Classification, epidemiology, clinical presentation, localization, and staging of pancreatic neuroendocrine neoplasms

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INTRODUCTION

Pancreatic neuroendocrine tumors (NETs), also known as islet cell tumors, are rare neoplasms that arise in the endocrine tissues of the pancreas (picture 1). They can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide, resulting in myriad clinical syndromes. In modern clinical series, however, between 50 and 75 percent of pancreatic NETs are nonfunctioning (ie, unassociated with a hormonal syndrome).

This topic review will cover the classification, clinical presentation, localization, and staging of well-differentiated pancreatic NETs. A discussion of surgical management of sporadic pancreatic NETs; the clinical features, diagnostic evaluation, and treatment of high-grade gastroenteropancreatic neuroendocrine carcinomas; and specific topics that address the presentation and management of functioning pancreatic NETs and neuroendocrine neoplasms of unknown primary site are all presented elsewhere:

- (See "Surgical resection of sporadic pancreatic neuroendocrine tumors".)
- (See "High-grade gastroenteropancreatic neuroendocrine neoplasms".)
- (See "Insulinoma".)
- (See "Glucagonoma and the glucagonoma syndrome".)

- (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Management and prognosis of the Zollinger-Ellison syndrome (gastrinoma)".)
- (See "VIPoma: Clinical manifestations, diagnosis, and management".)
- (See "Somatostatinoma: Clinical manifestations, diagnosis, and management".)
- (See "Neuroendocrine neoplasms of unknown primary site".)

CLASSIFICATION AND NOMENCLATURE

The nomenclature of pancreatic neuroendocrine neoplasms (NENs) has evolved considerably over the last two decades. Use of the term "islet cell tumor" (which denotes the presumed origination of pancreatic NENs in the islets of Langerhans) has declined. In more recent years, the term "pancreatic neuroendocrine tumor" (NET) has been adopted by most practitioners, as well as by the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO), for well-differentiated tumors regardless of histologic grade. The term "pancreatic neuroendocrine carcinoma" (NEC) is reserved for those cases with poorly differentiated histology and a high proliferative rate (table 1).

NENs arising at different sites within the body are classified according to their histologic features. While there are differences in terminology and grading for these tumors arising at different sites, all commonly used classification systems reflect a basic separation between more indolent, well-differentiated tumors and far more aggressive, poorly differentiated types, which behave clinically more like small cell carcinoma of the lung.

Measures of proliferative index (Ki-67 and mitotic index) are used to assign histologic grade for pancreatic NENs. Prior to 2017, well-differentiated pancreatic NETs were separated into low-grade (G1; Ki-67 index <3 percent) and intermediate-grade (G2; Ki-67 index 3 to 20 percent) categories according to proliferative rate. High-grade (G3; Ki-67 index >20 percent) tumors were considered equivalent to poorly differentiated carcinomas. However, it became apparent that not all G3 tumors were poorly differentiated and that some tumors, particularly those with a Ki-67 index in the 20 to 55 percent range, had relatively well-differentiated histology, relatively good prognosis (compared with poorly differentiated carcinomas), and relatively poor response to platinum-based chemotherapy. Therefore, the 2017 WHO classification of pancreatic NENs (table 1) includes a NET G3 category (Ki-67 >20 percent) that must be distinguished from the poorly differentiated pancreatic NEC category.

This subject is discussed in more detail elsewhere. (See "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on '2010 and 2019 World Health Organization classification'.)

Functionality and nomenclature — Functionality also impacts nomenclature. Pancreatic NETs that are functioning (hormone secreting) are classified according to the predominant hormone they secrete and the resulting clinical syndrome. Nearly all functioning NENs are well-differentiated NETs (see "Pathology, classification, and grading of neuroendocrine neoplasms arising in the digestive system", section on 'Functionality and nomenclature'):

- An insulin-producing pancreatic NET causing episodic hypoglycemia is considered to be an insulinoma. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology" and "Insulinoma".)
- A gastrin-producing tumor associated with Zollinger-Ellison syndrome is termed a gastrinoma. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis".)
- Other functioning pancreatic NETs that secrete glucagon (glucagonomas), somatostatin (somatostatinomas), or vasoactive intestinal polypeptide (VIPomas) are quite rare, with an estimated annual incidence of approximately 1 in 10 million. (See "Glucagonoma and the glucagonoma syndrome" and "VIPoma: Clinical manifestations, diagnosis, and management" and "Somatostatinoma: Clinical manifestations, diagnosis, and management".)

Of note, immunohistochemical staining is not a defining criterion for tumor classification. For example, if a tumor stains for gastrin but does not produce symptoms of Zollinger-Ellison syndrome, it is not considered a gastrinoma.

Although functionality may impact prognosis (eg, insulinomas are generally indolent tumors), the biologic behavior of most functioning pancreatic NETs is defined by the grade and stage of the tumor, as it is with nonfunctioning tumors. Thus, the pathologic diagnosis of a functioning pancreatic NET should be the same as for a nonfunctioning NET (ie, well-differentiated or poorly differentiated NET), with the descriptive functional designation appended to the diagnosis where there is knowledge of a clinical syndrome.

EPIDEMIOLOGY

Pancreatic neuroendocrine tumors (NETs) are overall rare; they have an incidence of ≤1 case per 100,000 individuals per year and account for 1 to 2 percent of all pancreatic tumors [1-3]. Pancreatic NETs represent less than 3 percent of primary pancreatic neoplasms [4]. Incidence rates have been increasing in the United States and elsewhere over the last two decades, but it

is likely that this is mainly related to increased detection of asymptomatic disease on cross-sectional imaging and endoscopy done for other reasons [2,3].

Although they may manifest at any age, they most often occur in the fourth to sixth decades of life.

Most pancreatic NETs are sporadic, but they can be associated with hereditary endocrinopathies, including multiple endocrine neoplasia type I (MEN1), von Hippel-Lindau (VHL) syndrome, neurofibromatosis type I (NF1), and tuberous sclerosis (table 2). Approximately 80 to 100 percent of patients with MEN1, up to 20 percent of patients with VHL, 10 percent of patients with NF1, and 1 percent of patients with tuberous sclerosis will develop a pancreatic NET within their lifetime [5]. Importantly, patients who develop a pancreatic NET in the context of an inherited syndrome must be considered separately with regard to prognosis, as these tumors tend to be associated with a more indolent course than are sporadic tumors. Furthermore, specific treatments may also be available that are not useful for treatment of sporadic tumors (eg, the hypoxia-inducible factor 2 alpha inhibitor belzutifan for VHL-associated pancreatic NETs). (See "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis" and "Clinical features, diagnosis, and management of von Hippel-Lindau disease", section on 'Pancreatic tumors' and "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis" and "Tuberous sclerosis complex: Genetics, clinical features, and diagnosis".)

Other potential risk factors for pancreatic NETs include smoking (albeit with weak evidence) [6], diabetes (although the cause versus effect relationship is not clear) [6-9], and a previous history of chronic pancreatitis [7].

CLINICAL PRESENTATION

The clinical presentation of pancreatic neuroendocrine tumors (NETs) has evolved in more recent years. Up until two decades ago, most pancreatic NETs were described as functioning and were detected following diagnostic evaluation of a hormonal syndrome. In contrast, more recent clinical series describe the majority (between 50 and 85 percent) of pancreatic NETs as nonfunctioning [10-18].

Functioning tumors — The clinical presentation of specific functional tumors is addressed in detail elsewhere and is outlined in the table (table 3). In brief:

- Insulinomas typically present with episodic hypoglycemia, which may cause confusion, visual change, unusual behavior, palpitations, diaphoresis, and tremulousness. Amnesia

for hypoglycemia is common. (See "Insulinoma", section on 'Symptoms and misdiagnosis'.)

- Gastrinomas typically present with peptic ulcer disease; diarrhea can also be a prominent feature. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

- The clinical syndrome classically associated with glucagonoma includes necrolytic migratory erythema, cheilitis, diabetes mellitus, anemia, weight loss, diarrhea, venous thrombosis, and neuropsychiatric symptoms. (See "Glucagonoma and the glucagonoma syndrome", section on 'Clinical features'.)

- The main clinical features of VIPoma syndrome are watery diarrhea, hypokalemia, and hypochlorhydria. (See "VIPoma: Clinical manifestations, diagnosis, and management", section on 'Clinical features'.)

Tumors presenting with a specific hormonal syndrome can develop additional syndromes subsequently due to secretion of more than one hormone [19].

Nonfunctioning tumors — Although nonfunctioning pancreatic NETs do secrete a number of substances, such as chromogranins, neuron-specific enolase, pancreatic polypeptide, and ghrelin, they do not present clinically with a hormonal syndrome as compared with their functional counterparts. As a result, they often present later in the course of the disease with symptoms of local compression or metastatic disease [20-22]. However, mean tumor diameter has decreased in the last two decades, attributed to the increased use of cross-sectional imaging, and a larger percentage of tumors (40 and 50 percent of nonmetastatic pancreatic NETs in two series [20,23]) are now detected incidentally in asymptomatic patients who undergo diagnostic evaluations for unrelated conditions.

Occasionally, patients with tumors that appear to be nonfunctional develop symptoms of hormone secretion later in their disease course [19].

When symptomatic, the most common presenting symptoms of a nonfunctioning pancreatic NET are abdominal pain (35 to 78 percent), weight loss (20 to 35 percent), and anorexia and nausea (45 percent) [24-27]. Less frequent signs include obstructive jaundice (17 to 50 percent), intra-abdominal hemorrhage (4 to 20 percent), or a palpable mass (7 to 40 percent). Symptoms may also be attributable to metastatic disease. In a variety of published reports, between 32 and 73 percent of cases are metastatic at diagnosis [3,12,28-30].

Metastatic disease — Uncommonly, patients present with metastatic NET and an unknown primary site. The most common site of metastatic disease involvement for pancreatic NET is the

liver [31]. (See "Neuroendocrine neoplasms of unknown primary site", section on 'Evaluation and management'.)

IMAGING STUDIES FOR DISEASE LOCALIZATION

Overview of the diagnostic approach — The diagnostic approach to a patient with a suspected pancreatic neuroendocrine tumor (NET) depends on the clinical scenario:

- Patients with a biopsy-proven pancreatic NET require appropriate radiographic staging studies in order to determine the extent of disease spread in order to plan appropriate treatment. In some cases, a patient may present with confirmed metastatic disease (most often in the liver; other less common sites include retroperitoneal lymph nodes and bone [32]), and the diagnostic approach focuses on identifying both the extent of disease spread and the likely primary site of disease. In patients with either metastatic or nonmetastatic disease, cross-sectional imaging studies, such as multiphasic computed tomography (CT) scan or magnetic resonance imaging (MRI), are indicated. Imaging should focus on the abdomen; the value of chest imaging is questionable.

- Diagnostic imaging using radiolabeled somatostatin analogs is recommended for most patients. Uptake of radiolabeled somatostatin analogs is predictive of a clinical response to therapy with somatostatin analogs and peptide receptor radionuclide therapy, and it can assist in identifying an otherwise occult primary site. Where available, functional imaging with gallium Ga-68 DOTATATE (68-Ga DOTATATE) positron emission tomography (PET)/CT is preferred over indium-111 (111-In) pentetreotide (OctreoScan) due to its greater sensitivity [33].

- Occasionally, patients present with a hormonal syndrome suggestive of a pancreatic NET (such as hypoglycemia with confirmed hyperinsulinemia on a monitored fast) but lack evidence of disease on conventional imaging. These patients may require highly specialized localizing evaluations that may include endoscopic ultrasonography (EUS) or arterial stimulation with venous sampling (ASVS). The combined use of conventional imaging and endoscopic studies for an occult hormonally functioning pancreatic NET (such as a subcentimeter insulinoma) has improved the sensitivity of preoperative detection to nearly 100 percent [34]. (See "Insulinoma", section on 'Tumor localization'.)

- In rare cases where there is strong clinical and biochemical evidence for an occult pancreatic NET that is undetectable on EUS, we recommend arterial stimulation with

transhepatic portal venous sampling (THPVS) if expertise in this technique is available. (See 'Arterial stimulation with venous sampling' below.)

The following sections will review the data on the utility of the available imaging techniques in patients with pancreatic NETs.

Computed tomography — CT scans are noninvasive and readily available. Helical (spiral), multiphasic, contrast-enhanced CT is recommended for evaluation of patients with pancreatic NETs.

Most NETs are highly vascular, and liver metastases may appear isodense with the liver on a noncontrasted study. Following the injection of intravenous contrast, pancreatic NETs often enhance with iodinated contrast during the early arterial phase (approximately 20 seconds after contrast injection), with washout during the portal venous imaging phase (approximately 70 seconds after contrast injection) [35]. 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 (image 1) [36].

CT scans are highly accurate for detecting primary pancreatic NETs; using modern multiphase imaging techniques, sensitivity is >80 percent [36-38]. Tumors as small as 4 mm have been visualized with CT scanning; however, sensitivity is decreased for tumors smaller than 2 cm in diameter compared with larger tumors [37]. Small tumors can often appear as rounded, enhancing vascular lesions (image 2); others may be hypodense or cystic (image 3).

Symptomatic but nonfunctioning tumors, VIPomas, and glucagonomas are usually large (>3 cm) at the time of diagnosis. The sensitivity of contrast-enhanced CT for these tumors approaches 100 percent, and it is considered the imaging study of choice [39,40].

Magnetic resonance imaging — On MRI, pancreatic NETs are typically characterized by low signal intensity on T1-weighted images (image 4) and by high signal intensity on T2-weighted images (image 5). Early series examining the role of MRI for the detection of NETs were disappointing. However, with the advent of newer techniques, such as short tau inversion recovery (STIR) sequences, sensitivity has improved substantially [41-43]:

- In one study of 28 consecutive patients with a clinically suspected functioning pancreatic NET, MRI detected a pancreatic NET in 17 of 20 patients in whom it was done (sensitivity 85 percent) [41]. Specificity was 100 percent, and the positive and negative predictive values were 100 and 73 percent, respectively. In this study, the gold standard for diagnosis of a pancreatic NET was either resection (n = 19) or clinical follow-up for at least a year.

- In another study of 64 patients with metastatic NETs, multiphasic MRI detected more hepatic lesions than either contrast-enhanced CT or somatostatin receptor scintigraphy [44]. As a result of this greater sensitivity for liver metastases, some clinicians prefer MRI over CT for assessing the status of the liver [43]. This subject is discussed in detail elsewhere. (See "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring", section on 'Cross-sectional imaging'.)

As with CT scans, early arterial phase imaging following the injection of gadolinium contrast is critical for the detection of small hypervascular liver metastases. In a study of 37 patients with liver metastases from gastroenteropancreatic NETs, the most sensitive sequences for detection of liver metastases were hepatic arterial phase and fast spin-echo T2-weighed images (image 5) [38].

Endoscopic ultrasonography — EUS provides high-resolution imaging of the pancreas, and it can detect lesions as small as 2 to 3 mm in diameter (image 6). Studies of EUS for detecting pancreatic NETs suggest high sensitivity for tumor detection [34,37,42,43,45-49]:

- In a systematic review of 17 cohort studies (612 patients), when it was performed, EUS identified pancreatic NETs in 97 percent of cases [49]. When the analysis was limited to cases where the pancreatic NET was not detected by CT with or without other modalities, a pancreatic NET was diagnosed solely by EUS in 28 percent of cases. Studies in which multidetector CT and/or spiral CT scans were known to have been performed before EUS noted a smaller incremental benefit for EUS.

- In another report, EUS was more sensitive than either CT or transabdominal ultrasonography for detection and localization of pancreatic NETs in patients with multiple endocrine neoplasia type 1 (MEN1) syndrome [48]. In this report, sensitivity for tumors less than 6 mm in diameter was poor, as determined by inspection of resected specimens by pathologists. However, others suggest acceptable reproducibility for EUS in detecting small pancreatic NETs in patients with MEN1 [50].

  Although routine screening of asymptomatic patients with MEN1 with EUS has been recommended, this is a controversial area, and the optimal screening strategy in these patients remains uncertain. (See "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis", section on 'Nonfunctioning pancreatic tumors' and "Multiple endocrine neoplasia type 1: Clinical manifestations and diagnosis", section on 'Monitoring for MEN1-associated tumors'.)

- EUS has also proven to be a useful tool for identifying pancreatic NETs such as gastrinomas that arise in the duodenal wall and have a high frequency of metastasis to the peripancreatic lymph nodes [51]. Duodenal gastrinomas are notoriously difficult to localize by CT.

Another benefit of EUS is that EUS-guided fine needle aspiration biopsy can often provide a nonoperative histologic diagnosis of pancreatic NET [51-53]. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract".)

EUS is limited by the requirement of a highly skilled endoscopist and by its inability to consistently visualize the pancreatic tail. Nevertheless, this technique has proven useful for the localization of primary pancreatic NETs in patients without metastatic disease.

Somatostatin-receptor-based imaging — Most well-differentiated NETs express high levels of somatostatin receptors and can therefore be imaged with radiolabeled somatostatin analogs. These scans allow for whole-body imaging. They also provide information on somatostatin receptor expression, which has important therapeutic implications regarding use of cold and radiolabeled somatostatin analogs. The first imaging technique to visualize somatostatin-receptor-expressing tumors used 111-In pentetreotide to produce a scintigraphic image (OctreoScan). The accuracy of 111-In pentetreotide improved with the addition of single-photon emission computed tomography (SPECT) to planar imaging (image 7) [54,55].

Several PET tracers for somatostatin receptor imaging have emerged (such as 68-Ga DOTATATE, 68-Ga DOTATOC, and copper Cu-64 DOTATATE), which, in combination with integrated PET/CT, improve the detection and staging of NETs over older methods of somatostatin receptor imaging such as OctreoScan [33,56-58]. These novel PET modalities offer higher spatial resolution than conventional 111-In pentetreotide scanning and are associated with improved sensitivity for detection of small lesions, including occult primary tumors (image 8). In our view (and that of others [59]), 68-Ga DOTATATE, 68-Ga DOTATOC, or 64-Cu DOTATATE PET/CT, where available, is preferred over conventional 111-In pentetreotide scanning for most NETs, especially for tumor localization in the setting of metastatic disease and an unknown primary site. This subject is discussed in detail elsewhere. (See "Neuroendocrine neoplasms of unknown primary site", section on 'Initial workup' and "Diagnosis and staging of small bowel neoplasms", section on 'Somatostatin receptor-based imaging'.)

The affinity of both 111-In pentetreotide and 68-Ga DOTATATE/68-Ga DOTATOC/64-Cu DOTATATE is highest for subtype 2 somatostatin receptors (SSTR2). Insulinomas, which are the most frequent type of functioning pancreatic NET, express relatively scant levels of SSTR2 and may be less likely to be detected with these scans [60-63].

Poorly differentiated neuroendocrine carcinomas (table 1) also express low somatostatin receptor levels and are unlikely to be detected. (See "Insulinoma", section on 'Diagnosis and staging' and "Insulinoma", section on 'Tumor localization' and "High-grade gastroenteropancreatic neuroendocrine neoplasms", section on 'Radiographic studies'.)

Arterial stimulation with venous sampling — For rare cases in which radiographically occult, hormonally functional tumors elude detection by conventional imaging modalities, invasive approaches may be employed to localize tumors to a particular region of the pancreas for treatment planning purposes (eg, tail, body/neck, head/uncinate). These include THPVS and ASVS [39,45]. These procedures have become relatively obsolete given the improved sensitivity of preoperative imaging, especially 68-Ga DOTATATE PET and EUS.

Intraoperative localization techniques — Intraoperative ultrasonography allows high-resolution examination of the pancreas. When combined with palpation of the organ, the sensitivity for tumor detection ranges from 83 to 100 percent [39,64,65]. Intraoperative transillumination has equivalent efficacy (sensitivity 83 percent) for the localization of duodenal wall gastrinomas [64].

Neither intraoperative ultrasonography nor illumination should replace preoperative imaging; they may be used as adjuncts to intraoperative palpation in patients who still have a suspected hormone-secreting pancreatic NET that cannot be identified or localized preoperatively.

Laboratory diagnostics — A variety of peptide markers, including chromogranin A (CgA) and pancreatic polypeptide (PP), may be used in the follow-up of patients with pancreatic NETs. However, due to suboptimal sensitivity and specificity (particularly for CgA in the setting of proton pump inhibitor use), the value of routine tumor marker measurement has been questioned. Guidelines from the National Comprehensive Cancer Network (NCCN) consider assay of either CgA or PP for any pancreatic NET to represent a class 3 recommendation (there is major disagreement within the guidelines panel that the intervention is appropriate).

Functioning tumors — Specific hormones secreted by functional tumors (ie, insulin, proinsulin, glucagon, gastrin, vasoactive intestinal polypeptide) can be measured and correlated with hormonal symptoms. Hormone levels also correspond to changes in tumor burden and can therefore serve as specific tumor markers. (See "Insulinoma" and "Somatostatinoma: Clinical manifestations, diagnosis, and management" and "VIPoma: Clinical manifestations, diagnosis, and management" and "Glucagonoma and the glucagonoma syndrome", section on 'Serum glucagon' and "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors", section on 'Hormones associated with pancreatic NETs'.)

Nonfunctioning tumors — We do not test nonspecific panels of hormone levels or nonhormonal tumor biomarkers such as CgA for patients with nonfunctioning tumors, which account for the majority of pancreatic NETs. (See "Overview of tumor biomarkers in gastroenteropancreatic neuroendocrine tumors".)

STAGING SYSTEM

Pancreatic neuroendocrine tumors (NETs) are staged using the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system, which is based on the definitions proposed by the European Neuroendocrine Tumor Society (ENETS) [66]. These staging systems are highly prognostic for both relapse-free and overall survival [67-69].

The newest release of the tumor, node, metastasis (TNM) staging classification of the AJCC/UICC (eighth edition, 2017) has a staging system for pancreatic NETs (table 4) that is separate from that used for exocrine pancreatic tumors for the first time [70]. Compared with earlier versions, it also incorporates the ENETS definitions for T stage and its prognostic stage groupings. A further modification of this combined ENETS/AJCC classification that may provide even better prognostic discrimination has been proposed based on an analysis of data from two large databases [71]. Importantly, this staging system does not apply to high-grade, poorly differentiated neuroendocrine carcinomas; these tumors are staged according to the classification for exocrine pancreatic cancer (table 5).

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 AND RECOMMENDATIONS

- **Classification and nomenclature** – The nomenclature of pancreatic neuroendocrine neoplasms (NENs) has evolved considerably over the last two decades. (See 'Classification and nomenclature' above.)
  - Use of the term "islet cell tumor" (which denotes the presumed origination of pancreatic NENs in the islets of Langerhans) has declined, and the term "pancreatic

neuroendocrine tumor" (NET) has been adopted by most practitioners, the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO), for well-differentiated tumors regardless of histologic grade.

- The term "pancreatic neuroendocrine carcinoma" is reserved for those cases with poorly differentiated histology and a high proliferative/mitotic rate (table 1). (See 'Classification and nomenclature' above.)

- **Clinical presentation** – Previously, most pancreatic NETs were functioning and detected following diagnostic evaluation of a hormonal syndrome. More recent clinical series describe the majority (50 to 85 percent) as nonfunctioning. (See 'Clinical presentation' above.)

- **Imaging and disease localization**

  - Cross-sectional imaging with multiphasic CT or MRI is highly sensitive for identification of primary pancreatic NETs as well as liver metastases. Early arterial phase imaging is particularly valuable for detection of hypervascular primary tumors and liver metastases. (See 'Computed tomography' above and 'Magnetic resonance imaging' above.)

  - Somatostatin receptor-based imaging offers whole-body imaging and functional information regarding tumoral expression of somatostatin receptors.

    - Where available, functional imaging with gallium Ga-68 DOTATATE (68-Ga DOTATATE), Ga-68 DOTATOC, or Cu-64 DOTATATE positron emission tomography (PET)/CT is preferred over indium-111 (111-In) pentetreotide (OctreoScan) due to the greater sensitivity of these radiotracers.

    - The sensitivity of somatostatin-receptor-based imaging may be lower for the detection of insulinomas and poorly differentiated or high-grade tumors. (See 'Somatostatin-receptor-based imaging' above.)

  - Endoscopic ultrasonography (EUS) is highly sensitive for detection of occult, subcentimeter pancreatic NETs and plays an important role in the evaluation of patients with functional NETs that are undetectable using conventional imaging techniques. Through endoscopic fine needle aspiration biopsy, EUS also offers the ability to obtain a nonoperative histopathologic diagnosis. (See 'Endoscopic ultrasonography' above.)

- Among patients presenting with hormonal syndromes such as hypoglycemia or Zollinger-Ellison syndrome, the diagnostic modalities listed above (CT, MRI, somatostatin-receptor-based imaging, EUS) can detect nearly 100 percent of pancreatic NETs. As a result, invasive localizing techniques (such as arterial stimulation with venous sampling [ASVS]) are rarely necessary in modern practice. (See 'Arterial stimulation with venous sampling' above.)

- Our approach to patients with suspected or biopsy-proven NETs is as follows (see 'Overview of the diagnostic approach' above):

  - For patients who present with hormonal syndromes suspicious for a pancreatic NET but who lack evidence of disease on conventional cross-sectional imaging, we recommend EUS. EUS with fine needle aspiration can also be used to establish a pathologic diagnosis, particularly in patients with early stage disease.

  - For patients who present with a biopsy-proven well-differentiated NET in the pancreas, we recommend helical triple-phase CT (arterial phase, portal venous phase, noncontrast) or multiphasic contrast-enhanced MRI of the abdomen to stage the extent of disease. If the results would potentially change management or the treatment plan, we perform somatostatin receptor-based imaging in order to assess for somatostatin receptor expression and evaluate for extra-abdominal (predominantly bone) metastases. Where available, functional imaging with 68-Ga DOTATATE, 68-Ga DOTATOC, or 64-Cu DOTATATE PET/CT is preferred over 111-In pentetreotide (OctreoScan) due to its greater sensitivity.

  - In rare cases where there is strong clinical and biochemical evidence for an occult pancreatic NET that is undetectable on EUS, we recommend arterial stimulation with hepatic venous sampling if expertise in this technique is available. (See 'Arterial stimulation with venous sampling' above.)

- **Staging** – Pancreatic NETs are staged using the combined AJCC/Union for International Cancer Control (UICC) staging system (table 4) which is separate from that used for exocrine pancreatic tumors. (See 'Staging system' above.)

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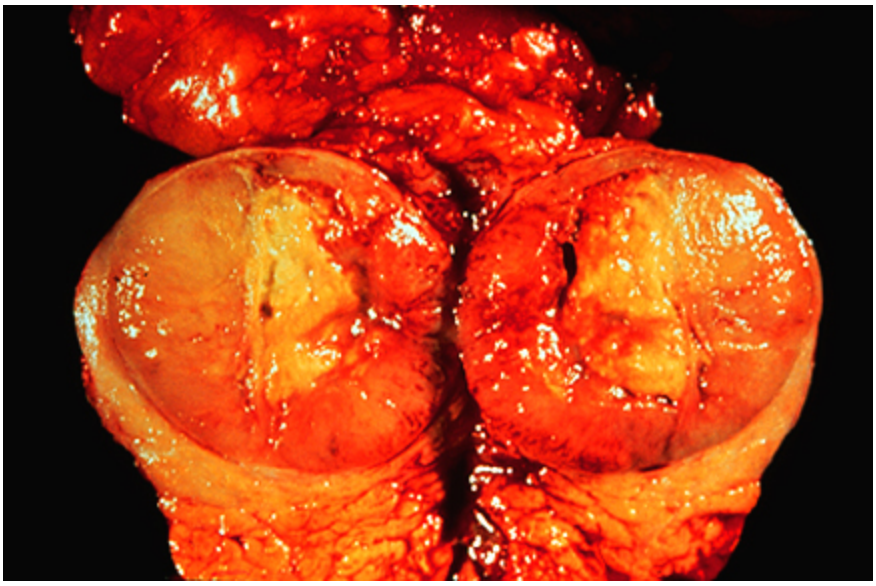
Topic 2612 Version 52.0

GRAPHICS

Pancreatic neuroendocrine neoplasm



Gross specimen of a pancreatic neuroendocrine neoplasm that has been surgically removed. The type of tumor cannot be determined from gross examination.

Courtesy of Robert Odze, MD.

Graphic 56960 Version 2.0

2017 World Health Organization (WHO) classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)

Classification/grade	Ki-67 proliferation index* (percent)	Mitotic index*
Well-differentiated PanNENs: Pancreatic neuroendocrine tumours (PanNETs)		
PanNET G1	<3	<2
PanNET G2	3 to 20	2 to 20
PanNET G3	>20	>20
Poorly differentiated PanNENs: Pancreatic neuroendocrine carcinomas (PanNECs)		
PanNEC (G3)	>20	>20
Small cell type		
Large cell type		
Mixed neuroendocrine-non-neuroendocrine neoplasm		

* The Ki-67 proliferation index is based on the evaluation of ≥500 cells in areas of higher nuclear labelling (so-called hotspots). The mitotic index is based on the evaluation of mitoses in 50 high-power fields (0.2 mm^2 each) in areas of higher density, and is expressed as mitoses per 10 high-power fields (2.0 mm^2). The final grade is determined based on whichever index (Ki-67 or mitotic) places the tumour in the highest grade category. For assessing Ki-67, casual visual estimation (eyeballing) is not recommended; manual counting using printed images is advocated.

Graphic 115945 Version 3.0

Inherited disorders associated with pancreatic neuroendocrine tumors

Syndrome	Associated clinical features	Chromosomal location	Pancreatic neuroendocrine tumor type
MEN1	Primary hyperparathyroidism Pituitary tumors Less commonly ▪ Adrenocortical tumors ▪ Carcinoid tumors ▪ Nonmedullary thyroid tumors	11q13	Nonfunctional Gastrinoma Insulinoma Various
Von Hippel-Lindau disease (VHL)	Pheochromocytoma (often bilateral) Retinal and cerebellar hemangioblastomas Renal cell carcinoma	3p25-26	Nonfunctional Various, including cystic tumors
Neurofibromatosis 1 (von Recklinghausen disease)	Neurofibromas Café au lait spots Pheochromocytoma	17q11.2	
Tuberous sclerosis	Cardiac rhabdomyomas Renal cysts Angiomyolipomas	9q33.34 and 16p13.3	

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Graphic 70019 Version 5.0

Clinical features of functional pancreatic neuroendocrine tumors

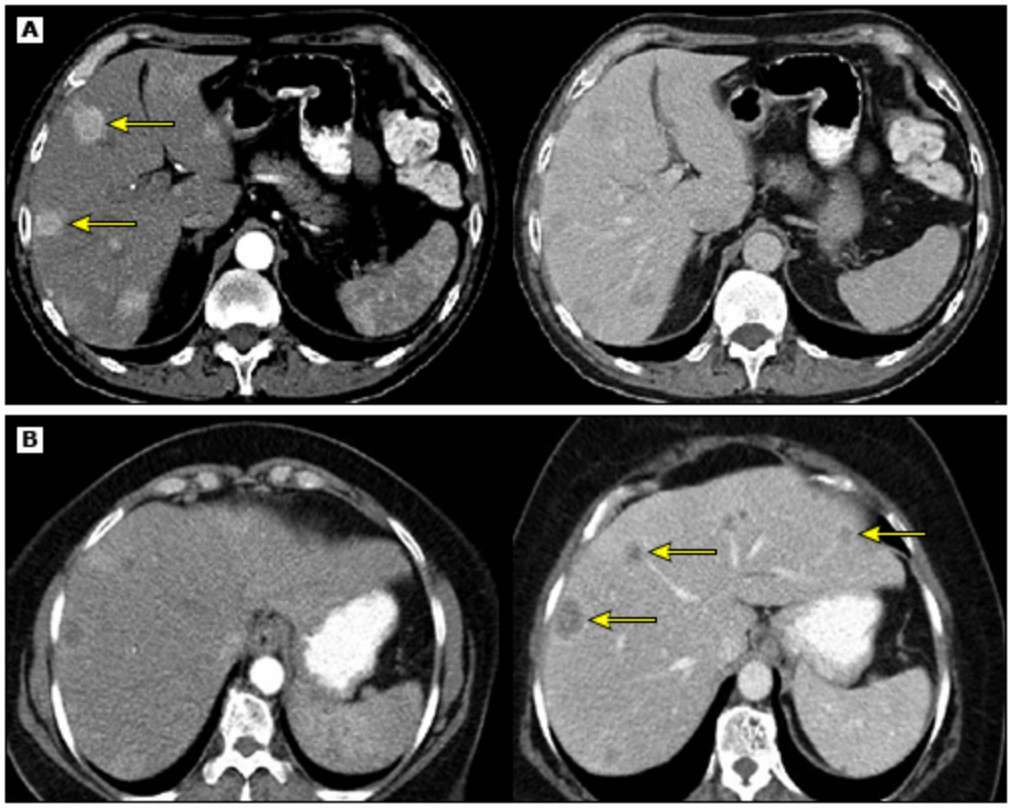
Name	Biologically active peptide(s)	Incidence (new cases/10^6 population/year)	Tumor location	Most com symptoms
Most common syndromes				
Insulinoma	Insulin	1 to 3	▪ Pancreas (>99%)	Hypoglycemi syndromes (Whipple's tri
Zollinger-Ellison syndrome	Gastrin	0.5 to 2	▪ Duodenum (70%) ▪ Pancreas (25%) ▪ Other sites (5%)	Abdominal pa gastroesopha reflux, diarrh duodenal ulc PUD/GERD
Less common syndromes (additional, rarer syndromes also exist)				
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA syndrome)	Vasoactive intestinal peptide	0.05 to 0.2	▪ Pancreas (90%, adult) ▪ Other (10%, neural, adrenal, periganglionic)	Diarrhea, hypokalemia, dehydration
Glucagonoma	Glucagon	0.01 to 0.1	▪ Pancreas (100%)	Rash, glucose intolerance, necrolytic mi erythema, we loss
Somatostatinoma	Somatostatin	Rare	▪ Pancreas (55%) ▪ Duodenum/jejunum (44%)	Diabetes mel cholelithiasis, diarrhea
ACTHoma/Cushing's syndrome	ACTH	Rare	▪ Pancreas (4 to 16% all ectopic Cushing's)	Cushing's syr
Pancreatic NET causing carcinoid syndrome	Serotonin	Rare	▪ Pancreas (<1% all carcinoid syndrome)	Flushing, diar
PTHrp-oma (hypercalcemia)	PTHrp, others unknown	Rare	▪ Pancreas	Symptoms du hypercalcemi (mimics prim hyperparathy

PUD: peptic ulcer disease; GERD: gastroesophageal reflux disease; WDHA: watery diarrhea, hypokalemia, and achlorhydria; NET: neuroendocrine tumor; PTHrp: parathyroid hormone-related protein.

Adapted with permission from: Jensen RT, Cadiot G, Brandi ML, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95:98. Copyright © 2012 S. Karger AG, Basel.

Graphic 111380 Version 4.0

CT of neuroendocrine tumor liver metastases

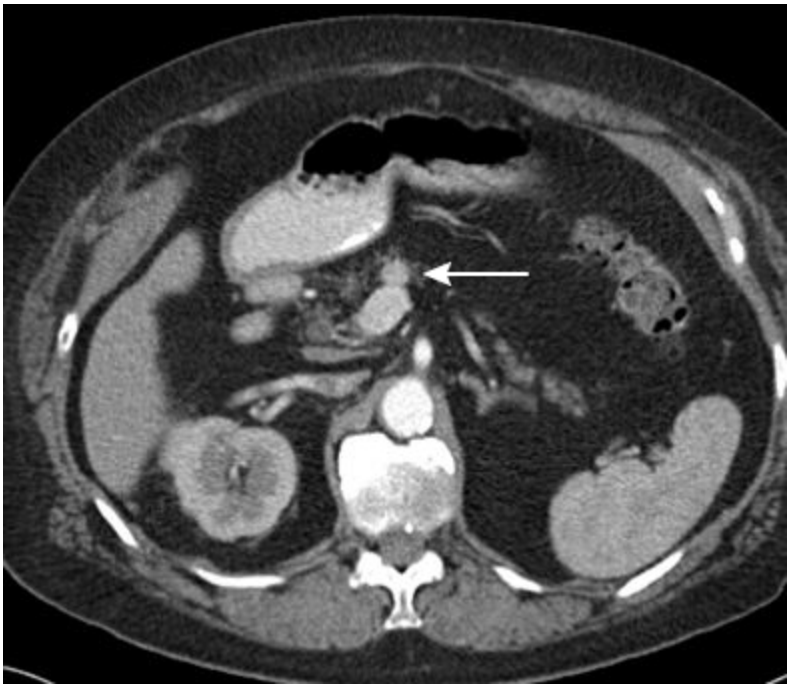


In patient A (top two images), the hypervascular liver metastases are more clearly observed on the arterial phase (left) compared to the portal venous phase (right); whereas in patient B (lower two images), the liver metastases are not as hypervascular and more clearly delineated on the portal venous phase (right) compared to the arterial phase (left).

CT: computed tomography.

Graphic 52935 Version 3.0

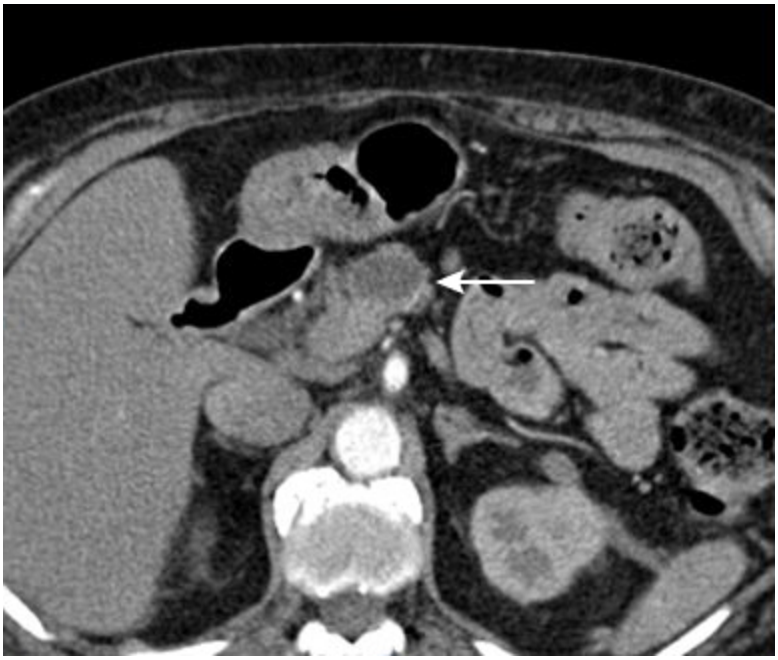
Axial image of a contrast-enhanced CT scan demonstrating a subcentimeter enhancing pancreatic neuroendocrine tumor



CT: computed tomography.

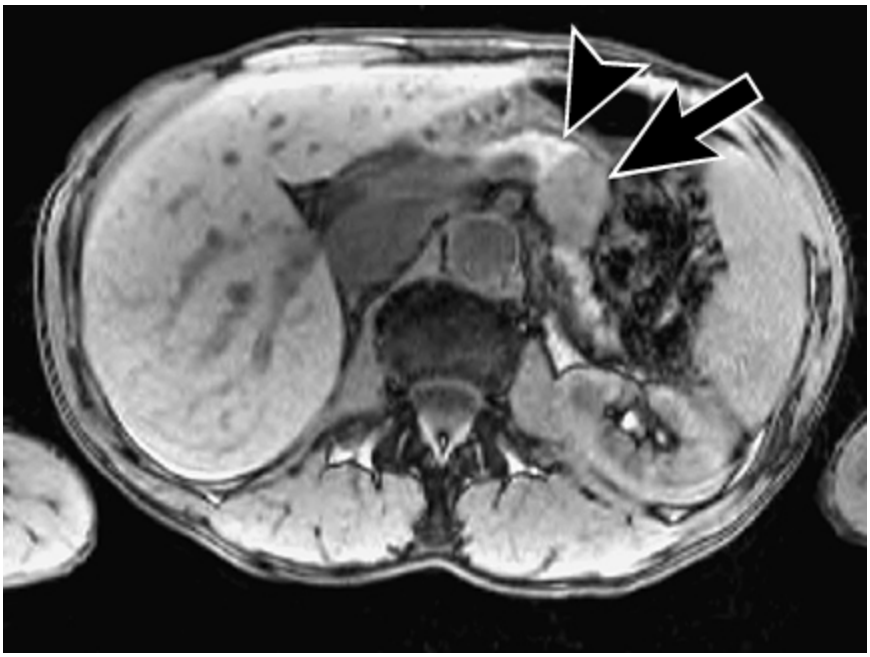
Graphic 69231 Version 3.0

Axial image of a contrast enhanced CT of the abdomen demonstrating a cystic pancreatic neuroendocrine tumor



Graphic 62453 Version 2.0

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

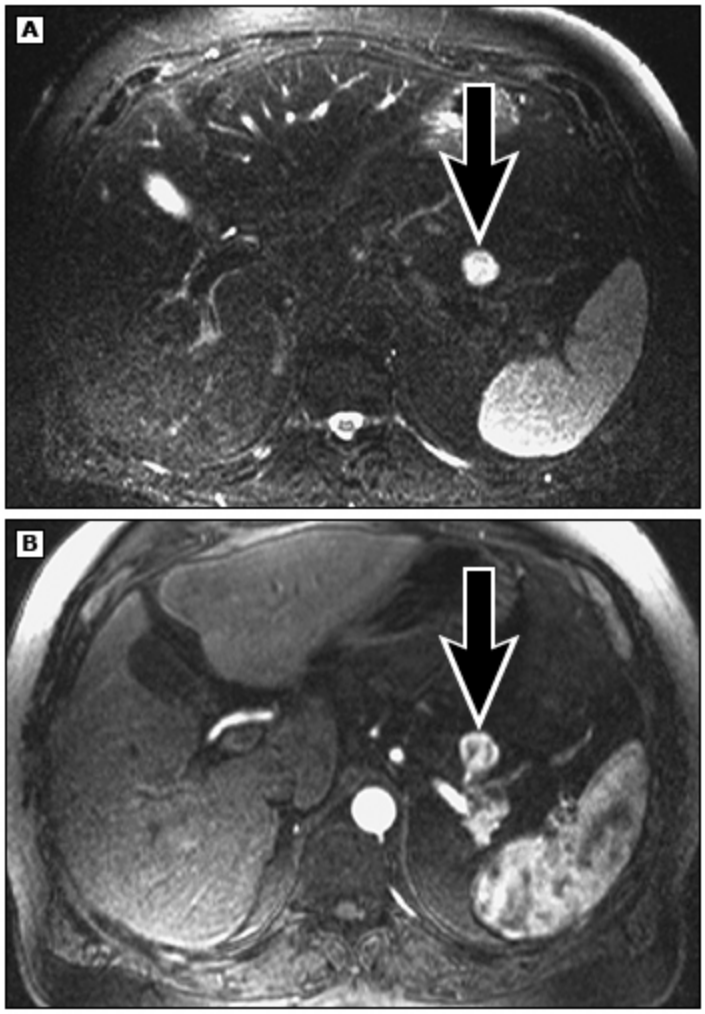


Malignant neuroendocrine tumor of the pancreas. T1-weighted gradient echo image of abdomen demonstrates mass (arrow) near junction of pancreatic body and tail. Note that mass (arrow) is lower in signal intensity than adjacent normal pancreatic parenchyma (arrowhead).

MRI: magnetic resonance imaging.

Graphic 59487 Version 5.0

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



Pancreatic neuroendocrine tumor.

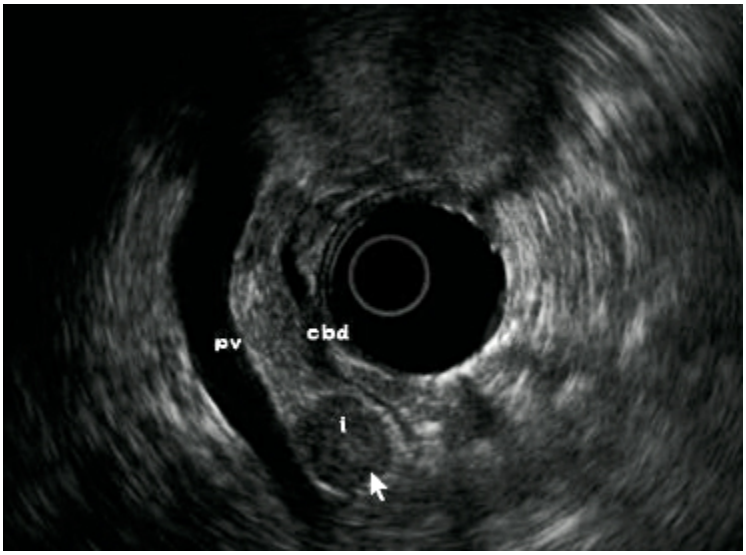
(A) Fat-suppressed T2-weighted image shows small high-signal intensity mass (arrow) involving tail of pancreas.

(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

Endosonographic image of an insulinoma

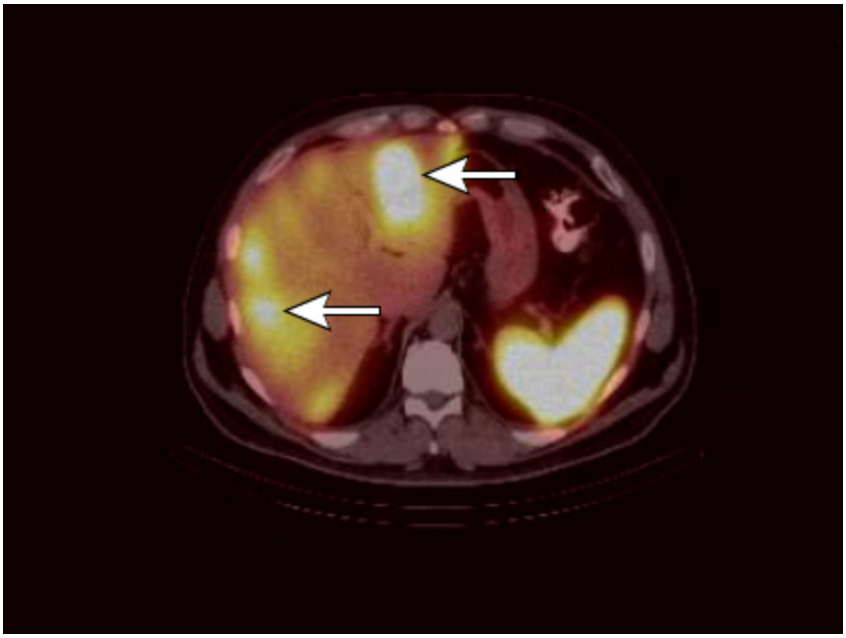


Endosonographic image of an insulinoma detected in a woman with recurrent episodes of hypoglycemia showing a well demarcated, homogenous hypoechoic mass lesion in the head of the pancreas adjacent to the common bile duct (CBD, above) and portal vein (PV, below) without invasion of these structures. The lesion had not been detected with other imaging modalities.

Courtesy of Maryam Moini, MD, and Seyed Alireza Taghavi, MD.

Graphic 74947 Version 2.0

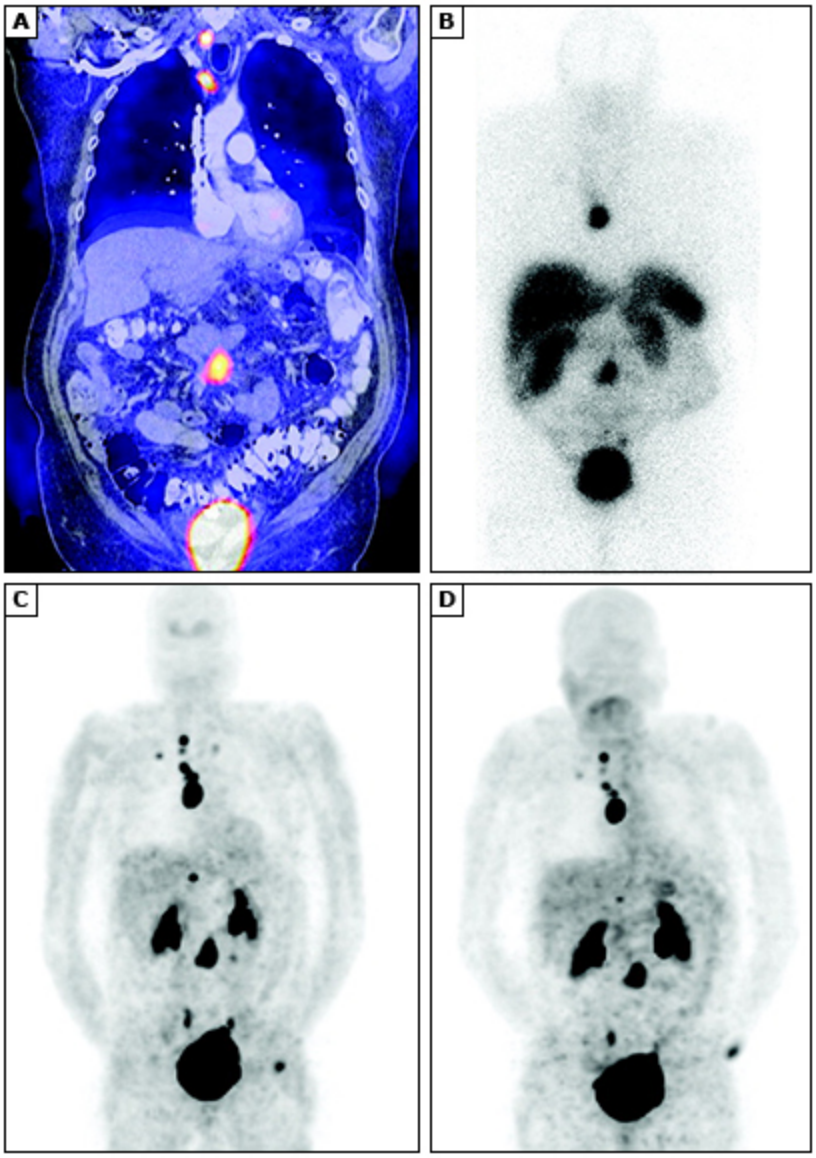
Liver metastases demonstrating high-grade radiotracer uptake on somatostatin receptor scintigraphy fused with SPECT/CT scan



SPECT: single photon emission computed tomography; CT: computed tomography.

Graphic 72923 Version 4.0

Functional PET imaging techniques for metastatic gastrointestinal tract neuroendocrine tumor



(A) Fused 18F-dihydroxy-phenyl-alanine (18F-DOPA) positron emission tomography (PET)/computed tomography scan

(B) Somatostatin receptor scintigraphy

(C) 18F-DOPA PET

(D) 11C-5-hydroxy-tryptophan (11C-5-HTP) PET of an 80-year-old male patient with metastatic neuroendocrine tumor of the gastrointestinal tract

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From: Koopmans KP, Neels OC, Kema IP, et al. Improved staging of patients with carcinoid and islet cell tumors with 18F-dihydroxy-phenyl-alanine and 11C-5-hydroxy-tryptophan positron emission tomography. J Clin Oncol 2008; 26:1489.

Graphic 81388 Version 6.0

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

Exocrine pancreatic cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*. This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia.
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 and <1 cm in greatest dimension
T1c	Tumor 1 to 2 cm in greatest dimension
T2	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0

T1	N0	M0	IA
T1	N1	M0	IIB
T1	N2	M0	III
T2	N0	M0	IB
T2	N1	M0	IIB
T2	N2	M0	III
T3	N0	M0	IIA
T3	N1	M0	IIB
T3	N2	M0	III
T4	Any N	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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Contributor Disclosures

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