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Hypervascular lesions of the pancreas: Think before you act

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ABSTRACT

Background: The "classic" CT appearance of pancreatic neuroendocrine tumors (PNETs) is a solid, hypervascular lesion; however, non-PNET diagnoses may appear similar. In addition, some PNETs have a "non-classic" appearance.
Methods: Demographic, imaging, endoscopic ultrasound-fine needle aspiration (EUS/FNA) results, and pathology data were analyzed for patients who underwent pancreatectomy for suspected or confirmed diagnosis of PNET from our institutional database.
Results: Forty-three patients with a hypervascular lesion on CT had pancreatectomy for a pre-operative diagnosis of PNET. Final pathology revealed PNET in 30 (70%) and non-PNET diagnoses in 13 (30%). EUS/FNA had a sensitivity of 82% for the pre-operative diagnosis of PNET in patients with "classic" CT. Of 13 non-PNET diagnoses, 7 were benign. Among a total of 41 patients with a final diagnosis of PNET, 11 (27%) had "non-classic" CT (5 hypodense solid lesions, 3 isodense solid lesions, and 3 cystic lesions). Among these patients, EUS/FNA had a sensitivity of 100% in diagnosing PNET.
Conclusions: Consideration of non-PNET diagnoses is important for patients with hypervascular lesions on CT. Appropriate pre-operative evaluation will optimize treatment plans.

Background

Pancreatic neuroendocrine tumors (PNETs) account for approximately 2% of pancreatic neoplasms.[1] While PNETs may be detected during evaluation of symptoms related to tumor size or functionality, they are often incidentally detected on cross-sectional imaging performed for other indications.[2] PNETs typically have a characteristic hypervascular appearance on contrast-enhanced computed tomography (CT). However, a variety of other types of pancreatic lesions may appear hypervascular on CT,[3,4] thereby limiting the specificity of CT alone for the diagnosis of PNETs. In addition, PNETs do not always appear as solid, hypervascular tumors but occasionally are isodense, hypodense, or cystic on contrast-enhanced CT.[5,6] Given the potential morbidity of pancreatectomy, accurate pre-operative diagnosis in patients with pancreatic lesions is critical to optimize the initial evaluation and avoid a possible unnecessary operation.

In the current institutional series, we evaluated the pre-operative diagnostic modalities performed and occurrence of PNET and non-PNET diagnoses identified after pancreatectomy for solid, hypervascular tumors identified on CT. We also examined the incidence of "non-classic" imaging features in patients with that underwent resection for PNETs. The purpose of this study was to better understand misdiagnoses in suspected PNETs and increase awareness of this potential pitfall.

Methods

After obtaining institutional review board approval, we performed a retrospective review of our pancreatic surgery database to identify patients with a suspected or confirmed pre-operative diagnosis of PNET as documented by the surgeon's pre-operative history and physical and/or operative note. We also collected data on all patients with a confirmed diagnosis of PNET on final pathology following pancreatectomy. Demographic, imaging, endoscopic, operative, and pathology data was collected. Tumor grade was assigned using World Health Organization (WHO 2010 Criteria) classification for NETs as low grade, G1 (Ki-67 < 3%),

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intermediate grade, G2 (Ki-67 3-20%), or high grade (Ki-67 > 20%). Patients with functional tumors, documented distant PNET metastases, and those with multiple endocrine neoplasia type 1, Von Hippel-Lindau disease, or neurofibromatosis type 1 were excluded. We also excluded patients undergoing resection from 2007 onward, as this was before endoscopic ultrasound (EUS) was routinely utilized at our institution.

Imaging and endoscopy

Preoperative evaluation including contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), ^{111}In-DTPA-octreotide scintigraphy (Octreoscan), and EUS with fine needle aspiration (EUS/FNA) was performed at the discretion of the evaluating physicians. All pre-operative CT scans and their reports were reviewed. Standard single phase intravenous contrasted CT consisted of 80–100 cc of isovue 300 at 3 ml/s with image acquisition 60 s after contrast administration with 2.5 mm cuts. Triple-phase pancreas protocol CT consisted of 5 mm non-contrasted images, and 1.25 mm arterial and venous images obtained after administration of 100 cc of isovue 370 at 4 ml/s. Lesions identified on CT were characterized as solid or cystic. Solid lesions were further characterized by contrast enhancement patterns as homogenously hyper-enhancing, heterogeneously hyper-enhancing, isodense, and hypodense. For purposes of this study, we defined solid hyper-enhancing lesions as having "classic" imaging and cystic, isodense, and hypodense tumors as having "non-classic" imaging. Contrast-enhanced MRI included multi-sequence, multi-phasic imaging after administration of 20 cc gadolinium-based contrast. Octreoscan included anterior and posterior whole body images obtained at 4 and 24 h after administration of ^{111}In-DTPA-octreotide with SPECT imaging performed on a hybrid SPECT/CT camera and low dose IV contrast given for improved anatomical localization. EUS/FNA was performed with the use of standard linear and/or radial array endoscopes with needle biopsy obtained using 4 to 5 passes with 22–25 gauge needles.

Statistical analysis

Comparisons were performed using Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. All statistical analyses were performed using SPSS, Version 23 (Chicago, IL). A p value of less than 0.05 was considered significant.

Results

Patients with solid, hypervascular tumors - "classic" imaging on CT

We identified 43 patients with a pre-operative diagnosis of PNET based on contrast-enhanced CT revealing a solid, well circumscribed, hypervascular lesion. Of these, 30 (70%) had a final diagnosis of PNET and 13 (30%) had an alternative diagnosis (Fig. 1). Non-PNET diagnoses included intrapancreatic accessory spleen (IPAS) (4), metastatic renal cell carcinoma (RCC) (2), solid pseudopapillary tumor (2), serous cystadenoma (1), duodenal GIST (1), adenocarcinoma (1) focal pancreatitis (1), and one patient had no tumor present (1). As shown in Table 1, there was no difference in age, gender, race, tumor size on CT, tumor location within the gland, the presence of pancreatic or biliary ductal dilation (as assessed by CT), tumor calcifications, or contrast enhancement patterns (homogeneous vs heterogeneous) between those with PNET and non-PNET diagnosis.

Each of these patients had undergone at least single phase contrast-enhanced CT, however, the extent of further pre-operative imaging with triple-phase pancreas protocol CT and/or contrast enhanced MRI was variable and not significantly different between patients found to have PNET versus non-PNET diagnoses. Furthermore, in each case these additional studies re-revealed a hyper-enhancing lesion and did not appear to alter the pre-operative diagnosis or operative plan.

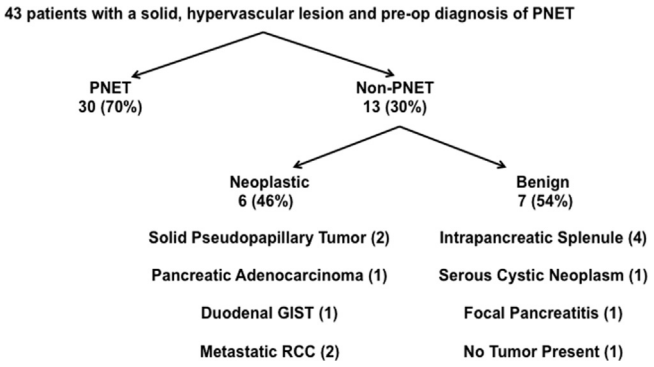

Fig. 1. Breakdown of patients included in analysis including those with solid hypervascular lesions on CT who underwent pancreatectomy and those with PNET without "classic" CT characteristics.

Among these 43 patients, 24 (56%) underwent pre-operative EUS/FNA. Of the 24 EUS/FNA procedures performed in this cohort, cytopathology was interpreted as PNET in 19 (79%) and was non-diagnostic because of "sparse" or "lack of adequate" cellularity within the sample in 5 (21%). Of those interpreted as PNET on EUS/FNA, 18/19 (95%) was confirmed as PNET on final pathology. The one false positive was in a patient found to have metastatic RCC on final pathology. Of the 5 patients with non-diagnostic cytopathology, none underwent repeat biopsy and on final pathology 4 had PNET and 1 had a serous cystadenoma. Thus, the overall sensitivity and specificity of EUS/FNA for diagnosing PNET in patients with "classic" CT was 82% and 50%, respectively. Notably, EUS/FNA was performed in 22/30 (73%) of patients with a final diagnosis of PNET compared to 2/13 (15%) of those with a non-PNET diagnosis ($p < 0.001$).

Among the 18 patients with EUS/FNA cytology interpreted as PNET and confirmed on final pathology, pre-operative octreoscan was only performed in 4 and positive in 2. Of note, 2 patients who did not have pre-operative EUS/FNA did have positive octreoscan, however neither had a PNET on final pathology (1 IPAS and 1 duodenal GIST).

PNET patients with "classic" versus "non-classic" CT

Within our database, we identified 41 patients with who had undergone pre-operative contrast-enhanced CT and had a diagnosis of PNET on final pathology. Thirty of these (73%) had a "classic" CT appearance and 11(27%) had "non-classic" CT findings. Of the patients with "non-classic" CT, 5 had a hypodense solid lesion, 3 had an isodense solid lesion, and 3 had a cystic lesion (Fig. 2). There were no differences between age, gender, race, tumor location, presence of pancreatic ductal dilation, or tumor grade (on final pathology) between those with "classic" vs. "non-classic" CT (Table 2).

Similar to patients with "classic" CT, the extent of further imaging evaluation in patients with "non-classic" CT was variable. Of the 5 patients with hypodense solid lesions, 3 underwent triple-phase pancreas protocol CT of which none enhanced during arterial image acquisition. One of these patients did demonstrate heterogeneous enhancement on MRI. Among the 3 patients with

Table 1
Comparison of demographics and imaging characteristics between patients with hypervascular solid appearing PNETs versus alternative diagnoses.

	PNET	Alternative Diagnoses	P value
Median Age (range)	55 (25-74)	60 (36-71)	0.164
Gender			
Female	15 (50%)	7 (54%)	0.817
Male	15 (50%)	6 (46%)	
Race			
Caucasian	14 (47%)	7 (54%)	0.810
African American	14 (47%)	6 (46%)	
Other	2 (6%)	–	
Median Tumor Size (range)	2.9 (0.6–9.4)	2.5 (1.0–3.1)	0.135
Tumor location			1.000
Head/Uncinate/Neck	8 (26.7%)	4 (31%)	
Body/Tail	22 (73.3%)	9 (69%)	
Pancreatic duct dilation	3 (10%)	2 (15%)	0.613
Bile duct dilation	1 (3%)	0 (0%)	0.488
Calcifications	6 (20%)	1 (8%)	0.315
Enhancement Pattern on CT			0.313
Homogenous hypervascular	21 (70%)	11 (85%)	
Heterogeneous hypervascular	9 (30%)	2 (15%)	

isodense solid lesions, none had a triple phase CT and 1 had contrast-enhanced MRI which demonstrated a hypodense mass. Of the 3 patients with a cystic lesion, 1 underwent triple phase CT and 1 contrast-enhanced MRI, neither of which contributed further to the diagnosis.

Among PNET patients with a "non-classic" CT, pre-operative EUS/FNA was performed in 8 (73%) with cytology interpreted as PNET in each. Thus, for patients with a final diagnosis of PNET, regardless of CT appearance, the overall sensitivity of EUS/FNA in was 87%. Pre-operative octreoscan was performed in 3 patients with "non-classic" CT and was positive in 2 (each with a solid lesion) and negative in 1 (with a cystic lesion).

Discussion

Although PNETs are typically reported as a "hypervascular" or "hyperintense" lesions on contrast-enhanced CT,[7] the current study emphasizes that other neoplastic and benign pancreatic lesions may have a similar appearance. Moreover, it was observed that nearly 30% of patients with a diagnosis of PNET did not have "classic" contrast enhanced CT features. Working to obtain a definitive diagnosis may alter further pre-operative evaluation and importantly, prevent unnecessary pancreatectomy in some patients.

In the current series 7 (16%) patients with a preoperative

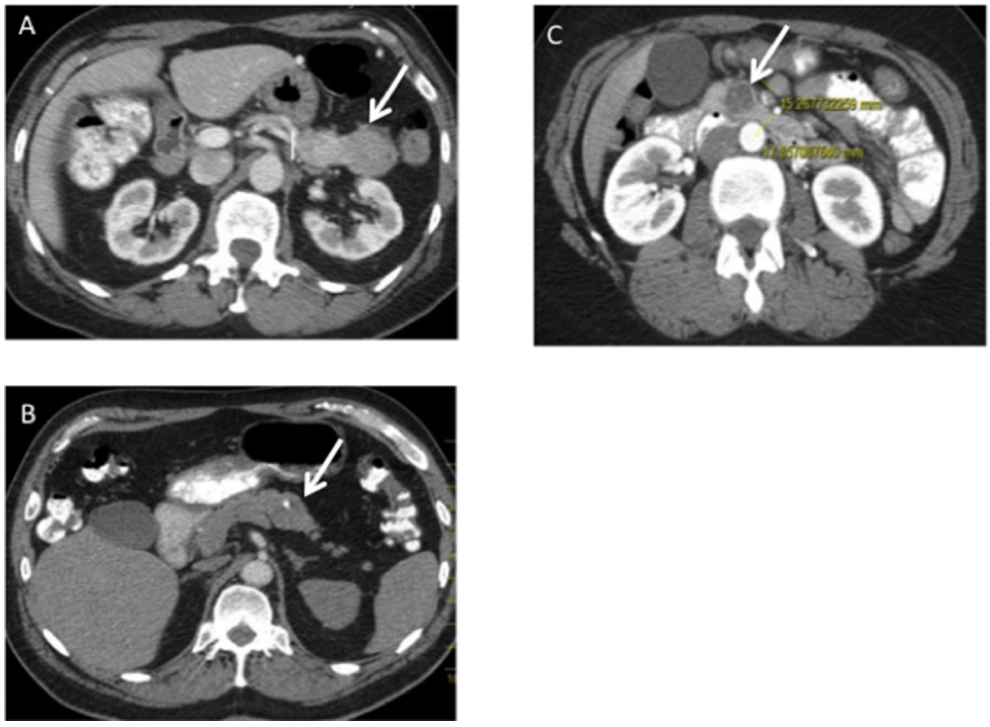

Fig. 2. Demonstration of the variable "non-classic" CT findings of pancreatic neuroendocrine tumors (a) a hypodense mass in the tail of the pancreas, (b) isodense mass with calcifications in the body of the pancreas, and (c) a cystic mass in the neck of the pancreas.

Table 2
Comparison of demographics, imaging characteristics, and tumor grade between PNET patients with "classic" and "non-classic" CT.

	"Classic" CT	"Non-classic" CT	P value
Median Age (range)	55 (25-74)	55 (33-71)	0.941
Gender			0.309
Female	15 (50%)	8 (73%)	
Male	15 (50%)	3 (27%)	
Race			1.000
Caucasian	15 (50%)	5 (45%)	
African American	13 (43%)	5 (45%)	
Other	2 (7%)	1 (9%)	
Median Tumor Size (range)	2.9 (0.6–9.4)	2.5 (1.0–3.6)	0.453
Tumor location			0.252
Head/Uncinate/Neck	8 (27%)	5 (45%)	
Body/Tail	22 (73%)	6 (55%)	
Pancreatic duct dilation	3 (10%)	5 (45%)	0.022
Bile duct dilation	1 (11%)	0 (0%)	1.000
Calcifications	6 (20%)	3 (27%)	0.680
Tumor Grade			0.500
G1	19 (63%)	6 (55%)	
G2	9 (30%)	5 (45%)	
G3	2 (7%)	0 (0%)	

diagnoses of PNET based on "classic" CT findings underwent pancreatectomy and ultimately had a benign diagnosis. The most common final diagnosis among this group of patients was IPAS. Although accessory splenic tissue is typically located within the splenic hilum, splenules within the gastro-splenic ligament, omentum, and intrapancreatic locations are well described.[8] In a report from the University of Louisville, Bhutiani et al. identified a diagnosis of intrapancreatic accessory spleen in 7/123 distal pancreatectomy specimens.[9] Similar to this report, the most common preoperative diagnosis in that series as well as additional case reports in the literature was non-functioning PNET.[10–12] These findings highlight the importance of considering a diagnosis of IPAS in patients with small, well-circumscribed, hypervascular lesions located in the tail of the pancreas (Fig. 3a). None of the 4 patients with IPAS in the current series underwent preoperative EUS/FNA. However, this technique can be utilized to correctly diagnosis IPAS based on cytologic findings of polymorphous mixed lymphoid cells and immunostaining for CD-8, which can reveal a sinusoidal pattern.[13] In distinguishing IPAS from PNET, it is important to appreciate that splenic lymphoid tissue harbors somatostatin receptors and thus somatostatin receptor based imaging (^{111}In-DTPA-octreotide and 68Ga-DOTATATE PET/CT) does not reliably differentiate these diagnoses.[10,14,15] However, Technetium-99 m sulfur colloid or heat-damaged red blood cell scintigraphy,[16] supramagnetic iron oxide-enhanced MRI,[17] and galactose/palmic acid microbubble contrasted ultrasound[18] are imaging modalities that depend contrast uptake within the reticuloendothelial system (RES) and can accurately diagnose IPAS.

One patient in this series presented with a 2.8 cm hypervascular, solid appearing mass in the head of the pancreas (Fig. 3b) with a nondiagnostic EUS/FNA and on final pathology was found to have a serous cystadenoma. Hypervascular, solid appearing serous cystic neoplasm (SCN) is rare but may mimic PNET on standard cross-sectional imaging.[4,19,20] In a study by Park et al. 15/206 (7.3%) resected SCN had a hypervascular, solid appearance during the arterial and portal venous phases of triple phase CT, similar to resected PNETs.[4] However, these authors noted that compared to PNETs, solid-appearing SCN had significantly lower attenuation values on the non-contrasted phase of CT and on MRI had bright signal intensity on T2 weighted images and lower apparent diffusion coefficient values. Although relatively uncommon, it is important to increase awareness of solid appearing SCN among pancreatic surgeons and radiologists given the subtleties in distinguishing these lesions from PNET as it can prevent unnecessary pancreatectomy.

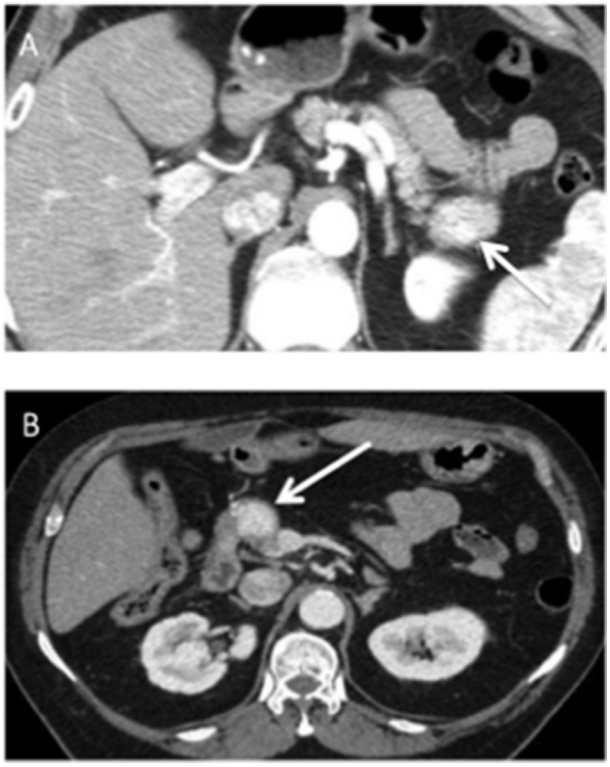

Fig. 3. (a) CT demonstrates a solid, well circumscribed, hypervascular mass in the tail of the pancreas, which on final pathology was found to be an intrapancreatic accessory spleen. (b) CT demonstrates a hypervascular mass in the head of the pancreas and on final pathology was found to have a serous cystic neoplasm.

Two patients in this series with a pre-operative diagnosis of PNET were found to have RCC on final pathology, one in whom a pre-operative EUS/FNA suggested PNET. RCC metastases to the pancreas have a similar appearance to PNETs on both contrast-enhanced CT and MRI[19] and may appear several years after resection of the primary tumor. Although resection of RCC oligometastases is supported and can result in prolonged disease free survival in appropriately selected patients,[21] pre-operatively distinguishing this diagnosis from PNET may impact further evaluation and management. For instance, in a patient with a history of clear cell RCC, a concomitant diagnosis of PNET should prompt consideration of Von Hippel Lindau (VHL) disease. Furthermore, in the setting of VHL, a patient's genotype may influence the management of PNET[22] and guide at risk family members to seek genetic counseling.

Other non-PNET neoplastic lesions in the current series included two solid pseudopapillary tumors, one duodenal GIST, and, surprisingly, one pancreatic ductal adenocarcinoma. The pre-operative suspicion for PNET in the adenocarcinoma patient was based on a single-phase contrast enhanced CT demonstrating a heterogeneously hyperenhancing tumor in the head of the pancreas without associated biliary or pancreatic ductal dilation and no further pre-operative diagnostic evaluation. Although resection was not contraindicated in these patients, accurate pre-operative diagnosis may have altered preoperative discussions with these individuals and potentially raised consideration of neoadjuvant therapy in the GIST and adenocarcinoma patients.

EUS/FNA is demonstrated as a highly sensitive and specific modality for the diagnosis of PNET[23–25] and is now widely available

at academic centers and most large community hospitals. In the current series, EUS/FNA was performed in only 56% of patients with a suspected PNET based on a "classic" CT. Among these patients, the sensitivity of EUS/FNA was for diagnosing PNET 82% in the current series, however, when an adequate cytology sample was obtained, the sensitivity was100%. In addition, for patients with a "non classic" CT who underwent EUS/FNA, PNET was accurately diagnosed in each case. Unfortunately, evaluation of specificity was limited in that only 2/13 patients with a non-PNET diagnosis had EUS/FNA. Referral for EUS/FNA was at the discretion of treating physicians and current consensus guidelines do not uniformly recommend its use in evaluating these patients.[26–28] Given its generally widespread availability, accuracy in diagnosis, and potential impact on further evaluation and management, it seems reasonable to have a low threshold for EUS/FNA prior to elective surgical intervention. However, there may be circumstances in which EUS/FNA is not required or likely to be helpful. For instance, if there is a localized mass with associated biliary and/or pancreatic ductal dilation or other symptoms attributable to the tumor that warrant resection regardless of pathology, EUS/FNA need not be pursued. Moreover, a small lesion located in the tail of the gland that is intimately associated with the splenic hilum may not be accessible for biopsy. Finally, EUS/FNA is not without risk of procedure related complications including pancreatitis, abdominal pain, and bleeding.[29,30] Although these events are rare, generally reported to occur in less than 3% of cases,[29] at least one study identified small tumors (<2 cm) and PNETs as independent risk factors for post-procedure complications.[30] Although no patient in the current series experienced a documented EUS/FNA-related complication, it is possible that hypervascular lesions are at higher risk for bleeding, which may result in pain and/or pancreatitis. When evaluating a patient with a solid, hypervascular lesion in the pancreas, the choice to perform EUS/FNA should be made on a case-by-case basis, considering these risks and the clinical implications of biopsy results. If EUS/FNA is performed, on-site and real-time evaluation of biopsy specimens and slide preparation is likely to minimize nondiagnostic samples. We noted that four of the five nondiagnostic EUS/FNA samples in our series were very early on in our experience when immediate evaluation of sample quality and preparation was not the institutional standard. In addition to confirming a diagnosis of suspected PNET, EUS/FNA can also be used to determine tumor grade, which may alter management.[25,31]

Somatostatin based nuclear imaging studies such as octreoscan and 68-Ga DOTATATE have a role in the evaluation of patients with PNETs, however, they are not diagnostic and should be performed only after a tissue diagnosis of well-differentiated PNET has been made. These studies are ideally used for clinical staging and assessment of the potential response of somatostatin analogue or peptide receptor radioligand therapy,[32,33] however, should not be relied upon to determine PNET from an alternative diagnosis.

Not all PNETs have "classic" CT findings and alternative imaging phenotypes including hypodense, isodense, and cystic lesions are well described.[5,6] In this series these represented 27% of PNET patients. Previous studies have reported that isodense, hypodense, or "less vascular" PNETs on multi-phasic contrast-enhanced CT were more likely higher-grade tumors.[5,34,35] Of the 8 patients in the current study with isodense or hypodense solid lesions, 4 were grade 1 and 4 were grade 2. This study was not designed to evaluate imaging as it related to grade and admittedly, a full appreciation of enhancement patterns in solid isodense or hypodense lesions was limited in that 5/8 patients with hypodense or isodense solid lesions only had a single phase contrast-enhanced CT. Cystic PNETs (Fig. 3b) were present in 3 patients and pre-operative EUS/FNA led to accurate diagnosis in each. Although cystic PNETs are rare, they should be considered in the differential diagnosis of patients presenting with cystic neoplasms of the pancreas and EUS/FNA can be useful in their detection. Mitra et al. reported a sensitivity of 70% in diagnosing cystic PNETs with EUS/FNA, however, found that the diagnostic yield improved from 20% from 2003 to 2007 to 100% between 2008 and 2011 and attributed this, in part, to increased awareness of the diagnosis among clinicians in their center.[36]

The limitations of this study include its retrospective nature, small sample size, and heterogeneity in the manner patients were evaluated. The small sample size prohibits any meaningful multivariable analysis to examine differences between PNET and non-PNET diagnoses in patients with solid, hypervascular pancreatic lesions. The patients in this study were treated over a 10-year period by multiple surgeons and gastroenterologists with variable training backgrounds and practice patterns within a multi-hospital healthcare system. Furthermore, availability, expertise, and awareness of the benefit of EUS/FNA have grown over this time. Despite these limitations, the data presented hopefully conveys a message of the value in standardizing the initial workup in patients with a pancreatic mass in an effort to establish an accurate preoperative diagnosis.

In conclusion, most PNETs are solid, hypervascular lesions on contrast-enhanced CT, however, it is important for clinicians to appreciate alternative diagnoses that may have a similar appearance. Moreover, up to 25% of PNETs may not have this "classic" imaging phenotype and can appear hypodense, isodense, or cystic. We recommend that clinicians have a low threshold for performing EUS/FNA for patients with solid, hypervascular pancreatic tumors, particularly if there are not other compelling reasons to proceed directly to resection. Accurate diagnosis may alter the management plan in patients with non-PNET neoplasms and avoid unnecessary pancreatectomy in patients with benign diagnoses.

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