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Pancreatic schwannoma, an extremely rare and challenging entity: Report of two cases and review of literature

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ABSTRACT

Pancreatic schwannoma is a rare benign tumor, for which the preoperative and intraoperative definitive diagnosis is quite challenging. We present the clinical, radiological and pathologic features of two primary pancreatic schwannomas identified in our pathology database over a period of 30 years at our tertiary care hospital. To better understand the clinico-pathological and radiological features of this entity, we provide a comprehensive review of 73 cases described in the English literature, along with our two cases. This review will especially focus on preoperative and intraoperative diagnosis to assess their accuracy for pancreatic schwannoma. The three most common preoperative diagnoses based on imaging for pancreatic schwannomas were cystic neoplasm (56%), pancreatic neuroendocrine tumor (29%) and mucinous cystic neoplasm (26%). Imaging could not definitely diagnose pancreatic schwannoma in any of the reported cases. To obtain a definite diagnosis before surgery, 25 cases underwent imaging-guided fine-needle aspiration (FNA)/biopsy, of which 60% were correctly reported as benign with definite diagnosis of pancreatic schwannoma in 48%. A higher diagnostic accuracy was observed in biopsies (71%) than FNA (37%). In addition, an intraoperative frozen section was carried out in 15 cases, and 47% were correctly diagnosed. Despite relatively low accuracy, preoperative histological assessment can be helpful in surgical managment. A core tissue specimen is recommended to improve the diagnostic accuracy in this setting.

Introduction

Schwannomas were first described in 1908 by a Uruguayan pathologist Dr. Jose Juan Verocay, who later introduced the name “neuroma” in 1910 [1]. In 1935, Dr. Stout [2] renamed these tumors as “neurilemmoma” for better illustration of their origin – nerve sheaths. Now-a-days, these tumors are more commonly referred to as schwannomas; as more specifically, they arise from Schwann cells which wrap around each axon to form the myelin sheath for myelinated nerve fibers. Histologically, a typical schwannoma has two main microscopic patterns of growth, namely Antoni A (hypercellular component) and Antoni B (hypocellular component), which were named after a Swedish neurologist who described those two patterns in 1920 [3]. Schwannomas are benign tumors that are usually slowly growing and encapsulated. About 90% of the cases are sporadic, while the remaining 10% are associated with genetic disorders, such as neurofibromatosis type 2 (NF2), multiple meningiomas and schwannomatosis. Rarely, they are associated with neurofibromatosis type 1 (NF1), in which case there is an increased risk of malignant transformation [4]. Majority of schwannomas arise in the subcutaneous tissue of the head and neck, as well as distal extremities, but virtually any part of the body can be involved [2]. Visceral schwannomas are uncommon. Even though schwannoma is one of the most commonly reported primary soft tissue tumors in pancreas [5–7], pancreatic schwannoma remains extremely rare.

According to PubMed database search, there have been only 75 cases of pancreatic schwannoma reported in the English literature [7–50], [51–76], among which a full text was available in 73 reported cases. Most of them underwent a radical surgical resection, such as Whipple or distal pancreatectomy with or without splenectomy. If a definitive diagnosis of pancreatic schwannoma can be

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made before or during the surgery, a limited resection or even observation of these tumors can be considered in a subset of cases. Therefore, improvement in the pre- or intra-operative diagnosis of these benign tumors is essential. Here, we present 2 cases of pancreatic schwannoma that were identified in our pathology database over a period of 30 years (1980–2018). In addition, we provide a comprehensive review of the prior reported cases with a focus on preoperative and intraoperative diagnosis.

Case 1

A 64-year-old female was incidentally found to have a pancreatic mass during the workup for her newly diagnosed follicular lymphoma. She was asymptomatic with unremarkable physical examination. A CT scan of the abdomen revealed a hypodense lesion in the pancreatic body. Subsequent MRI showed a complex cystic and solid mass in the pancreatic body with both high and low signal intensity components on T2-weighted images (Fig. 1A). This heterogenous mass appeared hypointense on T1-weighted images (Fig. 1B) and the solid components showed marked contrast enhancement after gadolinium administration (Fig. 1C). The cystic component did not communicate with the main pancreatic duct. The mass abutted the splenic artery and vein without encasement. The imaging findings favored a diagnosis of low-grade cystic and solid neuroendocrine tumor versus mucinous cystic neoplasm. A fluoro-deoxyglucose positron emission tomography (FDG-PET) was also performed and showed increased FDG uptake of the mass (Fig. 1D). She then underwent an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). The cytology showed small fragments of spindle cells, and could not exclude a spindle neoplasm of neural origin, as there was a rare fragment of spindle cells which stained positive for S-100 protein. The patient subsequently underwent a distal pancreatectomy with splenectomy because a definitive diagnosis couldn't be made, and the tumor abutted the splenic vessels for which a radical resection was warranted. Gross examination of the resected pancreas revealed a 2.8 cm encapsulated, ovoid, well-circumscribed mass with a tan-yellow cut surface (Fig. 2A). Histopathological examination showed a spindle cell lesion with variable cellularity (Fig. 2B–C). Scattered degenerated atypical nuclei were present, with no mitosis or necrosis identified. On immunohistochemistry, the spindle cells were strongly positive for S100 protein (Fig. 2D) and negative for CD34, KIT, DOG1, STAT6 and HMB45. These findings were consistent with a pancreatic schwannoma with ancient features.

The patient was discharged uneventfully following surgery. She was doing well at 2-month postoperative follow-up examination.

Case 2

A 46-year-old female presented with a one-month history of constant abdominal pain. It was accompanied by nausea and bilious vomiting. Her family members noted new development of scleral icterus and jaundice. She had lost 20 pounds in the past month. A CT scan was obtained at an outside hospital (not available for review), which revealed a homogeneous mass in the pancreatic head with coexisting pancreatitis and the duodenal lumen was highly compromised. She was referred to our institution for further evaluation. On physical examination, a palpable mass was noted in epigastrium. Her laboratory tests were remarkable for increased bilirubin and alkaline phosphatase. Her tumor markers (CA19-9 and CEA) were within normal range.

Based on the imaging findings and the fact that the patient was suffering from failure to thrive, she was taken to the operation room for Whipple procedure with a high suspicion of pancreatic adenocarcinoma. The specimen was sent to the pathology lab for an intraoperative evaluation of the pancreatic margin. In addition, a frozen section of the mass was also performed that revealed a fibroinflammatory lesion on one representative section. Postoperatively, gross examination revealed a 4 cm pancreatic head mass that was compressing the duodenum and pancreatic duct. On cut surface, the mass was tan-yellow, homogenous and well-circumscribed. Microscopically, the mass showed variable cellularity, with hypercellular areas composed of spindle cells with elongated nuclei. Peripheral lymphoid cuffs were present. There was no obvious cytological atypia or mitotic activity.

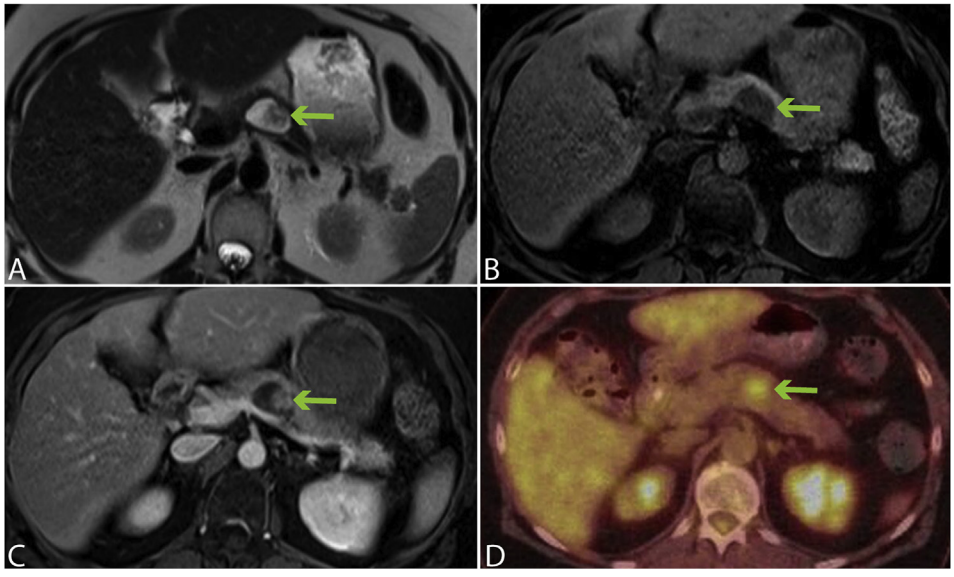

Fig. 1. Imaging findings of a pancreatic schwannoma in a 64-year old woman. A: T2-weighted fast spin-echo image shows a heterogenous mass with both high and low signal intensity (arrow) components. B–C: Axial fat suppressed T1-weighted images obtained before and after gadolinium administration show that the T2 hypointense components show enhancement (arrow). D: Corresponding FDG-PET image shows increased activity in the lateral aspect of the lesion (arrow) corresponding to the enhancing solid components shown in figure C. FDG-PET: Fluoro-deoxyglucose positron emission tomography.

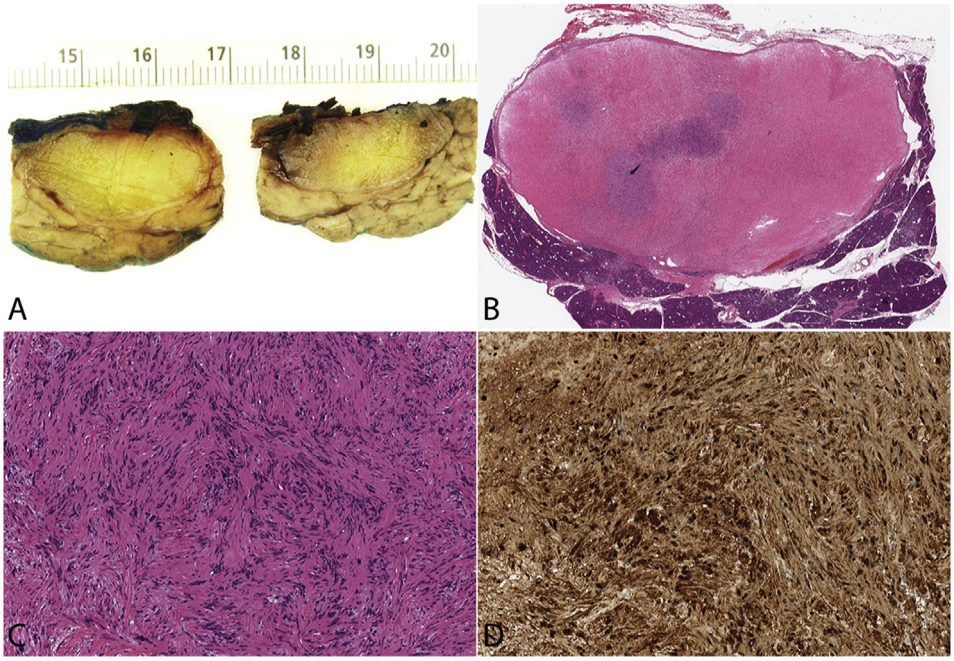

Fig. 2. Macroscopic and microscopic findings of a pancreatic schwannoma in a 64-year-old woman. The well-circumscribed mass (A) is surrounded by a capsule, with a tan-yellow cut surface. Microscopically, the tumor cells are spindle-shaped with variable cellularity (B, H&E, x4) and nuclear palisading in the hypercellular areas (C, H&E, x75). The spindle cells show nuclear and cytoplasmic immunoreactivity for S100 protein (D, x100). H&E: Hematoxylin and Eosin stain.

Immunohistochemical studies showed spindle cells to be positive for S100 protein and negative for ALK1, DOG1, SMA, KIT, Beta-catenin, Neurofilament, MITF, and Melan-A. Based on the morphology and immunohistochemical profile, a diagnosis of pancreatic schwannoma was made.

The patient had an uneventful postoperative course and at the postoperative 14-month follow-up visit, she was completely asymptomatic without any evidence of recurrence.

Discussion and literature review

Pancreatic schwannoma is an extremely rare benign soft tissue tumor with only 75 published cases in the English literature so far. In order to update the available knowledge in regard to the clinical, radiological and pathological characteristics, and to evaluate the accuracy of pre- and intra-operative diagnosis, we reviewed 68 literature citations of 73 pancreatic schwannoma cases in which a full text was available [7–19], [21,22], [24–50], [51–76]. The clinicopathological and radiological features of the prior 73 cases, combined with the features of our 2 cases are summarized in Table 1.

Clinical features

Pancreatic schwannomas tend to occur in adults with an average age of 55 years and slightly higher incidence in females than males (57% vs 43%). Most of the cases (72/75, 96%) were sporadic, however, association with neurofibromatosis type 1 (NF1, also called von Recklinghausen's disease) (2/75, 3%) and schwannomatosis (1/75, 1%) was also seen. Presenting symptoms and signs were nonspecific, with abdominal pain being the most common symptom (33/75, 44%). Approximately, one third of the patients (23/75, 31%) were asymptomatic. It was not uncommon to see presentations such as weight loss (13/75, 17%), a palpable mass (9/75, 12%) and jaundice (5/75, 7%), in patients with pancreatic schwannoma, that are clinically suspicious for a pancreatic adenocarcinoma. The laboratory tests including tumor markers were usually within reference range. Only two cases have been reported to have increased CA19-9 or CEA [7,24]. The tumors ranged in size from 1.0 cm to 30.0 cm with a mean size of 5.5 ± 5.0 cm. The most common locations were pancreatic head (33/75, 44%) and body (17/75, 23%).

Preoperative diagnosis- imaging modalities

A variety of diagnostic imaging modalities can be used to narrow the differential diagnosis of pancreatic tumors. However, there are no specific imaging features to diagnose pancreatic schwannomas. At least half of reported cases (39/75, 52%) were reported to have cystic component based on imaging studies (Table 1). The cystic appearance can mimic the whole spectrum of cystic pancreatic lesions [76].

The most common finding of pancreatic schwannomas on CT scan was an encapsulated hypodense lesion with or without cystic degeneration that correlated well with histological findings [50,62,77]. In areas of Antoni A, they appear heterogeneous, solid and hypodense due to their compact cellular organization and high lipid content of the tumor. On contrast-enhanced CT scan, Antoni A areas show heterogeneous enhancement because of well-developed reticular vascular component. Inversely, in areas of Antoni B, which are hypocellular with loose myxoid stroma, CT scan showed homogeneous pseudocystic appearance without significant contrast enhancement due to less vascularity [54]. Moreover, true cystic degeneration is often recognized in Antoni B areas resulting from vascular thrombosis and subsequent necrosis, especially when the tumor is large. Because of variable proportions of Antoni A and B areas, as well as various degrees of degenerations, pancreatic schwannomas show a variety of image findings.

On MRI, the characteristic findings of pancreatic schwannomas included encapsulation, hypointensity on T1-weighted images and inhomogeneous hyperintensity on T2-weighted images [32,50]. Most pancreatic schwannomas can be gradually enhanced on T1-

Table 1
Summary of clinicopathological findings of 75 patients (including prior reported 73 cases in which a full text was available and our 2 cases).

Sex (n = 75)		**Imaging feature**	
Male	32/75 (43%)	Solid	8/75 (11%)
Female	43/75 (57%)	With cystic component	39/75 (52%)
Age (n = 75)		Not specified	28/75 (37%)
Mean ± SD	55.2 ± 14.4 years		
Range	20–87 years	Increased FDG on PET/CT	5/5 (100%)
Sporadic	72/75 (96%)	**Gross findings**	
Syndromatic		Encapsulated	32/75 (43%)
Neurofibromatosis type 1	2/75 (3%)	Unencapsulated	1/75 (1%)
Schwannomatosis	1/75 (1%)	Capsulation not specified	42/75 (56%)
Clinical presentation		True cystic degeneration	27/75 (36%)
Asymptomatic	23/75 (31%)	**Histopathologic variants**	
Abdominal pain	33/75 (44%)	Conventional schwannoma	64/75 (85%)
Weight loss	13/75 (17%)	Ancient schwannoma	9/75 (12%)
Nausea/Vomiting	12/75 (16%)	Melanocytic schwannoma	2/75 (3%)
Palpable mass	9/75 (12%)	**Histology**	
Abdominal discomfort	6/75 (8%)	Benign	71/75 (95%)
Dyspepsia	6/75 (8%)	Malignant	4/75 (5%)
Jaundice	5/75 (7%)		
Back pain	3/75 (4%)	Peripheral lymphoid cuff	2/75 (3%)
Fever	2/75 (3%)	**Treatment**	
Size of tumor (n = 70)		Whipple	25/75 (33%)
Mean ± SD	5.5 ± 5.0 cm	Distal pancreatectomy with splenectomy	15/75 (20%)
Range	1.0–30.0 cm	Spleen-preserving distal pancreatectomy	3/75 (4%)
Location of tumor		Enucleation	11/75 (15%)
Head	33/75 (44%)	Central pancreatectomy	2/75 (3%)
Body	17/75 (23%)	Surgical resection not otherwise specified	14/75 (19%)
Tail	6/75 (8%)	No surgery[a]	5/75 (7%)
Uncinate	7/75 (9%)	**Prognosis (n = 38)**	
Body and tail	5/75 (7%)	Mean follow-up (months)	19.0 ± 17.2 (2–72)
Head and body	3/75 (4%)	Death[b]	1/38 (3%)
Not specified	4/75 (5%)	Recurrence or metastasis	0/38 (0%)

[a] 2 patients refused surgery; 1 patient's tumor was unresectable; 2 patients were managed by observation.
[b] Cause of death: postoperative complications.

weighted images after Gd-DTPA administration [32]. Degeneration with cystic change and hemorrhage might complicate the signal intensity characteristics. MRI is also helpful in assessing the vascular involvement, which can further characterize the biological behavior of these tumors and help determine the choice of surgical procedure. Encasement of superior mesenteric artery or portal vein, without invasion was reported in four cases (4/75, 5%).

Notably, a hypermetabolic appearance on FDG-PET has been reported in schwannomas including pancreatic schwannomas [78,79], even though they are benign. Of the five pancreatic schwannoma cases that underwent PET/CT, all of them had increased FDG uptake (5/5, 100%) [62,70,71,76]. Increased FDG uptake is thought to be due to glucose transporter type 3, which is the major glucose transporter on neuronal surface [76,80]. It is important to be aware that schwannomas can have increased FDG uptake so as to avoid over interpretation of a benign lesion as a malignancy process. Watanabe et al. [76] recently proposed that the FDG-PET findings and the imaging features of dilatation of the pancreatic duct are useful to narrow the list of differential diagnoses of cystic pancreatic lesions. According to their flowchart, if the tumor is accompanied by dilation of the pancreatic duct, intraductal papillary mucinous neoplasm (IPMN) should be suspected. If not, the FDG-PET might provide useful information. Serous cystic neoplasm and mucinous cystic neoplasm are less likely to have a hypermetabolic appearance on FDG-PET. In cases with positive FDG accumulation, pancreatic schwannoma needs to be differentiated from solid pseudopapillary neoplasm and pancreatic neuroendocrine tumor, as the latter two can also have an increased FDG uptake.

However, all those imaging features described above are nonspecific for pancreatic schwannomas and can be seen in other pancreatic tumors. Imaging could not definitely diagnose pancreatic schwannoma in any of the reported cases. In our review of literature (Table 2), the preoperative diagnoses based on imaging included, in descending order of frequency, cystic neoplasm (19/34, 56%), pancreatic neuroendocrine tumor (10/34, 29%), mucinous cystic neoplasm (9/34, 26%), solid pseudopapillary neoplasm (8/34, 24%), cystadenoma (7/34, 21%), mucinous cystadenocarcinoma (4/34, 12%), acinar cell carcinoma (3/34, 9%), ductal adenocarcinoma (3/34, 9%), pseudocyst (2/34, 6%), serous cystic neoplasm (1/34, 3%) and serous cystadenocarcinoma (1/34, 3%). Comparison of the common differential diagnoses is listed in Table 3. As these data suggest, precise preoperative diagnosis is nearly impossible by using imaging modalities only. Pancreatic schwannoma should be included in the differential diagnoses for a well-circumscribed lesion with or without cystic component, especially when there is increased FDG uptake.

Preoperative diagnosis-imaging-guided aspiration/biopsy

Various imaging-guided aspiration, such as ultrasound-guided fine needle aspiration (EUS-FNA) or CT-guided FNA, can be used to obtain material for the cytologic analysis of pancreatic tumors preoperatively [29,38,42,56,63,74]. New fine-needle biopsy (FNB) needles (Trucut, ProCore, SharkCore, Acquire, et al.) have been developed in order to increase the amount of tissue acquisition with preserved tissue architecture. However, high quality evidence from several studies showed no significant difference in diagnostic accuracy for malignancy [81,82] between FNA and FNB.

In the current review of 75 cases, 25 cases underwent imaging-guided FNA/biopsy preoperatively (including our case 1, Table 2), of which 12 cases (48%) were correctly diagnosed as pancreatic schwannoma, 3 cases (12%) were diagnosed as benign lesion, and 2 cases (8%) correctly reported the origin of the tumors as nerve sheath tumors. The final diagnosis in 4 cases (16%) was inconclusive due to inadequate sampling. Specifically, FNA was performed in 19

Table 2
Summary of pre- and intra-operative diagnosis.

Preoperative diagnosis based on radiological findings (N = 34)	
Cystic neoplasm	19/34 (56%)
Neuroendocrine tumor	10/34 (29%)
Mucinous cystic neoplasm	9/34 (26%)
Solid pseudopapillary neoplasm	8/34 (24%)
Cystadenoma	7/34 (21%)
Mucinous cystadenocarcinoma	4/34 (12%)
Acinar cell carcinoma	3/34 (9%)
Ductal adenocarcinoma	3/34 (9%)
Pseudocyst	2/34 (6%)
Serous cystic neoplasm	1/34 (3%)
Serous cystadenocarcinoma	1/34 (3%)
Preoperative diagnosis based on image-guided biopsy (N = 25)	
Schwannoma[a]	12/25 (48%)
Inconclusive	4/25 (16%)
Benign lesion	3/25 (12%)
Malignant tumor[b]	3/25 (12%)
Tumor of neural origin	2/25 (8%)
Low-grade spindle cell neoplasm	1/25 (4%)
Intraoperative diagnosis based on frozen diagnosis (N = 15)	
Schwannoma[a]	7/15 (47%)
Benign lesion	3/15 (20%)
Malignant tumor	3/15 (20%)
Benign spindle cell tumor	2/15 (13%)

[a] One case was diagnosed with pancreatic schwannoma by both preoperative FNA and intraoperative frozen section.
[b] One of the three cases was a true malignant pancreatic schwannoma based on final pathological examination. The other two cases were misdiagnosis.

cases and the diagnostic accuracy was 37% (7/19), whereas biopsy (FNB or core-needle biopsy, CNB) was done in 7 cases with 5 cases correctly diagnosed (71%, 5/7). This vast difference reflects the fact that a pancreatic schwannoma usually requires tissue diagnosis. Moreover, immunohistochemical staining, such as S100, is crucial for accurate diagnosis of schwannoma and a biopsy specimen is more likely to provide adequate material for ancillary testing. According to the European Society of Gastrointestinal Endoscopy (ESGE) technical guidelines [83], when the primary aim of sampling is to obtain a core tissue specimen, 19G FNA or FNB needles or 22G FNB needles are recommended. Sometimes, despite adequate material, precise diagnosis can be challanging due to various histological variants that can mimic other tumors. So far, only conventional (64/75, 85%), ancient (9/75, 12%) and melanocytic (2/75, 3%) variants have been reported in the pancreas [10,12,17,26,28,31,46]. As ancient schwannoma can demonstrate marked nuclear atypia of degenerative type, it can be misdiagnosed as a malignant lesion. In our review (Table 2), two cases of pancreatic schwannoma were misdiagnosed as malignant tumor based on FNA preoperatively [40,51]. One of them turned out to be an ancient schwannoma postoperatively. None of the cases were misdiagnosed on biopsy (FNB or CNB).

Core tissue specimen (e.g. FNB) tend to increase the diagnostic accuracy and is recommended along with FNA. Several guidelines [84–87] have shed light on the management of pancreatic cystic lesions and the indication of FNA/biopsy. However, there is no definite consensus to guide the diagnostic decision making of a solid or mixed solid and cystic pancreatic lesion. Hence, we propose a stepwise flow algorithm (Fig. 3) to facilitate accurate diagnosis of a well-circumscribed pancreatic lesion. We highly recommend preoperative FNA/biopsy for asymptomatic well-circumscribed lesions as it can alter surgical management. Karatzas et al. [88] suggested that a small incidental solid lesion (<2 cm) may simply be monitored without histological assessment, since pancreatic incidentolomas < 2 cm are likely to be benign in most series.

Intraoperative diagnosis

An intraoperative frozen section is frequently used by pancreatic surgeons to ensure negative resection margins, however, its usage in obtaining a histological diagnosis is controversial. In our review of the literature (Table 2), a total 15 cases of pancreatic schwannoma underwent intraoperative frozen section. Among them, 7 cases (47%) were rendered the correct diagnosis of pancreatic schwannoma, and 5 cases (33%) were reported as benign lesions. However, there were 2 cases that were misdiagnosed as malignant tumor on frozen section, both of which were ancient schwannoma on final pathological examination. The intraoperative frozen section diagnosis is usually straightforward in cases with characteristic histological features on the representative section, that being the most common scenario. Nonetheless, when there are atypical features, such as cytological atypia, ancient changes, cellular variant, etc., the diagnosis can be challenging.

In our review, only two reported cases underwent both preoperative FNA and intraoperative frozen assessment [17,29]. One of them was diagnosed with pancreatic schwannoma by FNA, which was then confirmed by intraoperative frozen section. The other case was thought to be a schwannoma on preoperative FNA; however, was diagnosed as malignant tumor on intraoperative frozen section. It was an ancient schwannoma on final pathological examination.

It is obvious that intraoperative diagnosis can have a critical influence in surgical decision-making. However, it is an imperfect test with a relatively low diagnostic accuracy for pancreatic schwannoma and misdiagnosis can potentially adversely impact patient outcomes. We suggest that if preoperative evaluation including imaging-guided FNA/biopsy cannot reach a definite diagnosis, intraoperative frozen section is justifiable only if the pathological findings caan substantially alter the surgical procedure (see Fig. 3), especially when clinical and radiological findings do not indicate a malignant process.

Histopathological features

Most of the reported cases (85%) are conventional schwannoma, microscopically characterized by Antoni A and Antoni B. Peripheral lymphoid cuffs are common in gastrointestinal schwannomas, and are reported to be as high as 70.3% [89]. Contrary to that, we found

Table 3
Differential diagnosis of pancreatic schwannomas (Cited and modified from Ref. [87] with permission, with additional data from Refs. [86] and [94,95]).

	Clinical features	Most common location	Imaging features	Fluid analysis	Cytology and ancillary stains	Malignant potential
Pancreatic schwannoma	% female: 57% Mean age: 55 Can cause abdominal pain (44%) or found incidentally (31%)	Head of pancreas	Well-circumscribed, encapsulated, cystic appearance in at least half of the cases; PET positive	N/A	Spindle cell lesion; stains positive for S100	None, unless associate with NF1
pNET	% female: 50% Mean age: 60-70 Can cause abdominal pain or found incidentally	No location predilection	Unilocular cyst occupies most of neoplasm; PET positive	Variable	Monomorphic endocrine tumor cells; stains positive for chromogranin and synaptophysin	Yes
MCN	% female: >95% Mean age: 47 Usually found incidentally but can cause abdominal pain and a palpable mass if large	Distal pancreas	Macrocystic, occasionally septated; peripheral calcifications, solid components and regional adenopathy when malignant; PET usually negative	Elevated CEA, low amylase	Mucinous columnar cells with variable atypia; fluid stains positive for mucin	Yes
SPN	% female: >80% Mean age: 30-40 Usually found incidentally; rarely causes abdominal discomfort	No location predilection	Solid and cystic components; PET positive	Variable	Monomorphic cells with round nuclei and eosinophilic or foamy cytoplasm; stains positive for vimentin and a-1-antitrypsin	Yes
SCN	% female: ~70% Mean age: 52-62 Usually found incidentally but can cause abdominal pain and a palpable mass if large	No location predilection	Microcystic with a “honeycomb” appearance; rarely has a macrocystic component; central calcification; PET usually negative	Low CEA and amylase	Cuboidal epithelium that stains positive for glycogen	Almost none (rare reports)
PDAC	% female: ~30% Mean age: 60-80 Presents with painless jaundice, abdominal/back pain or rarely pancreatitis	Head of pancreas	Primarily solid mass, can have cystic spaces; PET positive	Variable	Malignant adenocarcinoma may be seen, but varying degrees of atypia may be present in the specimen	Already present
Pseudocyst	% female: <25% Mean age: 40-50 History of moderate to severe pancreatitis	No location predilection	Anechoic, thick-walled, rare septations, regional inflammatory nodes may be seen; PET usually negative	Elevated amylase, low CEA	Neutrophils, macrophages, histiocytes; negative staining for mucin	None

Abbreviations: pNET, pancreatic neuroendocrine tumor; MCN, mucinous cystic neoplasm; SPN, solid pseudopapillary neoplasm; SCN, serous cystic neoplasm; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; CEA, carcinoembryonic antigen; NF1, neurofibromatosis type 1.

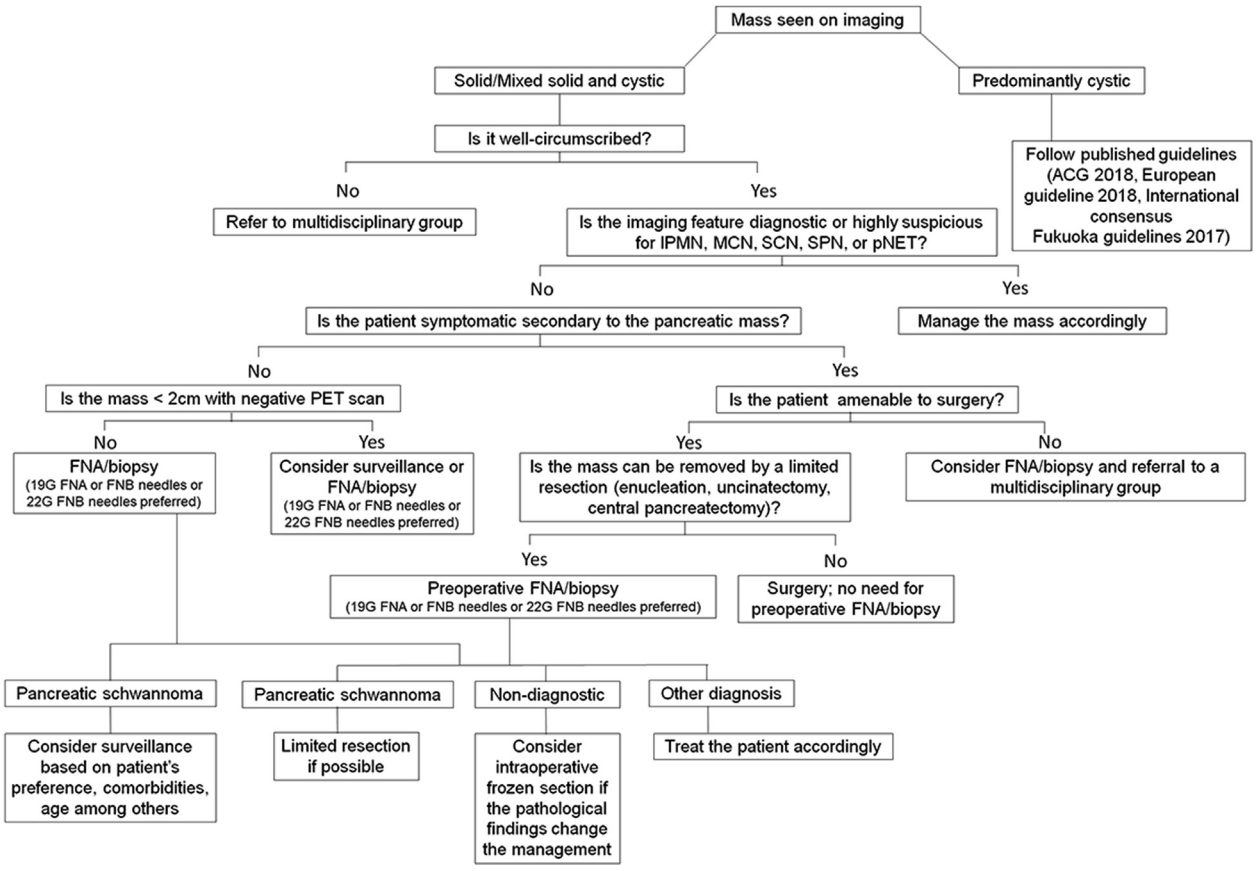

Fig. 3. Algorithm of management of a well-circumscribed solid/mixed solid and cystic pancreatic mass when pancreatic schwannoma is a possibility. (Abbreviations: IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; SPN, solid pseudopapillary neoplasm; pNET, pancreatic neuroendocrine tumor; PET, positron emission tomography; ACG, American College of Gastroenterology; FNA, fine-needle aspiration; FNB, fine-needle biopsy).

peripheral lymphoid cuff in only 2 pancreatic schwannomas (2/75, 3%, Table 1). Although at least half of the pancreatic schwannomas exhibit cystic component on imaging, the true cystic degeneration was found in 36% of cases on histopathological examination (Table 1). Histologically, the differential diagnosis of pancreatic schwannoma includes neurofibroma, gastrointestinal stromal tumor (GIST), melanoma, malignant peripheral nerve sheath tumor (MPNST), and other spindle cell tumors that can occur in pancreas. Neurofibroma is usually unencapsulated, lacks Antoni A areas and shows CD34 positivity. Immunostaining of neurofilament can highlight intratumoral axons for neurofibroma, which is absent in schwannoma. GIST and melanoma also lack the typical mixed Antoni A and Antoni B patterns. Immunohistochemistry is very important in distinguishing those entities. In addition to S100 and Sox10, melanoma expresses HMB-45 and Melan-A, which are negative in schwannoma. KIT and DOG1 proteins are positive in GISTs but negative in schwannoma. MPNST should be distinguished from ancient schwannoma or cellular schwannoma, but it often has a larger size with high mitotic activity and tumor necrosis. A total of 4 cases in this review were found to be malignant pancreatic schwannoma, for which the current designation should be MPNST.

Treatment and prognosis

Because of its rarity, there is no definite protocol or consensus regarding the treatment of pancreatic schwannoma. Give its benign nature, a relatively conservative strategy is recommended (Fig. 3). Several factors need to be considered for the decision making including the clinical presentation, size and site of the tumor, overall health status, comorbidities, and the life expectancy of the patient. For patients with symptoms secondary to a pancreatic mass, resection may be the most appropriate treatment regardless of the diagnosis. In these cases, pre- or intra-operative histological diagnosis is only essential if a limited resection (enucleation, uncinatectomy, central pancreatectomy) is anatomically feasible. Nevertheless, the size of the lesion (eg. >2 cm in terms of enucleation) and relationship to the pancreatic duct essentially exclude limited resection in many cases, for which the histological confirmation is likely unnecessary before surgical intervention. A review of the treatment choices (Table 1) showed that 11 cases (15%) received simple enucleation and 2 cases (3%) underwent central pancreatectomy. However, majority (at least 57%) of the patients with pancreatic schwannoma underwent either Whipple procedure or distal pancreatectomy with or without splenectomy, either because a definite diagnosis couldn't be made pre- or intra-operatively or due to the large tumor size.

By contrast, for an asymptomatic schwannoma, conservative management may be considered (Fig. 3). Several studies revealed that 58%–69% of schwannoma treated conservatively do not grow during observation period, and even if they do, the growth rate is only 0.9 mm–2 mm per year [90–93]. As such, Birk et al. [90] proposed a normal cost-effective management paradigm for asymptomatic peripheral nerve schwannomas. In their paradigm, observation with surveillance imaging is recommended for asymptomatic patients. Although data specifically for pancreatic schwannoma is lacking, given the common origin for those tumors, a more conservative approach with surveillance follow-up depending on various factors such as patient's age, comorbidities,

preference etc, can be an appropriate choice. In such scenarios, an accurate pre- or intra-operative histological diagnosis should be obtained to avoid unnecessary surgical interventions.

In our review of 18 patients with pancreatic schwannoma that were diagnosed correctly by preoperative FNA/biopsy and/or frozen, 8 patients underwent simple enucleation or partial pancreatectomy, 3 patients were managed with observation only, 3 patients received surgical excision (type not specified), and 4 patients underwent a radical resection either due to a large size (3 cases) or extensive vascular encasement (1 case). Unfortunately, one patient died of postoperative complications 12 days after Whipple procedure [51]. Most of the patients have a good prognosis, with no recurrence or metastasis reported over a mean follow-up of 19 months (Table 1).

In summary, a treatment strategy could be individualized for each patient with pancreatic schwannoma based upon the clinical presentation, patient's overall health state, his or her preference, and size/site of the tumor. Therefore, a multidisciplinary strategy for decision-making and surgical evaluation to provide the best care is essential for this rare benign entity.

Conclusion

In conclusion, pre- and intra-operative diagnosis of pancreatic schwannoma is quite challenging because of its rarity, lack of pathognomonic features on imaging, and a relatively low accuracy rate on FNA/biopsy and intraoperative frozen section. The incidence of this entity is higher than previously reported due to the availability of more sensitive imaging techniques. Pancreatic schwannoma should be considered in the differential diagnosis if radiological studies suggest a well-circumscribed lesion with or without cystic component that shows increased FDG uptake on a PET-CT scan. In these cases, a pre- or intra-operative histological assessment is suggested as it can change the surgical managment.

Conflicts of interest statement

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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