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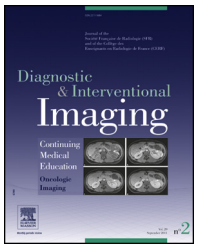

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Imaging of neuroendocrine tumors of the pancreas

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KEYWORDS
Neuroendocrine tumor;
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Abstract Pancreatic neuroendocrine tumors (PNETs) are rare and represent a heterogeneous disease. PNET can be functioning or non-functioning with different clinical presentations and different prognosis based on WHO and pTNM classifications. The role of imaging includes the localization of small functioning tumor, differentiation of these tumors from adenocarcinoma, identification of signs of malignancy and evaluation of extent. PNETs have a broad spectrum of appearance. On CT and MRI, most of functioning PNETs are well defined small tumors with intense and homogeneous enhancement on arterial and portal phases. However, some PNETs with a more fibrous content may have a more delayed enhancement that is best depicted on the delayed phase. Other PNETs can present as purely cystic, complex cystic and solid tumors and calcified tumors. Non-functioning PNETs are larger with less intense and more heterogeneous enhancement. Functional imaging is useful for disease staging, to detect disease recurrence or the primary but also to select patient candidate for peptide receptor radiometabolic treatment. Somatostatin receptor scintigraphy (SRS) (Octreoscan®) is still the most available technique. Gallium 68-SST analogue PET have been demonstrated to be more sensitive than SRS-SPEC and it will be the future of functional imaging for NET. Finally, ^{18}FDG PET/CT is indicated for more aggressive PNET as defined either by negative SRS and huge tumor burden or ki67 above 10% or poorly differentiated PNEC tumors.

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Pancreatic neuroendocrine tumors (PNETs) represent the second most common pancreatic cancer. Their incidence is below 1/100,000 persons, representing approximately 8—10% of all pancreatic carcinomas [1]. The incidence of PNET appears to be rising, due in part to heightened awareness of the disease, improved diagnostic techniques and an increased rate of incidental diagnoses during investigation for other conditions.

PNET exhibit a heterogeneous spectrum of clinical presentation and behaviors. PNETs can be functioning or non-functioning with different clinical presentation and different prognosis based on WHO and TNM classifications. Clinical presentation depends on the clinical impact of hormonal secretions, multiplicity and non-specificity of biomarkers and their potential association with tumor-predisposition syndromes. Furthermore, PNETs can be part of familial syndromes, such as multiple endocrine neoplasia (MEN), Von Hippel Lindau disease, tuberosclerosis and neurofibromatosis.

Well-differentiated PNETs have various evolutive profiles. Although some of these tumors may exert mostly a benign behavior, some are considered to be malignant. They are often slow growing, associated with long survival even when liver metastases are present [2,3].

Imaging plays a major role in the work-up of the primary tumor, its characterization and prognosis determination, the local and distant staging, the diagnosis of a cancer predisposition syndrome as well as the evaluation of treatment. Imaging endocrine tumors is extremely rich and varied combining conventional techniques of morphological imaging (ultrasound, computed tomography [CT], magnetic resonance imaging [MRI]), endoscopic explorations and functional imaging using radiopharmaceutical imaging techniques.

Our objective is to comprehensively review the current knowledge on imaging of PNET with a special emphasis on multidisciplinary approach to assess PNETs detection and diagnosis, characterization and prognosis.

Pathology

Diagnosis

PNET are considered to originate in the foregut. All PNETs, also sometimes known as pancreatic islet cell tumors, share a common phenotype with immunoreactivity for neuroendocrine markers, including chromogranin A and synaptophysin [4] (Fig. 1). Neuron-specific enolase (NSE) and CD56 are often positive in GEP-NETs, but are not specific for this tumor entity. Specific staining for hormones, such as serotonin, gastrin, insulin and glucagon, can be applied to confirm the source of a clinical symptomatology. However, immunohistochemical demonstration of a hormone alone is not proof of functionality of PNETs. Immunohistochemistry for Ki67 is also mandatory to grade the tumor according to the new 2010 WHO classification.

Grade and differentiation

PNET is first classified based on differentiation. Well differentiated PNETs have a typical organoid arrangement of cells with nesting, trabecular, or gyriform patterns. Well differentiated PNETs cells produce large amounts of secretory granules with diffuse immunoexpression of neuroendocrine markers (Fig. 1). In contrast, poorly differentiated PNETs have atypical, sheet-like, diffuse and irregular nuclei, less cytoplasmic secretory granules, and limited biomarker immunoexpression. Well differentiated PNETs are usually of low or intermediate grade whereas poorly differentiated PNETs are usually high grade.

The grade of a tumor refers to its biologic aggressiveness. For PNET, the grading system is based on the rate of proliferation, which is defined by the mitotic count or as the Ki67 index. PNETs are then classified into three categories: PNET-G1 (with a mitotic count < 2 per 10 high-power fields [HPF] and/or < 2% Ki67 index), PNET-G2 (with a mitotic count 2—20 per 10 HPF and/or 3—20% Ki67 index) and PNET-G3 (with a mitotic count > 20 per 10 HPF and/or > 20% Ki67 index). Briefly, low-grade tumors are characterized by low proliferative indices and are considered indolent in nature. High-grade tumors tend to be poorly differentiated, have high proliferative indices, and are thus very aggressive.

WHO 2010 classification

The WHO classification proposed in 2010 uses the grade proposed by the ENETS in 2006 [5] (Table 1).

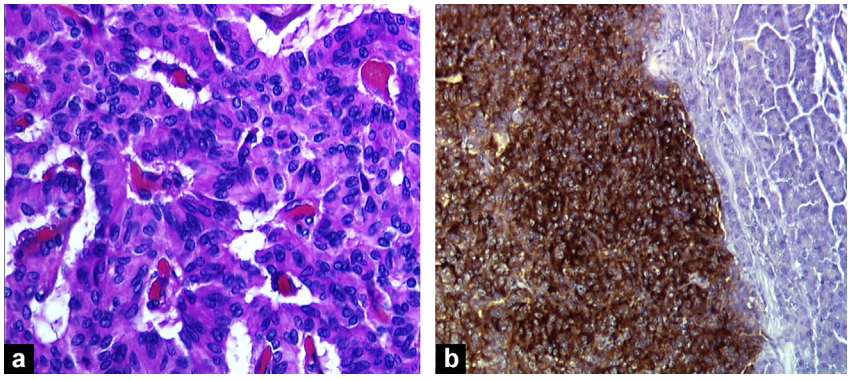

Figure 1. Typical histological appearance of a well differentiated neuroendocrine tumor of the pancreas on histopathology: monomorphic tumor cells are arranged in plates separated by thin fibrovascular septa (a). The strong expression of chromogranin A confirms the neuroendocrine nature of this well demarcated tumor of the pancreas (b).

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Table 1 2010 WHO classification of pNET.

Grade	Mitotic count (per 10 HPF)	Ki67 (%)		WHO classification
Grade 1	< 2	≤ 2	→	Neuroendocrine tumor (NET) G1: well-differentiated
Grade 2	2—20	3—20	→	Neuroendocrine tumor (NET) G2: well-differentiated
Grade 3	> 20	> 20	→	Neuroendocrine carcinoma (NEC)
				Small cells
				Large cells
				Mixed neuroadenocarcinoma (MANEC)
				Hyperplastic and preneoplastic lesions

HPF: high-power fields.

Clinical and biological presentation

A PNET should be suspected in case of:

- clinical endocrine syndrome (Fig. 2). Some PNETs are functional, which means they produce excess hormones that can lead to a variety of hormone-related symptoms (Table 2). In this case, diagnosis is considered early and allows the identification of the primary tumor when it is still small;
- clinical symptoms related to the growth of the tumor. Symptoms may include abdominal pain, diarrhea, stomach pain, a tired feeling all the time, fainting, or weight loss. Those cases usually concern non-functioning PNETs and do not lead to early symptoms;
- incidental diagnosis of a pancreatic mass.

Approximately 60% of functioning PNETs are insulinomas. Insulinomas are usually benign whereas other PNETs are often malignant. Insulinomas are characterized clinically by the Whipple triad, as follows: presence of symptoms of hypoglycemia (in about 85% of patients), low blood sugar at the time of symptoms, reversal of symptoms by glucose administration.

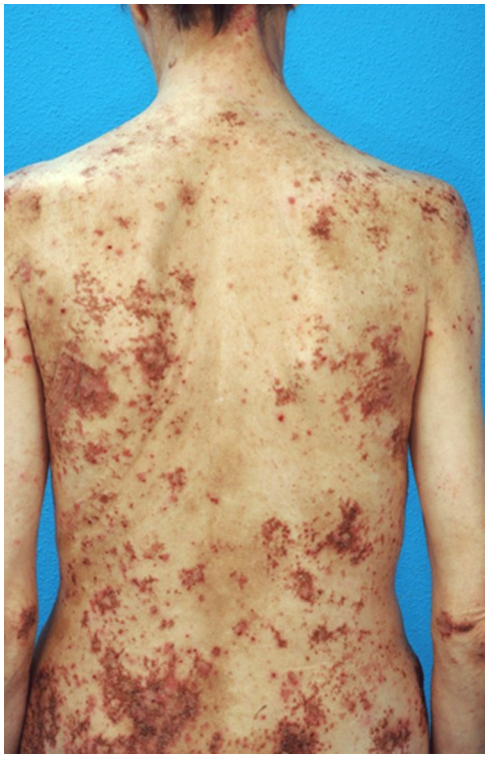

Figure 2. Necrolytic migratory erythema revealing a pancreatic glucanoma.

Gastrinomas are a gastrin-secreting tumor with symptoms similar to the symptoms of common peptic ulcer disease. Usually, persistent abdominal pain exists that is less responsive to medical treatment. Sometimes, symptoms may relate to a complication of peptic ulcer disease, such as bleeding (e.g., melena, hematemesis), gastric outlet obstruction (e.g., vomiting), and perforation (e.g., peritoneal irritation). The triad of gastrinomas, hypergastrinemia, and severe ulcer disease corresponds to the Zollinger-Ellison syndrome. Over 50% of gastrinomas are malignant and can metastasize to regional lymph nodes and the liver. Twenty percent of gastrinomas is related to multiple endocrine neoplasia (MEN) type I and are associated with hyperparathyroidism and pituitary adenomas. These MEN I associated tumors have been observed to occur at an earlier age than sporadic tumors and often follow a more benign course. Clinical symptoms of other functioning tumors are summarized in Table 2.

Because non-functioning tumors do not produce symptom-inducing hormones, they are often advanced before they are discovered with large size tumor and metastatic spread. Moreover, most functioning tumors (≈60% of pancreatic PNET) are benign, while more than 50% of non-functioning tumors (≈40% of PNET) are likely to be malignant.

Work-up of the primary tumor

Endoscopic ultrasonography

Endoscopic ultrasonography (EUS) is particularly suited to detect small size (2 to 5 mm) pancreatic lesions, such as gastrinomas and insulinomas with reported detection rates from 79% to 94% [6,7] (Fig. 3). Due to the proximity of the endoscope, the sensitivity for detection is higher in the head than in the tail.

Insulinomas are all located in the pancreas with an average size < 2 cm at diagnosis in 90% of cases. A gastrinoma can occur in the pancreas, but also in the duodenum in 40—50% of patients. When located in the duodenum, gastrinomas are frequently small and multiple. Sporadic tumors occurring in

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Table 2 Different subtypes of functioning PTNE according to the hormonal production.

Type	Hormone	Clinical symptoms	Diagnostic laboratory tests	Characteristics
Gastrinoma	Gastrin	Zollinger-Ellison syndrome (gastric ulcers)	Gastrin > 1000, secretin stimulation test	Location in the duodenal wall Often malignant Often associated with MEN1 (multiple lesions)
Insulinoma	Insulin	Hypoglycemia	Insulin, C-peptide	More often benign
Glucanoma	Glucagon	Diabetes, necrolytic migratory erythema (Fig. 2)	Glucagon, hyperglycemia	Often metastatic
VIPoma	Vasoactive intestinal peptide	Watery diarrhea, hypokalemia, achlorhydria syndrome	VIP	40% malignant
Somatostatinoma	Somatostatin	Diabetes, gallstones, inability to digest fats	Somatostatin	75% malignant
ACTHoma	Adrenocorticotropic hormones	Cushing syndrome weight gain, depression, easy bruising, increased risk of infection, and darkened skin		

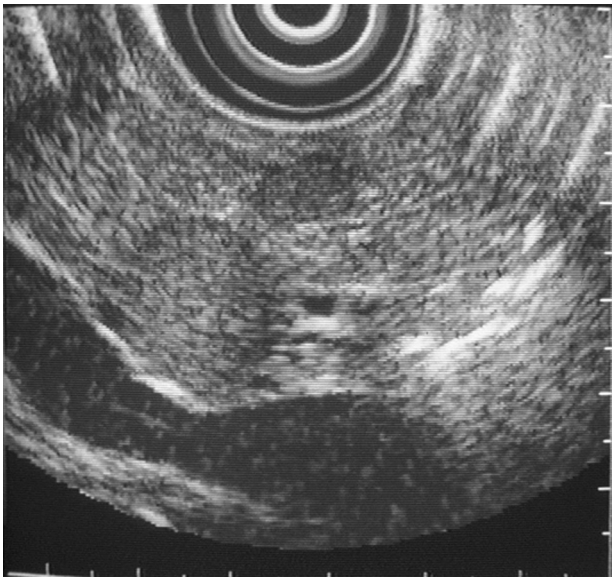

Figure 3. Small functioning pancreatic neuroendocrine tumor classified as insulinoma at histology. Echo-endoscopic image shows a small hyperechoic tumor with well circumscribed margins.

the pancreas tend to be solitary and have greater malignant potential as compared to duodenal gastrinomas. The sensitivity of EUS is higher for pancreatic gastrinoma than for extrapancreatic gastrinoma thought to be a result of their generally smaller sizes. EUS is also helpful for detection of adjacent metastatic lymph nodes within the gastrinoma triangle. The addition of contrast agent injection has been showed to increase potential detection of small pancreatic tumor by their ability to detect hypervascular enhancement [8].

EUS is also used to survey patients at increased risk of developing pNETs in particular in MEN type 1. A prospective multicentric study in 90 patients with MEN type 1 comparing EUS and pancreatic EUS has showed that 48 (53.3%) patients had at least one tumor $\geq$ 10 mm. EUS detected 86 tumors $\geq$ 10 mm vs. 67 tumors for MRI. EUS failed to identify 15.7% of patients with pancreatic tumor $\geq$ 10 mm, vs. 19.3% patients for MRI. The authors concluded that EUS and MRI are complementary and should be performed at initial evaluation in MEN type 1 patients [9].

Cross-sectional imaging

CT is the first-line imaging modalities of choice in the evaluation of patients with suspected PNETs allowing the investigation of the pancreas as well as the assessment of the disease extension. CT imaging should consist of multiphase imaging, including unenhanced, arterial/pancreatic phase, venous phase and delayed phase. The late arterial (30 s) or pancreatic phase (40 s) is mandatory allowing an increased detection of small functioning PNET in particular insulinoma [10]. Moreover, it also increases the detection of hepatic metastases [10—13]. The delayed phase is complementary of the arterial/pancreatic and the venous phase allowing the detection of delayed enhancement of some fibrous tumors [14].

MR imaging protocol should include T1-(T1W) and T2-weighted (T2W) MR sequences, dynamic three-dimensional (3D) sequence before and after intravenous administration of a gadolinium chelate with multiarterial, venous and delayed (> 5 min) acquisition and diffusion-weighted (DWI) sequences. Fat suppression on T1W and T2W images is useful to maximize the signal intensity differences between the pancreatic tumor and the adjacent normal pancreatic tissue. Similarly to CT, T1 W delayed (> 5 min) images are

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required to improve both characterization and detection [14]. Diffusion-weighted images increase the sensitivity for the detection of the primary pancreatic tumor as well as associated liver metastases [15].

Functioning tumors

Functioning PNETs are most often manifested by endocrine symptoms with an established or highly suspected clinical and biological diagnosis. The challenge of imaging is to localize the tumor that is often of small size.

Insulinomas are the most frequent functioning PNETs. Most insulinomas are < 2 cm in size, solitary and benign. They are located all over the pancreatic gland. On CT images, typical insulinomas are well defined, hypervascular and show intense enhancement during arterial/pancreatic phase (Fig. 4). The enhancement is usually uniform. Sometime, a rim of enhancement is depicted highly suggestive of the diagnosis [16].

Gastrinoma is the second more common PNET. Gastrinomas are also small pancreatic tumor (1—3 cm) arising in 80% within the ''gastrinoma triangle'' defined as the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially. Gastrinomas are the PNETs that are the more often associated with a MEN1 (Fig. 5). In these cases, they are often multicentric, and

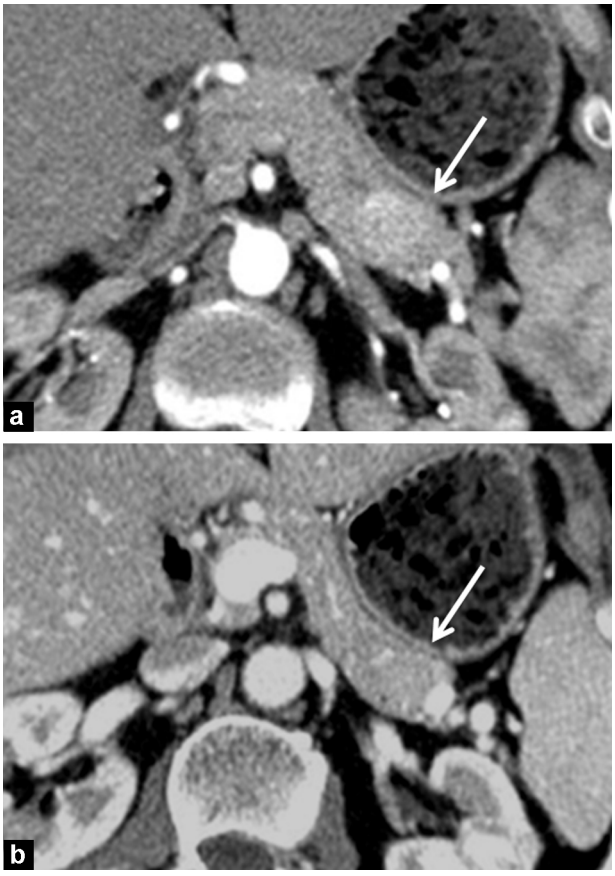

Figure 4. Benign insulinoma. CT images in the transverse plane during the arterial (a) and the portal venous phase (b) show a small pancreatic hypervascularized tumor of the pancreatic tail with sharp margin (arrow).

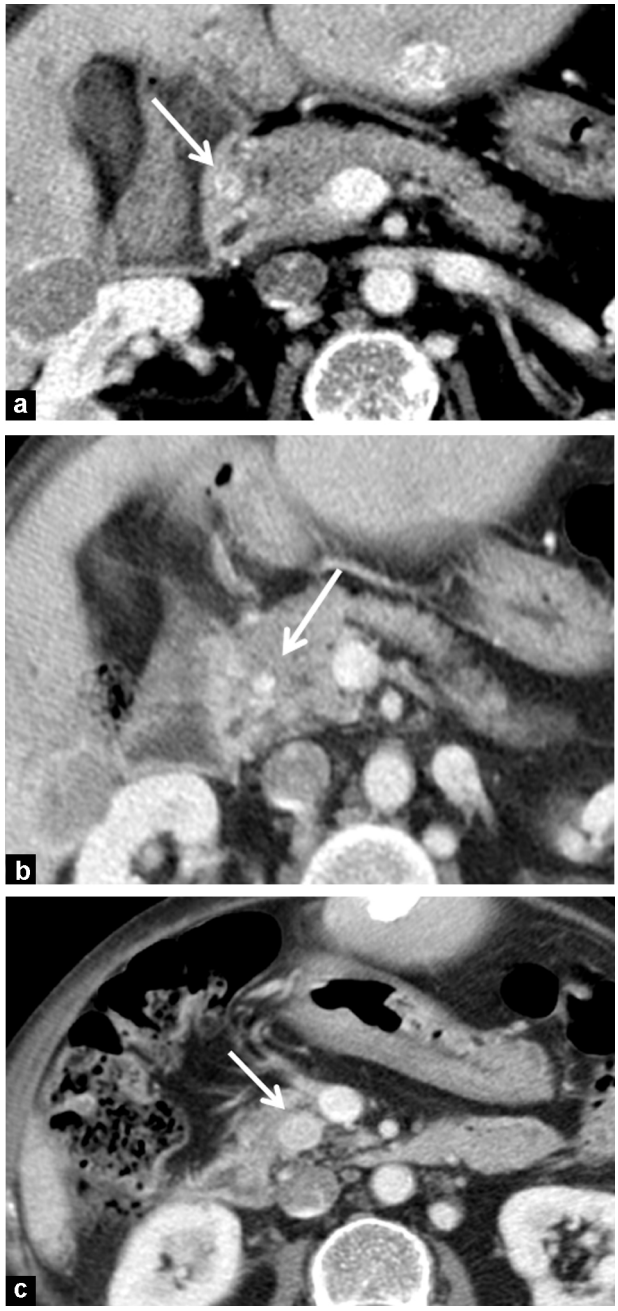

Figure 5. Multiple gastrinoma associated with a MEN1. CT images obtained in the transverse plane at different levels of the pancreatic gland during the arterial phase (a—c) show 3 hypervascular tumors located in the gastrinoma triangle defined by the confluence of the cystic and common bile duct superiorly, the second and third portions of the duodenum inferiorly, and the neck and body of the pancreas medially.

are associated with a major morbidity and mortality. After contrast injection, gastrinomas have more often a delayed enhancement persistent on delayed phase due to presence of fibrosis.

Other presentations of functioning PNETs include purely cystic tumors in 10% that is a common pattern of PNET associated with MEN1, complex solid and cystic pattern and calcified tumors in less than 5% (Fig. 6) [17].

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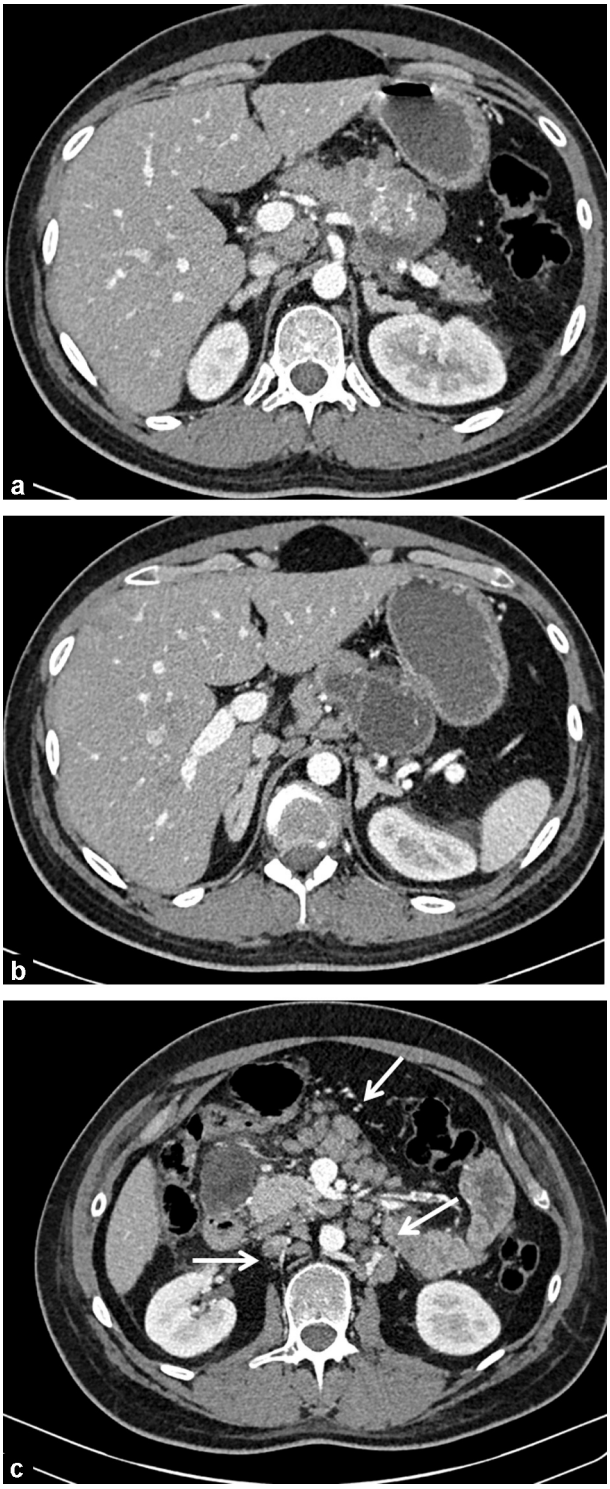

Figure 6. Malignant functioning pancreatic neuroendocrine tumor associated with ACTH secretion. CT images obtained during the arterial phase at different level of the pancreatic gland show a large mass with solid and cystic component associated with calcification and multiples mesenteric and retroperitoneal lymph nodes (arrows).

On MRI, most of functioning PNETs show low signal intensity on T1W, high signal intensity on T2W images and intense and early enhancement on dynamic T1W sequence after injection (Fig. 7). Hypervascular tumors (typically, insulinoma) are often better depicted on the T2W with fat suppression, whereas hypovascular tumors are better depicted on the T1W sequence during the arterial phase. This is probably explained by the high enhancement of the pancreas in the arterial phase, which concealed hypervascular tumours, whereas non-hypervascular tumours were surrounded by the enhanced normal pancreatic parenchyma [18]. DWI is helpful to depict small PNETs due to its greater image contrast. ADC values have been shown to be lower than adjacent pancreatic parenchyma in all cases of solid nodules [18]. However, higher ADC values can be obtained in case of cystic pattern [19].

Differential diagnosis of hypervascularized PNETs are pancreatic metastases (coming the most often from a renal cell carcinoma [RCC]) and intrapancreatic accessory spleen (Fig. 8). In addition, a splenic artery loop should not be misinterpreted as small PNET. With multiplicity, the relative percentage of washout of the tumor on CT could be helpful for differentiating pancreatic metastases from RCCs from hypervascular PNETs [20]. However, mulptiple hypervascular PNETs is frequent in case of NEM1.

Non-functioning tumors

Non-functioning PNETs are often detected incidentally or announced by non-specific symptoms. The challenge of imaging is not to detect the pancreatic tumor that is more often large but to differentiate this tumor from ductal adenocarcinoma or other type of pancreatic tumor and to determine the extent and the potential of resectability.

On CT and MR images, non-functioning PNET appears as a large pancreatic mass with heterogeneous enhancement due to necrotic and hemorrhagic changes. On MR images, in contrast to pancreatic adenocarcinoma most of PNETs are hyperintense on T2W images and hyper- or isointense during the arterial/pancreatic phase of the dynamic study [21]. Moreover, PNETs tend to have a higher rate of tumoral vein thrombosis (splenic, portal and superior mesenteric veins) and a lower rate of vascular encasement than pancreatic adenocarcinoma [18,21] (Fig. 9). Dilatation of the upstream pancreatic and common bile duct is rarer than in pancreatic adenocarcinoma present in 33% of cases for the main pancreatic duct and less than 9% for the common bile duct (Fig. 10) [22].

Radiopharmaceutical imaging techniques

Isotope-imaging modalities have become increasingly relevant for the management of PNET patients. Due to expression of multiple somatostatin receptors (SSTRS) in about 70% of PNETs, functional imaging with somatostatin (SST) analogue is recommended as a standard for imaging staging in NET patients [23]. Functional imaging with somatostatin analogue (SSA) is useful first to evaluate in vivo the expression of SSTRS, allowing to perform disease staging, to detect disease recurrence or the primary and finally to select patient candidate for peptide receptor radiometabolic treatment (PRRT) by Y90 (Yttrium-90) or Lu177 (Lutetium-177) SST analogues. Poorly differentiated neuroendocrine carcinomas on the other hand have a very low expression of SST receptors and functional imaging with SST analogue is very limited in this setting.

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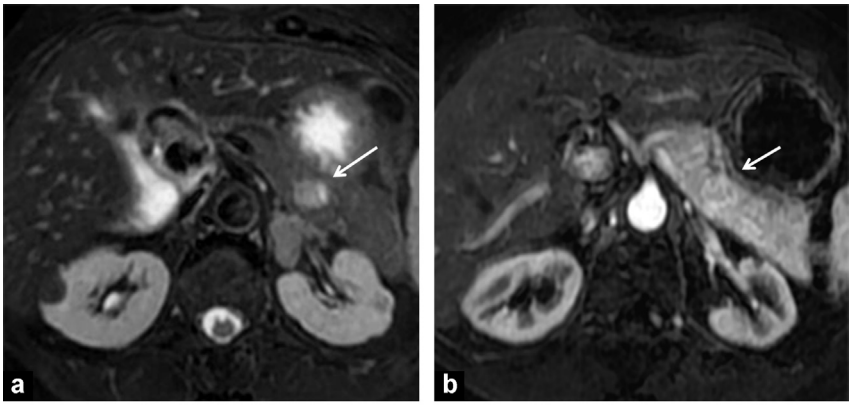

Figure 7. Small functioning pancreatic neuroendocrine tumor. T2-weighted MR image (a) shows a small lesion with well circumscribed margin and high signal intensity (arrow). On T1W acquired after contrast during the arterial phase, the lesion enhances with a rim like enhancement (arrow). Note that this hypervascularized PNET is better depicted on T2W because of the high enhancement of the pancreas in the arterial phase, which concealed hypervascular tumours.

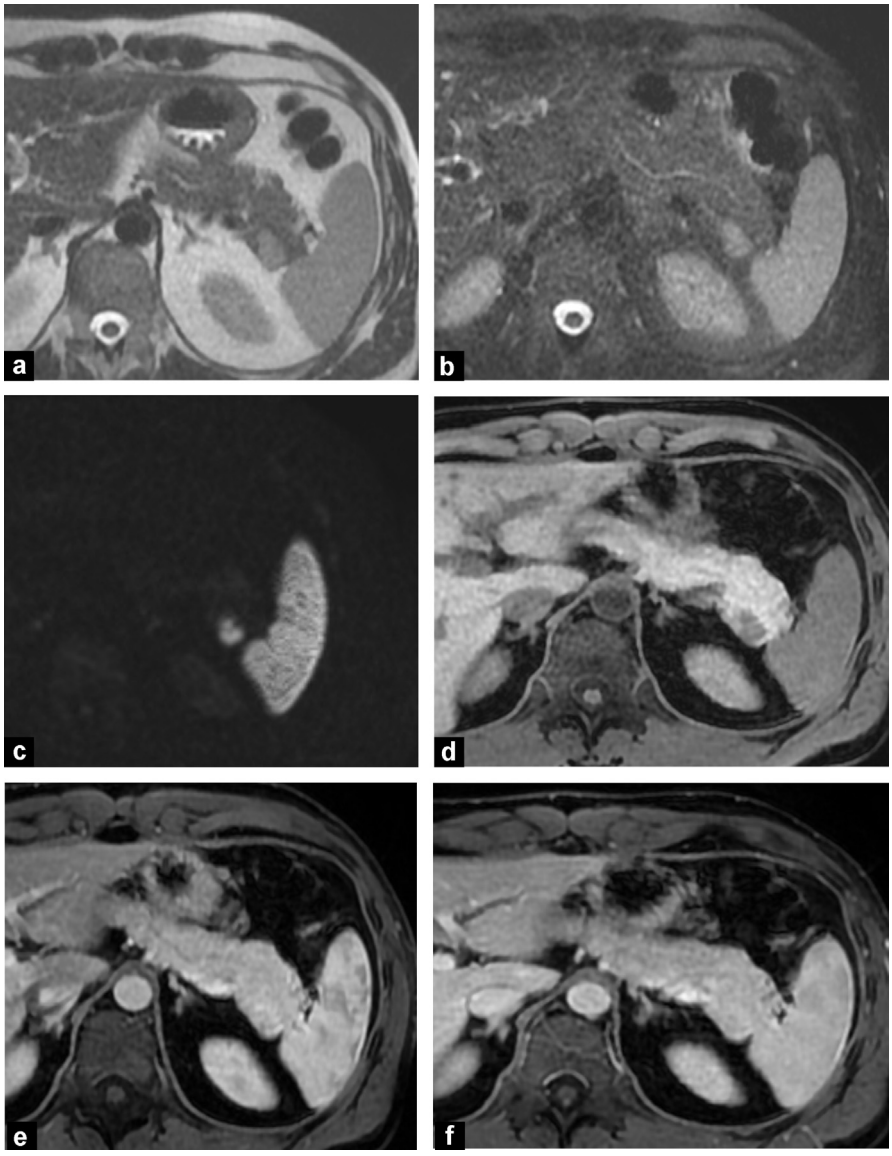

Figure 8. Intrapancreatic accessory spleen mimicking a pancreatic endocrine tumor. T2-weighted MR images without (a) and with (b) fat suppression show a hyperintense small lesion located in the pancreatic tail. On diffusion-weighted MR image with high *b* value (*b* = 1000), the lesion appears hyperintense. On T1-weighted dynamic sequence before (d) and after injection of contrast at the arterial (8) and venous (8) phase, the lesion enhances. The diagnosis is suggested by the similar intensity of signal of the lesion compared to the spleen in all sequences.

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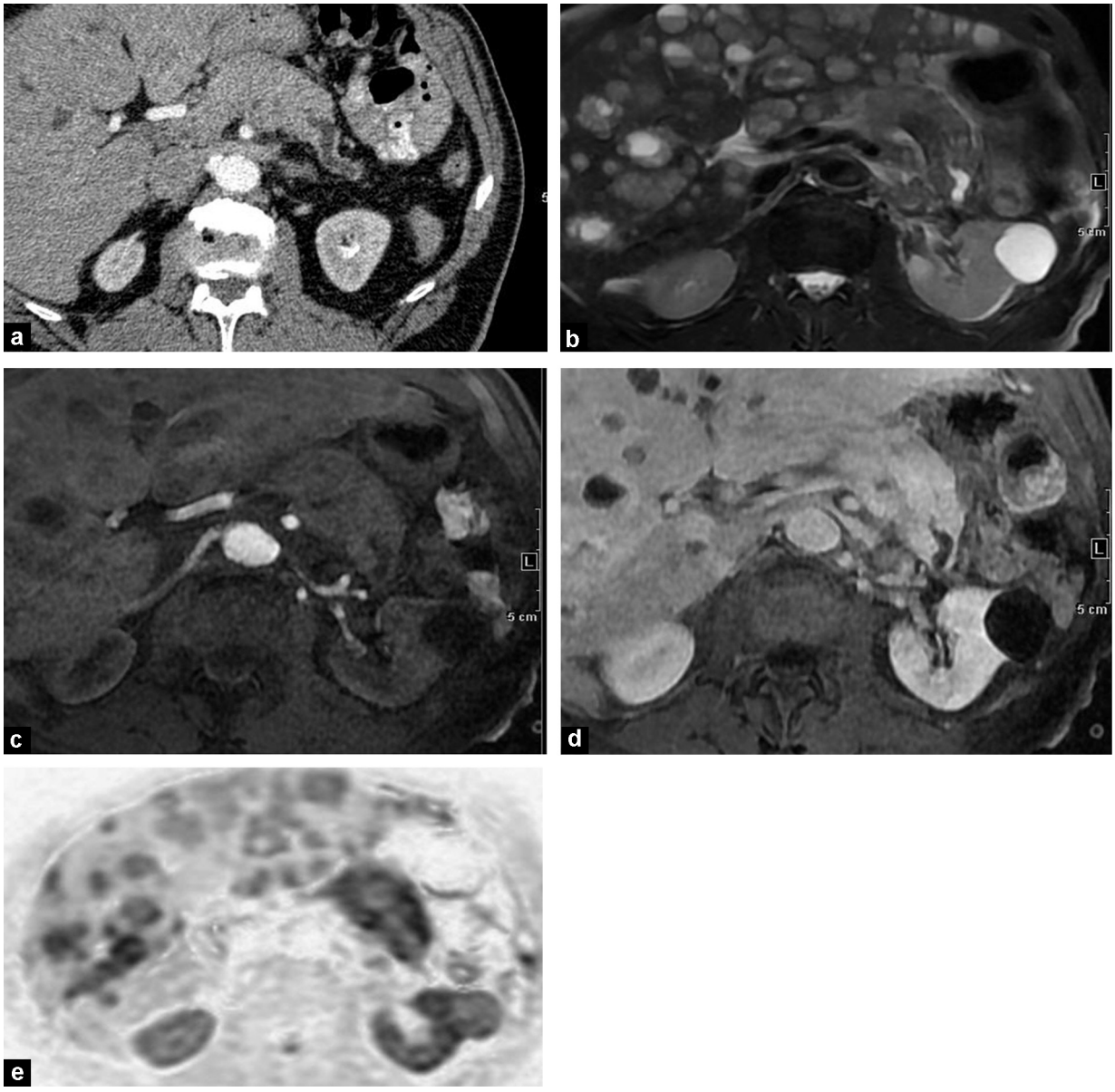

Figure 9. Malignant non-functioning pancreatic endocrine tumor. CT image (a) show a dilatation of the main pancreatic duct associated with an enlargement of the pancreatic gland, which remains isodense. T2-weighted image (b) shows a heterogenous hyperintensity associated with multiple liver metastases better depicted than on CT. The tumor is isointense on T1-weighted MR images at the arterial (c) and portal phase (d). The pancreatic tumor and liver metastases are also well depicted on DWI (e).

Somatostatin receptor functional imaging

111-pentetrotide single photon emission computed tomography (SPECT)-SRS (OCTREOSCAN; Mallinckrodt, St Louis, MO) is the most used and available somatostatine analog (SSA) tracer with high affinity for 2 and 5 subtype. Scintigraphic images require a 2-day protocol images acquisition (4 h and 24 h) with whole body 2D (anterior-posterior) evaluation at 24 h. Currently SPECT images can be performed to obtain 3D and fused images. This technique allows to a better evaluation of uptake foci and shows higher sensitivity than planar images to localize small size primary tumor or distant metastases (Fig. 11).

Ga 68-SSA-PET/CT presents some advantages comparing to scintigraphy (Fig. 11). First, the affinity for SST receptor is higher for PET tracer allowing for a higher detection rate. Actually 3 different tracers are available: DOTATATE (DOTA,Tyr(3)-octreotate), DOTANOC (DOTA,1-Nal(3)-octreotide) and DOTATOC (DOTA, D-Phe1, Tyr (3)-octreotide). In particular, DOTATATE shows 10-fold higher and selected affinity for SST-2 receptor, DOTATOC high affinity for SST-2 even if less than DOTATATE and also for SST5 receptor and DOTANOC high affinity for SST-2 SST-3 and SST5 subtype receptors [24]. Currently no substantial differences in patients staging have been demonstrated among the different tracers [25—27]. Second PET system resolution is higher comparing to SPECT with an incremental increase in sensitivity.

SRS scintigraphy may help detect the pancreatic primary tumor when morphological imaging and EUS show no lesions. SRS scintigraphy sensitivity value ranges between 40 and

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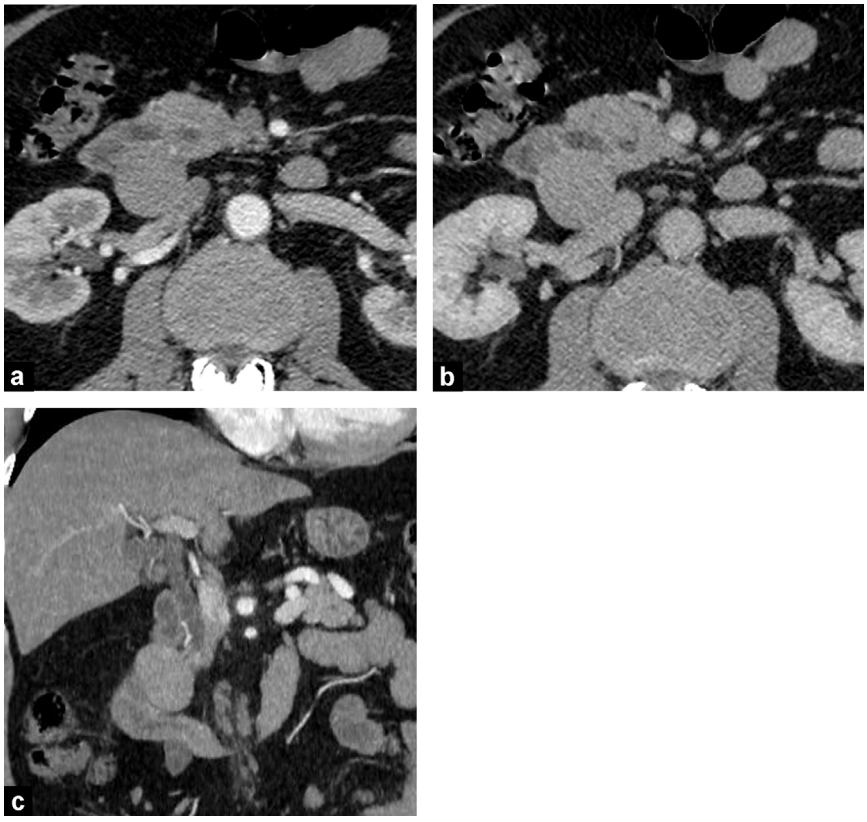

Figure 10. Non-functioning pancreatic neuroendocrine tumor. CT images in the transverse plane during the arterial (a) and portal phase (b) show a large mass developed between the second portion of the duodenum and the pancreatic head. This lesion is not hypervascular on arterial phase and is associated with a dilation of the common bile duct well depicted on the coronal reconstruction (c).

70% [28]. Sensitivity of SRS is first correlated to pathology and functioning status. It is more sensitive in detecting well differentiated gastrinoma, glucagonoma, VIPoma and not functioning PNET as it has a low sensitivity for detecting insulinoma or PNET due to lower SSTR 2 subtype expression. The small size of the tumor (< 2 cm) is an actual limitation for SSA scintigraphy detection of primary pancreatic tumor [29]. Ga 68-SSTA PET is more sensitive comparing to SRS in detecting primary GEPNET, pancreatic NET in particular, with sensitivity reported around 80—90%, even if false positive findings or false negative findings may occur [30—32]. One study reported a similar sensitivity of 92% for ^{68}Ga DOTA-TOC (92%) compared to multislices CT (91%) in detecting duodeno-pancreatic tumor in 19 patients [33]. The superiority of Ga 68-SSTA compared to MRI and in particular diffusion-weighted MRI in detecting primary pancreatic NET has not been establish and the available results from recent studies are discordant [34,35]. At this moment, the association of the two techniques is recommended to obtain the best performance.

Other PET tracers

FDG PET/CT is widely used in oncology but FDG it is not considered a good tracer for NET tumors. In particular, well differentiated G1 NETs are most likely to express SST receptor, to disclose high SSTA uptake and be negative at FDG PET/CT (Fig. 11e and f). On the other hand, for staging well differentiated NET with high Ki67 (> 10%) and poorly differentiated variant, FDG PET/CT is most indicated. In patients with well differentiated NET and Ki67 > 10%, Abgral et al. reported in 18 patients (7 pancreatic NET) higher sensitivity for FDG PET/CT compared to Octreoscan and CT with a higher number of detected lesions located in the lymph node and in the bone [36]. Furthermore, FDG uptake has been demonstrated to be an independent prognostic factor for PFS in patients with low-grade NET (mostly GEP NET) [37].

F-DOPA PET/CT has shown really excellent performances for staging midgut tumor but studies comparing F-DOPA to Octreoscan in non-midgut digestive NET showed a better performance of SSA imaging comparing to F-DOPA with sensitivity of Octreoscan of 75% vs. 25% for F-DOPA PET/CT [38]. Ga68-SSTA PET seems also to be superior to F-DOPA in small patient series with well differentiated NET, including pancreatic NET with sensitivity of 96% for Ga68-SSTA PET/CT vs. 56% for F-DOPA PET [39,40]. A comparison between the two techniques in homogeneous and selected patients group should be done to conclude.

Characterization and pre-therapeutic staging

Besides the diagnosis of the primary tumor, imaging has a major role in the staging, the diagnosis of a predisposition

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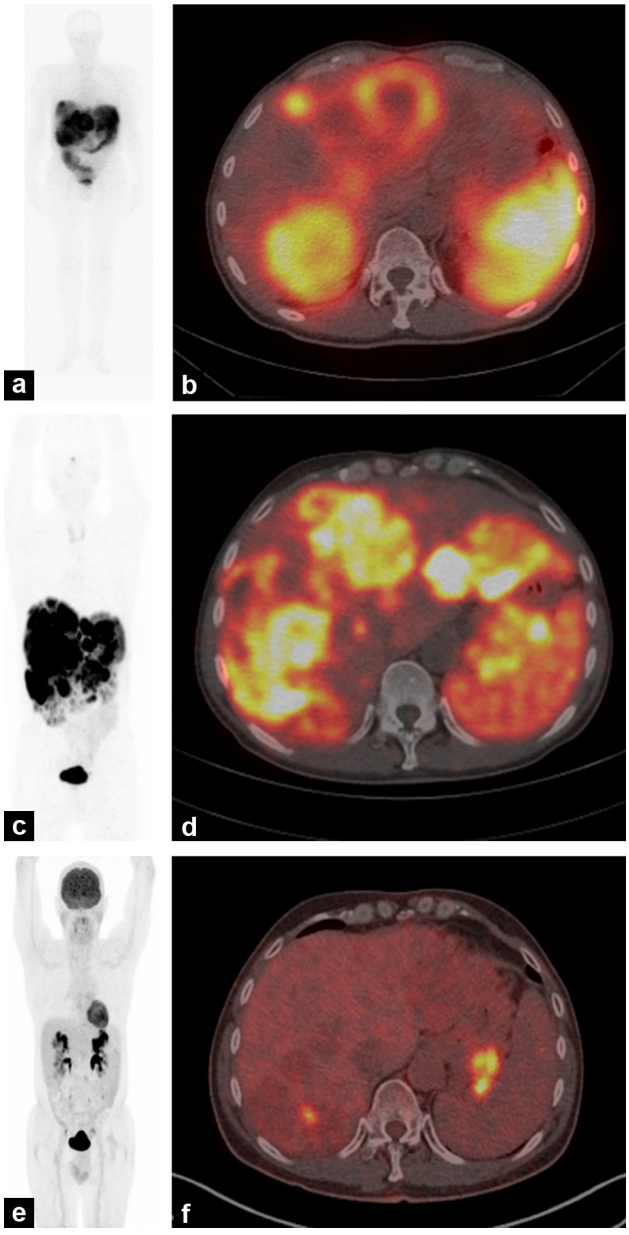

Figure 11. Patient with liver metastases from well differentiated pancreas neuroendocrine tumor. ^{111}In-pentetreotide single photon emission tomography (Octreoscan) (a and b) shows high uptake of somatostatine analogue in liver lesions. ^{68}GA DOTATOC PET/CT (c and d) shows more liver lesions compared to Octreoscan in the same patient. FDG PET/CT (e and f) was negative according to the well differentiated tumor feature.

syndrome, the work-up of multiple tumors, the prognosis characterization, the monitoring and prediction of response therapeutic. Grade or differentiation can be variable (G1—G3) based on Ki67 and mitotic count and morphological architecture and represent the most important prognostic factors. TNM and the extension of distant metastases especially in the liver constitute the second most important prognostic factor. Moreover, liver involvement at diagnosis in contrast to either metastatic disease at other sites has been shown to be correlated to the prognosis [41,42] and is a parameter of importance for the treatment management.

Metastases detection

Other metastatic sites of PNET metastases are the abdominal and mediastinum lymph nodes, peritoneum, bone, more rarely the lungs and even more rarely spleen, brain, thyroid, pituitary, breast, heart, meninges and the orbit. The frequency of metastatic sites depends on the primary tumor, the stage of the disease and the differentiation of the primary tumor [43].

CT scan complements somatostatin receptor scintigraphy (SRS) for PNET staging. CT is more sensitive for detecting lung, liver and brain metastases, while SRS excels at exploring bones and mediastinum [44—46]. MRI has several advantages over CT for evaluating PNET liver metastases, in addition to its high sensitivity: it is a non-radiant technique that can be repeated over time without any risk of cumulative irradiation; high MRI contrast between metastases and normal liver enables precise measurement of liver metastases on unenhanced sequences, independently of metastasis enhancement; and MR is the imaging technique with the best interobserver agreement and is more sensitive than US, CT, or SRS for liver metastases detection [11,12]. Its sensitivity is similar to that of intraoperative US assessment. However, about half of the liver metastases are not detected by any pre- and intraoperative imaging technique [47]. More recently, it has been showed in 32 patients with mainly small intestine PNETs that the addition of DW sequences to standard MRI revealed additional metastases and led to modifications of patient management. Adding DWI to standard liver MRI yielded additional findings for 45% of the patients with 1.78 times more new lesions, mainly infracentimetric; it induced a management change for 18% of the patients. DWI sequences added to whole body MRI yielded additional findings for 71% of the patients, with 1.72 times more lesions, mainly infracentimetric, and induced a change in management for 19% of the patients [48].

Ga 68 PET/CT has demonstrated to be more sensitive than Octreoscan with sensitivity of 90—100 vs. 50—80% for Octreoscan allowing for the detection of micrometastases not seen by Octreoscan, especially in the liver and in the locoregional lymph nodes [32—35,44,45,49]. Studies comparing directly Ga68-SSA Pet and Octreoscan in the same patients showed that PET tracers allowed for a more exhaustive disease staging, giving additional information to scintigraphy in two third of patients and having higher impact on therapeutical decision [50—52]. Several meta-analyses have reported a pooled sensitivity and specificity of Ga68-SST analogue of 91—93% and of 91—96%, respectively in patients with thoracic and GEP neuroendocrine [53—55]. Unfortunately, results among the studies are heterogeneous due to small number of patients included, due to heterogeneity in patient population including both thoracic and GEP NET and due to the lack of reliable gold standard to confirm PET findings. At this moment, it is not possible among the series to obtain results for PNET separately from other NET. The real superiority of Ga68-SSA PET comparing to morphological imaging in particular MRI is not clear and the association of the different techniques is still recommended. Some studies showed higher sensitivity of Ga68-SSTA PET

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tracers comparing to CT scan and/or MRI in detecting distant metastases, especially bone metastases in GEP neuroendocrine tumors with sensitivity around 95—100% for PET and 60—80% for CT but further studies comparing Ga68 PET and high quality morphological imaging are needed to define the role of each technique [32,56—58].

SSTA imaging is necessary to select patient as good candidate for PRRT that is currently under protocol evaluation as post first-line therapy in PNET patients. According to guidelines, Octreoscan is actually the reference and a visual analysis of tracer uptake according to Krenning scale is performed to classify patient as good candidate (grade 3—4 high uptake, homogeneous) or not to PPRT even if in most cases the uptake is heterogeneous among the lesions in the same given patients [59—61]. Indeed, in our experience, only 30% of advanced GEP NET patients qualify for PRRT based on grade 3—4 homogenous uptake of targets lesions [61]. In the future for this purpose, Ga68-SSTA tracers will probably substitute Octreoscan allowing for detection of higher number of lesions expressing SSTR, such as liver micrometastases and allowing for semi-quantitative evaluation [62]. In the future, new quantitative PET criteria will replace the visual analysis. On the other hand, the predictive value of positive SSTA imaging for response to cold SST analogue treatment is still not clear having the cold SSTA a therapeutic impact also in patient with low uptake on SSA imaging.

Peritoneal carcinomatosis is less often in PNET than in ileal NET. It is best explored by abdominopelvic CT and SSR-PET. Bone metastases are also rarer in PTNEs than in lung NETs, except in cases of huge hepatic involvement > 25%. Spine MRI or whole body MRI is here indicated. Finally, poorly differentiated G3 NECs are associated with brain metastases justifying a systematic brain MRI or CT.

Two TNM staging systems proposed by the European Neuroendocrine Tumor Society (ENETS) and the International Union for Cancer Control (UICC) are currently used (Table 3). The ENETS TNM staging has been proven to be more sensitive in predicting tumor-free survival when compared with the UICC TNM system [63].

Imaging prognostic factors

Few studies have addressed the value of imaging for assessing tumor aggressiveness and predictors of the biological tumor behavior in order to tailor the most appropriate treatment. Some parameters of importance, correlated with the patient prognosis in pNET are particularly important to mention in imaging reports:

The size of the primary tumor: it has been reported to be correlated with malignancy in non-functioning PNET [21,64]. In Manfredi at al. study, parameters associated with higher risk of malignant behavior non-functioning PNET were size > 30 mm, irregular margin, absence of cleavage plane with the main pancreatic duct, vascular encasement [21,65].

Vascularization of the pancreatic tumor. In PNET, mean vascular density has been reported to be higher in well differentiated benign endocrine tumor, small lesion < 2 cm, tumor with ki67 < 2%, non-metastatic tumor and in patients without disease progression [66]. Similar findings have been reported on CT and MR images. Well circumscribed hypervascular mass with homogeneous enhancement is more common in grade 1 tumor (Fig. 4). At the opposite ill-defined hypovascular tumor on arterial and portal phase with heterogeneous enhancement is more common in grade 2 or NEC [65,67] (Fig. 9). In agreement DCE-CT parameters were significantly correlated with prognostic histological characteristics of pancreatic NET [68]. Indeed, significant correlations existed between high blood flow and differentiation, proliferation index or microvascular density, and between longer mean transit time and lymph node or liver metastases. A link between blood flow and OS was also suggested but remains to be confirmed [68,69].

ADC values have been recently identified as a biomarker of tumor aggressiveness correlated with the histological

Table 3 TNM staging criteria.

TNM and stage	ENETS	UICC
T definition		
T1	Limited to the pancreas, < 2 cm	Limited to the pancreas, < 2 cm in greatest dimension
T2	Limited to the pancreas, 2—4 cm	Limited to the pancreas, > 2 cm in greatest dimension
T3	Limited to the pancreas, > 4 cm or invading duodenum or bile duct	Beyond the pancreas but without involvement of the superior mesenteric artery
T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)	Involvement of celiac axis or the superior mesenteric artery (unresectable tumor)
Lymph node (LN) status		
N0	No regional LN metastasis	
N1	Regional lymph node metastasis	
Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

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grade on PNET. In a recent paper, low ADC was a strong predictor of high tumor grade. A cut-off of 1.19×10^3 mm^2/s was associated with a sensitivity of 100% and a specificity of 92% [70] (Fig. 9).

Other imaging predictors of malignancy in PNET are vascular encasement, ill-defined margins, main pancreatic duct and common bile duct dilatation, complex cystic morphology and presence of calcification [17,21] (Figs. 6 and 10).

Tumor burden: the percentage of liver involvement and the number of metastasic sites are also prognostic parameters [41].

The spontaneous tumor progression slope assessed by the percentage of progression of the RECIST sum between 2 imaging examinations in metastatic patients. In the study of Durante et al., an independent statistical correlation was found between tumor slope before and survival of metastatic GEP tumors. Moreover, this parameter was found to better reflect tumor aggressiveness than disease-free interval or proliferative index. However, tumor slope assessment is not yet standardized in the field of endocrine tumors. Moreover, the period of time required for slope assessment delayed the prognostic classification and the treatment management. Most authors consider a low slope if RECIST sum < 20% over 1 year [11,12]. Another way to assess the spontaneous tumor growth is to measure the TGR (tumor growth rate) defined as an estimate of the increase/decrease of the tumor volume over time. TGR is expressed as the percentage change in tumor volume over 1 month. In post-hoc analyses, tumor measurements from CLARINET were re-evaluated to explore the clinical utility of TGR [71]. A pre-treatment TGR > 4%/month was associated with a 4.1-fold greater risk of progression than TGR $\leq$ 4%/month in the overall population (HR 4.1 [95% CI 2.5—6.5]; $P < 0.001$, $n = 187$). This study suggests than a higher prognostic role of TGR than the histologic grade.

The location and the size of the lesions are of importance if a local treatment (surgery, RFA) is considered.

Finally, if uptake intensity at SRS does not seems to be correlated with overall survival in GEP NET [61], one recent study shows that SUV_{max} at could be a valid prognostic factor for progression free survival in G1—G2 pancreatic NET with better prognosis for patient with high SSR uptake Ga68 DOTA NOC, low Ki67 score, absence of distant metastases and previous treatment by PRRT [72]. Validation on large-scale patient population has to be done on prognostic value of Ga68 SSR-PET.

Role of interventional radiology for treatment

Interventional radiology plays a key role for the treatment of PNET metastasis. Liver tumors constitute the most frequent secondary locations, and according to the ENETS recommendations, only G1 and G2 tumors are candidate for liver directed (locoregional) therapies whereas higher grade carcinoma are candidate for systemic treatment due to rapid progression of the disease and widespread metastases. Locoregional treatments of liver metastases include surgery, image guided ablative and hepatic intra-arterial therapies. Image guided therapies can be recommended in two different indications: control of tumor growth and control of secretory syndrome. For secretory syndrome, liver directed therapies are second line treatment after failure or insufficiency of somatostatin analogs. For control of tumor growth, liver directed therapies are used after tumor progression is demonstrated and in case of liver limited or predominant disease [73].

Lung, bone and miscellaneous locations can be treated with interventional radiology technics, in same way than other oligometastatic patients, diseases with long life expectancy and when functional prognostic is threatened [74]. Because many therapeutic options are actually approved for PNET and cumulative toxicity may preclude patients to receive all available treatments, it is crucial to determine the best treatment sequence. Specific secondary effects have to be evaluated for each therapeutic line [75]. It is also important to remind that most liver directed therapies are contraindicated in patients with bilioenteric anastomosis (Whipple's intervention, biliary drainage or prosthesis) [76].

Percutaneous ablation of liver metastases

Percutaneous ablation therapies are used to treat metastasis that cannot, or do not need to, be resected surgically. US and CT are the imaging techniques usually used to target liver metastases. RFA, microwave [77,78] and more recently, cryotherapy [79] are thermal ablation techniques delivering locally energy to destroy metastasis. Main limitations of thermal ablation are hilar location or proximity with bile ducts increasing the risk of complication and a large tumor volume not allowing safe complete ablation of all targeted metastases. According to Gustave-Roussy Institute algorithm, best indication for percutaneous ablative therapies is patients with less than 5 metastases, a sum of all tumors maximal diameters below 8 cm (with the larger one being less than 5 cm) and no significant extra-hepatic disease [74]. Although it is difficult to demonstrate ablation specific benefit on survival, as most of patients will receive several lines of treatment, the very low complication rate (0.5 to 5% according to different studies) make it a very early line treatment option [74]. Finally, the cost of such procedures remains low as percutaneous ablation can be done in outpatients under conscious sedation or during very short hospitalization time when general anesthesia is required.

Hepatic intra-arterial therapies

Because of the hyper-arterialization of PNET metastases, trans-arterial treatments are commonly used in first or second line in about 30% of PNET liver metastatic patients and in about half of them during the entire course of the disease [75]. Although no large randomized or prospective cohort study comparing trans-arterial chemoembolization (TACE), embolization (TAE), and radioembolization (TARE) is available [80], in the particular setting of PNET liver metastases, TACE (Fig. 12) seems to be the technic most commonly performed nowadays [74,81,82]. Several drugs have been used, such as doxorubicin [83] and streptozocin [84] (the latest requiring general anesthesia due to per-procedural pain) resulting in high clinical (50—90%) and radiological (22—100%) response rates. Response on the secretory

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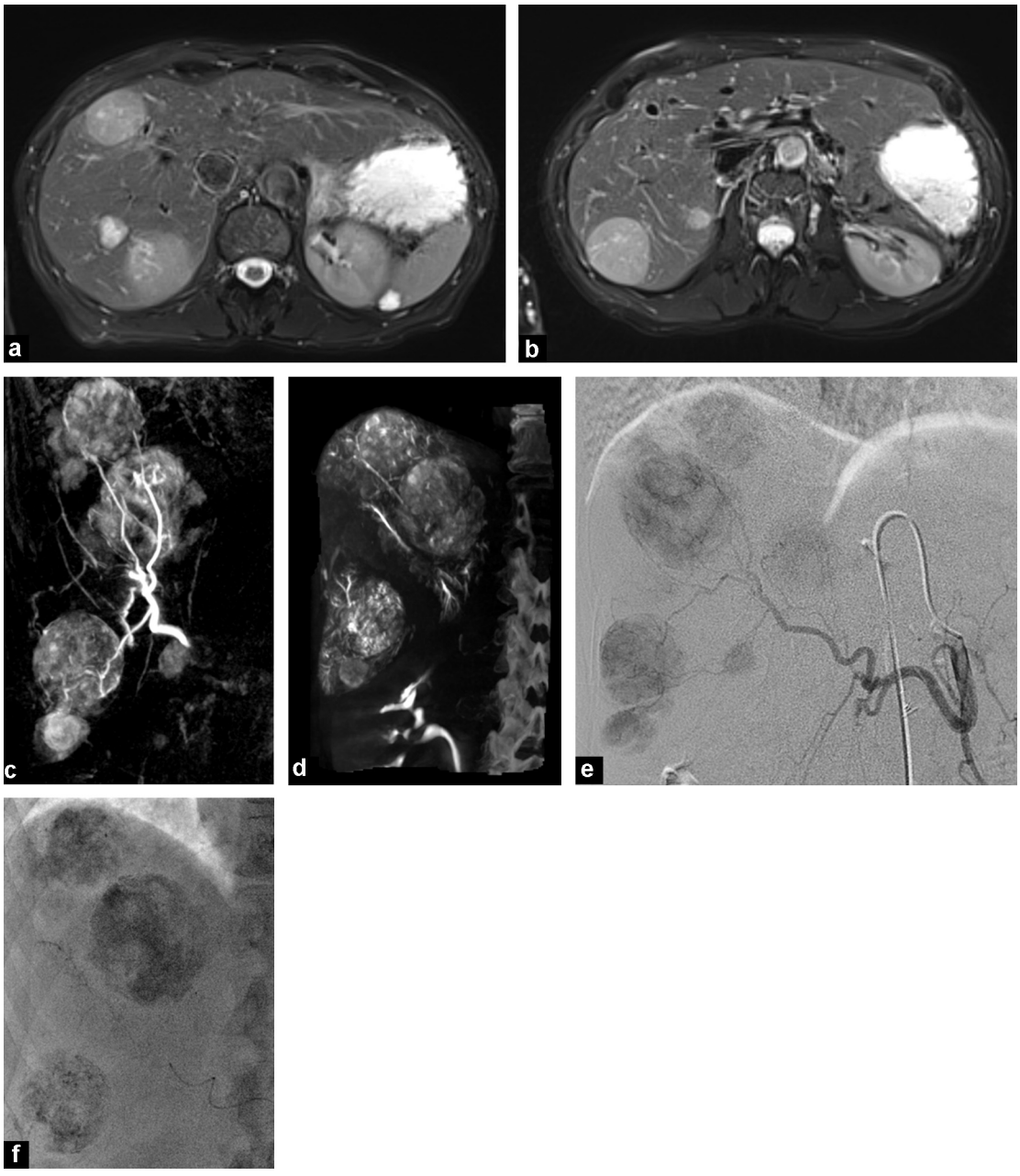

Figure 12. Liver metastases from a PNET treated with transcatheter arterial embolization (TACE) in a 35-year-old patient. A T2-weighted MR images in the transverse plane (a and b) show a 0% liver metastatic involvement. Liver metastases are hyperintense on T2-weighted images with saturation of fat signal (a and b), hypervascular on celiac trunk 2D (c) and 3D (d). Peroperative imaging during TACE using doxorubicin and Lipiodol® (e). Unenhanced volumetric reconstruction from CB-CT imaging immediately after TACE, showing intense Lipiodol® uptake (f).

syndrome is often longer than 1 year [74]. Median overall survival after TACE varies from 25 to 44 months [85—88] with results being worse than for other gastrointestinal NETs [81,89]. When tumor burden is greater than 30%, repeated courses of TACE targeting sequentially different areas of the liver have to be performed with a 4- to 8-week delay to avoid liver failure. Specific anesthesiology management is needed for these patients to avoid acute carcinoid crisis or kidney failure secondary to tumor necrosis and iodinated contrast agent. Lately, an increased risk of biliary and liver complications has been reported using drug eluting beads when compared to lipiodol® (Guerbet, Aulnay, France) [90,91] requiring a very careful selection of patients [92] before TACE.

Radioembolization (TARE) or selective internal radiation therapy (SIRT) could be a safe and effective alternative [93,94]. Recent studies report high response rates with median OS reaching 70 months in a large multicenter study in the US that included 148 patients [95]. Portal vein thrombosis and bilioenteric anastomosis are not formal contraindications for TARE but should be taken into consideration before treatment.

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Take-home messages

- PNET can be functioning or non-functioning with different clinical presentation and different prognosis from indolent to aggressive behavior based on WHO and TNM classifications.
- Endoscopic ultrasonography (EUS) is the imaging modality of reference to detect small size pancreatic lesions, such as gastrinomas and insulinomas.
- Typical insulinomas are well defined, hypervascular and show intense and homogenous or rim like enhancement during arterial/pancreatic phase.
- Gastrinomas are the PNET the more often associated with a MEN1. In these cases, they are located in the duodenum and often multicentric. After contrast injection, gastrinomas have more often a delayed enhancement persistent on delayed phase due to presence of fibrosis.
- Non-functioning PNET appears as a large pancreatic mass with heterogeneous enhancement due to necrotic and hemorrhagic changes. On MR images, in contrast to pancreatic adenocarcinoma, most of pNET are hyperintense on T2W images and hyper- or isointense during the arterial/pancreatic phase of the dynamic study.
- Somatostatin receptor scintigraphy (Octreoscan) is recommended to improve disease staging, to detect disease recurrence or the primary and finally to select patient candidate for Peptide Receptor Radiometabolic Treatment. However, Gallium 68-SST analogue PET have been demonstrated to be more sensitive than SRS-SPECT and it will be the future of functional imaging for PNET.
- Imaging predictors of aggressive behavior in PNET are large size, low vascularization, vascular encasement, ill-defined margins, pancreatic and/or bile duct dilatation, complex cystic morphology, important liver involvement, high number of metastasic sites and fast spontaneous tumor progression slope.

Disclosure of interest

C. Dromain: consultant for Ipsen (participation of advisory board meeting and sponsored clinical research protocols).

The other authors have not supplied their declaration of competing interest.

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