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State-Of-The-Art Imaging of Pancreatic Neuroendocrine Tumors

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Synopsis

Pancreatic neuroendocrine tumors are rare tumors that present many imaging challenges, ranging from detecting very small functional tumors, to fully staging large non-functioning tumors, including identifying all sites of metastatic disease, particularly nodal and hepatic, and depicting vascular involvement. The correct choice of imaging modalities requires knowledge of the tumor type (e.g. gastrinoma versus insulinoma), and also depends on histology (well versus poorly differentiated). Evolving techniques in CT, MR, EUS and nuclear medicine, such as dual energy CT, diffusion weighted MR imaging, liver specific MR contrast agents, and new nuclear medicine agents, offer new ways to better visualize, and ultimately manage, these tumors.

Keywords

Pancreatic neuroendocrine tumor; computed tomography; dual energy; CT; magnetic resonance imaging; MRI; PET/CT; octreotide; endoscopic ultrasound; imaging

Introduction

Pancreatic neuroendocrine tumors (PNET), account for only 3% of pancreatic malignancies, but have a rising incidence, currently 0.3-0.4/100,000.¹⁻³ They are notably more common in multiple endocrine neoplasia type I, von Hippel-Lindau syndrome, neurofibromatosis type I, and tuberous sclerosis.^{4, 5} PNET's can be divided into two groups: functional tumors, usually subcentimeter, that manifest because of the symptoms caused by the hormones they produce, and nonfunctional tumors, usually several centimeters in size, that manifest secondary to mass effect.

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State-of-the-art imaging plays a central role in the identification, diagnosis, and staging of PNET's. CT and MRI often used initially to detect and stage these lesions, and evolving nuclear medicine techniques provide improved specificity and whole body assessments for distant disease. A multimodality approach may be necessary to identify potentially very small primary tumors and to identify all sites of metastatic disease to optimize treatment planning.

Imaging techniques

CT—CT is often used for the initial evaluation of patients with abdominal pain or to identify suspected small functional PNET's because of its speed, resolution, and robustness. Recent advances allow for detailed multiplanar reconstructions, and new low kilovoltage imaging or multispectral imaging may improve the conspicuity of PNET's.

A typical abdominal multidetector CT (MDCT) exam for PNET is multiphasic (Fig. 1,2).⁶ Unenhanced images may be obtained to help identify calcifications or hemorrhage. At our institution, patients are then imaged following injection of iodinated intravenous contrast at 4-5 mL per second for an injection duration of approximately 30 seconds, with abdominal imaging obtained first at 40-45 seconds after the start of contrast injection for the late arterial phase of enhancement, and then 60-70 seconds after the start of contrast injection for the portal venous phase (Fig. 1, 2). Images are created at a slice thickness of 2-3 mm for diagnostic review, and at 0.625mm images for creating coronal and sagittal multiplanar reconstructions to facilitate problem-solving. CT has been reported in a 2009 consensus statement to have a mean sensitivity of 73% and specificity of 96%.⁷ Sensitivities for small functional tumors, such as insulinomas, vary by phase, approximately 83-88% for the arterial phase versus 11-76% for portal venous phase imaging though a small study of 13 patients evaluating the late arterial phase (pancreatic parenchymal phase) showed a sensitivity of 100% for that phase.⁸⁻¹¹ Detection is optimized by close evaluation of all phases.

New multispectral CT may improve detection of subtle differences in enhancement between lesions and background. Conventional multidetector CT utilizes a single polychromatic energy beam (e.g., “120 kVp”). Multispectral imaging uses either two polychromatic beams of high and low strengths (e.g. 80 kVp and 140 kVp) or a dual-layer detector that can discriminate between photons of high and low energy.^{12, 13} Multispectral imaging uses this additional data to mathematically create new types of images (Fig. 3, 4), two of the most common being monochromatic energy images (the equivalent of theoretically being scanned at a discrete single energy level), and material density or material decomposition, images (semi-quantitative images based on decomposing image data into representative amounts of just 2 or more materials to mimic the actual behavior at each image voxel).¹² The precise makeup of material decomposition images varies between vendors.

Low energy monochromatic images (i.e. 40-50 keV) improve the conspicuity of contrast enhancement. A small study investigating the detection of insulinoma compared 16 patients scanned with conventional dual phase multidetector CT with 23 patients scanned with rapid switching single source dual-energy dual phase multidetector CT.¹⁴ A sensitivity of 95.7% was obtained when a combination of low energy monochromatic energy images and iodine

(minus water) material decomposition images were used, compared to a sensitivity of 68.8% for conventional dual phase multidetector CT.¹⁴

Another related approach has been the use of a low polychromatic kVp (i.e. 80 kVp) technique which improved contrast to noise results when compared against conventional 140kVp imaging for overall pancreatic tumor imaging but did not statistically improve tumor detection.¹⁵ To our knowledge, no assessment has been published of this technique for pancreatic neuroendocrine tumors.

MRI—MRI offers several advantages for the imaging of PNETs including multiple different sequences that provide opportunities to differentiate tumor from normal pancreas. A typical abdominal protocol at our institution includes fat suppressed T2 weighted, fat suppressed pre-and post-contrast dynamically obtained T1-weighted, in and out of phase T1-weighted images, diffusion-weighted images with multiple b values and apparent diffusion coefficient (ADC) maps, and fat suppressed true FISP or FIESTA images (Fig. 5). An effective slice thickness of 3-6 mm is utilized to minimize volume averaging artifact and improve sensitivity. The overall sensitivity of MRI published in a consensus report was 93% with specificity of 88%.⁷ Limitations of MRI include greater frequency of motion related artifacts and a longer imaging time compared to CT. Benefits include good sensitivity even in the absence of administration of an intravenous contrast agent (making it a useful alternative for patients with renal impairment or allergy to iodine based CT contrast agents) and the absence of ionizing radiation, of particular concern in younger patients who may require surveillance. Recent studies of advances in diffusion-weighted imaging suggest potential for improving detection,¹⁶ differentiating accessory spleen from small islet cell tumors,¹⁷ differentiating near solid serous cystadenomas from neuroendocrine tumors,¹⁸ and potentially in evaluating tumor grade.^{19, 20} MRI also offers potential advantages over CT in regard to detection of liver metastases which will be discussed later.

Nuclear Medicine

The primary nuclear medicine imaging tool for PNET is somatostatin receptor scintigraphy performed with a radiolabeled somatostatin analogue. Somatostatin is a peptide hormone for which five types of receptors have been identified. Octreotide, a somatostatin analog, binds to receptors type 2 and 5.²¹ Octreotide is typically labeled with indium-111, administered intravenously, and patients are then imaged 4 hours and 24 hours after tracer administration using both planar imaging and single photon emission computed tomography (SPECT).²² At our institution, and in many centers, a CT study is performed concurrently with SPECT on a dedicated hybrid SPECT/CT camera, allowing for more precise anatomic localization of octreotide uptake (Fig. 6-8).²² Overall sensitivity for ¹¹¹In-octreotide for PNET is approximately 70-90% but varies with tumor type and diminishes particularly for subcentimeter lesions.^{22, 23} Sensitivity for insulinoma, which typically expresses receptor type 3, is notably limited (Fig. 9) at 50-70%²⁴.

While FDG PET/CT would offer potentially greater precision, PNET's don't typically demonstrate sufficient uptake unless they are poorly differentiated. FDG PET/CT, is therefore used as a complementary technique (Fig. 10) to SPECT/CT octreotide which

shows poor uptake in poorly differentiated tumors.²² New PET/CT agents that have been developed include gallium labeled somatostatin analogs such as DOTA-tyrosine-3-octreotide (DOTA-TOC), which has a higher affinity for somatostatin receptor type 2, and DOTA-1-NaI-octreotide (DOTA-NOC), which demonstrates a higher affinity for subtypes 2, 3, and 5 (Fig. 11).²⁴ Although these PET somatostatin radiotracers have faced many regulator barriers in the U.S., the somatostatin analog, Gallium 68 (Ga-68) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-octreotate (DOTATATE, GaTate), has recently been given orphan drug status by the US Food and Drug Administration. Somatostatin receptor imaging using positron emitting isotopes is attractive due to the improved spatial resolution of PET imaging compared to SPECT.²⁵ A recent meta-analysis of 22 studies of the broad category of somatostatin receptor PET/CT, including more than 2100 patients, showed a sensitivity of 93% and specificity of 95%.²⁶ The radiation dose to the patient is often lower with PET agents compared to conventional ¹¹¹In-labeled radiotracers. The radiation dose to the patient is often lower with PET agents compared to conventional ¹¹¹In-labeled radiotracers. Although Ga-68 has been used extensively, other radioisotopes are under investigation for imaging of neuroendocrine tumors, including Cu-64 and F-18. Using the approach of theragnostics, a therapeutic radioisotope (such as Y-90 or Lu-177) can be paired to the somatostatin-binding pharmaceuticals to deliver a high-dose radioisotope therapy to eligible patients, and trials are currently underway in the U.S. to achieve regulatory approval. Finally, metabolic pathways are being explored as a means to image PNET tumors, including PET imaging with amino acid precursors such as F-18 dihydroxyphenylalanine (DOPA), and C 11 labeled hydroxytryptophan (5-HTP).²⁷

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) reportedly has a mean detection rate for neuroendocrine tumors of 90%.⁷ EUS guided fine needle aspiration (FNA) has been reported to result in overall diagnostic accuracy of 90.1%.²⁸ Endoscopic ultrasound (Fig. 12) is particularly helpful for gastrinomas as many are located within bowel, a region which is poorly evaluated by both CT and MRI.²⁹ The primary limitations of endoscopic ultrasound are that it is dependent on the skill and experience of the operator, requires sedation, and the technique is relatively invasive.²⁹

A relatively recent development is that of intravenous contrast agents, namely blood-pool contrast agents (microbubbles) for ultrasound imaging, currently approved in the United States by the FDA for cardiac imaging but not abdominal imaging, though they have been approved for use more widely in other parts of the world.³⁰ A study of 37 insulinomas, using one such microbubble agent, sulfur hexafluoride lipid-type A microspheres, reportedly showed an improvement from a sensitivity of 24% for transabdominal unenhanced ultrasound to 87-89% following the administration of intravenous contrast.³⁰ To our knowledge, only very limited information is available regarding its use in the setting of pancreatic EUS. The already high sensitivity of EUS and high specificity of EUS-guided fine needle aspiration, likely account for contrast enhancement not being more widely utilized.

Imaging findings

The appearance of pancreatic neuroendocrine tumors can vary considerably, even within the same patient, and differs markedly between functional tumors, which are typically small, and nonfunctional tumors, which are typically several centimeters in size.

Functional Pancreatic Neuroendocrine Tumors

Functional pancreatic tumors, because they manifest with systemic symptoms, are usually 1-2cm in diameter at the time of imaging but can be smaller.^{8, 31, 32} The most common types are insulinoma (Fig. 9), and gastrinoma (Fig. 6, 11, 13). Their incidence is increased in syndromes such as the autosomally dominant multiple endocrine neoplasia type I (MEN-I), and von Hippel Lindau disease (vHL).^{4, 5}

Their classic appearance is that of a uniformly hypervascular, well defined, lesion (Fig. 9, 11) that is most notably prominent on arterial phases of contrast enhancement.^{8, 31, 33} Studies that have evaluated phases of contrast enhancement have shown a sensitivity of 83-88% for arterial phase imaging versus 11-76% for later portal venous phase imaging.^{8, 9, 34, 35} However, lesions may be seen on only one of these two phases.

Cystic changes are typically seen with larger lesions,³³ but even marked cystic transformation can occur with smaller lesions (Fig. 14). The presence of a hypervascular rim, sometimes very subtle, can be very helpful in suggesting the diagnosis of PNET.³⁶ Features such as heterogeneity, calcifications, and necrosis, become more notable with increasing tumor size.³³

Insulinomas

Knowledge of the suspected tumor type (e.g. insulinoma or gastrinoma) is important to guide assessment of the images. Insulinomas are typically solitary, 97% occur within the pancreas, are typically smaller than other functioning tumors at initial evaluation (40% are less than 1cm in size), and only 10% are malignant with malignancy usually seen in lesions greater than 3cm in size.^{32, 37, 38} Insulinomas are much more likely to be multiple in the setting of syndromes, notably MEN I.^{37, 39} CT and MRI are often used initially in this setting given their good sensitivity for intrapancreatic lesions and lack of invasiveness, and the poor sensitivity of octreotide as well as PET/CT. Invasive techniques such as arterial stimulation and venous sampling, and transhepatic portal venous sampling can be utilized to increase the likelihood of detection,³⁷ but may be controversial as intraoperative assessment has been reported to have high sensitivity.^{37, 40, 41} Non-invasive techniques such as CT and MRI, when able to localize lesions, can provide information that may be helpful in guiding decisions regarding surgery such as the extent of primary tumor, potential metastatic nodal involvement, or the identification of liver metastases.³²

Gastrinomas

Gastrinomas (Fig. 6, 11, 13) have a very different pattern of presentation from insulinomas. Only 60% are located within the pancreas, with the remainder most commonly located in the duodenum or peripancreatic nodes; overall about 90% are identified within the “gastrinoma triangle” bounded by the cystic duct junction with the common bile duct, the pancreatic neck

and the junction of the second and third portions of the duodenum.^{8, 32} Rarely, lesions have been reported in the stomach, and jejunum.⁸ While gastrinomas within the pancreas are typically 3-4cm and usually within the head,⁴² those within the duodenum are usually within the wall, multiple, and subcentimeter in size, making assessment by CT and MRI difficult.⁴² For this reason, endoscopic ultrasound is particularly useful for identifying gastrinomas preoperatively and to biopsy suspicious nodes.⁸ Because of the nature and high concentration of their somatostatin receptor expression, these lesions are more amenable to evaluation with nuclear medicine octreotide scanning.⁸ Unlike insulinomas, 60% of gastrinomas show malignant behavior at presentation requiring careful inspection for all sites of disease and close evaluation for potential liver metastases.⁸ Gastrinomas are the most common functioning pancreatic neuroendocrine tumor in the MEN 1 syndrome, in which case they are more likely to manifest with multifocal duodenal involvement.⁸

Nonfunctioning Pancreatic Neuroendocrine Tumors

Nonfunctioning pancreatic neuroendocrine tumors (Fig. 5, 15), typically manifest because of symptoms caused by mass effect, such as pain and weight loss, and as such typically present at a larger size.^{8, 33} These “nonfunctioning” tumors often secrete hormones, such as pancreatic polypeptide, but without causing an apparent clinical syndrome. Being larger, these lesions also more commonly manifest as heterogeneously enhancing lesions, may contain areas of necrosis/cystic change that can be markedly extensive, and can contain foci of calcification.³³ They are also more likely to be metastatic (Fig. 3) at presentation (60-80% of cases), most often to liver and lymph nodes (Fig. 7).^{32, 37, 43} The presence of calcifications is a useful indicator for potential malignancy.³¹ Duct obstruction can be seen secondary to mass effect, and occasionally tumor can be seen to have spread within a distended duct.^{8, 31, 44} In a study of 88 patients with nonfunctioning tumors, 33% were found to have venous tumor thrombus (Fig. 15), identification of which can alter surgical planning, and is a useful distinguishing feature from pancreatic ductal adenocarcinoma.⁴⁴

While most often solitary, nonfunctional PNET can be multiple in familial syndromes, and are the most common pancreatic endocrine tumor in patients with MEN1 and von Hippel Lindau disease.⁸ With the growing use generally of cross-sectional imaging, up to 35% of nonfunctional PNETs are now found incidentally, which often portends a better prognosis.⁴³

Poorly Differentiated Pancreatic Endocrine Tumors

An important criterion is poorly versus well differentiated PNET. The former is more likely associated with nodal and/or liver metastases, and have few somatostatin receptors and are therefore poorly visualized on octreotide studies, but are more likely visualizable (Fig. 10) on FDG PET/CT studies.^{8, 44, 45}

Recent studies have attempted to identify imaging biomarkers of aggressiveness. A study of 60 PNET's showed on dual phase imaging (arterial/portal venous) that atypical enhancement - persistent enhancement on portal venous phase imaging or increasing enhancement on that later phase compared to typical early enhancement with then washout on portal venous phase (Fig. 16) - were more likely to be carcinomas on histopathologic examination.⁴⁶ A study that evaluated similar characteristics and diffusion weighted imaging on MRI also

showed that malignant features were more likely to be hypovascular on the arterial phase of imaging, and also showed lower apparent diffusion coefficient (ADC) values.¹⁸ In one study, the presence of multiple factors such as poorly defined margin, upstream pancreatic duct dilatation, vascular invasion, tumor size, and enhancement features, were significant in predicting histopathologic grading of tumors,⁴⁷ while another study found that only identification of ill-defined boundaries between tumor and peripancreatic tissues or vessels was significantly associated with WHO 2010 pathologic classification.⁴⁸

Staging

The two most commonly used staging systems are the European Neuroendocrine Tumor Society system (ENETS, 2006) and the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC, 2009) system. Their differences are primarily in T staging as shown in Table 1.

Primary tumor

As noted earlier, the type of tumor being considered (i.e. insulinoma versus gastrinoma), and differentiation (well versus poorly differentiated) can have significant implications regarding the imaging modalities being chosen (nuclear medicine octreotide study, FDG PET/CT, EUS/CT/MRI).

The two primary modalities for assessing local extent of disease, including involvement of adjacent organs and vasculature, are MRI and CT. CT has the advantages of relative insensitivity to motion and submillimeter slice thickness, and therefore can produce detailed reconstructions useful for evaluating the relationship of tumors to adjacent structures (Fig. 17). MRI can image directly in multiple planes with good soft tissue contrast even when intravenous contrast agents cannot be administered.

Disease Beyond the Pancreas: Nodal and Distant Metastatic

Nodal disease—It is important to identify potential metastatic nodal sites of PNET preoperatively to improve the likelihood of resecting all sites of disease. The most commonly utilized techniques, are CT, MRI, and octreotide scanning (Fig. 7, 8, 18), with the latter being the most specific. Unfortunately, only limited information is available on nodal staging. As noted previously, CT provides high resolution imaging with few artifacts. A recent study of 181 patients undergoing pancreatic resection with curative intent showed a sensitivity and specificity of CT for detecting nodal metastases of 35% and 91% respectively.⁴⁹ PNET nodal metastases can be prominently hypervascular and therefore more conspicuous on the arterial phase of dynamic imaging.³⁵ In our experience, we have found such enhancement can also be similar to, and therefore difficult to distinguish from, adjacent vasculature. In this context, T2-weighted and diffusion-weighted MR imaging can be helpful, as vessels are typically black on images obtained with these techniques because of flow phenomena, while nodes (both metastatic and benign) are characteristically bright on both T2-weighted and diffusion imaging (Fig. 18). However, both CT and MRI are insensitive for micrometastases. Using size criteria of greater than 1 cm in short axis to identify adenopathy is relatively insensitive though somewhat specific. Octreotide scanning with single photon emission computed tomography with fusion with unenhanced CT images

can be very helpful for identifying small, avid, liver, node and bone metastases but is also insensitive for micrometastases.^{8, 24} A very recent study that compared Ga-DOTA-TOC PET/MRI with gadoxetate disodium against Ga-DOTA-TOC PET/CT showed an advantage for PET/CT for evaluation of involved lymph nodes.⁵⁰ As noted previously, conventional FDG PET/CT may be advantageous over octreotide scanning for identifying metastatic sites for poorly differentiated PNET.

Liver metastases—Multiphasic imaging on CT is also useful for liver metastases which have a variable appearance requiring careful inspection of all dynamic phases. The classic appearance (Fig. 2) is that of a hypervascular metastasis seen best on the arterial phase of imaging. However, metastases can also be hypoenhancing on all phases, portending a worse prognosis.⁵¹ A study of 64 patients in 2005 compared SPECT octreotide scanning, spiral CT, and MRI. SPECT octreotide identified 200 liver metastases, CT identified 325, and MRI identified 394 lesions.⁵² Newer developments since then include MRI diffusion-weighted imaging, and the development of liver specific agents. A study of MRI in 59 patients, 41 patients with 162 liver metastases from neuroendocrine tumors and 18 control subjects with no liver metastases, showed sensitivities of 72% for diffusion-weighted, 57.2% for T2 weighted and 48% for conventional intravenous gadolinium dynamic multiphasic imaging with decreasing sensitivities for decreasing size of metastases.⁵³ Gadoxetate disodium, a liver specific agent retained by normal liver parenchyma, washes out of liver metastases, making them notably conspicuous on 20 minute delayed images (Fig. 19).^{54, 55} While only very limited information is available regarding PNET liver metastases, a study has shown greater detection of colorectal liver metastases with gadoxetate disodium MRI than triphasic CT.⁵⁶ An interesting recent development has been combined Ga-DOTA-TOC PET/MRI with gadoxetate disodium.⁵⁰

Other distant metastases

PNET can also metastasize to bone, and lung. While CT has excellent sensitivity for assessing lung metastases, it is less capable at assessing bone metastases. MRI, is useful for characterizing and assessing limited regions of the skeleton, while nuclear medicine studies, provide the benefit of a whole body assessment.

Conclusion

State-of-the-art imaging for PNET continues to evolve with developments such as dual energy CT, new MRI techniques such as diffusion-weighted imaging, the increasingly greater use of endoscopic ultrasound for solid pancreatic lesions, and the evolving use of PET/CT including the role of FDG pet for poorly differentiated tumors and new pet agents that promise greater utility than conventional octreotide nuclear medicine imaging. Optimal use of imaging techniques (focused abdominal imaging and complementary whole body imaging) depends on such issues as functional versus nonfunctional tumors and well versus poorly differentiated tumors. Insulinomas, which are almost always confined to the pancreas, are typically best imaged by a combination of cross-sectional imaging techniques, such as CT or MRI, with cautious use of whole body nuclear medicine conventional octreotide imaging, given the often poor uptake of octreotide by this tumor. In contrast,

gastrinomas, which can be frequently extrapancreatic and octreotide avid, are best managed by a combination of CT or MRI, whole body octreotide imaging, and endoscopic ultrasound to evaluate for pancreatic and intraluminal lesions. In contrast, the typically large size of nonfunctional tumors is such that these are often best managed by cross-sectional imaging, CT or MRI, to provide detail with regard to staging with the type of whole body imaging depending on whether tumor is well differentiated (in which case whole body octreotide is utilized and FDG PET/CT has only limited utility) versus poorly differentiated (in which cases octreotide scanning often performs poorly, but FDG-PET can provide a useful whole body assessment).

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Key Points

1. Knowledge of the type of functional tumor, e.g. gastrinoma versus insulinoma, is important in choosing appropriate imaging strategies to identify primary lesions and their metastases.
2. FDG PET/CT has poor sensitivity for well differentiated pancreatic neuroendocrine tumors but good sensitivity for poorly differentiated types, and therefore has a complementary role to octreotide scanning.
3. To optimize treatment planning, it is important to inspect all potential sites of disease, particularly with regard to the extent of liver and nodal involvement, and potential distant metastases to lung and bone.
4. Metastatic adenopathy can show enhancement similar to adjacent vasculature structures and can be difficult to detect on CT. MRI, particularly diffusion weighted imaging, and nuclear medicine studies, can be helpful.

Fig. 1. Pancreatic tail neuroendocrine tumor (white arrows) on multiphasic CT. (A) is hyperdense to background on the arterial phase and (B) isodense on the portal venous phase.

Fig. 2. PNET liver metastases (white arrowheads) on multiphase CT are classically hyperdense to background on (A) early and (B) late arterial phases and either isodense or hypodense on (C) portal venous phase but can be variable.

Fig. 3. Pancreatic tail NET (white arrows) seen on late arterial phase CT, as seen (A) conventionally at 140kVp, and more conspicuously at dual energy CT (DECT) (B) low energy 50 keV and (C) iodine (minus water) material density images.

Fig. 4. PNET metastases to liver (white arrows) and nodes (thick white arrow) seen on DECT late arterial phase at (A) 70 keV and (B) more conspicuously on iodine (minus water) material density images. Uptake in these sites on (C) octreotide images is highly specific to neuroendocrine tumors.

Fig. 5. Nonfunctioning tail PNET (white arrows) seen on MRI on dynamic (A) arterial phase, (B) T2 and (C) diffusion weighted imaging. Diffusion imaging improves contrast, though resolution is less than other series.

Fig. 6. Patient with elevated gastrin levels and large pancreatic gastrinoma (white arrowheads) on multiphasic CT in (A) arterial phase with invasion of portal vein (curved black arrow) and (B) multiple liver metastases (white arrows). Octreotide scan (C) projection images show intense uptake in primary gastrinoma (black arrowhead), and liver metastases (black arrows).

Fig. 7. PNET (thick white arrow), adenopathy (long white arrow), liver metastases (white arrow) and tumor thrombus in vein (black arrowhead) as seen on arterial phase (A) 70keV (B) iodine material density and (C) portal venous phase imaging, the last showing metastases and portal vein thrombus. Octreotide fused SPECT CT (D), as a whole body study, identifies distant metastatic left supraclavicular node. Note similarity of some adenopathy to adjacent vessels.

Fig. 8. Metastatic PNET on whole body fused octreotide SPECT/CT with uptake in metastatic nodal disease (white arrows) in (A) mediastinum (B) retroperitoneum and (C) liver metastasis (thick white arrow).

Fig. 9.

Small pancreatic insulinoma on multiphasic CT and octreotide scan. Insulinoma (white arrow) here is uniformly hyperdense on late arterial phase but (B) near isodense to background on portal venous phase. On octreotide scan (C), it is not seen (normal uptake in liver, spleen and kidneys).

Fig. 10. Nonfunctioning poorly differentiated pancreatic body PNET (white arrows) on (A) axial late arterial phase CT and (B) showing intense uptake on PET/CT fused image as is a (C) liver metastasis.

Fig. 11.

Proximal duodenal histopathologically proven gastrinoma (white arrow) on (A) 50 keV dual energy CT, late arterial phase and (B) ^{68}Ga -DOTA-NOC fused PET/CT image has hypervascular appearance on CT and shows intense uptake of tracer. Water was used as negative contrast on CT.

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Fig. 12. Incidentally identified pancreatic tail mass (white arrows) on CT (A) similar to spleen (black asterisk) on multiphasic imaging, showed (B) no uptake of technetium sulfur colloid (therefore not an accessory spleen). (C) EUS with FNA showed well defined slightly hypoechoic mass, and PNET on histopathology.

Fig. 13. Peripancreatic adenopathy as site of gastrinoma. Portal venous phase CT shows enhancing adenopathy (white arrow) (A) anterior to transverse duodenum and (B) near aortocaval space, similar to aorta and opacified bowel loops.

Fig. 14.
Cystic pancreatic tail lesion (white arrows) on CT shows subtle peripheral enhancement.
EUS FNA confirmed PNET.

Fig. 15.

Large nonfunctioning pancreatic head PNET on CT (A) late arterial phase shows tumor (white arrows) extending anterior to a metallic biliary stent (black arrow), and (B) infiltrating (black arrowhead) the superior mesenteric vein.

Fig. 16.

A PNET (white arrow) and its liver metastases (black arrows) that is atypically hypodense on CT on (A) late arterial and (B) portal venous phases, that mimics pancreatic ductal adenocarcinoma.

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Fig. 17. Staging of pancreatic head PNET (white arrowheads) that on CT on (A) late arterial phase shows superior mesenteric vein (SMV) abutment. While PNET is not as well seen on (B) portal venous phase images, the SMV is clearly free of thrombus and coronal (C) reconstruction shows PNET not involving the portal vein and separate from superior mesenteric artery.

Fig. 18.

Metastatic PNET with liver metastases (short white arrows) and nodal disease (white arrowheads) appear bright as seen on typical (A) T2 fat suppressed imaging and (B) diffusion weighted imaging with B value of 500. Unlike CT, portal vein (long white arrow) is black, clearly distinguishable from nodes. Notably, metastatic and reactive nodes appear similar on both techniques.

Fig. 19.

PNET liver metastases (white arrows) on MRI on (A) arterial phase of dynamic, (B) portal venous phase, (C) 20 minute delayed post gadoxetate disodium and (D) diffusion weighted imaging. Conspicuity of liver metastases can vary greatly between arterial/portal venous images but because they lack hepatocytes, metastases are usually distinctly dark and well defined on (C) delayed gadobenate dimeglumine images. Diffusion weighted imaging also show lesions well.

Table 1

T Staging of Pancreatic Neuroendocrine Tumors: AJCC vs. ENETS

Stage	AJCC/UICC 2009	ENETS 2006
T1	Pancreatic confined primary tumor <2 cm	Pancreatic confined primary tumor <2 cm
T2	Pancreatic confined primary tumor >2 cm	Pancreatic confined primary tumor 2-4 cm
T3	Pancreatic tumor extending beyond pancreas without major vessel involvement	Pancreatic tumor >4 cm in size OR extending beyond pancreas with invasion limited to duodenum or bile duct
T4	Pancreatic tumor extending to involve major vessels such as celiac or superior mesenteric artery	Pancreatic tumor invading major vessels or invasion of adjacent organs other than duodenum or bile duct

Adapted from Rindi G, Klöppel G, Alhman H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Archiv.* 2006;449(4):395-401 and <https://cancerstaging.org/references-tools/quickreferences/Documents/PancreasSmall.pdf>.