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ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Neoplasms: Functional Pancreatic Endocrine Tumor Syndromes

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Introduction

Pancreatic endocrine tumors (p-NETs) include both pancreatic neuroendocrine tumors (p-NETs) associated with a functional syndrome (functional p-NETs) or those associated with no distinct clinical syndrome (non-functional p-NETs) [1–4]. Non-functional p-NETs frequently secrete pancreatic polypeptide, chromogranin A, neuron-specific enolase, human chorionic gonadotrophin subunits, calcitonin, neurotensin or other peptides, but they do not usually produce specific symptoms and thus are considered clinically to be non-functional tumors [2, 3, 5–7]. Only the functional p-NETs will be considered in this section. The two most common functional p-NETs (gastrinomas, insulinomas) are considered separately, whereas the other well-described and possible rare functional p-NETs are considered together as a group called rare functional p-NETs (RFTs) (table 1) [1–4].

Gastrinomas are neuroendocrine neoplasms, 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 peptic disease (peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD)) [8–10]. In this section, ZES due to both duodenal and pancreatic gastrinomas will be covered together because clinically they are similar [8, 10]. Specific points related to gastrinomas associated with the genetic syndrome of Multiple Endocrine Neoplasia type 1 (MEN1) (25% of cases) will also be mentioned [11, 12].

Insulinomas are neuroendocrine neoplasms located in the pancreas that secrete insulin, which causes a distinct syndrome characterized by symptoms due to hypoglyce-

[1] See list at the end of the paper.

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mia [2, 13–15]. The symptoms are typically associated with fasting and the majority of patients have symptoms secondary to hypoglycemic central nervous system (CNS) effects (headaches, confusion, visual disturbances, etc.) or due to catecholamine excess secondary to hypoglycemia (sweating, tremor, palpitations, etc.) [2, 3, 13–15].

RFTs can occur in the pancreas or in other locations (VIPomas, somatostatinomas, GRHomas, ACTHomas, p-NETs causing carcinoid syndrome or hypercalcemia (PTHrp-omas)) (table 1) [1–5, 7]. Each of the established RFT syndromes is associated with a distinct clinical syndrome reflecting the actions of the ectopically secreted hormone. Other RFTs are listed as causing a possible specific syndrome either because there are too few cases or there is disagreement about whether the described features are actually a distinct syndrome (table 1) [1–5, 7].

Epidemiology and Clinicopathological Features of Functional p-NETs

Gastrinomas: Minimal Consensus Statement on Epidemiology and Clinicopathological Features

Gastrinomas – Epidemiology and Site of Origin – Specific (table 1) [1–3, 8, 9, 16, 17]

The incidence of gastrinomas is 0.5–2/million population/year. They are the most common functional, malignant p-NET syndrome and comprise up to 30% of these [1, 2, 8, 9]. 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 [8, 16, 17] In rare cases, gastrinomas occur in other non-pancreatic, non-duodenal abdominal (stomach, liver, bile duct, ovary) (5–15%) and extra-abdominal (heart, small cell lung cancer) locations [8, 16–18]. The exact site of origin of sporadic gastrinomas is unknown, however, in MEN1/ZES patients the duodenal gastrinomas (which occur in 70–100%) originate from diffuse gastrin cell proliferations [16, 19].

Gastrinomas – Clinicopathological Features – Specific

Similar to other gastroenteropancreatic neuroendocrine neoplasms, gastrinomas can be classified both using the current WHO classification system with TNM classification and grading [20] based on the ENETS TNM and grading [21], which both proved to have prognostic significance [3, 22–30]. According to WHO 2010, gastrinomas are NET G1-G2, usually >1 cm, showing local invasion and/or proximal lymph node metastases [8, 16, 17, 20, 31]. Liver metastases (LM) occur much more frequently with pancreatic gastrinomas (22–35%) than duodenal gastrinomas (0–10%) [8, 17, 18, 31]. 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) [8, 31–33]. 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 [8, 17, 18, 31]. At surgery, 70–85% of gastrinomas are found in the right upper quadrant (duodenal and pancreatic head area), the so-called 'gastrinoma triangle' [8, 17, 18, 34].

MEN1 is an autosomal-dominant syndrome that is present in 20–30% of patients with ZES [11, 12]. In these patients duodenal tumors are usually (70–100%) responsible for the ZES. The duodenal tumors are almost always multiple [11, 16, 17, 35, 36]. Histologically, most gastrinomas are well differentiated and show a trabecular and pseudoglandular pattern. Their proliferative activity (i.e. the Ki67 index) varies between 2 and 10%, but is mostly close to 2%. Immunohistochemically, almost all gastrinomas stain for gastrin [8, 17].

Insulinomas: Minimal Consensus Statement on Epidemiology and Clinicopathological Features (table 1)

Insulinomas: Minimal Consensus Statement on Epidemiology and Clinicopathological Features – Specific (table 1)

Insulinomas are the most common functioning neuroendocrine tumor of the pancreas, with an estimated incidence of 1–3/million population/year [1–3, 13–15]. Less than 10% are malignant. There is an age-specific incidence peak in the fifth decade of life and the incidence is slightly higher in women than in men. Approximately 10% are multiple, and approximately 5% are associated with the MEN1 syndrome [1, 2, 11, 13, 13, 15, 26]. Isolated sporadic insulinomas are generally cured by pancreatic resection [13–15, 26]. A multidisciplinary team approach is required [13–15, 26].

Rare Functioning Tumors (table 1): *Minimal Consensus Statements on Epidemiology and Clinicopathological Features* [1–5, 37, 38]

Rare Functioning Tumors (table 1): Minimal Consensus Statements on Epidemiology and Clinicopathological Features – Specific

RFTs include the established RFT syndromes: glucagonomas, VIPomas, somatostatinomas, GRHomas, ACTHomas, p-NETs causing carcinoid syndrome or hypercalcemia (PTHrp-omas). RFTs also include five possible RFT syndromes: p-NETs secreting calcitonin, renin, luteinizing hormone, erythropoietin and insulin-like growth factor II (table 1) [1–5, 7, 37, 38] whose status is unclear whether they represent a specific syndrome because of the small numbers of cases (table 1) [1–3, 5, 7, 37, 38]. RFTs represent less than 10% of all p-NETs [2, 5]. The majority of patients with RFTs of the pancreas present with metastatic disease (40–90%) in the liver. Somatostatinomas can occur in the pancreas or upper small intestine, however, the duodenal somatostatinomas are rarely associated with a functional clinical syndrome (the somatostatinoma syndrome) (table 1) [2, 37, 39]. In addition to somatostatinomas, a number of the other RFTs occur in extrapancreatic locations also (table 1). Most RFTs are

Table 1. Functional pancreatic endocrine tumor (PET) syndromes

Name	Biologically active peptide(s) secreted	Incidence (new cases/10^6 population/year)	Tumor location	Malignant %	Associated with MEN-1, %	Main symptoms/signs
A. Most common functional PET syndromes						
Insulinoma	insulin	1–3	pancreas (>99%)	<10	4–5	hypoglycemic symptoms (100%)
Zollinger-Ellison syndrome	gastrin	0.5–2	duodenum (70%); pancreas (25%); other sites (5%)	60–90	20–25	pain (79–100%); diarrhea (30–75%); esophageal symptoms (31–56%)
B. Established rare functional PET syndromes (RFTs)						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	vasoactive intestinal peptide	0.05–0.2	pancreas (90%, adult); other (10%, neural, adrenal, periganglionic)	40–70	6	diarrhea (90–100%); hypokalemic (80–100%); dehydration (83%)
Glucagonoma	glucagon	0.01–0.1	pancreas (100%)	50–80	1–20	rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%)
Somatostatinoma	somatostatin	rare	pancreas (55%); duodenum/jejunum (44%)	>70	45	diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%)
GRHoma	growth hormone-releasing hormone	unknown	pancreas (30%); lung (54%); jejunum (7%); other (13%)	>60	16	acromegaly (100%)
ACTHoma	ACTH	rare	pancreas (4–16% all ectopic Cushing's)	>95	rare	Cushing's syndrome (100%)
PET causing carcinoid syndrome	serotonin? tachykinins	rare (43 cases)	pancreas (<1% all carcinoids)	60–88	rare	same as carcinoid syndrome above
PET causing hypercalcemia (PTHrp-oma)	PTHrp; others unknown	rare	pancreas (rare cause of hypercalcemia)	84	rare	abdominal pain due to hepatic metastases, symptoms due to hypercalcemia
Possible rare functional PET syndromes						
PET secreting calcitonin	calcitonin	rare	pancreas (rare cause of hypercalcitonemia)	>80	16	diarrhea (50%)
PET secreting renin	renin	rare	pancreas	unknown	no	hypertension
PET secreting luteinizing hormone	luteinizing hormone	rare	pancreas	unknown	no	anovulation, virilization (female): reduced libido (male)
PET secreting erythropoietin	erythropoietin	rare	pancreas	100	no	polycythemia
PET secreting IF-II	insulin-like growth factor II	rare	pancreas	unknown	no	hypoglycemia

diagnosed as WHO group 2. Not enough data in the literature is currently available to give accurate estimates on survival. The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with RFT is MEN1, with glucagonomas occurring in 3% of MEN1 patients, VIPomas in 3%, GRHomas, somatostatinomas in <1% [11, 40]. Somatostatinomas (especially periampullary) are seen in up to 10% of patients with von Recklinghausen's disease (neurofibromatosis 1) but in almost all cases they are not associated with a functional syndrome (somatostatinoma syndrome) [5, 11, 39].

Prognosis and Survival in Functional p-NETs and MEN1

Minimal Consensus Statement on Prognosis and Survival in Functional p-NETs and MEN1

Gastrinomas: Minimal Consensus Statement on Prognosis and Survival – Specific [8, 9, 18, 41, 42]

Prospective studies show in approximately 25% of patients with sporadic ZES and in 15% with MEN1/ZES the gastrinomas demonstrate aggressive growth [8, 9, 31, 41, 43]. Approximately 30–40% of gastrinomas are associated with LM [44]. At diagnosis, 5–10% of duodenal gastrinomas and 20–25% of pancreatic gastrinomas are associated with LM [8, 9, 31, 41]. LM are the

most important prognostic factor, the 10-year survival being 90–100% without LM and 10–20% with LM [8, 9, 31, 41, 42]. Poor prognostic factors besides LM 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 (1–3 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, advanced TNM classification status; 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, Ki67 index >2, poor differentiation [8, 9, 18, 25, 31, 41, 42, 45–48].

Insulinomas: Minimal Consensus Statement on Prognosis and Survival – Specific

Greater than 90–95% of insulinomas are benign at presentation, and 95–100% of these can be surgically cured [1, 2, 13–15, 26, 49]. The <10% with LM have a median survival of less than 2 years [13, 15, 50]. Tumor size ≥2 cm, Ki67 >2% and various molecular features (chromosomal instability; chromosomal loss of 3p or 6q; chromosomal gain on 7q, 12q or 14q) all are predictors of metastatic disease, which is associated with decreased survival [51].

RFTs: Minimal Consensus Statement on Prognosis and Survival – Specific

Most RFTs present with metastatic disease and their 5-year survival is increasingly determined by the growth of the tumor, rather than the hormone excess state. Five-year survival for the group with advanced disease is 29–45% [1, 2, 4, 5]. All of the survival/prognostic data on the individual RFTs comes from retrospective studies and in recent studies their results are often included in non-insulinoma/non-gastrinoma series that include non-functional p-NETs. These studies demonstrate tumor Ki67 ≥2%, presence of LM, presence of cytokeratin-19 staining and various molecular features (chromosome 7p gain), chromosomal instability) were associated with a poor prognosis [2, 42, 51].

MEN1: Minimal Consensus Statement on Prognosis and Survival – Specific

The prognostic significance of MEN1 in patients with p-NETs is not entirely clear. Some studies in patients with gastrinomas suggest these patients have a better prognosis, even though the gastrinomas are almost always multiple [8, 31, 41, 43]. However, because the patients present at an earlier age, this could affect the survival results [31, 41]. Patients with MEN1 frequently have multiple insulinomas, however, these are usually cured surgically [11, 52]. There are no comparative studies on survival in MEN1 patients with insulinomas compared to sporadic cases. In older studies, survival was primarily determined by the development and adequacy of treatment of ZES, development of renal failure from inadequately treated hyperparathyroidism and the malignant nature of the p-NETs [11, 53]. With the ability to treat both the ZES and the hyperparathyroidism, recent studies show in patients with MEN1, the natural history of the p-NET increasingly becoming a determinant of survival [11]. In the French registry that included 758 patients with MEN1, thymic tumors and duodenopancreatic tumors, including non-secreting pancreatic tumors but not insulinomas, increased the risk of death [53, 54]. Thymic carcinoid occur primarily in males (>90%) and are a particularly aggressive tumor causing not only local encasement of vital structures in the mediastinum, but also the early development of distal metastases to liver and bone [11, 53, 55].

Clinical Presentation of Functional p-NETs

Minimal Consensus Statement on Clinical Presentation of Functional p-NETs

Gastrinomas: Minimal Consensus Statement on Clinical Presentation – Specific (table 1) [3, 8–10, 12, 32, 56–59]

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, peptic symptoms, GERD symptoms or ulcer complications and diarrhea. Multiple ulcers or ulcers in unusual locations are a less frequent presenting feature than in the past [3, 8–10, 12, 32, 56–59]. With the widespread use of gastric antisecretory drugs, particularly proton pump inhibitors (PPIs), symptoms may be masked and the diagnosis most often suggested by the long history of PUD/GERD symptoms or their recurrence after treatment [3, 32, 57, 59, 60]. 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% [8, 10, 57]. At presentation, >97% of patients have an elevated fasting serum gastrin (FSG) level, 87–90% have marked gastric acid hypersecretion (basal acid output >15 mEq/h) and 100% have a gastric acid pH <2 [61]. Patients with MEN1 with ZES (20–30%) present at an earlier age (mean 32–35 years) than patients without MEN1 (i.e. sporadic disease) [11, 12]. In up to 45% of MEN1/ZES patients, the symptoms of ZES precede those of hyperparathyroidism, and they can be the initial symptoms these patients present with [11, 12, 62]. 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 [11, 12] or an oral calcium challenge test [63]. Of all MEN1/ZES patients, 25% lack a family history of MEN1, supporting the need to screen all ZES patients for MEN1 [11, 12].

Insulinomas: Minimal Consensus Statement on Clinical Presentation – Specific (table 1)

Insulinomas characteristically present between ages 40 and 45 years, 60% occur in females, and the symptoms are due to hypoglycemia [1–3, 13–15, 50]. The majority of symptoms are related to the effects of hypoglycemia on the CNS and include confusion, visual disturbances, headaches, behavioral changes, or coma. Most patients also have symptoms due to adrenergic

stimulation secondary to the hypoglycemia, which include sweating, tremor, palpitations and irritability. The mean duration of symptoms at diagnosis is 3 years and a recent increase in body weight is present in the majority of patients [1–3, 13–15, 50].

Rare Functioning Tumors: Minimal Consensus Statement on Clinical Presentation – Specific (table 1)

RFTs characteristically present with the symptoms of the specific hormone excess state (table 1), and in most cases present late in the disease course when advanced disease is already present [2, 4, 5]. In a small percentage of patients with a functional p-NET, a second functional syndrome may develop over time [64, 65].

Diagnosis of Functional p-NETs and MEN1

Diagnosis of Functional p-NETs – General

The diagnosis of all functional p-NETs requires the demonstration of an inappropriate elevation of the appropriate, specific serum hormonal marker (i.e. gastrin in ZES, insulin in insulinomas, etc.) combined with clinical/laboratory evidence of oversecretion of the appropriate hormone (such as gastric acid hypersecretion in ZES, hypoglycemia in insulinomas, etc.) (table 1) [1–3, 57, 66]. The diagnosis of functional p-NET requires clinical evidence of hormonal overexpression (table 1) and is not based only on immunohistochemical results [1–3, 57, 66].

Diagnosis of ZES – General

While the diagnosis of ZES generally requires the demonstration of an inappropriate elevation of FSG by demonstrating hypergastrinemia in the presence of hyperchlorhydria or an acidic pH (preferably ≤ 2), in most cases today the first study done today is the FSG determination [2, 8, 32, 57, 60, 66, 67]. 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) [2, 8, 32, 57, 60, 66, 67]. No level of FSG alone can distinguish ZES from that seen in achlorhydric states. A recent study [68] demonstrates that it is particularly important that a known, reliable assay be used to determine the fasting gastrin levels. In this study [68] of 12 available gastrin assays examined (7 RIAs, 5 ELISAs), only 5 of the 12 kits accurately measured plasma gastrin concentrations with the others either over- or underreporting the value from the true value [68].

Recent data show that the widespread use of PPIs is making the diagnosis of ZES more difficult and delaying the diagnosis [2, 8, 32, 57 59, 60, 66, 67]. 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 [2, 8, 32, 57, 59, 60, 66, 67]. 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 and must be done carefully as discussed below in the specific recommendations for ZES diagnosis. 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 H_2 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 break through symptoms which may lead to a suspicion of ZES and are frequently seen with H_2 blockers, are infrequent with PPIs [2, 8, 32, 57, 59, 60, 66, 67].

Patients with ZES with PUD have *H. pylori* infection 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 PUD not taking gastrotoxic drugs [8, 57, 69].

Minimal Consensus Statement on Diagnosis with or without MEN1 – Specific ZES

Suspect ZES Diagnosis [3, 8, 10, 57, 60, 66, 67]

ZES should be suspected if: recurrent, severe or familial PUD is present; PUD without *H. pylori* or other risk factors (NSAIDs, aspirin) is present; PUD associated with severe GERD is present; PUD resistant to treatment or associated with complications (perforation, penetration, bleeding) is present; PUD occurs with endocrinopathies or diarrhea; PUD occurring with prominent gastric folds at endoscopy (present –92% of ZES patients), or with hypercalcemia or hypergastrinemia [3, 8, 10, 57, 60, 66]. It should be sought for in all patients with MEN1 [8, 11]. ZES should also be suspected in PUD patients in whom diarrhea promptly resolved with treatment with PPIs.

ZES Diagnosis: Biochemistry/Laboratory Studies

Whereas the initial study usually performed to support the clinical suspicion of ZES is a FSG level, which is an excellent screening test because it is elevated in >98% of all ZES patients, it alone does not establish the diagnosis because of the many other causes of hypergastrinemia [2, 32, 58, 60, 66, 67, 70]. The

fasting gastrin assay should be performed by a known, reliable laboratory [68]. To establish the diagnosis of ZES, FSG and gastric pH should be determined (following interruption of PPI for at least 1 week with H_2 blocker coverage, if possible). If FSG levels are >10-fold elevated and gastric pH <2, the diagnosis of ZES can be made, because the possibility of retained gastric antrum can usually be eliminated by history [2, 8, 57, 58, 66]. Sixty percent of ZES patients do not have very elevated FSG levels (<10-fold), and they are in the range that is frequently seen with other diagnoses, including with PPI treatment in non-ZES patients (<10-fold elevated) [2, 32, 58, 60, 66, 67, 70]. Many centers do not have the capability of measuring gastric acid secretory rates, however, gastric pH can be initially measured and a method to perform this at endoscopy has recently been described which may facilitate measurement [71]. If FSG is <10-fold elevated and gastric pH <2, then a secretin test and basal acid output (BAO) should be performed. Also, if repeated FSG 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 [61]. The criterion for a positive secretin test (2 U/kg rapid infusion) is a >120 pg/ml increase over the basal FSG, which has a sensitivity of 94% and a specificity of 100% [72]. A second way to perform the secretin test has been described using a 1-hour infusion of 3 U/kg secretin with assessment of acid output and serum gastrin levels [73]. This method has been shown to be very effective with thresholds of 99% specificity for gastrin levels and acid outputs, but it necessitates the measurement of gastric acid outputs for at least 2 h and therefore is now less frequently used. Calcium stimulation of gastrin release can also be used to diagnose ZES, but because of its lower sensitivity, specificity and higher side-effect profile, it is now rarely used, except in situations where secretin is not available or the diagnosis of ZES is strongly suspected, but the secretin test is negative [57, 72, 74, 75]. PPIs can complicate the diagnosis of ZES because they can cause elevations of FSG in patients without ZES, can lead to false positive secretin tests [76] and can also mask the symptoms of a patient with ZES [3, 32, 57, 59, 60, 77]. PPIs presence can delay the diagnosis of ZES as discussed above. Because of this it is generally not possible to diagnose ZES while a patient is taking PPIs. Therefore to make the diagnosis of ZES, patients are usually switched to H_2 receptor antagonists to replace the PPI for at least 1 week. This needs to be performed with caution because some patients will require high, frequent doses, and because stopping PPI can cause complications due to acid hypersecretion in ZES patients (ulcer bleeding, diarrhea with dehydration or hypokalemia) [222]. Therefore, it is best performed by a specialty unit experienced in diagnosing ZES.

The diagnosis of ZES in patients with MEN1 has a number of unusual features and is discussed below in the MEN1 section.

Minimal Consensus Statement on Diagnosis in a Patient with ZES, Insulinomas or RFTs – Specific MEN1

ZES: Suspect MEN1 [11, 12]

The presence of MEN1 should be particularly sought in patients with ZES because 20–25% have MEN1 and the patient may present with symptomatic ZES only [11, 12, 62]. In a patient with ZES, MEN1 should be suspected if there is a family or personal history of endocrinopathies or familial history of recurrent peptic disease; other endocrinopathies are found during the evaluation; there is a history of renal colic or nephrolithiases; history of hypercalcemia or p-NET syndromes, or if multiple p-NETs/duodenal NETs are present. Furthermore, if carcinoid tumors of the thymus, lung or stomach (type 2) are found, MEN1 should be suspected because these are rarely present in sporadic ZES, but are much more frequent with MEN1 [12, 53, 55, 78, 79].

Insulinomas, RFTs: Suspect MEN1 [11]

MEN1 should be suspected in a patient with insulinomas with a personal or family history of any endocrinopathy, especially hyperparathyroidism; a concomitant gastrinoma or other RFT is present or develops with time; a non-functional p-NET is present; or if there are multiple insulinomas or recurrent disease occurs after resection.

Biochemistry/Laboratory Studies to Diagnose MEN1 in a Patient with a p-NET

Because of the frequency of MEN1 in ZES (20–25%) and because up to 40% of MEN1/ZES patients have no family history [10–12], all patients with ZES should have biochemical studies for MEN1. Serum parathormone levels (preferably an intact molecule assay – IRMA), ionized calcium levels and prolactin levels should be performed when initially seen and during yearly follow-up. Ionized calcium levels are much more sensitive than a total calcium- or albumin-corrected calcium determination [11, 12, 63]. In some cases, an oral tolerance calcium test might be performed [63]. ZES can be difficult to diagnose in MEN1 patients after a parathyroidectomy, because if successful, the serum calcium can return to the normal range as well as the serum gastrin, and the secretin test can become negative, masking the presence of the gastrinoma [11, 12, 80–83]. Furthermore, an effective parathyroidectomy can result in a marked decrease in acid secretory rates [80], further masking the presence of ZES and making the diagnosis more difficult.

Genetic Study for MEN1 and Other Inherited Syndromes Associated with p-NETs

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 considered. Genetic testing for MEN1 should include sequencing of the entire gene and its splice variants. If genetic testing is considered, genetic counseling should be performed, prior to testing [11, 84, 85].

If clinical features suggest von Hippel-Lindau disease (VHL), tuberous sclerosis or NF-1, appropriate gene testing should be considered after genetic counseling [11].

Diagnosis of Insulinomas – General

Suspect Insulinoma Diagnosis

Hypoglycemic symptoms can be grouped into those resulting from neuroglycopenia (commonly including headache, diplopia, blurred vision, confusion, dizziness, abnormal behavior, lethargy, amnesia, whereas, rarely, hypoglycemia may result in seizures and coma) and those resulting from the autonomic ner-

vous system (including sweating, weakness, hunger, tremor, nausea, feelings of warmth, anxiety, and palpitations) [13–15, 50]. Because occasionally symptoms are not specific and insulinoma can mimic several pathological conditions, a broad differential diagnosis should be considered. A major distinction should be made between patients with insulinoma and non-insulinoma pancreatogenous hypoglycemia [86] and from hypoglycemia occurring after various gastric bypass surgeries for obesity. The latter is usually not fasting in nature, but is postprandial, and in some cases is caused by nesidioblastosis [2, 87, 88]. However, the original description of Whipple's triad to suspect insulinoma remains fundamentally sound [15]. This triad consists of: (1) symptoms of hypoglycemia, (2) plasma glucose level ≤2.2 mmol/l (≤40 mg/dl), and (3) relief of symptoms with administration of glucose.

Minimal Consensus Statements for Diagnosis of Insulinomas – Specific [1–3, 13–15, 50, 66, 67, 89, 90]

Classically, clinical symptoms are required for the diagnosis of insulinoma and the diagnosis of insulinoma is absolutely established using the following six criteria: (1) documented blood glucose levels ≤2.2 mmol/l (≤40 mg/dl); (2) concomitant insulin levels ≥6 μU/ml (≥36 pmol/l; ≥3 U/l by ICMA); (3) C-peptide levels ≥200 pmol/l; (4) proinsulin levels ≥5 pmol/l; (5) β-hydroxybutyrate levels ≤2.7 mmol/l, and (6) absence of sulfonylurea (metabolites) in the plasma and/or urine.

Further controlled testing includes the 72-hour fast, which is the classical gold standard for establishing the diagnosis of insulinoma, although some studies, but not others, report a 48-hour fast may be adequate [1–3, 13–15, 50, 66, 67, 89, 90]. When the patient develops symptoms and the blood glucose levels are ≤2.2 mmol/l (≤40 mg/dl), blood is also drawn for C-peptide, proinsulin and insulin. Failure of appropriate insulin suppression in the presence of hypoglycemia substantiates an autonomously secreting insulinoma [1–3, 13–15, 50, 66, 67, 89, 90].

Recently, increasingly, instead of using the standard insulin radioimmunoassay, which can cross-react in many cases with proinsulin, insulin-specific assays (immunoradiometiric, immunochemiluminescent assays) are being used which have no cross-reactivity with proinsulin and give lower insulin values (up to 60% of patients with insulinomas has insulin levels ≤6 μU/ml with these assays). In one recent comparative study the most sensitive criterion for diagnosing insulinomas using these assays was the combination of an elevated proinsulin level with a fasting glucose value <45 mg/dl (<2.5 mmol/l) [91].

Minimal Consensus Statement on Diagnosis of RFTs – Specific

The minimal biochemical work-up for RFTs includes specific biochemical analyses related to the specific hormonal activity (example: serum glucagon in suspicion of glucagonoma), clinical symptoms of the disease and evidence of a hormone excess state. General markers such as serum chromogranin A may support the presence of a neuroendocrine tumor, be helpful for monitoring during the disease's course, but do not establish the diagnosis of a given RFT syndrome [1, 3, 66, 67]. All biochemical tests should be performed at first visit. p-NETs causing Cushing's syndrome should be suspected from the clinical examination and history, and the diagnosis established by performing 24-hour urinary cortisol determinations, midnight plasma or salivary cortisol assessments and dexamethasone suppression tests as needed [7, 66].

Minimal Consensus Statement on Diagnosis of Other Hormonal Syndromes in ZES Patients

Ectopic Cushing's syndrome develops in 5–15% of patients with advanced metastatic disease and has a very poor prognosis [41, 45]. It should be routinely assessed for in patients with advanced metastatic disease by careful clinical examination, history and, if clinically suspected, routine 24-hour urinary cortisol determinations and serum cortisol assessment after dexamethasone suppression [7, 66]. A secondary hormonal syndrome develops in 1–10% of patients, especially those with metastatic disease or MEN1 [64, 65]. These should be assessed for by a careful clinical history and routine hormonal assays are not recommended.

Localization of Tumor/Tumor Extent in Patients with Functional p-NETs [1, 2, 5, 8, 13–15, 92–95]

p-NET: Tumor Localization – General

Tumor localization studies are required in all patients with p-NETs. All aspects of their management require knowledge of tumor extent. It is important to remember that the majority of all functional p-NETs (except insulinomas) (table 1) are malignant and that the natural history of p-NET is now the most important determinant of long-term survival in many studies, whereas in the past it was the control of the hormone excess state [1, 2, 28, 31, 41]. Accurate localization of the tumor can result in complete surgical resection with cure of most insulinomas and a percentage of gastrinomas and other RFTs (10–40%). In gastrinoma patients, surgical resection whenever possible has been shown to decrease the subsequent rate of developing LM and increase survival [1, 2, 26, 50, 96–98].

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 or calcium stimulation and assessment of hepatic venous gastrin gradients, portal venous sampling for hormonal gradients), somatostatin receptor scintigraphy (SRS) and endoscopic ultrasound (EUS) as well as various intraoperative localization methods including intraoperative ultra-

sound (IOUS), and in patients with gastrinomas, intraoperative transillumination of the duodenum and routine use of a duodenotomy [2, 5, 8, 9, 15, 18, 92–95, 99–101].

Most prospective studies show the sensitivity of conventional imaging studies for localizing the primary tumor is 10–50%, angiography 20–50% and SRS 30–70% (except non-metastatic insulinomas) [2, 3, 5, 8, 15, 94]. The use of SRS changes management in 15–45% of patients with gastrinomas and other RFTs [2, 8, 9, 18, 100–102]. For SRS as well as all conventional studies, tumor size is an important variable and tumors <1 cm are missed in >50% of cases [8, 103]. Therefore, because most duodenal gastrinomas are <1 cm, they are frequently missed. SRS has a much lower sensitivity in patients with localized insulinomas because they have lower densities of somatostatin receptors that bind the radiolabeled somatostatin analogue with high affinity (sst2, sst3, sst5) [3, 14, 15, 93]. EUS is particularly sensitive for pancreatic NETs, however, its ability to detect small duodenal tumor is controversial [8, 15, 47, 104–106, 119]. Functional localization studies are not limited by tumor size but are invasive studies, and are now primarily reserved for insulinomas (intra-arterial calcium with hepatic venous insulin sampling) that are negative on other localization methods [8, 101, 107, 108]. Prospective studies show for metastatic disease from a malignant p-NET to the liver that CT and ultrasound detect their presence in 30–80% of patients with metastases, MRI and angiography in 50–85% and SRS in 70–95% [1, 2, 8, 93, 109, 110]. In patients that might have duodenal NETs such as those with ZES, at surgical exploration, duodenotomy is essential to detect up to one-half of duodenal tumors and its use increases the cure rate. IOUS should be routinely used to assess and identify pancreatic lesions [5, 8, 15, 99, 111].

Recently, a number of studies have demonstrated that positron emission tomography (PET) especially with gallium-68-labelled somatostatin analogues when combined with CT has high specificity and is more sensitive that SRS or other modalities [1, 94, 112–118]. At present it is not available in many centers and the exact place in the localization algorithm it should be used has not been clearly defined. Standard PET with ^{18}F-glucose is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive poorly differentiated pancreatic neuroendocrine carcinomas (p-NECs) [5].

A striking wide discrepancy with regard to the results for localization between different centers for each of these techniques presumably reflects the specialist expertise and the availability of equipment. Still, no single modality is 100% effective. Any proposed imaging algorithm should take into account cost, sensitivity, availability and local expertise [15].

ZES: Minimal Consensus Statement on Gastrinoma Localization [1–3, 8, 9, 18, 47, 92–96, 100, 106, 110, 119]

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 mdCT or MRI and SRS [8, 18, 94, 96, 100, 110]. If these studies are negative and surgery is being considered, EUS should be performed which will detect most pancreatic gastrinomas, but misses up to 50% of duodenal tumors [47, 106, 119]. If results are still negative (<10%), selective angiography with secretin stimulation and hepatic venous gastrin sampling should be considered and should be performed in experienced centers [101]. SRS is the best study to initially stage the disease and detect both liver and distant metastases, however, SRS will miss 50% of tumors <1 cm [103]. Recent studies show that MRI is a sensitive method for detecting LM of endocrine tumors [120]. IOUS and routine duodenotomy for duodenal lesions preferably preceded by transillumination of the duodenum should be done in all patients at surgery [8, 47, 96]. Bone metastases occur in up to one-third of patients with LM and should be sought in all patients by using SRS and an MRI of the spine [8, 121, 122]. PET scanning, especially combined with CT scanning (PET-CT), for gastrinomas as well as other p-NETs/duodenal NETs, is receiving increased attention because of its enhanced sensitivity/specificity. The results of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT imaging of gastrinomas are disappointing, presumably because of their low proliferative potential. Promising results reporting greater sensitivity than other modalities, however, have been obtained using ^{11}C-5-HTP, ^{18}F-DOPA, and ^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (^{68}Ga-DOTATOC), however, all of these are investigational at present [94, 115, 123].

MEN1: Minimal Consensus Statement on Neuroendocrine Tumor Localization – Specific [1, 2, 8, 11, 84, 85]

Patients with MEN1 not only develop p-NETs/duodenal NETs (functional and non-functional), but also tumors/hyperplasia of the parathyroid, pituitary, adrenal, skin, thyroid, CNS, smooth muscles as well as carcinoids (lung, thymus, gastric) [8, 11, 12, 53, 55, 79, 84, 85]. In addition to initially screening for functional p-NETs/duodenal NETs, hyperparathyroidism and functional pituitary adenomas, as outlined in a previous section, all MEN1 patients need to be carefully assessed by physical examination and imaging studies for the other tumors, which are generally non-functional [8, 11, 84, 85]. Specific parathyroid localization studies are required if hyperparathyroidism is found (ultrasound, CT/MRI, ^{99m}Tc-sestamibi scan) [84]. All patients require MRI of the sella turcica region and after 20 years of age require CT of the chest/abdomen [53, 55, 84]. If MEN1/ZES is present, UGI endoscopy for gastric carcinoids is recommended [8, 11, 79]. Routine SRS is not recommended if other imaging studies for NET are negative. EUS is more sensitive than cross-sectional imaging studies (CT, MRI, US) for the detection of small non-functional pancreatic NETs, especially in the pancre-

atic head/body region and to determine their size. Furthermore, the presence of multiple pancreatic tumors with EUS is very suspicious of MEN1. However, EUS is not generally recommended at present in all MEN1 patients, because routine surgical resection of small p-NETs (<2 cm) is not recommended and the EUS criteria on when to operate on these patients are not established [8, 11, 124, 125]. Some experts recommended pancreatic EUS in selected MEN1 patients, especially if they have ZES or small non-functional p-NETs on other imaging studies and are being followed without surgery, in an attempt to detect small non-functional tumors and to follow their growth in order to offer earlier surgery [8, 124–126]. ^{68}Ga-PET/CT is more sensitive than any of the other modalities, however its use remains investigational, and its role has not been defined in MEN1 patients [94].

Insulinoma: Minimal Consensus Statement on Tumor Localization – Specific [13–15, 47, 92, 106, 108]

Insulinomas are almost universally within the pancreas (1/3 head – 1/3 body – 1/3 tail) and are characteristically small p-NETs (82% <2 cm, 47% <1 cm) and thus can be difficult to detect [1, 2, 13–15, 50]. Ultrasound, CT, and MRI are widely available but positive in many studies in only 10–40% of cases. US or CT is usually the first study performed to rule out LM which occur in <10% [13–15, 26, 95]. SRS is positive in only 50% of localized insulinoma cases because of either a low density or lack of somatostatin receptors that bind octreotide with high affinity (sst2, sst5) [1, 2, 13–15, 93, 110]. Endoscopic US is positive in 70–95% of all cases if an experienced endoscopist is available and is thus is the imaging study of choice if the other non-invasive studies are negative [13, 15, 47, 106]. Furthermore, EUS can help to determine if tumor enucleation is possible because it can evaluate the distance between the tumor and the pancreatic duct. Insulinomas like other p-NETs are vascular tumors, and selective angiography is positive in 60%, however if combined with hepatic venous sampling for insulin after intra-arterial calcium administration, it is positive in 88–100% of cases [13, 50, 107, 108]. This is an invasive study and requires specific expertise that may be only available in experienced centers. Recently, insulinomas have been shown to overexpress GLP-1 receptors and it has been shown that radiolabeled GLP-1 analogues can localize the insulinoma [127]. However, at present this study has only been performed in small number of cases and its possible general utility is unclear. IOUS is essential for localizing the insulinoma at surgery and determining the correct surgical procedure. PET with ^{18}F-FDG PET imaging of insulinomas is disappointing, presumably because of their low proliferative potential. Promising results, however, have been obtained using various PET/CT methods including ^{11}C-5-HTP, and ^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (^{68}Ga-DOTATOC) [94, 115, 123, 128]. Although PET/CT remains investigational, in the small percentage of patients with insulinomas with negative imaging by the other methodologies (2–10%), PET/CT with ^{68}Ga-radiolabelebed somatostatin analogues (^{68}Ga-DOTA-D-Phe^{1}-Tyr^{3}-octreotide (^{68}Ga-DOTA-TOC)) should be considered in an experienced center.

Rare Functioning Tumors: Minimal Consensus Statement on Tumor Localization – Specific [1–3, 5, 92, 106]

The combined use of mdCT scan (or MRI) and SRS-SPECT is always recommended [2, 5, 92, 95, 120]. Conventional imaging studies suggesting vascular or tissue invasion may provide important information on whether surgical resection is contraindicated [2, 5, 92, 95, 120, 123]. EUS is not universally recommended as a first-line procedure in the investigation of RFT of the pancreas; it may be used in circumstances where mdCT, MRI and SRS-SPECT are inconclusive, especially preoperatively; however, in patients with RFTs presenting with LM, EUS is rarely necessary. EUS may be helpful in patients with large or aggressive tumors to more clearly define the tumor involvement where surgery is considered. EUS-guided fine-needle aspiration is an effective and safe way to obtain tissue for pathological analysis of p-NETs [5, 106, 126]. Insufficient data is available to recommend PET/CT methods on a routine basis, its use remains investigational and availability is limited. If results with the above-recommended imaging are unclear or negative in a patient with RFT, gallium-68-labeled somatostatin analogue PET should be considered with performance by an experienced center. Other examinations which may be useful are ^{18}F-DOPA-PET or ^{11}C-5-HTP-PET (although availability and costs may have to be considered) [1, 2, 94, 115, 123].

Histopathology and Genetics of Functional p-NETs [5, 8, 15, 17, 30, 129–132]

Histopathology/Genetics – General

The diagnosis of a specific functional p-NET type (table 1) requires the presence of a functional syndrome, combined with the appropriate diagnostic hormonal and functional studies and is supported by presence of a NET immunohistochemically expressing the appropriate hormone [5, 8, 130, 131]. Immunohistochemistry is not essential for the diagnosis of a functional p-NET syndrome (table 1), but it provides verification of hormonal production, it may identify specific cell types, and it may provide information on the source of LM [130, 131]. Like other GI-NETs, p-NETs frequently produce multiple peptides, but they may or may not be released in sufficient quantities to cause serum elevations or a respective hormonal syndrome [2, 8, 129–131]. Hormone-producing NETs without a clinical syndrome are not considered a functional tumor syndrome. One exception is that most somatostatinomas in the literature are diagnosed only by immunohistochemistry and have no clinical or biochemical evidence of somatostatin ectopic release [2, 3, 37], and thus because of the widespread occurrence of this practice, it has been suggested the term somatostatinoma syndrome be used for those with a functional tumor [2, 3].

In general, p-NETs do not show any histological features that specifically distinguish them from other foregut NETs. The histological features that are predictive of the biologic behavior of a given p-NET are discussed among the clinicopathological features and include an-

gioinvasion, mitotic activity and the proliferative index determined by Ki67 staining.

In MEN1 with functional p-NETs the diagnosis of the functional p-NET is complicated by the multiple p-NETs that are invariably present microscopically and can become macroscopically [5, 8, 16, 17]. Similarly in MEN1 patients with ZES due to a duodenal gastrinoma, they are almost invariably multiple [8, 11, 16, 17]. In MEN1 patients with insulinomas the insulin-secreting tumors are intrapancreatic in location and frequently multiple [11, 15]. In most MEN1 patients with ZES (80–100% in various series) the gastrinoma(s) are in the duodenum and the pancreatic lesions seen on imaging studies are usually non-functional p-NETs [11, 16, 17]. In these patients, immunohistochemical studies with multiple hormones should be done on all primaries and metastases to help determine their origin [17, 131].

Pathological diagnosis can be obtained on tumor biopsy performed either in cases of hepatic metastases (e.g., ultrasound-guided biopsy) or of the primary tumor (preferably using EUS-FNA if locally advanced, or at surgery). Pathological diagnosis of RFTs is performed using conventional hematoxylin and eosin (HE) staining, and immunohistochemical staining with chromogranin A and synaptophysin [5, 8, 131]. Determination of mitotic index by counting 10 HPF and/or calculation of Ki67 index by immunohistochemistry are mandatory as is assessment of the degree of invasion [5, 8, 131]. Recently, for p-NETs, WHO and ENETS TNM classification systems with grading have been proposed and numerous studies have validated their prognostic significance; therefore, it is important p-NETs be appropriate classified by these systems [21, 24, 25, 29, 30, 48, 133–136].

Genetic testing for hereditary tumor syndromes should be performed in case of suspected familial predisposition to MEN1 or if the presence of other associated endocrinopathies (e.g., elevated serum calcium or PTH suggesting hyperparathyroidism and prolactin, respectively) after appropriate genetic counseling [11, 84, 85].

Minimal Consensus Statement on Pathology and Genetics of Gastrinomas – Specific [1, 2, 8, 11, 84, 85, 130]

Pathology

A detailed description of the macroscopic, microscopic and immunohistochemical findings are mandatory in order to support the diagnosis of gastrinoma and to allow for its correct classification using the current WHO TNM classification [20, 21, 30, 130–132, 137]. Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, and gastrin. Occasionally, immunohistochemistry using antibodies against bioactive products may be negative even in a case of the correct diagnosis [17, 138]. Both a mitotic index using a mitotic count and a Ki67 index are mandatory. Immunohistochemistry for p53, SSR, and lymphovascular markers are optional. In MEN1 patients, all primaries and metastases should also be stained for the hormones responsible for the syndrome [131]. Cytology may be helpful, particularly in metastatic disease.

Genetics [11, 84, 85, 139]

Germline DNA testing for hereditary tumor syndromes in a patient with gastrinoma is only recommended in specific situations: a familial history or clinical/laboratory findings suggesting MEN1, VHL, tuberous sclerosis or the presence of multiple tumors. Mutational analysis should be performed to test for menin, VHL or tuberous sclerosis mutations (following informed consent). Genetic testing should be done according to approved methodology and prior to any genetic testing, genetic counseling should be performed.

Minimal Consensus Statement on Pathology and Genetics of Insulinomas – Specific [1, 2, 15, 85, 130]

Pathology

A detailed description of the macroscopic, microscopic and immunohistochemical findings is mandatory in order to support the diagnosis of insulinoma and to allow for its correct classification using the current WHO TNM classification [20, 21, 30, 130–132, 137]. Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, and insulin. Both a mitotic index using a mitotic count and a Ki67 index are mandatory. The immunohistochemical determination of insulin expression by tumor cells is not absolutely necessary for diagnosis. Some insulinomas do not stain positively for insulin despite the correct diagnosis. This might be caused by the rapid release of insulin from the insulin-producing cells [15]. In patients with MEN1 with insulinomas, all primaries and metastases should be stained for insulin, whereas immunohistochemistry for PP, glucagon, and somatostatin to determine their full hormone expression, as well as for p53, SSR, and lymphovascular markers are optional. Cytology may be helpful, particularly in metastatic disease. In patients without MEN1 but with multiple insulinomas or multiple recurrences, insulinomatosis should be suspected [140].

Genetics [11, 84, 85, 139]

Germline DNA testing for hereditary tumor syndromes in a patient with insulinoma is only recommended in specific situations: a familial history or clinical findings suggesting MEN1, tuberous sclerosis or VHL, the presence of multiple tumors, or the demonstration of precursor lesions in the peritumoral pancreatic tissue. Mutational analysis should be performed to test for menin, VHL or tuberous sclerosis mutations (following informed consent). Genetic testing should be done according to approved methodology and prior to any genetic testing, genetic counseling should be performed.

Minimal Consensus Statement on Pathology and Genetics of RTFs – Specific [1, 2, 5, 85, 130]

Pathology

A detailed description of the macroscopic, microscopic and immunohistochemical findings is mandatory in order to support the diagnosis of RFT and to allow for its correct classification using the current WHO TNM classification [20, 21, 30, 130–132, 137]. Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, and the specific hormonal syndrome suspected clinically. Both a mitotic index using a mitotic count and a Ki67 index are mandatory. Immunohistochemistry for p53, SSR, and lymphovascular markers are optional. In patients with MEN1 with RFTs, all primaries and metastases should be stained for insulin, in addition to PP, gastrin, glucagon and somatostatin to determine their full hormone expression. Cytology may be helpful, particularly in metastatic disease. In MEN1 patients, all primaries and metastases should also be stained for the hormones (gastrin, PP, glucagon, insulin, somatostatin) to determine the full spectrum of hormone expression. In the presence of multiple glucagon-containing tumors, glucagon cell adenomatosis should be considered [141].

Genetics [11, 84, 85, 139]

Germline DNA testing is only recommended in the presence of a positive family history of MEN1, if there are suspicious clinical findings or if multiple tumors or precursor lesions are present. Genetic analysis should also be performed in suspected cases of MEN1, VHL, neurofibromatosis-1, and tuberous sclerosis. Genetic testing, when performed, should include mutational screening and sequencing allowing the analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Genetic testing should be done according to approved methodology. Somatic (tumor) DNA testing is not recommended.

Surgery with Functional p-NETs
[5, 8, 15, 111, 142–144]

Surgical Treatment of ZES[E1] – General
[2, 8, 9, 47, 96, 145, 146]

There is now general agreement that patients with sporadic ZES with potentially resectable disease and without serious contraindications to surgery should undergo routine surgical exploration for cure [2, 8, 9, 47, 96, 145–147]. In both sporadic ZES and MEN1/ZES patients, 60–90% of patients will be found to have duodenal gastrinomas, which are frequently small, are associated with positive lymph nodes in 40–60% of cases, are not seen on preoperative imaging studies or EUS, and can only be found at surgery if a duodenotomy is performed [9, 33, 36, 47, 96, 103, 147]. Surgery should be performed by surgeons experienced in treating these tumors. Surgical exploration with duodenotomy should be performed at a laparotomy and not laparoscopically [8, 47, 96]. The role of surgery, type, and timing of surgery in patients with MEN1/ZES remains controversial [11, 36, 47, 83, 146–149].

Total gastrectomy is no longer indicated unless in rare patients who cannot or will not take oral antisecretory drugs (<1–2%) [8, 47, 96, 150]. Parietal cell vagotomy at the time of exploratory surgery is now rarely indicated, but patients who undergo surgery should receive antisecretory drugs in the preoperative period to avoid complications related to acid residual secretion [8, 47]. In highly selected patients, pancreaticoduodenotomy may be indicated and Whipple resections can result in cure in patients with pancreatic head/duodenal gastrinomas in both sporadic and MEN1/ZES patients [8, 47, 111, 142, 147, 148]. 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 [8, 47, 142, 147]. After curative resection it is essential to regularly evaluate patients for continuing cure by performing both FSG assessments as well as secretin testing [8, 18, 151]. Repeated conventional imaging studies are not needed if the fasting gastrin and secretin test remain normal [8, 18, 151]. Whether SRS will detect recurrent tumor before fasting gastrin elevations or a return of a positive secretin test is unknown at present [8, 47, 103, 151].

Minimal Consensus Statement on Surgical Treatment for Gastrinoma – Specific [3, 8, 9, 11, 47, 96, 111, 142, 145, 146, 148, 150]

Due to efficacy of PPIs, total or partial gastrectomy is no longer indicated [8, 47, 75, 96, 150]. For sporadic gastrinoma, surgery including complete resection of the primary and involved lymph nodes is the only curative treatment [8, 47, 96, 145, 147]. Surgery has been shown to decrease the rate of development of LM which is the most important prognostic factor for long-term survival and to increase disease-related survival [97, 98, 152]. Therefore, surgery for cure is recommended in patients with sporadic ZES without LM or comorbidity limiting life expectancy. Long-term cure after surgery (excluding pancreaticoduodenectomy) occurs in 20–45% of patients with sporadic ZES, but in 0–1% of patients with MEN1/ZES [18, 47, 147, 149]. Pancreatic tumors distant from the pancreatic duct can be enucleated. Resections are required when tumor is close to pancreatic duct (<3 mm). Distal pancreatic resection should be performed for caudally located tumors and duodenotomy performed routinely to detect small duodenal gastrinomas [8, 47, 96, 99, 142, 145, 153]. For sporadic left-sided pancreatic gastrinoma, central or distal pancreatectomy (with or without splenectomy) can be proposed [8, 47, 96, 99, 142, 145, 153]. In highly selected patients with pancreatic head

gastrinoma and those with local recurrence or persisting tumor after previous surgery, pancreaticoduodenectomy may be an alternative [8, 47, 142, 148, 154]. For sporadic gastrinomas, independent of the primary location, both routine regional lymphadenectomy and intraoperative liver exploration should be performed, because lymph node and LM from duodenal/pancreatic gastrinomas are frequent and lymph node and hepatic primary tumors are reported, although controversial [8, 47, 96, 155]. Up to 30% of sporadic gastrinomas are not located precisely by preoperative explorations. In this setting, surgical exploration may be controversial and a multidisciplinary discussion should review the case and decide whether or not to perform surgery. When decided, surgery should include complete abdominal cavity exploration through laparotomy, intraoperative pancreatic ultrasound, duodenotomy (with duodenal transillumination) and routine lymphadenectomy (at least in the gastrinoma triangle) [2, 3, 8, 96, 145, 155, 156].

In MEN1/ZES, surgery without a Whipple resection is associated with >90% of recurrence [8, 11, 47, 52, 147, 149, 157]. Therefore, routine surgical exploration is controversial in patients with MEN1/ZES [8, 11, 47, 52, 146–148, 157]. Indeed, these patients usually have multiple duodenal gastrinomas, frequently with lymph node metastases, with other p-NETs (non-functional primarily), are rarely cured and have an excellent life expectancy if only small tumors (<2 cm) or no tumors are present on preoperative imaging studies [8, 11, 36, 52, 96, 125]. However, surgery is the only approach that might lead to prevent (or cure) malignant transformation [157]. Since MEN1 patients with pancreatic tumors <2 cm have spontaneous good long-term life expectancy, it has been generally recommended that surgery for prevention of metastatic dissemination could be restricted to MEN1 pancreatic tumors >2 cm [8, 11, 47, 52, 125]. Even if some limited series reported potential long-term biochemical remission after pancreaticoduodenotomy in MEN1-ZES patients, the real impact on the long-term survival remains controversial and the long-term side effects of pancreaticoduodenotomy remain largely undefined [8, 9, 96, 142, 146, 148, 157].

In contrast to the case for insulinomas, laparoscopic resection of gastrinomas is controversial and not generally 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 [8, 47, 96, 158].

Surgical Treatment of Insulinomas – General
[2, 13–15, 26, 50, 159]

In contrast to gastrinomas and some RFTs (somatostatinomas, GRHomas) (table 1), insulinomas are often unique in that they are in benign in 90% and located, similar to a few other RFTs (table 1) (i.e. glucagonomas, >90% VIPomas) entirely within the pancreas [2, 13–15]. This intrapancreatic location facilitates the localization with EUS, which has a greater sensitivity/specificity for intrapancreatic than extrapancreatic localization of p-NETs. However, when insulinomas are small (<1 cm), which is not infrequent, preoperative localization and detection at surgery can be difficult. Furthermore, insulinomas have a lower detection rate with SRS because of lower densities of somatostatin receptors and therefore are frequently (>50%) missed during SRS studies preoperatively [2, 13–15, 26, 47, 50]. Insulinomas also differ from the other PETs in that they are malignant in <10% of cases (table 1) and therefore have a very high probability of cure (>90%) [2, 13–15, 26, 50, 159]. In contrast to the other PETs, laparoscopic resection is increasingly used in patients with insulinomas in whom the tumor can be localized preoperatively [26, 158–161].

Minimal Consensus Statement on Surgical Treatment of Insulinoma – Specific
[3, 8, 9, 11, 47, 96, 111, 142, 145, 146, 148, 150]

For sporadic insulinoma, the standard surgical treatment should include pancreas exploration by both palpation and IOUS. When the tumor is located further than 2–3 mm from the pancreatic duct, an enucleation is preferred to pancreatic resection. Otherwise, a partial pancreatic resection (central or distal or pancreatic head resection) is needed. In all settings, no lymphadenectomy is needed [3, 8, 9, 11, 47, 96, 111, 142, 145, 146, 148, 150]. If the insulinoma is localized preoperatively, enucleation from the pancreatic body/tail and distal pancreatectomy can be performed safely by laparoscopy [8, 26, 158, 159, 161, 162]. When a sporadic insulinoma is not localized preoperatively, surgical exploration is indicated [3, 8, 9, 11, 47, 96, 111, 142, 145, 146, 148, 150]. Intraoperative tumor location can require, additionally to IOUS, intraoperative insulin sampling and frozen section [163]. In rare patients with suspicion of malignant insulinoma or recurrence, a radical surgery aiming to treat either locoregional recurrence and/or LM is indicated. When insulinoma is not located either preoperatively or intraoperatively including samplings, blind distal resection is not recommended [3, 8, 9, 11, 47, 96, 111, 142, 145, 146, 148, 150].

In the presence of MEN1, in which multiple tumors are frequently present, the aim of surgery is to control inappropriate insulin secretion by excising all insulinomas. Preoperative localization of which pancreatic tumors are the insulinomas is mandatory, because these patients frequently have other pancreatic NETs (which are usually non-functional) [2, 11, 52, 142]. In these patients, preoperative intra-arterial calcium injections with hepatic venous insulin sampling as well as intraoperative insulin sampling may be required [8, 11, 50, 107, 163].

Surgical Treatment of RFTs – General
[2, 5, 111, 142, 144]

Indications for surgery depend on clinical symptom control, tumor size/location/extent, malignancy and metastatic spread [1, 2, 5, 111, 142, 144]. Curative surgery should be sought whenever possible, even in the presence of metastatic disease, including 'localized' metastatic disease to the liver, if thought potentially resectable and the patient can tolerate the surgery [1, 2, 5, 111, 142, 144]. The type of surgery depends on the location of the primary

tumor – pancreaticoduodenal resection (Whipple's operation), distal pancreatic resection, tumor enucleation or enucleation in combination with resection. Since malignancy is frequent in RFTs, adequate lymph node clearance is mandatory [1, 2, 5, 111, 142, 144]. In the case of localized LM or more extensive disease spread, surgery should also be considered if at least 90% of gross tumor is thought resectable [8, 98, 142, 152, 164–169], as discussed in a latter section.

Minimal Consensus Statement on Surgical Treatment of RFTs – Specific [2, 5, 98, 111, 142, 144, 167]

Curative surgery is always recommended whenever feasible after optimal symptomatic control of the clinical syndrome by medical treatment. Due to the usually large size of the tumor and the high prevalence of LM in RFT, curative surgery should include pancreatic resection with lymphadenectomy through laparotomy. Laparoscopic resection is not recommended because of the need for lymphadenectomy and careful inspection for invasion/metastases [5]. Bilateral adrenalectomy can be indicated in some selected patients with Cushing syndrome [2, 5, 111]. Surgery of LM may be performed during treatment of the primary tumor. Cytoreductive surgery should be considered when the metastatic disease is localized or if >90% of tumor load is thought resectable which may help to improve hormonal control and perhaps extend survival, although this is not proven [8, 142, 152, 164–169]. This will be discussed in the next section.

Minimal Consensus Statement on Surgical Treatment of Advanced Symptomatic p-NETs – Specific [2, 5, 8, 15, 98, 111, 142, 144, 164, 165, 167–169]

Symptomatic control of the hormone excess state of all functional p-NETs may be facilitated by therapy directed against the tumor per se in the form of cytoreductive surgery either alone or combined with RFA. Cytoreductive surgery should be considered when the metastatic disease is localized or if >90% of tumor load is thought resectable [8, 98, 142, 152, 164–169]. RFA can also be used with resection or alone through laparoscopic approach if there are <10 lesions seen in the liver and if the largest tumor is <5 cm (ideally <3 cm) in diameter [5, 152, 170]. Laparoscopic RFA has resulted in control of symptoms in >90% of patients with malignant p-NETs [170].

Medical Treatment of Functional p-NETs

[1, 2, 5, 8, 13–15, 57, 168, 169, 171]

Medical Treatment of ZES: Treatment of the Gastric Acid Hypersecretion – General [2, 3, 8, 32, 57, 172, 173]

It is essential to control the gastric acid hypersecretion in all patients to prevent peptic complications which can rapidly develop in these patients, because the basal gastric acid output can be >5 normal in many patients with ZES (mean 45 mEq/h) [8, 61]. Both H_2 blockers and PPIs can control acid hypersecretion in all patients who can take oral medications and are cooperative [2, 8, 32, 57, 172, 173]. The preferred drugs are now PPIs, because of their long duration of action [8, 32, 57, 172, 174–178]. H_2 blockers to be effective are usually required at higher doses than used in conventional peptic disease (frequently up to 10 times the usual dose) and 4–6 h dosing is frequent [2, 3, 57, 75]. Patients have been treated for up to 15 years with PPIs with no evidence of tachyphylaxis and no dose-related side effects. Vitamin B_{12} deficiency but not iron deficiency has been reported with long-term PPI use in ZES, but it is unclear if it causes clinically significant vitamin B_{12} deficiency [8, 179–181]. Although either intravenous PPIs (intermittent use) or continuous infusion of high doses of H_2 blockers can satisfactorily control acid secretion when parenteral drug is needed [2, 3, 8, 32, 57, 75], because of the intermittent use parenteral PPIs are recommended. In patients with MEN1/ZES the correction of the hyperparathyroidism can reduce the fasting gastrin level, BAO, and increase the sensitivity to acid antisecretory drugs [82, 83]. Gastric acid hypersecretion can continue even after a curative resection in up to 40% of the patients and require low doses of antisecretory drugs [182, 183]. Although rarely used at present, a parietal cell vagotomy can reduce the BAO long term and decrease the dosage of antisecretory drug needed [8].

Minimal Consensus Statement on Medical Treatment of the Gastric Acid Hypersecretion in ZES Patients – Specific

Acid hypersecretion needs to be controlled acutely and long-term in all ZES patients to prevent acid-related peptic complications [8, 57, 75, 172, 173, 175, 176]. PPIs are the drugs of choice because of their long duration of action allowing once or twice a day dosing in most patients. Studies show all available PPIs (omeprazole, lansoprazole, pantoprazole, rabeprezole, esomeprazole) are effective [8, 32, 57, 172, 174–178]. The recommended starting dose is equivalent to omeprazole 60 mg once per day in sporadic ZES and 40–60 mg b.i.d. in MEN1/ZES [8, 57, 75, 172, 173, 175, 176]. To control acid hypersecretion in ZES patients with complicated disease (presence of MEN1 with hypercalcemia, presence of severe GERD symptoms, presence of previous Billroth II resection), higher doses of all antisecretory drugs are required and more frequent dosing may be needed, even with PPIs [8, 75, 82, 83, 184]. In these patients, PPIs should be started at equivalent to 40–60 mg b.i.d of omeprazole. On follow-up visits, PPI drug dosage can be reduced in most patients with sporadic ZES and in 30–50% of MEN1/ZES patients. With long-term treatment, serum vitamin B_{12} levels should be

monitored once per year [8, 179–181]. Recent studies suggest an increased incidence of bone fractures, particularly of the hip in patients on continuous long-term PPIs, although no studies have been performed specifically on ZES patients [179, 180]. The exact mechanism that PPIs may be producing bone fractures is unclear and no specific recommendations have been generally accepted for the follow up of patients maintained long term on PPIs. Oral doses of histamine H_2 receptor antagonists can also be effective, but high, frequent dosing is required [8, 57, 75]. During periods when oral drugs cannot be taken such as during surgery, parenteral PPIs are the drugs of choice, although a continuous infusion of histamine H_2 receptor antagonist can also be effective but high doses are required [8, 57, 75]. Long-acting somatostatin analogues also control acid secretion, but they are not recommended for this purpose in ZES, because of the ease and effectiveness of PPIs, which can be given orally.

Medical Treatment of Insulinoma: General [13–15, 185]

Appropriate dietary management can help prevent prolonged periods of fasting. Because the vast majority of patients with insulinomas can be cured surgically, medical management is reserved only for preoperative control of blood glucose levels, for patients with unresectable metastatic disease, or for patients who are unable or unwilling to undergo surgical treatment [13–15, 26, 50].

Minimal Consensus Statement on Medical Treatment of Insulinoma – Specific

Prior to surgery or in patients with metastatic insulinomas, in addition to frequent small feedings and intravenous glucose administration, the hypoglycemia frequently needs to be controlled by drug therapy. Diazoxide (50–300 mg/day, can be increased up to 600 mg/day) inhibits insulin release by direct action on the β cells [2, 13–15]. Diazoxide is the most effective drug for controlling hypoglycemia [2, 13–15]. However, side effects are: edema, weight gain, renal impairment, and hirsutism. Verapamil and diphenylhydantoin have also been reported to be successful in the control of hypoglycemia. In refractory cases, glucocorticoids such as prednisolone can be effective as well. Somatostatin analogues like octreotide and lanreotide can be useful in preventing hypoglycemia in those patients with somatostatin receptor subtype 2-positive tumors, but can worsen hypoglycemia in some patients [185]. Interferon-α has been shown to be beneficial in selected cases. Recently, in a small number of cases with malignant insulinomas, mTOR inhibitors (everolimus, rapamycin) have controlled the insulin secretion and hypoglycemia [2, 3, 186–188].

Medical Treatment of RFT Functional Syndrome – General [2, 3, 5, 171]

In the past, patients frequently died from the untreated effects of the hormone excess state, therefore it is important it be controlled [2, 5, 42]. This can be accomplished in most cases at present by using a combination of medical, surgical, radiological approaches. Only the medical aspects are dealt with in detail here because treatment directed at the tumor per se which can also help control the functional aspects of the p-NET in patients with advanced disease is dealt with in a separate chapter. Both somatostatin analogues and interferon have been shown to be effective in the control of symptoms in functioning p-NETs and this also includes RFTs [1–3, 5, 171]. Approximately 80–90% of patients with VIPomas and glucagonoma improve very promptly, overcoming diarrhea and skin rash, and 60–80% have a reduction in VIP and glucagon levels [1–3, 5, 171]. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily [1–3, 5, 171]. Somatostatin analogues can also have anti-growth effects on p-NETs, and that is covered in the chapter on the treatment of advanced disease. For the control of symptoms, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 μg s.c. × 2–3) for 1–2 days with titration according to clinical response. Then the patient can be transferred to slow-release Lanreotide-SR® i.m. Lanreotide autogel® s.c. or Sandostatin-LAR® i.m. (every 4 weeks) [5, 189]. Likewise, interferon-α treatment may help control symptoms of the hormone excess state in functional low proliferating tumors although it has been less well studied than the use of somatostatin analogues. It is reported to be effective in VIPomas not responding to somatostatin analogues and also in isolated cases when combined with somatostatin to control the symptoms of a functional p-NET, which with somatostatin treatment alone there was inadequate symptom control, however, this requires confirmation in a controlled manner [1, 5, 190].

Minimal Consensus Statements on Medical Treatment of RFT Functional Syndrome – Specific [2, 3, 5, 171]

Somatostatin analogues are an effective treatment in the control of symptoms in RFTs, especially in patients with VIPomas, GRHomas and glucagonomas [2, 3, 5, 50, 171]. Long-acting somatostatin analogues are also reported to be effective in controlling the ectopic hormone secretion in some cases of somatostatinomas. In patients with Cushing's syndrome, the majority of which have metastatic disease at presentation, primarily adrenal-blocking agents (ketoconazole, metyrapone) are used prior to adrenectomy. In some cases long-acting somatostatin ana-

logues may be effective and there is increased interest in the use of glucocorticoid receptor antagonists, like mifepristone, which are investigational at present [191, 192]. If somatostatin analogues are ineffective or lose efficacy in controlling the hormone excess state, treatment with interferon-α may be effective at controlling the symptoms either alone or in combination with somatostatin analogues. Promising results with the multiligand somatostatin receptor congener pasireotide have recently been presented. Also, the dopamine agonist cabergoline might have a role in controlling ectopic ACTH secretion [191, 193, 194].

Medical Treatment of Functional p-NET Syndromes in Patients with Advanced, Metastatic Disease – General

Treatment of advanced disease is updated in a separate and comprehensive chapter [195]. Here, is a brief summary.

Somatostatin analogues may be of value also in subgroups of patients with slowly progressive low proliferative NET (G1) of pancreatic and gastroduodenal origin and its use is supported by literature data on retrospective and non-randomized prospective trials in more than 500 patients [171, 196–198]. In patients with gastric carcinoids, somatostatin analogues have been shown to exert anti-proliferative effects in animals and in man, however, data is not available in cases of LM [199].

Two prospective randomized trials in metastatic gastroenteropancreatic NET have shown that somatostatin analogues, IFN or the combination of both have comparable anti-proliferative effects when used after prior disease progression [196, 197].

Chemotherapy is recommended in pancreatic NET, G2 foregut NET of extrapancreatic site, and in neuroendocrine carcinoma (G3) of any site. Systemic cytotoxics are indicated in patients with inoperable progressive LM from well-differentiated NET of pancreatic tumor origin using combinations of streptozotocin and 5-FU and/or doxorubicin with objective response rates in the order of 35–40% [199–201]. These response rates are considerably lower than the 69% reported by Moertel et al. [202] in 1992. There is long-standing experience with streptozotocin-based chemotherapy since the 1980s. Other newer chemotherapy regimens report higher response rates with various regimens and thus show promise, but larger confirmatory studies are needed (5-fluorouracil, dacarbazine, epirubicin [203] or capecitabine and temozolomide) [204]. Also transarterial embolization and/or chemoembolization as well as liver-directed therapy with radiolabeled particles, each of which have been shown to have tumor response rates of ≥50%, should be considered in patients with liver predominate metastases, especially with functional pNETs difficult to control [205–207].

PRRT is considered in both functioning and non-functioning NET and irrespective of the primary tumor site. Based upon small phase II trials and retrospective data, partial remission rates range between 0 and 33% [208, 209] and are higher in pancreatic compared to midgut NET. In a prospective multicenter phase II trial with ^{90}Y-edotreotide in patients with refractory carcinoid syndrome, partial remission rate was 4% and disease stabilization rate 70%. PFS was favorable with 16.3 months [210].

Regarding new molecular targeted therapies, both drugs, everolimus and sunitinib, are novel treatment options in advanced p-NET. Everolimus is thus a treatment option after failure of chemotherapy in p-NET, but can be considered as first-line therapy in selected cases as an alternative treatment to locoregional therapies or chemotherapy.

The RADIANT-3 study (everolimus) included 40% therapy-naive patients, and efficacy was equally good in therapy-naive patients as in patients with previous therapies [211]. An early unselected use of the drug cannot be recommended, because long-term toxicity data are lacking, however, it is licensed in many countries for use in progessive p-NETs.

Results from a phase III placebo-controlled trial support the efficacy of sunitinib, a multiple tyrosine kinase inhibitor that targets PDGF-R, VEGF-R, c-kit, RET and FLT-3, in progressive p-NET [223, 224].

The majority of the patients had undergone prior systemic therapy, especially systemic chemotherapy. The main indication of sunitinib is its use as a second- or third-line therapy. Sunitinib should be considered as first-line therapy only in selected cases as an alternative treatment option if somatostatin analogues, chemotherapy and/or locoregional therapies are not feasible or promising. The role of everolimus and sunitinib in advanced disease is discussed in detail in the chapter on treatment of advanced progressive p-NETs.

Minimal Consensus Statements on Medical Treatment of Functional p-NET Syndromes in Patients with Advanced, Metastatic Disease – Specific [5, 8, 15, 212, 213]

The control of the hormone excess state in patients with advanced disease is similar to that outlined above for the typical patient with a p-NET, except that some added features need to be considered. Not infrequently a patient with advanced disease (non-gastrinoma) becomes refractory to the effect of medical therapy (somatostatin analogues and/or interferon, etc.) and the hormone excess state cannot be satisfactorily controlled. This does not occur with gastrinomas because PPIs are effective even

with extensive disease. If symptomatic refractory disease develops this can be an indication to consider various anti-tumor therapies including liver directed therapies (embolization, chemoembolization, RFA, radiolabeled microspheres), PRRT or cytoreductive surgery, all of which are reported to improve symptomatic control in many patients [8, 15, 111, 142, 152, 164, 166–169, 212–218]. With these different modalities, symptoms improve in 40–80% of patients [167–169, 208, 218, 219].

The early combination use of somatostatin analogues and IFN for anti-proliferative purposes is not recommended. Also, the use of PRRT cannot be recommended as first-line therapy, but after failure of medical therapy. The presence of a strong expression of sstr2 as visualized by somatostatin receptor imaging is a prerequisite for the use of PPRT. The minimum requirements for PRRT are reported in a separate consensus guideline [220]. Everolimus and sunitinib represent novel therapeutic options in patients with surgically non-resectable progressive pancreatic NET as alternative or after progression following chemotherapy [211, 223, 224].

Follow-Up of Patients with Functional p-NETs (table 1) [2, 3, 5, 8, 221]

Follow-Up of Patients with Functional p-NETs – General

Patients with functional p-NETs with MEN1, with advanced metastatic disease, post-curative resection, or with active disease problems frequently require a different follow-up schedule than the typical p-NET patient with active but limited disease. Patients with MEN1 after initial treatment of the MEN1 problems (hyperparathyroidism, pituitary disease) should be seen at 6- to 12-month intervals and other MEN1 problems also investigated. Patients post-curative resection can be evaluated yearly unless symptoms of recurrence occur. Patients with metastatic disease require a relatively short follow-up initially (3–6 months) to determine whether progressive disease is present and interfering with symptomatic control and whether anti-tumor treatment might be needed to facilitate symptom control.

Minimal Consensus Statement on Follow-Up of Patients with Gastrinoma – Specific [2, 3, 8, 18, 75, 221]

All patients with active non-metastatic disease should be seen initially at 3–6 months and then if stable yearly. At each evaluation, biochemical studies (vitamin B_{12} level, ionized calcium, PTH, gastrin), assessment of acid control if possible and tumor imaging studies (abdominal CT or MRI yearly, SRS at least every 3 years) should be done. For patients with MEN1/ZES, follow-up should be yearly with an assessment of tumor extent with imaging (CT/MRI abdomen and chest CT (rule out thymic carcinoid, especially in men every 3–5 years), SRS at least every 3 years, pituitary MRI every 3–5 years), biochemical assessment for MEN1 diseases (ionized calcium, serum PTH, prolactin, insulin), FSG, acid control if possible, UGI endoscopy to evaluate for gastric carcinoid [8, 11, 55, 79, 83, 84]. 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/H_2 blockers [8, 18, 151]. Imaging modalities should be performed if ZES is not cured, according to previous indications.

For patients with advanced metastatic disease, follow-up should be at 3- to 6-monthly intervals with tumor imaging (CT or MRI and SRS (when clinically indicated)), FSG 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. Treatment of advanced disease is dealt with separately in a later chapter.

Minimal Consensus Statement on Follow-Up in Patients with Insulinoma – Specific [2, 3, 13, 15, 221]

Follow-up for insulinoma patients without MEN1 post-resection should be at 3–6 months and then if continued cured only if symptoms recur [213]. Post-curative resection patients with multiple insulinomas or with MEN1 should be followed yearly and also re-evaluated at any time symptoms recur. At follow-up in addition to a careful history for fasting hypoglycemic symptoms, a fasting glucose, insulin, C-peptide and proinsulin measurement should be done.

Minimal Consensus Statement on Follow-Up for Patients with RFTs – Specific [2, 3, 5, 213]

Follow-up for patients with RFTs should be at 3- to 6-month intervals with metastatic disease and yearly in patients without metastatic disease. Following treatment, in patients with no evidence of residual disease, pertinent biochemical assessment (i.e. hormones known to be elevated prior to treatment, both specific and non-specific) should be initially performed and, when negative, further tests are not usually required. For patients with residual disease, specific markers coupled with contrast-enhanced mdCT scan or MRI and SRS (when clinically indicated) should be performed.

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