Recent updates on pancreatic neuroendocrine tumors (PNET)

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Learning objectives

• To provide a review of different types of pancreatic neuroendocrine tumours and the role of imaging techniques (CT, US, MRI and Nuclear imaging) in the initial diagnosis and management.
• To list the imaging features that help characterize pancreatic neuroendocrine tumors and describe molecular changes that correlate with prognosis.
Background

Pancreatic neuroendocrine tumours (pNET) are rare entities that arise from pancreatic islet cells, with a reported prevalence of approximately one in 100,000 people. They account for 1%-2% of all pancreatic neoplasms and may manifest at any age, but are higher among patients in their third to sixth decades, with no clear gender predilection. [1,2].

The majority of pNETs occur sporadically, with 1-2% associated with familiar syndromes, most commonly multiple endocrine neoplasia (MEN) type 1, von Hippel-Lindau syndrome (VHL), neurofibromatosis type 1 and tuberous sclerosis.

PNETs may be classified as functioning (F-pNETs) or non-functioning (NF-pNETs), according to their associated clinical symptoms. The widespread use of high-quality imaging techniques has allowed a large increase in diagnosis of non-NF-pNETs. More than 70% of pNETs are non-functional, which are generally diagnosed at advanced stages because of their absence of symptoms and slow growth. [3].

The WHO 2010 classification has been shown to have important prognostic value for pNET. Grading and correct histological diagnosis is now essential to manage these patients. Patients with pNET have favorable prognosis than those with pancreatic adenocarcinoma because of the more indolent and slow-growing tumor biology. [1,4].

Computed tomography (CT) and magnetic resonance imaging (MRI) are often used initially to detect and stage these lesions. Ecoendoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) allows a pathological. In addition, nuclear medicine techniques such as somatostatin receptor imaging (SRI) provide improved sensitivity, specificity and whole-body assessments for distant disease.

PNETs comprise a mixed group with variable incidence, natural history, presentation and behavior, where imaging plays a pivotal role. The following section will summarize the most representative radiological features of pancreatic neuroendocrine tumors.
Findings and procedure details

Most pancreatic neuroendocrine tumours are more indolent than pancreatic adenocarcinomas but may have a malignant course. The biological behavior of an individual pNET is uncertain [6]. PNETs in patients with MEN 1 may remain stable for several years. Higher tumor grade, liver and lymph node metastasis and a larger primary tumor give less favorable prognosis.

From a clinical point of view, pNETs can be divided into two groups: syndromic (functioning) or nonsyndromic (non-functioning), depending on if they cause hormonal hypersecretion syndrome. Functioning tumours are usually smaller and manifest because of the symptoms caused by the hormones they produce. Large non-functioning pNETs, which are usually bigger, cause non-specific symptoms and can be an incidental finding (Fig 1). They produce symptoms related to mass effect (such as abdominal pain, weight loss and jaundice), local invasion or metastasis (Fig 7) and are more likely to present cystic features, calcifications or hemorrhage. [5-7]. (Table 1).

Functioning tumours produce multiple hormones, but the predominant hormone usually determines the clinical syndrome. The two most common types are insulinoma followed by gastrinoma, most of which occurs in patients with MEN-1. Other types include glucagonoma, vipoma (Fig 4), and somatostatinoma. Non-functioning pNET shows no clinical evidence of hormone production, but frequently secrete pancreatic polypeptide, chromogranin A, neuron-specific enolase, neurotensin or other peptides.

To guide assessment of the images is important to know which tumour type is suspected. Insulinomas are usually solitary, in 90-97% occur within the pancreas and typically are smaller than other syndromic tumours. About 90% are benign, but when insulinomas are larger than 3 cm, malignancy is more common. On the other hand, gastrinomas have a different pattern of presentation. About 90% are located within the gastrinoma triangle limited 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].

Staging and grading

The current diagnosis and management has been modified due to the classification proposed by the World Health Organization (WHO) in 2010. WHO classification system
divided pancreatic neuroendocrine tumors into well-differentiated (WDNETs) grade 1 (G1) and grade 2 (G2); and poorly differentiated (PDNECs) grade 3 (G3). [2].

The grading of pNETs is based on two findings: (1) mitotic count and (2) Ki-67 labeling index. MIB1 antibody is used to classify them according Ki-67 index. [4,9]. (Table 2).

For the mitotic calculation, it is advisable to count at least 50 high-power fields (HPF). To obtain the Ki-67 index the optimum is to count a minimum of 500 tumor cells in tumor hot spots. If the assigned grade is discordant between the mitotic count and Ki-67 score, the higher grade should be used.

The staging of pNET is now done separately from the grade, unlike the WHO-2004 system where the two were combined to determine the category.

There are two different staging protocols for pNETs that are widely used in managing pancreatic neuroendocrine tumors. Their differences are essentially in T staging. The one from The American Joint Comission / Union of International Center Control / College of American Pathologists (AJCC/UICC/CAP) is similar to that used for exocrine tumors. In contrast, the European Neuroendocrine Tumor Society (ENETS) staging system is based on more reproducible criteria such as tumor size rather than irreproducible parameters like peripancreatic extension. [10,11].

However, there is no widely acceptable staging system for pNETs. The ENETS system (2006) was validated to risk stratify patients and to identify prognostic groups but several studies demonstrated that patients with Stage 1 disease show a similar prognosis than those with Stage IIA disease [10]. For the other hand, AJCC defines stage III disease based on tumoral involvement of the celiac axis or superior mesenteric artery (unresectable tumor) without distant metastases. But in contrast to pancreatic adenocarcinoma, pNETs often do not show invasive growth into the celiac or mesenteric vessels. [10,12].

Despite the discrepancies between both systems, recent studies have shown that they do not imply significative effects in the diagnosis and management. [11]. (Table 3, Table 4, Table 5).

**Imaging techniques and findings**

**Computed Tomography (CT)**
CT scan is the first line imaging modality in the evaluation of pNET, because of its speed, resolution and robustness. A typical abdominal multidetector CT examination for pNET is multiphasic. The study of the upper abdomen is performed before and after the injection of an iodinated contrast agent, in the late arterial phase (40 to 45 seconds after the start of contrast administration), and the whole abdomen in the venous phase (60 to 70 seconds after the start of contrast injection).[4]. CT was reported to have a mean sensitivity of 73% and specificity of 96%. [7].

At imaging, the appearance of pNETs can differ considerably but typically characterized by a well-defined hypervascular mass best visualized on arterial phase imaging (Fig 1). [8].

Smaller tumours usually are more homogeneous, hypervascular and well-circumscribed; whereas larger tumours more commonly have heterogeneous enhancement, with areas of cystic change (Fig 4), necrosis, fibrosis and calcification (Fig 5), associated with poorer prognosis and a higher prevalence of local and vascular invasion and metastases. [13]. However, some neoplasms may appear hypoattenuating relative to the enhancing pancreas and therefore are better identifiable in the portal venous phase (Fig 3). [8].

Lymph nodes and liver are the most metastases locations of pNET, and also are hypervascular demonstrating ringlike enhancement. All of them are potentially malignant, but many well-differentiated pNETs usually follow an indolent course. [13].

**Magnetic Resonance Imaging (MRI)**

MRI is a diagnostic tool that aids in the evaluation of pNETs because his superior soft tissue contrast resolution and the ability, including multiple different sequences, to differentiate the structures based on their signal intensity characteristics. [4].

The protocol includes sequences before and after intravenous administration of gadolinium-based chelates in late arterial, portal venous and usually in equilibrium phase.

MRI evaluation also tends to include "fat-suppressed T2-weighted; in-phase and out-of-phase T1-weighted; diffusion-weighted with multiple b values and apparent diffusion coefficient (ADC) maps". [7].

On unenhanced fat-suppressed T1-weighted image, pNET usually is hypointense relative to adjacent parenchyma while on T2-weighted image that appears hiperintense relative
to pancreas. Liver metastasis may show ring-like early enhancement on MRI. However, when pNETs are non-functioning, do not always show hypervascularity. [4].

MRI was reported to have a mean sensitivity of 93% and specificity of 88%. [7]. MRI is superior to CT in terms of evaluating extra-pancreatic extension.

Recent studies suggest that morphological and functional MR findings have predictive value for pNET tumor grade, especially for the differentiation between G3 and G1-2 tumors, and the prediction of tumor grade has been shown to be strongly associated with size. [14].

Ultrasound (US)

The detection of an increasing number of pNETs is incidental during an abdominal ultrasound because the widespread use of high-quality imaging techniques, even though it may be difficult due to the small size of tumors, gas interposition and patients who are frequently obese.

PNET tumors are typically hypoechoic and well defined, without calcifications or necrosis, but they can also appear as isoechoic mass, in which case can only be detected by contour changes. On the contrary, larger tumors may contain calcifications or areas of necrosis, which usually are associated with malignancy, and can be irregular, hypoechoic or echogenic. Metastatic lesions tend to be echogenic. [15]

Recent experience with endoscopic ultrasonography (EUS) has allowed more reliable detection of these neoplasms, as it may discover very small pancreatic lesions, ranging from 0.2-0.5 cm in diameter. Indeed, a higher sensitivity is found in the EUS, with a mean of detection rate of 79-100% for pNETs, and therefore it is particularly useful for evidencing also small tumours. Consequently, EUS is recommended as the most accurate diagnostic tool for pNETs when performed by experienced operators. In addition, the EUS-FNA suggests the NET nature of the pancreatic lesion. Therefore, it has to be considered as the procedure for detection and categorization of these lesions.

The following characteristics are listed to be evaluated and combined with the WHO 2010 classification of pNETs when performing an EUS: tumor size, echogenicity (hypoechoic or isoechoic), tumor margin (regular or irregular), internal echo pattern (homogeneous or heterogeneous), existence of cystic component, presence or absence of vascularity, and main pancreatic duct (MPD) obstruction. [1]
Intraoperative ultrasound improved the sensitivity of sonographic detection, which has been reported to achieve 100% when combined with palpation, and 84% alone. It can also outline the relation of the tumor to the pancreatic or common bile duct [15].

It has long remained unclear if the Ki-67 index obtained from EUS-FNA samples truly reflects the one obtained from surgical specimens, as it does not represent the entire tumor.

The concordance rates between grades in different studies are consistently between 70 to 80%, and the concordance in differentiating lesions as neuroendocrine is 98.5%. As it is demonstrated that the mean diameter of G2/G3 tumors is larger than that of G1 tumors, the Ki-67 index might be underestimated owing to tumor heterogeneity in the larger ones, especially when it comes to G2 tumors. It has been reported that heterogeneous ultrasonographic texture is associated with malignant pNET, but this is not the case with MPD obstruction [16].

However, a good concordance rate of grading has been observed between EUS-FNA and surgery specimens, which makes it useful for diagnosis and deciding treatment options. The Ki-67 index is a predictive factor for the effect of chemotherapy and correlates with the prognosis of pNET [1,16]. Recently there have been some reports about K-ras mutations in certain pNET patients, which might be correlated with malignancy in the future. [16].

**Nuclear medicine**

The main nuclear imaging technique for pNET is somatostatin receptor imaging (SRI) based on the overexpression of somatostatin receptors by a large variety of pNET (80%). SRI includes single photon emission tomography (SPECT) with $^{111}$In-pentetotide or more recently positron emission tomography (PET) with $^{68}$Ga-labeled somatostatin analogs; DOTA-tyrosine-3.octreotide (DOTATOC - DOTATATE) and DOTA-1-Nal-octreotide (DOTA-NOC). These SPECT and PET radioligands show a high affinity for somatostatin receptors specially subtype 2 and 5. [19]. Because of the large variability between pNETs, in proliferation rate (Ki-67) and somatostatin receptor subtype profile, no modality alone is entirely effective and overall sensitivity and specificity are 80-90%. This sensitivity varies according with tumour type and size. Bening insulinoma, the most common pNET, expresses receptor type 3 and SRI shows low sensitivity (50-70%) in this subtype [7].
SRI is used in detection the primary tumour, tumour staging, diagnosis of recurrent disease and for evaluating eligibility for treatment with somatostatin analogs such as peptide receptor radionuclide therapy (PPRT). When tumor is poorly differentiacted or Ki-67>15-20%, SRI is not very useful, and FDG/PET provide a good whole-body assessment with prognostic information in terms of overall survival (OS) and progression free survival (PFS).

**Differential diagnosis**

It is important to differentiate pNETs from other hypervascular lesions, such as primary exocrine tumors, solid serous cystadenomas, hypervascular metastases from renal cell or medullary thyroid carcinomas, neurogenic tumors, vascular lesions and developmental lesions such as intrapancreatic splenule, because they all share some imaging features with pNETs. It is suggested to use MRI when depicting cystic nature of hypervascular serous cystic neoplasms, as this finding differentiates solid-looking serous cystadenomas from other solid hypervascular tumors of the pancreas because of their high signal intensity and internal septation on T2-weighted MR images. [20]. In any case, endoscopic US is performed in patients with unclear or negative CT/MR findings and clinical suspicion of NET. [21]

An intrapancreatic accessory spleen (IPAS) measures usually less than 3 cm and is generally innocuous, which is why it is important to characterize accessory spleens and to differentiate them from solid pancreatic tumors as noninvasively as possible.

**Treatment**

Because most pNETs are indolent, a "wait and see" approach has historically predominated, but in the last 10-20 years, an aggressive approach has become popular. Unlike patients with adenocarcinoma of the pancreas, those with pNET who undergo surgical resection may achieve long-term survival. [6].

The treatment for pNETs is based on four components: surgery, locoregional therapy, systemic therapy, and complication control.

Observation can be considered in case of tumors < 1cm, incidentally discovered but for most patients with localized pNETs surgery is the best choice. The role of surgery in MEN1 remains controversial because patients often show multifocal microscopic disease requiring extensive resections. [2].
The type of surgery depends on parameters such as location, number of size, tumor size, relationship of the tumor with the main pancreatic duct and major vessels.

The best choice for patients with syndromic pancreatic neuroendocrine tumors without metastases is a complete surgical resection. When lesion is located in the tail of the pancreas a distal pancreatectomy can be executed. In contrast, lesions in the pancreatic head require Whipple surgery. The smaller lesions (<2cm), especially if they are exophytic, can be submitted to laparoscopic enucleation.

The treatment for patients with liver metastases and a symptomatic primary tumor may also be a surgery approach if it is possible, because the symptomatology frequently decreases after resection. In addition, some studies have shown that use of hepatic artery embolization or radiofrequency ablation for control of liver metastases may be considered. [19]. Nonetheless, recurrence ratio when hepatic metastases are present is very high.

In patients with poorer prognosis, with unresectable or residual disease, somatostin analogues such as octreotide may be beneficial. Somatostatin analogues (SSAs) have been increasingly used over the last one to two decades and have been shown to be very active in ameliorating symptoms of hormone overproduction. An alternative is peptide receptor radionuclide therapy (PRRT) using $^{177}\text{Lu}$-DOTATATE. PRRT is a molecular targeted therapy which is performed by using a small peptide (a somatostatin analog similar to octreotide) that is coupled with a radionuclide emitting beta radiation. The results reported have showed an improved in PFS and OS in patients with advanced midgut neuroendocrine tumors.

Recent trials show that targeted therapies are serious alternative consideration. Everolimus is a mTOR inhibitor blocking PI3K/Akt/mTOR pathway. Some studies show that everolimus, as compared with placebo, improves progression-free survival in patients with advanced pancreatic neuroendocrine tumors with alterations of the mTOR pathways have demonstrated. [24].

Cabozantinib, a tyrosine kinase inhibitor, and sunitinib, a tyrosine kinase inhibitor against vascular endothelial growth factor (VEGFR, PDGFR) have also demonstrated similar outcomes. [2].
Table 1. Classification of pancreatic neuroendocrine tumours (PNET)

<table>
<thead>
<tr>
<th>PNET</th>
<th>Clinical presentation</th>
<th>Malignancy</th>
<th>Origin</th>
<th>Most common location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulinoma</td>
<td>Whipple triad: fasting serum glucose levels less than 50 mg/dL, symptoms of hypoglycaemia that include diastole, blurred vision, palpitations, or weakness, and relief of symptoms after glucose administration.</td>
<td>10%</td>
<td>Beta-cells</td>
<td>Intrapancreatic (90%)</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Zollinger Ellison syndrome: abdominal pain, peptic ulcer disease, diarrhea and esophagitis</td>
<td>60%</td>
<td>Gastrin-cells</td>
<td>Duodenum or pancreas</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>4D syndrome: diabetes, dermatitis, deep vein thrombosis and depression</td>
<td>80%</td>
<td>Alpha-cells</td>
<td>Head and tail of pancreas</td>
</tr>
<tr>
<td>Vipoma</td>
<td>WDHA syndrome: watery, diarrhea, hypokalemia and achlorhydria</td>
<td>75%</td>
<td>Delta-cells</td>
<td>Body or tail of pancreas</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Inhibitory syndrome: abdominal pain, diarrhea, cholelithiasis, indigestion, and diabetes</td>
<td>75%</td>
<td>Delta-cells</td>
<td>Head of pancreas</td>
</tr>
<tr>
<td>Non functioning</td>
<td>Mass effect, abdominal pain, cachexia</td>
<td>&lt;2 mm: 6%</td>
<td></td>
<td>Head of pancreas</td>
</tr>
<tr>
<td></td>
<td>Larger: 80%</td>
<td>&gt;20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Classification system for pancreatic neuroendocrine tumors. Modified from WHO 2010.

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitosis/10HPF</th>
<th>Ki-67 proliferation index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated pNET</td>
<td>Grade 1</td>
<td>&lt;2</td>
<td>&lt;3</td>
</tr>
<tr>
<td></td>
<td>Grade 2</td>
<td>2-20</td>
<td>3-20</td>
</tr>
<tr>
<td>Poorly-differentiated pNET</td>
<td>Grade 3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>


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Table 3. T staging of PNETs: AJCC versus ENETS

<table>
<thead>
<tr>
<th>Stage</th>
<th>AJCC/UICC 2009</th>
<th>ENETS 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Pancreatic confined primary tumor ≤ 2 cm</td>
<td>Pancreatic confined primary tumor ≤ 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Pancreatic confined primary tumor &gt; 2 cm</td>
<td>Pancreatic confined primary tumor &gt; 2 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Pancreatic tumor extending beyond pancreas without major vessel involvement</td>
<td>Pancreatic tumor &gt; 4 cm in size or extending beyond pancreas with invasion limited to duodenum or bile duct</td>
</tr>
<tr>
<td>T4</td>
<td>Pancreatic tumor involving major vessels such as celiac or superior mesenteric artery</td>
<td>Pancreatic tumor invading major vessels or invasion of adjacent organs other than duodenum or bile duct</td>
</tr>
</tbody>
</table>


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Table 4: Consensus for a TNM classification for pNETs

<table>
<thead>
<tr>
<th>ENETS</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>T</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III A</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>III B</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AJCC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td>T</td>
<td>N</td>
<td>M</td>
</tr>
<tr>
<td>I A</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>T1-3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>


Table 5: WHO grading system and ENETS staging system for pNETs.

<table>
<thead>
<tr>
<th>Grade</th>
<th>5-year survival</th>
<th>ENETS Staging system</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>85%</td>
<td>I</td>
<td>97%</td>
</tr>
<tr>
<td>G2</td>
<td>78%</td>
<td>II</td>
<td>87%</td>
</tr>
<tr>
<td>G3</td>
<td>9%</td>
<td>III</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>56%</td>
</tr>
</tbody>
</table>


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**Case 1**

74-year-old woman with lung mass and incidentally discovered small pancreatic mass (arrow). Right hilum mass shows fat content within the lesion in keeping with pulmonary hamartoma.

CT scan (a) showed typical hypervascular enhancement consistent with pNET. OctreoScan (b) depicts a tiny focal uptake in keeping with the CT finding. Further $^{18}$F-FDG PET/CT scan (c) did not show any uptake. Laparoscopic enucleation was performed.

Pathology: Well-differentiated (G1) pNET
No mitotic figures, Ki-67 1%
Follow-up: No evidence of relapse 1y after surgery

* Incidentally discovered pNETs are common in clinical practice due to the widespread use of high-quality imaging techniques*

**Fig. 1**

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Case 2

79-year-old man with multiple comorbidities as well as an abdominal aortic aneurysm (a) and a pituitary macroadenoma – giant prolactinoma (b).

CT scan shows an incidentally discovered small hyperenhancing pancreatic mass (c) consistent with pNET. No further action has been taken.

Previous scans were reviewed and even though it is an unenhanced CT scan, small nodularity is noted in 2010 (d).

Probably a well-differentiated (G1) pNET
No pathological data has been obtained
Follow-up: stable for at least 6 years

* Well-differentiated pNETs usually follow a slowly growing and indolent course*

Fig. 2
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Case 3

31-year-old woman with multiple episodes of hypoglycemia, CT scan showed a small pancreatic hyperenhancing lesion consistent with pNET, probably insulinoma. Note typical hyperenhancement in late arterial phase (AP) and isoattenuation on portal venous phase (PV).

Multiple bilateral renal and pulmonary arterio-venous fistulas were also depicted (arrows). Laparoscopic distal pancreatectomy was performed.

Pathology: Well-differentiated (G2) pNET
3 mitotic figures, Ki-67 6%
Follow-up: No evidence of relapse 6mo after surgery

* Late arterial venous phase is mandatory when pNET is suspected, as they may be isoattenuating in portal venous phase*

Fig. 3
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Case 4

39-year-old woman with long standing watery diarrhea and weight loss. CT (a) scan showed a heterogenous pancreatic mass with cystic component (arrows) consistent with cystic pNET, probably VIPoma in keeping with clinical features. No hyperenhancement is noted.

Pathology: Well-differentiated (G2) pNET <2 mitotic figures, Ki-67 16%
Follow-up: No evidence of relapse 3y after surgery

* Some pNETs may show atypical features such as isoattenuation or cystic component *

Additional Case

Different appearance of cystic pNET in a 41-year-old woman with a palpable abdominal mass.

Fig. 4

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Case 5

68-year-old woman with abdominal pain and multiple liver masses on abdominal ultrasound. CT scan (a; late arterial, portal venous and delayed phases) showed a large heterogenous hyperenhancing pancreatic mass with dystrophic calcifications. Multiple liver masses (not shown) in the right lobe were also depicted, in keeping with metastatic pNET.

Pathology: Well-differentiated (G2) metastasic pNET
Ki-67 2,2%
Follow-up: No evidence of relapse 18mo after surgery

*Patients with liver metastases may be also considered candidates for surgery with good overall survival rates *

Further OctreoScan (b) and CT-fused images (c) revealed avid abdominal uptake consistent with pancreatic mass and liver lesions. Open corpo-caudal pancreatectomy and right hepatectomy was performed.

Fig. 5

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**Case 6**

64-year-old man with pancreatic neuroendocrine tumour relapse with mesenteric root mass. $^{68}$Ga-DOTATATE PET/CT (a) showed intense uptake in the mesenteric root mass (arrows), as well as in the retroperitoneal lymph nodes (arrowheads). Maximum intensity projection image also showed focal uptake in liver and mediastinic lymphadenopathy. OctreoScan CT-fused images (b) showed moderate radiotracer uptake in the mesenteric root mass, not other significant uptake was visible.

Pathology: Well-differentiated (G2) metastatic pNET
Ki-67 8%
Relapse 2y after diagnosis, currently on chemotherapy

* $^{68}$Ga-DOTATATE PET/CT provides incremental diagnostic information compared to OctreoScan*

Courtesy of Department of Clinical Physiology, Nuclear Medicine and PET (Dr. Mortensen / Dr. Puig), Rigshospitalet, Copenhagen. Denmark

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**Fig. 6:** Courtesy of Department of Clinical Physiology, Nuclear Medicine and PET (Dr. Mortensen / Dr. Puig). Rigshospitalet, Copenhagen. Denmark

**Case 7**

52-year-old woman with previous enucleation of pancreatic head pNET in 2001 and left hepatectomy for liver metastases in 2007. Surveillance CT scan (a) showed a pancreatic mass in primary tumour’s surgical bed (arrows). Subsequent OctreoScan (b) did not showed any abdominal uptake within the pancreatic lesion. EUS-FNA was positive for neuroendocrine differentiation.

Pathology: Well-differentiated (G2) metastatic pNET
Ki-67 4%
Follow-up: No evidence of macroscopic disease 15y after diagnosis

Patient started chemotherapy (Somatostatine Analogs). Follow-up CT scans (c-d) 3 and 6 years after local relapse showed distrophic calcifications (arrows) with no evidence of viable tumour. Patient remains asymptomatic.

* Metastatic pNETs may achieve long-term survival rates*

**Fig. 7**
Case 8

66-year-old woman with previous enucleation of pancreatic neuroendocrine tumour 3 years ago and recently detected mesenteric mass. $^{68}$Ga-DOTATATE PET/CT (a) showed intense uptake in the mesenteric mass (arrows). $^{18}$F-FDG PET/CT (b) did not showed any uptake.

Pathology: Well-differentiated (G2) pNET relapse
Ki-67 14%
Relapse 3y after diagnosis, currently on chemotherapy

* Well-differentiated pNETs may negative on $^{18}$F-FDG PET/CT *

Fig. 8: Courtesy of Department of Clinical Physiology, Nuclear Medicine and PET (Dr. Mortensen / Dr. Puig). Rigshopitalet, Copenhagen. Denmark

Case 9

59-year-old woman with acute onset of clonic movements and hemiparesis. Brain MRI showed a right pre-rolandic focal lesion consistent with metastasis. Subsequent CT scan (b) showed a large pancreatic head mass with liver metastases (not shown). Further EUS-FNA was positive for neuroendocrine differentiation.

Further OctreoScan (c) did not revealed significant abdominal uptake, but showed intense uptake within the brain lesion, in keeping with neuroendocrine brain metastasis.

Probably poorly-differentiated (G3) metastatic pNET
No Ki-67 reference data was obtained
Patient passed away 3 months after clinical onset

* Large non-functioning pNETs usually produce symptoms related to mass effect, local invasion or metastasis *
Case 10

70-year-old man with recently resected pancreatic neuroendocrine tumour. $^{68}$Ga-DOTATATE PET/CT showed liver subcapsular lesions and several bone metastases, not previously depicted on conventional CT imaging. Vertebral body with slight sclerosis and right rib with no visible anomaly on CT (arrows).

Pathology: Poorly-differentiated (G3) metastatic pNET

Ki-67 35%

Metastatic neuroendocrine tumour, currently undergoing chemo

* $^{68}$Ga-DOTATATE PET/CT provides incremental diagnostic information compared to conventional imaging*

Fig. 10: Courtesy of Department of Clinical Physiology, Nuclear Medicine and PET (Dr. Mortensen / Dr. Puig). Rigshospitalet, Copenhagen. Denmark

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Differential diagnosis

**Autoimmune pancreatitis**

48-year-old man with long standing abdominal pain. CT scan showed a bulging pancreatic head. Pathology proven autoimmune pancreatitis.

**Adenocarcinoma**

54-year-old man with abdominal pain and malaise. CT scan showed an ill defined pancreatic mass with peripancreatic fat stranding. Pathology proven pancreatic adenocarcinoma.

**Hypervascular metastases**

78-year-old man with previous nephrectomy and multiple hyperenhancing pancreatic masses. Pancreatic metastases from renal cell carcinoma.

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Fig. 11
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Intrapancreatic accessory spleen

38-year-old man with incidentally discovered pancreatic tail mass. CT scan (a), MRI (b) and spleen scintigraphy with iv injection of $^{99}$Tc labeled heat-damaged red blood cells, showed exact same features as the spleen.

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Fig. 12
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Conclusion

- PNET are becoming an increasing clinical problem, which in some cases are diagnosed with advanced disease that requires distinct diagnostic and treatment approaches.
- Although a wide range of options for imaging are available for the localization of the tumor, careful selection of a particular modality should be based on different factors such as cost-effectiveness, expertise of radiologists and endosonographers, and history of prior pancreatic surgeries. An adequate combination of morphological and nuclear imaging techniques is the best choice for pNET diagnosis.
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