Seminars in ULTRASOUND CT and MRI

Multimodality Imaging of the Pancreatic Neuroendocrine Tumors

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Pancreatic neuroendocrine tumors (PNETs) are uncommon pancreatic masses which arise from amine precursor and uptake decarboxylation cells. They are classified as functional or nonfunctional based on the associated clinical symptoms. Insulinomas and gastrinomas are the most common functional tumors. PNETs are also classified based on their biologic behavior as benign or malignant. While most PNETs are sporadic, a small percentage are associated with syndromes such as multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, and are usually multiple in those cases. On imaging, most PNETs are circumscribed and hypervascular masses; however, larger tumors are often heterogeneous. The presence of calcification, cystic degeneration, and necrosis increases the likelihood of malignancy and carries a poor prognosis. Metastases have similar imaging appearance to the primary lesion and are most commonly seen in the liver, locoregional lymph nodes, and bone. This article reviews the pathologic and radiologic features of pancreatic neuroendocrine tumors as well as imaging mimics and their distinguishing features.
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Introduction

Pancreatic neuroendocrine tumors (PNETs) are a subset of gastroenteropancreatic neuroendocrine tumors as classified by the World Health Organization. Neuroendocrine tumors of the foregut are most commonly found in the pancreas, duodenum, or stomach. PNETs were formerly called islet cell neoplasms; however, they are now thought to arise from pluripotential cells in ductal epithelium.[1] PNETs are a heterogeneous group of tumors, presenting with a wide variety of symptoms and biological behavior which can range from indolent to aggressive.[2] PNETs are typically slow-growing masses, representing 1%-10% of all pancreatic neoplasms, with an incidence of 4-5/1,000,000 population.[3,4] On average, they occur between the ages of 51 and 57 and have an equal sex predilection.[1] The incidence of PNETs has increased over the past 30 years, with advances in cross-sectional imaging and discovery of incidental asymptomatic lesions likely contributing to this trend.[2] Most PNETs are sporadic but a small percentage are part of an inherited syndrome, including multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau syndrome (Fig. 1), and neurofibromatosis type 1 (NF-1). PNETs associated with these syndromes tend to be multiple.

PNETs can be hyperfunctioning, producing metabolically active hormones such as insulin, glucagon, gastrin, vasoactive intestinal peptide (VIP) and somatostatin, which give rise to diverse clinical symptoms. Hyperfunctioning tumors tend to present at a smaller size due to the accompanying clinical symptoms. Insulinomas are the most common functioning neuroendocrine tumors, accounting for at least 40% of all functioning PNETs.[5] Patients with an insulinoma may present with hypoglycemic attacks, with biochemical workup showing low-fasting serum glucose and elevated insulin levels. Gastrinomas are the second most common functioning PNETs. While most gastrinomas arise from the pancreas, 10% are extrapancreatic, often located in an anatomic segment defined by the common duct and cystic duct superiorly, the third portion of the duodenum inferiorly, and the pancreatic head and uncinate process medially, the so-called gastrinoma triangle (Fig. 2). Patients can sometimes present with Zollinger-Ellison syndrome, characterized by severe gastroesophageal reflux and ulcer disease precipitated by elevated gastrin levels. The remainder of functioning PNETs account for at most 5% of this tumor class, and include glucagonomas, somatostatinomas, corticotropinomas, and VIPomas.

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Figure 1 von Hippel-Lindau disease with PNET. (a, b) Axial arterial phase CT images demonstrates a hypervascular pancreatic head mass (white arrow), consistent with a neuroendocrine tumor. Also present are enhancing spinal cord lesions representing hemangioblastomas (black arrowheads), multiple renal cysts (white arrowheads) and pancreatic cystic lesions (black arrows), which could represent simple cysts vs serous cystadenomas.

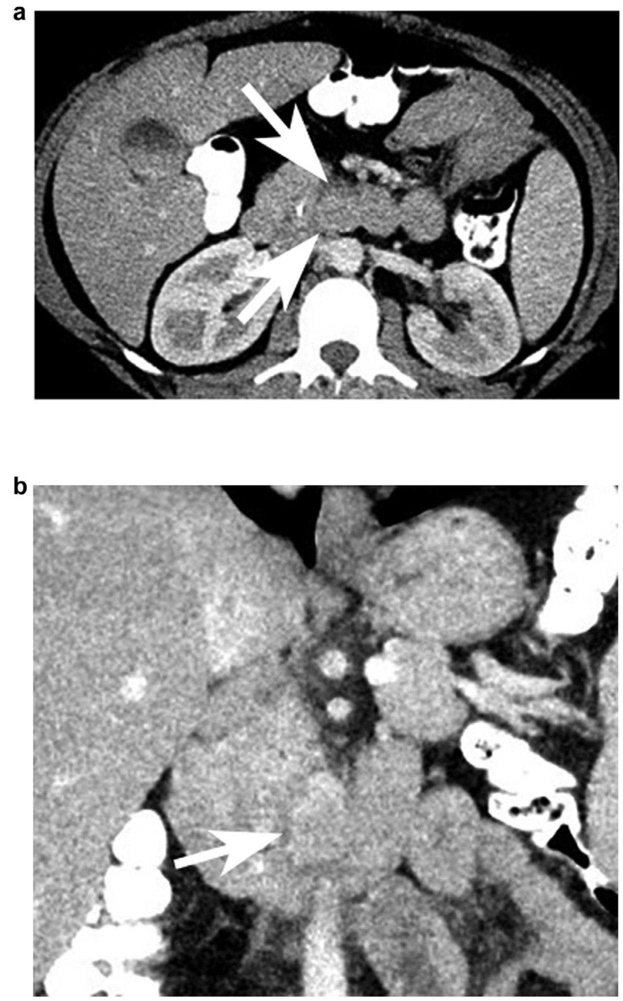

Figure 2 Peripancreatic NET. 41-year-old woman with abdominal pain and choledocholithiasis. A peripancreatic mass was incidentally found on EUS performed to evaluate the common bile duct. Axial (a) and coronal (b) CT contrast-enhanced images in portal venous phase demonstrate a nearly isointense pancreatic mass (arrow) in the medial aspect of the gastrinoma triangle. The patient underwent Whipple procedure and was found to have a well-differentiated peripancreatic (G1) NET at pathologic analysis.

Glucagonomas are associated with migratory necrolytic dermatitis and diabetes. Symptoms of VIPomas include watery diarrhea and flushing. Both glucagonomas and VIPomas often manifest as large solid pancreatic masses.[6]

Nonfunctioning tumors account for 65%-85% of newly diagnosed PNETs.[7] Nonfunctioning tumors do not produce active hormones and therefore are more likely to present with larger lesion size and locally advanced disease. Large tumors have a higher malignant potential with metastases most commonly to peripancreatic lymph nodes, liver and, less commonly, bone.[7]

A variety of noninvasive imaging modalities have been utilized for diagnosis and staging of neuroendocrine tumors. These can be broadly divided into anatomical or morphologic imaging, such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), and functional imaging, including nuclear scintigraphy methods such as somatostatin receptor scintigraphy, conventional ^{18}F-FDG PET-CT, and ^{68}Gallium-DOTATATE PET. Surgery is the treatment of choice for PNETs, consisting of either partial pancreatectomy or enucleation of the primary tumor. Tumor characterization and staging are important to determine treatment planning. CT and MRI are the mainstay imaging modalities used for tumor detection and evaluation of extent of disease, due to easy availability and better contrast and spatial resolution compared to US and nuclear scintigraphy. In this review article, we discuss the pathologic basis, biological behavior, imaging features, treatment options and prognosis of PNETs, as well as potential pitfalls and mimics on cross-sectional imaging.

Pathologic Evaluation

PNETs have malignant potential and therefore, pathologic characterization of tumor grade and cell differentiation is necessary

Table 1 Summary of WHO Classification of PNETs (Adapted From Lewis et al)[7]

Classification	WHO Grade	Features
Well differentiated	G1	Benign, confined to the pancreas, +/- vascular or perineural invasion
Well differentiated	G2	Low-grade malignant—gross local invasion or metastasis
Poorly differentiated (neuroendocrine cancer)	G3	High-grade malignant—>10 mitoses per 10 high-power fields

to predict biological behavior and potential for metastases. Tumor grading and risk for malignancy take into account factors such as tumor size, mitotic rate, presence of metastatic disease, local invasion, perineural spread, angioinvasion, and Ki-67 proliferation index. While histopathologic classification plays an important role in risk stratification and prognosis for the patient, it cannot be used to diagnose malignancy; malignancy can only be confirmed by the presence of local spread, vascular invasion, lymphadenopathy, or metastatic disease, rather than on specific microscopic features of the tumor. The World Health Organization (WHO) classification was modified in 2010 to include the tumor grade and differentiation[4,8,9] (Table 1).

The European Neuroendocrine Tumor Society factors in TNM staging, tumor grade[4,8,10,11,12], mitotic count, and Ki-67 labeling index.[11-13]

The TNM staging classifies PNETs based on tumor location and size, nodal status, and metastasis.[2]

The tumor (T) stage is classified as

- T0 (no primary tumor evident),
- T1 (<2 cm and confined to the pancreas),
- T2 (>2 cm, confined to the pancreas),
- T3 (tumor spread beyond the pancreas, without celiac or SMA involvement), and
- T4 (vascular involvement).

Nodal status (N) can be classified as

- N0 (no lymph node involvement) and
- N1 (lymph nodes are involved).

Metastatic stage (M) is either

- M0 (absence of metastases) and
- M1 (metastases present).

Role of Imaging

Recent advances in CT and MRI imaging have allowed for increased detection of small PNETs. The majority of small tumors are nonfunctioning, accounting for 60%-80% of newly diagnosed PNETs.[14] Noninvasive imaging plays a crucial role in primary detection, staging of PNETs and surgical planning, especially nonfunctioning tumors which may be clinically occult. Detection of local extrapancreatic disease and distant metastases can be accomplished with CT, MRI, and nuclear scintigraphy. Similarly, evaluation of treatment response can be assessed with imaging follow-up.

Imaging Modalities

US

Transabdominal US can be used in detection of PNETs; however, it plays a limited role. In many cases, visualization of the pancreatic body and tail is suboptimal due to obscuration by bowel gas, which reduces sensitivity of tumor detection. The sensitivity of transabdominal US for detection of PNETs ranges between 20% and 80%.[15-18] On transabdominal US, PNETs are typically seen as circumscribed masses with smooth margins (Fig. 3).[7] Large PNETs can appear heterogeneous with areas of cystic degeneration or necrosis. Although visualization of the upper abdomen is limited, occasionally regional lymphadenopathy and hepatic metastases can be detected.

Endoscopic US (EUS) performed with a high frequency probe can improve tumor detection in a close proximity organ such as the pancreas. A detection rate of 80%-100% is reported for PNETs with EUS,[19-22] with a slightly lower sensitivity for insulinomas.[23] Sensitivity for pancreatic tail tumors may be decreased due to limited visualization of the pancreatic tail.[24] EUS depicts similar features as transabdominal US, however with improved spatial resolution due to proximity to the lesion. EUS may also identify peripancreatic lymphadenopathy consistent with regional spread of disease.

CT

CT is the most widely available modality for initial evaluation of PNETs. Recent advances in CT technique and image acquisition have resulted in improved spatial resolution and shortened scanning time. Multiphase multidetector CT can now be utilized to dynamically visualize the pancreas in different phases of enhancement, and increase sensitivity of tumor detection. The scanning protocol can be tailored to the specific indication, such as initial tumor detection, staging, or surveillance of treatment response. Multiphase CT protocol typically includes an arterial dominant acquisition followed by a portal venous phase obtained at 60-80 seconds after injection. The arterial dominant phase can be performed either early (angiographic phase, 20-30 seconds) or slightly later, in the pancreatic phase, typically 20 seconds after the early arterial phase. Both of these phases are effective in detection of PNETs, and based on current literature, it is uncertain whether there is a clear advantage of using one over the other.[17] A rapid infusion of intravenous contrast (3-4 cc/s) is needed for optimal arterial phase imaging. Attention to proper arterial phase technique with regard to both contrast bolus administration and timing is absolutely critical for detection of PNETs. Arterial phase imaging increases the

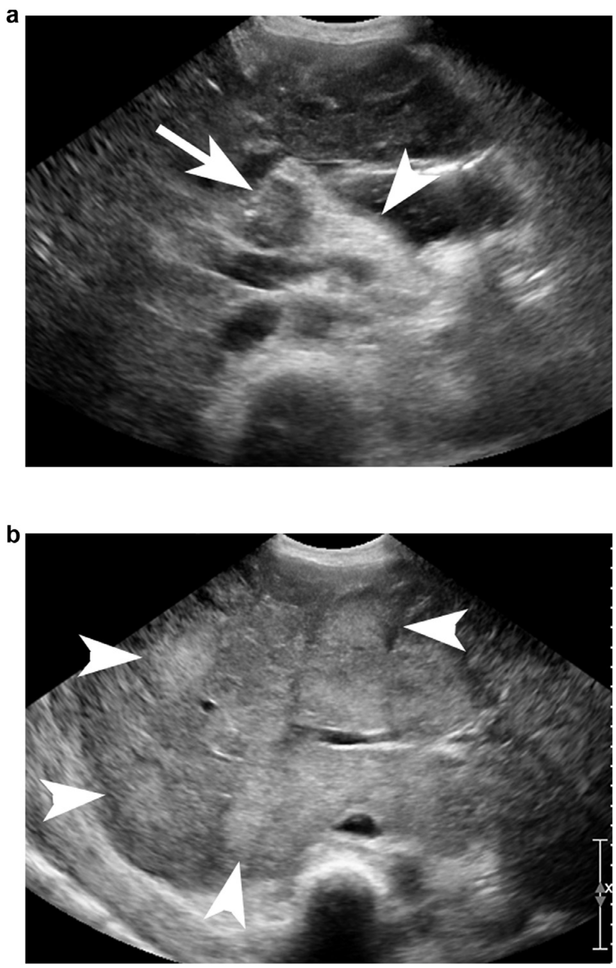

Figure 3 Metastatic PNET on US. (a) Grayscale US image demonstrates a hypoechoic mass in the pancreatic head (arrowhead) and normal upstream pancreas (arrow). (b) Additional image demonstrates multiple echogenic hepatic masses (arrows) consistent with metastases.

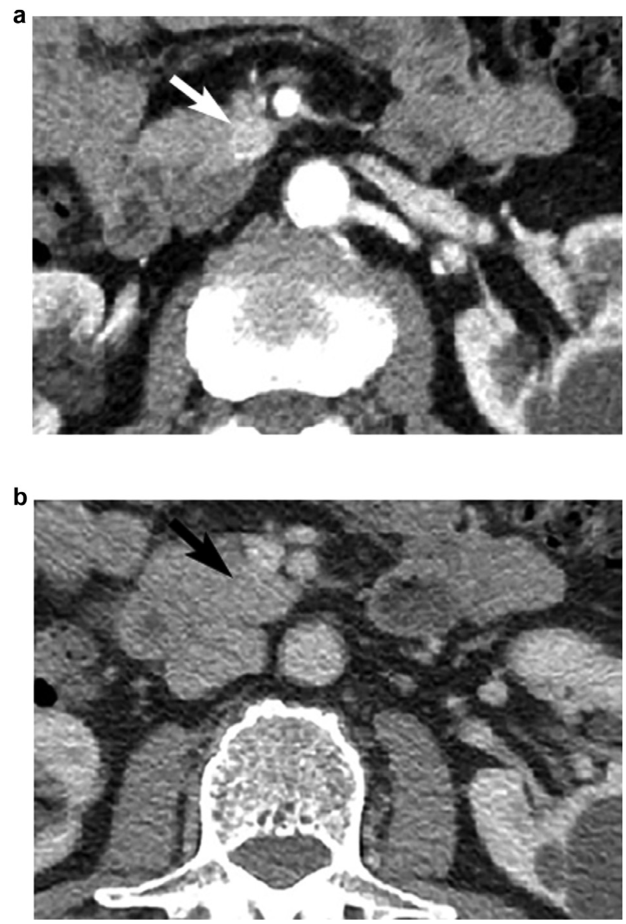

Figure 4 Insulinoma. 70-year-old man with hypoglycemia. (a) Axial CT image acquired in the arterial phase demonstrates a hypervascular pancreatic uncinate process mass, intensely enhancing as compared to pancreatic parenchyma (white arrow). (b) Note that the mass equilibrates with pancreatic parenchyma (black arrow) in the venous phase, making it very difficult to detect, as it is causing only minimal contour deformity of the uncinate process. Pathologic analysis revealed an insulinoma.

conspicuity of small PNETs, as they are usually hypervascular, and frequently very difficult to detect on portal venous phase imaging, due to washout of contrast from the tumor and equilibration with pancreatic parenchyma (Fig. 4). In comparison, studies between arterial phase and portal venous phase imaging for tumor detection, a sensitivity of 83%-88% was reported with arterial phase compared to 11%-76% with portal venous phase.[17,20,25,26] CT also plays a critical role in staging and detection of advanced locoregional disease and distant metastases. Promising results for detection of neuroendocrine tumors have been reported using dual-energy CT, with one study showing a combination of monochromatic imaging and iodine maps resulting in a 96% sensitivity for insulinoma detection, compared to 69% for conventional CT.[27]

PNETs are generally well defined, uniformly hypervascular masses on arterial phase CT images, due to their rich capillary network, which results in more rapid and intense enhancement than pancreatic parenchyma (Fig. 4). The hypervascularity of these tumors is essential in detection, as small PNETs may not disturb the contour of the pancreas. This is also a key characteristic in distinguishing PNETs from pancreatic adenocarcinoma, which is almost always hypoenhancing on arterial phase imaging. On portal phase imaging, PNETs can be hypo-, iso-, or hyperdense as compared to normal pancreatic tissue. While the majority of masses are hypervascular on arterial or pancreatic phase imaging, PNET enhancement is variable, and some will be hypovascular. Studies have shown that a minority of tumors will be better seen, or only seen, on portal venous phase imaging.[17] In the study by Fidler et al, which only included insulinomas, 3/25 tumors were hypoattenuating, and the same number were more conspicuous on portal venous phase imaging. Additionally, some PNETs show delayed enhancement, best visualized on portal phase imaging. These variabilities in enhancement kinetics make multiphase imaging essential for detection of PNETs. Functioning PNETs, which are less common compared to the nonfunctioning variety, are typically small in size at the time of presentation. Nonfunctioning tumors are diagnosed at a larger size (mean size 4 cm), and tend to show heterogeneous enhancement with areas of necrosis or cystic degeneration.

Masses which are more biologically aggressive tend to spread to regional lymph nodes, locally invade structures such as the retroperitoneum, and metastasize to the liver. Bone metastases from neuroendocrine tumors are not uncommon, observed in 42% of patients at autopsy.[27] Risk for bone metastases may vary depending on the organ of neuroendocrine tumor origin, with a suspected higher risk from pulmonary tumors. Metastases can be osteolytic or osteoblastic; osteolytic metastases are associated with worse survival than osteoblastic lesions.[28,29]

Several studies have looked at CT findings to preoperatively stratify tumors by pathologic (WHO) grade. Takumi et al showed that G1 tumors were more likely to be hyperattenuating on portal venous phase than G2 tumors.[30] Belousova et al found that G2 tumors had statistically significant decreased arterial phase enhancement (tumor:pancreas ratio of <1.1), delayed venous enhancement, and larger size (20 mm), than their G1 counterparts.[30] Zamboni et al found that G1 tumors were more often hypervascular on arterial phase imaging, while G3 tumors were larger (>20 mm) and more heterogeneous.[31,32]

Occasionally, PNETs can be cystic, especially larger and nonhyperfunctioning tumors (Fig. 5). In such cases, a hypervascular rim may be seen after contrast administration in up to 90% of cases (Figs. 5 and 6).[33] This is a crucial finding in considering PNET in the differential diagnosis, rather than mistakenly categorizing the lesion as a more commonly encountered cystic pancreatic tumor, such as an intraductal papillary neoplasm, serous cystadenoma or mucinous cystadenoma/cystadenocarcinoma. Pancreatic duct involvement is not a typical feature of PNETs and is often a distinguishing feature between a pancreatic adenocarcinoma and a neuroendocrine tumor. PNETs can uncommonly cause upstream main pancreatic duct dilatation due to mass effect in large tumors.[1,34,35] Ductal dilatation can also be seen in the setting of small tumors due to fibrotic stricture caused by release of serotonin and related metabolites (Fig. 7).[36]

Other atypical CT imaging features include the presence of calcifications and vascular encasement. Calcifications can be seen in up to 20% of nonfunctioning PNETs, and are often a sign of malignancy (Fig. 8).[14] Detection of vascular involvement is important for staging and presurgical workup. Arterial encasement is more commonly seen than venous encasement and can be reliably identified with thin section arterial phase imaging as soft tissue attenuation surrounding the vessels.

Tumor thrombus from direct invasion is a relatively distinct finding in PNETs, as opposed to other pancreatic malignancies (Fig. 9). The true incidence of tumor thrombus in PNETs is difficult to derive from the literature due to the sparsity of reports. A 3.8% incidence of portal venous thrombectomy at surgery has been reported and portal vein invasion[37] was found in 3.9% of patients on angiography.[38] However, more recent literature suggests that this finding may be more common than previously thought. A study looking at dual-phase CT of nonfunctioning PNETs found a 17% incidence[25] and a retrospective study from 2012 reviewing preoperative CT scans in patients with nonfunctioning PNETs found tumor thrombus in 30% of cases.[39] These studies suggest that technical improvements in cross-sectional imaging may make this a more commonly seen finding going forward. The portal vein is probably the most commonly affected vessel, with the superior mesenteric and splenic veins also at risk. PNETs are known for abundant production of proangiogenic and vascular growth factors, which may account for the predilection for vascular invasion; however, this has not been proven. On MRI or CT, intraluminal enhancement will be seen in cases of tumor thrombus, and the vessel is often expanded (Fig. 9). In contradistinction, bland thrombus will not demonstrate enhancement, and the vessel will be narrowed if tumor encasement is the cause of the bland thrombus.[40] Given the rarity of this finding in other pancreatic tumors, the presence of vascular invasion should elevate PNET in the differential diagnosis of a pancreatic tumor.

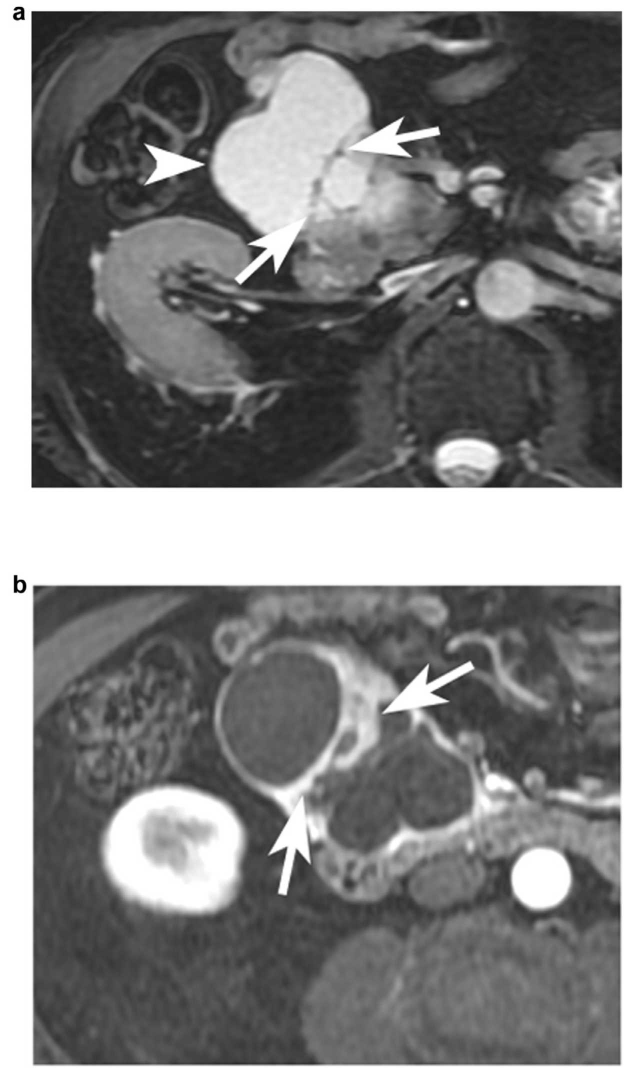

Figure 5 Cystic nonfunctioning PNET. (a) Axial balanced gradient echo and (b) axial fat-suppressed postcontrast MR images demonstrate a large cystic mass in the pancreatic head (arrowhead) with thick irregular septae (arrows). The septations demonstrate avid enhancement on postcontrast imaging (arrows in image b), a finding which should make the radiologist suspect a cystic neuroendocrine tumor over other cystic pancreatic neoplasms.

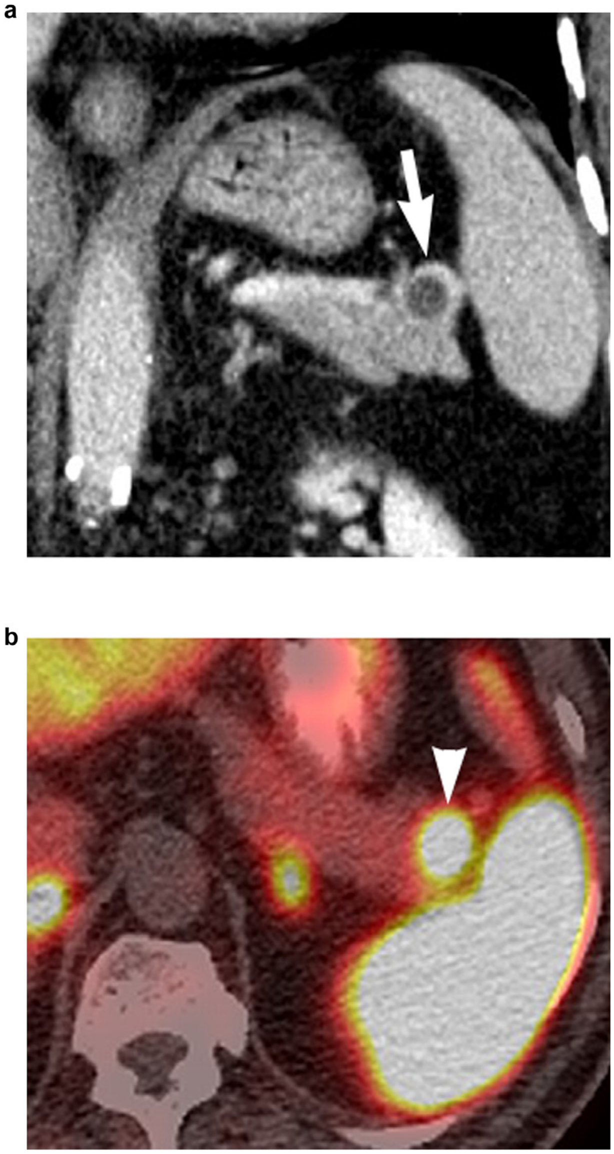

Figure 6 58-year-old with abdominal pain. (a) Coronal contrast-enhanced CT image shows a cystic pancreatic tail mass with a thin peripheral hyperenhancing rim (arrow). (b) Axial ^{68}Ga-Dotatate PET/CT-fused image demonstrates avid radiotracer uptake in the pancreatic tail mass (arrowhead), consistent with a neuroendocrine tumor.

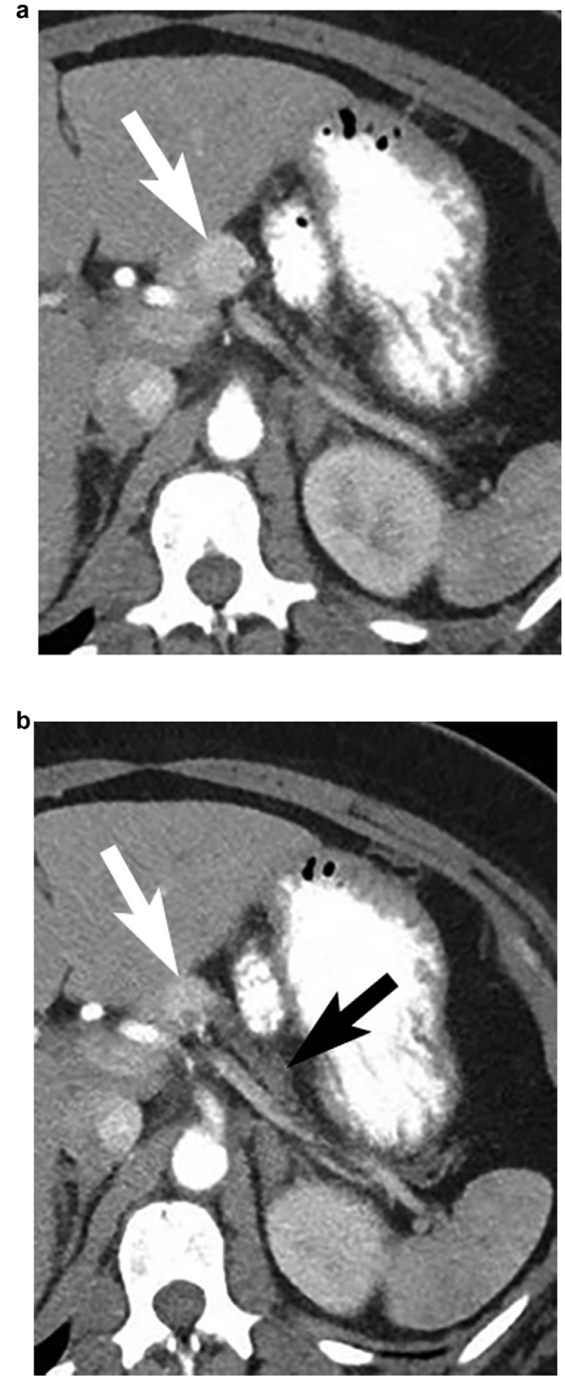

Figure 7 PNET causing pancreatic ductal dilatation. (a) Axial contrast-enhanced CT image demonstrates an intensely enhancing pancreatic mass in the pancreatic neck which was pathologically proven to be neuroendocrine tumor (white arrow). (b) Axial CT image at a slightly higher level shows the mass (white arrow) and upstream pancreatic ductal dilatation (black arrow). Neuroendocrine tumors can cause pancreatic ductal dilatation from either mass effect or desmoplastic reaction.

MRI

MRI, along with CT, is a mainstay of pancreatic imaging. Recent advances in MRI technique which allows for faster image acquisition with breath hold sequences and reduced artifacts have made MRI an effective tool for problem solving and evaluating equivocal findings on CT. MRI uses nonionizing radiation and has better contrast resolution compared to CT; however, MRI is not widely available and remains an expensive exam. There is an overall sensitivity of 74%-94% and specificity of 78%-100% for tumor detection with MRI.[41-43] Typical MR protocol for pancreatic imaging includes axial and coronal breath hold half-Fourier spin echo, axial fat-suppressed T2 fast spin echo, diffusion-weighted imaging (DWI) (with short and long b values and corresponding ADC map), and T1-weighted fat-suppressed sequences before contrast administration. Multiphase dynamic gadolinium-enhanced imaging is performed with arterial phase T1-weighted 3D fat-suppressed images at 20-25 seconds, followed by additional venous and delayed phase series.

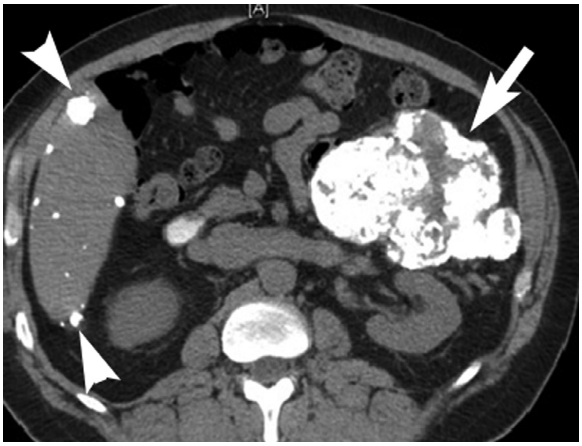

Figure 8 Calcified PNET. Axial unenhanced CT image demonstrates a heavily calcified PNET in the pancreatic tail (arrow) and widespread calcified liver metastases (arrowheads). The presence of calcification is often a sign of a biologically aggressive tumor.

a

b

Figure 9 PNET with vascular invasion. 34-year-old man with abdominal pain. Axial (a) and coronal (b) CT contrast-enhanced images obtained in the late arterial phase demonstrate a large hypervascular left upper quadrant mass centered on the pancreatic tail (curved arrow in image a) and invading the spleen (arrows). There is invasion into the splenic vein (arrowhead) and large perisplenic varices due to splenic vein occlusion. The patient underwent distal pancreatectomy and splenectomy and was found to have a G1 PNET with splenic invasion.

Normal pancreatic signal on T1-weighted imaging is hyperintense due to an abundance of proteinaceous material, making PNETs hypointense to background pancreatic parenchyma on unenhanced T1-weighted images (with or without fat suppression). In a study conducted by Theoni et al, unenhanced T1-weighted fat-suppressed sequence had the highest sensitivity at 75% for optimal PNET imaging. On T2-weighted images, PNETs have variable signal; most are hyperintense, however intermediate to low signal may be seen in some cases. DWI images may also help in tumor detection. DeRobertis et al found that DWI was more sensitive than conventional sequences for PNET detection.[44] The enhancement characteristics on MR are similar to CT. PNETs are usually hypervascular on arterial phase imaging (Fig. 10); however, a minority of tumors may only be visible on the venous or unenhanced phases.[45] Similar to CT, small tumors tend to enhance homogeneously, whereas larger neoplasms demonstrate heterogeneous enhancement (Fig. 11). Larger masses or peripancreatic metastases may cause local mass effect resulting in biliary or pancreatic duct dilation.

As with CT, MRI appears to have the ability to predict tumor biology. Similar to CT, higher grade (G2-G3) tumors are more likely be hypovascular on arterial phase MR imaging as compared to G1 tumors, and more likely to be larger and enhance heterogeneously.[45] Several authors have found an inverse correlation with tumor grade and ADC values[45-49], and between ADC values and tumor Ki-67 labeling index.[46,50] Kim et al also showed an inverse relationship between ADC values and WHO grade, however found that ADC values were not accurate in predicting recurrence-free survival.[51] Ill-defined tumor borders on MRI also show a consistent correlation with higher pathologic grade.[45,46,48,49] While CT and MR characteristics of PNETs with regard to histologic composition and biologic behavior are still being worked out, the growing body of literature suggests there is potential for both modalities to guide management and stratify tumors according to extent of resection or malignancy.

Liver and peripancreatic lymph nodes are the most common sites of metastases. Liver metastases have similar T1- and T2-weighted features as the primary lesion (Fig. 11). They also demonstrate moderate to intense early ring-like enhancement.[52] Cystic degeneration may be present in larger lesions.

Nuclear Imaging

Somatostatin Scintigraphy

PNETs often have increased expression of somatostatin receptors (SSR) which makes them an ideal target for nuclear imaging. Five somatostatin receptor subtypes have been identified, of which the subtype 2 is the most commonly expressed. The most common somatostatin scintigraphy technique is octreoscan using indium-diethylenetriaminepentaacetic acid-octreotide 111 (^{111}In-octreotide). Planar and 3D single photon emission computed tomography (SPECT) imaging is performed for detection and localization of PNETs (Fig. 12). The time between radiotracer injection and imaging can span between 4 and 24 hours. The sensitivity of this technique depends on the specific hormone being overexpressed and the overall SSR

Figure 10 PNET on CT, MRI, and DOTATATE-PET/CT. Axial post-contrast CT (a) and MR (b) images demonstrate an avidly enhancing mass in the pancreatic tail (white arrow and arrowhead). (c) Axial ^{68}Ga-DOTATATE PET/CT-fused image shows a hypermetabolic mass in the pancreatic tail (black arrow). No regional or distant metastases were seen on any of the imaging studies. The patient underwent resection with distal pancreatectomy and splenectomy.

expression. The sensitivity is highest for gastrinomas and lowest (50%-70%) for insulinomas, due to low expression of somatostatin receptor scintigraphies.[53]

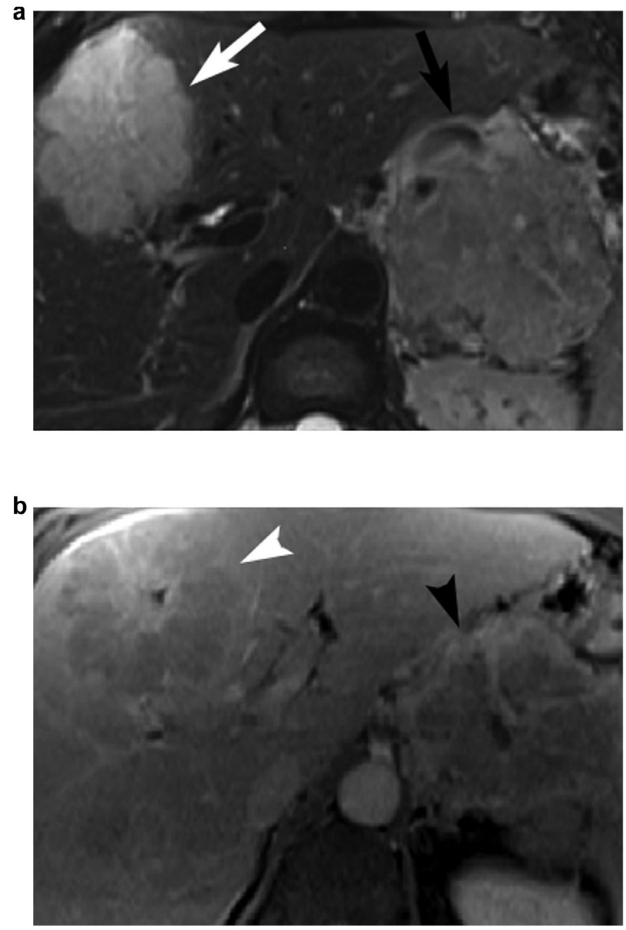

Figure 11 Metastatic PNET on MRI. (a) Axial T2 fat-suppressed image shows a hyperintense mass in the right hepatic lobe (white arrow) and a T2 hyperintense pancreatic body mass (black arrow). (b) On axial delayed postcontrast image, both the hepatic mass (white arrowhead) and the pancreatic body mass (black arrowhead) enhance heterogeneously. Additional similar masses in both hepatic lobes were also present, but are not shown. Biopsy of the hepatic masses revealed well-differentiated neuroendocrine tumor.

Positron Emission Tomography

Positron emission tomography (PET) imaging combined with CT has the advantage of improved lesion localization compared to ^{111}In-Octreoscan. Similar to nuclear scintigraphy, PNETs with increased SSR expression can be localized using positron emitter ^{68}Ga conjugated with octreotide (Fig. 10). The 3 main radiotracers include ^{68}Ga-tetraazacyclododecane tetraacetic acid-octreotate (^{68}Ga-DOTA-TATE), ^{68}Ga-edotreotride, and ^{68}Ga-DOTA-NOC. These octreotide analogs bind to the surface somatostatin receptors within the tumor while being rapidly excreted from nontarget sites. ^{68}Ga-DOTA-TATE has affinity for the somatostatin receptor subtype 2 and therefore may have low sensitivity for detection SSR-subtype 2 poor lesions. Other octreotide analogs such as DOTA-1-NaI-octreotide (DOTA-NOC) have a higher affinity for subtypes 2, 3, and 5.[53] PET allows for high-contrast imaging and detection of occult primary lesions and small liver, lymph node, and bone metastases.

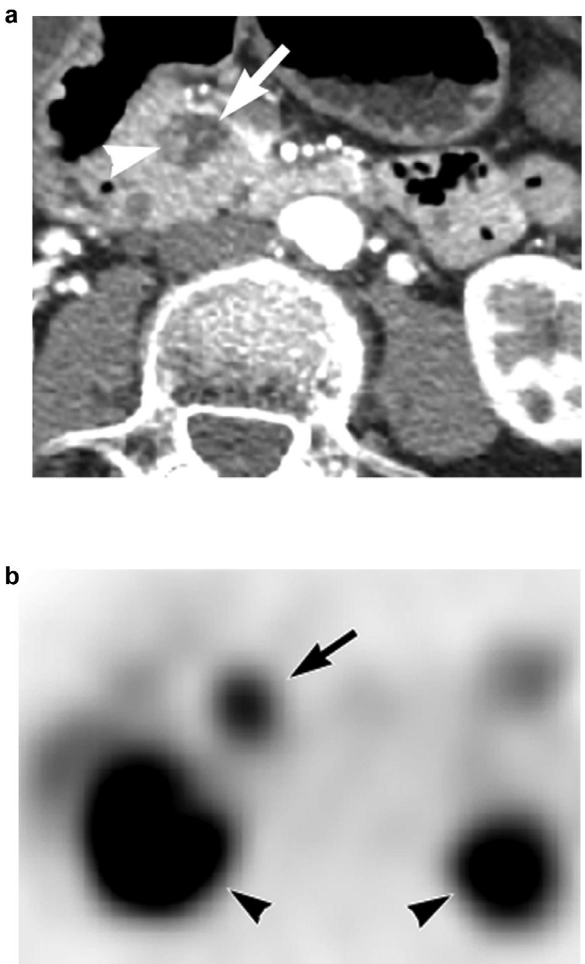

Figure 12 PNET on CT and Octreoscan. (a) Axial contrast-enhanced CT image demonstrates a cystic mass (white arrow) with a solid component (white arrowhead). (b) Axial SPECT image from an octreoscan at the same level as CT shows avid pentetreotide uptake within the pancreatic mass (black arrow), consistent with a neuroendocrine tumor. Physiologic radiotracer uptake is seen in the kidneys (black arrowheads).

A second class of radiotracers commonly used in oncologic imaging, rely on tumor metabolism. ^{18}F-FDG is widely available and a commonly used tracer, in which signal reflects increased glucose turnover within a tumor. ^{18}F-FDG is best suited for detecting poorly differentiated (G3) or aggressive tumors with decreased or no SSR expression (Fig. 13). Evaluation of well-differentiated tumors is limited with ^{18}F due to near normal levels of glucose metabolism.

Typically, PNETs or metastases with either increased somatostatin receptor expression or high-glucose metabolism have increased radiotracer uptake on ^{68}Ga-DOTA-TATE or ^{18}F-FDG PET imaging, respectively. When coupled with SPECT or CT imaging, the lesion can be accurately localized. Multiple comparative studies have shown that ^{68}Ga-DOTA PET/CT imaging outperforms Octreoscan for PNET detection.[23] A recent meta-analysis looking at the performance of somatostatin receptor PET/CT for neuroendocrine tumor detection showed 93% sensitivity and 96% specificity.[54] Nuclear imaging plays an important role in follow-up imaging

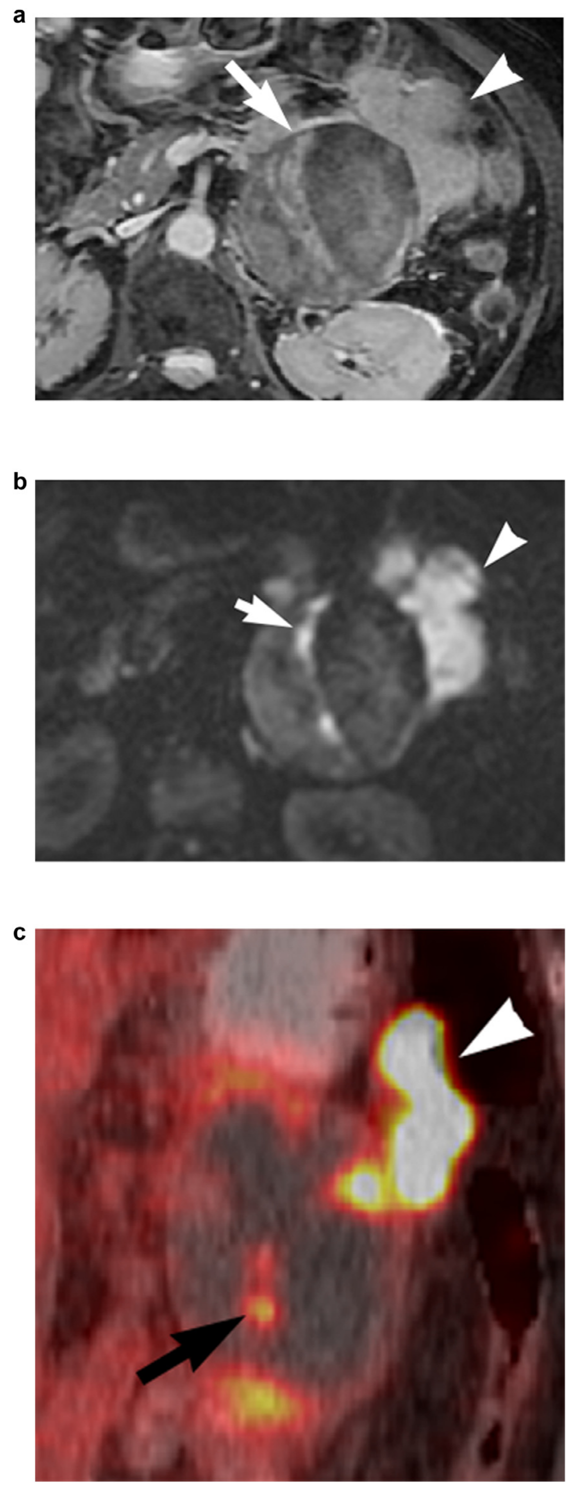

Figure 13 Metastatic PNET on MRI and FDG-PET/CT. (a) Axial postcontrast venous phase MR image demonstrates a heterogeneous pancreatic tail mass (white arrow). (b) Axial DWI image demonstrates restricted diffusion within the pancreatic mass (short white arrow). (c) Coronal FDG PET/CT-fused image shows focal areas of intense FDG activity within the pancreatic mass (black arrow). Regional metastatic retroperitoneal adenopathy (a-c, white arrowhead) demonstrates restricted diffusion and increased FDG radiotracer activity. A destructive T9 vertebral body mass (not shown) was also found. Pathology revealed metastatic high-grade PNET. Patient underwent chemotherapy and radiation treatment.

to detect small metastases that may be occult on CT or MRI. Prasad et al demonstrated that ^{68}Ga-DOTANOC PET helped identify lymph node involvement in all patients, whereas CT identified nodal involvement in only 50% (only 16 of 30 patients).[55] Recently, ^{68}Ga-DOTATOC PET has demonstrated high sensitivity (97%) and specificity (92%) for early detection of bone metastases.[56] Functional imaging using ^{18}F-FDG PET can help identify early metastases and aggressive lesions with high proliferation index and low SSR expression.

Imaging Mimics

PNETs are uncommon pancreatic neoplasms that are hypervascular on arterial phase of imaging. The masses tend to equilibrate with background pancreatic parenchyma on venous phase imaging. Although the imaging features are often distinct from other pancreatic masses, several benign and malignant pancreatic and peripancreatic lesions can mimic the imaging appearance of PNETs. Differentiation between benign masses mimicking PNETs is important for treatment planning, since surgical excision of PNETs is the primary treatment.

Intrapancreatic Splenule

Intrapancreatic or accessory pancreatic splenule arises from ectopic splenic tissue implanted within the pancreatic parenchyma. The lesion is incidentally noted as an intrapancreatic mass, most commonly in the pancreatic tail and usually smaller than 3 cm.[57] The enhancement characteristics of the splenule follow the spleen on all phases or sequences of imaging. On arterial phase imaging, a splenule may demonstrate hypervascularity mimicking a hypervascular PNET. However, owing to its origin and vascular supply, a splenule follows the spleen on all phases of imaging. Classic arterial phase serpiginous enhancement of the splenule can help distinguish between a neuroendocrine tumor and benign splenule. Pancreatic lesions that are indeterminate on anatomic imaging can be definitively characterized as accessory splenules by ^{99m}Tc-labeled sulfur colloid scan or ^{99m}Tc-labeled heat-damaged RBC scan (Fig. 14).

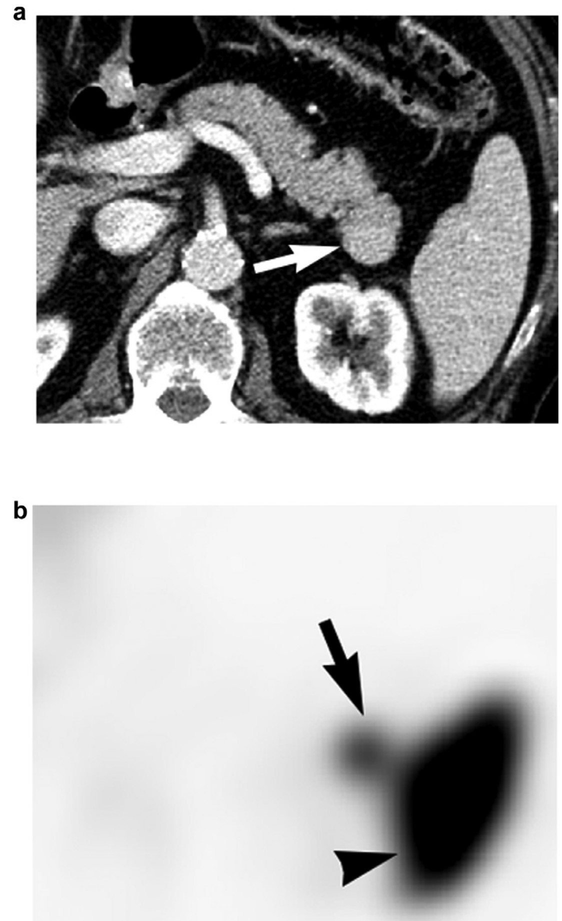

Figure 14 Intrapancreatic accessory spleen. (a) Axial contrast-enhanced CT image in portal venous phase demonstrates a hypervascular mass in the pancreatic tail (white arrow). (b) Axial SPECT image from a ^{99m}Tc-labeled heat-damaged RBC scan shows avid uptake in the pancreatic tail (black arrow), consistent with an intrapancreatic splenule. Physiologic RBC uptake is seen in the spleen (black arrowhead).

Pancreatic Metastases

Pancreatic metastases are rare lesions that account for 2%-4% of all pancreatic masses.[57] The common primary tumors that metastasize to the pancreas include renal cell carcinoma, melanoma, breast cancer, and lung cancer. Renal cell carcinoma is the most common metastasis to the pancreas and typically presents as a hypervascular mass(es), which can be similar to a PNET (Fig. 15). The presence of multiple hypervascular pancreatic tumors in the absence of history of MEN1, von Hippel-Lindau (Fig. 1) or other syndromes and history of malignancy, should raise strong suspicion of metastases rather than a neuroendocrine tumor, especially in patients with a history of a malignant tumor.

Serous Cystadenoma

Pancreatic serous cystadenomas are benign neoplasms composed of numerous small cysts, measuring less than 2 cm and arranged in a honeycomb pattern. Classic CT findings include a central stellate scar with coarse calcification, although this is seen in a minority of patients. Serous cystadenomas account for approximately 20% of all cystic pancreatic lesions and have a predilection for elderly females.[57] Even though serous cystadenomas contain multiple small cysts, they can sometimes appear as solid masses on CT due to the small size of the cysts and intervening stroma (Fig. 16). The vascularized stroma may cause these neoplasms to hyperenhance on arterial phase similar to a PNET, and the cysts may be difficult to resolve due to their size.[58] In these cases, MRI is often helpful for accurate characterization, by virtue of the numerous small cysts appearing markedly T2 hyperintense, which helps to distinguish these tumors from a solid mass, such as a PNET, which will typically not have T2 signal as bright as a fluid containing structure. The utility of MRI in differentiating a truly solid serous tumor from a PNET, however, may be limited, although a recent study showed promising results with the use of DWI with ADC values.[59]

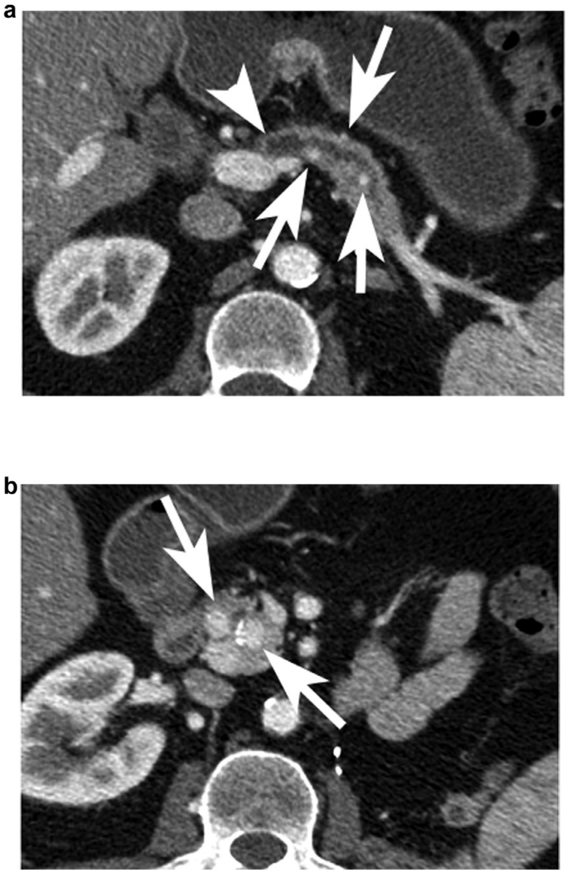

Figure 15 Renal cell carcinoma with pancreatic metastases. (a,b) Axial contrast-enhanced CT images show multiple hypervascular pancreatic body masses (arrows) and pancreatic duct dilatation (arrowhead) from pancreatic head masses (arrows in image b). The patient underwent left nephrectomy for renal cell carcinoma and the pancreatic masses represent metastatic disease.

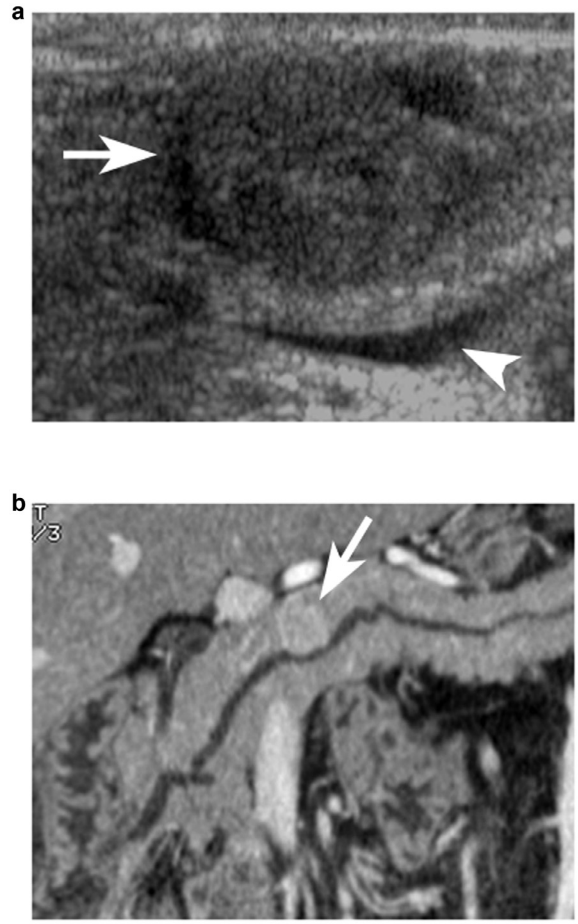

Figure 16 "Solid type" serous cystadenoma. (a) Transverse EUS image and (b) axial contrast-enhanced CT image demonstrate a serous cystadenoma in the pancreatic body (arrows) with a solid hyperattenuating appearance on CT, but with a characteristic cystic "honeycomb" appearance on EUS. This lesion does not communicate with the main pancreatic duct (arrowhead), as confirmed on US. Lack of communication with pancreatic duct is characteristic of serous cystadenoma.

Solid Pseudopapillary Epithelial Neoplasm

Solid pseudopapillary epithelial neoplasms (SPENs) are rare pancreatic neoplasms with a predilection for the pancreatic tail in young females in their second to third decade. These lesions are thought to arise from pancreatic ductal cells or pluripotent stem cells. Their CT and MR appearance is variable; however, they are often large and heterogeneous with internal hemorrhage, necrosis, or cystic areas (Fig. 17). The peripheral solid components enhance after administration of contrast. Compared to SPENs, PNETs tend to be smaller in size and demonstrate more avid enhancement on arterial phase imaging.

Other

Due to their variable degree of enhancement, PNETs can justifiably be included in the differential diagnosis of any enhancing soft tissue attenuation pancreatic mass, and can be indistinguishable from non-neuroendocrine tumors with a rich blood supply. In addition to the more common examples discussed above, other lesions that can have findings in the spectrum of PNETs include groove pancreatitis, retroperitoneal paraganglioma, or gastrointestinal tumor in close proximity to the pancreas, solitary fibrous tumor, lymphoma, and acinar cell cancer.[57] An aneurysm of the splenic artery or any other peripancreatic artery may bear a resemblance to a PNET; however, these lesions should follow attenuation of blood pool on multiphase imaging, allowing for proper diagnosis.

Prognosis

Characterization of tumor histology as well as extent of disease on imaging plays a crucial role in determining patient prognosis. Extrapancreatic invasion and metastatic disease are reliable predictors of malignancy.[6] Poor prognostic predictors in well-differentiated PNETs are tumors larger than 2-4 cm, vascular and/or neural invasion, high mitotic rate, high Ki-67 index, and necrosis.[7] In general, insulinomas, the most common functioning PNET, tend to be benign and have a better prognosis than patients with other types of neuroendocrine tumors. In contradistinction, noninsulinoma PNETs may recur or metastasize in 50%-80% of patients, and these patients have a 5-year

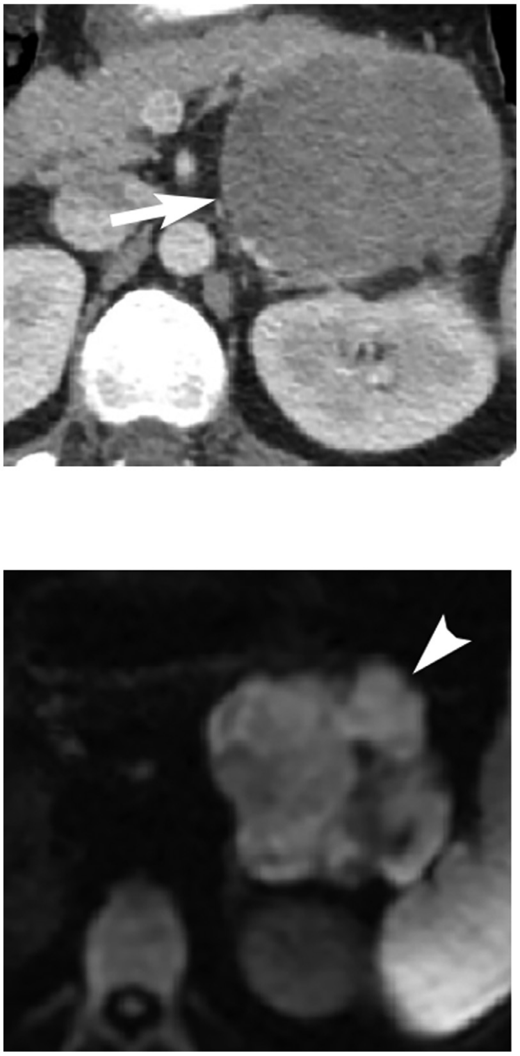

Figure 17 Solid pseudopapillary epithelial neoplasm. (a) Axial contrast-enhanced CT image shows a large poorly enhancing pancreatic mass (arrow). (b) On axial DWI, the pancreatic mass shows restricted diffusion (arrowhead). Pathology revealed SPEN.

survival rate of 50%-65%.[5] Liver metastases are the single most important predictor of survival, with liver failure being the most common cause of death.[14]

Treatment

Surgical excision is the mainstay of treatment for PNETs; however, curative surgical resection is an option in only 50% of patients due to advanced stage at diagnosis.[23] Resection of a solitary PNET without metastases is potentially curative; however, partial pancreatectomy may be required for deep or extensive lesions.[7] In patients with noncurative disease, surgery may be performed to debulk the tumor and alleviate symptoms. Surgical treatment options for patients with syndromic PNETs may be limited due to multiplicity of tumors.

Although the presence of hepatic metastases carries a worse prognosis, surgical excision can still be considered a potential treatment. Partial hepatic resection can be performed for limited disease along with primary tumor enucleation. Harring et al reported a 5-year survival rate of 60%-80% in patients undergoing surgical resection of liver metastases.[60] In general, liver resection is not considered when multiple metastases are present. Patients who are not candidates for resection of hepatic metastases can be considered for targeted liver therapies such as radiofrequency ablation or chemoebolization. Targeted therapies can be used to provide symptom relief in patients with refractory disease.

The biochemical profile of PNETs, including SSR expression, makes them unique for development of targeted radionuclide therapies for extrapancreatic disease. Somatostatin expression can be detected by ^{111}In Octreoscan and those tumors can be specifically treated with receptor-targeted radionuclide agents. Patients with well-differentiated tumors and low proliferation index of primary tumor or metastases are ideal for these agents.[3,61,62] Systemic chemotherapy is a consideration in patients with aggressive tumors or metastases that lack somatostatin receptor expression.[3,63]

Conclusion

PNETs are uncommon neoplasms with distinctive imaging findings on multiple modalities. Multimodality assessment with morphologic imaging (CT, MRI, and US) is complementary with functional imaging (^{111}In-Octreoscan, ^{68}Ga-DOTA-TATE, ^{18}F-FDG PET, etc.) for primary PNET detection, staging of regional and distant metastases, assessment of local invasion, and surveillance for recurrent disease. Proper imaging technique must be strictly adhered to on CT and MR examinations for accurate assessment of the primary tumor, local spread of disease, and liver and lymph node metastases. The radiologist must be aware of the typical and atypical imaging findings of PNETs, as well as the multiple pathologic entities that can mimic this tumor.

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