Original Article

B-mode and contrast-enhancement characteristics of small nonincidental neuroendocrine pancreatic tumors

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ABSTRACT

Background and Objectives: Imaging of the pancreas for detection of neuroendocrine tumors is indicated as surveillance in multiple endocrine neoplasia type 1 (MEN1) or if typical clinical symptoms combined with hormone production raise the suspicion of a neuroendocrine tumor. Endoscopic ultrasound (EUS) is considered the best imaging modality to detect small pancreatic tumors. However, little is known about how small pancreatic neuroendocrine tumors (pNETs) present on EUS. **Patients and Methods:** In this multicenter study, we retrospectively analyzed the endosonographic characteristics of small pNETs which had been detected due to typical biochemistry and clinical symptoms or during surveillance of MEN 1. Only small pancreatic tumors ≤15 mm with histological confirmation as pNET were included. B-mode and contrast-enhanced ultrasound- and EUS patterns were analyzed. **Results:** Among 32 patients with histologically proven small pNETs, 7 patients had known MEN1. Among the pNETs, 20 were insulinoma, 2 gastrinoma, 3 glucagonoma, 6 nonfunctional in MEN1, and one PPoma. 94% of the pNET appeared hypoechogenic, only 1 isoechogenic and 1 hyperechogenic. After contrast injection, 90% of the pNETS showed hyperenhancement compared to the surrounding pancreatic parenchyma. **Conclusion:** The high spatial resolution of EUS allows detection and even cytological confirmation of pNET <7 mm diameter. Hypoechogenicity in B-mode and hyperenhancement after injection of contrast agents are endosonographic characteristics of small pNET and present in >90% of pNETs.

Key words: Contrast-enhanced endoscopic ultrasound, endoscopic ultrasound, fine needle aspiration, guidelines, pancreatic ductal adenocarcinoma, solid pancreatic lesions

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INTRODUCTION

Due to its high spatial resolution, endoscopic ultrasound (EUS) is recommended as the method of choice for detection of very small pancreatic tumors; it is also useful to obtain cytopathology by fine needle aspiration (FNA).[1] The diagnostic potential of cross-sectional imaging, especially of magnetic resonance imaging (MRI) is well-known, but the accuracy of EUS still remains superior.[2]

Pancreatic neuroendocrine tumors (PNETs) are a rare entity with an incidence of 1–10 per million in the general population.[3,4] However, the prevalence in patients with multiple neuroendocrine neoplasia type 1 (multiple endocrine neoplasia type 1 [MEN-1]) is up to 75%, while pNETs are the main cause of MEN1-related death.[5] Therefore, early detection and surveillance is mandatory as surgery is the only curative treatment.

Imaging of the pancreas for detection of neuroendocrine tumors is indicated as surveillance in MEN1 or if typical clinical symptoms combined with hormone production raise the suspicion of a neuroendocrine tumor. EUS is considered the best imaging modality to detect small pancreatic tumors in particular in MEN1.[6-12] Moreover, EUS is increasingly used for active surveillance of very small nonfunctioning pNET, which carry a low oncological risk.[13-15]

However, little is known about how small pNETs present on EUS.

In a previous multicenter study, we could show that contrast enhanced transabdominal ultrasound (CE-US) and contrast-enhanced endoscopic ultrasound (CE-EUS) are helpful in characterizing small pancreatic tumors which are incidentally found on other imaging; however, in this study hormone-active tumors and pNETS in patients with MEN1 were excluded from this study.[12] The aim of the present study was to characterize small pancreatic tumors found in patients with known MEN1 or with clinical symptoms combined with biochemical elevation of typical neuroendocrine hormones such as insulin, glucagon, or gastrin.

PATIENTS AND METHODS

From 30 tertiary referral centers invited to participate in the study, 7 centers sent their cases of small pNETs found on annual surveillance of patients with MEN type 1 or due to typical hormone alterations and clinical symptoms.

Symptom evaluation, computer tomography (CT) and MRI or octreotide scans were performed as part of

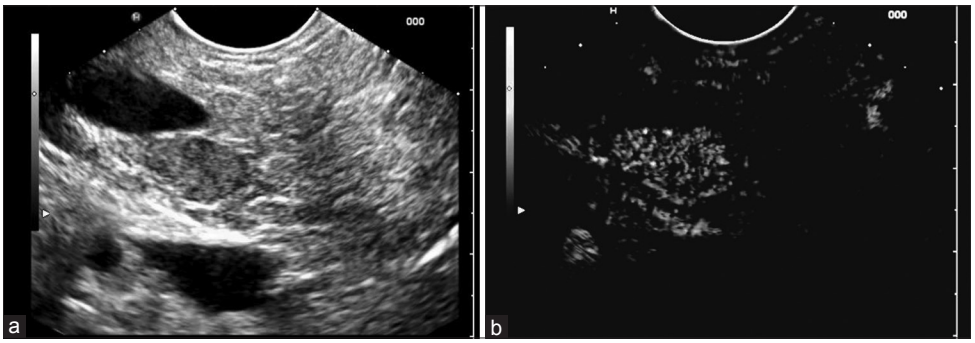

Figure 1. Insulinoma in the pancreatic head using B-mode (a) and contrast-enhanced endoscopic ultrasound with early hyperenhacnement in comparison to the surrounding pancreatic parenchyma (b). Portal vein and inferior vena cava do not show enhancement during this very early contrast phase

Table 1. Clinical and pathologic characterization of 32 patients with small neuroendocrine pancreatic lesions

	All (%)	Insulinoma (%)	MEN 1 (%)	Glucagonoma (%)	Gastrinoma (%)	PPoma
n	32	20/32 (63)	7/32 (22)	3/32 (9)	1 (3)	1 (3)
Age (years)	54 [18-78]	52 [18-86]	28 [18-57]	60/71/78	65	74
Sex (male/female)	12/20	6/14	3/4	2/1	female	male
Size (mm)	10 [4-15]	10 [5-15]	12 [4-15]	11/12/12	7	6
Surgery	26/32 (81)	19/20 (95)	3/7 (43)	3/3 (100)	1	1

Minimum – maximum given in square brackets; percentage given in round brackets. MEN 1: Multiple endocrine neoplasia Type1

the clinical workup but not for the purpose of this study.

All patients included underwent transabdominal US and EUS of the pancreas. CE-US or CE-EUS, as well as EUS elastography, were performed depending on the availability of these imaging in the different centers. EUS was performed using radial (EG-3670URK) and/or linear (EG-3870UTK) echoendoscopes (Pentax Medical, Hamburg, Germany) with high-end ultrasound systems HI Vision Preirus and HI Vision Ascendus (Hitachi Medical Systems, Wiesbaden, Germany).

The use of EUS-guided FNA (EUS-FNA) and the particular EUS-guided sampling technique, as well as the choice of echoendoscope (radial or linear), were at the discretion of the endoscopist in the participating centers. Furthermore, the indication for surgery and the preferred surgical techniques for management of pNET varied between the centers. As some of the centers were only referral centers for EUS, they did not perform cross-sectional imaging for follow-up.

The localization in caput (head), corpus (body), or cauda (tail) was defined according to tumor node metastasis classification: cauda between the left side of the aorta and the splenic hilum; the corpus between the left lateral border of the superior mesenteric vein and left side of the aorta and the caput between the left lateral border of the mesenteric vein and right side of the head/duodenum.

Evaluation criteria

The anonymized data collection over a 10-year period included age, sex, final diagnosis (etiology of the lesion[s]), benign or malignant nature, size, location (head, body, tail), and echogenicity (hypoechoic, isoechoic, mixed echogenicity, hyperechoic).

Contrast enhancement was assessed after intravenous injection of 4.8 mL SonoVue® (Bracco SpA, Milan, Italy); hyper-, iso-, or hypo-enhancement compared to the surrounding pancreatic parenchyma was documented. All contrast enhanced examinations were performed as described in the guidelines of the European Federation of Societies for Ultrasound in Medicine and Biology.[16]

Data analysis and statistics

All data were analyzed according to the pathological diagnosis. Dimensions were given as median (minimum – maximum) as appropriate. Institutional Board approval according to the ethical guidelines from Helsinki was obtained. Only patients older than 18 years were included into the study.

RESULTS

Histological or cytological confirmation

Among 32 patients with histologically or cytologically proven small pNETs, 7 patients had known MEN1. Among the pNETs, 20 were insulinoma, 2 gastrinoma, 3 glucagonoma, 6 nonfunctional in MEN1, and one PPoma [Table 1].

In 13 patients, the diagnosis of a pNET had been obtained by EUS-FNA and cytology.[17] In this subgroup, the median tumor size was 10 mm ranging from 5 to 15 mm. Five of the pNETs diagnosed by EUS-FNA were ≤7 mm.

In 26 patients, the diagnosis of pNET was confirmed after surgery; thereof, seven patients had already positive cytology by EUS-FNA before surgery.

Location of the tumor in the pancreas

Most of the neuroendocrine tumors were found in the pancreatic head (56%), this was also true for insulinoma (65%) [Table 2].

B-mode echogenicity

Only one glucagonoma showed isoechogenicity compared to the surrounding pancreatic parenchyma, and one insulinoma was reported as hyperechogenic, while 94% of the pNETs appeared hypoechogenic on B-mode ultrasound examination [Table 2].

Contrast enhancement

Contrast enhancement studies were performed in 19 patients with small pNETs. CE - EUS was performed in 10 patients, CE-US in 9 patients and both methods in 5 patients. In one of the five patients, who underwent both, CE - US and CE-EUS, the pNET in the pancreatic tail has only been visualized endosonographically.

After intravenous injection of contrast agents, 90% of the pNETS showed hyperenhancement compared to the enhancement of the surrounding pancreatic parenchyma [Figure 1 and Table 2]. Only one 11 mm sized glucagonoma appeared hypoenhancing on CE-EUS and a 5 mm sized insulinoma was isoenhancing.

Table 2. Localization, B-mode characteristics and contrast enhancement pattern of patients with small solid neuroendocrine pancreatic lesions

	All (%)	Insulinoma	MEN 1	Glucagonoma	Gastrinoma	PPoma
Localization						
Caput	18/32 (56)	13/20 (65%)	3/7 (43)	1/3 (33)	1	
Corpus	9/32 (28)	6/20 (30)	1/7 (14)	1/3 (33)		1
Cauda	5/32 (16)	1/20 (5)	3/7 (43)	1/3 (33)		
Echogenicity						
Hyperechogenic	1/32 (3)	1/20 (5)	0/7 (0)	0/3 (0)		
Isoechogenic	1/32 (3)	0/20 (0)	0/7 (0)	1/3 (33)		
Hypoechogenic	30/32 (94)	19/20 (95)	7/7 (100)	2/3 (67)	1	1
Contrast enhancement						
Hyper-enhancement	17/19 (90)	13/15 (86%)	2/2 (100)	2/2 (100)		
Iso-enhancement	1/19 (5)	1/15 (7)	0/2 (0)	0/2 (0)		
Hypo-enhancement	1/19 (5)	1/15 (7)	0/2 (0)	0/2 (0)		

Percentage given in round brackets. CE-EUS: Contrast enhancement tested in 19 patients; MEN 1: Multiple endocrine neoplasia Type 1, CE-EUS: Contrast-enhanced endoscopic ultrasound

DISCUSSION

The detection and exact localization of hormone-producing pNETs which are often only minuscule is crucial for further organ-preserving surgical management,[18] active surveillance[13-15] or modern ablative methods. In the hands of an experienced operator, EUS has a high sensitivity to detect even minute pancreatic tumors which is also pivotal in the surveillance of high-risk patients such as patients with MEN type, von Hippel-Lindau disease, neurofibromatosis type 1 or tuberous sclerosis.[10,13-15,19,20] As soon as, the diagnosis of MEN type 1 has been confirmed in an individual by genetic testing and/or clinical manifestation and/or affected family members, an active surveillance program is commenced including annual pancreatic imaging with CT, MR or EUS depending on the local expertise and availability.[21]

Conventional imaging such as transabdominal ultrasound, CT, and MRI have a lower sensitivity than EUS[6,8-11] and have disappointing results in further characterization of small pancreatic lesions.

CE-EUS has proved to be a helpful new technique in the differential diagnosis of pancreatic masses,[12,22-26] but little is known about the EUS characteristics of small (<15 mm) pNET which are usually found due to their hormone production or during surveillance of patients with MEN type 1.

Recognition of the typical imaging features of pNETs is important for early detection and appropriate patient management. In this retrospective multicenter study, we could demonstrate that the vast majority of small pNET are predominantly hypoechogenic in B-mode (94%) and demonstrate hyperenhancement compared to the surrounding pancreatic parenchyma after contrast injection (90%). The hyperenhancement in the arterial phase is likely explained by the abundant arterial vascularization in neuroendocrine tumors.[22,27,28] and could be visualized even in diminutive tumors. Dilatation of the pancreatic duct or signs of vascular infiltration were not observed.

Currently, the best prognostic parameter for the behavior of a detected pNET is the tumor grade which underlines the important role of the cytology obtained by EUS-FNA.[11,29,30] pNET can be categorized in well-differentiated endocrine tumor of generally benign behavior or poorly differentiated endocrine carcinoma (high grade of malignancy).[31] In our study, even in minuscule pNETs as small as 5 mm, the cytological confirmation by EUS-FNA was possible, underlining the immense diagnostic potential of the EUS technique owing to its high spatial resolution which enables very precise targeting.[9,11,29,32,33]

An emerging role of EUS in the management of pNET is the EUS-guided tattooing or placement of fiducials which mark the exact localization of small pNET. This technique has proved useful for parenchyma-saving pancreatic surgery.[34-36] Moreover, in selected cases, EUS-guided ablation techniques have proven effective in symptomatic functional pNET.[37-44]

Potential limitations of our study are its retrospective nature and the limited number of patients undergoing contrast studies.

CONCLUSION

Due to the high spatial resolution provided by EUS, even very small pNET of a few mm diameter can be detected. EUS also enables cytological confirmation of very small pNET <7 mm diameter. Typical endosonographic features of small pNETs are hypoechogenicity in B-mode and hyperenhancement after injection of ultrasound contrast agents; these characteristics are present in >90% of pNETs.

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Conflicts of interest
There are no conflicts of interest.

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