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ORIGINAL ARTICLE

EUS-FNA for Pancreatic Neuroendocrine Tumors: A Tertiary Cancer Center Experience

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Abstract
Objectives Pancreatic neuroendocrine tumors (PNET) are fairly uncommon. Recent data highlight the importance of EUS in diagnosis of PNET. With this background, we decided to review our experience from a tertiary cancer center with regard to the presentation and clinical features of PNET and the diagnostic utility of EUS-FNA in this scenario.
Methods We identified patients who underwent EUS at our institution between January 1st 2001 and December 31st 2009 for a suspected PNET. Data on clinical features, cross-sectional imaging findings, EUS findings, and cytology results were collected.
Results A total of 81 patients were referred for EUS-FNA for a suspected PNET. Mean age was 58.1 years. There were 41 (50.6%) males. PNET was found incidentally in 38 (46.9%) patients. Computed tomography scanning identified a pancreatic mass in 72 out of 79 (91.1%) cases. Mean diameter of the largest lesion seen on EUS was 27.5 mm (range: 6.9–80 mm). The most common site (34; 42%) was the head of the pancreas. EUS-FNA correctly confirmed a PNET in 73 out of 81 cases with diagnostic accuracy of 90.1%. Seven (8.6%) out of 81 patients had functional lesions, including three gastrinomas and four insulinomas. Liver metastases were found in 31 out of 81 (38.3%) cases. Of the 31 patients with liver metastasis, the mean diameter of lesions on EUS was 33.9 mm compared with 23.5 mm in patients without liver metastasis ($P = 0.005$).
Conclusion EUS-FNA is a reliable modality for further characterization of suspected lesions and for establishing a tissue diagnosis. The occurrence of complications of EUS-FNA in this setting is low. Non-functional PNET are more frequently encountered than functional PNET.

Keywords Pancreatic neuroendocrine tumors · Endoscopic ultrasound · Fine needle aspiration · MEN-1 · Insulinomas

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Introduction

Pancreatic neuroendocrine tumors (PNET) are fairly uncommon, accounting for less than 5% of all primary pancreatic malignancies [1]. The incidence of PNET has been steadily growing over the past two decades, with an incidence of 1–1.5/100,000 [2]. They are heterogeneous tumors with varying tumor biology and prognosis [3]. PNET may present with clinical symptoms and syndromes

related to substances released from these tumors (Zollinger–Ellison syndrome from gastrinoma, hypoglycemia from insulinoma, necrolytic migratory erythema from glucagonoma, etc.) or they may be nonfunctioning tumors presenting with symptoms of obstruction, jaundice, bleeding, or abdominal discomfort [4]. Diagnosis of these tumors may be challenging, requiring a combination of careful history, physical examination, laboratory tests, imaging studies, and tissue acquisition [5].

Pancreatic neuroendocrine tumors can be sporadic or associated with a genetic syndrome. Genetic syndromes associated with endocrine tumors include multiple endocrine neoplasia type 1 (MEN-1), von Hippel–Lindau disease, von Recklinghausen disease, and tuberous sclerosis [6]. PNET have been diagnosed in 15–25% of cases with MEN-1; and 20–25% of patients with Zollinger–Ellison syndrome have MEN-1 [3].

On imaging, PNET typically appear as well-defined hypervascular masses. Cystic change, calcification, and necrosis are common in large tumors [7]. Typical microscopic findings include an organized pattern of growth, with cells containing scant to moderate amounts of cytoplasm, and nuclei with dispersed chromatin, and inconspicuous nucleoli. However, these tumors may have wide spectrum of histologic and cytologic features, and, in some cases, the differential diagnosis could include chronic pancreatitis with neuroendocrine hyperplasia, ductal adenocarcinoma, solid pseudopapillary tumor, acinar cell carcinoma, and pancreatoblastoma [8].

There has been a discrepancy in the literature regarding the prevalence of functioning neoplasms as several studies report a high prevalence of these lesions [9]. Functional lesions come to the attention because of signs and symptoms attributed to the specific hormone production and the resulting manifestation of a clinical syndrome. However, recent studies report a higher prevalence of non-functioning neoplasms [10–12].

Pancreatic neuroendocrine tumors can be detected, with variable sensitivity, by imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), abdominal ultrasonography, and somatostatin receptor scanning (SRS) [13, 14]. Abdominal CT is the imaging modality most commonly employed to first investigate a known or suspected mass lesion of the pancreas [15]. Endoscopic ultrasound (EUS) is usually performed in conjunction with other imaging modalities. EUS can assist in confirming the size and characteristics of these lesions, and in obtaining tissue diagnosis in the same setting. In selected cases, it may also identify lesions that are not seen on imaging modalities such as CT scan or SRS. Whether EUS is of significant additional value in the detection of suspected PNET is still unclear. A recent large series demonstrates significantly greater sensitivity and incremental benefit of EUS over CT [12]. A number of older studies have also reported the superiority of EUS over CT for detecting PNET [16–18]. We sought to identify the presenting symptoms, characteristic findings on imaging studies, and the utility of EUS for diagnosis of PNET at our institution.

Methods

Study Population

This study was approved by the institutional review board of MD Anderson Cancer Center. We identified patients who underwent EUS at our institution between January 1st 2001 and December 31st 2009 for a suspected PNET, or who were found to have a PNET after EUS-FNA. PNET was suspected if a patient presented with clinical features associated with a functional neuroendocrine tumor, for example hypoglycemia, refractory GERD, peptic ulcer disease, and diarrhea, with an imaging study suggesting a lesion in the pancreas. Characteristic CT findings prompting EUS included a well circumscribed, hypervascular mass lesion in the pancreas. The clinical information reviewed included: age, sex, symptoms, and diagnosed familial syndromes. Laboratory data including hormone levels (e.g. gastrin, insulin, VIP, glucagon, vaso-active intestinal poly-peptide, chromogranin, and neuron specific enolase) were recorded. Radiological imaging including CT, MRI, and SRS were reviewed. EUS features reviewed were tumor size, location within the pancreas (i.e. head, uncinate process, neck, body, tail, or multifocal), number, echogenicity, and margins. Surgical pathology and final cytology were also recorded.

CT Imaging

At MD Anderson, the pancreatic protocol includes a dual-phase multidetector CT (MDCT) exam of the abdomen, including the liver and pancreas, at both the peak-pancreatic and portal-venous phases of enhancement. Post-contrast axial images are reconstructed at 2.5, 1.3, or 0.6 mm thickness, the last two depending on the capabilities of the scanner. Because patients underwent several diagnostic exams, we only considered the CT imaging which was done immediately before the EUS exam (Fig. 1).

EUS-FNA Examination

All procedures were performed by one of six experienced gastroenterologists after informed consent was obtained. All EUS exams were performed after EGD, using radial or linear echoendoscopes, or both; Pentax 32-UA, Pentax

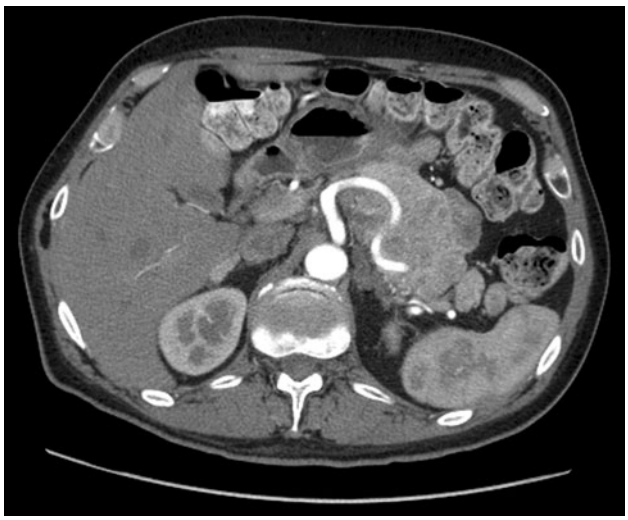

Fig. 1 CT: a large lobulated, well circumscribed mass arising from the body of the pancreas and measuring 8.4 × 5.6 cm

36-UX (Pentax Medical, Montvale, NJ, USA), Olympus GF-UC30P, Olympus GF-UC140P-AL5 (Olympus America, Center Valley, PA, USA), ProSound Alpha 5, or Alpha 10 (Aloka). When performed, EUS-FNA was repeated until a definitive diagnosis was made or the endosonographer felt that more sampling would not increase the yield (Figs. 2, 3). An attending cytopathologist provided immediate assessment of the cytologic features on direct smears (air-dried and Papanicolaou-stained slides) while the patient was kept under sedation. Patients routinely received one dose of intravenous antibiotics followed by 3–5 days of oral antibiotics when the lesion was cystic.

Cytology Examination

FNA diagnosis of PNET was considered if tumor cells were of relatively uniform size and shape with a moderately large, round nucleus, and finely dispersed chromatin. Immunohistochemical (IHC) staining of chromogranin and synaptophysin was subsequently performed on cytologic samples to confirm their neuroendocrine nature. Histopathology on surgical specimen or cytology findings (from percutaneous, intraoperative, or EUS-guided FNA) was considered diagnostic when confirmed by an attending cytopatholgist (Figs. 4, 5).

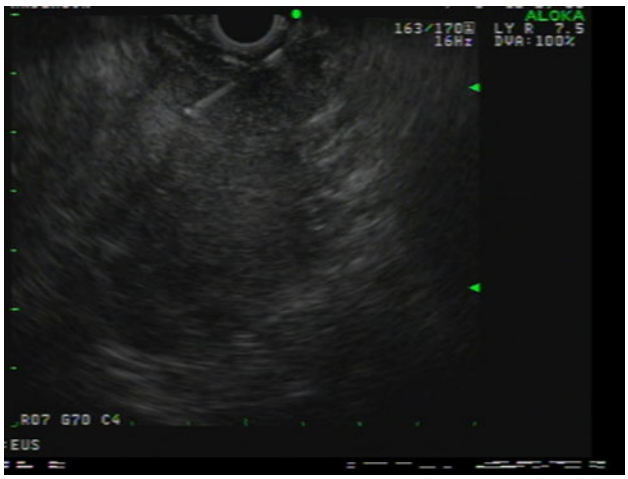

Fig. 3 EUS-FNA

Classification of PNET

The American Joint Committee on Cancer (AJCC) Version 7 was used for staging.

Statistical Analysis

Fisher's exact test was used to assess the association between two categorical variables. The Wilcoxon rank-sum

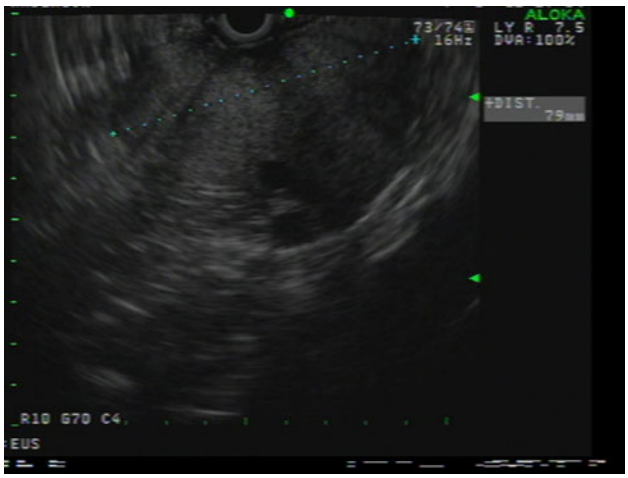

Fig. 2 EUS: large irregular hypoechoic mass in the body of the pancreas

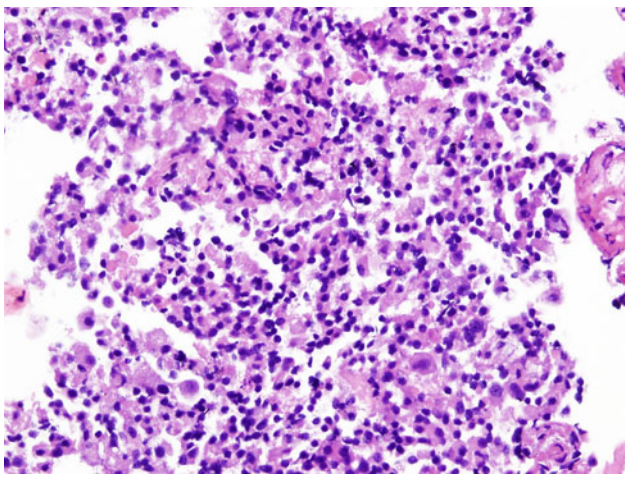

Fig. 4 Cell block showing monomorphic population of uniform tumor cells with nesting growth pattern (H&E stain, ×200)

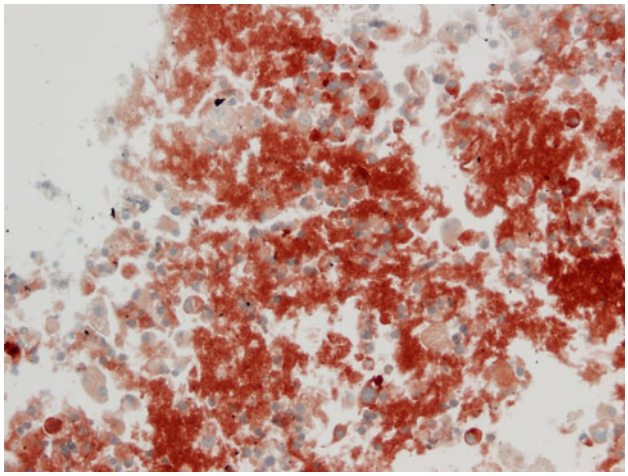

Fig. 5 Synaptophysin immunostaining on a cell block showed diffuse and strong staining in tumor cells (synaptophysin immunostain, ×200)

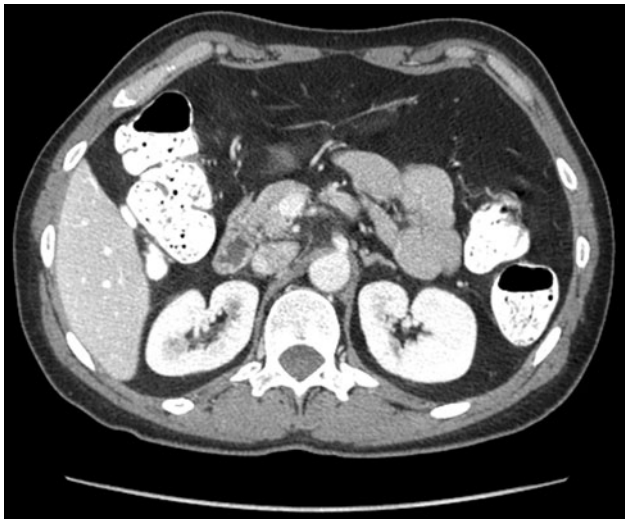

Fig. 6 CT: no discrete mass lesions seen in the head of the pancreas

test was used to evaluate the difference between two groups in regard to a continuous variable. *P* values less than 0.05 were deemed statistically significant. All statistical analysis was performed using SAS 9.0 (Cary, NC, USA).

Results

A total of 81 patients were referred for EUS-FNA for a suspected PNET. Mean age was 58.1 years. There were 41 (50.6%) males. Clinical presentation included abdominal pain in 26 (32.1%) patients, jaundice in nine (11.1%), diarrhea in three (3.7%), hypoglycemia in two (2.5%), weight loss in three (3.7%). PNET was found as an incidental finding in 38 (46.9%) patients (Figs. 7, 8).

Radiological Investigations

Computed tomography scan identified a pancreatic mass in 72 out of 79 (91.1%) cases. Sixty of 81 (75.9%) patients had a pancreatic protocol CT with 1.3 or 0.6 mm collimation images. Five of nine (55.5%) patients who were not found to have a definitive mass lesion in the pancreas had undergone a pancreatic protocol CT (Figs. 6, 7).

Forty patients underwent SRS for evaluation of suspected neuroendocrine tumor. In 28 of 40 cases (70.0%), SRS located a lesion in the pancreas (Figs. 9, 10, 11).

EUS Findings

All 81 patients had pancreatic lesions detected by EUS. Mean diameter of the largest lesion seen on EUS was 27.5 mm (range: 6.9–80 mm); median diameter was 25 mm. The distribution of the lesions on EUS exam was 34 (42%) in the head, 26 (32.1%) in the body, 16 (19.8%) in the tail, two (2.5%) in the uncinate process, and three (3.7%) in the neck. Seventy-five of 81 patients underwent FNA. In six patients, FNA was not attempted because of blood vessels in the projected needle path or lack of a specific indication. Cytology evaluation of the specimens from EUS-FNA correctly confirmed a PNET in 73 out of 81 cases with diagnostic accuracy of 90.1% (Fig. 8). Two biopsies were non-diagnostic. When analyzing only those who underwent FNA, the yield was 97.3%.

A solitary lesion was seen in 73 (90.1%), and multiple in eight (9.8%). Of the eight cases with multiple lesions, two patients had MEN-1 syndrome whereas five patients had

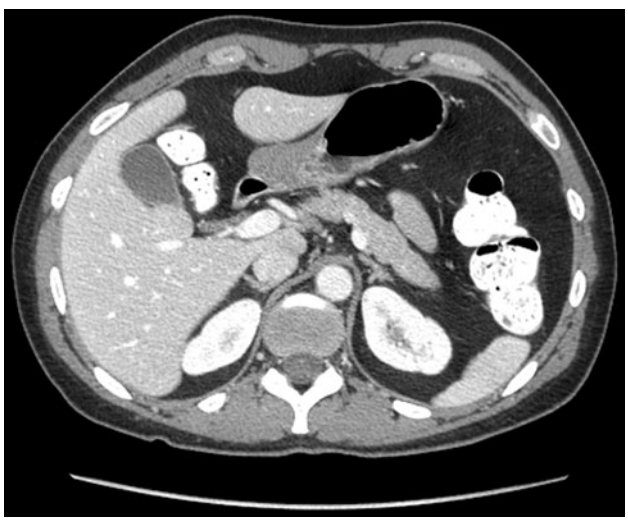

Fig. 7 CT: no discrete mass lesions seen in the body or tail of the pancreas

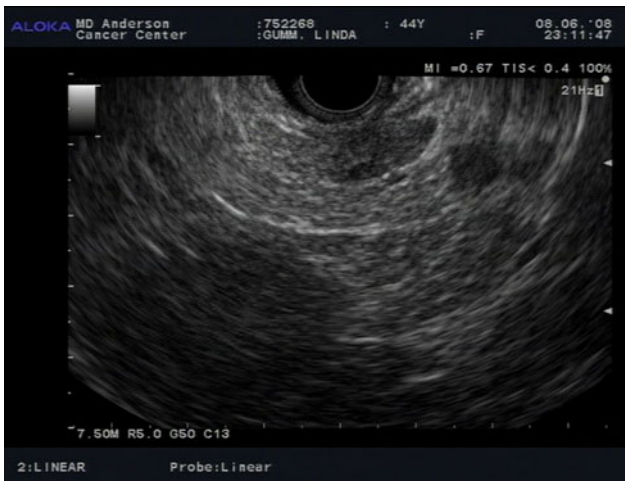

Fig. 8 EUS showing a well-circumscribed, hypoechoic mass in the tail of the pancreas

Table 1 Comparison of clinical and EUS features of patients with functional and non-functional PNET

	Functional	Non functional	*P* value
Age (mean)	48.0 (35–60)	59.0 (18–65)	0.03
Men	2 (28.6%)	39 (52.7%)	0.26
Location (EUS)		0.28	
Head	3	31	
Uncinate	1	1	
Neck	0	3	
Body	1	25	
Tail	2	14	
Mean size of lesion on CT (mm)	33.7 (8–68)	29.7 (6–84)	0.91
Mean size of lesion on EUS (mm)	23.9 (8–66)	27.9 (6.9–80)	0.28
Echogenicity			0.68
Hypoechoic	5	56	
Hyperechoic	0	0	
Isoechoic	0	1	
Anechoic	1	5	
Mixed echogenicity	0	1	
Not documented	1	11	

sporadic PNET. One patient was found to have pancreatic microadenomatosis.

Eight out of 81 (9.9%) PNET were proven to be cystic neuroendocrine tumors (CNET). The mean size of these lesions was 25.0 mm (10.4–70.0 mm), with a median size of 18.0 mm. Most of these lesions were located in the body of the pancreas.

Functional Versus Non-Functional Lesions

Seven (8.6%) out of 81 patients had functional lesions (Table 1, Figs. 9, 10, 11). These included three gastrinomas and four insulinomas. Among the patients with gastrinomas, two patients had MEN-1 and one had a sporadic gastrinoma. Of the four patients with insulinoma, one had pancreatic endocrine microadenomatosis and three had sporadic insulinomas. In two of the four patients with insulinoma, CT (three performed with the pancreatic protocol) was unable to detect a definitive mass lesion in the pancreas. Mean size of the insulinomas was 15.2 mm (8–20 mm) on EUS.

Patients with functional lesions were younger than those with non-functional tumors (mean age: 48.0 years vs. 59.0 years; *P* value 0.03). Three of the seven patients (42.9%) with functional tumors had liver metastasis at the time of presentation, including two with insulinoma and one with gastrinoma. Twenty-eight (37.4%) patients with non-functional tumors had liver metastasis. Co-existing genetic syndromes were found in six (7.4%) cases, including four cases of MEN-1, one case of Von Hippel Lindau syndrome, and one case of tuberous sclerosis.

Clinical Staging

By the AJCC staging system, 18 (22.2%) of the 81 patients were stage IA at the time of EUS, 15 (18.5%) patients were stage IB, three (3.7%) patients were stage IIA, nine (11.1%) patients were stage IIB, three (3.7%) patient were stage III, and 33 (40.7%) patients were stage IV.

Correlation of Liver Metastasis and Size of Lesion on EUS

Liver metastases were found in 31 out of 81 (38.3%) cases. Of the 31 patients with liver metastasis, the mean diameter of lesions on EUS was 33.9 mm compared with 23.5 mm in patients without liver metastasis ($P = 0.005$). Four out of 31 (12.9%) patients with lesion size <2 cm on EUS had liver metastasis, compared with 27 out of 50 (54.0%) patients with ≥2 cm lesion ($P < 0.01$) (Table 2).

Complications

One patient developed right upper quadrant abdominal pain 1 day after EUS-FNA. He was evaluated in our emergency center and was discharged after pain control and observation.

Discussion

Pancreatic neuroendocrine tumors are a heterogeneous group of tumors with clinical presentation and biological

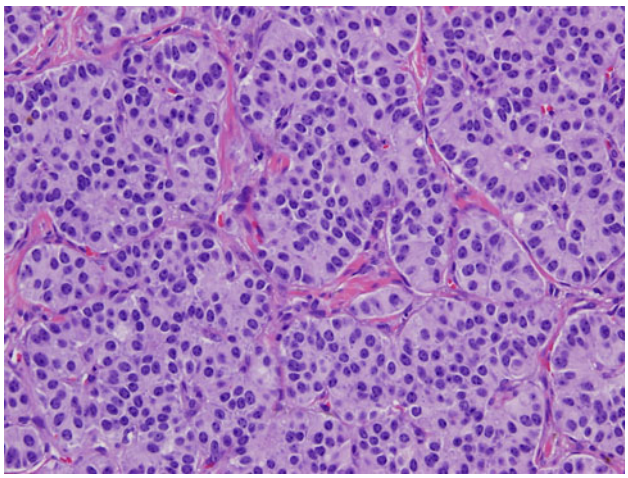

Fig. 9 A representative pancreatic neuroendocrine carcinoma showing uniform tumor cells with nesting growth pattern and fine-granular chromatin pattern (H&E stain, ×200)

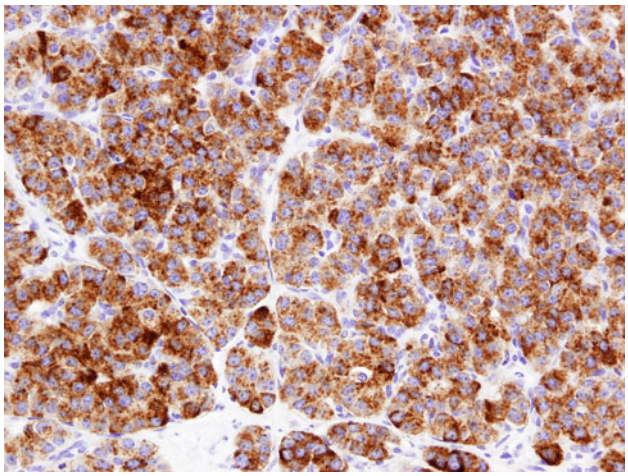

Fig. 10 Insulin immunostaining showed diffuse and strong staining in tumor cells, consistent with insulinoma (insulin immunostain, ×200)

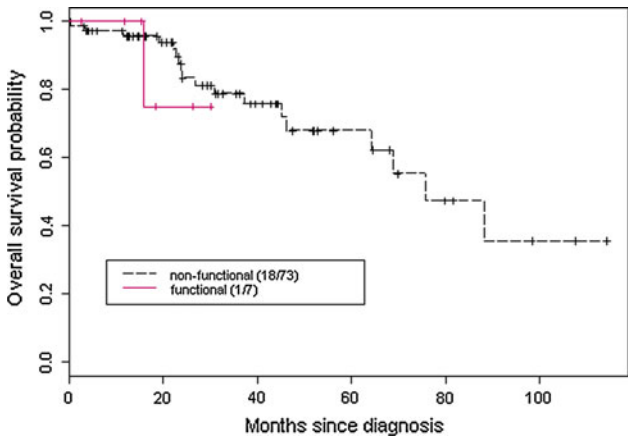

Fig. 11 Kaplan–Meier estimates for OS by functional versus non-functional lesions

behavior different from pancreatic adenocarcinoma. These tumors have increased in overall incidence in recent years, partly because of the increased use of screening CT imaging [19].

Our study reports a significantly higher proportion of patients with non-functional tumors. This trend has been identified in most recent reports [10–12]. This may be related to early detection of non-functional tumors by sophisticated imaging modalities, for example CT scan, which may otherwise go undiagnosed in the absence of symptoms. Interestingly, two of four patients with insulinoma presented with symptoms of hypoglycemia. The other two patients began to have symptoms of hypoglycemia only after diagnosis of PNET. Most patients in the current series (73/81; 90.3%) presented with a solitary lesion. Of the eight patients with multiple lesions, one patient was diagnosed with pancreatic endocrine microadenomatosis. She initially presented with hypoglycemia. CT imaging revealed multiple hypervascular nodules in the head, neck, and tail of the pancreas. EUS identified three subcentimeter, hypoechoic lesions in the pancreas. Surgical specimen (total pancreaticoduodenectomy) showed multiple well-circumscribed, tan to brown, firm nodules (2–3 mm) randomly distributed in the pancreas.

A large number of patients in this series presented with distant metastasis, including 31 patients with hepatic metastasis, two with pulmonary metastasis, and one with a scalene node metastasis. In a large SEER dataset of 6,447, fifteen percent of patients presented with metastasis [19].

Nine of 81 patients (11.1%) did not have a definitive mass in the pancreas on CT imaging. Investigators from Johns Hopkins found that the CT-negative lesions identified on EUS were, on average, significantly smaller than those seen on CT imaging [12]. In our experience, functional lesions were more likely to be missed on CT imaging; however the small number of functional tumors limits our ability to derive a definitive inference from this finding.

We noticed that tumor size ≥2 cm was associated with the presence of liver metastases. In the 2004 World Health Organization (WHO) classification, PNET with a diameter greater than 2 cm are classified as "PNET with uncertain behavior." In a recent report, however, PNET with a diameter greater than 2 cm were also reported to be associated with aggressive behavior [20]. On the other hand, the authors also identified a few cases where PNET smaller than 2 cm were associated with invasion of vasculature or lymph node metastases, indicating that tumor size alone is insufficient to indicate malignancy. We noticed that four of 31 patients with primary lesion smaller than 2 cm had concurrent liver metastasis. Figueiredo et al. [21] reported EUS-FNA may help predict five-year survival in patients with PNET if WHO classification is used to define the neruroendocrine tumors as well-differentiated endocrine

Table 2 Comparison of clinical and EUS features of patients with and without liver metastasis

	No liver metastases	Liver metastases	*P* value
Mean age (years)	58.7 (18–85)	57.1 (28–81)	0.65
Men	23 (56.1%)	18 (43.9%)	0.65
Location (EUS)			0.75
Head	20	14	
Uncinate	1	1	
Neck	1	2	
Body	18	8	
Tail	10	6	
Mean size of lesion on CT (mm)	24.9 (6.0–68.0)	39.2 (8.0–84.0)	0.0054
Mean size of lesion on EUS (mm)	23.5 (6.9–66)	33.9 (9.2–80.0)	0.005
Echogenicity			0.24
Hypoechoic	39	22	
Hyperechoic	0	0	
Isoechoic	0	1	
Anechoic	5	1	
Mixed echogenicity	0	1	
Not documented	6	6	

Table 3 Comparison of clinical and EUS characteristics of patients with cystic and non-cystic NET

	Cystic lesions ($n = 8$)	Non-cystic lesions ($n = 73$)	*P* value
Mean age (years)	55.0 (33–74)	58.4 (18.0–85.0)	0.52
Men	4 (50%)	37 (50.7%)	1.00
Presentation			0.09
Incidental finding	8	30	
Abdominal pain	0	26	
Jaundice	0	9	
Hypoglycemia	0	2	
Diarrhea	0	3	
Weight loss	0	3	
Location (EUS)			0.28
Head	1	33	
Uncinate	0	2	
Neck	0	3	
Body	4	22	
Tail	3	13	
Mean size of lesion on EUS (mm)	25.0 (10.4–70.0)	27.8 (6.9–80.0)	0.36
Functional lesion ($n = 7$)			0.53
No	7	67	
Yes	1	6	

carcinoma or poorly differentiated endocrine carcinoma based on EUS-FNA results. In our experience, EUS-FNA analysis does not always help make that distinction.

It has been suggested that heterogeneous ultrasonographic features and filling defects on contrast enhanced EUS corresponding to hemorrhage or necrosis on pathologic examination may predict more aggressive behavior [20]. In another small study, complete obstruction of the main pancreatic duct in addition to heterogeneous internal structures was regarded as an important EUS feature suggestive of aggressive nature in nonfunctioning pancreatic islet cell tumors [22].

Ultimately, molecular classification-based analysis of cells obtained from EUS-guided aspiration could be used to guide therapy in patients with PNET, particularly when the tumors are small, in the setting of inherited conditions such as MEN1, or in the presence of established metastatic disease [23–25].

Table 4 Clinical and EUS characteristics of eight patients with CNET

Patient	Age/ sex	Presenting symptom	EUS appearance (septations/mural nodule)	Size (mm)	Location	No. of passes/ needle (gauge)	Cyst fluid CEA (ng/ml)	Cyst fluid amylase (IU/l)	String sign (mm)	Follow up
1	54/f	None	Unilocular cyst No septations	11	Body	1/22	<1	NA	NA	Spleen preserving distal pancreatectomy
2	74/m	None	Unilocular cyst No septations Intra-cystic wall thickening (+)	25	Body	1/22	NA	268	2	Distal pancreatectomy and splenectomy
3	60/f	None	Multi-cystic Thin septations Mural nodule	32	Head	NA	<1	114	NA	Lost to follow up
4	48/m	None	Cyst No septations	16	Tail	1/25	NA	NA	NA	Lost to follow up
5	33/f	None; surveillance for MEN-1	Unilocular cyst Intra-cystic wall thickening (+) Intra-cystic components (+)	10.4	Tail	1/25	NA	NA	3	Observation
6	55/m	None	Unilocular cyst	17.9	Body	1/22	1.3	83	Negative	Observation
7	59/f	None; surveillance for MEN-1	Unilocular cyst Intra-cystic wall thickening (−) Intra-cystic components (−)	18.1	Tail	1/NA	<1	NA	2	Spleen preserving distal pancreatectomy
8	58/m	None	Thick septations Intra-cystic wall thickening (+)	70	Body	4/NA	11.5	49	Non-viscous	Whipple's operation

Eight of 81 (9.9%) PNET had a cystic appearance (Tables 3, 4). This finding coincides to the findings of previously reported series [26–28]. Seven of our eight cystic PNET patients had non-functional tumors. As high as 81% of the reported cystic PNET in the literature have been found to be non-functional [26]. It is quite challenging to distinguish cystic PNET from other pancreatic cysts based on imaging studies alone [27, 28]. Similarly, EUS imaging seems unlikely to reliably differentiate PNET from other cystic pancreatic lesions [26, 29]. Moreover, cyst fluid analysis is not always useful. However, results from our study and those from other investigators showed that good cytology specimens and an expert cytologist's opinion are more reliable than fluid analysis [26, 29].

The diagnostic yield of EUS-FNA in our study was 90.1%. This is in line with other published data. In a large series, EUS correctly localized PNET in 93% of cases [30]. Others have reported detection of PNET by EUS to be in the range 82–100% [9, 16, 18, 31–35]. In a case–control study including 36 patients who underwent surgical exploration without undergoing an EUS, EUS was found to be highly accurate and cost-effective when used early in the preoperative location strategy. EUS reduced the need for additional invasive tests and avoided unnecessary morbidity and resource consumption [36]. Finally, the complication rate with EUS-FNA, as evidenced in our experience, is quite low.

Conclusion

Careful history taking, physical examination, high index of clinical suspicion, and correlation with CT and EUS images assist in the diagnosis of PNET. EUS-FNA is a reliable modality for further characterization of suspected lesions and for establishing a tissue diagnosis. The rate of complications of EUS-FNA in this setting is low. Non-functional PNET are more frequently encountered than functional PNET.

Limitations

Potential limitations in our study include a retrospective design limiting adequate comparison of EUS and CT imaging in a blinded fashion, and referral bias, because our facility is a tertiary cancer center. However, the latter helps provide a perspective for managing complex cases of PNET.

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