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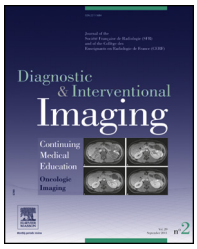

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Imaging of neuroendocrine tumors of the pancreas

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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).

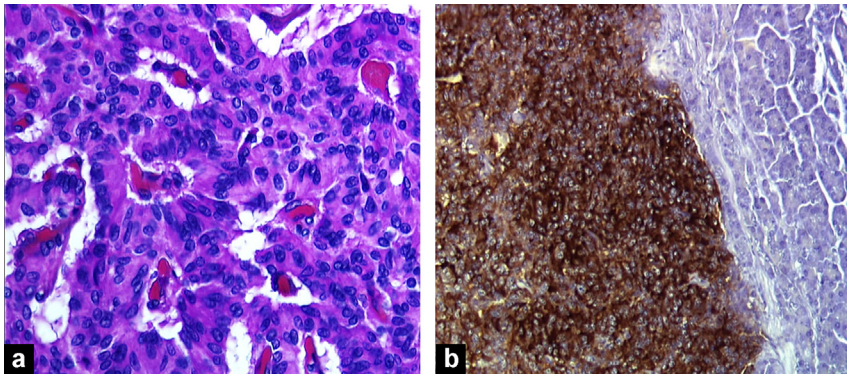

Figure 1. Typical histological appearance of a well differentiated neuroendocrine tumor of the pancreas on histopathology: monomorphic tumor cells are arranged in plates separated by thin fibrovascular septa (a). The strong expression of chromogranin A confirms the neuroendocrine nature of this well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

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