

Gastrinoma (Duodenal and Pancreatic)

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Introduction

Gastrinomas are neuroendocrine tumors (NETs), usually located in the duodenum or pancreas, that secrete gastrin and cause a clinical syndrome known as Zollinger-Ellison syndrome (ZES). ZES is characterized by gastric acid hypersecretion resulting in severe acid-related peptic disease (peptic ulcer disease, PUD; gastro-esophageal reflux disease, GERD) [1–3] and diarrhea. In this section ZES, due to both duodenal and pancreatic gastrinomas, will be covered together because clinically they are similar [2, 3]. Specific points related to gastrinomas associated with the genetic syndrome of multiple endocrine neoplasia type 1 (MEN1) will also be mentioned. Some specific points related to duodenal gastrinomas will also be covered in the duodenal carcinoid section.

Epidemiology and Clinicopathological Features

Minimal Consensus Statement on Epidemiology and Clinicopathological Features

Epidemiology and Site of Origin [3, 4]

The incidence of gastrinomas is 0.5–3/million population/year. They are the most common functional and, malignant pancreatic endocrine tumor (PET) syndrome and comprise up to 30% of these tumors [3, 4]. Duodenal tumors, which were originally thought to be uncommon (i.e. <20%), now make up 50–88% of gastrinomas in sporadic ZES patients and 70–100% of gastrinomas in MEN1/ZES patients. In rare cases, gastrinomas occur in other nonpancreatic, nonduodenal abdominal (stomach, liver, bile duct, ovary) (5–15%) and extra-abdominal (heart, small cell lung cancer) locations [5–8].

Clinicopathological Features [1, 9, 10]

The WHO classification [10] subdivides gastrinomas, similar to other gastroenteropancreatic neuroendocrine tumors (GEP-NETs), into three general categories: (1) well-differentiated endocrine tumors with benign or uncertain behavior at the time of diagnosis (10–30%); (2) well-differentiated endocrine carcinomas with low-grade malignant behavior (50–80%), and (3) poorly dif-

differentiated endocrine carcinomas with high-grade malignant behavior (1–3%). The 50–80% of gastrinomas of the pancreas and duodenum that fall into the category of well-differentiated endocrine carcinomas are usually larger than 1 cm and show local invasion and/or proximal lymph node metastases [6, 11]. Liver metastases occur much more frequently with pancreatic gastrinomas (22–35%) than duodenal gastrinomas (0–10%) [6, 12]. Pancreatic gastrinomas are generally large in size (mean 3.8 cm, 6% <1 cm), whereas duodenal gastrinomas are usually small (mean 0.93 cm, 77% <1 cm). While the pancreatic gastrinomas may occur in any portion of the pancreas, duodenal gastrinomas are predominantly found in the first part of the duodenum including the bulb [7]. At surgery 70–85% of gastrinomas are found in the right upper quadrant (duodenal and pancreatic head area), the so-called ‘gastrinoma triangle’ [4, 5, 13]. MEN1 is an autosomal-dominant syndrome that is present in 20–30% of patients with ZES [14]. In these patients duodenal tumors are usually (70–100%) responsible for the ZES. The duodenal tumors are almost always multiple [15–17] and originate from diffuse gastrin cell proliferations [18].

Histologically, most gastrinomas are well-differentiated and show a trabecular and pseudoglandular pattern. Their proliferative activity (i.e. the Ki-67 index) varies between 2 and 10%, but is mostly close to 2%. Immunohistochemically, all gastrinomas stain for gastrin.

Prognosis and Survival [5, 6, 19–22]

Approximately one fourth of ZES patients have gastrinomas that pursue an aggressive course and aggressive growth occurs in 40% of patients with liver metastases. At diagnosis, 5–10% of duodenal gastrinomas and 20–25% of pancreatic gastrinomas are associated with liver metastases. Liver metastases are the most important prognostic factor, the 10-year survival being 90–100% without liver metastases and 10–20% with. Poor prognostic factors besides liver metastases include: inadequate control of gastric acid hypersecretion; presence of lymph node metastases ($p = 0.03$); female gender ($p < 0.001$); absence of MEN1 ($p < 0.001$); short disease history from onset to diagnosis ($p < 0.001$); markedly increased fasting gastrin levels ($p < 0.001$); presence of a large primary tumor (>3 cm) ($p < 0.001$); a pancreatic primary gastrinoma ($p < 0.001$); development of ectopic Cushing’s syndrome or bone metastases ($p < 0.001$); the presence of various flow cytometric features, molecular features (high HER2/neu gene expression ($p = 0.03$), high 1q LOH, increased EGF of IGF1 receptor expression), or histological features including angioinvasion, perineural invasion, >2 mitoses per 20 HPF, Ki-67 index >2 [5, 6, 19–24].

Clinical Presentation [2, 14, 25–28]

At the onset of symptoms, the mean age of patients with sporadic gastrinomas is 48–55 years; 54–56% are males, and the mean delay in diagnosis from the onset of symptoms is 5.2 years. All of the symptoms except those late in the disease course are due to gastric acid hypersecretion. The majority of ZES patients present with a single duodenal ulcer or GERD symptoms and ulcer complications. Multiple ulcers or ulcers in unusual locations are a less frequent presenting feature than in the past. Abdominal pain primarily due to PUD or GERD occurs in 75–98% of the cases, diarrhea in 30–73%, heartburn in 44–56%, bleeding in 44–75%, nausea/vomiting in 12–30% and weight loss in 7–53%. At presentation, $>98\%$ of patients have an elevated fasting serum gastrin level, 87–90% have marked gastric acid hypersecretion (basal acid

output greater than 15 mEq/h) and 100% have a gastric acid pH ≤ 2 . Patients with MEN1 with ZES (20–30%) present at an earlier age (mean 32–35 years) than patients without MEN1 (i.e. sporadic disease). In 45% of MEN1/ZES patients, the symptoms of ZES precede those of hyperparathyroidism, and they can be the initial symptoms these patients present with. However, almost all MEN1/ZES patients have hyperparathyroidism at the time the ZES is diagnosed, although in many patients it can be asymptomatic and mild and therefore can be easily missed if ionized calcium and serum parathormone levels are not performed. Twenty five percent of all MEN1/ZES patients lack a family history of MEN1, supporting the need to screen all ZES patients for MEN1.

Diagnostic Procedures for ZES and MEN1: Laboratory Tests, Imaging and Nuclear Medicine [2, 27, 29, 30]

Diagnosis of ZES – General

The diagnosis of ZES generally requires the demonstration of an inappropriate elevation of fasting serum gastrin by demonstrating hypergastrinemia in the presence of hyperchlorhydria or an acidic pH (preferably ≤ 2). In most cases the first study done nowadays is the fasting serum gastrin (FSG) determination. The FSG alone is not adequate to make the diagnosis of ZES because hypergastrinemia can be caused by hypochlorhydria/achlorhydria (chronic atrophic fundus gastritis, often associated with pernicious anemia) as well as other disorders causing hypergastrinemia with hyperchlorhydria besides ZES (*Helicobacter pylori* infection, gastric outlet obstruction, renal failure, antral G cell syndromes, short bowel syndrome, retained antrum). No level of FSG alone can distinguish ZES from that seen in achlorhydric states.

Recent data show that the widespread use of proton pump inhibitors (PPIs) is making the diagnosis of ZES more difficult and is delaying the diagnosis. This is occurring with PPIs because they are potent inhibitors of acid secretion with a long duration of action (i.e. up to 1 week), which has two effects that can lead to misdiagnosis of ZES. First, this results in hypergastrinemia in patients without ZES frequently with peptic symptom history thus mimicking ZES. This means the PPI needs to be stopped to make the proper diagnosis; however, it can be difficult to stop the drug in some patients, especially those with severe GERD. Second, the potent inhibition of acid secretion results in control of symptoms in most ZES patients with conventional doses used in idiopathic peptic disease, in contrast to H2 blockers where conventional doses were frequently not adequate. The result is that PPIs mask the diagnosis of ZES by controlling the symptoms in most patients and that breakthrough symptoms,

which may lead to a suspicion of ZES and are frequently seen with H2 blockers, are infrequent with PPIs.

Patients with ZES with PUD have *H. pylori* infections in 24–48% in contrast to patients with idiopathic peptic disease who have *H. pylori* in >90%. Therefore, lack of *H. pylori* should lead to a suspicion of ZES in a patient with recurrent peptic ulcer disease [30].

Minimal Consensus Statement on Diagnosis of ZES and MEN1 – Specific ZES [2, 27, 29, 30]

ZES should be suspected if: recurrent, severe or familial PUD is present; PUD without *H. pylori* is present; PUD resistant to treatment or associated with complications (perforation, penetration, bleeding) is present; PUD occurs with endocrinopathies or diarrhea; PUD occurs with prominent gastric folds on barium studies or at endoscopy (present –92% of ZES patients), or with hypercalcemia or hypergastrinemia [25].

Biochemistry/Laboratory Studies for ZES

Initially to make the diagnosis, FSG and gastric pH should be determined (following interruption of PPI for at least 1 week with H2-blocker coverage, if possible). If FSG is <10-fold elevated and gastric pH ≤ 2 , then a secretin test and basal acid output should be performed. Also, if repeated fasting serum gastrin are performed on different days <0.5% of ZES patients will have all normal values. If a BAO is performed, >85% of patients without previous gastric acid-reducing surgery will have a value >15 mEq/h [26].

MEN1 [14, 17, 31]

MEN1 should be suspected if there is a family or personal history of endocrinopathies or recurrent peptic disease; history of renal colic or nephrolithiasis; history of hypercalcemia or pancreatic endocrine tumor syndromes.

Biochemistry/Laboratory Studies for MEN1

All patients with ZES should have serum parathormone levels (preferably an intact molecule assay – IRMA), fasting calcium levels and prolactin levels. Recent studies show that an ionized calcium level is much more sensitive than a total calcium- or albumin corrected-calcium determination.

Genetic Study for MEN1

If the family history is positive for MEN1, suspicious clinical or laboratory data for MEN1 are found or multiple tumors are present raising the possibility of MEN1, then MEN1 genetic testing should be done. If the genetic testing is positive for MEN1, genetic counseling should be performed.

Minimal Consensus Statement on Diagnosis of Other Hormonal Syndromes in ZES Patients [5, 23, 32]

Ectopic Cushing's syndrome develops in 5–15% of patients with advanced metastatic disease and has a very poor prognosis. It should be routinely assessed for in patients with advanced met-

astatic disease by careful clinical examination, history and routine 24-hour urinary cortisol determinations and serum cortisol assessment.

A secondary hormonal syndrome develops in 1–10% of patients, especially those with metastatic disease or MEN1. These should be assessed for by a careful clinical history and routine hormonal assays are not recommended.

Imaging – General [33, 34]

Tumor localization studies are required in all patients with ZES. All aspects of management of ZES require knowledge of tumor extent. It is important to remember that 60–90% of gastrinomas are malignant and that the natural history of the gastrinoma is now the most important determinant of long-term survival in many studies.

Tumor localization studies are necessary to determine whether surgical resection is indicated; to localize the primary tumor; to determine the extent of the disease and whether metastatic disease to the liver or distant sites is present, and to assess changes in tumor extent with treatments.

Numerous localization studies have been recommended including conventional imaging studies (CT, MRI, ultrasound), selective angiography, functional localization methods (angiography with secretin stimulation for hepatic venous gastrin gradients, portal venous sampling for gastrin gradients), somatostatin receptor scintigraphy (SRS) and endoscopic ultrasound (EUS) as well as various intraoperative localization methods, including intraoperative ultrasound, intraoperative transillumination of the duodenum [35] and routine use of a duodenotomy [21, 33, 34, 36–39]. Prospective studies show for primary gastrinomas that conventional imaging studies localize 10–40%, angiography 20–50% and SRS 60–70%. The use of SRS changes management in 15–45% of patients [33, 34, 40]. SRS's sensitivity is equal to all conventional imaging studies combined [34]. For SRS, as well as all conventional studies, tumor size is an important variable and tumors <1 cm are missed in >50% of cases [41, 42]. Therefore, because most duodenal tumors are <1 cm they are frequently missed. EUS is particularly sensitive for pancreatic lesions; however, its ability to detect small duodenal tumors is controversial [21, 43, 44]. Functional localization studies are not limited by tumor size but are invasive studies [45, 46]. Prospective studies show for metastatic gastrinoma to the liver that CT and ultrasound detect their presence in 30–50% of patients with metastases, MRI and angiography in 60–75% and SRS in 92% [33, 34]. At surgical exploration duodenotomy is essential to detect up to one-half of duodenal tumors and its use increases the cure rate.

Intraoperative transillumination of the duodenum is frequently used to help identify the site for the duodenotomy. Intraoperative ultrasound should be routinely used to assess and identify pancreatic lesions [35, 37, 38].

Minimal Consensus Statement on Imaging – Specific

Tumor localization studies are required in all patients with ZES biochemically established. Most recommend initially a UGI endoscopy with careful inspection of the duodenum followed by a helical CT and SRS. If these studies are negative and surgery is being considered, endoscopic ultrasound should be performed. If results are still negative, selective angiography with secretin stimulation and hepatic venous sampling should be considered. SRS is the best study to initially stage the disease and detect both liver and distant metastases. Intraoperative ultrasound and routine duodenotomy for duodenal lesions preferably preceded by transillumination of the duodenum should be done in all patients at surgery. Bone metastases occur in up to one-third of patients with liver metastases and should be sought in all patients by using SRS and an MRI of the spine [47, 48].

Pathology [1, 9]

Histopathology – General

The diagnosis of a gastrinoma requires the presence of a NET immunohistochemically expressing gastrin and associated with ZES. Gastrin-producing NETs without ZES are not considered gastrinomas. Gastrinomas do not show any histological features that distinguish them from other NETs. The histological features that are predictive of the biological behavior of a gastrinoma are discussed in the section on clinicopathological features and include angioinvasion, mitotic activity and the proliferative index determined by Ki-67 staining. Approximately 50% of gastrinomas, like other NETs, may produce hormonal peptides other than gastrin, but they may or may not be released in sufficient quantities to cause serum elevations or a respective hormonal syndrome. In MEN1/ZES patients with duodenal gastrinomas, multiple pancreatic endocrine tumors are invariably present microscopically and often also macroscopically. In almost 100% of these patients the gastrinoma is in the duodenum, and only exceptionally in the pancreas. In these patients, immunohistochemical studies with multiple hormones should be done on all primaries and metastases to help determine their origin.

Minimal Consensus Statement on Histopathology – Specific

Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, gastrin and Ki-67. Both a mitotic index using a mitotic count and a Ki-67 index are recommended. In MEN1 patients, all primaries and metastases should also be stained for other hormones (PP, glucagon, insulin, somatostatin) to determine the full spectrum of hormone expression. Cytology is generally not useful except in an intraoperative setting for tumor confirmation.

Medical Therapy (Gastric Acid Hypersecretion)

Medical Treatment – General

Gastric acid hypersecretion can be >10 normal in ZES (mean 45 mEq/h) and it is essential it be controlled acutely and long-term in all patients to prevent peptic complications [2, 26]. Both H₂-blockers and PPIs can control acid hypersecretion in all patients who can take oral medications and are cooperative [27, 49, 50]. PPIs are the drugs of choice because of their long duration of action allowing once or twice a day dosing to control symptoms in >98% of patients. H₂ blockers, to be effective, are usually required at higher doses than are those drugs used in conventional peptic disease (frequently up to 10 times the usual dose) and 4- to 6-hourly dosing is frequently needed [49–52]. Patients with complicated disease (presence of MEN1 with hypercalcemia, presence of severe GERD symptoms, presence of previous Billroth II resection) need higher doses of all antisecretory drugs and may need more frequent dosing even with PPIs [53–56]. Patients have been treated for up to 15 years with PPIs with no evidence of tachyphylaxis and no dose-related side effects. Vitamin B₁₂ deficiency but not iron deficiency has been reported with long-term PPI use in ZES, but it is unclear if it causes clinically important vitamin B₁₂ deficiency [57–59]. Both intravenous PPIs (intermittent use) and continuous infusion of high doses of H₂ blockers satisfactorily control acid secretion when parenteral drugs are needed. Because of this intermittent use, PPIs are recommended [52, 60]. In MEN1/ZES patients, correction of hyperparathyroidism can reduce the fasting gastrin level and BAO, and increase the sensitivity to acid antisecretory drugs [54, 61]. Postcurative resection in up to 40%, the patients continue to show mild acid hypersecretion and require low doses of antisecretory drugs [62]. Parietal cell vagotomy can reduce the BAO long-term and decrease the dosage of antisecretory drugs needed [63].

Minimal Consensus Statement about Medical Treatment – Specific

Acid hypersecretion needs to be controlled acutely and long-term in all ZES patients to prevent acid-related peptic complications. PPIs are the drugs of choice because of their long duration of action allowing once or twice a day dosing to control symptoms in >98% of patients. The recommended starting dose is equivalent to omeprazole 60 mg q.d. in sporadic ZES and 40–60 mg b.i.d. in MEN1/ZES. Patients with complicated disease (presence of MEN1 with hypercalcemia, presence of severe GERD symptoms, and presence of previous Billroth II resection) need higher doses of PPIs and should be started on 40–60 mg b.i.d. On follow-up visits, PPI drug dosage can be reduced in most patients with sporadic ZES and a 30–50% of MEN1/ZES patients. Patients have been treated for up to 15 years with PPIs with no evidence of tachyphylaxis. With long-term treatment serum vitamin B₁₂ levels should be monitored once per year.

Surgical Therapy

Surgical Therapy – General [21, 64]

In contrast to the past, there is now general agreement that patients with sporadic ZES, with resectable disease and without serious contraindications to surgery or with concomitant illnesses limiting life expectancy, should undergo routine surgical exploration for cure by a surgeon experienced in treating these tumors. Surgical resection should be performed at laparotomy and not laparoscopically. The role of surgery, type of surgery, and timing of surgery in patients with MEN1/ZES remains controversial [21, 61, 65, 66]. Total gastrectomy should only be performed in patients who cannot or will not take oral antisecretory drugs (<1–2%). Parietal cell vagotomy at the time of exploratory surgery is generally not performed but it may have a role in selected patients because it reduces the acid secretory rate and drug dosage in patients who are not cured [63, 67]. Whipple resections can result in curing patients with pancreatic head/duodenal gastrinomas in both sporadic and MEN1/ZES patients. However, its use is not generally recommended. It may have a role in the few selected patients with long life expectancy with multiple or large gastrinomas in this region that are not removable by enucleation [21].

After curative resection it is essential to regularly evaluate patients for continuing cure by performing both fasting serum gastrin assessments as well as secretin testing. Repeated conventional imaging studies are not needed if the fasting gastrin and secretin test remain normal. Whether SRSs will detect recurrent tumors before fasting gastrin elevations or a return of a positive secretin test is unknown at present [68].

Minimal Consensus Statement on Surgical Treatment – Specific

Surgery is the only treatment that can cure gastrinomas. Surgery has been shown to decrease the rate of development of liver metastases which is the most important prognostic factor for long-term survival [5, 19, 69] and to increase survival [89]. Long-term curative resection without a pancreaticoduodenectomy (Whipple resection) occurs in 20–45% of patients with sporadic ZES when the surgery is performed by a surgeon skilled in the treatment of this disease, but in 0–1% of patients with MEN1/ZES [16, 21, 65, 70, 71]. Tumors in the pancreatic head area should be enucleated, distal pancreatic resection performed for caudally-located tumors and duodenotomy performed routinely to detect small duodenal gastrinomas. A lymph node dissection should be performed even if no primary tumor is found because lymph node primary tumors are reported, although controversial [21, 72]. Surgery for attempted cures is recommended in patients with sporadic ZES without liver metastases or concurrent illnesses limiting life expectancy. Routine surgical exploration is controversial in patients with MEN1/ZES since these patients usually have multiple duodenal gastrinomas, frequently with lymph node metastases, are rarely cured and have an excellent life-expectancy if only small tumors (<2 cm) or no tumors are present on preoperative imaging studies. Surgery is recommended if imaging studies identify tumors >2 cm in diameter to possibly decrease the subsequent development of metastatic spread to the liver. However, the efficacy of this approach remains unproven [65].

In contrast to insulinomas, laparoscopic resection of gastrinomas is not recommended because frequently the primary is not seen on preoperative imaging studies, the tumors are submucosal in the duodenum and they frequently have lymph node metastases [21]. Whipple resections are not generally recommended. It may have a role in the few selected patients with long life expectancy who have multiple or large gastrinomas in this region that are not removable by enucleation [21].

Integrated Therapy of Advanced Disease

Advanced Disease Treatment – General

It is important to consider treatment for advanced disease because it is becoming the main determinant of long-term survival in ZES patients now that acid hypersecretion can be controlled medically [5, 19]. The presence of any liver metastases decreases life expectancy in ZES patients. Ten-year survival with no liver metastases is 96%, single or limited metastases in both lobes (<5/lobe) is 78–80% and with the presence of diffuse metastases it is 16%. The survival of a patient who develops liver metastases during follow-up when there were no liver metastases at the initial evaluation is decreased to 85% [5, 19]. In 40% of patients with unresectable liver metastases the tumor demonstrated aggressive growth and all of the deaths due to disease progression occurred in these

patients [73]. One fourth of ZES patients have tumors that demonstrate aggressive growth and progress to cause death while in the remaining 75% the tumor growth is indolent and death from tumor is uncommon [6, 19]. Cytoreductive surgery, chemotherapy, hepatic artery embolization or chemo-embolization, biotherapy (somatostatin analogues/interferon), peptide receptor radionuclide therapy and liver transplantation have all been recommended as valuable in ZES patients with advanced disease [74–76].

Minimal Consensus Statement on Advanced Disease Therapy – Specific

Cytoreductive Surgery/Radiofrequency Ablation (RFA)

Cytoreductive surgery should be considered for the 5–15% of patients with liver metastases confined to one lobe or who have liver metastases that could be completely removed or $\geq 90\%$ removed at surgery [64, 77–79]. At the time of cytoreductive surgery RFA can be used for isolated metastases. RFA can also be used alone if there are < 10 lesions seen in the liver.

Hepatic Artery Embolization or Chemoembolization [79, 80]

This treatment should be considered in a patient with unresectable liver metastases if they are symptomatic or the hepatic deposits are increasing in size, the portal vein is patent and distant disease is not present. Selective embolization of peripheral arteries is usually preferred. There are no studies that show this methodology prolongs life in these patients.

Chemotherapy [76]

Streptozotocin and doxorubicin with or without 5-fluorouracil should be considered for patients with rapidly growing diffuse liver metastases that fail embolization or chemoembolization or have distant metastases outside the liver. The response rate varies from 5 to 50% in various series. Whether chemotherapy extends survival is controversial at present.

Biotherapy (Somatostatin Analogues/Interferon) [81–84]

Both interferon-alpha and somatostatin analogues have been used for their anti-tumor effects in patients with metastatic gastrinomas. Anti-growth effects are reported in 30–50% of patients with almost all cases responding by showing stabilization of tumors that had been growing prior to treatment. Both interferon and somatostatin are reported to be more effective in slow-growing tumors with low proliferative rates. Less than 10% of gastrinomas demonstrate a decrease in tumor size with treatment with either somatostatin or interferon-alpha. At present, the use of these biotherapy agents for anti-growth effects is controversial and their routine is not recommended until ongoing randomized trials clarify their role.

Peptide Receptor Radionuclide Therapy [85]

In patients with metastatic, inoperable tumors that are positive with SRS, of which most gastrinomas are, there may be a role

for PRRT. Until this is more carefully studied with larger numbers of patients, its exact role at present is unclear.

Liver Transplantation [86]

In patients with disease confined to the liver who are young and otherwise generally healthy, liver transplantation may be considered. Patients with a Whipple resection or aggressive gastrinoma should be excluded.

Follow-Up

Long-Term Follow-Up – General

Patients with advanced metastatic disease, post-curative resection, with MEN1/ZES, and with active acid-related peptic disease problems frequently require a different follow-up schedule than the typical ZES patient with active but limited disease. Patients with metastatic disease require a relatively short follow-up initially (3–6 months) to determine whether progressive disease is present and antitumor treatment is indicated. Patients receiving antitumor treatment need follow-ups at 3- to 6-month intervals to assess the effect of treatment and to evaluate toxicity. Patients with MEN1/ZES after initial treatment of the MEN1 problems (hyperparathyroidism, pituitary disease) should be seen in 6- to 12-month intervals. Patients with postcurative resection can be evaluated yearly unless symptoms of recurrence occur.

Minimal Consensus Statement on Follow-Up – Specific

For patients with advanced metastatic disease follow-up should be at 3- to 6-monthly intervals with tumor imaging (CT, SRS), fasting serum gastrin and acid secretory control (6 months). At least yearly, assessment for ectopic Cushing's with a urinary cortisol and serum cortisol should be considered. For patients with advanced metastatic disease or who are receiving chemotherapy or other antitumor treatments, follow-up may need to be shorter to assess for specific toxicities. For patients with MEN1/ZES, follow-up should be yearly with an assessment of tumor extent with imaging (CT abdomen and chest [rule out thymic carcinoid], SRS), biochemical assessment for MEN1 diseases (ionized calcium, serum PTH, prolactin, glucagon), fasting serum gastrin, acid control, UGI endoscopy to evaluate for gastric carcinoid [14, 87, 88]. For patients with post-curative resection, yearly evaluation with fasting gastrin levels, secretin provocative test and acid secretory control should be done if the patient is still taking PPIs/H2 blockers. SRSs should be performed at 2-year intervals. Typical ZES patients without any of the above-mentioned special problems should be seen yearly with tumor assessment (CT, SRS), fasting gastrin determination, and acid control.

Final Remarks

The management of gastrinomas has many similarities to that of the management of other pancreatic endocrine tumor syndromes; however, it also has some important specific areas that need attention. First, the gastric acid hypersecretion is unique to ZES and requires appropriate management initially and at every phase of follow-up. Although PPIs have greatly simplified management, special circumstances such as the need for parenteral drugs, patients with MEN1, severe GERD or a previous Billroth II resection require special attention. The possible long-term effects of PPI treatment, such as the development of vitamin B₁₂ deficiency or possibly increased development of gastric carcinoids, are also requiring special attention. Second, gastrinomas have the highest percentage of any GEP-NET of patients with MEN1 (20–30%). Its identification and management initially and during follow-up are critical because both differ from that of the nonMEN1/ZES patient. Particularly important are possible genetic counseling, assessment for thymic and gastric carcinoid, multiple hormonal syndromes, management of the hyperparathyroidism, and assessment for other tumors these patients are increasingly developing (soft tissues and muscle tumors, CNS tumors such as meningiomas, melanomas). Third, ZES is the most common malignant functional PET and in contrast to the other less common PETs the patients often present with minimal tumor burdens and the primary tumors can be difficult to find. Therefore, careful imaging and an appreciation of the prognosis of the disease with different tumor extents are essential in determining the appropriate treatment at a given stage. Fourth, in contrast to the other symptomatic PETs, the role of surgery in patients with MEN1/ZES is controversial. Fifth, in contrast to other functional PETs with advanced disease the symptoms of the hormone excess state can be controlled in almost every patient with PPIs. Therefore the indication for treatment of the advanced disease is either the symptoms due to the tumor mass per se or tumor progression, not refractory hormonal symptoms.

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