MINIREVIEWS

Current update on imaging for pancreatic neuroendocrine neoplasms

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Abstract

Pancreatic neuroendocrine neoplasms (panNEN) are a heterogeneous group of tumors with differing pathological, genetic, and clinical features. Based on clinical findings, they may be categorized into functioning and nonfunctioning tumors. Adoption of the 2017 World Health Organization classification system, particularly its differentiation between grade 3, well-differentiated pancreatic neuroendocrine tumors (panNET) and grade 3, poorly-differentiated pancreatic neuroendocrine carcinomas (panNEC) has emphasized the role imaging plays in characterizing these lesions. Endoscopic ultrasound can help obtain biopsy specimen and assess tumor margins and local spread. Enhancement patterns on computed tomography (CT) and magnetic resonance imaging (MRI) may be used to classify panNEN. Contrast enhanced MRI and diffusion-weighted imaging have been reported to be useful for characterization of panNEN and quantifying metastatic burden. Current and emerging radiotracers have broadened the utility of functional imaging in evaluating panNEN. Fluorine-18 fluorodeoxyglucose positron emission tomography (PET)/CT and somatostatin receptor imaging such as Gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate PET/CT may be useful for improved identification of panNEN in comparison to anatomic modalities. These new techniques can also play a direct role in optimizing the selection of treatment for individuals and predicting tumor response based on somatostatin receptor expression. In addition, emerging methods of radiomics such as texture analysis may be a potential tool for staging and outcome prediction in panNEN, however further investigation is required before clinical implementation.

Core Tip: Imaging plays a critical role in the diagnosis and management of pancreatic neuroendocrine neoplasms. Enhancement patterns and diffusion-weighted imaging aid the detection and classification of these lesions. Contrast-enhanced magnetic resonance imaging is useful for the evaluation of hepatic metastases. Dual-tracer positron emission tomography/computed tomography with Gallium-68 1,4,7,10-tetraazacyclodo-decane-1,4,7,10-tetraacetic acid–octreotate and Fluorine-18 fluorodeoxyglucose may be particularly useful for distinguishing grade 3 pancreatic neuroendocrine tumor from pancreatic neuroendocrine carcinoma. Furthermore, these advanced imaging tech-niques can help in the staging and detection of distant metastases. Evaluation of somatostatin receptor expression and metabolic activity with functional imaging can help select optimal treatment.

INTRODUCTION

Pancreatic neuroendocrine neoplasms (panNEN) represent a rare, diverse group of neoplasms[1]. These tumors account for less than 2% of pancreatic cancers and only 7% of all neuroendocrine tumors. These entities can manifest at any age but are most often diagnosed in individuals between 40 and 65 years old. The majority of panNEN are sporadic[2]. Up to 10% are associated with hereditary disorders including Von Hippel-Lindau disease, neurofibromatosis type 1, tuberous sclerosis complex, and multiple endocrine neoplasia type 1 (MEN1) syndrome, which increase a patient's predilection for neoplasms. PanNEN can be categorized into functioning and nonfunc-tioning neoplasms based on clinical findings. Recent discoveries on the mechanisms behind panNEN pathogenesis and molecular cytogenetics have resulted in significant changes regarding their classification, diagnosis, and treatment. In particular, new distinctions in classification between well-differentiated pancreatic neuroendocrine tumors (panNET) and poorly-differentiated pancreatic neuroendocrine carcinomas (panNEC) has emphasized the need for more advanced imaging techniques to guide diagnosis and follow-up[1]. In this review, we will discuss the most current classific-ations of panNEN based on pathology, genetic, and clinical features. In addition, we will review the use of anatomic imaging modalities like ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) for initial detection and management, along with molecular imaging techniques that have proven useful for identifying occult tumors and further characterization. The potential use of CT, MRI, and positron emission tomography (PET)/CT texture analysis to grade tumors and predict clinical outcome will also be briefly highlighted.

PATHOLOGY

PanNEN demonstrate two histopathological classifications: panNET and panNEC. PanNET account for more than 90% of panNEN and are characterized as well-differen-tiated neoplasms that manifest with little to moderate atypia. On gross examination, they appear well-circumscribed by a thin capsule. Cystic changes and hemorrhage may be identified. PanNEC can manifest as a small cell or large cell variant. The large cell variation comprises 60% of panNEC and exhibits expansile growth. Small cell panNEC exhibit more infiltrative growth. Necrosis and vascular invasion are com-

monly observed[3].

The 2010 World Health Organization (WHO) classification system for panNEN based categorization on a neoplasm's Ki-67 proliferation index and mitotic index. In this system, when both indices are greater than 20, the tumor is classified as panNEC. Subsequently, many large studies showed the existence of well-differentiated panNET presenting high mitotic and Ki-67 indices. Thus, the 2017 WHO classification system (Table 1) accounts for both the level of proliferation and differentiation of neoplasms, distinguishing a well-differentiated grade 3 panNET from a poorly-differentiated grade 3 panNEC[1,4]. Additional changes include the renaming of mixed adenoneuroendocrine carcinomas to mixed neuroendocrine-nonneuroendocrine neoplasms (MiNEN), in order to reflect their capacity to manifest not only as high-grade, malignant neoplasms, but also as low-grade, benign tumors. MiNEN are composed of both neuroendocrine and non-neuroendocrine components and have relatively non-specific features, tending to mimic panNEC[1].

Although WHO classification relies on pathological features to distinguish grading, single location biopsy may not be an accurate representation of all tumor burden due to the variance within and between lesions. In addition, grade transformation can occur following biopsy. Thus, imaging evaluation and follow-up often play an important role in dictating ongoing and future management, regardless of initial grading.

MOLECULAR CYTOGENETICS

Research focusing on the study of panNEN pathogenesis has significantly broadened the knowledge behind genetic mutations which may influence these lesions and their prognosis. The most common genetic alterations seen in panNET include mutations of the tumor suppressor gene *MEN1*, and chromatin-remodeling genes *ATRX* and *DAXX* [3]. *MEN1* encodes the protein menin, which is involved in histone methylation and cell cycle inhibition. *MEN1* mutations are seen in 31% to 44% of grade 3 panNET, resulting in the disruption of tumor suppression[5]. The majority of these mutations are sporadic, but some may be inherited and seen in association with MEN1 syndrome, Von Hippel Lindau syndrome, neurofibromatosis type 1 and tuberous sclerosis. *ATRX* and *DAXX* mutations are strongly associated with high grade tumors and poor outcomes. A mutation in one of the two genes is observed in more than 45% of well-differentiated neoplasms, and result in an alternative lengthening of telomeres phenotype which correlates with aggressive behavior. *DAXX* abnormalities are also associated with low expression of *TP53*, a tumor suppressor gene that is involved in apoptosis, cell proliferation, and DNA repair. Other molecular abnormalities that may be observed in panNET are mutations in *TSC1* and *TSC2*, *PTEN*, *PIK3CA*, and *DEPDC5*, which all play a role in the mammalian target rapamycin (mTOR) pathway. These mutations occur in approximately 15% of tumors[1,3].

The molecular abnormalities driving panNET do not usually occur in panNEC. Instead, these neoplasms commonly feature mutations in *TP53* and *Rb1*. *KRAS* and *SMAD4* mutations can also occur, but these are less frequent[1].

CLINICAL FEATURES

PanNEN have a wide range of clinical findings, depending on the subtype. The clinical presentation of functioning panNET is influenced by their characteristic hypersecretion of various hormones. Insulinomas account for 60% of functioning panNET and are composed of insulin-producing β cells[3]. They typically manifest with Whipple's Triad (*i.e.* fasting hypoglycemia, symptoms of hypoglycemia, and relief of symptoms following administration of IV glucose)[2]. About 10% of cases will present multiple insulinomas, usually in association with MEN1 syndrome. Gastrinomas represent the second most common functioning panNET. They usually arise in the gastrinoma triangle, a region enclosed by the pancreatic head and neck, the second and third part of the duodenum, and the cystic and common bile duct[1]. Overproduction of gastrin leads to the onset of Zollinger-Ellison syndrome, resulting in peptic ulcer disease, secretory diarrhea, or gastroesophageal reflux disease[3]. Glucagonoma is characterized by its hypersecretion of glucagon. Common manifestations include necrolytic migratory erythema, diabetes mellitus, deep vein thrombosis, and depression[3,6,7]. Other functioning panNET are somatostatinomas, vasoactive intestinal peptide-secreting tumors, and adrenocorticotropic hormone-secreting tumors, which comprise

Table 1 Comparison of 2010 and 2017 World Health Organization classification system for pancreatic neuroendocrine tumors

WHO 2010 Classification system	WHO 2017 Classification system	Ki-67 index (%)	Mitotic index[1]
Well-differentiated PanNET G1	Well-differentiated PanNET G1	< 3	< 2
Well-differentiated PanNET G2	Well-differentiated PanNET G2	3-20	2-20
	Well-differentiated PanNET G3	> 20	> 20
Poorly-differentiated PanNEC G3 (*i.e.* small cell carcinoma, large cell carcinoma)	Poorly-differentiated PanNEC G3 (*i.e.* small cell carcinoma, large cell carcinoma)	> 20	> 20
MiNEN	MANEC		

[1]Per 10 high-power fields. WHO: World Health Organization; PanNEN: Pancreatic neuroendocrine neoplasms; PanNET: Pancreatic neuroendocrine tumors; PanNEC: Pancreatic neuroendocrine carcinomas; MiNEN: mixed neuroendocrine-nonneuroendocrine neoplasms; MANEC: Mixed adenoneuroendocrine carcinomas.

less than 20% of cases[8].

Nonfunctioning panNET are usually asymptomatic until advanced stages, resulting in later presentation and diagnosis. These tumors can secrete polypeptides; however, such secretions do not lead to any associated clinical findings. When symptoms do appear, they are often a result of tumor burden and its mass effect. Up to 50% of nonfunctioning panNET present distant metastases, particularly in the liver, although other locations include the lungs, bone, peritoneum, adrenal glands, brain, and spleen [3]. Similarly, metastatic disease is a common clinical feature of panNEC. A retrospective study reported 88% of panNEC in their cohort demonstrated metastases upon diagnosis[9].

IMAGING FEATURES

Imaging plays a critical role in diagnosing and evaluating panNEN. Conventional modalities like US, CT, and MRI are often used in the initial detection of panNEN. Techniques using PET/CT and novel radiotracers have proven to be extremely useful in the identification and classification of these tumors.

US

On sonography, panNEN usually appear as a well-defined, solid, heterogeneous hypoechoic mass (Figure 1). Some lesions may present with cystic regions[8,10]. Hepatic metastases from panNEN are often hyperechoic in comparison to surrounding liver parenchyma, however they can also manifest as hypoechoic and targetoid lesions. Doppler US reveals increased vascularity. Endoscopic US (EUS) is the preferred modality for detecting small, occult panNEN that are difficult to see with noninvasive techniques[1]. EUS has been reported to have 80% to 90% sensitivity towards panNET, including those that remain undetected on CT and transabdominal US[11-14]. EUS sensitivity towards small insulinomas and duodenal gastrinomas is particularly useful, as these lesions can often be overlooked by other modalities. Following microbubble contrast, panNET show early, intense enhancement on EUS, differentiating these tumors from panNEC or pancreatic ductal adenocarcinoma (PDAC) which are generally hypovascular. Homogeneous enhancement typically indicates a lower Ki-67 index[1]. Other benefits of EUS include its capacity for tissue acquisition using fine needle aspiration or core biopsy; EUS-guided biopsies agree with surgical Ki-67 evaluation in up to 84% of cases[15-18]. Intraoperative US also plays a useful role in some cases by allowing for accurate localization of neoplasms in relation to adjacent structure, thus reducing the risk of postoperative fistulas[1].

CT

CT is commonly used for initial assessment of suspected panNET. Given its high spatial resolution, CT provides excellent diagnostic information with regards to the detection and characterization of the primary tumor and allows assessment of local vascular spread and distant metastatic spread. Typical CT protocol involves multiphasic imaging with pre-contrast acquisition and arterial, pancreatic, and venous phase acquisition following contrast[19]. Pre-contrast images may be useful in cases where there is hemorrhage. Following contrast administration panNEN are generally
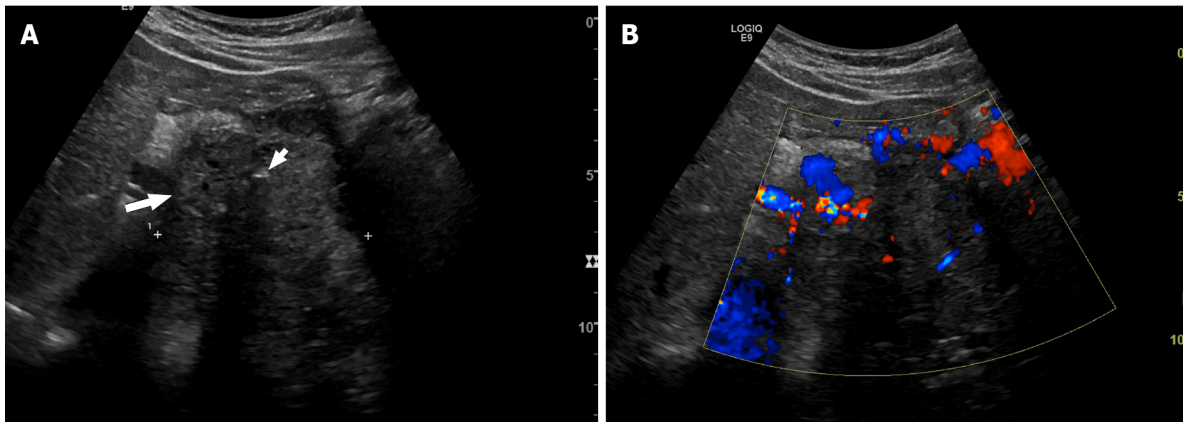
Figure 1 Forty-year-old man with pancreatic neuroendocrine neoplasm. A: Axial ultrasound shows a large solid heterogeneous mass (long arrow). Internal calcification (small arrow) is seen, causing posterior acoustic shadowing; B: Doppler ultrasound shows increased vascularity within the pancreatic tumor.

hyperenhancing (Figure 2) in comparison to surrounding pancreatic tissue on arterial phase and remain mildly hyperattenuating on venous and delayed phases. However, more subtle discrimination of enhancement patterns may allow further classification. Intense, homogeneous enhancement is typical of lower grade panNEN. Grade 1 and 2 neoplasms often appear as small, well-circumscribed lesions, best depicted on arterial phase. These tumors may contain cystic regions in up to 15%-20% of cases[20,21], and are more common in cases associated with MEN1. Pancreatic ductal dilation is more commonly seen in high-grade neoplasms and mixed tumors than well-differentiated panNEN; however, ductal dilation in low-grade tumors may be seen with secretion of serotonin. Grade 3 tumors are characterized as large, ill-defined masses that manifest with mild to low enhancement on arterial phase. They are typically hypointense on portal venous phase imaging. Heterogeneous attenuation due to necrosis and cystic change and the presence of lymphadenopathy or metastatic disease is common.

CT radiomics may be useful for distinguishing the grade of panNEN based on tumor heterogeneity and spatial variation when imaging findings are ambiguous. Texture analysis interprets the distribution of pixel values and position within an image to provide objective, quantitative evaluation of tissue heterogeneity. Guo *et al* [22] found texture parameters such as mean grey-level intensity, entropy, and uniformity demonstrated adequate sensitivity (73%-91%) and specificity (85%-100%) when differentiating grade 1 and 2 panNET from grade 3 panNEC, suggesting texture analysis may be useful for staging panNEN. Mean grey-level intensity showed up to a 100% sensitivity and 91% specificity for distinguishing grade 1 and grade 2 panNET. Canellas and colleagues reported significant differences between low-grade (grade 1) and high-grade (grade 2 and 3) panNEN in texture parameters including skewness, mean of positive pixels, and entropy. However, the only parameter that was an independent predictor of tumor grade was entropy. In addition, further investigation and standardization of postprocessing techniques is required before texture analysis can be applied in a clinical setting[23].

In conjunction with clinical findings, CT can also aid distinguishing functioning from nonfunctioning panNET. Functioning panNET tend to be smaller and more homogenous lesions. Gastrinomas may present ring-like enhancement. Nonfunctioning panNET are usually larger, heterogeneously enhancing masses, and are more likely to exhibit local or vascular spread. Necrosis, cystic changes, and calcifications may be observed[1,8]. Larger nonfunctioning panNET are more likely to exhibit aggressive behavior and often present with metastatic disease.

Hepatic metastases demonstrate intense enhancement on arterial phase imaging and only mildly enhance during the portal venous phase. Similar to gastrinoma, ring-like enhancement may also be seen and can be useful for differentiating panNEN-related metastatic disease from other hepatic lesions[1,11].

MRI

MRI provides improved detection of panNEN and hepatic metastases over abdominal sonography and CT given its superior contrast resolution (Figure 3). MRI enhancement patterns on arterial, venous, and delayed sequences are similar to those seen on CT. Fat-suppressed and diffusion-weighted imaging are particularly useful for identifying small, occult lesions and recognizing associated edema[11]. On MRI,
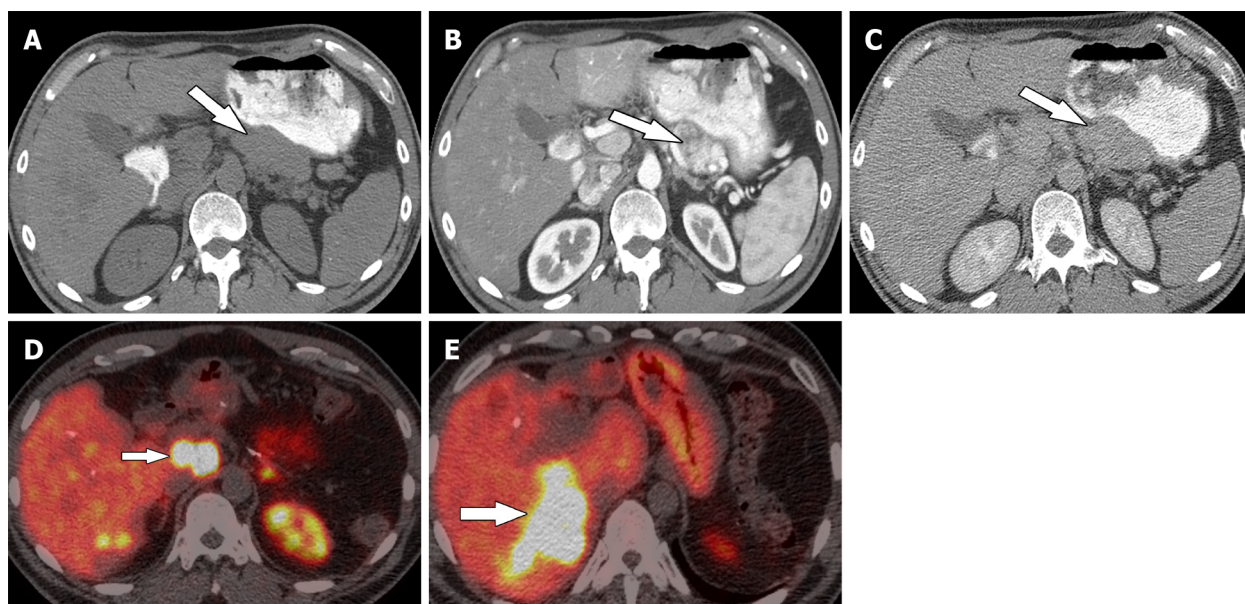
Figure 2 Thirty-eight-year-old woman with pancreatic neuroendocrine neoplasm. A: Axial precontrast computed tomography; B and C: Contrast-enhanced computed tomography in the arterial phase (B) and delayed phase (C) demonstrate pancreatic neuroendocrine neoplasm (arrow). Patient underwent surgical resection; D and E: Follow-up Gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate positron emission tomography/computed tomography shows metastatic adenopathy (short arrow) and liver metastases (long arrow).
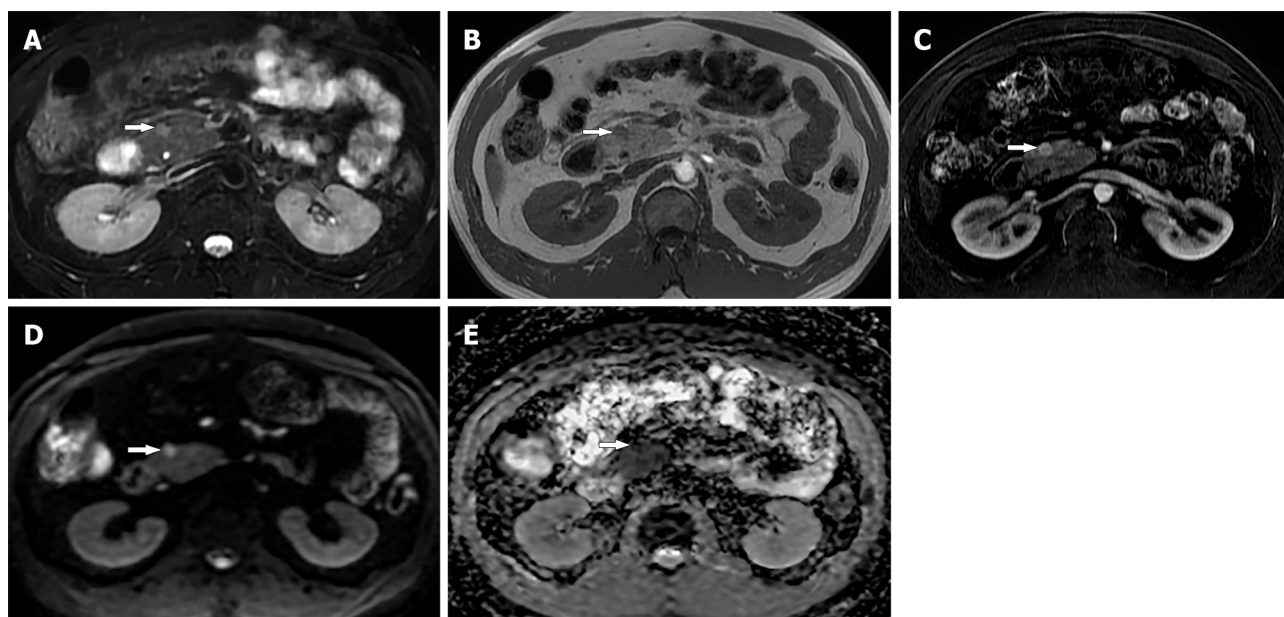

Figure 3 Thirty-five-year-old male with small pancreatic neuroendocrine neoplasm. A: Axial magnetic resonance T2 weighted image; B: T1 weighted image show a small 1 cm mass (arrow) in the head of pancreas; C: Arterial phase image shows avid enhancement in the tumor; D: Diffusion-weighted image; E: Apparent diffusion coefficient map show restricted diffusion within the tumor (arrow). Biopsy confirmed diagnosis of pancreatic neuroendocrine neoplasm.

panNEN typically manifest as hypointense on T1-weighted imaging and isointense on portal venous and delayed phases. Low-grade panNEN tend to exhibit high T2 signal while high-grade neoplasms typically exhibit low to intermediate hyperintensity on T2-weighted imaging[1].

Differentiating between panNEC and grade 3 panNET is challenging on imaging alone (Table 2). PanNEC usually share similar enhancement patterns to grade 3 panNET. Imaging features such as hypoenhancement or rim-like enhancement on arterial phase, persistent enhancement on portal venous phase, and hyperenhancement on delayed phase imaging may favor a diagnosis of panNEC over panNET. On diffusion-weighted imaging, panNEC also demonstrate high signal intensity and low apparent diffusion coefficient (ADC) in comparison to grade 3 panNET[1];

Table 2 Imaging features of grade 3 pancreatic neuroendocrine tumors *vs* grade 3 pancreatic neuroendocrine carcinomas

Grade 3 PanNET	Grade 3 PanNEC
Smaller, more defined lesions	Larger, ill-defined lesions
Absence of ductal dilation or metastatic disease	Ductal dilation or metastatic disease
Low to moderate homogeneous enhancement on arterial phase imaging	Heterogeneous or rim-like enhancement on arterial phase imaging
Hypointense on delayed phase imaging	Atypical persistence of enhancement on delayed phase imaging
Higher ADC values	Signal hyperintensity on diffusion-weighted MRI and lower ADC value
Low uptake on ^{18}F-FDG PET/CT	High uptake on ^{18}F-FDG PET/CT
Moderate uptake on ^{68}Ga-DOTATATE PET/CT	Low uptake on ^{68}Ga-DOTATATE PET/CT

MRI: Magnetic resonance imaging; ADC: Apparent diffusion coefficient; PanNET: Pancreatic neuroendocrine tumors; PanNEC: Pancreatic neuroendocrine carcinomas; ADC: Apparent diffusion coefficient; ^{18}F-FDG: Fluorine-18 fluorodeoxyglucose; PET/CT: positron emission tomography/computed tomography; ^{68}Ga-DOTATATE: Gallium-68 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid–octreotate.

however exact ADC cutoffs vary between studies and are not typically used in clinical practice to differentiate between panNEC and panNET[24-26]. The presence of ductal dilation and metastatic disease may indicate panNEC rather than panNET[1].

MRI is very helpful towards assessing the spread of panNEN to the liver[27]. Hepatic metastases are usually heterogeneously hyperintense on T2-weighted imaging, though atypical presentations include low to moderate T2 intensity. PanNEN hepatic metastases are typically hyperintense on the arterial phase of MRI. A peripheral ring of enhancement with gradual internal enhancement may also occur[1, 11,28]. The apparent size of metastases can also vary depending on the dynamic contrast phase on which the dimension is measured. For estimation of tumor load, measurements on the hepatobiliary phase of gadoxetate MRI may be more accurate[29, 30]. Histogram analysis of ADC maps could be useful for further indicating the aggressiveness and spread of panNEN. ADC entropy and kurotsis were reported to increase with tumor grade and vascular invasion. These parameters may also be useful for distinguishing panNEN with lymph node or distant metastasis, as both increase with the presence of metastases[31].

Functional imaging

The majority of panNEN express somatostatin receptors, allowing for excellent detection and characterization of these lesions using somatostatin analogs (SSA) coupled with radionuclide tracers. These techniques represent the forefront of panNEN imaging and can help to select patients for peptide receptor radionuclide therapy (PRRT)[1].

Somatostatin receptor scintigraphy (SRS) with Indium 111 (^{111}In)-pentetreotide can identify primary or metastatic disease throughout the body with 77% sensitivity and provides functional information on tumor somatostatin receptor expression[1,8]. However, SRS is limited due to its nonspecific uptake in other organs and inflammatory tissues. In addition, its poor spatial resolution and comparatively low affinity for somatostatin receptors has led to the adoption of substantially superior PET/CT techniques[32].

Gallium-68 (^{68}Ga) 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)–octreotate, more commonly called ^{68}Ga-DOTATATE, has demonstrated consistently high specificity (81%-100%) and sensitivity (90%-100%) as a PET agent for panNET[33,34] (Figure 4). ^{68}Ga-DOTATATE PET/CT is particularly useful for distinguishing low-grade, well-differentiated panNEN, which show greater ^{68}Ga-DOTATATE uptake than high-grade panNEN. Grade 3 panNET exhibit moderate uptake, while panNEC exhibit relatively poor uptake[1]. Physiological uptake in the pancreatic uncinate process is observed in up to one-third of individuals. The European Association of Nuclear Medicine (EANM) recommends disregarding uptake in the pancreatic uncinate process unless corresponding imaging findings are seen [35]. Other ^{68}Ga-DOTA-peptides include DOTATOC and DOTANOC, which are reported to have similar diagnostic yields as to ^{68}Ga-DOTATATE.

The decrease of somatostatin receptors seen in higher grade, less differentiated neoplasms is accompanied by an increase in metabolic activity, making Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET an ideal technique for identifying these lesions. Grade 3 tumors have a reported median maximum standardized uptake value of 11.7
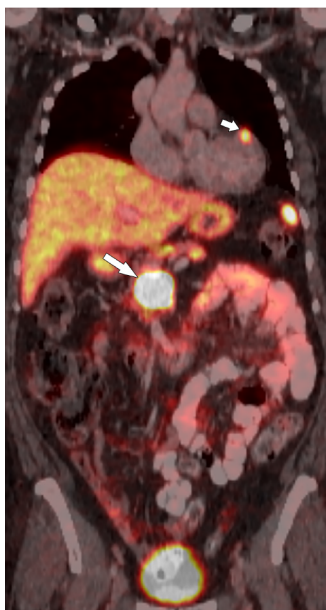
Figure 4 Sixty-two-year-old female with metastatic pancreatic neuroendocrine neoplasm. Coronal fused Gallium-68 1,4,7,10-tetraazacyclodo-decane-1,4,7,10-tetraacetic acid–octreotate (DOTATATE) positron emission tomography/computed tomography shows a large soft tissue mass in the pancreatic head with intensely avid DOTATATE uptake. Note the subtle metastatic lesion in the pericardium (short arrow) along the left atrium.

for ^{18}F-FDG, *vs* 4.4 for ^{68}Ga-DOTATATE[1]. Conversely, tumors with a Ki-67 index lower than 10% showed minimal ^{18}F-FDG uptake, but high ^{68}Ga-DOTATATE uptake [36]. Dual-tracer PET/CT with ^{68}Ga-DOTATATE and ^{18}F-FDG may be useful for distinguishing grade 3 panNET from panNEC, as higher uptake of ^{68}Ga-DOTATATE indicates grade 3 panNET, while higher uptake of ^{18}F-FDG indicates panNEC[1,35]. The use of SSA-PET/CT combined with texture analysis may also be a useful indicator of prognosis. A multi-center retrospective study demonstrated higher entropy could predict greater overall survival[37].

A minority of insulinomas (< 10%) are negative on all conventional modalities due to their small size[35]. In such instances, SSA-PET/CT is a poor alternative, with a reported 25% sensitivity and specificity[38-43]. ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA) PET/CT may aid localization of insulinomas, offering high sensitivity in cases of hyperinsulinemic hypoglycemia. However, this technique frequently results in positive findings for non-neuroendocrine pancreatic lesions and is only indicated for detecting non-pancreatic NENs by 2017 EANM guidelines[44]. Carbidopa premedication may increase ^{18}F-DOPA specificity towards insulinomas by inhibiting physiologic uptake. Multiple retrospective studies with small cohorts using ^{18}F-DOPA and carbidopa premedication have demonstrated insulinoma detection rates of 70-85% [45-47]. However, further investigation into the role of ^{18}F-DOPA PET/CT in panNEN is required.

Glucagon-like peptide receptor (GLP-1R) PET/CT may also prove useful for detecting insulinomas. The majority of benign insulinoma express GLP-1R, resulting in a sensitivity on GLP-1R -based PET/CT of more than 95%[47,48]. However, uptake in the pancreatic tail can be mistaken for physiological renal accumulation of radio-nuclides; uptake by duodenal Brunner gland may be mistaken for an insulinoma in the pancreatico-duodenal groove. In addition, malignant insulinomas express GLP-1R considerably less than their benign counterparts [35,49].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for panNEN includes other hypervascular pancreatic lesions. Pancreatic metastases from renal cell carcinoma, melanoma, and sarcoma may often appear as hypervascular masses resembling panNEN. In particular, renal cell carcinoma may present with late onset metastasis in pancreas, even 5 to 10 years following treatment of the primary tumor, causing diagnostic dilemma. A history of previous primary malignancies should alert to the possibility of pancreatic metastases over panNEN. Serous cystadenomas represent another possible mimic of panNEN,

particularly the rare subset of cases which may appear solid on CT. T2-weighted usually reveals presence of multiple septated cysts in serous cystadenomas which may occasionally not be apparent on CT. Lack of uptake on ^{68}Ga-DOTATATE PET/CT is also useful for separating serous cystadenomas from panNEN. Intrapancreatic accessory splenules in the pancreatic tail may be another potential pitfall causing diagnostic confusion, especially if only a single-phase CT is available. However, on MRI this diagnosis is generally straightforward. Splenules will have the same appearance as normal spleen on all MR sequences including T1-weighted, T2-weighted, diffusion-weighted and postcontrast sequences. In cases of diagnostic difficulty, uptake on technetium 99m (^{99m}Tc)-labeled heat-damaged red blood cell-tagged or ^{99m}Tc-labeled sulfur colloid scans may help. Cystic panNEN may be mistaken for other cystic pancreatic entities such as mucinous cystic neoplasms, in which case EUS-guided fine needle aspiration might be necessary to confirm diagnosis [1].

Distinguishing the typical well-differentiated panNET from PDAC is usually straightforward, as panNET typically are hypervascular, well-defined and do not typically cause ductal obstruction. Nevertheless, the imaging appearance of panNEC often overlap with PDAC given their shared hypovascularity and ill-defined borders. These similar radiologic findings may result in misdiagnosis of up to 57% of panNEC as PDAC[31]. Decreased portal phase enhancement and a lower enhancement ratio between arterial and portal phase may raise suspicion for PDAC over nonhyper-vascular panNEN[50-52]. Features that are more common in panNEC include tumoral calcification and vascular invasion[1,31]. CT texture analysis may be useful as panNEC typically demonstrate more intratumoral homogeneity than PDAC. Consequently, panNEC demonstrate higher uniformity and lower entropy than PDAC at portal phase imaging[50]. Texture analysis based on ADC values may also improve diagnostic capabilities; ADC histogram analysis of diffusion-weighted imaging revealed PDAC demonstrate higher kurtosis and skewness on ADC_{400} and ADC_{800} than panNEN, overall. PanNEN exhibited significantly lower entropy regardless of *b* value [31]. However, definitive discrimination between panNEC and PDAC using imaging alone is difficult, and histological diagnosis is usually warranted.

MANAGEMENT

The management of panNEN varies with their classification and the degree of local and metastatic spread. Localized, asymptomatic panNET less than 2 cm in size are usually treated conservatively with active surveillance[53]. However, larger or symptomatic panNEN require more comprehensive treatment such as symptom-directed therapy, SSA therapy, molecularly-targeted and conventional chemotherapy, or peptide receptor radionuclide therapy. Liver-specific therapy may be used to treat hepatic metastases[54,55].

Surgical resection and debulking

Surgical resection is currently used for nonfunctioning tumors larger than 2 cm, and functioning panNET of any size. Accurate tumor localization is critical for operative success. ^{68}Ga-DOTATATE PET/CT is the preferred imaging study for evaluating the spread of noninsulinoma panNET[54]. Selective arterial calcium stimulation with hepatic venous sampling is occasionally used to localize insulinomas that are difficult to assess on anatomic imaging. The emergence of GLP-1R PET/CT represents a superior alternative to this technique[54,56,57]. Simple enucleation may be sufficient for smaller, low-grade tumors that are at least 2-3 mm away from the main pancreatic duct. MR cholangiopancreatography and EUS are useful for estimating this distance [54]. The majority of functioning panNET require more extensive resection and lymphadenectomy[1]. A total pancreatectomy may be considered for multifocal disease. Noncurative surgical debulking may be pursued in cases of unresectable, metastatic panNEN to palliate symptoms and extend survival[1]. However, advanced disease is typically managed with non-surgical treatment strategies (Figure 5).

SAA therapy

SSA such as octreotide or lanreotide is often used in the management of advanced, progressive tumors. In addition to their antisecretory benefits these drugs have cytostatic effects on the tumor, as proven by the multicenter, phase III CLARINET and PROMID trials which demonstrated an increase in estimated progression-free survival [58,59]. However, this effect appears to be diminished in tumors that do not show adequate uptake on somatostatin imaging techniques. Koch *et al*[60] reported a 2.9-fold
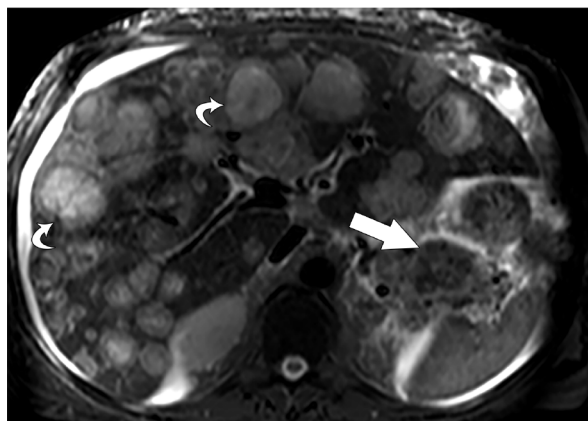
Figure 5 Thirty-nine-year-old male with metastatic pancreatic neuroendocrine neoplasm. Axial T2 weighted image shows innumerable bilobar metastases (curved arrows). Note the heterogeneous primary pancreatic neuroendocrine tumor (straight arrow). Patient was treated with capecitabine and temozolomide.

increased probability of achieving stable disease following SSA therapy in neuroendocrine tumors with high uptake on ^{68}Ga-DOTATATE PET, in comparison to tumors with low uptake. Thus, a multidisciplinary panel of experts convened by the Society for Medicine and Molecular Imaging (SNMMI) suggested the potential utility of ^{68}Ga-DOTATATE PET/CT in selecting patients with nonfunctioning panNET for somatostatin analog therapy. However, the SNMMI expert panel agreed that in the case of symptomatic manifestations, SSA therapy is indicated regardless of imaging findings [61].

Molecularly targeted chemotherapy

Molecularly targeted chemotherapy using agents such as everolimus, an mTOR inhibitor, and sunitinib, a tyrosine kinase inhibitor, have been reported to improve progression-free survival of individuals with grade 3 panNET and metastatic disease [1]. Early studies on emerging agents including multi-targeted kinase inhibitors and a combination of temsirolimus and bevacizumab, also show positive results[55,62].

Conventional chemotherapy

Although SSA and molecular therapies have shown significant benefits in patients with panNEN, conventional chemotherapy or PRRT is preferred for highly symptomatic patients and those with rapidly growing metastases. A streptozocin-based regimen or a combination of temozolomide and capecitabine is the optimal approach for panNET[55]. Platinum-based chemotherapies such as cisplatin with etoposide or irinotecan are the regimen of choice for panNEC, with reported response rates of 60% [1,63].

Peptide receptor radionuclide therapy

Peptide receptor radionuclide therapy (PRRT) uses SSA to deliver radionuclides such as yttrium-90 (^{90}Y) and lutetium-177 (^{177}Lu). These agents deliver beta radiation or high energy electrons, causing localized cellular necrosis at the site of accumulation, and have been associated with promising outcomes in grade 1 and 2 panNET. One phase II, single-center clinical trial demonstrated an increase in median survival by 26 mo in neuroendocrine tumor patients treated with PRRT[64-68]. However, PRRT may be less useful in panNEC due to their lower somatostatin receptor expression[1]. In addition, panNET with lower expression of somatostatin receptors may be susceptible to a similar decrease in response rate. Multiple studies propose the use of the "NETPET" scoring system developed by Chan and colleagues, and similar PET/CT-dependent classification, to select patients for PRRT[69-72]. In the NETPET system, tumors are graded from P1 to P5 based on their avidity on ^{68}Ga-DOTATATE and ^{18}F-FDG PET, with a score of 1 indicating positive results on ^{68}Ga-DOTATATE but not ^{18}F-FDG PET, and a score of 5 indicating positive results on ^{18}F-FDG PET but not on ^{68}Ga-DOTATATE PET. However, further investigation into the correlation between PRRT outcome and NETPET scores must be done to establish if such imaging-based classification systems have a role in clinical settings. Other methods for predicting PRRT response include the measurement of skewness and kurtosis based off ^{68}Ga-DOTATATE imaging; Önner *et al*[73] reported significantly higher skewness and

kurtosis in tumors which did not response to treatment that those that did. Nevertheless, the diagnostic ability of the two metrics to indicate poor PRRT response remained moderate to low.

Liver-specific therapy

In the presence of hepatic metastases, liver-directed therapies including partial hepatectomy, ablation, or arterial chemo- and radioembolization may be useful. Resection is usually contraindicated in the presence of multifocal extrahepatic metastases, high-grade and poorly-differentiated carcinoma, liver disfunction, or diffuse bilobar involvement[55]. Previously, resection was only recommended if more than 90% of disease could be removed but more recent literature supports lowering this threshold to 70%[74-76]. Ablation is often reserved for the treatment of small metastases that do not qualify for surgical resection or may be done in addition to resection in the presence of multifocal disease. Arterial embolization, radioembolization, and chemoembolization can be used to diminish the secretory effects of functioning panNET. Liver transplantation is only considered in patients with significant hepatic tumor burden, without the presence of extrahepatic metastases, and is not routinely undertaken in metastatic panNET[1,55]. ^{68}Ga-DOTATATE PET/CT may be useful for determining suitability of patients for transplantation, as this technique allows for a whole-body acquisition in order to assess potential extrahepatic metastatic disease[35].

Symptom-directed therapy

Symptom-directed therapy plays an important role in the management of functioning panNETs. Treatment varies with each functioning panNET; common interventions include the use of diazoxide to suppress insulin secretion in insulinomas, and proton pump inhibitors to suppress hypersecretion by gastrinomas. Long-acting SSA may also be useful for controlling the secretory effects of these tumors, particularly vasoactive intestinal peptide-secreting tumors and glucagonomas[55].

CONCLUSION

Better understanding of the genetic and biological features of panNEN has led to significant changes in the diagnosis and management of these tumors. Imaging is crucial for diagnosing and staging of panNEN. CT and MR play a vital role in differentiating these tumors from other benign and malignant lesions of the pancreas. Recent studies indicate enhancement pattern of panNEN on cross sectional imaging and texture analysis may also be helpful in classifying these tumors or indicating prognosis. Diagnosis of panNEN is typically confirmed with EUS guided biopsy. Functional imaging techniques including SRS and PET/CT are very helpful in the management of panNEN. ^{68}Ga-DOTATATE and GLP-1R-based PET/CT may improve detection of occult lesions and their characterization. These techniques also have the potential to guide management, as information on somatostatin receptor expression and metabolic activity are useful for determining optimal treatment.

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