Neuroendocrine Tumors of the Pancreas

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Pancreatic endocrine tumors are rare neoplasms accounting for less than 5% of pancreatic malignancies. They are broadly classified into either functioning tumors (insulinomas, gastrinomas, glucagonomas, VIPomas, and somatostatinomas) or nonfunctioning tumors. The diagnosis of these tumors is difficult and requires a careful history and examination combined with laboratory tests and radiologic imaging. Signs and symptoms are usually related to hormone hypersecretion in the case of functioning tumors and to tumor size or metastases with nonfunctioning tumors. Surgical resection remains the treatment of choice even in the face of metastatic disease. Further development of novel diagnostic and treatment modalities offers potential to greatly improve quality of life and prolong disease-free survival for patients with pancreatic endocrine tumors.

Introduction

In 1902, Nicholls [1] described a tumor originating from pancreatic islet cell lineage; this was the first report of a pancreatic endocrine tumor (PET). PETs are an uncommon neoplasm of the pancreas, accounting for less than 5% of pancreatic malignancies [2]. The incidence in unselected autopsy studies is as high as 1.6% and rises to 10% in autopsies at which the whole pancreas is examined both grossly and microscopically [3]. Pancreatic adenocarcinoma is much more common, with a ratio of 25:1. It is important to distinguish between the two, however, as the outcome for a PET is superior to that of a ductal carcinoma even in the presence of metastatic disease.

In the third month of fetal development, parenchymal pancreatic cells begin to differentiate into the Islets of Langerhans; this process is usually complete by the fifth month. The cell of origin for PETs is controversial. Many authors consider that neuroendocrine tumors originate from the pluripotent cells in the ductal epithelium, which maintain their ability to differentiate toward the different hormone-producing neoplasms. PETs can be broadly divided into two groups: 1) functional PETs such as insulinoma, gastrinoma, glucagonoma, somatostatinoma, and VIPoma, which present with symptoms of hormonal hypersecretion; and 2) nonfunctioning PETs, which present no clinical manifestations of hormonal hypersecretion. Although nonfunctioning PETs produce no clinical signs of hormonal excess, they may produce a precursor hormone that is functionally inert or occurs in amounts too small to be clinically relevant. These patients tend to present late, with symptoms due to mass effect or metastasis [4].

The pathologic diagnosis depends on the confirmation of the neuroendocrine nature of the tumor cells. Microscopic features can be heterogenous, and immunohistochemical staining with markers such as chromogranin A, synaptophysin, and neuron-specific enolase can confirm the origin of the PET. It is difficult to determine the biologic behavior of PETs. By assessing the site and extent of disease, histologic differentiation, mitotic rate, and proliferation, the World Health Organization attempts to classify the tumors into benign behavior, uncertain behavior, low-grade malignant, and high-grade malignant (Table 1). Others have attempted to simplify this classification by combining tumor size and the presence or absence of metastases with a simple grading system based on necrosis and mitotic rate [5•].

Insulinoma

The first operative intervention for a suspected PET was described in 1927 [6]. The patient was an orthopaedic surgeon with an 18-month history of unpredictable hypoglycemia. Laparotomy revealed an unresectable mass with hepatic metastases, and the patient died not long after the operation. In 1929, a benign insulinoma was successfully resected [7]; this patient was thought to have survived for 20 years after the initial operation.

Epidemiology

Insulinomas, which arise from the insulin-producing β islet cells, are the commonest form of functioning PET, with an annual incidence of 0.7 to 4.0 cases per million. They account for 30% to 45% of all PETs [8].

Table 1. World Health Organization classification of gastroenteropancreatic neuroendocrine tumors

	Well-differentiated endocrine tumor (benign behavior)	Well-differentiated endocrine tumor (uncertain behavior)	Well-differentiated endocrine carcinoma (low-grade malignant)	Poorly differentiated endocrine carcinoma (high-grade malignant)
Pancreas	Confined to pancreas	Confined to pancreas	Well to moderately differentiated	Small cell carcinoma
	< 2 cm	≥ 2 cm	Gross local invasion and/or metastases	Necrosis common
	< 2 mitoses per 10 HPF	> 2 mitoses per 10 HPF	Mitotic rate often higher (2–10 per 10 HPF)	> 10 mitoses per HPF
	< 2% Ki-67–positive cells; no vascular invasion	> 2% Ki-67–positive cells or vascular invasion	Ki-67 index > 5%	> 15% Ki-67–positive cells; prominent vascular and/or perineural invasion
Stomach	Confined to mucosa–submucosa, ≤ 1 cm; no vascular invasion	Confined to mucosa–submucosa, > 1 cm or vascular invasion	Well to moderately differentiated; invasion to muscularis propria or beyond, or metastases	Small cell carcinoma
Duodenum, upper jejunum	Confined to mucosa–submucosa, ≤ 1 cm; no vascular invasion	Confined to mucosa–submucosa, > 1 cm or vascular invasion	Well to moderately differentiated; invasion to muscularis propria or beyond, or metastases	Small cell carcinoma
Ileum, colon, rectum	Confined to mucosa–submucosa, ≤ 1 cm (small intestine)	Confined to mucosa–submucosa, > 1 cm (small intestine)	Well to moderately differentiated; invasion to muscularis propria or beyond, or metastases	Small cell carcinoma
	≤ 2 cm (large intestine); no vascular invasion	> 2 cm (large intestine) or vascular invasion		
Appendix	Nonfunctioning, confined to appendiceal wall	Enteroglucagon-producing, confined to subserosa	Well to moderately differentiated; invasion to mesoappendix or beyond, or metastases	Small cell carcinoma
	≤ 2 cm; no vascular invasion	> 2 cm or vascular invasion		

HPF—high-power field.

They are usually solitary, occurring within the pancreatic parenchyma throughout the gland. Less than 5% will be located in ectopic sites such as the duodenum, splenic hilum, and gastrocolic ligament [9]. The median age of presentation is 47 years (range 8–82), with a slight female preponderance (female to male ratio of 1.4:1) [10]. Most insulinomas are sporadic, but 5% to 8% are associated with multiple endocrine neoplasia type 1 (MEN-1), an autosomal-dominant inherited condition usually characterized by multiple tumors of the parathyroids, enteropancreatic endocrine tissues, and the anterior pituitary gland. The syndrome results from inactivation of the *Menin* gene, a tumor-suppressor gene located on chromosome 11q13. It is not unusual for multiple lesions to be identified in these patients.

Diagnosis

Patients with insulinoma usually present with symptoms related to episodic hypoglycemia. Common symptoms are neuroglycopenic (behavioral changes, blurred vision, fatigue, seizures, and coma) and neurogenic (hunger, sweating, anxiety, tremor, and palpitations due to activation of the autonomic nervous system) [11]. An insulinoma is an uncommon cause of hypoglycemia, however, so careful examination should be carried out to rule out other causes such as administration of exogenous insulin or antidiabetic drugs such as the sulphonylureases. A recent review of the Massachusetts General Hospital experience over a 25-year period identified 61 patients with insulinoma who required surgery [12•]. MEN-1 syndrome was present in 7 patients (11%). The most common presenting complaints were confusion (67%), visual disturbances (42%), and diaphoresis (30%). The median duration of symptoms before a diagnosis was made was 18 months. These findings are similar to those reported by investigators at Memorial Sloan-Kettering Cancer Center, who noted that patients with nonfunctioning tumors had a significantly shorter symptom duration prior to evaluation and treatment (90 days) than those with a functional tumor (365 days) [13].

When insulinoma is suspected, it is our practice to admit patients to hospital and conduct a supervised fast in which glucose, insulin, and C-peptide levels are measured every 6 hours or when symptoms occur. Blood glucose 2.5 mmol/L or lower, insulin 41.7 pmol/L or higher,

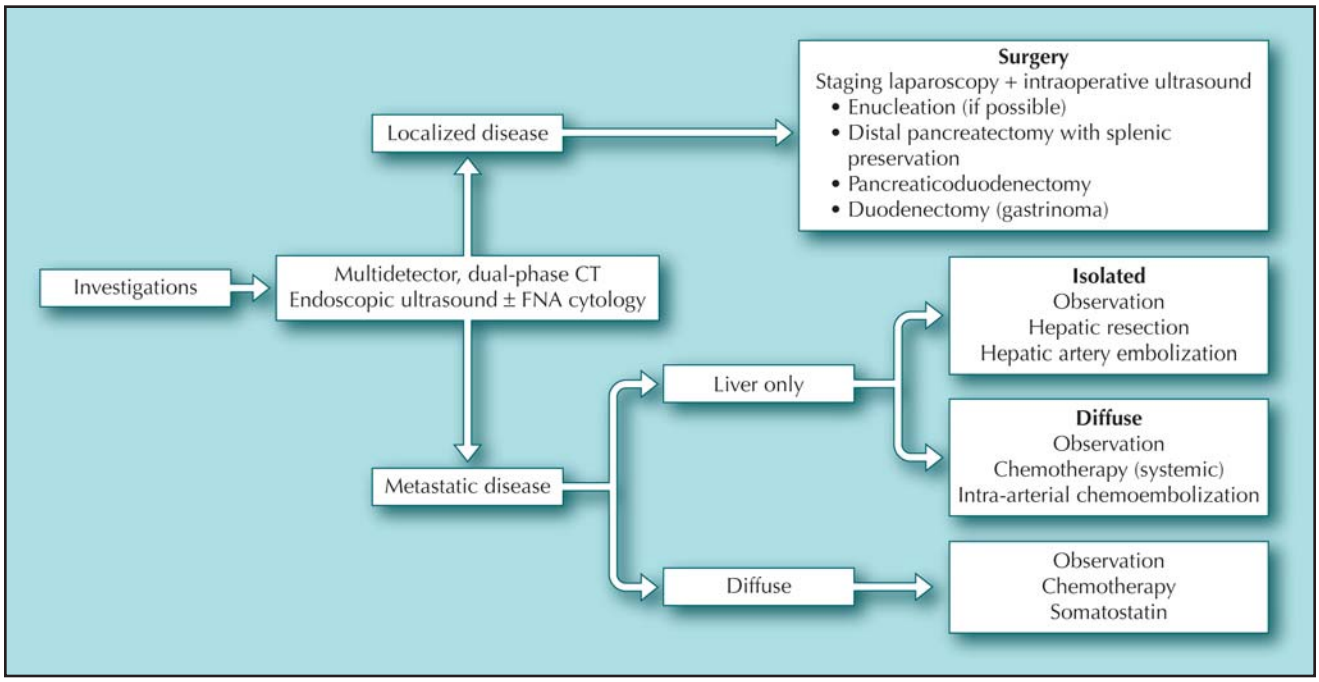

Figure 1. Current algorithm for the diagnosis and treatment of pancreatic endocrine tumors. FNA—fine needle aspiration. (*Adapted from* O'Grady and Conlon [14], with permission from Elsevier.)

C-peptide 0.2 nmol/L or higher, and a negative sulphonylurea screen are diagnostic for insulinoma. Traditionally, a 72-hour fast has been recommended, but this is rarely necessary, as 30% of patients develop symptoms within 12 hours, 80% within 24 hours, 90% within 48 hours, and almost 100% within 72 hours [14].

Localization

Modern radiologic imaging facilitates the localization of the tumor, avoiding the need for a "blind" pancreatic resection (Fig. 1). Multidetector CT is the imaging modality of choice. Thin-slice, dual-phase images from arterial and portal phases are used to image the pancreas and display the peripancreatic vasculature. Early arterial imaging enhances detection, but false negative results can occur when the tumor is close to a major vessel or is nonhyperattenuating. MRI has been reported to have a role in detecting small insulinomas. The use of fast spin-echo, fat saturation, and contrast-enhanced techniques facilitates optimal tumor detection. PETs typically express low signal density on T1-weighted images and high signal density on T2-weighted images. Gadolinium as contrast offers greater sensitivity for vascular lesions than standard iodine agents [15]. This protocol identified 50% of lesions between 1 and 2 cm and 100% of tumors larger than 3 cm.

Somatostatin-receptor scintigraphy, which has a major role in imaging other PETs, is less useful in locating insulinomas, as they have a low density of somatostatin receptors and generally do not express the somatostatin subtype-2 cell-surface receptor. Early reports suggest that positron emission tomography using fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) may be useful in detecting insulin-secreting tumors, particularly when conventional imaging such as CT or MRI is negative. However, further data are required before this type of imaging can be recommended.

Endoscopic ultrasound (EUS) allows a high-frequency ultrasound probe (7.5–10 mHz) to be placed endoscopically in close proximity to the pancreas [16,17]. The result is improved image resolution and sensitivity for the detection and localization of small tumors. The pancreatic head and duodenum are scanned with the probe positioned in the duodenum, and the body and tail are scanned through the stomach. This technique is particularly useful in demonstrating small tumors in the pancreatic head (which may be impalpable at surgery), lesions in the duodenal wall, and regional lymphadenopathy. However, EUS is technically challenging and is not widely available. Lesions in extrapancreatic locations and in the tail of the pancreas are difficult to demonstrate, and the liver cannot be fully assessed. Despite these difficulties, the technique is very successful in expert hands, with reported sensitivities as high as 79% to 100%. The Massachusetts General Hospital experience suggests that improvements in noninvasive imaging in combination with EUS have increased the sensitivity of preoperative tumor detection to 98% [12•].

Invasive investigations such as percutaneous transhepatic portal venous sampling (PTPVS) and arterial stimulation with venous sampling (ASVS) may be used if all noninvasive localization tests are negative and an insulinoma is strongly suspected. PTPVS requires placing a catheter percutaneously in the portal system. Multiple samples are taken from the draining veins of the pancreas to localize the region of the tumor.

False-positive results are low, but because of high operator dependency, sensitivity ranges from 63% to 94%. ASVS using selective arteriographic injection of calcium while measuring hepatic venous insulin levels has yielded excellent tumor localization rates and is less operator-dependent; it is becoming the invasive localization study of choice [18]. Roland and coworkers [19] reported on 16 patients who underwent selective arterial cannulation and calcium stimulation with a success rate of 88%.

The gold standard of tumor localization remains a combination of imaging studies with intraoperative ultrasound and operator palpation. In the Massachusetts General Hospital study, a combination of palpation and intraoperative ultrasound scanning detected 92% of tumors [12•]. It is critical for the surgeon to completely mobilize the entire pancreas to facilitate bimanual palpation. Norton [20] reported that only one third of tumors in the head of the pancreas were palpable, but all were detected using intraoperative ultrasound. In the event that the tumor is not localized, blind pancreatic resection should not be performed. The surgical procedure should be terminated and the diagnosis confirmed.

Treatment

Surgical resection offers the highest chance of cure. Open or laparoscopic techniques may be used. Enucleation is indicated for small, benign tumors at least 2 to 3 mm from the pancreatic duct. Intraoperative ultrasonography helps to confirm the anatomic relationship of the tumor to surrounding structures. Should the lesion be unsuitable for enucleation, resection by means of a pancreaticoduodenectomy, central pancreatic resection, or distal pancreatectomy (with or without splenic preservation) can be performed. Because patients undergoing a distal pancreatectomy with splenectomy have significantly increased perioperative infective complications, a spleen-preserving procedure is recommended [21]. Resection is associated with low mortality and morbidity and achieves long-term overall survival in 75% to 98% of patients, with prognosis dependent on the disease stage at presentation and whether a complete resection was achieved.

Laparoscopic resection for insulinomas is achievable and safe. Multiple series of laparoscopic resection have been reported since 1996. As in open surgery, the size and relationship of the primary tumor to the pancreatic duct and major vessels is critical in determining whether local resection is feasible. Laparoscopic ultrasonography is essential for this determination, and in our experience it also aids in achieving adequate margins of resection by clearly demarcating the boundaries of the lesion. Studies have reported conversion rates to open surgery of 3% to 40% and pancreatic fistula rates of 2% to 20%. Recently, Fernández-Cruz and colleagues [22•] reported on their experience with laparoscopic resection. Over a 10-year period, 49 consecutive patients underwent laparoscopic resection at their institution in Barcelona. Of these, 20 patients had sporadic insulinomas. The mean age was 40 years and the mean tumor size was 1.4 cm. Laparoscopic enucleation was performed in 15 patients and a laparoscopic splenic-preserving distal pancreatectomy in 4 patients. One patient was converted to open surgery because the tumor could not be found with laparoscopy. There was no mortality, and morbidity was comparable to that with open surgery. All patients appear disease-free at a mean follow-up of 36 months. The authors concluded that the advantages of a minimal-access approach (decreased pain, reduced hospital stay, and enhanced postoperative recovery) make it a viable option for selected patients with PETs.

Laparoscopic resection is currently not indicated if malignancy is suspected. Lymphatic involvement is common, and an oncologic resection with en bloc lymphadenectomy is indicated for localized, nonmetastatic tumors.

An aggressive approach is warranted in patients who have insulinomas associated with MEN-1. Most have multiple pancreatic tumors and thus may require a distal pancreatectomy, enucleation of any palpable or ultrasonographically detected lesions in the head of the gland, and regional lymphadenectomy. A pancreaticoduodenectomy is required for lesions in the pancreatic head that are not suitable for enucleation—those that are large or invasive, or that involve the pancreatic duct.

Gastrinoma

In 1955, Zollinger and Ellison [23] described a syndrome of upper jejunal ulceration, gastric acid hypersecretion, and non–β-cell tumors of the endocrine pancreas. This syndrome was described as recalcitrant to medical or surgical therapy, persistent, and associated with significant risk of mortality. Since that initial report, gastrin has been identified as the agent responsible for the Zollinger-Ellison syndrome (ZES).

Epidemiology

Gastrinomas are the second most common PET, occurring in 1% of patients with peptic ulcer disease. Most patients are diagnosed between the fifth and sixth decade; there is a male to female preponderance of 2:1 [24]. In contrast to insulinomas, 16% to 35% of gastrinomas are associated with MEN-1. Up to half of these tumors are found to be malignant at diagnosis.

Diagnosis

The clinical presentation of gastrin hypersecretion includes abdominal pain and secondary gastric acid hypersecretion leading to peptic ulceration. Diarrhea is also a common symptom because of the large volume of acid secretion; the low intraluminal pH damages the walls of the intestines, leading to malabsorption and steatorrhea.

The diagnosis of a gastrinoma is based on an elevated fasting gastrin level, acid secretory studies, and the results of secretin and calcium provocative tests. Over 90% of

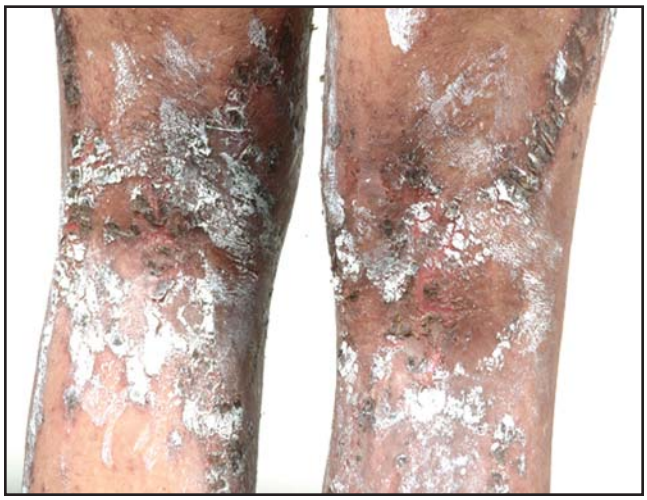

Figure 2. Necrolytic migratory erythema as seen in a patient with a metastatic glucagonoma.

patients with ZES will have an elevated fasting gastrin level. This test should be repeated and gastric pH should be measured. If the pH is higher than 2.5, ZES is unlikely to be the correct diagnosis. A full description of the other causes of hypochlorhydria or achlorhydria is outside the scope of this review. In a patient with no prior gastric surgical history, if the serum gastrin is greater than 1000 pg/mL and the gastric pH is less than 2.5, the diagnosis of ZES is likely and no further biochemical tests are required. However, about 60% of patients will have an elevated gastrin level lower than 1000 pg/mL. For these patients, assessment of basal acid output and either a secretin or calcium provocative test is required [25].

Localization

Once a biochemical diagnosis is confirmed, a workup for localization and extent of disease is performed using upper gastrointestinal endoscopy, EUS, and conventional cross-sectional imaging, similar to other PETs. In addition, somatostatin-receptor scintigraphy using ^{111}In-DTPA-DPhe^{1} octreotide with whole-body views and single-photon emission computed tomography (SPECT) views are helpful. Most tumors will be identified in the area referred to as the "Gastrinoma Triangle," the junction of the pancreatic body and neck, the second and third portion of the duodenum, and the confluence of the common hepatic and common bile ducts [26]. At presentation, up to one third of patients will have liver metastases, so cross-sectional imaging studies must include this area. Patients with pancreatic primary tumors are more likely to present with advanced disease and therefore are less likely to undergo surgical exploration. Laparoscopy can prevent unnecessary exploration in this group of patients [27].

Treatment

Proton pump inhibitors can control the symptoms of acid hypersecretion in virtually all patients with ZES, so there is controversy about the role of surgery. As surgery offers the only potential for long-term disease-free survival, our practice is to offer resection to all patients with localized disease who are fit for operative intervention. Norton and coworkers [28•] have demonstrated that surgical exploration with disease resection increases disease-specific survival and reduces the development of advanced disease. They compared 160 patients undergoing surgery with 35 nonsurgical patients. In the surgical group, 94% of patients had their tumor resected. After 15 years, overall survival (72% vs 46%) and disease-related survival (98% vs 74%) were significantly improved in the operative group, and the development of liver metastases was also reduced in these patients. The authors concluded that surgery should be offered to all ZES patients with a resectable tumor and all MEN-1/ZES patients with a tumor larger than 2 to 2.5 cm.

Glucagonoma

Glucagon is produced by the α cells of the pancreas. In 1942, Becker and Kahn [29] were the first to describe the symptoms. The association with a raised glucagon level was made by McGarvan in 1966 [30].

Epidemiology

Glucagon-secreting tumors are very rare; the annual incidence is estimated to be less than 0.1 per million population. These tumors occur in the pancreas (predominantly in the body and tail of the gland) and appear to have an equal sex distribution. About 75% are malignant, and they are rarely associated with the MEN-1 syndrome. At presentation, they are generally large (> 4 cm) and the radiologic diagnosis is commonly made with CT scanning.

Diagnosis

Patients often present with diabetes, weight loss, generalized weakness, and a characteristic skin rash termed *necrolytic migratory erythema* (NME) (Fig. 2). This rash occurs in 70% of patients and consists of erythematous papules or plaques that classically appear on the perineum, legs, or face, with areas of blistering, crusting, or scaling that can be intensely pruritic and painful [31].

The syndrome is diagnosed by measuring the serum glucagon level. A level greater than 1000 pg/mL is usually sufficient for a diagnosis. The differential diagnosis of hyperglucagonemia includes fasting, sepsis, pancreatitis, and renal or hepatic failure, although levels rarely exceed 500 pg/mL.

Localization

Tumors tend to be large, with CT scanning being the imaging modality of choice. Somatostatin-receptor scintigraphy is helpful in confirming the diagnosis and excluding metastatic disease, which may be present in up to 50% of patients [32].

Treatment
Patients are at increased risk for developing a deep venous thrombosis. Therefore, prophylactic anticoagulation or placement of a vena caval filter should be considered.

In patients with localized disease, surgical resection is the treatment of choice. As patients may be severely nutritionally depleted, nutritional supplementation should be considered. Additionally, somatostatin analogs should be considered in preoperative preparation, as they will reduce the glucagon levels and partly reverse the catabolic state.

Extended survival can occur even in the presence of metastatic disease. To achieve palliation, an aggressive approach may be appropriate, including resection of the primary tumor and metastatic lesions. For patients with unresectable hepatic metastases, selective hepatic artery chemoembolization has been shown to control the hormonal effects but not to increase survival. The use of somatostatin analogs can improve the symptoms of hormonal excess in patients who are not surgical candidates. Systemic chemotherapy with agents such as doxorubicin and streptozocin has had limited success.

VIPoma

In 1958, Verner and Morrison [33] described a syndrome of severe watery diarrhea, hypokalemia, and achlorhydria associated with a non–β-cell tumor of the pancreas. This syndrome is now known to be due to excess production by the tumor of vasoactive intestinal polypeptide (VIP). VIPomas are very rare tumors, with an estimated incidence of 1 per 10,000,000 per year [33]. The pancreas is the most common site of origin. Extrapancreatic sites such as the adrenals, colon, bronchus, liver, and sympathetic ganglia have been reported.

Diagnosis and localization
The predominant presenting complaint is profuse watery diarrhea and dehydration. Patients can produce up to 10 L per day of straw-colored stool, resulting in significant hypokalemia and acidosis. The diarrhea is unresponsive to fasting.

In many cases, the diagnosis is delayed while more common causes of diarrhea are excluded. A fasting serum VIP level greater than 200 pg/mL is diagnostic. Localization is achieved in most cases with CT scanning. In addition, somatostatin-receptor scintigraphy is useful in confirming the location and identifying metastatic disease.

Treatment
Once the diagnosis is confirmed, aggressive resuscitation is required to correct the electrolyte and fluid derangements. The use of somatostatin analogs has greatly facilitated the correction of the hypokalemia and dehydration associated with these tumors.

Complete surgical excision is the only curative option. Patients with localized disease who are fit candidates for surgery should undergo exploration and an oncologic resection of the primary tumor and regional lymph nodes. For patients with locally advanced or metastatic disease, debulking of the primary tumor and resection of the metastatic disease should be considered, as this may result in significant symptomatic palliation. Medical therapy with the somatostatin analog octreotide or chemotherapy with streptozocin has also been shown to achieve a limited palliative response rate.

Somatostatinoma

Somatostatin-secreting tumors of the pancreas have been described but are exceedingly rare. They typically present in patients 40 to 50 years of age and have an equal sex distribution. About 30% occur outside the pancreas, with the commonest extrapancreatic sites being the duodenum, ampulla of Vater, and proximal small bowel.

Diagnosis and localization
In 1977, Ganda and colleagues [34] reported the case of a female patient with diabetes, cholelithiasis, and a pancreatic tumor who was noted to have elevated somatostatin levels.

Patients generally present incidentally with diarrhea/steatorrhea, diabetes, and gallstones. Diarrhea and steatorrhea result from decreased secretion of pancreatic enzyme and bicarbonate. Somatostatin also inhibits cholecystokinin, decreasing gallbladder contractility and leading to the formation of gallstones. Inhibition of insulin results in mild hyperglycemia. Extrapancreatic somatostatinomas are often incidentally identified or may present with obstructive symptoms due to their anatomic location.

Diagnosis of somatostatinomas is often delayed because of their rarity. The diagnosis can be confirmed by elevated fasting serum somatostatin levels: a value greater than 100 pg/mL is considered diagnostic. The tumors are usually solitary and are predominantly situated in the head of the pancreas. Standard imaging modalities such as CT, MRI, and EUS are useful for localization and staging.

Treatment
Surgical resection for localized tumors offers the potential for long-term survival, but most patients have metastatic disease at presentation. Surgical debulking of the metastatic deposits has been shown to palliate symptoms and prolong disease-specific survival [35]. Overall, prognosis is poor due to the disease status at presentation.

Rare Functional Tumors

Islet cell tumors have been described that produce adrenocorticotropin, corticotrophin-releasing hormone, growth hormone–releasing factor, neurotensin, or parathyroid

hormone–related protein. These tumors are exceedingly uncommon and present with symptoms related to the specific hormone excess. In all cases, resection may be curative if the disease is localized. If metastatic disease is present, limited palliation may be achieved with somatostatin analogs such as octreotide.

Nonfunctioning Tumors

Nonfunctioning PETs are pancreatic tumors with endocrine differentiation but without clinical evidence of hormonal excess. Some actually do produce increased serum levels of hormone but remain clinically inert for various reasons: the hormone secreted, even in excess, causes no specific clinical signs; the hormone is produced in quantities too small to cause significant symptoms; or the hormone produced is functionally inert.

Epidemiology

The proportion of nonfunctional tumors varies in individual series. A recent Japanese review classified 48% of PETs as nonfunctional [36], whereas Kazanjian and coworkers from the University of California, Los Angeles [37], reporting on a series of 70 consecutive patients undergoing pancreatic resection for PET, classified 71% as nonfunctional. The explanation for this variation is complex and includes referral bias, improved diagnostic imaging resulting in increased identification of occult lesions, differing definitions of "nonfunctional" PET, and increased awareness of PETs.

Diagnosis

Most lesions are located in the head of the gland [13]. Clinical presentation relates to the anatomic site of the lesion. Predominant symptoms are abdominal pain, weight loss, and jaundice [14]. Tumors are generally large and the presence of metastatic disease at presentation is not uncommon.

As the presenting symptoms are similar to those of other pancreatic tumors, the major concern is distinguishing these tumors from other lesions, particularly the more common pancreatic ductal adenocarcinoma. Multidetector CT is the imaging modality of choice. The differences between a nonfunctioning PET and adenocarcinoma of the pancreas may be subtle. PETs generally are hypervascular and may enhance in the early arterial phase of the CT scan. Additionally, pancreatic duct obstruction is usually absent even though the lesion is quite large. Necrosis and dystrophic calcification may be present. Metastases may be present in regional nodes and the liver. MRI and EUS are also useful, particularly in problematic cases. Laparoscopic exploration with or without liver biopsy has been shown to have added value, obviating unnecessary exploration in patients with metastatic disease [28•].

Tumor markers for nonfunctioning PETs have low sensitivity and specificity, but a number are used in clinical practice. These include serum pancreatic polypeptide [38] and chromogranin A, which is elevated in 72% to 100% of patients, particularly those with a large tumor burden or metastatic disease [39,40].

Treatment

As mentioned, the natural history for nonfunctioning PETs remains unclear. Classification using the World Health Organization system helps determine therapy [5•]. For well-differentiated, localized tumors in patients fit for surgery, resection with curative intent offers the best option for long-term disease-free survival. Whether a pancreaticoduodenectomy, central pancreatectomy, or distal pancreatectomy is required depends on the site of the tumor.

The treatment of patients with hepatic metastases is somewhat controversial. For asymptomatic patients with well-differentiated metastatic disease, in whom the natural history may be prolonged, many would suggest a conservative approach, waiting until the disease progresses or symptoms occur before initiating therapies such as systemic chemotherapy, hormonal therapy, radiofrequency ablation, or selective transcutaneous arterial chemoembolization (TACE) or transplantation [32,41,42]. Others advocate a more aggressive surgical approach, suggesting that complete surgical resection of hepatic metastases is associated with prolonged overall and disease-free survival [43,44].

Conclusions

PETs present many problems in diagnosis, classification, therapy, and follow-up. Improved understanding of the natural history of these uncommon tumors permits a more rational approach to therapy. Complete surgical resection of the primary disease remains the mainstay of therapy, but the outlook for patients with metastatic disease has been improved by advances in medical therapy, radio-labelled somatostatin therapy, TACE, radiofrequency ablation, and selective use of hepatic resection. Further understanding of the biology of these lesions and the development of specific targeted therapies will offer further improvements in quality of life and disease-specific survival to patients with this group of tumors.

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Disclosure

No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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