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SPECIAL SECTION: NEUROENDOCRINE NEOPLASMS

Pancreatic neuroendocrine neoplasms: a 2022 update for radiologists

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Abstract
Pancreatic neuroendocrine neoplasms (PaNENs) are a unique group of pancreatic neoplasms with a wide range of clinical presentations and behaviors. Given their heterogeneous appearance and increasing detection on cross-sectional imaging, it is essential that radiologists understand the variable presentation and distinctions PaNENs display compared to other pancreatic neoplasms. Additionally, some of these neoplasms may be hormonally functional, and it is imperative that radiologists be aware of the common clinical presentations of hormonally active PaNENs. Knowledge of PaNEN pathology and treatments may influence which imaging modality is optimal for each patient. Each imaging modality used for PaNENs has distinct advantages and disadvantages, particularly in different treatment settings. Thus, the focus of this manuscript is to provide an update for the radiologist on PaNEN pathology, imaging, and treatments.

Keywords Neuroendocrine · Pancreas · PaNEN

Introduction

Pancreatic neuroendocrine neoplasms (PaNENs) represent a unique class of neoplasm that are distinct from the more common pancreatic adenocarcinoma in histology, management, and prognosis. PaNENs are relatively rare, making up just 3–5% of all pancreatic cancers with an incidence of 2.5–5 per 100,000 globally [1] and 0.48 per 100,000 population annually in the USA [2]. During 2000–2016, the incidence of PaNEN significantly rose from 0.27 to 1.06 per 100,000 persons with an average annual percentage change of 9.4 [3]. There is some speculation that the increased incidence may be partly related to widespread increase in the use of cross-sectional diagnostic imaging [namely computed tomography (CT) and magnetic resonance imaging (MRI)] during that period. Although the majority of PaNENs are

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sporadic, approximately 10% are associated with familial or hereditary syndromes, such as multiple endocrine neoplasia type 1, von Hippel–Lindau disease, neurofibromatosis type 1, and tuberous sclerosis [4].

The presentation and clinical course of PaNENs are protean, with substantial variability in aggressiveness and metastatic frequency, as well as potential syndromic manifestations secondary to pancreatic hormone hypersecretion. PaNENs are more likely to be diagnosed with distant metastases at the time of initial presentation, a pattern that has been increasing. This is in contrast to other primary sites of NENs of the gastrointestinal tract, such as the rectum and small intestine, which are more likely to be diagnosed with local or locoregional disease at the time of presentation, respectively [5]. Most commonly, patients with PaNENs present in their seventh or eighth decade. The 5-year survival for PaNENs is improving such that patients with metastatic disease are now surviving for a median of 60 months [2], but with significant heterogeneity in survival rates and persistent poor prognosis for late-stage PaNENs [3].

PaNENs represent a unique and challenging scenario for patients and their healthcare providers given heterogeneity in tumor biology between patients and even within a single patient. In this review, the Neuroendocrine Disease Focused Panel of the Society of Abdominal Radiology aims to provide a comprehensive review and guidance for abdominal radiologists, in an effort to optimize imaging strategies, pathology, staging, and treatment for patients with these neoplasms.

Tumor differentiation, grade, and heterogeneity

Pathologic classification is essential in the diagnostic assessment and clinical management of PaNENs and therefore tissue sampling is nearly always performed to confirm the diagnosis of NEN. Modern pathologic classification of NENs includes two components, namely differentiation and grade. Differentiation is a histologic classification by the pathologist as either well differentiated or poorly differentiated, based on resemblance to normal endocrine cells (Fig. 1). When interpreted independently, such histologic classification is necessary but not sufficient to predict biological behavior given that well-differentiated NETs have highly variable natural histories even with identical pathologic findings. Tumor grade reflects tumor proliferation rate, which is determined by the mitotic rate or by the percentage of tumor cells staining positively for Ki-67. This evaluation may be inaccurate in small biopsy specimens due to heterogeneity in proliferation or due to limited number of tumor cells present (as at least 500 to 2000 tumor cells should be present within an area of maximal Ki-67 labeling to determine proliferative index) [6]. In the 2017 nomenclature for the pancreas and 2019 nomenclature for all of the gastroenteropancreatic neuroendocrine neoplasms, well-differentiated tumors are subdivided by the World Health Organization (WHO) into three pathologic grades (G1–3) based on the Ki-67 proliferative index and/or the number of mitoses/2mm^2 [7]. The PaNENs with a Ki-67 index of less than 3% and/or a mitotic count of less than 2 mitoses/2 mm^2 are defined as low grade or grade 1 (G1) tumors. Intermediate grade or grade 2 (G2) tumors have a Ki-67 index between 3 and 20% or a mitotic count between 2 and 20 mitoses/2 mm^2, while high grade or grade

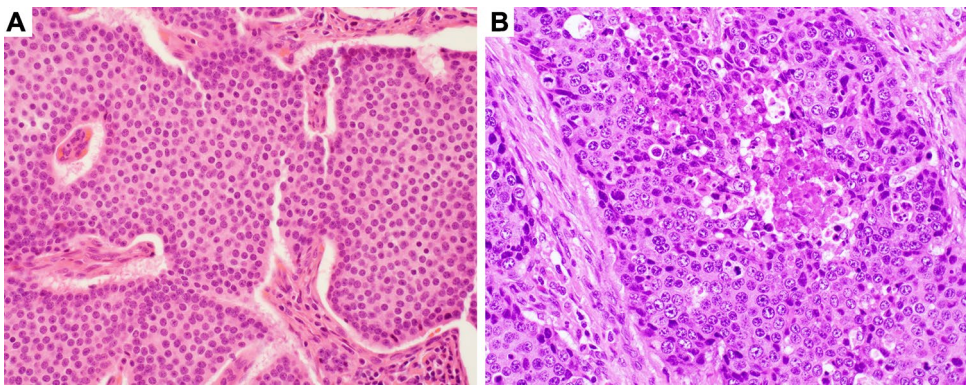

Fig. 1 Hematoxylin and eosin photomicrograph of well differentiated (**a**) vs. poorly differentiated pancreatic neuroendocrine neoplasm (**b**). Image **a** tumor cells that are monomorphic, with rounded to oval nuclei, granular chromatin, rare mitosis, or apoptosis/necrosis. Cytoplasm is moderate, amphophilic, or eosinophilic. Tumor cells have an organoid arrangement, disposed in nests, trabeculae, or glandular formation. Image **b** tumor cells show pleomorphism, hyperchromasia, frequent mitosis, and apoptosis as well as confluent necrosis. In large cell subtype, the nuclei are vesicular, with prominent nucleoli, and cytoplasm is scant to moderate, amphophilic to eosinophilic

3 (G3) tumors have a Ki-67 index of greater than 20% or a mitotic count of greater than 20 mitoses/2 mm^2. Critically, the 2017 WHO criteria separated these well-differentiated G3 PaNENs from poorly differentiated G3 neuroendocrine carcinoma based on tumor cell morphology. Histologic subdivisions of poorly differentiated neuroendocrine carcinomas are either large cell or small cell variants. A mixed neoplasm with a neuroendocrine component (either well- or poorly differentiated) and a non-neuroendocrine component (such as an adenocarcinoma or acinar cell carcinoma) are collectively categorized as mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs) [8–10] (Table 1).

NENs may demonstrate *intratumoral* heterogeneity as previously discussed, wherein different portions of the same tumor mass demonstrate differing density of Ki-67 positivity, which may or may not be accurately reflected in the small biopsy specimen. Furthermore, NENs may also demonstrate *intertumoral* heterogeneity wherein separate tumor sites demonstrate differing grades or differentiation. The complexity of patient management can be further complicated by changes in tumor grade or differentiation over the course of time, as NENs may also demonstrate *temporal* heterogeneity [11]. Thus, a small biopsy sample in a single location at a single time point may not be representative of the overall aggressiveness of the patient's tumor burden and sampling from multiple sites may be indicated over time [12].

Tumor Markers in PaNENs

A minority of PaNENs are functional, designated as such due to the functional hormones they secrete. Hormones secreted in excess by these tumors, include insulin, gastrin, glucagon, vasoactive intestinal peptide, and ACTH, and each are associated with a clinical syndrome [13]. An underlying functional tumor tends to be discovered when they are small in size as compared to nonfunctional tumors. However, most PaNENs are nonfunctional and are either detected incidentally or due to bulk symptoms from the large size of the pancreatic mass or hepatic metastatic disease.

Functional or not, all PaNENs derive from a similar cell lineage and therefore secrete substances which can be used as biomarkers [14]. Chromogranin A is a protein released from neuroendocrine cells that circulates in the blood and is often elevated in cases of PaNENs. However, serum levels of chromogranin A can also be falsely elevated with certain medical conditions (atrophic gastritis, renal insufficiency) and with drugs, including proton pump inhibitors. The current National Comprehensive Cancer Network (NCCN) guidelines state that routine measurement of chromogranin A can be considered, but states that the recommendation falls under NCCN Evidence and Consensus Category 3 (major disagreement that the intervention is appropriate) and current North America Neuroendocrine Tumor Society (NANETS) guidelines do not recommend the routine use of chromogranin A measurements [15, 16]. Pancreastatin is a new serum biomarker that is overexpressed by PaNENs and potentially less susceptible to false elevations from proton pump inhibitors, but no studies exist that indicate that pancreastatin measurements offer any additional value above conventional imaging [16]. Novel transcriptomic markers, circulating DNA cells, and cell-free tumor DNA are emerging options, but remain investigational at this time. In cases of high grade or poorly differentiated PaNENs where the imaging features of the tumor may overlap with pancreatic ductal adenocarcinoma, measurements of serum CA 19-9 may be useful as elevations in CA 19-9 may suggest the tumor represents adenocarcinoma rather than PaNEN.

Imaging of PaNENs

Multiphasic CT imaging with intravenous contrast is the most common initial and useful preoperative imaging exam in patients with PaNENs [17]. The sensitivity of CT for detection of PaNENs is 64–81%, mainly depending on the size of the tumor [17]. Both CT and MRI can be utilized in the characterization of the pancreatic mass. *Importantly, there is no single characteristic imaging appearance of PaNEN* (Fig. 2). Tumor size can range from a few millimeters to many centimeters, enhancement can vary from hyperenhancing to hypoenhancing, and tumor margins can vary from round and well defined to ill-defined and infiltrative [18]. Tumor composition can range from entirely solid to entirely cystic and tumors may also demonstrate

Table 1 2019 WHO classification of gastroenteropancreatic neuroendocrine neoplasms

WHO category	Neuroendocrine tumors			Neuroendocrine carcinomas	MiNeNs
Tumor grade	Low (G1)	Intermediate (G2)	High (G3)	High	Variable
Degree of differentiation	Well	Well	Well	Poorly	Well or poorly
Ki-67 index	< 3%	3–20%	> 20%	> 20	Variable
Mitotic count	< 2/2 mm^2	2–20/2 mm^2	> 20/2 mm^2	> 20/2 mm^2	Variable

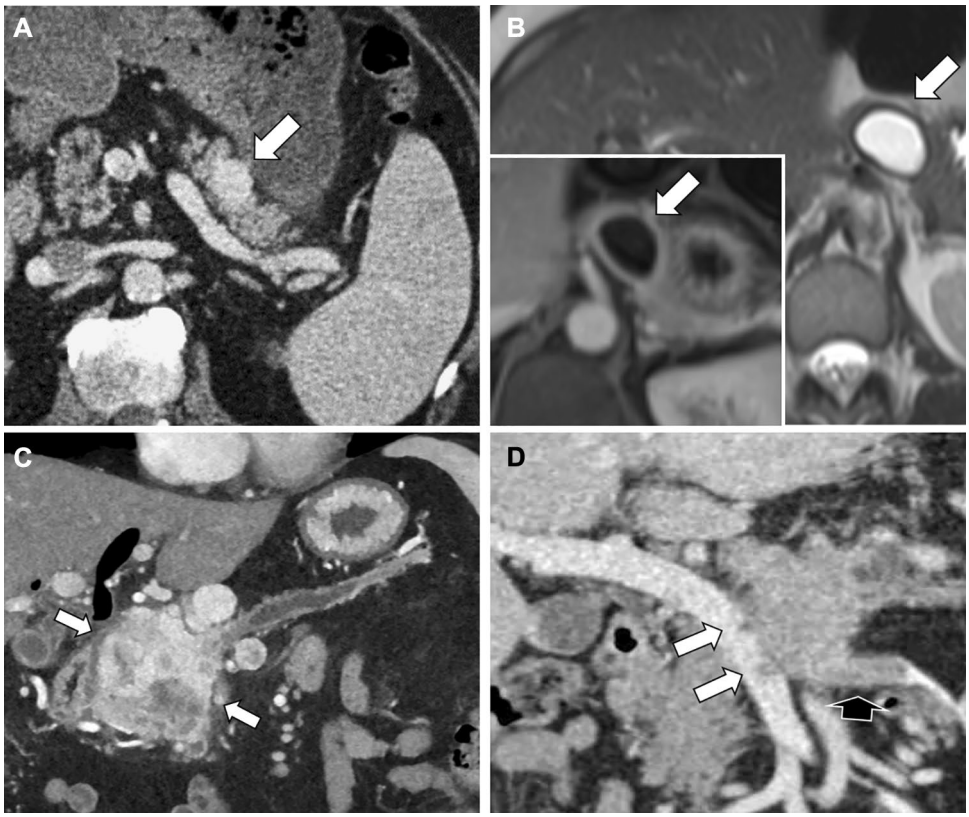

Fig. 2 Imaging examples demonstrate the wide variability in appearance of pancreatic neuroendocrine neoplasms. **a** Round, homogeneously hyperenhancing pancreatic lesion (arrow) on contrast-enhanced portal venous phase CT corresponds to a well-differentiated grade 1 PaNEN. **b** T2-weighted MR image with post-contrast T1 fat-saturated image inset shows T2 hyperintense unilocular cystic lesion (arrow) with thick peripheral enhancement, compatible with a cystic well-differentiated grade 1 PaNEN. **c** Curved planar reformatted contrast-enhanced CT image through the pancreatic duct demonstrates a large heterogeneously enhancing pancreatic head mass (flanked by arrows) which extends into the pancreatic duct and results in upstream ductal dilatation and pancreatic parenchymal atrophy. This mass was a well-differentiated grade 2 PaNEN. **d** Curved planar reformatted contrast-enhanced CT image through the mesenteric veins demonstrates a heterogeneously hypoenhancing pancreatic mass with contiguous tumor thrombus in the inferior mesenteric vein (short arrow) and the superior mesenteric vein (two arrows). This mass also results in upstream pancreatic ductal dilatation (partially imaged). This mass was a well-differentiated grade 2 PaNEN

calcifications [19, 20]. Although typically associated with the more common pancreatic adenocarcinoma, PaNEN may also cause ductal obstruction and vascular occlusion [21, 22]. Specifically, serotonin-producing PaNENs can cause prominent stromal fibrosis, leading to pancreatic ductal stenosis and upstream ductal dilation out of proportion to the size of the pancreatic mass. When tumor thrombus is discovered contiguous with a pancreatic mass, the underlying histologic diagnosis is most likely PaNEN [23]. On non-contrast CT, PaNENs typically demonstrate a Hounsfield Unit (HU) greater than 20. This feature may be useful in differentiating these tumors from small serous cystadenomas. Dual-energy CT is a novel imaging modality that allows for potential increased detection and conspicuity of enhancing PaNENs through use of low-energy monochromatic energy images that approach the *k*-edge of iodine [24]. The reported sensitivity of MRI for the detection of PaNENs is 93% with a specificity of 88% [25]. On MRI, PaNENs also have variable enhancement and morphologic features as on CT. MR-specific characteristics include low signal intensity on T1-weighted images compared to the normal high background T1 signal intensity of the pancreas. T2 signal is variable and may be intermediate to high. Some PaNENs can be completely cystic and demonstrate high T2 signal, while others demonstrate rim enhancement. Most solid tumors demonstrate diffusion restriction, although generally not to the degree demonstrated by the spleen [26]. While MRI may be utilized to characterize the pancreatic mass, it is probably more commonly utilized to characterize indeterminate liver lesions in these patients [27]. In patients with suspected PaNEN not detected on cross-sectional imaging or for confirmation of a diagnosis, endoscopic ultrasound (EUS) with or without fine-needle aspiration (FNA) is frequently performed, with a reported accuracy of 90–97% for the diagnosis of PaNEN [28].

Unfortunately, many patients with PaNEN present with metastatic disease. The most common sites for metastases include locoregional peripancreatic lymph nodes and the liver. Hepatic and lymph node metastases have similar enhancement pattern to PaNENs, and both hepatic and lymph node metastases often show early, avid arterial enhancement. Hepatic metastases from PaNENs are usually hypodense on unenhanced CT, hyperenhancing on post-contrast images (approximately 70%), and frequently demonstrate washout, all of which can be helpful in differentiating PaNEN metastases from adenocarcinoma metastases [29, 30] (Fig. 3). Liver metastases have high signal on the T2-weighted sequence, enhance in the arterial phase, and have variable degree of enhancement on the portal venous and delayed phase of contrast enhancement when using conventional intravenous extracellular MRI contrast agents. Hepatic metastases may have a high signal on the T1-weighted sequence due to internal hemorrhage and fluid–fluid levels on the T2-weighted sequences. On DWI, hepatic metastases may have a high signal intensity and often have a low signal intensity on the corresponding ADC map unless they are centrally necrotic. On hepatobiliary phase when using hepatobiliary-specific contrast agents, hepatic metastases have a low signal compared to the liver parenchyma and become more conspicuous on the delayed hepatobiliary or hepatocyte-specific post-contrast phase. However, these metastases may demonstrate hepatobiliary phase enhancement in varying amounts, with central enhancement being the most commonly seen pattern with NET metastases [31]. Hepatobiliary phase contrast-enhanced MRI has also been shown to detect more liver metastases as compared to all the other sequences on MRI and currently is the preferred agent for imaging neuroendocrine liver metastases.

Tumor biology prognostication with imaging

Imaging may help navigate the clinical management of complex NEN tumor biology. Some qualitative and quantitative imaging features have been found useful in predicting grade, differentiation, and prognosis of PaNENs. Low to intermediate-grade tumors tend to have well-defined margins compared to high-grade NETs or NECs on cross-sectional imaging. Low-grade tumors also tend to have T2W hyperintense signal on MRI [32, 33] and show moderate to strong enhancement due to high microvascularity compared to hypo, iso, or mild hyperenhancement of the higher-grade PaNENs on the pancreatic phase of contrast-enhanced CT [34, 35].

PaNENs associated with pancreatic ductal dilation are more aggressive [21, 36]. The large (≥ 3 cm) tumors, irregular or lobulated tumors, necrotic tumors, presence of pancreatic ductal dilation and/or vascular invasion, and liver metastasis tend to be significantly associated with high grade and aggressive tumors with poor survival [33, 37]. On DWI MRI, ADC values have inverse correlation with the tumor grade and ADC of $> 1.19 \times 10^{-3}$ mm^2/s indicate lower-grade (G1, G2) PaNENs [38]. Among the high-grade PaNENs, poorly differentiated NECs tend to have lower ADC values compared to well-differentiated tumors [38]. Cystic components within PaNEN do not necessarily reflect tumor necrosis. Rather, a recent meta-analysis on cystic PaNEN shows that tumors with cystic components are associated with more indolent behavior [39].

Molecular imaging with both ^{68}Ga-DOTA-conjugated peptides (DOTATATE, DOTATOC, and DOTANOC) and ^{18}F-FDG PET may offer non-invasive evaluation of tumoral phenotype and provide information as to whether a patient will benefit from somatostatin receptor-based therapeutic agents [40, 41]. Ki-67 index and tumor grade tend to have an inverse relationship with DOTATATE avidity on PET. DOTATATE PET avid neoplasms tend to be low-grade well-differentiated tumors which express somatostatin receptors,

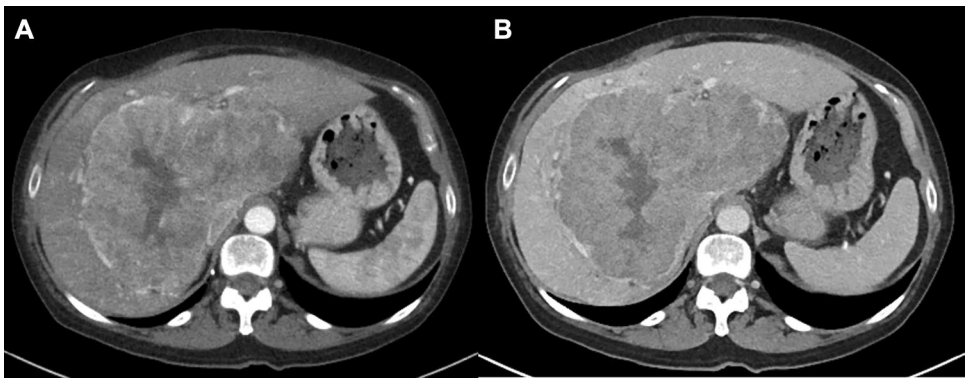

Fig. 3 Axial contrast CT in arterial (**a**) and portal venous (**b**) phases demonstrating a large, avidly enhancing hepatic metastasis on arterial phase with washout on portal venous phase, typical for a PaNEN hepatic metastasis. Central necrosis was present in this lesion, likely due to large size

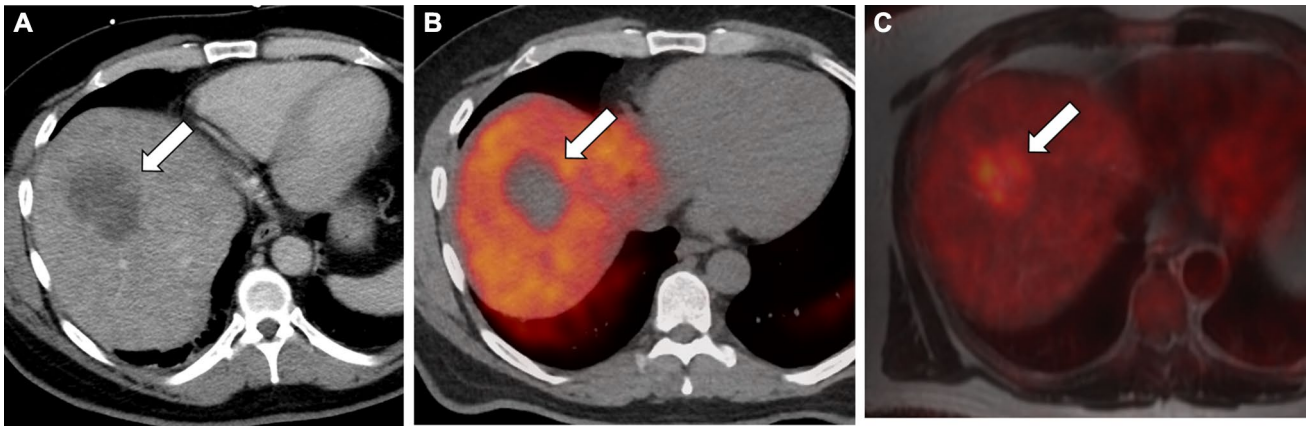

Fig. 4 Patient with extensive neuroendocrine tumor of the liver manifesting on contrast-enhanced CT (**a**) as diffuse nodular heterogeneous enhancement of the liver, with several larger-rounded hypoenhancing lesions, such as that shown in the right hepatic lobe (arrow). ^{68}Ga-DOTATATE PET/CT (**b**) demonstrated mottled, increased tracer uptake in the background liver consistent with biopsy-proven diffuse disease. Superimposed on this, there is a larger focal lesion (arrow) in the right hepatic, also a pathologically proven site of neuroendocrine tumor, which fails to demonstrate significant tracer uptake. FDG PET/MR (**c**) shows heterogeneous uptake within the right hepatic lobe lesion (arrows) where DOTATATE uptake was absent, presumed to be a site of more aggressive tumor with greater Ki-67 index

whereas high grade and poorly differentiated tumors tend to be more FDG avid [42]. Both conventional and molecular imaging may help direct tissue sampling to confirm the presence of a more aggressive component of the tumor (Fig. 4). However, these features are not exclusive, as there may be overlap in the imaging appearance of low- and high-grade NENs. PET/MRI is a novel imaging modality that utilizes the previously discussed advantages of both molecular imaging and MRI to optimize detection of metastatic disease, particularly in the abdomen and pelvis. Given the simultaneous acquisition of both PET and MRI imaging data, PET/MRI offers less co-registration errors and may allow for detection of smaller metastatic deposits when compared to PET/CT [43–45]. Additionally, PET/MRI offers the potential for increased detection of small hepatic metastases compared to PET/CT, particularly when combined with hepatocyte-specific contrast-enhanced MRI and diffusion-weighted imaging [44].

Some analytic techniques like CT or MRI radiomics and radiogenomics are mostly limited to research at this time. Radiomics with tumor texture analysis may allow objective and quantitative assessment of tissue microenvironment and heterogeneity within the PaNENs beyond what is possible with qualitative assessment or tissue sampling [33, 46]. According to some studies, this approach may also outperform traditional imaging characteristics in grading and differentiation of various PaNENs [47, 48]. However, these features are still being explored and need formal prospective confirmation in large sample studies.

Diagnosis, staging, and management of PaNENs

Following identification of a suspected PaNEN on CT or MRI, a histopathologic diagnosis is most frequently obtained by a EUS-guided approach. These EUS-guided biopsies can be performed as either a FNA or fine-needle biopsy (FNB), with FNB demonstrating superior histologic yield and diagnostic accuracy [49]. As with any percutaneous or endoscopic biopsy performed, there are some limitations with this technique for heterogeneous neoplasms. This is particularly important in cases where CT, MRI, or molecular imaging suggest a poorly defined neoplasm or portion of the neoplasm, as non-targeted biopsy may only reveal a more indolent pathology, whereas a targeted biopsy to the suspicious portion of the tumor may significantly alter pathologic grading. Additional endoscopic information regarding locoregional staging can also be performed at the time of diagnosis, including the additional biopsy of peripancreatic lymph nodes.

Staging of PaNENs most commonly utilizes the American Joint Committee on Cancer TNM system, which is based on the size and extent of the tumor (T) and presence of metastatic disease in lymph nodes (N) or distant organs (M) [50] (Table 2). Unique to PaNENs, the size of the primary tumor is one of the key determinants in staging, with tumors localized to the pancreas measuring less than 2 cm classified as stage I and larger localized tumors classified as stage II. The presence of nodal metastatic disease or local invasion of adjacent structures (excluding duodenum and common bile duct) or vasculature places the patient in stage III, while distant metastatic disease represents stage IV disease. Current

Table 2 AJCC 8th Edition TNM staging of pancreatic neuroendocrine neoplasms

AJCC stage	TNM stage	Description
I	T1 N0 M0	Tumor < 2 cm localized to pancreas, no nodal or distant metastases
II	T2 N0 M0 or T3 N0 M0	Tumor 2–4 cm (T2) or > 4 cm (T3) localized to pancreas, can invade duodenum or common bile duct (T3), no nodal or distant metastases
III	T4 N0 M0 or any T N1 M0	Tumor invades adjacent organs or blood vessels (T4), can spread to nearby lymph nodes (N1), no distant metastases
IV	Any T any N M1	Distant metastases present, can be any T or N stage

NANETS and European Neuroendocrine Tumor Society (ENETS) guidelines advise that nonfunctional PaNENs that measure less than 2 cm are likely benign with a low risk of metastatic potential and can safely be observed [27, 51]. For nonfunctional PaNENs larger than 2 cm, surgical resection is recommended if technically possible to achieve a durable cure and minimize risk of subsequent metastatic disease. Alternatively, for functional PaNENs, resection may be indicated at any size criteria to provide symptomatic relief. If definitive surgical treatment is desired for small (< 2 cm) PaNENs, enucleation offers the potential for a cure and subjects the patients to a less extensive operation, but this is dependent on the location of the tumor relative to the pancreatic duct [52]. A formal surgical resection of tumor localized to the pancreas via pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy usually includes regional lymphadenectomy of 11 to 15 lymph nodes regardless of their imaging appearance, as this enables accurate pathologic nodal staging [27]. Currently, the efficacy of neoadjuvant chemotherapy for localized PaNENs is uncertain but there may be some benefit in downstaging for palliative cytoreductive surgery [27].

Systemic therapy for patients with unresectable metastatic disease will depend on the underlying tumor differentiation and grade. Somatostatin analogs such as octreotide and lanreotide are considered first-line agents which are effective for control of tumor growth and hormonal symptoms. Typically, somatostatin analog treatment will lead to stability of tumor size or decrease in rate of growth rather than volumetric radiographic response, as these are not cytotoxic agents. Other systemic therapies include everolimus, an mTOR inhibitor, and sunitinib, a multi-targeted tyrosine kinase inhibitor, which have also been proven to reduce the rate of progression or death, with responses seen less commonly. Cytotoxic chemotherapy also holds a role, with temozolomide with capecitabine being most commonly used for patients with bulky or progressive well-differentiated PNETs, while platinum and fluoropyrimidine-based chemotherapy are preferred for poorly differentiated carcinomas [53, 54]. Peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE represents another systemic therapeutic option for patients with well-differentiated, somatostatin receptor-positive metastatic disease who have progressed on prior therapy [55].

In patients with metastatic disease, the liver represents the most common organ for metastasis and therefore liver-directed therapies may also be utilized in disease management. These are typically used for bulk symptoms or in cases of focally progressive disease despite medical management and include ablation, bland embolization, chemoembolization, and radioembolization. While ablation lends itself to oligometastatic disease typically smaller than 4 cm in size, embolization can be utilized for diffuse disease, with treatment to one lobe at a time in a staged fashion. Each of these procedures has its own safety and toxicity profiles [56]. Depending on the distribution of tumor burden within the liver, cytoreductive surgery may also be considered, and survival appears to be longer in patients for whom 70% of the tumor can be resected [27]. In general, the approach to evaluating response to therapy in patients with metastatic NEN is challenging and often depends on the treatments that the patient is undergoing. Thus, a prescriptive one-size-fits-all approach is not possible and both anatomic and functional imaging play key roles in evaluating both response and progression [57].

Conclusion

PaNENs are complex, heterogeneous tumors and range in behavior from indolent lesions to aggressive lesions with potential to metastasize. Thus, knowledge of PaNEN pathology is essential to direct imaging and treatment decisions. Use of cross-sectional imaging with multiphasic CT or MRI and functional imaging utilizing several PET tracers provides comprehensive staging information and allows for accurate non-invasive evaluation of metastatic disease. Understanding both NCCN and NANETS guidelines is helpful in understanding the management and follow-up of patients with PaNENs and helps to bridge the gap between radiologists and treating clinicians.

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