

## Endoscopic Ultrasound in Pancreatic Neuroendocrine Neoplasms

M Saidi Idrissi<sup>1\*</sup>, N Benjelloun<sup>1</sup>, M Salihoun<sup>1</sup>, M Acharki<sup>1</sup>, I Serraj<sup>1</sup>, I Elouarith<sup>2</sup>, K Znati<sup>2</sup> and N Kabbaj<sup>1</sup>

<sup>1</sup>Unit of Gastroenterology “EFD-HGE”, Ibn Sina University Hospital, Rabat, Morocco

<sup>2</sup>Unit of Anatomical Pathology, Ibn Sina University Hospital, Rabat, Morocco

### \*Corresponding author:

Saidi Idrissi Maroua,  
Unit of Gastroenterology “EFD-HGE”, Ibn Sina  
University Hospital, Rabat, Morocco,  
E-mail: si.maroua12@gmail.com

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## 1. Abstract

**1.1. Background:** Pancreatic neuroendocrine neoplasms (PNENs) are exceedingly rare, often diagnosed incidentally or with nonspecific symptoms, rarely with symptoms of hormone overproduction. The aim of this study is to evaluate the role of endoscopic ultrasound (EUS) in the diagnosis of these tumors.

**1.2. Materials and methods:** 5 PNENs cases were identified, between March 2017 and February 2022. EUS was performed in all patients and tissue samples were obtained using EUS -fine needle aspiration (FNA).

**1.3. Results:** mean age was 51 years, 80% were male, 80 % of the tumors were non-functioning PNENs. The median size was 45 mm, located in the pancreatic head in 60 % of cases. The echoendoscopic aspect was heterogeneous hypoechoic in all cases. 40% had metastases. EUS- FNA allowed tissue acquisition.

**1.4. Conclusion:** EUS is a sensitive tool in the diagnosis of PNENs, it identifies the lesions, evaluates their extension and allows tissue acquisition for diagnosis confirmation and prognosis.

## 2. Introduction

PNENs are relatively rare, accounting for 1 to 2 % of all pancreatic neoplasm [1]. They form a very heterogeneous group of tumors and are classically divided into functional and non-functional tumors. They can be diagnosed incidentally or with nonspecific symptoms, rarely with symptoms of hormone overproduction in case of functional-PNENs.

The aim of the study is to report 5 case PNENs and to evaluate the role of EUS in the diagnosis of these neoplasms.

## 3. Materials and Methods

A monocentric study included 5 patients with PNENs, from march 2017 to march 2022. The medical records of the patients were

reviewed to conduct this study. The variables analyzed were: age, sex, symptomatology, results of imaging, EUS, and histopathology following EUS-FNA. All EUS were performed with propofol sedation with or without tracheal intubation, using a radial and/or a linear echoendoscope (Pentax®) and a ultrasound processor (Aloka-Hitachi®). All EUS examinations were performed by experienced endoscopists. EUS-FNA was performed in all cases using a 19, 22 or 25 (G) needle. Cytology and immunohistochemical studies were performed on the specimens obtained through EUS-FNA, using Immunocystochemical staining for chromogranin A, Synaptophysin. The 2017 World Health Organization (WHO) guidelines [2] based on the degree of differentiation and Ki-67 index, were followed for the analysis

## 4. Results

Out of 132 EUS identifying solid and cystic pancreatic masses ; 5 cases (3,8%) of PNENs were collected. The mean age was 51,2 years [range :37-70 years] and 80% were men. 80% off PNENs were non-functional : revealed by cholestatic jaundice in 40% of cases and abdominal pain with melena in 20% of cases. The patients that presented with incidentalomas (20%) were asymptomatic. 20% of the PNENs were functional revealed by severe hypoglycemia.

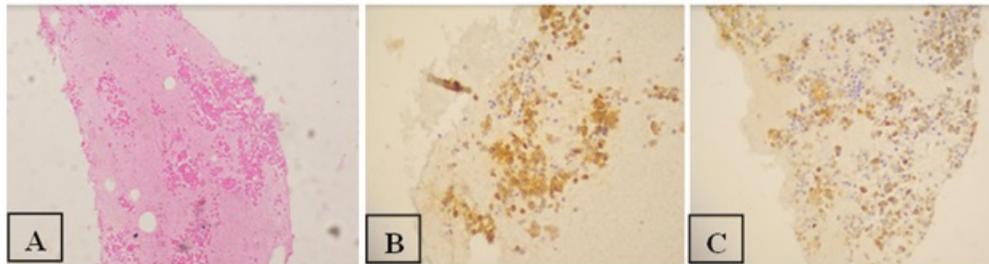
Abdominal Computed tomography (CT scan) and /or Magnetic resonance imaging (MRI) were used to locate the tumor in symptomatic patients (80%) and in the asymptomatic patients (20%). EUS identified a heterogeneous, hypoechoic and well defined lesion in 100% of cases, with necrotic areas in 40% of cases. The mean lesion size was 45 mm [range 15.7-60], located in the pancreatic head in 60% of cases and extending to the body in 20%, located in the body in 20% of cases and in the tail in 20% of cases. The tumor was localized, advanced (with vascular invasion) and

metastatic (liver metastases) in 40%, 20% and 40% of cases respectively (Figure 1). EUS-FNA has been successfully performed in 100% of cases, using a 22 G needle in 60% of cases, 25 G in 20% and 19 G in 20%, through the duodenal bulb (40%); through the gastric wall (40%) and through the second duodenal portion (20%), with an average number of passes of 3 [2-4]. No major or minor complications – particularly hemorrhage- occurred during or after the sampling procedure. FNA was feasible in all cases.

Cytology and immunocytochemistry studies were performed on the samples obtained through EUS-FNA, carrying out histologic staining for chromogranin A and Synaptophysin. The 2017 WHO guidelines were followed for the ki-67 analysis and were based on ki-67 index value and mitotic count. The tumor cells were positive for chromagranin A and synoptophysin, and classified into grade 1 (Ki-67  $\leq$ 2%) in 40% of cases, grade 2 (Ki-67 3-20%) in 40%, and small cell neuroendocrine carcinoma in 20 % of cases (Figure 2,3 and 4).

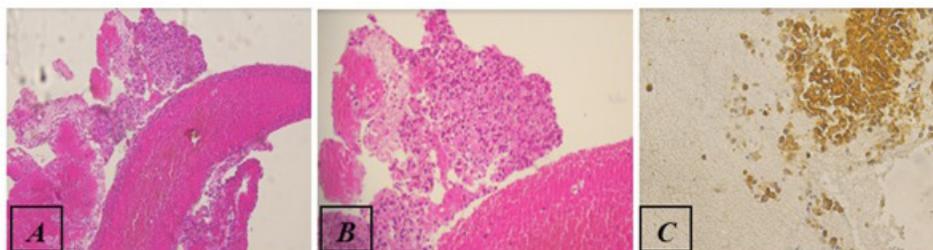


**Figure 1 :** EUS showing a well defined hypoechoic heterogenous mass in the pancreatic tail (Well-differentiated PNEN, Grade 1)



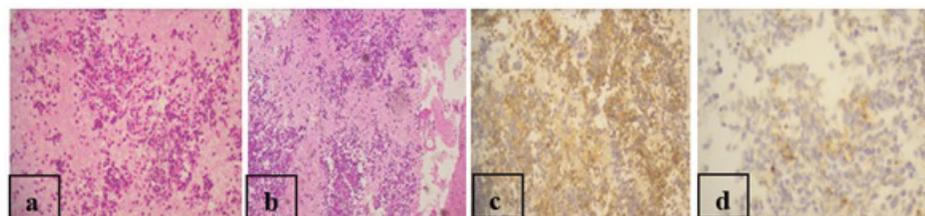
**Figure 2: Cytological and immunohistochemical findings of a well-differentiated PNEN**

Sheets of medium-sized cells showing uniform round nuclei, finely stippled chromatin and no nucleoli (A, hematoxylin and eosin [H&E], x 100), Cells are positive for synaptophysin (B, x200) and chromogranin (C, x200)



**Figure 3: Histological results of a well-differentiated PNEN**

A,B) Hematoxylin & Eosin stain show clusters of small round monotonous cells with coarse, salt and pepper nuclear chromatin and eosinophilic cytoplasm (A : x 100 ,Bx200). C ) Tumor cells show positive staining for synaptophysin.(Cx200).



**Figure 4: Poorly differentiated neuroendocrine carcinoma:**

a – b) Diffuse sheets of small cells with high N/C ratio and nuclear hyperchromasia (a: hematoxylin and eosin [H&E], x100 and b : H&E, x200). The cells are positive for synaptophysin (C, x200) and focally positive for chromogranin (d, x400)

## 5. Discussion

PNENs are exceedingly rare. They occur in approximately 1 per 100,000 population and account for 1 to 2 % of all pancreatic neoplasm [1]. There is a slight male predominance (55% of cases). Most patients present in their 50s [3]. In our study the percentage of PNENs was slightly higher than reported in literature (3%) Mean age (51 years) and the sex ratio (4M:1F) were in accordance with other series. Most P-NENs occur as sporadic tumors (95% of cases), although a proportion occurs as part of an inherited syndrome such as multiple endocrine neoplasia type 1 or Von Hippel Lindau disease [3,4]. All the PNENs in our study were sporadic. The rarity of PNENs makes it difficult to identify risk factors. However, a meta-analysis has highlighted the following risk factors: family history of first degree cancer, smoking, significant chronic alcoholism and diabetes [5]. We didn't identify any risk factor in our study. Clinically, PNENs are classified as non-functional (NF-PNENs) and functional tumors (F-PNENs), depending on the presence or absence of a clinical hormonal hypersecretion syndrome [6]. 80% of our cases were NF-PNENs. Patients with F-PNENs present earlier than patients with NF-PNENs, with a mean age of presentation 55 vs. 59 years [3]. In our study, only 1 patient (20%) had a F-PNENs, at the age of 31. NF-PNENs are more prevalent (85%) than F-PNENs [7]. They are usually asymptomatic until the occurrence of nonspecific symptoms due to mass effect or until metastasis occurs [8]. This explains the delay in the usual significant diagnosis for these tumors and their larger appearance and more often malignant presentation than functioning PNENs. However, small size asymptomatic NF-PNENs (pancreatic incidentalomas) are more often accidentally discovered, representing up to nearly 70% of NF-PNENs [9]. Only 10-20% of PNENs are functional. The results of our study was in accordance with this percentage. The most common functional syndromes are those related to hypersecretion of insulin (insulinoma) and gastrin (gastrinoma), then glucagon (glucagonoma) and vasointestinal peptide (vasoactive intestinal peptide-producing tumors). Other hormones are rarely involved (Somatostatin, ACTH, PTHrp) [10]. In our study, 1 patient (20%) had severe recurring hypoglycemia.

Insulinomas are the most common F-PNENs, they tend to be smaller than other F-PNENs. at diagnosis, 90% of insulinomas being < 2 cm in diameter and 40% being < 1 cm [11]. Most insulinomas occur in the pancreas, and are distributed evenly in the pancreatic head, body, and tail [12]. Insulinoma can be malignant in 5 to 15% of cases, whereas the other PNENs are malignant in 50–90% of cases, with metastases developing in the regional lymph nodes initially, in the liver later and at distant sites [13]. In our study, the insulinoma presented in EUS as a hypoechoic, round well defined lesion measuring 15,7 × 15,4 mm, located in the pancreatic head. The WHO (2017) classifies PNENs according to differentiation and tumor grade and distinguish 5 categories and 3 grades based

on mitotic index and Ki-67 index (G1, G2, G3, and NEC according to the mitotic index and Ki-67 index). Unlike the previous version dating from 2010, in the 2017 revision a new subset of well-differentiated neuroendocrine tumors has been recognized, which are lesions that are morphologically well-differentiated and often identical to grade 1 or grade 2 NEN but have a high Ki-67 index (> 20%) and should probably be treated as well-differentiated grade 2 PNENs [2].

In our study PNENs were classified using the 2017 WHO classification into : grade 1 PNENs (Ki-67 ≤ 2%) in 40% of cases, grade 2 PNENs (Ki-67 3-20%) in 40%, and small cell neuroendocrine carcinoma in 20 % of cases.

PNENs can also be classified according to the TNM classification systems with grading, of which there are 2 different classifications (ENETS and UICC / AJCC) ; ENETS classification would be better correlated to the prognosis [14].

The prognosis of PNENs, depends on multiple factors, the main being the tumor stage and the presence of distant lesions. PNENs are discovered at a localized or locally advanced stage in about 25% each, and metastatic in about half of the cases [15, 16]. The main histological prognostic factors are the tumor differentiation and the proliferation index. Also, high levels of tumor markers (chromogranin A, specific hormones) are associated with a poor prognosis. The presence of extra-hepatic metastases, and in particular peritoneal and/or bone, is associated with a poor prognosis [12,15,17,18,19].

The diagnosis of PNENs is often delayed, most of them are small, initially asymptomatic and slow in evolution. Depending on their location, PNENs can cause jaundice (17-50%) or acute pancreatitis, in addition to nonspecific signs such as abdominal pain (35-78%), transit disorders, nausea (45%), weight loss (20-35%) and/or a palpable mass (7-40%) [16]. In our study, 40% of PNENs were revealed by cholestatic jaundice and abdominal pain with melena in 20%. PNENs were incidentalomas in 20% of the cases. In F-PNENs, the presenting symptoms depend on the particular hormone that is being overproduced: Insulinomas present with symptoms of episodic hyperinsulinemia classically referred to as Whipple's triad: symptoms of fasting hypoglycemia (weakness, sweating, tremors, palpitations, confusion, visual changes etc.), documented hypoglycemia at time of symptoms, and immediate relief of symptoms after the glucose administration [13,20]. Gastrinomas hypersecrete gastrin and causes hyperchlorhydria resulting in Zollinger Ellison syndrome. The classic symptoms are refractory peptic ulcer disease and secretory diarrhea [13,20].

Glucagonomas presents commonly with migratory necrolytic erythema [21], glucose intolerance, weight loss, diarrhea, and deep vein thrombosis. VIPomas secrete vasoactive intestinal polypeptide and presents with large volume watery diarrhea and hypokalemia. Somatostatinomas secrete somatostatin (ST) and can result in diabetes mellitus, gallbladder disease, diarrhea or steatorrhea,

anemia, and weight loss [13,20]. The dosage of hormones responsible for hormonal syndromes (insulin, vasoactive intestinal polypeptide, glucagon, ... is useless in the initial assessment of a NF-PNEN, but can be useful in the cases of occurrence of symptoms suggestive of hormonal hypersecretion [22].

A variety of tumor markers have been proposed for F-PNENs and NF-PNENs. The most common of these is chromogranin A : the main serum marker of PNENs, used in the diagnosis and the follow up of especially NF-PNENs with a sensitivity of 60–100% in metastatic disease and < 50% for local disease [13]. Cross-sectional imaging methods (CT scan and MRI) are key examinations for initial diagnosis, staging and monitoring PNENs. Due to their typically hypervascular nature, PNENs and possible metastatic lesions are enhanced after iodinated contrast media injection in the arterial phase and wash out during the portal phase. Triple-phase contrast (without injection, early arterial and portal) with images centered on the pancreatic region is the optimal study [12,23,17]. It allows the detection of the primary tumor and lymph node and /or liver metastases and allows the measurement of tumor progression under treatment, one of the most important prognostic factors in clinical practice, however CT scan can fail in the detection of smaller PNENs. In a large study it failed to detect 68.4% of PNENs < 10mm and a further 15% of PNENs  $\leq$  20 mm in diameter [24].

In our study, CT scan failed to detect an insulinoma measuring 15,7  $\times$  15,4 mm, located in the pancreatic head in a patient presenting with severe recurring hypoglycemia. EUS with EUS-FNA allowed the diagnosis.

Pancreatic MRI has a good sensitivity for detecting PNENs, especially those measuring more than 2 cm. However, its sensitivity remains lower than that of EUS. MRI is more effective than CT scan and Somatostatin receptor scintigraphy (SRS) for the detection of distant lesions, in particular liver metastases. In a study, these three techniques detected respectively 394, 325 and 204 liver metastasis [25]. Well-differentiated PNENs often express somatostatin receptors on their surface, which can be visualized by binding a radioactive ST analogue. It identifies 50–70% of primary tumors, except insulinomas that express somatostatin receptors in only 50% of cases [13]. In-pentetreotide SRS has a sensitivity and specificity of 90% and 80% respectively for the diagnosis of PNEN > 1 cm. Nevertheless, its sensitivity is low for tumor <1 cm and its spatial resolution is poor. It can be coupled with CT scans, which makes it possible to locate focal points of fixation and reduce false positives. SRS allows a whole-body mapping of ST receptors and thus to highlight fixations related to intra- and extra-abdominal metastases [12,23,17].

The place of 18F-Fluorodeoxyglucose (FDG)-PET in the assessment of PNENs depends on the degree of tumor differentiation. The diagnostic yield is low for low-grade PNENs and is better for tumors with a high proliferation index expressing little or no ST receptors [26]. Therefore 18FDG-PET is useful for staging and

monitoring poorly differentiated neuroendocrine carcinomas and well-differentiated PNENs that do not fix in SRS [12,23].

PET with gallium-labeled somatostatin analog allows for the detection of smaller lesions and/or detection of lesions with moderate somatostatin receptors expression, resulting in a higher sensitivity and diagnostic accuracy [27].

EUS is one of the most invaluable tools for the diagnosis of pancreatic lesions, allowing a high resolution detailed observation of the entire pancreas, and offering an additional benefit of tissue acquisition. EUS has a sensitivity of 87.2% and a specificity of 98.0% for detecting PNENs [28], and can detect lesions up to 2-5 mm in diameter [29], it can provide detailed information about location, diagnosis, grading and relationships with nearby structures such as the main pancreatic duct and vessels. A Meta-analysis showed that preoperative EUS increased the overall PNENs detection rate by > 25% after CT scan, with or without additional investigative modalities such as MRI [30] and was more accurate in identifying as well as characterizing PNENs. PNENs appear as a hypoechoic, homogeneous lesions with distinct margins [31]. However, cystic degeneration and calcification as PNENs size increases may appear. In these cases, PNENs often present a heterogeneous pattern. The majority appear as solid lesions, but they may also appear as cystic or mixed solid-cystic masses, showing features as: unilocular cysts, septated cysts, microcystic-appearing cysts, and mixed solid-cystic masses [32]. In our study, PNENs appeared as hypoechoic and well defined lesion in 100% of cases, with necrotic areas in 40% of cases. Some tumors need to be differentiated from PNENs such as solid pseudopapillary neoplasms, serous cystic neoplasm, pancreatic metastasis and pancreatic carcinoma, differential diagnosis using imaging techniques alone may prove difficult, thus the need for tissue diagnosis. Tissue acquisition using EUS is the primary sampling technique for pancreatic tumors with a sensitivity of 80%-90%, a specificity close to 100%, and a sampling adequacy rate of 83–93% [33]. It allows cytologic or immunocytochemical studies for confirmation and grading.

EUS-FNA can be performed using a 22 G or 25 G needle. The choice of needle caliber depends on the diameter and site of the lesion, whether it is predominantly solid or cystic. If the lesion is cystic, a biopsy microforceps able to pass through a standard 19 G needle, and obtain histological specimens of the cystic lesion wall, can be used [34]. A systematic review reported a concordance rate of the Ki-67 index between PNENs measured from EUS-FNA samples and surgical specimens of 83% [35].

A study also suggested the ability of EUS-FNA specimens of PNENs to accurately predict prognosis. Malignant PETs contained significantly greater DNA microsatellite losses than benign lesions, which was associated with a lower 5-year survival [36]. However, the accuracy of the technique is dependent upon the size and location of the pancreatic mass and expertise of the endoscopist [37]. EUS-FNB (fine-needle biopsy) can be performed to obtain

core biopsies and improve histological diagnoses. Recent studies showed that EUS-FNB outperformed EUS-FNA for diagnosis of PNENs. A 2019 study demonstrated higher diagnostic sensitivity : 94.3% for EUS-FNB over 88.4% for EUS-FNA, indicating that EUS-FNB improves diagnostic sensitivity and confers additional information to cytological assessment of PNENs [38]. In our study, EUS-FNA allowed the diagnosis and cytological assessment of all cases of PNENs.

Contrast-enhanced EUS (CE-EUS) allows the observation of the hemodynamics of pancreatic masses in real time. Typical PNENs show hypervascular contrast in the early phase, persisting until the delayed phase. CE-EUS has a sensitivity of 78.9%–95.1% and 98.7% specificity in the identification of PNENs [39,40]. It can also help finding a specific site within a lesion that would be suitable for EUS-FNA. A study reported that a heterogeneous ultrasonographic texture point to a malignant disease [39], Another reported that contrast-enhanced harmonic EUS can predict an aggressive tumor behavior by evaluating the heterogeneous patterns of PNENs, with a high sensitivity and specificity (86% and 96% respectively) [41]. It also demonstrated that In PNENs, CH-EUS has the ability to classify tumors according to their aggressiveness with an excellent overall accuracy and a high negative predictive value. EUS elastography (EUS-E) is a non-invasive method allowing the characterization and differential diagnosis of solid pancreatic lesions [42] and has been proven to differentiate between benign and malignant solid pancreatic masses. PNENs are portrayed as blue in EUS-E, they are homogeneous and harder than the surrounding pancreatic parenchyma [43]. A study showed a sensitivity of 100% and specificity of 88% for quantitative elastography in differentiating pancreatic ductal adenocarcinoma from PNENs when the cut-off value of strain ratio was 26.6 [44].

## 6. Conclusion

EUS has become an invaluable tool in the diagnosis of PNENs. It allows detection of the tumor when other non-invasive procedures have failed such as CT scan and provides additional informations for tumor staging. The addition of FNA or FNB to EUS has enables tissue confirmation and prognosis prediction, allowing for proper therapeutic management.

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