Somatostatinoma: Clinical manifestations, diagnosis, and management

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INTRODUCTION

Somatostatinomas are rare neuroendocrine tumors of D-cell origin that contain and sometimes secrete excessive amounts of somatostatin (figure 1) [1]. This topic will review the clinical manifestations, diagnosis, and management of somatostatinomas. An overview of the clinical manifestations, diagnosis, and management of pancreatic neuroendocrine tumors is discussed in detail separately. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms" and "Surgical resection of sporadic pancreatic neuroendocrine tumors" and "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion" and "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion" and "Insulinoma" and "Glucagonoma and the glucagonoma syndrome" and "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)" and "VIPoma: Clinical manifestations, diagnosis, and management".)

EPIDEMIOLOGY

Somatostatinomas are rare neuroendocrine tumors with an annual incidence of 1 in 40 million [2]. The mean age at diagnosis of somatostatinomas is 50 to 55 years (range 26 to 84), with a

roughly equal sex distribution [3]. Approximately 55 percent of somatostatinomas are in the pancreas, and, of these, two-thirds arise within the head of the pancreas. The remainder arises in the ampulla and periampullary region of the duodenum or rarely in the jejunum [4]. Other rare primary sites include the liver, colon, and rectum [3,5]. Approximately 75 percent of somatostatinomas are malignant, and 70 to 92 percent present with metastatic disease [6].

Although 35 to 45 percent of somatostatinomas occur in association with multiple endocrine neoplasia (MEN)-1 syndrome or other familial syndrome, somatostatinomas are among the least common functioning pancreatic neuroendocrine tumors in patients with MEN-1 syndrome, occurring in less than 1 percent of patients [7]. Hereditary pancreatic somatostatinomas also occur in the setting of von-Hippel Lindau syndrome [8,9]. Up to 10 percent of patients with neurofibromatosis I (NF-1; von Recklinghausen disease) develop somatostatinomas. NF-1-associated somatostatinomas are characteristically duodenal, are rarely associated with somatostatinoma syndrome, and are less likely to metastasize as compared with sporadic somatostatinomas [4,7,10]. Interestingly, pheochromocytomas and paragangliomas also sometimes produce and secrete somatostatin, but hormone excess is not typically associated with somatostatinoma syndrome [11].

PATHOPHYSIOLOGY

Somatostatin is a tetradecapeptide that normally acts in a paracrine manner to inhibit secretion of many hormones, including insulin, glucagon, gastrin, and growth hormone. It also has direct effects on a number of gastrointestinal functions [12]. In patients with somatostatinomas, cholelithiasis may result from inhibition of cholecystokinin release, which reduces gallbladder contractility [13]. Diarrhea and steatorrhea result from inhibition of pancreatic enzyme and bicarbonate secretion and intestinal absorption of lipids. Many patients with somatostatinomas also have gastric hypochlorhydria due to decreased gastrin secretion. (See 'Clinical manifestations' below and "Physiology of somatostatin and its analogues".)

Some somatostatinomas, particularly those arising in the ampullary and periampullary area, contain immunoreactive granules but are not associated with any functional syndrome [10,14,15]. In contrast, those arising in the pancreas may secrete large amounts of somatostatin, resulting in a constellation of symptoms of somatostatinoma syndrome. (See 'Clinical manifestations' below.)

CLINICAL MANIFESTATIONS

While these tumors secrete somatostatin, clinical symptoms related to high somatostatin levels are found in less than 10 percent of cases, depending on the location of the tumor (pancreas >duodenal), and the likely intermittent nature of somatostatin secretion from the tumor [16]. When present, the most common symptoms in patients with somatostatinomas, regardless of their location, are abdominal pain (50 percent) and weight loss (20 to 30 percent) [16]. Less often, patients present with somatostatinoma syndrome, characterized by diabetes mellitus or glucose intolerance, hypochlorhydria, cholelithiasis, and diarrhea/steatorrhea. Somatostatinoma syndrome is more common in patients with pancreatic somatostatinomas as compared with duodenal somatostatinomas (19 versus 2 percent), due to differences in their secretion of somatostatin [4,17,18]. (See 'Pathophysiology' above.)

Duodenal somatostatinomas usually present with symptoms caused by local complications [10,17]. These symptoms include abdominal pain, obstructive jaundice, and gastrointestinal bleeding. Duodenal somatostatinomas can also be associated with multiple paragangliomas, and polycythemia is due to somatic gain of function of HIF2a, which activates the erythropoietin gene, causing polycythemia [16,19,20].

DIAGNOSIS

Somatostatinoma syndrome should be suspected in patients with the classical presentation of diabetes/glucose intolerance, cholelithiasis, and diarrhea/steatorrhea. In patients with somatostatinoma syndrome, providers should look for elevated plasma somatostatin concentrations at least three times over the upper limit of the reference range [16,18]. However, somatostatinoma syndrome is rare, and most somatostatinomas are detected as pancreatic or duodenal masses during the course of evaluation of abdominal pain, jaundice, or weight loss. In such patients, the diagnosis is often established by histopathology of the surgical specimen that demonstrates well-differentiated islet cells that stain positive for somatostatin on immunohistochemistry. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Biopsy and establishing the diagnosis'.)

TUMOR LOCALIZATION

Approach to imaging — Imaging can localize the tumor and stage the extent of disease. Like other neuroendocrine tumors, glucagonomas express somatostatin receptors, thus they are amenable to localization using somatostatin analogs. We begin with helical (spiral) multiphasic contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) for evaluation of patients with a somatostatinoma. In patients with inconclusive

cross-sectional imaging, we perform endoscopic ultrasound (EUS). We perform integrated PET/CT using Gallium-68-DOTA-0-Phe^1-Tyr^3-Octreotate (Gallium Ga-68 DOTATATE) or Gallium-68-DOTA-0-Phe^1-Tyr^3-Octreotide (Gallium Ga-68 DOTATOC) for indeterminate lesions, to work up occult primary tumors, and to fully stage neuroendocrine tumors. Because of its greater sensitivity, DOTA-PET/CT or MRI is preferred over conventional somatostatin receptor scintigraphy (SRS), when available [21-26]. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Computed tomography'.)

- **Computed tomography** – Since the primary tumor is usually large (>3 cm diameter) by the time of diagnosis, it is localizable by CT in the majority of cases. Intravenous contrast enhances the detection of smaller lesions, especially when images are obtained during the arterial phase. In addition, arterial phase and portal venous phase sequences can be used to maximize the conspicuity of liver metastases compared with the surrounding normal liver parenchyma.

- **Magnetic resonance imaging** – On MRI, pancreatic neuroendocrine tumors are typically characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (image 1 and image 2). MRI may have a higher sensitivity for liver metastases as compared with CT. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Computed tomography' and "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Magnetic resonance imaging'.)

- **Endoscopic ultrasound** – EUS can detect pancreatic tumors as small as 2 to 3 mm, provides accurate information on the local extent of disease, and allows transmucosal needle biopsy of pancreatic lesions in patients with locally advanced tumors. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Endoscopic ultrasonography'.)

- **Somatostatin receptor scintigraphy** – SRS (OctreoScan) using radiolabeled form of the somatostatin analog octreotide (Indium-111 [111-In] pentetreotide) has the advantage of instantaneous whole body scanning, which also allows detection of metastases outside of the abdominal region [14,27]. While SRS can be used for localization and staging of well-differentiated neuroendocrine tumors, it has largely been replaced by functional PET, which has a higher specificity and sensitivity [23-26]. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Somatostatin-receptor-based imaging'.)

- **Functional PET imaging with Ga-68 DOTATATE and Ga-68 DOTATOC** – Several positron emission tomography (PET) tracers for functional imaging have emerged (18-F-dihydroxy-phenyl-alanine [18F-DOPA], 11-C-5-hydroxytryptophan [11-C-5-HTP], Ga-68-DOTA-D-Phe^{1}-Tyr^{3}-Octreotide [gallium Ga-68-DOTATOC], copper Cu-64-DOTATATE (Cu-64 DOTATATE), and Ga-68-DOTA-D-Phe^{1}-Tyr^{3}-Octreotate [gallium Ga-68 DOTATATE]) that offer higher spatial resolution than conventional SRS and are associated with improved sensitivity for detection of small lesions [28]. Both Ga-68 DOTATATE and Ga-68 DOTATOC are approved in the United States for use with PET for localization of somatostatin receptor positive neuroendocrine tumors. Integrated PET/CT scanning using Ga-68 DOTATATE or Ga-68 DOTATOC is the functional imaging modality of choice for staging and localization of most well differentiated neuroendocrine tumors (where available). (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Somatostatin receptor-based imaging techniques'.)

STAGING

The American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) have proposed the staging systems for neuroendocrine tumors. The newest release of the AJCC/UICC tumor, node, metastasis (TNM) staging classification has a staging system for neuroendocrine tumors of the pancreas (table 1) that is separate from that used for exocrine pancreatic tumors [29]. It integrates advances in staging previously proposed by the European Neuroendocrine Tumor Society (ENETS), which is prognostic for both relapse-free and overall survival [30-33]. (See "Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms", section on 'Staging system'.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of somatostatinoma varies based on the clinical presentation. Somatostatinoma can be differentiated from other pancreatic and small intestine tumors by somatostatin levels and by histology.

- The differential diagnosis of a pancreatic mass includes primary exocrine pancreatic cancer, other pancreatic neuroendocrine tumors, lymphoma, metastatic cancer, focal chronic pancreatitis, and autoimmune pancreatitis. Evaluation of a patient with a pancreatic mass is presented in detail separately. (See "Clinical manifestations, diagnosis,

and staging of exocrine pancreatic cancer", section on 'Pancreatic mass seen on an imaging study'.)

- The differential diagnosis of steatorrhea include cirrhosis, chronic cholestasis, bacterial overgrowth, ileal resection, or ileal disease. The evaluation of chronic diarrhea and steatorrhea are discussed in detail separately. (See "Overview of nutrient absorption and etiopathogenesis of malabsorption", section on 'Fat' and "Approach to the adult with chronic diarrhea in resource-abundant settings".)

TREATMENT

Pancreatic resection — Surgical resection is the treatment of choice [13]. Most somatostatinomas are solitary and located in the head of the pancreas or duodenum and can be managed with pancreaticoduodenectomy. However, as 70 to 92 percent of patients present with metastatic disease, curative surgery is often not possible [6,34]. (See "Surgical resection of sporadic pancreatic neuroendocrine tumors" and "Surgical resection of sporadic pancreatic neuroendocrine tumors", section on 'Others'.)

Treatment of advanced/metastatic disease

Somatostatin analogue — Somatostatin and its analogues (eg, octreotide, lanreotide) inhibit the secretion of somatostatin and are first-line therapy for symptomatic disease in patients with unresectable tumors. Although somatostatin analogues are highly effective at controlling the symptoms of hormone hypersecretion, objective evidence of antitumor activity has not specifically been demonstrated in somatostatinomas. Control of tumor growth is expected, extrapolating from randomized controlled studies in metastatic midgut neuroendocrine tumors (octreotide) and gastroenteropancreatic neuroendocrine tumors without hormone-mediated symptoms (lanreotide) [16,35,36]. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Somatostatin analogs'.)

Liver-directed therapy for metastatic disease

- **Surgery** – Hepatic resection is indicated for the treatment of metastatic liver disease in the absence of diffuse bilobar involvement, compromised liver function, or extrahepatic metastases (eg, pulmonary, peritoneal). Although cure is unlikely, resection may increase survival (eg, by "setting the clock back" in a slow-growing disease) and has the benefit of symptom palliation) [37-41]. (See "Surgical resection of sporadic pancreatic neuroendocrine tumors" and "Overview of hepatic resection" and "Metastatic

gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Surgical resection'.)

- **Hepatic artery embolization and chemoembolization** – Hepatic arterial embolization, with or without selective hepatic artery infusion of chemotherapy, is a palliative technique in patients with symptomatic hepatic metastases who are not candidates for surgical resection. Embolization can be performed via the infusion of Gelfoam powder into the hepatic artery through an angiography catheter (bland embolization) or in conjunction with chemotherapy (ie, doxorubicin, cisplatin, or streptozocin, or drug-eluting beads) administered via the hepatic artery (chemoembolization). A third embolization technique uses radioactive isotopes (eg, yttrium-90 [90-Y]) that are tagged to glass or resin microspheres and delivered selectively to the tumor via the hepatic artery. Response rates, as measured by a decrease in hormonal secretion or by radiographic regression, are generally over 50 percent [42-55]. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Hepatic arterial embolization'.)

- **Radiofrequency ablation, microwave ablation, and cryoablation** – Ablation can be used as a primary treatment modality for neuroendocrine liver metastases or as an adjunct to surgical resection [40,41,56,57]. Ablation can be performed percutaneously or laparoscopically and is less invasive than either hepatic resection or hepatic artery embolization. However, ablation is applicable only to smaller lesions (typically <3 cm), and its long-term efficacy is somewhat uncertain [56]. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Ablation'.)

- **Liver transplantation** – Liver transplantation is considered an investigational approach for metastatic pancreatic neuroendocrine tumors, as the number of patients with liver-isolated metastatic disease in whom orthotopic liver transplantation has been attempted is small, and follow-up data are insufficient to judge whether a complete cure has truly been achieved [58-61]. (See "Metastatic gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion", section on 'Liver transplantation'.)

Molecularly targeted therapy — Molecularly targeted agents (eg, everolimus, sunitinib) have a role in the management of patients with progressive advanced somatostatinomas and have proven anti-tumor efficacy in progressive pancreatic neuroendocrine tumors [62,63]. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to

control tumor growth and symptoms of hormone hypersecretion", section on 'Molecularly targeted therapy'.)

Peptide receptor radioligand therapy — A form of peptide receptor radioligand therapy with a radiolabeled somatostatin analog (Lu177 dotatate) is now approved for use in panNETs and is discussed in detail elsewhere. Activity has been noted in patients with glucagonoma [64,65].

Cytotoxic chemotherapy — For patients who are highly symptomatic due to tumor bulk or who have rapidly enlarging metastases, chemotherapy has been used as initial treatment together with a somatostatin analogue. However, experience with systemic chemotherapy in patients with somatostatinomas is limited, and few patients have been included in chemotherapy series. The use of cytotoxic chemotherapy in patients with pancreatic neuroendocrine tumors typically includes streptozocin- or temozolomide-based chemotherapy and is discussed in detail elsewhere [66-68]. (See "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion", section on 'Cytotoxic chemotherapy'.)

PROGNOSIS

The prognosis of somatostatinomas with any therapy is poor when metastatic disease is present [34]. There are not enough survival data for somatostatinoma specifically to give accurate estimates of survival [4,69,70].

POST-TREATMENT SURVEILLANCE

There is limited evidence from which to make recommendations for follow-up after resection of a somatostatinoma, and guidelines are based on expert consensus [26,70-72]. Our approach for follow-up after treatment of a somatostatinoma is consistent with guidelines from the National Comprehensive Cancer Network and consists of the following [73]:

- Three to 12 months post-resection – History and physical examination, serum somatostatin level, and abdominal multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) (and chest CT scan +/- contrast as clinically indicated).
- >1 year post-resection to a maximum of 10 years – History and physical examination with serum somatostatin level every 6 to 12 months. Consider abdominal multiphasic CT or MRI (and chest CT scan +/- contrast) as clinically indicated.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Well-differentiated gastroenteropancreatic neuroendocrine tumors".)

SUMMARY

- Somatostatinomas are rare neuroendocrine tumors of D-cell origin that contain and sometimes secrete excessive amounts of somatostatin (figure 1). The mean age at diagnosis of somatostatinomas is 50 to 55 years. Approximately 55 percent of somatostatinomas are in the pancreas, and, of these, two-thirds arise within the head of the pancreas. The remainder arises in the ampullary and periampullary area of the duodenum and rarely in the jejunum. (See 'Epidemiology' above.)

- In patients with somatostatinomas, cholelithiasis may result from inhibition of cholecystokinin release, which reduces gallbladder contractility. Diminished insulin secretion leads to glucose intolerance/diabetes. Inhibition of pancreatic enzyme and bicarbonate secretion and intestinal absorption of lipids causes diarrhea and steatorrhea. (See 'Pathophysiology' above.)

- While often asymptomatic, the most common symptoms in patients with somatostatinomas, regardless of their location, are abdominal pain and weight loss. Less often, patients present with somatostatinoma syndrome characterized by diabetes mellitus/glucose intolerance, cholelithiasis, and diarrhea/steatorrhea. Somatostatinoma syndrome is more common in patients with pancreatic somatostatinomas as compared with duodenal somatostatinomas (19 versus 2 percent). Duodenal somatostatinomas usually present with obstructive jaundice, weight loss, and gastrointestinal bleeding. (See 'Clinical manifestations' above.)

- Somatostatinoma syndrome should be suspected in patients with the classical presentation of diabetes/glucose intolerance, cholelithiasis, and diarrhea/steatorrhea. In patients with somatostatinoma syndrome, the diagnosis is established by the presence of a fasting plasma somatostatin level over three times the upper limit of normal. However, somatostatinoma syndrome is rare, and most somatostatinomas are detected as pancreatic or duodenal masses during the course of evaluation of abdominal pain, jaundice, or weight loss. In such patients, the diagnosis is often established by

histopathology of the surgical specimen that demonstrates well-differentiated islet cells that stain positive for somatostatin on immunohistochemistry. (See 'Diagnosis' above.)

- Somatostatinomas can occur in the setting of the Multiple Endocrine Neoplasia-Type I (MEN-1), von Hippel-Lindau syndrome, or NF-1. At such, patients should be evaluated for a personal or family history consistent with MEN-1 or other inherited syndrome. Duodenal somatostatinomas can also be associated multiple paragangliomas and polycythemia is due to somatic gain of function of HIF2a which activates the erythropoietin gene causing polycythemia.

- Cross-sectional imaging with multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen can localize the tumor and stage the extent of disease. If cross-sectional imaging is inconclusive, endoscopic ultrasound or functional imaging with integrated PET/CT using Gallium Ga-68 DOTATATE or Ga-68 DOTATOC imaging should be performed to identify the tumor. In addition, we perform Ga-68 DOTA-PET imaging (or, if not available, somatostatin-receptor scintigraphy) to fully stage patients at risk for metastatic disease. (See 'Tumor localization' above.)

- As with other neuroendocrine tumors, surgical resection is the treatment of choice. However, because 75 percent of patients have tumors that have metastasized by the time the diagnosis is made, curative surgery is often not possible. (See 'Pancreatic resection' above and "Surgical resection of sporadic pancreatic neuroendocrine tumors", section on 'Others'.)

- Hepatic resection (with or without ablation) can be considered in patients with metastatic disease in the absence of diffuse bilobar involvement, compromised liver function, or extensive extrahepatic metastases. Radiofrequency hepatic arterial embolization, with or without selective hepatic artery infusion of chemotherapy, may be used for palliation in patients with symptomatic hepatic metastases who are not candidates for surgical resection. Experience with orthotopic liver transplantation is limited.

- In the setting of unresectable disease, somatostatin analogs are used to delay progression. In addition, benefit has been shown for cytotoxic chemotherapy and molecularly targeted agents such as sunitinib and everolimus. Peptide receptor radioligand therapy with Lu177 dotatate is also an approved option for patients harboring locally advanced or metastatic somatostatin receptor-positive tumors by functional imaging. (See 'Treatment of advanced/metastatic disease' above and "Metastatic well-differentiated pancreatic neuroendocrine tumors: Systemic therapy options to control tumor growth and symptoms of hormone hypersecretion" and "Metastatic

gastroenteropancreatic neuroendocrine tumors: Local options to control tumor growth and symptoms of hormone hypersecretion".)

- Prognosis is generally poor when patients present with metastatic disease. Our approach for follow-up after treatment of a somatostatinoma is consistent with guidelines from the National Comprehensive Cancer Network and consists of the following (see 'Prognosis' above and 'Post-treatment surveillance' above):
  - Three to 12 months post-resection – History and physical examination, serum somatostatin level, and abdominal multiphasic CT or MRI (and chest CT scan +/- contrast as clinically indicated).
  - >1 year post-resection to a maximum of 10 years – History and physical examination with serum glucagon level every 6 to 12 months. Consider abdominal multiphasic CT or MRI (and chest CT scan +/- contrast) as clinically indicated.

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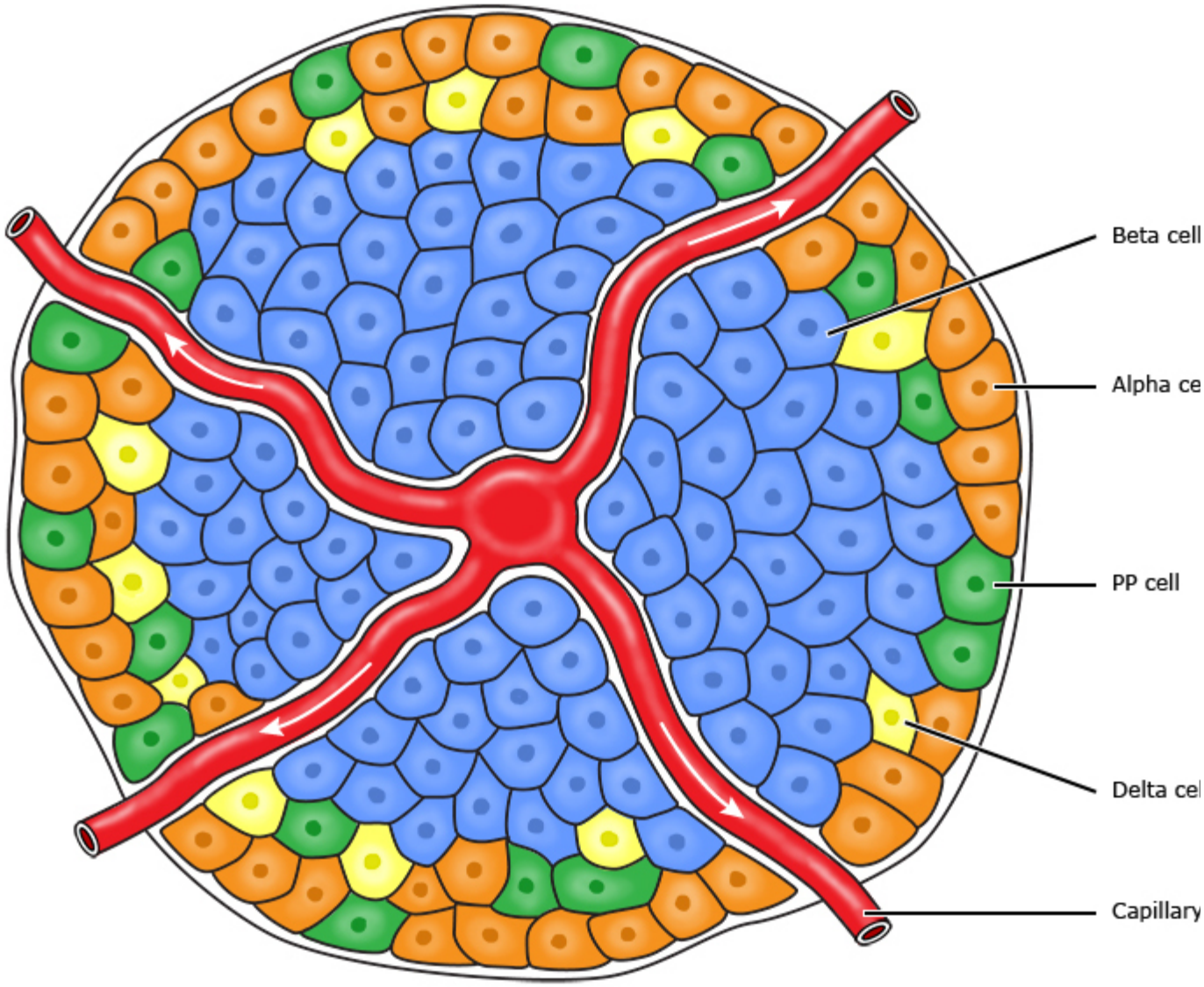
Topic 2608 Version 36.0

GRAPHICS

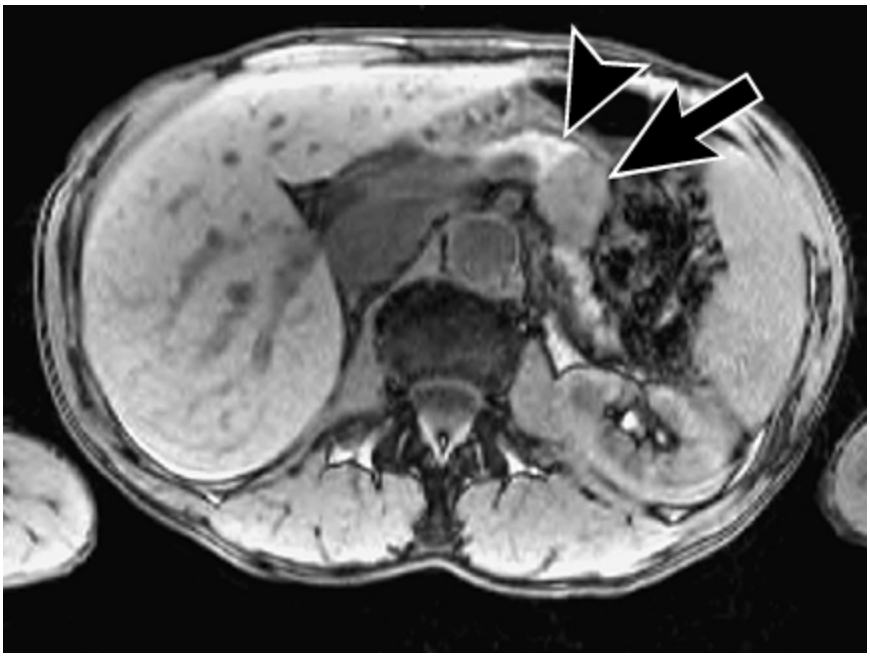
Islets of Langerhans



Schematic representation of the anatomic relationships in an islet of Langerhans. The insulin-producing bet cells (in blue) are mostly in the center closest to the systemic blood supply from pancreatic arterioles and ar surrounded by the glucagon-producing alpha cells (in orange). On the outside are the delta cells (in yellow), which make somatostatin, and the PP cells (in green), which make pancreatic polypeptide. Periportal blood flow within the islet is from beta to alpha to delta cells.

Graphic 80502 Version 3.0

T1-weighted MRI image of a neuroendocrine tumor of the pancreas

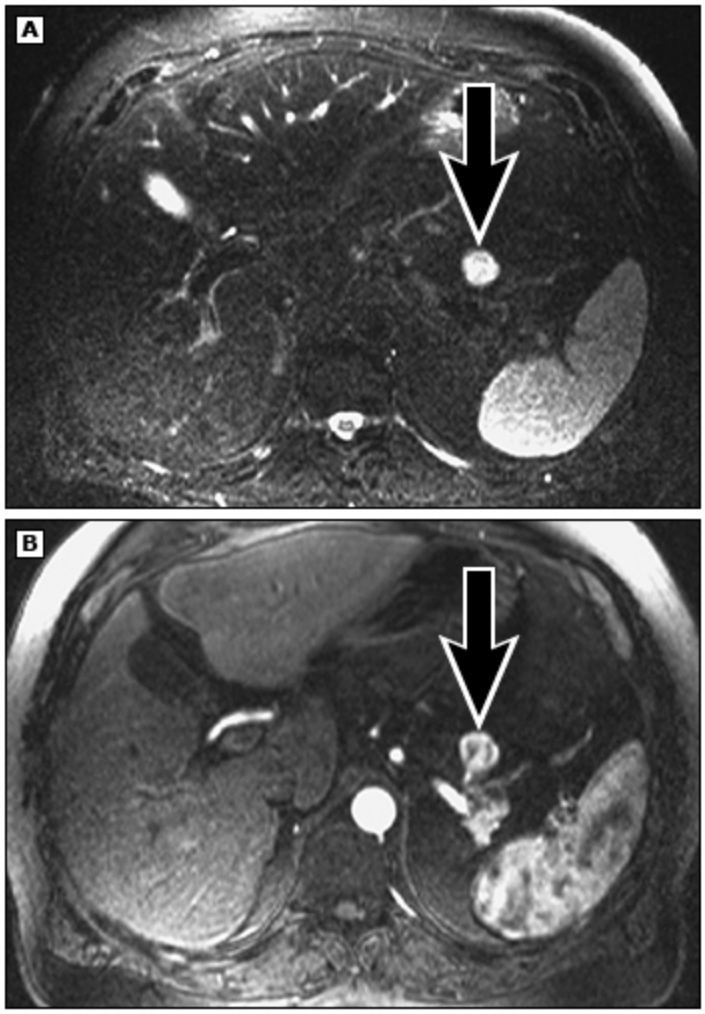


Malignant neuroendocrine tumor of the pancreas. T1-weighted gradient echo image of abdomen demonstrates mass (arrow) near junction of pancreatic body and tail. Note that mass (arrow) is lower in signal intensity than adjacent normal pancreatic parenchyma (arrowhead).

MRI: magnetic resonance imaging.

Graphic 59487 Version 5.0

T2-weighted MRI image of a neuroendocrine tumor of the pancreas



Pancreatic neuroendocrine tumor.

(A) Fat-suppressed T2-weighted image shows small high-signal intensity mass (arrow) involving tail of pancreas.

(B) Arterial phase fat-suppressed gradient echo image from dynamic examination reveals mass (arrow) to be hypervascular.

MRI: magnetic resonance imaging.

Graphic 72303 Version 5.0

Neuroendocrine tumors of the pancreas TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Tumor cannot be assessed
T1	Tumor limited to the pancreas,* <2 cm
T2	Tumor limited to the pancreas,* 2 to 4 cm
T3	Tumor limited to the pancreas,* >4 cm; or tumor invading the duodenum or common bile duct
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)
* *Limited to the pancreas* means there is no invasion of adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of tumor into peripancreatic adipose tissue is NOT a basis for staging. *NOTE:* Multiple tumors should be designated as such (the largest tumor should be used to assign T category): ▪ If the number of tumors is known, use T(#); eg, pT3(4) N0 M0. ▪ If the number of tumors is unavailable or too numerous, use the *m* suffix, T(m); eg, pT3(m) N0 M0.	
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group**

			is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer control.

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Graphic 111355 Version 9.0

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