnosis of ZES by their ability to cause a false suspicion for ZES by inducing hypergastrinemia in normal subjects (56,515). However, the characteristic of PPIs which has most complicated the ability to diagnose ZES is their long duration of action which makes it difficult to take patients off the PPI, especially if ZES is present and can lead to complications (25,51,55,57,59,77,78,563) as will be discussed below.

If the gastric fluid is sampled in a patient with an elevated FSG while the patient is being treated with a PPI, and the gastric pH is >2 it is not possible with this information alone, to determine whether the hypergastrinemia is physiological or pathological. To resolve this problem, both historically and in the more recent American NANETs and European ENETs guidelines, as well as recommendation by experts for the diagnosis of ZES, it was recommended to stop the PPI for up to one week and then determining gastric pH and FSG (7,9,27,55,78,79,103,181,182,235,517,564). This approach should be performed with caution (25,55-57,59,77,520). In each of the above guidelines, it is pointed that this must be performed only after taking a careful history of the prior effects of stopping the PPIs, that high-dose H_2R antagonists be substituted for the PPI (equivalent to ranitidine-300-600-every 4-6 hours), and this only be performed after it is established that acute PUD/GERD lesions are healed and the patient can be carefully followed during this time (55,56,59,77,520). After 5-7 days, the H_2R can be stopped, antacids used and on the following day the repeat testing performed. A recent study (77) reported two patients with ZES who developed severe PUD/GERD complications when PPIs were suddenly stopped and recommended the diagnosis of ZES should be established by not stopping the PPI. A number of subsequently papers (55,56,59) have pointed out that it may be possible in some patients to decrease the dose/frequency of PPI to obtain gastric pH≤2 or use other findings (presence of gastrinoma) to establish the diagnosis; however, in most cases this will not be possible. The only established criteria, which usually require discontinuation of PPIs, are listed in Table 8 (Part I). Because of the potential risk in a patient who does have ZES, it has been recommended that in a patient suspected of having ZES on PPIs, that the trial off PPIs in such a patient is best performed at experienced centers (9,55,56,181,565).

In the past, gastric acid secretory studies were performed in most centers and the results used for ZES diagnosis. A study of gastric acid secretory results in 234 NIH ZES patients and 984 ZES patients from the literature reported study found that most ZES patients without previous gastric acid-reducing surgery have elevated basal and maximal acid outputs (BAO, MAO) with a mean BAO=42mEq/hr (normal<10 mEq/hr) and mean MAO=62.7 mEq/hr. (normal 48 mEq/hr. (men)/ 30 mEq/hr. (women) (70). In this study various levels of BAO, MAO, BAO/MAO ratios as well as basal gastric fluid volume and basal/maximal acid concentration or pH were proposed to identify ZES patients (70). A number of these secretory criteria had high sensitivity for identifying ZES patients with the commonly used BAO criteria of ≥15 mEq/hr. (no previous gastric surgery) or ≥5 mEq/hr (with previous gastric surgery) having a sensitivity of 87-90% and 81-100%, respectively (70). However, gastric acid secretion studies are now performed by very few centers, and thus not generally available, so these secretory criteria are no longer used. However, the above NIH study (70) demonstrated that >99% of ZES had a fasting gastric pH ≤2 off antisecretory drugs; therefore, this is a useful criterion that can be applied widely today. A recent study (566) described the validity of measuring gastric pH at the time of gastrointestinal endoscopy in ZES patients, so this criterion can be generally applied (70).

In a patient suspected of having ZES, who is found to have a FSG level >10-fold elevated and a gastric pH≤2 (which in 40% of ZES patients), the diagnosis is established without further testing (Table 8 (part I)), if the possibility of a retained antrum syndrome, which can mimic ZES (Table 7), has been ruled out by previous history/records (27,552,567). Unfortunately, most ZES patients (60%) present with a FSG<10-fold elevated (27,73,75,212) and are found to have a gastric-pH ≤2, which overlaps with a number of other disorders that can cause hyperchlorhydria with hypergastrinemia (Table 7, 8 (part b)) (7,28,81,105,134,183,184,527). The most frequent of this group are patients with H. pylori infection, which is most frequently thought to be associated with acid hyposecretion, but which can also result in hyperchlorhydria with hypergastrinemia (485,527,568,569), and may thus be particularly confusing. To exclude these other disorders (Table 7,8 (part b)) it is now recommended that a BAO and a secretin provocative test be performed (Table 8 (part b)). In the past, a number of gastrin provocative tests were reported to help identity the patients with ZES, which included tests using secretin (27,28,74,75,381,384,570), calcium (28,40,74,75,384,390,390,570) or a standard meal (27,28,74,384,391). The secretin/calcium tests were based on the finding that these agents stimulated an increase in serum gastrin in ZES patients compared to normal subjects (381,390), while with the standard meal test, ZES patients generally show <100%-increase in serum gastrin (74,384,391), whereas patients with antral G-cell hyperfunction/hyperplasia have an augmented and much larger response (74,384,391,571). At present, only the secretin test is widely used because of its convenience, sensitivity, specificity, and lack of side effects (33,61,74,83). A NIH study of 293 ZES patients (NIH) and 537 ZES cases(literature) (74) demonstrated that a value of 120 pg/mL increase with secretin had a sensitivity of 94% and specificity of 100% for ZES (74), and was more sensitive than previously proposed criteria of increases of 200 pg/ml, 50% over basal or 110 pg./ml (75,382,384,570), and therefore is the criterion recommended today (29,84,181,182). In some countries, secretin is not available, and a glucagon stimulation test has been proposed as an alternative (572); however, there is much less experience with the glucagon stimulation test. Unfortunately, the secretin tests results can be affected by PPI-inducted hypo/achlorhydria or by the presence of hypo/achlorhydria for other reasons; therefore, it

cannot be reliably performed while the patient is taking PPIs or is hypo- or achlorhydric (573,574).

The availability of a reliable serum/plasma gastrin-assay is essential in all phases of the diagnostic evaluation of a patient with possible ZES. Unfortunately, a recent study (516) examined the accuracy of 12 widely used commercial assays for FSG assessment used by laboratories in both the US and Europe demonstrated and reported that only 5 assays reliably measured gastrin concentrations, with the others either overestimating or under-estimating the true value. Hence, 7 assays produced FSG values that could lead to false diagnoses or missed diagnoses (56,516,521). The inaccuracy occurred because inadequately characterized antibodies were used that either recognized precursor/inactive fragments or did not interact with all biologically active forms. The lack of a reliable FSG assay invalidates both the assessment of the FSG levels and the results of the secretin test. This is a potential major problem, and the best approach is to check to see if the laboratory performing the FSG assay for your patients uses one of the 5 reliable gastrin-assays listed in this paper or to obtain advice from a center that routinely performs FSG studies in your area for the assay they recommend. A recent study (82) reports a rapid method to measure serum G17 an G34 using liquid chromatography-tandem mass spectroscopy which might prove useful to circumvent the above problems using RIA's.

A recent study (55) pointed out in regular practice the criteria that most physicians are using to make the diagnosis of ZES are not those outlined above. This report (55) for the first time proposing new criteria which would support the diagnosis of ZES that did not involve the assessment of gastric pH, because it was found that in the last 20 cases of ZES reported in the literature, in only 5% (1/20) was an assessment of gastric acidity used in establishing the proposed ZES diagnosis of the cases reported in these studies. This has occurred primarily because of the difficulty physicians are having in assessing the gastric fluid acidity in these patients. The failure to measure gastric acidity in newly selected patients is due to a number of different contributing factors. First, In almost all community as well as many university hospitals, the assessment of gastric acid acidity is complicated by the general lack of its availability and the widespread use of PPIs. Secondly the vast majority of newly diagnosed ZES patients when the diagnosis is first suspected, the patients are almost all being treated with PPIs. As discussed above, these drugs have a long duration of action (up to 1 week), making it is difficult to assess the unsuppressed gastric acidity which can only be done by stopping the PPI for up to one week (40,55,70,74,75,254,553,555,556) which makes it difficult to take patients off the PPI. Third, because in a patient who has ZES, this approach is not without potential risk (51,55-57,59,77) and must be performed under control conditions, often using high doses of histamine H_2 receptor antagonists, hence it is uncommonly performed. Although many current reports use the presence of an elevated FSG in combination with a positive SRI study to make the diagnosis of ZES (55), unfortunately, this is not specific for ZES, as patients can be achlorhydric/hypochlorhydria and have a non-gastrinoma neuroendocrine tumor that will be positive on SRI, and thus not have ZES. Furthermore, some propose the use of provocative test on PPIs to circumvent the need to stop the PPI to assess gastric pH (55), however a number of studies (573,574), but not all (61) conclude this is not a reliable alternative as the secretin test results are not reliable in a patient taking PPIs which frequently cause achlorhydria/marked hypochlorhydria which causes unreliable results (573,574). In a recent study (61) this conclusion has been challenged, because in 28 patients taking PPIs, no false positive or false negative secretin tests occurred and the sensitivity, specificity and positive predictive values for the secretin test were the same in patients taking or not taking PPIs.

It is important to remember that the new criteria (55) have been proposed to support the diagnosis of ZES, have not been widely evaluated and are not as strong as the classical criteria requiring increased FSG and gastric pH<2. These criteria were only proposed because 95% of physicians are not using the established criteria for the diagnosis of ZES (Table 8 (Part I)), and it is not apparent this practice will be reversed in the future. At present, it is best to refer these patients to a center that has expertise in the diagnosis of ZES to firmly establish the diagnosis by the established criteria. This is importance because it will dictate the course of management acutely and long term in the patient if ZES is present or not present (9,50,55).

TUMOR LOCALIZATION: ASSESSMENT OF PRIMARY LOCATION AND DISEASE

An assessment of both the primary tumor location and the tumor extent by various tumor localization modalities is needed at all steps in the management of ZES patients, similar to patients with other malignant NENS (9,27,29,33,53,135,140,140,142,181,575-582). It is initial needed in ZES patients to determine whether surgery should be considered and if so, to determine the extent of surgery; to determine the location, extent and in some cases the rate of growth of metastatic disease prior to any anti-tumor treatment; to assess in MEN1 patients the possible presence of extra-duodenal-pancreatic NENs, such as carcinoid tumors (especially of the lung/thymus); to assess post-resection status; and to assess changes in tumor load with antitumor therapies or extent of recurrence, with time (9,27,29,33,53,129,135,140,140,142,142,181,291,575-578,578,579,579-582). Generally, more than one imaging modalities is used in different patients with the most frequent cross-sectional imaging study being a being a triphasic CT scan with intravenous contrast. In the case of SRI, in the past primarily somatostatin receptor scintigraphy (SRS) using ^{111}Indium-labeled somatostatin analogues with SPECT imaging was used (141,582). But now in most centers it is replaced by the use of SRI with ^{68}Gallium-labeled somatostatin analogues with positron emission tomographic imaging (PET-scanning) (45,129,134-137,139,141,157,291,293,578,582).

A wide range of different imaging modalities have been used in the evaluation of ZES patients (Table 9) (9,130,134,135,141,291,293,576,582,583). These include cross-sectional imaging (CT scanning, magnetic-resonance imaging (MRI), transabdominal ultrasound); selective angiography; somatostatin receptor scintigraphy (SRS) using ^{111}Indium-labeled somatostatin analogues with SPECT imaging or ^{68}Gallium-labeled somatostatin analogues with positron emission tomographic imaging (PET-scanning); endoscopic ultrasound (EUS); and the assessment of serum gastrin gradients either determined in the portal venous drainage through transhepatic venous sampling or in hepatic veins after selective, intra-arterial secretin injections (9,27,29,37,130-132,135,138,142,153,181,291,293,323,577,583-592) vary in sensitivities for detection of the primary tumor, as well as metastatic tumor (Table 9).

Table 9. Tumor Localization Results in Patients with ZES			
	NIH studies Mean(range)	**Literature Mean(range)**	**Literature Mean(range)**
Extra-hepatic lesions			
Ultrasound	13 (9-16)	24 (0-28)	92 (92-93)
MRI	40 (30-57)	22 (20-25)	100 (99-100)
CT scan	38 (31-51)	38 (0-59)	90 (83-100)
Angiography	43 (28-57)	68 (35-68)	89 (84-94)
SRS	69 (58-78)	72 (57-77)	86 (86-100)
PVS	71	68 (60-94)	ND
Intra-arterial Secretin test	86	89 (40-100)	ND
EUS	ND	70 (28-86)	85 (80-93)
IOUS	83	83 (75-100)	
Liver Metastases			
Ultrasound	46	40 (15-77)	100 (99-100)
MRI	71	63 (60-75)	92 (88-100)
CT scan	42	48 (37-56)	99 (99-100)
Angiography	65	62 (33-86)	98 96-100
SRS	92	97 (92-100)	95 (90-100)
Intra-art. Secretin test	40	ND	ND

Data are from (9,27,40,119,129,133,142,295,525,591,593).
ND-no data.

At present, most patients when initially evaluated have performed a cross-sectional imaging study (CT, MRI. Ultrasound) and an SRI study to determine whether surgical resection should be considered (6,9,44,88,181,182,584). Gastrinomas, similar to other pNEN, are hypervascular and are thus their detection on imaging studies can be enhanced by the of administration of contrast; hence, in most patients, either a triphasic CT with intravenous contrast or an MRI with intravenous contrast (gadolinium (129,291,576,577,583). With the cross-sectional imaging modalities, the detection of lesions is influenced by their (40,141,525,577,591). In patients with gastrinoma lesions <1 cm in diameter, only <10-20% are detected, with 1-3 cm in diameter it increases to 15-40%, and with tumor lesions >3 cm, >80-90% are detected (40,525,577,591). Therefore, cross-sectional imaging studies will miss most primary duodenal gastrinomas, which are characteristically <1 cm in diameter; however, they detect most pancreatic primaries which are frequently > 3 cm in diameter (43,45,109,110,175,176,577). As summarized in Table 9, the sensitivity of cross-sectional imaging for detection of primary gastrinomas varies markedly among different series, with generally excellent specificity. In general, they detect <50% of the primaries, with lower yields in series with a high percentage of duodenal gastrinomas. For detection of a patient with liver metastases, cross-sectional CT/ultrasound identify approximately one-half the patients, whereas MRI detects nearly three-quarters (Table 9).

Selective angiography was widely used in the past, but is infrequently used now, however it is a sensitive method to image gastrinomas,

(27,43,241,525,591,593). In most studies angiography was more sensitive than cross-sectional imaging studies for localizing primary gastrinomas, but it still did not localized approximately half of all primary gastrinomas, particularly missing small duodenal gastrinomas (40,43,175,241,525,591) (Table 9). However, angiography is increasingly not used, because it is an invasive procedure, but more importantly because of the increasing sensitivity of both cross-sectional imaging, and the increased availability of SRI which has a significantly higher sensitivity of SRS (Table 9). In the past frequently at the time of angiography, selective hormonal sampling was also used, and still used today in some centers for patients with ZES who have negative cross-sectional imaging and negative SRI studies (138,323,585,588,589,593-597) Two different methods for gastrin hormonal sampling have been used, with the first being the transhepatic catheterization of portal venous tributaries draining the pancreas (portal venous sampling (PVS)) (323,593,595) and the second, which is more frequently used, is the assessment of hepatic venous gastrin concentrations performed after secretin injection into selective arteries to various pancreatic/duodenal regions (585,588,589,593,594,596,597). This method is not dependent on tumor size and involves functional localization which can be very sensitive (Table 9), however, it is now rarely used being replaced by cross sectional imaging and SRI (588,589).

Greater than 90% of NENs/NTs including gastrinomas are well differentiated tumors which overexpress or ectopically express one of the subtypes of somatostatin receptors (sst1-5) in >90% of cases (primarily sst2) with the result that somatostatin receptor imaging (SRI) with various radiolabeled various somatostatin analogues is now widely used (90,134-137,139,141,153,291,292,582,598,599). This method is particularly sensitive method to identify both the primary and metastatic gastrinoma location (181,401,525,576,600-602). Of the five classes of somatostatin receptors (sst1-5), all can be detected in various gastrinomas; however, sst2(80-100%) and sst5 (30-60%) are the most often overexpressed (603). Whereas native somatostatin (som14) interacts with all 5 receptor subtypes with high affinity; it is rapidly degraded in the circulation, hence is not useful therapeutically or for radio-imaging studies (601,603). Two synthetic analogues of somatostatin, octreotide and lanreotide, which have high affinity only for sst2 and sst5, are metabolically stable, and are now widely used for both SRI, for their anti-tumor effects both alone or coupled to radiolabels that are cytotoxic to the tumor and will be discussed in the treatment section later (see PRRT) (90,129,292,601,603-609). Specifically in gastrinomas, in the NIH ZES prospective studies (Table 9), SRS using ^{111}In-labeled somatostatin analogues (Octreoscan) and single photon emission computed tomographic scanning (SPECT) imaging detected primaries in 69% of patients and in one prospective study of 80 consecutive ZES patients (133), SRS was more sensitive than any single cross-sectional imaging study or angiography, and was equal in sensitivity to the combination of all three cross-sectional imaging studies (US, CT, MRI) and angiography together (58% vs 48%)(133). The sensitivity of SRS, similar to cross-sectional imaging, is influence by the size of the gastrinoma, with SRS using ^{111}In-labeled somatostatin analogues (Octreoscan) and SPECT imaging visualizing only 20% of gastrinomas <0.5 cm in diameter, 30-40% <1 cm in diameter (610). Because the mean size of duodenal gastrinomas is <1 cm, SRS detects only 32% of duodenal gastrinomas (175,610). The use of ^{68}Ga-labelled somatostatin analogues with positron emission tomography (PET-scanning) has greater resolution with increased sensitivity (129,134,141,290-292,582) and thus is an important recent advance. In the US and in many countries, the most commonly used ligand for SRI is now ^{68}Gallium DOTA (9,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid) labeled somatostatin analogue

(generally ^{68}Ga-DOTATOC PET/CT) with positron-emission tomography detection (129,134,141,290,582). This SRI method has generally replaced the use of ^{111}Indium (diethylenediamine penta-acetic-D-phenylalanine-1) octreotide with single photon emission CT (SPECT) detection, because of it greater sensitivity (129,134,290-292). SRI at present is the most sensitive method for assessing whole body localization of advanced NENs (129,134,290,292).

SRI is of particularly valuable for detecting distant metastases both to the liver and more distant, especially to bone, with a detection rate of 97% for identifying a patient with metastatic disease in the liver (Table 9). Studies demonstrate that bone metastases are relatively common in patients with advanced NENs including gastrinomas, in which they occur in up to 31% of ZES patients with liver metastases (58,112,294,611,612). The detection of bone metastases in ZES patient has been shown to have a high clinical importance, because they may not only require specific treatment, they also have important prognostic significance) (109,294,299,612,613). In one prospective study from NIH (112), SRS had greater sensitivity than bone scans for detecting bone metastases, and for imaging metastases in the spine was equal in sensitivity to MRI (112). Because 15-25% of the initial metastases occur outside the axial skeleton, SRI is recommended as the initial study over MRI to detect bone metastases (112).

Whereas endoscopic ultrasound (EUS) has proven to be one of the most sensitive modalities for detecting insulinomas/NF-pNEN and is reported to be sensitive for localizing gastrinomas in some studies, its use is controversial in gastrinomas (40,119,245,614-616). EUS detected a mean of 70% of gastrinomas in different studies (Table 9) and has the advantage of allowing histological verification of the presence of a NEN as well as obtaining samples for determining the grade of the NEN which is particularly important for prognosis (617,618). However, EUS's result is operator-dependent and false positives can occur (119,133,245,615). An important issue in patients with ZES is EUS's sensitivity for detecting gastrinomas in different locations such as the duodenum, which is the source of controversy in is use in ZES as opposed to its general use in patients with entirely intra-pancreatic NENs (insulinoma, NF-pNEN, etc.). In one review of EUS in ZES patients, EUS detected a pancreatic gastrinoma in 83%, whereas it detected a duodenal gastrinoma in only 43 % (119). This is a major problem for EUS in patients with ZES because in recent studies 3-10 times more gastrinomas are found duodenal than pancreatic (9,181,182). Because of this difference, many experts do not recommend EUS as a routine preoperative imaging study in patients with ZES, especially in the 75-85% of patients with sporadic ZES (119). As will be discussed further in a later section, serial EUS studies may be used in patients with MEN1/ZES to evaluate the possible growth of the pNETs in patients who do not undergo routine exploration (30,44,88,90,619,620). At present it is recommended that a cross-sectional imaging study and SRS with SPECT imaging be performed in all ZES patients to evaluate tumor location/extent (9,42,50,181,182). If negative, but where the diagnosis of ZES has otherwise been confirmed, MEN1/ZES is not present and surgery is being considered, there is not complete agreement on which if any localization procedure should be performed prior to surgery (45,119,254). This issue will be discussed further under the section on surgical management.

Recently, there has been increased interest in pNENs, including gastrinomas, as well as NENs in other locations of the use of ^{18}F-Fluordeoxyglucose (^{18}F-FDG) PET imaging particularly as a prognostic marker (42,90,115,116,129,134,291,621-623). ^{18}F-FDG PET/CT assesses tumor metabolic activity by determining the glucose uptake and therefore measures a different tumor parameter than SRI which is assessing somatostatin receptor expression.

Although ^{18}F-FDG PET/CT is widely used in oncology, until recently, it was generally not thought helpful in patients with pNENs/NETs (134,624). However, numerous recent studies report high uptake by a proportion of NETs (291,625-627). In a number of studies, the high uptake/SUV of ^{18}F-FDG PET/CT was reported to be associated with higher Ki67 values and was a predictor of overall survival as well as PFS (42,115,116,134,291,621-623). Lately there have been an increasing number of papers advocating either the use of FDG either alone or combined in dual imaging with ^{68}Ga-DOTA-SSA PET/CT (42,622,623,625-631). Similar to its increasing use in other pNENs/NENs the use of ^{18}F-FDG PET/CT in patients with gastrinomas may help in identifying those with aggressive disease, particular as a postoperative tool to stratify patients that may benefit by more aggressive postoperative treatments.

TREATMENT (ACID SECRETION/LOCALIZED DISEASE)

General Aspects (Not Advanced Metastatic Disease)

Like patients with other F-NEN syndrome, patients with ZES have two different aspects that require treatment and often can't be controlled by a single treatment strategy (25,48,54,158,632-634): control of the hormone excess state and treatment directed at the NEN per se, because, except for insulinomas, but similar for gastrinomas and the other F-NEN, these NENs are malignant in 50-100% of cases and require treatment. Specifically, in the case of ZES treatment needs to be directed at two different problems: the control of the marked acid hypersecretion and the gastrinoma itself. Whereas a curative resection would solve both problems; unfortunately, it is possible in <30% of patients. Furthermore, in patients with MEN1/ZES which comprise 20-25%, treatment must be also directed at the other endocrinopathies these patients frequently develop, as well as genetic family counseling (30,65,96,99,100,203,463,505). The first section will discuss management of the acid hypersecretion, followed by the surgical management of the gastrinoma in patients without advanced metastatic disease. In the last section of treatment, the management of patients with advanced/metastatic disease will be discussed.

Management of Gastric Hypersecretion

GENERAL MANAGEMENT OF GASTRIC HYPERSECRETION

Numerous studies, especially older studies prior to adequate drug therapy to control the gastric acid hypersecretion in ZES patients, demonstrate that both the acute and long-term control of the acid hypersecretion is essential for long-term survival (9,46,72,89,103,181,184,205,313,635-637). Prior to the availability of effective acid antisecretory drugs, most ZES patients who did not have a total gastrectomy, eventually developed complications of the gastric acid hypersecretion, and the majority died from these complications rather than from tumor progression (1,27,28,46,72,89,103,184,205,235,313,635,638). This occurred largely because of the direct effect of the marked acid hypersecretion, with the mean basal-acid output (BAO) in ZES patients typically 4-times normal but reaching as high as 12-times the upper limit of normal in some patients (40,70). In a given patient it is not possible to predict when these elevated acid levels will overcome the defense mechanism (increased bicarbonate secretion, increased duodenal secretion, etc.), thus in all patients it is essential to acutely control the acid hypersecretion as soon as ZES is suspected and as the initial step in management (1,9,28,51,56,72,181,182,313,558,639).

SURGICAL TREATMENT OF GASTRIC HYPERSECRETION

While surgical management of the gastric acid hypersecretion in ZES patients is now rarely used, in the past (prior to the 1970' s), the only effective means of adequately controlling gastric acid hypersecretion in these patients was by total gastrectomy (1,28,205,207,237,620,638,640-642). Lesser operations were almost invariably inadequate to prevent recurrence long-term (1,28,237,403,620,638,641). Because in ZES patients prior to any other means of controlling the acid hypersecretion, the total gastrectomy was often performed as an emergency procedure and was associated with considerable morbidity/mortality (1,40,205,638). However, later with the availability of histamine H_2 receptor antagonists, starting in the 1970's, allowing preoperatively control of the acid hypersecretion medically in most patients, the total gastrectomy could then be performed electively and was relatively safe, with an overall mortality of 5.8% in 248 cases since 1980, and 2.4% for elective cases (207). However, the long-term morbidity remained unclear, and in some studies up to 50% of patients have moderate or severe side-effects, including weight loss, pain, stenosis of the anastomoses, vomiting and early satiety (27,40,643). At present, because of the effectiveness of medical therapy especially the PPIs, total gastrectomy is rarely performed and reserved for patients (<0.2%) (9,27,51,71,103,108,644,645) who cannot or will not regularly take oral antisecretory drugs.

Both vagotomy, as well as medical treatment with anticholinergic agents, can reduce the levels of gastric acid hypersecretion in ZES patients and also, they can potentiate the effectiveness of histamine H_2R antagonists when added (27,40,646-648). After the availability of histamine H_2R antagonists (1970+), but prior to the availability of PPIs(mid-1980s), most ZES patients were not cured at surgery, and because many continued to require frequent histamine H_2R antagonists, it was proposed that parietal cell vagotomy, be performed at the time of surgery in ZES patients (211). In ZES patients that underwent selective vagotomy, (211,648), the BAO decreased by a mean of 50%, the histamine H_2R antagonist dosage could be reduced by 40%, and in 36% of patients all antisecretory drugs could be stopped postoperatively. Today, with the development and availability of PPIs, which are highly effective in ZES patients, a form of vagotomy is rarely necessary or used.

In patients with MEN1/ZES with hyperparathyroidism, an effective parathyroidectomy can markedly reduce fasting gastrin levels (FSG), the BAO and can increase the sensitivity to gastric antisecretory drugs (190,508,509,533), with a mean decrease in BAO of 56% and the FSG of 55% (40,190,508,509). Moreover, in some patients, the FSG levels can decrease to the normal range, as well as a positive secretin-test can become negative (40,190,508,509). MEN1 patients, with or without ZES, have parathyroid hyperplasia which involves all four parathyroid glands, if recurrent hyperparathyroidism is to be avoided post-parathyroidectomy, it is recommend that either a 3.5 parathyroid gland resection or a 4-gland resection, with a parathyroid implant, should be performed in these patients (463,508,509,649-653).

Long-term, curative gastrinoma resection is possible in < 40% of patients with sporadic ZES undergoing surgery with the recommended surgical approaches in most guidelines with no-aggressive resections (non-Whipple resection) (6,43,175,254); and even when curative, it does not completely correct the gastric acid hypersecretion in some patients (654-656). In the NIH prospective studies of acid hypersecretion post-curative resection, the MAO decreased 50%, BAO decreased 75% within 6-12 mos. and then remained unchanged for up to 4 years, and the histamine H_2R antagonists' dose could be reduced by >60% (654-656). However, even though the BAO decreased by

75% after curative resection for up to 4 years, 60% of the patients remained acid hypersecretors (654,655). This group included 34% who were mild hypersecretors (BAO-15-24.9 mEq/hr.) and 28% who had marked to extreme hypersecretion (≥25 mEq/hr. (range-25-69 mEq/hr.)) (655). The mechanism of this continued hypersecretion post-curative resection is unclear (655). Practically, it means that all ZES patients should continue to be followed carefully post-curative resection and many will continue to need low doses of antisecretory drugs (655).

MEDICAL TREATMENT OF GASTRIC HYPERSECRETION

In all recent guidelines, medical treatment with oral gastric acid antisecretory drugs is the recommended method to control the gastric acid hypersecretion seen in ZES patients, both acutely and long-term (9,29,103,157,164,180,181). PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) are the recommended drug of choice because of their long durations of action and potency (7,9,25,29,40,72,103,157,164,180-182,657,658).
Most ZES patients without complicated disease (MEN1/ZES, moderate-severe GERD, post-Billroth II surgery) require only once a day dosing and many are controlled on PPI doses equivalent to those used in idiopathic PUD disease (i.e., equivalent to 20 mg/day omeprazole) (103,184,518,519,557). In patients with complicated disease (MEN1/ZES (especially with active hyperparathyroidism), moderate-severe GERD, post-Billroth II surgery) higher doses/frequency are usually needed (72,184,518,519,557,659). For patients requiring higher doses, in general, increasing the dose frequency is more effective than increasing the dosage once-per-day (72,518,519). Most long-term studies were performed with omeprazole or lansoprazole as the PPI, however; other PPIs (pantoprazole, rabeprazole, esomeprazole) are effective in ZES, and it is not apparent anyone has an advantage over the others (103,184,660-662). There is no complete agreement on the starting dose of PPI to be recommended. This becomes an important point in patients with ZES because many of the PPI formulations are acid-labile and thus starting a patient on a low PPI-dose could delay its action, and in acutely ill ZES-patients with PUD this could result in complications (663). One study attempted to address this question (663) by starting patients with ZES on a low dose of omeprazole (20 mg/day) and found that in 32% acid secretion was not controlled and higher omeprazole doses were needed. This study proposed that ZES patients with uncomplicated ZES (no MEN1/ZES, moderate-severe-GERD, post-Billroth II surgery) be started on higher PPI doses (equivalent to omeprazole 60 mg/day) and then doses reduced during follow-up. Both the US NANETs guidelines (182) and the European ENETs guidelines (181) recommend that ZES patients with uncomplicated disease (no-MEN1/ZES, moderate-severe GERD, post-Billroth II surgery) be started on the equivalent of 60 mg/day of omeprazole and that patients with complicated disease be started on PPI doses equivalent to omeprazole 40-60 mg BID and then, with time, dose reduction be attempted. It is ideal to titrate the PPI dose to control the acid output (<10 mEq/hr for no gastric surgery, <5 mEq/hr for previous gastric surgery) (27,40,72,103,106,184,503,660), but few physicians now have access to units measuring gastric acid output. Symptom control (particularly diarrhea, pain, heartburn) can be used to guide management, and if mucosal disease is present, repeat UGI endoscopy should be performed after 6-8 weeks. Because of their potency, dose titration is less important with PPIs; however, it is essential with histamine H_2R antagonists (see comments below in this section).

Only a few studies have reported the long-term results of continuous treatment with PPIs in ZES patients for 9-15 years (72,76,518,557,661). Tachyphylaxis does not develop with long-term PPI treatment in ZES patients, and on average <20% of patients require a

PPI-dose increase/year (rate-0.13/patient), whereas with long-term histamine H_2R antagonist treatment, an average of at least one dose increase/year was required (27,72,103,104,518,558-561). Long-term PPI use has proven safe; with fewer than 0.1% of patients stopping treatment because of a side-effect (103). A potential concern of long-term PPI-treatment is the drug-induced hypo-/achlorhydria, which may lead to effects on nutrient absorption (vitamin B_{12}, iron, calcium) as well as enhanced hypergastrinemia resulting in an increased risk of gastric carcinoid tumors (76,502,664-669). Low vitamin B_{12} levels are frequent in ZES patients (666,667,670,671), are more frequent in ZES patients treated with PPIs, and correlate with the PPI-induced hypo/achlorhydria (670). While the PPI induced decrease in serum VB_{12} levels in ZES patients in the above study (670) was established in a prospective study of these patients, the question of whether PPIs systematically decrease VB_{12} levels in the nonZES, general population and thus should be monitored for, remains controversial (76,667,672).

In another study of ZES patients (673), deficiencies in body iron stores were not found with long-term PPI treatment. Recently, epidemiological, and various correlative studies report in the general population that long-term PPI use may result in an increased incidence of bone fractures, particularly in the spine/ hip, but there are no specific studies in ZES patients (76,666,667,674). In addition, in similar correlative studies in the general population a number of other possible side effects of long-term PPI treatment have been proposed: these are controversial and except for malabsorption of vitamin B_{12} have not been reported with increased occurrence in ZES patients (76,667). The proposed PPI-side-effects include an increased occurrence of such diverse problems as: dementia, chronic renal disease, hypomagnesemia, malabsorption of various nutrients (vitamin B_{12}, iron, etc.), well as increased growth of various other cancers including gastric, pancreatic, and colorectal tumors (76,502,667,668,675,676). Hypomagnesemia has been rarely reported (3 case reports) in ZES patients (76,645,672,677) and in the prospective NIH studies involving 250 ZES patients, only a single patient developed hypomagnesemia despite chronic, continuous PPI with many patients taking higher PPI doses and with a mean treatment time >10 years, for rate of 0.4% over the treatment period (76). On the basis of these studies, it has been proposed (76,181,673) that only the serum vitamin B_{12}-levels should be periodically assessed once a year in ZES patients with long-term PPI treatment, especially the group of patients who might have low vitamin B_{12} level initially or a poorer nutritional status (elderly patients with a long history of malabsorption).

Recently, there have been an increasing number of reports of medical failure in ZES patients of the long-term use of H_2R (27,558,562,586,678) for maintenance acid control, and also even problems controlling acid with PPI therapy long-term (71,71,95,102,108,136,285,403,494,644,645,672,679-686). This is occurring in large part due to the lack of data from any extended long-term/ lifetime treatment studies (i.e., >10 yrs.-lifetime) of antisecretory acid control in ZES patients. This is in contrast to a number of studies of acute acid control and short-term (<5-6 yrs.) control with small number of ZES patients (225,518,519,554,561,661,662,677,687-693). This lack of information about the long-term efficacy of acid antisecretory drug's in ZES is a particular problem because of the unique acid secretory condition in ZES. In ZES there is a constant hypersecretory drive due to constant ectopic secretion of gastrinoma from the gastrinoma, resulting in a constant acid hypersecretory state, which results in a constant requirement to inhibit the acid secretion, which because it is unique to ZES, its treatment can only be addressed by long-term/lifetime study data in these patients. In contrast to ZES, there are numerous long-term PPI studies in nonZES patients, particularly in patients with advanced idiopathic GERD, and these

can provide evidence for safety issues that might occur with lifetime PPI treatment (76,667,694-696), which is applicable to chronic treatment of ZES patients, however, this is not the case with long-term/lifetime efficacy data in ZES. Another important variable contributing to the need to have data on long-term/lifelong antisecretory efficacy in ZES patients, occurs because of the marked variation of the dose requirement between individual ZES patients as well as in each patient, which has been well-examined in short-term ZES acid secretory studies (225,518,519,554,561,661,662,677,687-689,697).
This issue was recently addressed (72) in an analysis of the results of acid antisecretory treatment in ZES patients, which examined in detailed the efficacy/pharmacology of long-term/lifetime medical treatment of acid hypersecretion in a large cohort of ZES patients. This study included results from all 303 patients with established ZES who were prospectively followed and had acid antisecretory treatment with either H_2Rs or PPIs who had antisecretory doses individually titrated by the results of regular gastric acid testing. It includes both patients treated for short-term periods (<5 years), as well as patients treated long-term (>5 yrs.), and with lifetime treatment (30%), followed for up to 48 yrs. (mean-14 yrs.). Long-term/lifelong acid antisecretory treatment with H_2Rs/PPIs could be successfully carried out in all patients with both uncomplicated and complicated ZES (i.e., with MEN1/ZES, previous Billroth 2, severe GERD). Successful treatment in this study was only possible because the drug doses were individually set by assessing acid secretory control by measuring the acid secretory rate and adjusting the various drug doses to establish proven criteria, with regular reassessments and readjustments. Frequent dose changes both up and down were needed; as well as regulation of dose-frequency and a primary reliance on the use of PPs. In this study (72) prognostic factors predicting patients who required PPI dose-changes were identified which need to be studied prospectively to develop a useful predictive algorithm which could be clinically useful for tailored long-term/lifetime therapy in these patients. These results clearly establish that long-term/lifelong medical control of the acid hypersecretion is possible in all ZES patients who can take acid antisecretory drugs, but requires it be performed in centers with the capability of titrating the drug dose over time by assessing the acid secretory rate, thus it is best if these patients are referred to centers with this capability.

Chronic hypergastrinemia in animals and man stimulates gastric enterochromaffin-like (ECL) cell proliferation and in animal models, gastric carcinoid tumors (ECLomas) can develop, some of which are malignant (76,217,224,227,502,665,666,698-701). In patients with ZES, ECL cell proliferative changes develop in >90% (76,217,227). However, patients with sporadic ZES (no MEN1) (75-80%), rarely develop gastric carcinoids (76,103,217,502), whereas MEN1/ZES patients have >70 greater risk of developing a gastric carcinoid (227). In one prospective study (227), 23% of MEN1/ZES patients had gastric carcinoids and other studies have indicated that these can be malignant in 10-30% of patients (76,227,502,666,702,703). In a similar prospective study of 106 patients (217) with sporadic ZES, none of the patients had a gastric carcinoid tumor, although 99% had ECL cell hyperplasia, and 50% had advanced ECL cell proliferative changes, including 7% with dysplasia. Even though there are a few case reports of gastric carcinoids found in sporadic ZES patients (76,212,228,229,232,233,704-709), the prospective NIH study discussed above(217), demonstrates that this is very uncommon, and differs markedly from the chronic atrophic gastritis patients in which 0.4-7% have gastric carcinoids on a routine endoscopy, and 5-35% in some series with long-term follow-up (76,710,711). There is no evidence the long-term use of PPIs accelerates gastric carcinoids development either in patients with sporadic ZES or with MEN1/ZES (76,103,502). However, because of the association of

hypergastrinemia with gastric carcinoids, all patients with ZES should undergo an initial upper gastrointestinal endoscopy; those with MEN1/ZES should have a repeat UGI endoscopy yearly, while in those with sporadic ZES, if there are no upper GI symptoms, follow-up UGI endoscopy can be less frequent.

During the subsequent clinical course of many ZES patients after diagnosis, for their frequently occurs brief periods where they cannot take the oral antisecretory drugs (e.g., after surgery, chemotherapy, etc.) and during this period a parenterally administered gastric antisecretory drug may be necessary. Parental histamine H_2R antagonists can be used, however, continuous infusions of high doses are required (27,103,105,586,712,713). In contrast, with parenteral PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, etc.), because of their long durations of action, intermittent parenteral administration (every 6-12 hours) can be used (103,555,714-716).

At present histamine H_2R antagonists are much less frequently used than in the past (76). Although histamine H_2R antagonists can be effective if properly administered, they usually have to be taken every 4-6 hours, and the oral dose needs to be titrated so that acid hypersecretion one hour prior to the next dose is decreased to <10 mEq/hr (no previous-gastric-surgery, <5 mEq/hr.-previous gastric-acid surgery) (28,103-105,558,560,562,717). In most patients at this level of control, symptoms will be controlled, and mucosal lesions heal (27,103,105,106,586). For patients with complicated ZES (MEN1/ZES, moderate-severe GERD, previous Billroth II surgery), acid hypersecretion may have to be reduced to <1 mEq/hr in order to achieve complete healing (27,105,503,519,659). Using dose-titration, the average daily doses needed of oral histamine H_2R antagonists in the prospective NIH studies were 4.9, 2.2 and 0.33 g/day for cimetidine, ranitidine, and famotidine, respectively (40,103). Despite these high doses, the drugs were generally free of dose related side effects, except for anti-androgen effects with cimetidine (gynecomastia, impotence) and were effective long-term, although approximately one dose-increase/ year was needed (27,40,103,104,558,561,718). Because of this need to titrate the histamine H_2R antagonist dose for each patient, the need for frequent, high dosing and the need to adjust of dosage with time, PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) have now largely replaced the use of histamine H_2R antagonists, and are currently the recommended drugs of choice, because of their long durations of action and potency (7,9,29,40,76,103,157,180-182,657,719). Most ZES patients without complicated disease (MEN1/ZES, moderate-severe GERD, post-Billroth II surgery) require only once a day dosing and many are controlled on PPI doses equivalent to those used in idiopathic PUD disease (i.e., equivalent to 20 mg/day omeprazole) (103,184,518,519,557). In patients with complicated disease (MEN1/ZES (especially with active hyperparathyroidism), moderate-severe GERD, post-Billroth II surgery) higher doses/frequency are usually needed (184,518,519,557).

Currently, somatostatin analogues are uncommonly used to control acid hypersecretion in ZES patient, because they must be given parenterally, whereas effective inexpensive long-acting, oral antisecretory agents such as PPIs are available and are the drugs of choice (29,103,142,151,181,182,396).

SURGICAL TREATMENT (NOT FOR ADVANCED METASTATIC DISEASE)

At presents most authorities, as well as all guidelines, agree that surgical resection for attempted cure should be performed in ZES patients whenever possible without undue risk, similar to the treatment of other potentially resectable pNENs

(9,43,46,95,99,102,119,120,122,157,180,182,267,461,720-728). This approach is, in contrast to that in the recent past, wherein the role of routine surgery for cure was controversial, with some recommending that surgery not routinely be performed, because gastrinomas were frequently not found at surgery and cure was uncommon (729-731). In addition, many patients had negative preoperative imaging, and most patients with non-imaged or small gastrinomas had a good prognosis without surgery (729,731). The situation has changed because of results from a number of more systematic studies. In a NIH prospective surgical study (43) of sporadic ZES patients (n=123), the immediate postoperative cure rate was 51% and after 10-years was 34%. A number of other NIH surgical studies (45,175,176,241,254,258,732,733), as well as studies from other institutions (46,95,99,102,122,177,724) have provided additional support for routine surgery. This approach is further supported by two NIH studies on survival/disease course post-surgical resection of the primary gastrinoma, with the one study (732) demonstrating that patients who underwent routine exploration had a lower incidence of developing liver metastases post-resection (3% vs 23%, $p<0.003$). A subsequent NIH study (733) with more patients (n=160) and a longer follow-up (mean 12 yrs. postresection) demonstrated that patients undergoing surgery had a better overall survival (15 yrs., 98% vs 74%, $p=0.0002$); the survival advantage was disease-related ($p=0.0012$), due to less tumor progression, and fewer patients developed liver metastases (5% vs 29%, $p=0.0002$). This is a particularly important finding, because two NIH studies (109,110) in patients with gastrinomas, as well as a number of other studies both in patients with gastrinomas and other pNEN (115,116,235,276,433,639,734), have demonstrated that the development/presence of liver metastases is one of the most important prognostic markers of long-term survival in these patients. Neither of above NIH studies were randomized, but in each case the comparative groups were well matched (109,110,242,733).

In the past, imaging studies were not infrequently all negative on preoperative studies, and because these ZES patients had an excellent prognosis without surgery, and because surgery was often negative in these patients, this led a number of investigators to recommend against surgical exploration in this group (45,515,729-731,735-737). A subsequent NIH study (45) provided important information to challenge this approach by reporting the value of surgery in patients with preoperative negative imaging in an expert treatment center. In this study (45), in 58 ZES patients with negative preoperative imaging (40%=negative SRS), at surgical exploration, a gastrinoma was found in almost every patient (98%), and nearly 50% were cured. The postoperative cure rate was not different from ZES patients with positive preoperative imaging studies treated in a similar manner (45). This study demonstrated that if the diagnosis of ZES is appropriately established, that an experienced surgeon can find gastrinoma in almost every patient, even if imaging studies and negative, and almost one-half will be cured (45). This improvement in the surgical success of finding and curing gastrinomas in sporadic ZES patients has occurred because of a number of factors: particularly important is the appreciation that the majority of gastrinomas are not in the pancreas, as previously thought, and are, in fact, small duodenal tumors (often <1 cm) (6,109,110,175,177,236,286,738), which are frequently missed on even the most sensitive pre-operative imaging studies, including SRI (293); which will be missed at standard surgical operations if special duodenal gastrinoma localization procedures are not used, such as duodenotomy with or without duodenal-transillumination (175,176,244,247); the use of improved imaging including SRI (549); at surgical exploration the routine resection of pancreatic head area lymph nodes because of the possibility of lymph node primaries

(258,259,268,269,269-272,739); and an understanding that patients with sporadic ZES have a different surgical outcome than those with MEN1/ZES (9,30,43,179,723).

The standard operation includes besides a careful inspection of the duodenum, pancreas and general abdominal inspection, a Kocher maneuver to explore the pancreatic/head; a duodenotomy with or without duodenal transillumination; routine resection of pancreatic/duodenal lymph nodes; careful inspection of biliary tract and liver, and an intra-operative ultrasound(IOUS) examination of the pancreas (43,95,120,175,176,247,249,258,288,738,740-743).
This detailed examination is based on the fact that the relative order of occurrence of gastrinomas is duodenum>>pancreas>lymph node primary>primary liver/biliary tract> other (ovary, mesentery, gastric, etc.) (27,40,50,744). The most important procedure is a careful inspection of the duodenum. This requires the performance of a duodenotomy which is characteristically a 3-cm longitudinal duodenotomy centered on the anterolateral surface of the descending part (second portion) of the duodenum accompanied in the NIH protocol with transillumination of the duodenum (175,176,244,247). A duodenotomy is required to carefully inspect the duodenum because intraoperative ultrasound (IOUS) has been found to be relatively insensitive for duodenal wall tumors in patients with ZES (740). The use of a duodenotomy was proposed by Norman Thompson, University of Michigan in 1989 (246) at a time when most physicians though gastrinomas were primarily intrapancreatic, similar to insulinomas and its benefits and risks for detecting occult duodenal gastrinomas was debated (175,175,246,247,721). Its routine use was firmly established by a prospective study at NIH involving 35 patients with ZES in which all patients first had the standard exploration for a duodenal tumor involving careful palpation without a duodenotomy/or intraoperative transillumination of duodenum, followed IOUS, then duodenal transillumination and finally a duodenotomy (244). Standard palpation identified only 61% of all duodenal tumors found by any method, IOUS found only 26% and no new lesions; transillumination identified 64% of all duodenal tumors and 6 of these were new tumors, whereas duodenotomy identified all 31 duodenal tumors of which 5 were not identified by any other method.

This result was corroborated by another NIH study (176) which compared the surgical results from 36 patients (Group 1) who underwent the standard laparotomy (1980-1986) without duodenotomy (prior to its routine use) to a group receiving the same operation but with transillumination and a duodenotomy (19987-1990-37 patients) (Group 2). Gastrinomas were found in significantly more patients in Group 2(92% vs 64%, $p<0.01$); this increase was due to more duodenal gastrinomas detected in Group 2 (43% vs 11%, $p<0.01$) which resulted in an increased disease-free rate in group 2 (176). Most importantly, a NIH 2004 study (175) examined the long-term effects of adding a duodenotomy on the long-term cure rate. This study (176) compared results in 143 ZES patients, of which all had the standard exploration protocol, but 79 had a duodenotomy and the others had not had one. Gastrinomas were found in a higher percentage of patients who had underwent a duodenotomy (98 vs 76%, $p<0.000011$); as were duodenal gastrinomas (62 vs 18%, $p<0.00001$), whereas the detection rate of pancreatic tumors was similar; the duodenotomy group had a postoperative cure rate that was higher (62 vs 44%, $p=0.010$) as well as the long-term cure rate (52 vs 26%, $p=0.0012$). These results have established the need for all patients to have duodenotomy at exploration (9,157,181,182,745).

The routine resection of peri-duodena/peripancreatic lymph nodes is recommend for two reasons. First, as discussed earlier, a number of different groups have reported lymph node primary gastrinomas (27,40,43,258,259,266-274) which in the NIH series

(258) was the third largest primary tumor group after pancreaticoduodenal tumors, comprising 10 % and their resection resulted in a disease-free state. Secondly, lymphadenopathy is reported to increase the disease-free rate postresection in ZES patients, as well as to increase overall survival in patients with sporadic ZES (746).

In contrast to the situation with sporadic ZES (no MEN1), the surgical management of MEN1/ZES patients remains controversial (9,30,87,92,93,95,95,96,99,120,122,123,128,157,181,182,745,747). This has occurred because almost all studies demonstrate that these patients are rarely cured by the standard ZES operation involving local tumor resection/enucleation even with a duodenotomy, and that cure only occurs if a Whipple resection is performed, which is not routinely recommended (9,43,44,88,89,92,122,181,182,747,748). Even though pancreaticoduodenectomy (Whipple resection) will cure the ZES in MEN1 patients (30,92,119,747,748), it is not routinely or generally recommended by most groups or in most guidelines in patients with MEN1/ZES, primarily because of the long-term potential complications (119,748,749). Also, in patients with NF-pNEN, because of the multiplicity of small adenomas, a total pancreatectomy would be required, which because of its morbidity, is not recommended (30,750). This low cure rate with nonaggressive resections occurs because MEN1/ZES patients almost invariably have multiple, duodenal gastrinomas which are microscopic to small in size (many <0.5 cm) and thus difficult to find at surgery, as well as >50% have metastatic lymph nodes at surgery (43,95,119,178,179,191,284). On preoperative imaging studies in MEN1/ZES patients, duodenal-pancreatic NENs are frequently visualized, however, the peripancreatic tumors are often not the primary but an adjacent positive metastatic lymph node, whereas the pancreatic NENs frequently visualized are usually not gastrinomas (0-<15%) (mostly-nonfunctional-pNEN) (88,191,284). Numerous studies report that if the preoperative imaging studies identify a tumor <1.5-2 cm in diameter, that these patients have an excellent long-term prognosis; in fact, survival is not different from MEN1 patients without a pNEN seen in some studies (9,27,191,751).

A number of other points complicate the decision for surgery and the management of the pancreatic-duodenal lesions in MEN1 patients and have particularly importance in recommending a more conserve approach than aggressive surgical resection in MEN1/ZES patients. First, pNEN present approximately 10-years earlier in MEN1 than sporadic cases (30,87), even occasionally occurring in patients < 20 years old (101,752). This has led to added controversy on whether such young patients should undergo surgery or have continued surveillance. Second, MEN1 patients have an increased incidence of glucose intolerance and diabetes (753,754). This could become an important consideration, particularly in younger patients if they underwent extensive pancreatic resections such as Whipple resection, because the occurrence of glucose intolerance/diabetes after such procedures is reported in different series as, 10% (749), 34 % (755),40% (102) and 86%(756) if MEN1 patients underwent a major pancreatic resection and in 8-27 % of any patients undergoing pancreaticoduodenectomy (102,757,758). Furthermore, pancreatic insufficiency develops in 41-50% after major resections or un 40% after Whipple resections (102) which can complicate the post-surgical clinical management. Third, is the potential importance of continued radiation exposure in MEN1 patients who require life-long monitoring (90). This could become an important issue if these patients are followed, and continued imaging surveillance is required. Some recommend endoscopic ultrasound (EUS) for this purpose (90), which is the most sensitive modality, however, it is an invasive procedure which is done under general anesthesia in many centers, and therefore other imaging modalities that allow serial

assessment of changes in pNEN size, would be of value, such as repeated cross-sectional imaging studies (MRI, CT scanning), however they are less sensitive. These cross-sectional imaging modalities (CT, MRI) very frequently miss small pNEN<1.5-2 cm in diameter, a group that numerous studies shows do not have an increased mortality from pNEN (181,505,751,759,760). For the above reasons, there has been increased interest in MEN1 patients, especially younger patients, in imaging studies not involving radiation such as MRI, but because MRI does not detect a significant number of small pNEN in MEN1 patients, there also is increased interest in more sensitive imaging studies such as ^{68}Ga-DOTATOC positron emission tomographic/CT imaging (^{68}Ga-DOTATOC-PET/CT) which involve radiation. This interest has especially increased with recent studies reporting for the first time prospective (549,761,762) and non-prospective studies (763,764) demonstrating enhanced sensitivity/specificity for localizing NETs, including pNEN, in MEN1 patients, using ^{68}Ga-DOTATOC-PET/CT. Lifetime exposure to radiation may be a particular issue in MEN1 patients because basic science studies demonstrate that menin, the protein altered in patients with MEN1, is involved in DNA repair, cell cycle control and transcriptional regulation, and when there is a loss of menin activity, as occurs in MEN1 patients, cells become more sensitive to the effects of ionizing radiation as well as other cell damaging injuries (765-767). As a result, a number of studies have raised concerns about the use of imaging studies involving radiation in younger patients (without MEN1) (768-770), and whether younger MEN1 patients are at increased risk is unclear. These points raise controversies about when and how frequent these serial imaging studies should be used.

For these reasons, most current guidelines, and expert opinions (9,44,88,157,180-182) for the treatment of pNEN in MEN1 patients recommend that MEN1/ZES patients with preoperative imaging studies demonstrating pNETs <1.5-2 cm in diameter not undergo routine surgical exploration. These guidelines also recommend that when surgical exploration is performed that Whipple resections not be routinely performed.

There are however, increasing concerns raised by the number of recent studies with this general conservative approach. Important points being raised is that these patients have a markedly shortened life-expectancy (i.e., 55 yrs. in the large prospective NIH review (89) with the major cause of death being malignant NENs, although presumed pNEN in origin it is not proven at this point (89). A second major point reviewed above is the enhanced ability to localize the primary NENs and their extent preoperative with the availability of SLI, allowing an enhanced ability to plan the operation and extend of surgery needed and likely enhancing the probability of cure. A third major point is that there have been a number of series (95,99,102) from different institutions reporting high cure rates and excellent long term survival in these patients after Whipple resections (95,99,102,119,178,191,683,747,748,771-801) . Furthermore, in a number of these studies the rate of post operative diabetes is less than previous reported in some studies and even not higher than seen with the recommended more conservative resections (273).

Increasingly, both patients with sporadic ZES, as well as those with MEN1/ZES, who had undergone an initial surgical resection, are being reoperated with time for either a recurrence after being initial rendered disease-free or due to increasing tumor growth with persistent disease (92,127,254,747,802-805). In a recent prospective NIH study of 52 ZES patients (254) with recurrence who underwent reoperation, the reoperation occurred a mean of 6 years after the initial surgery. After the reoperation, 35% were disease-free immediately postoperative and on the last follow-up after the repeat surgery (mean-8 years), 25%

remained disease free, which are lower percentages than seen with the initial operation in NIH studies (43,45,175,254,805). In this study (254), the 20-year survival was 84% and the presence or absence of MEN1/ZES did not affect survival, but the length of the disease-free interval postresection and presence of liver metastases did. A recent study (127) reported recurrence in 108 sporadic ZES patients who had underwent an initial elective surgery between 2000-2020 in 15 different European hospitals. In these patients (127) 68 had duodenal gastrinomas, 19 (18%) had pancreatic gastrinomas, and 21 (19%) had a primary lymph node gastrinoma in the original surgery. During the initial surgery 74% of the patients with duodenal gastrinomas had a pancreaticoduodenectomy (Whipple Resection). For all gastrinoma patients (127) their mean OS was 173 mos., 5-yr survival 94%, and no predictive factors were found. The median DF-survival was 93 mos., and the 5 yr DF survival rate was 63%. For recurrence, significant prognostic factors were tumor size> 2 cm, (P=0.00001), tumor grade (p=0.00001) and pancreatic gastrinoma location (p=0.0001), however on multivariate analysis only tumor size >2 cm (p=0.005) and grade (p-0.013) were significant. Specifically, not a significant prognostic factor was age, sex, preoperative gastrin level, lymphadenopathy <10 nodes or metastatic lymph nodes in resected nodes. Also, for duodenal gastrinoma the recurrence rate was similar in patients with a Whipple operation to that in patients with excisions of duodenal tumors and lymphadenectomy (127).

A recent study also reported the results of duodenopancreatic reoperations in patients with MEN1(12 patients), of whom 5 patients (42%) had MEN1/ZES (92,747). In this study (92,747) the mean time to reoperation was 5.5 yrs., and with a long-term mean follow-up of 18 years, 83% (10/12) remained alive. The authors (92,747) concluded reoperations in this group of patients are not uncommon, there is no increased perioperative morbidity with reoperation in a specialty center, the patients can have prolonged survival after reoperation and that organ-sparing resections are preferred in these patients.

TREATMENT OF ADVANCED METASTATIC DISEASE

General Points

With the increased ability to medically control the gastric acid hypersecretory state in ZES patients, the natural history/growth of the gastrinoma is becoming the major determinant of long-term survival in ZES patients (46,89,109,110,314,433). Natural history studies show that gastrinomas are malignant in 60-90% of patients, and at present, approximately one-third of ZES patients present with metastatic disease to the liver, and because most patients are not cured surgically, an increasing proportion develop advanced metastatic disease over time (40,46,89,109,110,254,314,433,639). Overall, in NIH prospective studies, 25% of patients with sporadic ZES (109,110) and 15% of MEN1/ZES patients (111) have tumors showing an aggressive growth pattern, and in 40% of patients with hepatic metastases, aggressive growth occurs (429). As a result, currently one-half of ZES patients have tumor-related deaths (109).

A number of clinical, laboratory, pathological and other tumoral features in ZES patients are associated with a poor prognosis and are summarized in Table 10. A number of studies report one of the most important prognostic factors is the presence of any liver metastases (initially or their development) (Table 10). For example, in the NIH studies, the 10-year survival of ZES patients with no liver metastases initially is 96%, with liver metastases limited to one hepatic lobe is 78%, and with diffuse liver metastases is 16% (109,110). If liver metastases develop for the first time during the follow-up period after an initial evaluation wherein no liver metastases were present, the ten-

year survival is decreased to 85% (110). However, in different studies at different times in the NIH cohort of ZES patients, the presence of lymph node metastases alone was, at best, only a weak predictor of poor prognosis, and in fact, was not predictive in a number of early studies (Table 10) (109,110,314,806). In a detailed analysis (806) of 216 pNEN patients at NIH in which >90% were ZES, with a prolonged follow-up (mean 11 years), overall survival decreased not only in patients with any lymph node positive, but also the extent of decrease in survival correlated with the number of positive lymph nodes. This result is consistent with some general studies in patients with various pNEN (807-809), but differs from others, which found no effect of lymph node metastases on survival in patients with various pNEN (130,314,806,810-813).

Numerous characteristics of the gastrinoma itself correlate with decreased survival including (Table 10): pancreatic location over duodenal location; increasing primary size; rate of growth overtime; in addition to the presence of liver or lymph node metastases the development of bone metastases has a poor prognosis. The development of ectopic, Cushing's syndrome or bone-metastases has a particularly poor prognosis with survival averaging only one year (109,113,294,611). The fact that duodenal and pancreatic gastrinomas are equally malignant (40-70%=lymph node metastases), but not equally aggressive, with liver metastases present in 25-40% of pancreatic gastrinomas, but in only 2% of duodenal gastrinomas; results in pancreatic gastrinomas having a worse prognosis (Table 10) (27,109,110,314,433). Other features of gastrinomas associated with a poor prognosis including advanced ENET/WHO classification, higher ENET/WHO grade, poor differentiation, other histological features, and rapid growth (Table 10) (65,142,301,814).

As mentioned earlier in the pathology section of this paper, both the recently developed TNM tumor classification systems (ENETs, UICC/AJCC/WHO) and the tumor grading systems have been shown to be the most important single factors in numerous multivariate analyses for predicting overall survival or disease-free survival in all NENs (pNEN, GI-NENs (Carcinoids) (Table 10) (115,116,142,815-817). Most (>90%) of gastrinomas are well differentiated NENs (Grade G1 or G2), and at present there is only one study just including only gastrinomas showing the importance prognostic effect of grade on survival of ZES patients (65). However, because of the almost universal importance of these classification/grading systems in studies involving all pNEN, it is almost certain this will be true of gastrinomas also.

Table 10. Prognostic Factors in Patients with Gastrinomas (overall survival or associated with increased development liver metastases)

Prognostic factor for decreased survival	**Reference(s)**
I. GASTRINOMAS ONLY	
I.A. Acid Control	
Uncontrolled acid hypersecretion	(1,27,205,433,638)
I.B. Demographic Features	
Female gender (p=0.024)	(109,110)
Diagnosis before 1980 (p=0.010)	(315)
Older age at diagnosis (p=0.001)	(65,315)
I.C. Disease Clinical/Lab Features	
MEN1 absent (sporadic ZES) (p<0.03) (Fig.3.D)	(64,65,110,207,734,818)

Short disease history prior diagnosis (<3 yrs.) (p<0.001)	(109,110,819)
High gastrin (p=0.022)	(109,110,191,507,819)
I.D. Disease Course	
Recurrence postop with short disease-free interval	(254)
Develop ectopic Cushing's syndrome (p=0.0049)	(109,113)
Primary gastrinoma location	
Pancreatic >duodenal (p<0.004)	(109,110,281,315,734,819)
I.E. Tumor size, Location, Extent, Growth Rate	
Large primary tumor size (>2-3 cm)	(109,110,315,433,507,819)
Gastrinoma located to the Left of the SMA> right of SMA (gastrinoma triangle)	(415)
Presence of Lymph node metastases (p<0.004)	(109,734,806)
Extent/presence of liver metastases (p<0.0001)	(27,64,109,110,254,314,314,433,507,734)
Diffuse>localized (p<0.0001)	
Diffuse>both lobes>single lobe>none	
Rate of growth of liver metastases or tumor	
Rapid> slow, none	(111,402,429)
Time liver metastases diagnosed	
Present initially>develop on follow-up (p=0.02)	(109)
Develop bone or extrahepatic metastases (p<0.0001)	(65,109,112,433,611)
I.F. Specific Tumor Features	
Flow cytometric results	
High S phase, low % nontetraploid aneuploid, multiple stem line aneuploid frequent	(820)
Molecular changes	(821)
(Chromosome 1qLOH) (p=0.019))	(822)
(Chromosome XLOH) (p=0.042))	
Tumor grade	(65)
II. ADDITIONAL FEATURES SHARED WITH OTHER pNEN	
II.A. Classification	
Advanced TNM classification (ENETs, UICC/AJCC/WHO)	(41,115,116,142,816,817,823)
IIB. Histological Features	
Poorly differentiated	(41,115,116,142,824,825)
High Ki_{67}>low Ki_{67} proliferative index	(115,116,142,815-817)
Cytokeratin 19-IR positivity	(115,116,826-828)
Vascular, neural invasion	(115,116,639,829)
Decreased expression of autophagic genes	(117)
Alternative lengthening of telomeres, ATRX/DAXX loss	(444)
Alpha cell origin over Beta cell origin	(444)

IIC. Other Features	
Age	(41,825)
Gender	(825)
Poor symptom control post-resection	(32)
No surgical resection	(41,825)
NF-pNEN rather than F-pNEN	(825)
Tumor size	(825)

Abbreviations: SMA, superior mesenteric artery; LOH, loss of heterozygosity; IR, immunoreactivity; ENETs, European Neuroendocrine Tumor network; postop-postoperative

A wide range of different anti-tumor treatments is used in patients with advanced pNEN, which are similar to that used in all advanced NENs. These include: surgical resection including cytoreductive (debunking) surgery; liver-directed therapies including radio-frequency ablation (RFA)/other local ablative therapies; trans-arterial embolization (TAE) or chemo-embolization (TACE), radio-embolization or selective internal radiation therapy (SIRT); chemotherapy; biotherapy with somatostatin analogues or interferon-Alfa; molecular targeted therapy with mTOR (everolimus) or tyrosine kinase inhibitors; peptide radio-receptor therapy (PRRT), liver transplantation and immunotherapy (38,50,142,158,604,830-839). There are only a few small, specific studies including only patients with metastatic gastrinomas as they are usually included in series with other metastatic pNEN, and in some cases even with GI-NENs (Carcinoids). Thus, below the results will primarily be from series containing pNEN with some gastrinomas.

One of the main problems with all forms of anti-tumor treatment in patients with advanced pNENs and other NENs, is the development of resistant to the therapies with time. This occurs to varying degrees at different times with all of the current therapies except complete surgical removal without recurrence (840,841). Numerous experimental approaches have been tried after failure of the different primary therapies, with the most frequent approach used is to switch to another primary established approach (840,841). The development of resistant with treatment and approaches recommended to deal with it will be briefly covered in each of the following sections dealing with the various established specific primary anti-tumor therapies.

Cytoreductive Surgery

In patients with gastrinomas with advanced metastatic disease, similar to all malignant NENs, it is recommended that the possibility of surgical removal of all resectable tumor (cytoreductive surgery, debunking surgery) should be considered by many authorities although there are no controlled studies to support its value (9,41,128,142,143,157,171,181,191,258,288,831,842-862,862-864). Surgery is generally recommended if ≥90% of all imageable disease can be removed, although others, have recommended lower numbers. There are only a few reports containing primarily gastrinomas treated with this approach (122,258,288,403,842-844,865), with most studies reporting results from different malignant pNEN and in some cases combined with GI-NENs (carcinoids). In various studies using this approach five-year survivals of 75-80% are reported and increased survival over patients not undergoing such surgery (128,142,143,157,831,849-859,861,862,862,864,866). This approach is primarily used in patients with well differentiated NENs, which is the case in >90% of gastrinomas (G1, G2,G3NET). Unfortunately, this approach is possible in the minority of even patients with advanced well differentiated

gastrinomas or other NENs (<15-20%), and because of lack of control studies establishing its efficacy, it is not uniformly used. In only a small minority of G3NEC patients, is such an approach considered and even then, it is controversial (857,867).

At the time of any abdominal surgery, it is generally recommended that prophylactic cholecystectomy be performed because of the widespread use of somatostatin analogues for their anti-tumor activity and the ability of long-term treatment with them to cause biliary stasis and gallstones (143,180,849,868). Lastly, recent non-controlled studies, report that removal of the primary tumor increases the survival rate with PRRT and suggest it routinely be performed, although this approach is not widely used at present (869).

Liver Directed Therapies

GENERAL

These approaches include the use of local ablative techniques (radiofrequency ablation (RFA), ethanol injections, cryotherapy), which are frequently used in combination with other anti-tumor treatments, as well as various more general hepatic cytotoxic approaches using trans-arterial embolization (TAE)/chemo-embolization (TACE) or radioembolization (42,142,143,831,834,851,859,870-872,872-877). The embolization approaches in gastrinoma patients are generally reserved for patients who have metastatic unresectable hepatic metastases either limited to the liver or with liver-predominant disease, particularly if locally symptomatic, whereas in patients with other F-NENs, they are also frequently used for patients in whom the symptoms due to F-NEN excess-state not controlled by other modalities (25,142,143,831,834,851,870-872,876,878,879).

RADIOFREQUENCY AND OTHER ABLATIVE THERAPIES

Of the all of the liver-directed therapies, RFA is the most widely used, which converts RF waves to heat resulting in cellular destruction (142,831,880-883). RFA and other ablative techniques (cryotherapy, ethanol injections) are administered either at the time of surgery (+/- laparoscopic) to ablate isolated metastases or by radiological techniques for guidance (25,142,844,847,881,882,884-887).In different studies, relative contra-indications to its use are the presence of large lesions (>3.5-5 cm), a large number of lesions (>5-15), and he presence of metastases near vital structures (831,848,880,880,881,883,885,887-889). RFA has response rates of 80-95% which last up to 3 years, has the lowest complication rate of all liver-directed therapies (<15%), and can be used alone for a palliative procedure or to supplement a surgical resection by removing additional isolated liver metastases (25,831,880,885,888).

Embolization and Chemoembolization

Embolization of advanced metastases in the liver in patients with metastatic gastrinomas or other NENs, can be used because the blood supply to the tumor is primarily arterial, whereas in normal liver only 20-25% is arterial, with the majority coming from the portal vein (42,142,831,870,872-876,880,882). Therefore, interrupting the tumoral area arterial supply preferentially affects metastases (142,870,880,882). At present, this procedure is usually performed radiological, rather than at surgery and can be done alone (trans-arterial embolization or TAE) or accompanied by administration of chemotherapeutic agents (trans-arterial chemoembolization or TACE) such as doxorubicin, cisplatin, 5-fluorouracil, mitomycin C or streptozotocin (42,142,837,870,872,872,873,875,876,880,882,888,890). TAE or TACE is performed using gel foam powder or polyvinyl alcohol particles. In various studies a response is seen in 55-100% of symptomatic

patients, 25-85% have an objective tumor response, and responses last from 6-45 mos. (142,831,834,870,872,880,891). Five-year survival rates for TAE/TACE are 20-35% and the progression free survival is 1.5 years (142,870,892). Contra-indications are the presence of portal venous occlusion, liver failure, extensive liver involvement (>50-75%), poor performance score, and previous biliary surgical reconstruction (142,870,880,888,890-893). Both TAE and TACE are associated with side-effects including a mortality rate of <6%, complications in 10-80%, particularly post embolization syndrome (pain, fever, nausea/vomiting), and occasionally gallbladder necrosis, hepatic failure, abscess formation and liver/renal failure (831,834,870,880,882,888,890,891,894). TAE/TACE are generally considered for palliative therapy in patients with non-resectable liver metastases with hepatic predominant disease (142,143,180,834,872,891). There are no prospective studies that have established the value of TAE/TACE; however, both the NANETS and ENETs guidelines recommend TAE/TACE be considered for palliative treatment in an experienced center if the patient has hepatic-only or hepatic-predominant disease that is not surgically resectable (142,143,180,182,834,848,891).

Radioembolization or Selective Internal Radiation Therapy (SIRT)

Radio-embolization or selective internal radiation therapy (SIRT) utilizes ^{90}Yttrium-labeled microspheres (Sir-spheres-20-60 um diameter, load-50Bq/sphere or Theraspheres-glass sphere, 20-30um diameter, 2500 Bq/sphere), which are administered by selective intra-arterial injection after a pretreatment angiogram to allow correct catheter localization (9,142,181,182,831,848,871,872,876,876-878,895-905). Prior to their administration, the position of the catheter tip needs to be properly established so that microsphere administration does not enter the cystic or duodenal arteries, which can result in cholecystitis or ulceration, and the amount of lung shunting must be determined to avoid radiation pneumonitis (142,831,871,871,872). Contraindications include: the presence of excessive shunting to the lung/GI tract; inadequate liver reserve; and the inability to isolate the liver arterial tree from the gastric/small intestinal branches (142,831,871,872,905,906). The mean objective response rate from 12 studies in patients with advanced NENs was 55% (range-12-90%) with stable disease seen in 32% (range-10-60% (142,831,871,905,907) and the disease control rate was 91% in a recent multicenter international study (908). The mean survival is 30-months and 50% of patients have symptomatic improvement in quality-of-life indices (142,871,897-899). Side-effects include post-embolization (fever, nausea, vomiting, abdominal pain) (25-45%), \and rarely ulceration or cholecystitis (<1%) if the catheter is not properly positioned (142,831,871,905,907,909).

At present the exact embolization procedure that is preferable in which clinical situation is not clear because of lack of prospective comparative studies. There have been no randomized control trials comparing radioembolization to the other liver-directed therapies, so at present at is unclear which should be preferred.

Medical Treatment of Advanced Metastatic Disease

CHEMOTHERAPY

Chemotherapy has a poor response rate (<15%) in well-differentiated NENs outside the pancreas (lung/GI-NETs, carcinoids) and thus is uncommonly used for these tumors, it has higher response rates in different series of malignant, well-differentiated pNEN, varying from 25% to 70 % (9,147,181,182,832,848,893,904,910-920). Until recently the generally used chemotherapeutic regimen

was streptozotocin (STZ) based for advanced pNEN (most frequently combined with doxorubicin, 5-FU or cyclophosphamide) (9,142,147,181,182,832,878,893,910,916-919,921). STZ is a glycosamine-nitrourea derivative which was found to have cytotoxic effect on pancreatic islets (28), and since 1968 has been used for the treatment of patients with metastatic pNEN/gastrinomas (9,142,181,182,878,893,916-918,921). However, recent studies report temozolomide and capecitabine may have at least similar if not better activity than STX based regimens (827,830,911-913,918-920,922-927). Recently, in a randomized, prospective trial (ECOG-ACRIN E2211) (928) the Eastern Cooperative Oncology group compared the combination of temozolomide (TMZ) and capecitabine (CAP)(CAPTEM) to TMZ alone in 144 patients with advanced G1/G2 pNENs. At the interim analysis the mean PFS was 14.4 mos. in the TMZ alone group and 22.7 MS FR CAPTEM (P=0.022). At the final analysis the mean S was 53,6 mos. for TMZ and 58.7. mos. with CAPTEM. MGMT deficiency was associated with the response in this study. The authors concluded that the CAPTEM combination was superior to TMZ alone and that MGMT deficiency correlated with a response (928). In a recent systematic review of CAPTEM treatment of patients with advanced NENs, involving 42 articles with 1818 patients the overall disease control rate was 77% (range 44-100%), the median PFS ranged from 4 to 38 mos., and the media OS ranged from 8 to 103 mos. In this review (920) the safety analysis showed an occurrence of G3-G4 toxicities in 16% of the patients treated. The most common toxicities were hematological (27%), gastrointestinal (8%) and cutaneous (3%). This systematic analysis (920) concluded CAPTEM was an effective and relatively safe treatment for patients with well-moderately differentiated NENs of pancreatic, GI, lung and unknown origin.

STZ-based regimens have considerable morbidity with 70-100% developing some side-effect including nausea/vomiting (70-100%), abnormalities in hepatic function, leukopenia, and thrombocytopenia in 6%, and 15-40% developing some degree of renal toxicity including proteinuria (40-60%) and decreased creatinine clearance (893,913,916,917). The combination of STZ/doxorubicin (±5-FU) has an objective response rate of 20-45%, but complete responses are rare, and the median-response duration is 5-20 months (9,142,181,182,830,878,893,914,916-919,921). In patients with advanced gastrinomas only, the response rate varied from 5 to 40% (147,929).

Poorly differentiated pNETs comprise only 2-6.5% of all pNETs; however, it is important that they be identified because they have an aggressive course and poor prognoses and are generally treated differently than well-differentiated pNEN (54,142,848,912,913,918,930-935). The recommended chemotherapeutic drug combinations for treatment of well differentiated pNEN differs from that for treatment of poorly differentiated NENs (Grade 3) in any location (142,143,180,912,913,932,935-937). In contrast to the combinations listed above to treat advanced well differentiated pNEN, in patients with poorly differentiated NENs, a cisplatin-based drug combination with etoposide is generally the initial treatment (142,143,180,848,912,913,918,919,931,932,936,938,939). This combination results in an objective response in 30-80% of patients with mean duration of <12 months (142,143,180,912,932,936). The median survival is 4-16 mos., and the 5-year survival is 11% (range 0-31%) (142,143,180,912,913,918,931,932,936,938). This chemotherapeutic regiment can be associated with significant toxicity including GI toxicity (nausea/vomiting), myeloid-suppression and renal toxicity (142,143,180,912,913,931,932,936,938,939). In a recent multicenter study promising results were reported with the use of temozolomide/capecitabine (92%/8%=TMZ alone) (CAPTEM) in patients with Gr3

GP-NENs (933). In this study (933) the results of treatment with CAPTEM were reported from 130 patients (67% pNENs) and a radiological response was seen in 36%, the median TTF was 3.6 mos., OS was 9.2 mos., with the TTF being longer in pNENs than patients with GI-NENs Gr 3 tumors (5.8 vs 1.8 m0s, p=0.04). The role of surgery in patients with high grade NENs is controversial (940), although it is reported to be associated with higher survival in those with Gr3 WDs in some studies (940).

Recently, some studies (926,928,941-948) report that the effectiveness of alkylating agents in NENs correlated with the expression of, but not all (489,945,949-951) the DNA repair enzyme, O^6-methylguanine DNA methyl transferase (MGMT) in these tumors. MGMT, in its role as a DNA repair enzyme, specifically removes the methyl/alkyl group form the O^6 position of guanine, whereas alkylating agents induce methylation at this site which leads to DNA mismatch occurring and results in cell death/apoptosis. Some studies show that pNEN have a higher response rate to alkylating agents due to their low level of MGMT (926) compared to GI-NENs (carcinoids) having higher MGMT levels and lower response rate. Perspective studies are needed before recommending the routine determination of NEN tumoral MGMTs to help predict, for a given patient the subsequent response to an alkylating agent, and therefore its routine use is not generally recommended at this time (928,945-948).

BIOTHERAPY

Somatostatin Analogues

Similar to NENs in general, most well-differentiated G1, G2 pNEN, as well as a proportion of G3 pNEN, overexpress one of the 5 subtypes of somatostatin receptors (sst1-5) (most frequently sst2) (142,851,952-955). Numerous studies, including both non- controlled and randomized controlled studies (PROMID, CLARINET studies) on NENs and pNEN(including gastrinomas) (142,954,956,957), demonstrate that somatostatin agonist analogs (octreotide, lanreotide) are not only are effective for controlling the hormone-excess state in F-NENs(discussed in a previous section), but also have anti-tumor growth effects in NENs (25,142,155,402,603,609,848,851,952-955,958-965). The exact molecular basis for this antiproliferative-effect is not entirely clear, but somatostatin analogues inhibit the release of growth factors from NETs, have antiproliferative effects on neighboring cells (stromal, immune, vascular, etc.) and activate intracellular cascades that have antiproliferative effects (phosphatases, inhibition of adenylate -cyclase, etc.) (603,954,959,962-964). In these studies the anti-tumor effect of the somatostatin analogues is almost entirely a tumoristatic effect (only 10-15% show decreased tumor-size), resulting in disease stabilization with prolongation of progressive free survival, and because of study design and the multiple treatments the patients received, an effect on overall survival has not been established (155,402,603,609,848,956,958,961-964,966).
However, these agents are very well tolerated, and are generally the first line treatment of patients with advanced well-differentiated gastrinomas and other pNEN as well as with lung/GI-NENs(carcinoids) (25,142,143,150,164,180,833,851,952-956). In a recent study of the use somatostatin analogs (SSAs) on tumor progression in 12 ZES patients (WD, G1, G2) (155), 67% had a sustained response to SSAs and 33% showed early progression. There was a significant difference in PFS between the early and late progression groups (84 vs 2 mos., p=0.004) (155). However, there was no difference OS or PFS between these 12 SSA treated ZES patients and 21 other ZES patients not treated with SSA analogues (155).

With time the tumor may become refractory to the antigrowth effect of the somatostatin analogue, and its efficacy may be restored by either increasing the

dosage or shortening the time interval between doses (965). Side effects that result in somatostatin analogue therapy discontinuation are rare with any side-effect occurring in 50% of patients (including pain at injection site, GI symptoms), which may improve with continued treatment (25,29,142,848,954,955,958,961,964,967). Long-term more serious side-effects include the development of biliary sludge/gallstones which cause symptomatic disease in <1%, developing glucose intolerance/diabetes or developing steatorrhea which is usually mild (25,29,142,142,848,868,954,955,958,961,964,967).

Interferon

Interferon-alpha, similar to somatostatin analogues, is able to control symptoms of the hormone hypersecretory state and has anti-proliferative effects in pNEN/NENs which result in primarily disease stabilization, rather than a decrease in tumor size (<15%) (142,848,961,968-973). In the only study of interferon limited to gastrinoma patients (13 patients, advanced metastatic progressive disease) (972), 46% of patients showed disease stabilization, and in 23% it lasted almost 2 years. The antiproliferative effect on pNENs/NETs of interferon is partially mediated by blocking cell-cycle progression in G1, inhibiting DNA synthesis, stimulating an increase in Bcl-2, inhibiting protein synthesis, inhibiting angiogenesis, and induction of apoptosis (961,968,970,971). Side effects develop in the majority of patients (>70%) with the most frequent being flu-like symptoms (40-80%), weight loss/anorexia (60%), and fatigue (51%), which frequently decrease in severity with continued treatment or with decreased dose (848,961,970-972). More serious side effects include hepatotoxicity (31%), hyperlipemia (31%), and bone marrow toxicity; autoimmune disorders particularly thyroid disease and rarely CNS side effects such as depression or mental disorders (142,961,968,970-972). While interferon-alpha was frequently used in the past either alone or with somatostatin, at present it is uncommonly used because of the availability of other agents with fewer side effects.

MOLECULAR TARGETED THERAPIES

mTor-Inhibitors (Everolimus)

Both extensive in vitro and in vivo studies demonstrate that activation of the mTOR cascade, plays and important role in the proliferation, growth, and apoptosis of pNEN, as well as NENs in other locations (142,150,479,882,915,957,964,974-979). mTor is a serine-threonine kinase critically involved in a variety of cellular functions including apoptosis, cell-growth, and proliferation (150,957,974,977,978,980). A number of different mTOR antagonists have been developed and shown to have anti-proliferative effects in NENs in various in vitro and in vivo studies, however, only one, everolimus, has been approved by the FDA for patients with advanced NENs (pNEN (including gastrinomas) and GI-NENs (carcinoids) (142,150,480,974-976,978-981). The approval of everolimus for use in both advanced pNEN and GI-NENs(carcinoids) was based on the positive results of two randomized, double-blind, prospective, placebo-controlled studies, RADIANT-3 (pNEN) (480) and RADIANT-4 (lung/GI-NENs) (982), which each demonstrated almost a 3-fold increase in PFS ($p<0.001$). There are no specific studies on the effects of everolimus on gastrinomas only, and the only data comes from general trials of all pNEN.

Everolimus treatment was associated with a 2-fold increase in adverse events, the majority being grade 1 or 2, with grade 3 or 4 side effects occurring in 3-7% (primarily hematological, stomatitis, or hyperglycemia) which could be managed by dose-reduction or drug interruption (480). At present, it is not established whether everolimus' ability to increase progression-free survival will result in an increase in overall survival (142,981).

Long-term treatment with everolimus is associated with primary and acquired resistance, which has frequently limited its long-term benefit for patients with advanced NEN (150,983-985). Numerous mechanisms for this have been described but none has been sufficiently successful to lead to its widespread use or its ability to function as a biomarker for the occurrence of resistance (983-985).

Numerous studies have provided information on the importance of angiogenesis in the pathogenesis of pNENs as well as other NENs (986). A recent randomized Phase II study compared the effectiveness of everolimus alone versus everolimus plus the anti-VEGF agent, bevacizumab in 150 patients with advanced pNENs (987). The combination resulted in improved PFS compared to everolimus alone (16.7 mos. vs 14 mos., complete tumor response in 31% with the combination compared to 12% with everolimus alone (p=0.0053), with similar median overall responses. Toxicities were more frequently seen in the combination group (987). The authors concluded that these results support the need for continued evaluation of VEGF pathway inhibitors for the treatment of advanced pNENs (987).

Tyrosine Kinase Receptor Inhibitors (Sunitinib and Surufatinib)

PNEN including gastrinomas, similar to other NENs, as well as other neoplasms and normal tissues, frequently possess multiple tyrosine kinase (TK) receptors, which are important in mediating growth, angiogenesis, differentiation, and apoptosis (26,142,848,895,957,964,988-995). TK receptors comprise >20 families of transmembrane receptors that mediate the actions of a number of different growth factors that include the receptors for insulin-like growth factor (IGF1R), epidermal growth factor family (EGFRs); hepatocyte growth factor (c-Met); platelet-derived growth factor family (PDGFRs); vascular endothelial growth factor family (VEGFRs); stem cell factor (c-Kit) and a number of others (142,957,992,994). A number to tyrosine kinase receptor antagonists (sunitinib, axitinib, cabozantinib, famitinib, nintedanib, pazopanib, sorafinib, sulfatinib, surufatinib) (979,994,996-998,998-1001) have been shown to have anti-growth/anti-angiogenic effects on pNEN/NENs in both in vitro and in vivo animal studies, however, at present the only two are approved for use in various countries which are sunitinib (US, Europe, other countries) which is an inhibitor of a number of tyrosine kinase receptors (PDGFR, VEGFR1/2,c-KIT, FLT-3) (142,914,989,991,994,996,1002-1004) and surufatinib (approved in China) which is an inhibitor of VEGFR, FGFR1, and colony stimulating factor 1 (CSF1R) (998,998-1001). In a Phase 3 double blind, randomized trial (1002) in 171 patients with progressive well-differentiated nonresectable pancreatic NENs (including 19 patients with ZES), sunitinib resulted in a doubling of PFS (11.4 vs. 4.5 mos., p<0.001), which lead to its approval for advanced pNEN. There are no specific studies on the effects of sunitinib on gastrinomas only, and the only data comes from general trials of all pNEN.

Sunitinib treatment is associated with frequent grade 1/2 side effects and some grade 3/4 side effects particularly neutropenia (12%) and hypertension (10%) (994,1002,1005). A quality-of -life analysis (1002) showed sunitinib did not have a significant effect, with most side-effects able to be managed by dose-reduction and/or temporary cessation of treatment.

Surufatinib was evaluated in two multicenter studies, one a randomized, double-blind, placebo controlled Phase III involving 172 patients with advanced pNENs in 21 different Chinese hospitals (999) and a second study (SANET-ep) involving 198 patients with advanced extra-pancreatic NENs 1in 24 hospitals in China (998), In the first study in patients with pNENs (999) the PFS was 19.3 mos. with surufatinib vs 3.7 with placebo (p=0.00110) with the most common Gr ¾

side-effects being hypertension (38% vs 7%), proteinuria (10% vs 1%) and hypertriglyceridemia (7% vs 0%). In the second study on patients with advanced extra-pancreatic NENs (998) the PFS was 9.2 mos. with surufatinib vs 3.8 with placebo ($p<0.0001$) with the most common Gr ¾ side-effects being hypertension (47% vs 13%) and proteinuria (19% vs 0%). Currently, surufatinib is not approved by either the FDA or European regulatory agencies.

Long-term treatment with sunitinib is associated with primary and acquired resistance, which has frequently limited their long-term benefit for patients with advanced NEN (840,841,983,984,994,995). Numerous mechanisms for this have been described but none has been sufficiently successful to lead to its widespread use or its ability to function as a biomarker for the occurrence of resistance (840,841,983,984,995).

Peptide Radioreceptor Therapy (PRRT) Using Radiolabeled Somatostatin Analogues

PRRT utilizes the fact that almost all well-differentiated NENs, as well as a proportion of G3NECs, overexpress somatostatin receptors (sst1-5) particularly sst2, which can bind radiolabeled somatostatin analogues resulting in the targeted delivery of cytotoxic radiation to the tumor cells (142,154,603-605,607,608,836,952,953,1006-1018). Two different isotopes have been used in most studies: ^{90}Yttrium(^{90}Y)- or ^{177}Lutetium(^{177}Lu)- labeled somatostatin analogues (142,154,836,1008-1016,1018). ^{177}Lu emits beta-particles and gamma rays, has a maximum tissue penetration of 2 mm, and a half-life of 6.7 days, whereas ^{90}Y strongly emits beta-particles, has a maximal tissue penetration of 12 mm, and a half-life of 2.7 days (1011-1015). A number of different synthetic somatostatin analogues have been used, with the most frequent being octreotide or octreotate coupled to the radiolabel by different chelators, including diethylene triamine penta-acetic acid (DTPA) and 1,4,7,10-tetraazaacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (142,1010,1011,1013,1014).

At present the only approved formulation for pNEN is ^{177}Lu-DOTATATE (604,605,607,608,1006-1010). The approval of this therapy is based on results of a double-blinded, control phase 3 trial (NETTER-1) (1019) in patients with advanced unresectable, midgut carcinoids which showed a marked prolongation of PFS (from 8.4 mos. to >40 mos., $p<0.0001$), with an increased overall survival from 3 to 18%, combined with the results of treatment of 510 patients with advanced pNEN and other NENs, in Rotterdam which showed complete response in 2%, partial response in 28%, and tumor stabilization in 35% (404,1015). Of 440 patients (10 studies) with various malignant pNEN/NETs, including gastrinomas, treated with ^{90}Y-labeled somatostatin analogues, complete tumor remission was rare (0-6%), partial remission occurred in 7-37%, and tumor stabilization in 40-86% (29,142,1011,1013,1014). In a recent meta-analysis of 22 studies (1758 patients) with advanced NENs treated with PRRT the pooled disease response rate (complete/partial tumor response) was 33% with RECIST criteria, and the pooled disease control rate (compete/partial response or stable disease) was 79% (1020). In a second recent meta-analysis of PRRT results (1018) involving 15 studies selected from 715 references in patients with advanced NENs, the pooled response rate was 27.6% by RECIST criteria, and 20.6 % by SWOG criteria, with respective DCR rates of 79.1% and 78.3% by the two criteria demonstrating excellent agreement with these two different criteria of response.

In two different studies there was no significant difference in the PFS overall survival rates between NEN patients treated with PRRT with advanced pNEN compared to NENs in other sites (869,1010).

Gastrinomas are one of the malignant pNEN/NETs that were most responsive to PRRT (42%-3mos); however, they also had one of the highest recurrence rates leading to a poorer prognosis (142,404,1011,1013-1015,1021). In one detailed study of 11 patients with metastatic ZES (1022) treated with either ^{90}Y-and/or ^{177}Lu-labeled somatostatin analogues, the mean serum gastrin decreased by 81%, compete response occurred in 9%, partial tumor response in 45%, tumor stabilization in 45%, and in 64% the antitumor effect persisted for a median period of 14 months. In a second study (1023) involving 30 gastrinoma patients treated with ^{90}Y- labeled somatostatin analogues the tumoral partial response rate was 33% with a mean overall survival time of 40 mos.

The treatment was well tolerated when given with renal protective amino acid infusions, with no Grade 3/4 nephrotoxicity. In various studies the most serious side effects are hematological (15%-transient, 0.8% developing a myeloproliferative disorder), liver toxicity (0.6%) and renal toxicity, with the latter occurring primarily in patients receiving ^{90}Y-labeled somatostatin analogues (154,404,604,605,607,608,1006,1007,1010,1015,1019).

Recent studies show that in patients with refractory hormonal symptoms due to a F-NEN, PRRT may be of great help in control the hormone excess state's symptoms independent of its effect on tumor proliferation (25,148,350,860,1010,1024). Although this is almost never an issue in patients with gastrinoma because of the effectiveness of PPIs in controlling the symptoms of the gastric acid hypersecretion, numerous recent studies suggest that PRRT may be particularly helpful in patients with refractory advanced F-NEN syndromes in controlling the hormone excess state, particularly in patients with carcinoid syndrome, VIPomas and insulinomas (25,148,350,860,1010,1024).

With ^{177}Lu-(DOTA^{0}, Tyr^{3}) octreotate, a number of prognostic factors were identified which predicted a poor outcome after PRRT, which included; presence of progressive metastatic disease prior to treatment; Karnofsky performance score of ≤70; no tumor-response to PRRT; weight loss at the time of treatment; presence of bone metastases; extensive liver involvement; poor uptake of the radiolabeled analogue by the tumor; the presence of malignant gastrinoma, VIPoma, or insulinoma and the presence of positive lesions on ^{18}F-FDG Pet scans (142,404,612,1011,1013-1015,1021,1025,1026).

Recent studies support the conclusion that retreatment of NEN patients with PRRT who develop progressive disease after an initial PRRT treatment, is a feasible option with good efficacy and acceptable toxicity (1027,1028). This conclusion was supported by two recent systematic reviews and met analyses (1027,1029). In the report by (1027) 9 articles with 426 patients were analyzed and the ORR after retreatment was 17.1%, DCR was 76.9%, PFS was 14.1 mos. and OS was 26.9 mos. Pooled proportions of hematologic and renal toxicities were 11% and 0.7%. In a subgroup allowing direct comparison to initial PRRT treatment data, the salvage PRRT had a lower therapeutic efficacy (ORR, DCR, $p<0.001$) and shorter PFS ($P=0.03$), despite similar hematologic and renal toxicity. In a second analysis (1029) 13 studies were identified containing retreatment data (^{177}Lu-PRRT, or ^{90}Y-PRRT) from 567 original studies. With ^{177}Lu-PRRT retreatment in 7 studies PFS was 12.5 mos., mean OS was 26.8 mos., and DCT was 71%. Grade ¾ toxicity occurred in 5% of 177Lu-PRRT retreated patients, with no Gr ¾ renal toxicity and no myelodysplastic and acute myeloid leukemia incidence.

Liver Transplantation

In contrast to many metastatic tumors, liver transplantation is both recommended for pNEN/NENs

(including patients with advanced gastrinomas) and is selectively used in a small number of patients with metastatic advance metastatic pNEN/NENs, although it use remains controversial (142,143,1030-1038). In one recent systematic analysis of reported NEN series the 1-,3- and 5-yr survival rates were 89%, 69% and 63% with a recurrence rate after transplantation of 31-57% (1032). In another recent (2020) review of 206 patients with metastatic pNEN/NENs who underwent liver transplantation the overall survival rates at 1,3,5 and 10 years were 89%,75%, 65% and 46% respectively (1039). In this study (1039) the recurrence rate was 34% with a mean time to recurrence of 28 mos. Important prognostic factors in the systematic analysis (1032) were >50% liver involvement by tumor, high Ki_{67}, or the presence of a pancreatic primary over a GI-NEN. In other studies important other factors predict a poorer prognosis include: older age of patient(>50), older age of donor, cold ischemic time MELD score, tumor recurrence, presence of a symptomatic tumor, a primary tumor in the pancreas as opposed to an extra-pancreatic NEN (carcinoid), poor tumor differentiation, transplantation associated with a simultaneous and extensive digestive tract resection, presence of hepatomegaly, presence of extra-hepatic metastases and a patient with a primary tumor not resected (1034-1036,1039). Liver transplantation is generally reserved for patients with life-threatening hormonal disturbances refractory to other treatments (which is very rare in ZES) or to selected patients with pNEN/NENs with diffuse liver involvement refractory to all other treatments (26,142,1033-1040).

If liver transplantation is considered, important selection criteria include the presence of a well-differentiated NEN/pNEN; age <45-50; a Ki-67 index <10%; <50% liver involvement; the absence of extra-hepatic metastases as determined using the most sensitive methodology (^{68}Ga-labeled somatostatin-analogues and PET imaging) ; the absence of extra-hepatic disease(resected primary tumor); the absence of other resections at the time of liver-transplantation; and some groups consider various histological features such as E-cadherin-tumor staining characteristics (142,848,930,1032,1034-1039,1041,1042).

Immunotherapy

Since the recent widespread effectiveness of immune check point inhibitors in a number of tumors (melanomas, etc.), including in patients with poorly differentiated lung NENs with small cell neuroendocrine tumors, there have been several studies of the efficacy and safety in other tumors such as patients with advanced NENs including pNEN such as advanced gastrinomas (995,1043-1049).

A number of these studies suggest single agent (Anti-PDL1) immunotherapy may be a useful approach in only small subset of patients with advanced disease (12% in Keynote 02 study (1047) , 0-5% in other studies not selecting for PD-L1 activity (1049-1051) and this subset is primarily patients with high-grade poorly differentiated NENs (995,1043-1046). In various GEP-NENs the presence of high tumor-infiltrating lymphocyte (TILs) numbers and high PD-1 expression show a significant correlation with decreased survival and higher grading of the tumor supporting the finding that immunotherapy might be most promising in GEP-NENs with high TILs (1044). In other tumors particularly melanomas, renal cell carcinoma and non-small cell lung tumors, a combination of immunotherapies using anti-PD-L1 and CTLA-4 blockade resulted in increased efficacy, and a recent study in patients with various advanced NENs reported an objective response rate of 24 % with increased activity in patients with both atypical lung NENs and with high-grade pNEN (1046). Other studies report ORR of 14.7-25% almost entirely in patients with high grade NENs (995). Ongoing and future studies are in progress to exactly define the best

combinations as well as define which specific NEN types will best respond (995,1043-1045).

Neoadjuvant Therapy

Because the large majority (>80%) of patients with advanced gastrinomas or other advanced NENs present with surgically unresectable disease, primarily with widespread liver metastases or unresectable locally invasive tumors, the possible benefit of surgical resection is not an option. Therefore, with the increasingly effectiveness of various anti-tumor modalities, there is increasing interest in a possible role of neoadjuvant treatments which could allow tumor downsizing to the point surgical resection can become an option (1052,1053). In one recent systematic review and meta-analysis of 9 studies from the literature (1052), involving 468 patients with advanced pNENs who had adjuvant therapies, there were no complete responders, 43.6% had a partial response; 51.3% had stable disease; and 4.3% had progressive disease. The estimated resection rate was 68.2%, and the RO resection rate was 60.2% (1052). There was no difference in the resection rate between different chemotherapy regimens (41% vs 34%), as well as the RO resection rate (62% to 68%) and the ORR was similar with CAPTEM and FAS (42% and 34%). PRRT showed a higher numerical ORR than chemotherapy although the difference did not reach statistical significance (49% vs 37%, p=0.154). The authors concluded these results were promising for some patients, however the best neoadjuvant regime to use remains unclear (1052).

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