

QUALITY IMPROVEMENT

Solid Pseudopapillary Neoplasm: A Single Institutional Case Series of a Rare Pancreatic Tumor

KRISTEN OASE,¹ MS, PA-C, CHERYL MEGUID,¹ DNP, ACNP, ATSUSHI OBA,^{1,2} MOHAMMED H. AL-MUSAWI,¹ MD, MSC, FIBMS-CTV, FRCS (GLASG), ALISON SHERIDAN,¹ MD, EVAN NORRIS,¹ MD, SANJANA MEHROTRA,¹ MD, MARK A. LOVELL,³ MD, RICHARD D. SCHULICK,¹ MD, MBA, FACS, STEVEN A. AHRENDT,¹ MD, and MARCO DEL CHIARO,¹ MD, PhD, FACS

From ¹University of Colorado Hospital, Aurora, Colorado; ²Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; ³Children's Hospital Colorado, Aurora, Colorado

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Kristen Oase, MS, PA-C, 13001 E. 17th Place, Aurora, CO 80045.
E-mail: kristen.oase@cuanschutz.edu

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Abstract

Purpose: Solid pseudopapillary neoplasms (SPN) are rare pancreatic cystic neoplasms with low malignant potential that tend to occur in young women. Due to the rarity of this disease, there are few large case series in the literature, and the exact pathophysiology remains unknown. In this article, we aim to share our institutional experience.

Methods: Retrospective clinical data collection and analysis was performed on all patients with a diagnosis of SPN at the University of Colorado Hospital and Children's Hospital of Colorado (n = 28). **Results:** Twenty-eight patients were diagnosed with SPN during the study period. The median age was 21.5 years, and the majority of patients were female (89.3%) and Caucasian (60.7%). Six patients were diagnosed incidentally (21.4%). The majority of tumors were in the pancreatic tail (46.4%), and most underwent distal pancreatectomy (64.3%). The mean tumor size was 5.4 cm, and R0 resection was achieved in 25 patients (89.3%). Ten patients underwent laparoscopic resection (35.7%). The median hospital length of stay was 8.5 days, and postoperative complication rate was 39.3%. Median follow-up was 41 months, with 78.6% of patients alive without evidence of disease, while 2 patients were lost to follow-up. Two patients developed recurrence/metastases, which were resected; both are alive without evidence of disease. **Conclusion:** SPN are rare pancreatic tumors diagnosed most frequently in young women. Surgical resection is the mainstay of treatment, and outcomes are excellent if complete resection is achieved. Predictors of malignant disease are inconsistent in current literature. Considerations should be made for a minimally invasive approach in patients with SPN. Multidisciplinary clinics may be helpful in the diagnosis, management, and surveillance of pancreatic cystic lesions, with major potential for the advanced practitioner role.

The incidental finding of pancreatic cystic lesions has increased with the use of cross-sectional imaging, with prevalence up to 3% in CT and up to 20% in MRI (Laffan et al., 2008). Pancreatic cystic neoplasms (PCN) are a subtype accounting for approximately 15% of pancreatic cystic lesions (Kromrey et al., 2018). While most pancreatic cystic lesions are benign, PCN have biological behaviors ranging from benign to potentially malignant, and treatment varies based on diagnosis. Solid pseudopapillary neoplasms (SPN) are an exceedingly rare subtype of PCN accounting for 3% of PCN and 1% to 2% of all exocrine pancreatic tumors (Limaïem et al., 2014). They most commonly occur in young females (Lubezky et al., 2017) and appear as large, heterogenous pancreatic masses with mixed solid and cystic features (Kawamoto et al., 2011). Typical presentation includes vague, nonspecific abdominal pain or palpable mass, while 15% of patients are asymptomatic (Dinarvand & Lai, 2017). Solid pseudopapillary neoplasms have low malignant potential and can be cured with surgical resection. However, 10% to 15% of patients will develop locally recurrent or metastatic disease (Hao et al., 2018; Naar et al., 2017), and surgical resection is recommended even in these cases (European Study Group on Cystic Tumours of the Pancreas, 2018).

The current literature contains multiple single case studies on SPN and fewer larger institutional case series. Due to the rarity of this neoplasm, the exact pathophysiology is not well understood. In this article, we discuss clinical presentation, diagnostic workup, radiographic and pathologic characteristics, type of surgical resection, and long-term outcomes of patients with SPN at our single institution. In addition, we consider the role of multidisciplinary clinics in the diagnosis, management, and surveillance of PCN, and the role of the advanced practitioner (AP).

METHODS

We retrospectively collected clinical data from all patients diagnosed and treated for SPN at the University of Colorado Hospital and Children's Hospital of Colorado between January 2008 and June 2020 (n = 28). Descriptive statistical analysis was performed on clinical data, including demo-

graphic information, clinical presentation, diagnostic workup, pathological features, radiographic features, surgical strategy, surgical outcomes, and long-term outcomes. Radiographic review was performed retrospectively by an attending and a resident radiologist (Sheridan, A.; Norris, E.). Radiographic features included tumor size, anatomic location, and presence of abutment of vascular structures, pseudocapsule, calcifications, or hemorrhage. Pathologic review was performed retrospectively by attending pathologists (Mehrotra, S.; Lovell, M.). The diagnosis of SPN was made by histologic and immunohistochemical findings. Main pathologic features included tumor size, resection margins, presence of perineural invasion (PNI) or lymphovascular invasion (LVI), the number of positive lymph nodes, and immunohistochemistry (IHC). Complications were graded using the Clavien-Dindo classification (Dindo et al., 2004; Table 1). Follow-up time was defined as the interval between the date of first operation and the date of last follow-up or imaging. This study was exempt by the Colorado Multiple Institutional Review Board (#20-1358).

RESULTS

Patient Demographics and Clinical Presentation

During the study period 2008 to 2020, 28 patients underwent resection for histologically diagnosed SPN at our institution (Table 2). The median age at diagnosis was 21.5 years (range 14–67 years), and the majority were adults (n = 18, 75%) and female (n = 25, 89.3%). Median age in females was 20 years, while median age in males was 43 years. The most common race was Caucasian (n = 17, 60.7%) followed by Hispanic (n = 6, 21.4%). At the time of diagnosis, 22 patients were symptomatic (78.6%), with abdominal pain as the most common presenting symptom (n = 4, 14.3%). Abdominal pain locations included the right upper quadrant (n = 3), epigastric region (n = 2), left upper quadrant (n = 1), left abdomen (n = 1), and unspecified (n = 14). Abdominal pain quality included bloating (n = 1), indigestion (n = 1), and unspecified (n = 20). Six patients were asymptomatic (21.4%), and SPN was diagnosed incidentally on diagnostic workup for trauma (n = 2), appendicitis (n = 1), nephrolithiasis (n = 1), and cholelithiasis (n = 1).

Table 1. The Clavien-Dindo Classification of Surgical Complications

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacologic treatment with drugs other than such allowed for grade I complications Blood transfusion and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiologic intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under anesthesia
Grade IV	Life-threatening complication (including CNS complications) ^a requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Note. CNS = central nervous system; IC = intermediate care; ICU = intensive care unit. Information from Dindo et al. (2004).
^aBrain hemorrhage, ischemic stroke, or subarachnoid bleeding, but excluding transient ischemic attacks.

Diagnostic Workup and Radiographic Characteristics

All 28 patients had preoperative cross-sectional imaging, and 19 patients underwent preoperative tissue biopsy. Seventeen patients had endoscopic ultrasound (EUS) with fine needle aspiration (FNA), and two had CT-guided biopsies.

All 28 patients had at least one preoperative imaging study, and 12 had an additional preoperative radiological study, totaling 41 reviewed scans. The 41 studies included a combination of outside hospital and in-house CT (n = 26), ultrasound (n = 10), MRI (n = 4), and PET-CT (n = 1). The most common tumor location was in the pancreas tail (46.4%), followed by the head (42.8%), body (10.7%), and neck (3.6%; Figure 1A). The average tumor size was 5.4 cm x 5.2 cm x 4.1 cm (volume 145.3 cm³). The most common imaging features included pseudocapsule (76%), vascular involvement by either abutment or compression of adjacent structures (59.3%), calcifications (13.8%), and hemorrhage (3.4%; Figure 2).

Pathologic Characteristics

Most SPN express a variety of proteins, including alpha-1-antitrypsin, alpha-1-antichymotrypsin, neuron-specific enolase, vimentin, progesterone receptors, CD10, CD56, claudins 5 and 7, galectin 3, cyclin D1, synaptophysin, and nuclear/cytoplasmic β -catenin (La Rosa & Bongiovanni, 2020).

These tumors are typically negative for expression of the markers chromogranin, Bcl-10, and trypsin. Based on morphology, the differential diagnoses include pancreatic neuroendocrine tumors and acinar cell carcinoma. Due to the diversity of positive and negative IHC staining, a core panel of

Table 2. Patient Demographics and Clinical Presentation (N = 28)

Demographic	n	%
Age, median, yr	21.5	-
Adult (> 18 yr)	18	75
Pediatric (< 18 yr)	10	25
Female	25	89.3
Male	3	10.7
Race		
Caucasian	17	60.7
Hispanic	6	21.4
African American	3	10.7
Asian	2	7.1
Symptomatic	22	78.6
Abdominal pain	21	75.0
Pancreatitis	4	14.3
Nausea, vomiting	1	3.6
Palpable mass	2	7.1
Weight loss	1	3.6

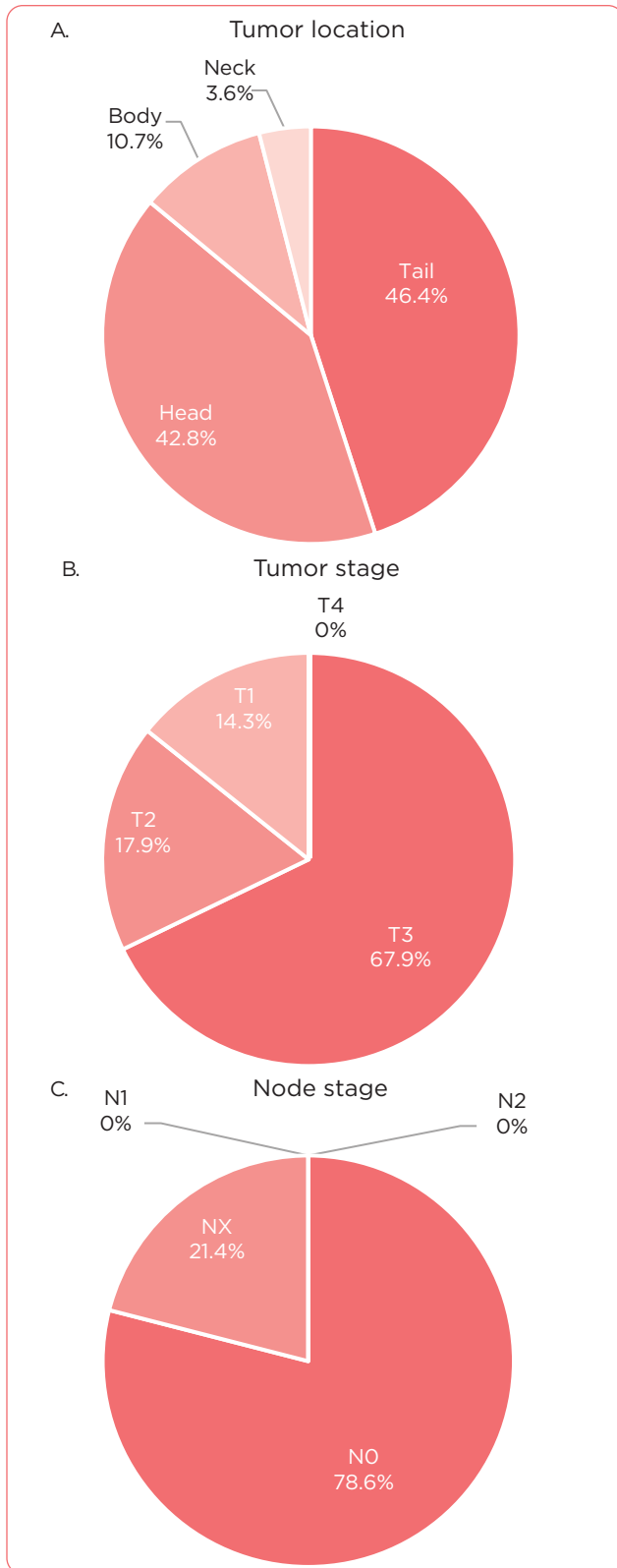


Figure 1. Tumor location and staging characteristics (N = 28). (A) Tumor location; (B) tumor stage; (C) node stage.

markers including β -catenin, CD10, chromogranin, and vimentin was used to support the morphologic impression of SPN (Figure 3). T stage was determined using the American Joint Committee on Cancer Guidelines (Kakar et al., 2017), with T1 defined as tumor size in greatest dimension ≤ 2 cm, T2 as > 2 cm and ≤ 4 cm, T3 as > 4 cm, and T4 as tumor involving celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size. N stage was determined by evaluating for presence of SPN cells in lymph nodes, with N0 defined as no regional lymph node metastases, N1 as metastases to 1 to 3 regional lymph nodes, N2 metastases in 4 or more regional lymph nodes, and NX as regional lymph nodes unable to be assessed.

The most common positive IHC stains included CD56 (n = 25, 3 unknown), CD10 (n = 24, 4 unknown), β -catenin (n = 22, 6 unknown), vimentin (n = 10, 18 unknown), and progesterone receptor (n = 9, 1 negative, 18 unknown). The most common negative IHC stain was chromogranin (n = 17, 11 unknown). The majority of tumors were stage T3 (n = 19, 67.9%), followed by T2 (n = 5, 17.9%), and T1 (n = 4, 14.3%). Zero patients had T4 stage tumors. (Figure 1B). The majority of lymph nodes were N0 (n = 22, 78.6%), followed by NX (n = 6, 21.4%; Figure 1C). Perineural invasion (PNI) was absent in 25 patients (89.3%), present in 2 patients (7.1%), and unknown in one patient (3.6%). Lymphovascular invasion (LVI) was absent in 25 patients (89.3%) and present in 3 patients (10.7%). Peripancreatic extension was present in 10 patients (35.7%), absent in 7 patients (25%), and unknown in 11 patients (39.3%). Surgical margins were negative in 25 patients (89.3%) and positive in 3 patients (10.7%).

Operative and Postoperative Courses

All 28 patients underwent surgical resection, which included distal pancreatectomy in 18 (64.3%), pancreaticoduodenectomy in 9 (Whipple; 32.1%), and enucleation in 1 (3.6%). One of the 9 pancreaticoduodenectomies required a simultaneous resection and reconstruction of the superior mesenteric vein. In 4 of the 18 distal pancreatectomies, the spleen was preserved. Eighteen patients underwent open resection (64.3%), and 10 patients underwent laparoscopic resection (35.7%; Table 3). All 28 patients had resectable disease without evidence of distant metastases at the time of initial diagnosis or



Figure 2. CT images of solid pseudopapillary neoplasms in the pancreatic head (A and B) and tail (C and D).

resection. Median hospital length of stay after resection was 8.5 days. Postoperative complication rate was 39.3%, with the most common complications including pancreatic leak ($n = 4$, 36.4%), abscess ($n = 2$, 18.2%), and chyle leak ($n = 2$, 18.2%). The majority of complications were grade 1 ($n = 7$, 63.6%), followed by grade 2 ($n = 3$, 27.3%) and grade 3 ($n = 1$, 9.1%). There were no grade 4 complications (Table 4). In-hospital mortality, 30-day mortality, and 90-day mortality was zero. There were no known deaths secondary to SPN or other disease, excluding 2 patients lost to follow-up.

Long-Term Follow-Up and Survival

At a median follow-up of 41 months, 22 patients are alive without evidence of disease (78.6%), 4 patients are alive with unknown disease status (14.3%), and 2 patients have been lost to follow-up (7.1%). The median disease-free survival has not been reached. Two patients developed recurrence or metastases (7.1%). One of these patients, a 48-year-old female, developed liver metastases 126

months after initial resection of a 9.7-cm primary tumor with LVI and positive surgical margins. The patient underwent metastasectomy and was alive with no evidence of disease 12 months postoperatively. Another patient, a 43-year-old male, developed local recurrence/peritoneal metastases at 43 months after initial resection, which was treated surgically. Initial tumor size was 12.5 cm, PNI negative, LVI negative, and surgical margins negative. This same patient developed another local recurrence/peritoneal metastases 22 months after re-resection, which was resected and had no evidence of disease 6.5 months later. There were no known deaths related to solid pseudopapillary tumor recurrence or metastases in the study group.

DISCUSSION

Solid pseudopapillary neoplasm is a rare subtype of PCN that occurs most commonly in young women. A large retrospective review of 340 patients with SPN from the National Cancer Database showed that 82% of patients were female and median age

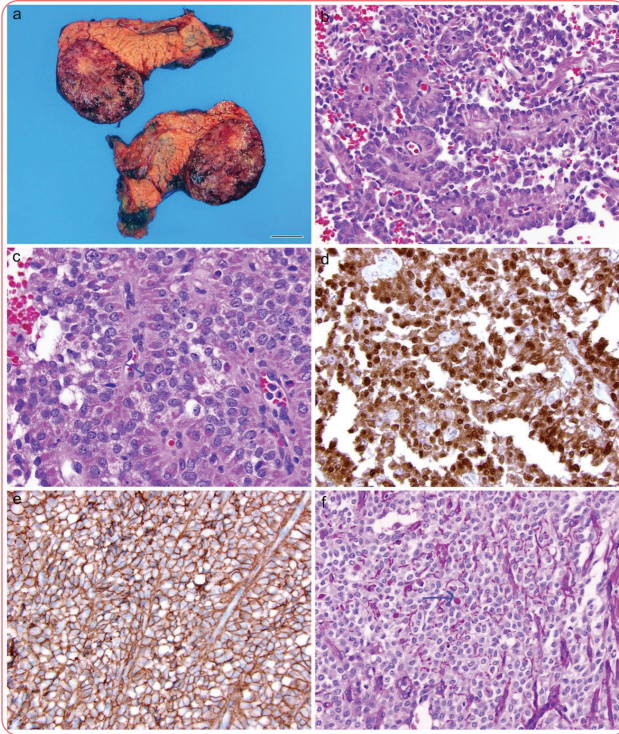


Figure 3. Gross and histopathologic characteristics of solid pseudopapillary neoplasm.

was 39 years (Jutric et al., 2017). The exact reason for female predilection is unclear, but literature suggests that sex hormones may be part of the pathogenesis (Naar et al., 2017; Pettinato et al., 2002). Multiple studies have identified strong immunoreactivity for progesterone in SPN (Nguyen, et al., 2011; Yeh et al., 2002; Zou et al. 2020). Other case reports show that SPN grew rapidly during pregnancy (Huang et al., 2013, 2018; Ganepola et al., 1999). Solid pseudopapillary neoplasm in females seems to have a bimodal distribution with peaks at age 28 and age 64, while SPN in males tends to occur later with unimodal distribution and peak at age 64 (Wu et al., 2020). Earlier age of onset in females than males may be related to exposure to progesterone and/or estrogen during the reproductive age, while the later onset in females may be related to accumulated lifetime environmental exposure. Male patients also have significantly poorer overall survival and disease-free survival than female patients, the reason for which is unclear but may be related to older age at diagnosis.

The differential diagnosis of PCN is broad and includes serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neo-

Table 3. Resection Type and Approach (N = 28)

Resection type	n	%
Whipple	9	32.1
Distal pancreatectomy	18	64.3
Enucleation	1	3.6
Surgical approach		
Open	18	64.3
Laparoscopic	10	35.7
Vascular resection		
Yes	1	3.6
No	27	96.4

plasm (MCN), pancreatic neuroendocrine tumor (PNET), cystic adenocarcinoma, and SPN. Accurate diagnosis is critical since malignant potential and management varies within this group (Figure 4; Lennon et al., 2014). Diagnostic workup should include cross-sectional imaging, like pancreas protocol CT or pancreatic MRI, and EUS (European Study Group on Cystic Tumours of the Pancreas, 2018). Typical radiographic appearance of SPN are large, encapsulated, heterogeneous masses in the pancreatic tail (Cantisani et al., 2003). All 28 patients in the study had preoperative cross-sectional imaging and had a similar incidence of SPNs located in the pancreatic tail (n = 13) and pancreatic head (n = 12). The majority of the SPNs in the study demonstrated a pseudocapsule (76%), which is the most commonly cited imaging feature. Intertumoral hemorrhage is a pathognomonic characteristic of SPN, yet hemorrhage was only identified in 3.4% of our cases. This may be due to the relatively low incidence of MRI imaging in our population (n = 4), which has a higher sensitivity and specificity for detecting blood products. Fine needle aspiration can be performed with EUS if diagnosis is unclear or diagnosis will change management. Cyst fluid can be sent for cytology and additional fluid studies, like fluid carcinoembryonic antigen and fluid lipase, if differentiating between mucinous and nonmucinous neoplasms. Nineteen patients in our study had a preoperative pathologic diagnosis (17 EUS with FNA, 2 CT-guided biopsy). Subtle morphologic differences and IHC can be helpful in distinguishing between neuroendocrine tumors, acinar cell carcinoma, and pancreatoblastoma (Hansen et al., 2019). None of the pediatric patients in our study underwent preoperative EUS

or biopsy. This may be related to the higher clinical suspicion of malignancy in the pediatric and adolescent population, and the lower likelihood of other benign pancreatic cystic neoplasms that would not require surgical resection.

The mainstay of treatment for SPN is aggressive surgical resection if technically possible and if the patient is fit for surgery (Del Chiaro et al., 2013). There is no current role for chemotherapy since no studies prove its efficacy. A minimally invasive approach should be considered for patients undergoing resection for SPN. All of our 28 patients underwent surgical resection with 64.3% open approach and 35.7% laparoscopic approach. There are reported similar outcomes with laparoscopic pancreatectomy compared with open pancreatectomy in patients with SPN, including length of surgery, complication rate, and length of stay (Stewart et al., 2016).

Solid pseudopapillary neoplasm is generally associated with excellent long-term prognosis if complete surgical resection is performed, with a reported 10-year disease specific survival rate of 96% (Estrella et al., 2014). They have low malignant potential of 10% to 15% but can metastasize to the liver and peritoneum. Patients with recurrence and metastases experience long-term survival similar to that of patients without metastases treated surgically (Jutric et al., 2017). In our series, all 28 patients had localized disease at diagnosis, and the majority

Table 4. Postoperative Outcomes (N = 28)

	n	%
Complication (N = 28)		
Yes	11	39.3
No	17	60.7
Complication type (N = 11)		
Pancreatic leak	4	36.4
Chyle leak	2	18.2
Abscess	2	18.2
Ileus	1	9.1
Other	2	18.2
Complication grade		
Grade 1	7	63.6
Grade 2	3	27.3
Grade 3	1	9.1
Grade 4	0	0
Grade 5	0	0

of patients had no lymph node metastases, while lymph node status was not reported in 6 patients. Prognostic criteria for SPN are not well defined in current literature. Some studies suggest male gender, younger age, larger tumor size > 5 cm, venous invasion, and advanced nuclear grade to be associated with malignant disease (Wright et al., 2020; Lee et al., 2008). Other studies suggest only unresectable tumor and metastases within 36 months as poor

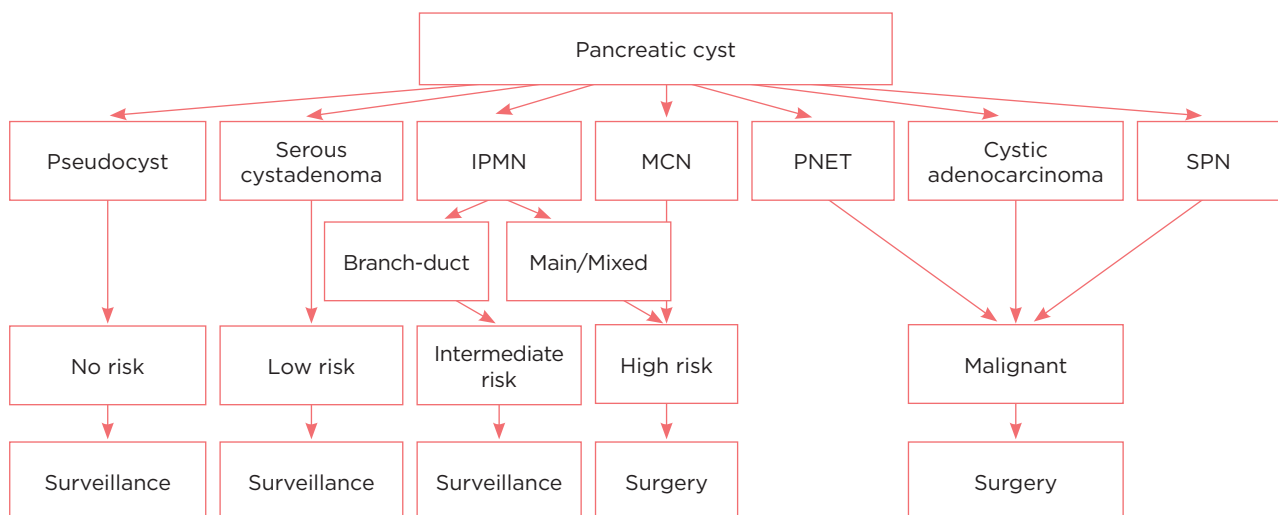


Figure 4. Pancreatic cyst risk stratification and management. IPMN = intraductal papillary mucinous neoplasm; MCN = mucinous cystic neoplasms; PNET = pancreatic neuroendocrine tumor; SPN = solid pseudopapillary neoplasm. Adapted from Lennon et al. (2014).

predictors of survival (Hao et al., 2018). Two patients in our study developed recurrence or metastases after initial resection (7.1%). After median follow-up of 41 months, excluding 2 patients who were lost to follow-up, all remaining 26 patients were alive without evidence of disease. There were no known deaths from SPN in our case series suggesting that these tumors generally have favorable prognosis.

There is no clear consensus in the literature regarding surveillance modality, interval, duration, or age-adjusted guidelines for SPN. The European Study Group on Cystic Tumours of the Pancreas advocates for yearly life-long follow-up with cross-sectional imaging as long as the patient is fit for surgery. Surveillance imaging modalities in our study included ultrasound, CT, and MRI, with varying intervals between 6 months, 12 months, and 2 years. Duration of surveillance also varied with most pediatric patients undergoing one follow-up imaging study, while most adult patients had imaging for a few years then stopped, and others who continue to have surveillance imaging presently. A cost-effective and personalized approach should be used in the development of a surveillance strategy. It is reasonable to perform life-long annual surveillance in fit patients with either pancreas protocol CT or pancreas MRI, depending on patient contraindications like kidney disease, body metal, or claustrophobia. If recurrence or metastases is detected, the lesions are technically resectable, and the patient is fit for surgery, these should be aggressively resected.

IMPLICATIONS FOR THE AP

Multidisciplinary clinics may be beneficial in the accurate diagnosis and management of pancreatic cystic neoplasms. A study from Johns Hopkins University showed that their multidisciplinary pancreatic cyst clinic resulted in altered management of 30.2% of patients (Lennon et al., 2014). Another study from the University of Colorado Hospital demonstrated their multidisciplinary clinic for pancreatic and biliary cancers resulted in 38% diagnosis change and 35% management change (Meguid et al., 2016). With increasing use of multidisciplinary clinics for diagnosis, treatment, and surveillance of pancreatic lesions, there is major potential for the AP role. Our institution developed a pancreatic cyst clinic in 2014 and currently utilizes a dedicated pancreatic cyst multidisciplinary clinic that is led by APs.

CONCLUSION

In summary, this is a large series of SPN published by a single institution spanning more than 10 years. The results confirm that SPN occurs mainly in young women. All patients were treated with resection with average morbidity and no postoperative mortality. The majority of patients were alive at last follow-up, a low percentage experienced disease recurrence, and zero experienced death from disease. A minimally invasive approach to resection could be considered for select patients at high-volume minimally invasive pancreatic surgery institutions. There is an opportunity for APs to lead multidisciplinary pancreas cyst clinics to ensure accurate diagnosis, management, and surveillance of pancreatic cysts, including SPN. Institutions should continue to publish their experiences to improve our collective knowledge and understanding of the pathophysiology of this rare disease. Through further meta-analysis, it may be possible to identify risk factors and attempt to predict which patients will develop malignant disease in the future. ●

Disclosure

The authors have no conflicts of interest to disclose.

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