

## Current perspectives on pancreatic serous cystic neoplasms: Diagnosis, management and beyond

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### Abstract

Pancreatic cystic neoplasms have been increasingly recognized recently. Comprising about 16% of all resected pancreatic cystic neoplasms, serous cystic neoplasms are uncommon benign lesions that are usually asymptomatic and found incidentally. Despite overall low risk of malignancy, these pancreatic cysts still generate anxiety, leading to intensive medical investigations with considerable financial cost to health care systems. This review discusses the general background of serous cystic neoplasms, including epidemiology and clinical characteristics, and provides an updated overview of diagnostic approaches based on clinical features, relevant imaging studies and new findings that are being discovered pertaining to diagnostic evaluation. We also concisely discuss and propose management strategies for better quality of life.

**Key words:** Pancreatic cystic neoplasm; Serous cystic neoplasm; Diagnosis; Management strategy; Surgery

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**Core tip:** Pancreatic cystic neoplasms (PCNs) have been more frequently recognized clinically in recent years and serous cystic neoplasms (SCNs) account for a large proportion of all PCN cases. Recent reviews have paid much attention to general aspects of PCNs and have discussed various subtypes of PCNs, but there is still a lack of comprehensive review exclusively focused on SCNs. This review attempts to provide a concise overview and outlook of pancreatic SCN and propose management strategies.

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## INTRODUCTION

Pancreatic cystic neoplasms (PCNs) are increasingly being recognized incidentally with widespread use of advanced imaging techniques, including computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). According to the most recent WHO classification<sup>[1]</sup>, PCNs comprise serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs) and solid pseudopapillary neoplasms (SPENs). SCNs account for nearly 16% of surgically resected PCNs and > 30% of all clinically diagnosed PCNs<sup>[2-4]</sup>, hence, they have become of concern and have posed a challenge to primary care clinicians and general practitioners. Not surprisingly, SCNs harbor some already known epidemiological characteristics. SCNs largely affect women (approximately 75% of all cases), and the mean age of patients who underwent pancreatic surgery for SCNs was 56 years in Europe, 58 years in Asia and 62 years in the United States<sup>[5,6]</sup>. SCNs tend to be larger if they occur in male patients<sup>[4]</sup>. In contrast with other premalignant or malignant PCNs (MCNs, IPMNs and SPENs), SCNs are usually benign, and the malignant variant serous cystadenocarcinoma is rare. To date, only approximately 30 cases of serous cystadenocarcinoma are reported in the literature<sup>[7]</sup>. Therefore, correct diagnosis is needed to avoid unnecessary surgical interventions and exclude other malignancies.

Morphologically, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic (< 10% of cases), mixed form (micro-macrocystic) and a solid variant form<sup>[8]</sup>. SCNs may arise in any part of the pancreas and occasionally can spread throughout the organ. The majority of SCNs are the microcystic lesions, which occur predominantly in the body and tail of the pancreas, whereas the oligocystic lesions normally arise from the head of the pancreas<sup>[9,10]</sup>. When multiple lesions are identified, Von Hippel-Lindau (VHL)-disease-associated pancreatic cysts should be taken into consideration<sup>[11]</sup>. VHL disease is a genetic disease, driven by mutation of the VHL tumor suppressor gene located on chromosome 3, which leads to development of several tumors, primarily hemangioblastoma of the central nervous system, retinal hemangioblastoma, renal cell carcinoma, adrenal pheochromocytoma and pancreatic tumors, mainly represented by pancreatic endocrine tumors and cystic tumors<sup>[12]</sup>. It is reported that SCNs are involved in 2.7%-9.5% of patients with VHL disease<sup>[13]</sup>.

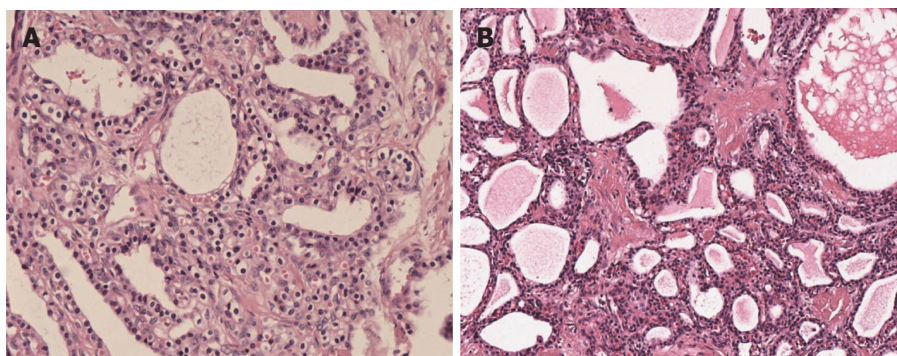
Histologically, SCN cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells<sup>[14]</sup> (Figure 1). The cytoplasm is

either clear or eosinophilic and the nuclei are normally centrally located, small and hyperchromatic; mitoses are not commonly found<sup>[15]</sup>. Although some controversy still exists, it is widely accepted that SCNs originate from the centroacinar cells<sup>[16]</sup>. They normally express cytokeratins AE1/AE3, CAM 5.2, CK7, CK8, CK18 and CK19, epithelial membrane antigen,  $\alpha$ -inhibin, and mucin 6<sup>[16,17]</sup>.

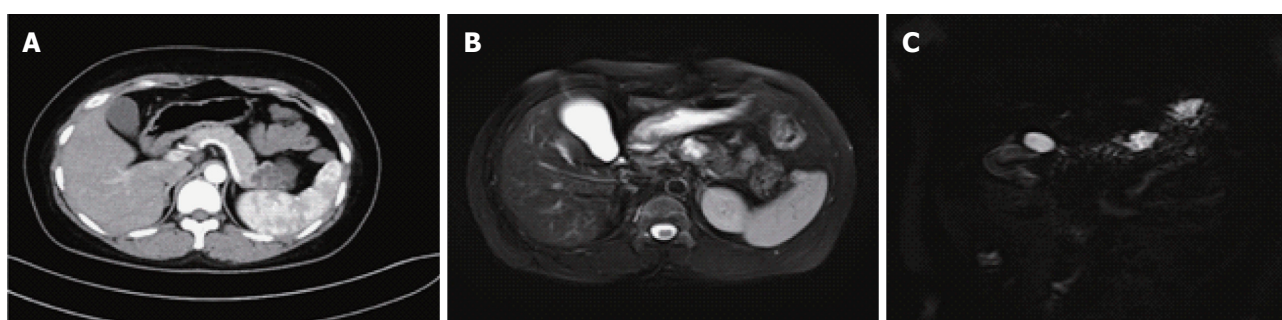
## CLINICAL PRESENTATION AND DIAGNOSIS OF SCN

According to a study led by Tseng *et al.*<sup>[4]</sup>, approximately 47% of patients with SCN were asymptomatic and diagnosed incidentally. As for symptoms, they are not specific and often attributed to mass effects or to infiltration of adjacent structures. Abdominal pain (25%), palpable mass (10%) and jaundice (7%) are the main clinical manifestations. It also has been shown that when lesions are > 4 cm, symptoms do occur more frequently if compared to lesions < 4 cm (72% vs 22%,  $P < 0.001$ )<sup>[4]</sup>, which is in line with several studies reported elsewhere<sup>[18,19]</sup>. A more recent multinational study of 2622 cases of SCN revealed that patients could present with nonspecific abdominal pain (27%), pancreaticobiliary symptoms (9%), diabetes mellitus (5%), or other symptoms (4%), with the remaining patients being asymptomatic (61%)<sup>[20]</sup>.

Given that SCNs are usually benign and asymptomatic, better surveillance and management strategies for these cysts call for accurate preoperative diagnosis. CT, MRI and EUS are three most commonly used imaging techniques for revealing SCNs. A recent study stated that the accuracy of preoperative diagnosis of PCN remains low, reaching approximately 60%, and in light of the exact diagnosis by pathology, surgical resection, most of which were Whipple resections, should not have been performed in approximately 8% of patients<sup>[21]</sup>. In another study cohort, 9% of PCN patients underwent pancreatic resection for a non-neoplastic condition<sup>[22]</sup>, which further demonstrated the difficulty in differentiation between benign and premalignant lesions and that better preoperative diagnosis is urgently needed. Pancreatic cysts are readily identified in up to 20% of MRI studies, and 3% of CT scans<sup>[23,24]</sup>. Both CT and MRI predict the presence of malignancy in pancreatic cysts with 73%-79% accuracy<sup>[25]</sup>. In addition to routine radiological studies, EUS has emerged as a useful tool because it provides high-resolution imaging of the pancreas through the lumen of the stomach or duodenum and helps obtain detailed information of the cystic lesions, such as wall, margins, internal structures and parenchyma<sup>[26,27]</sup>. In a recent prospective cross-sectional study of the prevalence of incidental pancreatic cysts during routine outpatient EUS, the prevalence of incidental pancreatic cyst was 9.4% and most were < 1 cm<sup>[28]</sup>. The accuracy of EUS to differentiate benign from malignant neoplastic tumors and from non-neoplastic



**Figure 1** Pathological examinations revealing that serous cystic neoplasm cystic walls are lined with cubic flat epithelia consisting of glycogen-rich, watery-fluid-producing cells (hematoxylin and eosin  $\times 100$  ). A: Pathology of a microcystic SCN of the pancreas; B: Pathology of a macrocystic SCN of the pancreas. SCN: Serous cystic neoplasm.



**Figure 2** Microcystic pancreatic serous cystic neoplasm presentation on computed tomography/magnetic resonance imaging. A: A microcystic pancreatic SCN lesion was revealed in the tail of the pancreas; B: MRI showed a microcystic lesion in the body of pancreas; C: A microcystic SCN lesion was revealed by magnetic resonance cholangiopancreatography. Images B and C came from the same patient. SCN: Serous cystic neoplasm; MRI: Magnetic resonance imaging.

cysts remains debatable. Some studies have stated an accuracy of  $> 90\%$ , while others have expressed doubt, especially when there is a lack of evidence of a solid mass or invasive tumor<sup>[29-31]</sup>. Despite this debate, another major advantage of EUS is its ability to collect fluid from cystic lesions *via* fine-needle aspiration (FNA) for cytological and biochemical analysis, such as carcinoembryonic antigen (CEA), amylase, and *KRAS* mutations<sup>[32]</sup>.

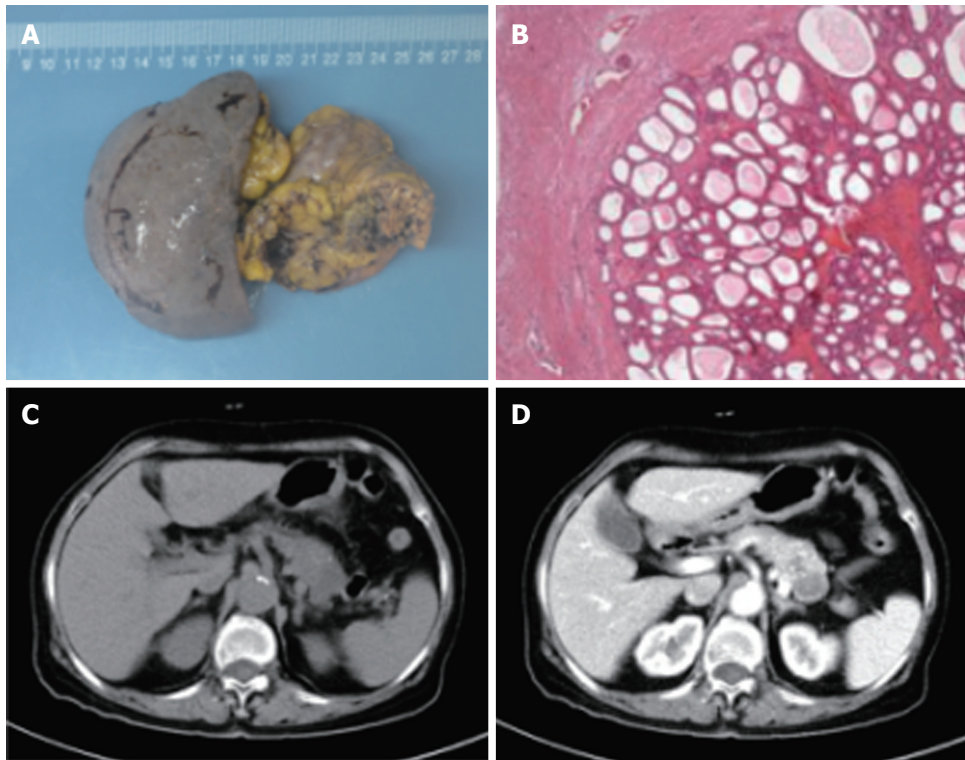
Compared to other cystic neoplasms, accurate preoperative diagnosis of SCNs seems more feasible. As mentioned before, SCNs can be divided into four subtypes: Microcystic, macrocystic or oligocystic ( $< 10\%$  of cases), mixed form (micro-macrocystic) and solid variant form<sup>[8]</sup>. VHL-disease-associated pancreatic cysts should be considered when other cystic lesions exist. A Japanese multicenter study of 172 SCNs diagnosed by resection and typical imaging findings noted highest diagnostic accuracy for microcystic SCN (85%), with lower diagnostic rates (17%-50%) for macrocystic and mixed types. CT alone is approximately 23% accurate at diagnosing SCN<sup>[33]</sup>. Diffusion-weighted MRI has proved to be a powerful tool with 100% sensitivity and 97% specificity for differentiating mucinous cysts from SCNs<sup>[34]</sup>. The pathognomonic central scar, which is formed by central coalescence of the septa and commonly contains foci of calcification on imaging, is present in only approximately 30% of these

cysts<sup>[35]</sup>.

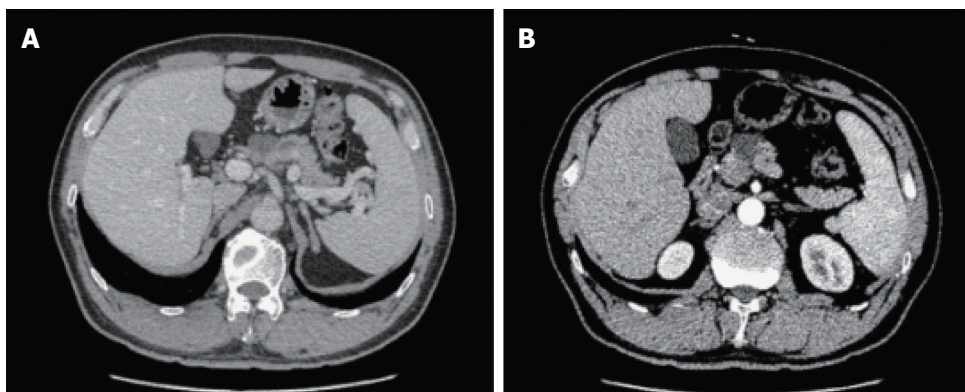
On CT/MRI, microcystic SCN typically appears as an isolated, lobulated, well-marginated, multilocular lesion, comprising a cluster of multiple (usually  $> 6$ ) small cysts separated by a thin septum<sup>[26,36]</sup> (Figure 2). Each of the small cysts is usually  $< 2$  cm<sup>[37]</sup>. Occasionally, the "honeycomb" pattern, characterized by numerous, sub-centimeter cysts appears as a solid mass on CT (Figure 3), but has high signal intensity when T2-weighted MRI is applied<sup>[37]</sup>. Macrocystic SCN is characterized by a limited number of cysts, usually  $< 6$ , showing a diameter  $> 2$  cm, or even one single cyst<sup>[38]</sup> (Figure 4). This subtype can be seen in approximately 10% of all cases of SCN but poses difficulty for differentiating it from MCN and branch-duct (BD)-IPMN, based on the findings of CT or MRI<sup>[39]</sup>. In addition, if a patient has a reported history of pancreatitis, pseudocyst should be considered<sup>[40]</sup>. The mixed micro-macrocystic type is depicted as a combination of the above two types of lesions. As for the solid variant, it consists of small cysts separated by multiple, thick fibrous septa<sup>[41]</sup>. VHL-disease-associated pancreatic cysts, which can occur in 50%-80% of the patients with VHL disease, and are occasionally misdiagnosed as macrocystic SCNs, tend to form multiple lesions and are even diffuse throughout the pancreas<sup>[42,43]</sup>.

Generally, microcystic SCNs on EUS are imaged as numerous ( $> 6$ ) small ( $< 1-2$  cm) fluid-filled cysts with





**Figure 3 Solid variant microcystic serous cystic neoplasm with honeycomb characteristics.** A: Gross pathology of a solid variant microcystic SCN; B: Histology of solid variant microcystic SCN; C: Solid variant lesion was detected by CT; D: Solid variant lesion was detected by contrast-enhanced CT. These four images were acquired from the same patient. SCN: Serous cystic neoplasm; CT: Computed tomography.



**Figure 4** A macrocystic pancreatic serous cystic neoplasm was detected on computed tomography with (B) and without enhancement (A).

thin-walled septa and possibly calcification of the central septum<sup>[44,45]</sup> (Figure 5). The honeycomb variants are interspersed within dense fibrous septa, with or without central fibrosis or calcification<sup>[46,47]</sup>. The less common oligocystic SCNs usually contain larger (> 2 cm) cysts<sup>[48]</sup>. However, the solid variant, which is defined when lesions are predominantly solid (< 10% cystic portion) and might resemble a ductal carcinoma on CT, contains numerous tiny cysts (1-2 mm) and appears as a hypoechoic mass on EUS<sup>[49]</sup>.

Management and surveillance of SCNs depend on correct preoperative diagnosis. One major concern is potential misdiagnosis of a malignancy or premalignancy as a benign SCN, which was more frequent in the past;

it was reported in seven of 28 patients in one study and in two of 49 patients in another<sup>[50,51]</sup>. Among SCNs, macrocystic SCNs are frequently undistinguishable from MCNs and BD-IPMNs. BD-IPMNs may also present in a polycystic pattern, similar to microcystic SCNs<sup>[52]</sup>. Typically, unlike IPMNs, SCNs are characterized by lack of communication with the main pancreatic duct. However, the absence of communication does not allow for the exclusion of IPMN, although this absence may favor the diagnosis of MCN over SCN<sup>[53,54]</sup>. In contrast to MCNs, which usually exhibit a smooth oval shape and varied signal intensity (depending on the fluid viscosity of each lobule), macrocystic SCNs typically present with a thin wall and lobulated contours and can be

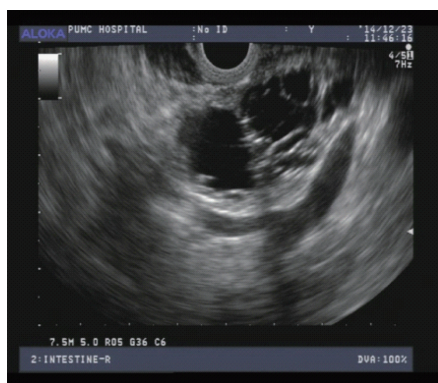


Figure 5 A microcystic pancreatic serous cystic neoplasm was discovered by endoscopic ultrasonography.

found in the head of the pancreas<sup>[55]</sup>. A central calcified scar is virtually pathognomonic for SCNs (Figure 6), whereas peripheral calcifications are frequently observed in MCNs<sup>[56]</sup>. Many solid variant SCNs show arterial hypervascularity on imaging studies and are frequently misdiagnosed as pancreatic neuroendocrine tumors (pNETs)<sup>[57-59]</sup>. A recent study found that the frequency of hypervascular solid-appearing SCNs was 7.3% among surgically confirmed SCNs and unenhanced CT and MR features can help to differentiate solid variant SCNs from pNETs<sup>[60]</sup>.

Despite various potential complications of EUS-FNA, such as bleeding caused by injury of the subepithelial vascular plexus of SCNs, pancreatitis, infection, and even the seeding of malignant cells along the tract of the needle have been suggested<sup>[61-63]</sup>, EUS-FNA-related morbidity and mortality rates have remained low<sup>[64]</sup> and the widespread use of EUS-FNA has yielded a wealth of information for cytological, chemical and molecular analysis of SCNs.

A 22- or 25-gauge needle is often used when aspirating cyst fluid during EUS-FNA. SCNs usually contain little fluid and the fluid usually contains few cellular components, and FNA cytological analysis has an unreliable sensitivity of only 30%-40%<sup>[65]</sup>. For chemical analysis, assessment of tumor markers such as CEA, carbohydrate antigen (CA)19-9, CA15-3, CA72-4, and enzymes like amylase and lipase is often carried out, although it has proved of limited diagnostic value<sup>[66]</sup>. Fluid from SCNs universally has low CEA levels. A level < 5 ng/mL is 95% specific for SCN, pseudocyst or pNET<sup>[67]</sup>. However, an elevated CEA level favors a mucinous lesion, although the exact cut-off level is still in debate. It is also important to mention that the CEA threshold varies in different centers, ranging from 5 ng/mL to > 100 ng/mL<sup>[68]</sup>. When a classic CEA cut-off level of 192 ng/mL is applied, it yields 73% sensitivity and 84% specificity for mucinous cysts<sup>[69]</sup>. An amylase level < 250 U/L favors diagnosis of SCN over pseudocyst, with a sensitivity of 44%, specificity of 98% and overall accuracy of 65%<sup>[68]</sup>. Other than CEA and amylase, recent studies have revealed that levels of cystic fluid

metabolites glucose and kynurenine are markedly elevated in SCNs compared to MCNs, which aids the diagnosis of SCNs<sup>[70,71]</sup>. Although large prospective studies are warranted to validate these promising results, they shed light on a new path to seek better biomarkers. Molecular analysis of cystic fluid has gained in interest in recent years, in parallel with the advent of new techniques on sequencing. DNA analysis of KRAS mutations may help identify mucinous cysts with 54% sensitivity and 100% specificity, as demonstrated in a study containing 142 surgically resected cysts. When CEA and KRAS analysis were collectively applied, the sensitivity climbed to 83% while the specificity dropped to 85%<sup>[72]</sup>. More interestingly, data from whole-exome sequencing of PCNs revealed that the application of a panel of five genes (*VHL*, *RNF43*, *KRAS*, *GNAS* and *CTNNB1*) allowed correct distinction of mucinous from nonmucinous cysts. All eight SCNs had intragenic mutations of *VHL* or loss of heterozygosity in or adjacent to *VHL* and did not contain mutations of the other four genes. Furthermore, point mutations of *VHL* gene were detected in cystic fluid analysis in half of the SCNs. Nevertheless, IPMNs had alterations of *RNF43*, *GNAS* or *KRAS* and never had *VHL* or *CTNNB1* mutations. MCNs always harbored *KRAS* or *RNF43* mutations but never contained *GNAS*, *CTNNB1* or *VHL* mutations<sup>[73]</sup>. Another study stated that *GNAS* mutations were present in 10% of their cases of SCN, which was still significantly lower than in IPMNs<sup>[74]</sup>. Thereafter, the identification of *GNAS* mutation may help discrimination of SCN from IPMN. Another mainstay of research of cystic molecular analysis gives insights into miRNAs. A panel of four miRNAs comprised miR-31-5p, miR-483-5p, miR-99a-5p and miR-375 has been developed to differentiate SCNs accurately from mucinous lesions, with 90% sensitivity and 100% specificity<sup>[75]</sup>. While promising, these results were based on surgically archived specimens but not on cystic fluid, therefore, validation in cystic fluid samples should be addressed in future studies to fit these findings better in preoperative scenarios.

## MANAGEMENT AND INTERVENTION

### STRATEGY FOR SCNs

As mentioned before, most SCNs follow a benign course and malignant SCNs (serous cystadenocarcinoma) are rare (< 1% of all cases). According to an investigation of 193 SCNs, along with a literature review, the clinicopathological characteristics of solid and macrocystic SCN variants are similar to those of their microcystic counterpart, and there are no deaths that are directly attributable to dissemination/malignant behavior of SCNs<sup>[76]</sup>. It is also recommended to consider and manage SCNs as benign neoplasms initially<sup>[77]</sup>. For this reason, correct preoperative diagnosis of SCNs could spare many unnecessary interventions and guide optimal management strategies. Currently, there



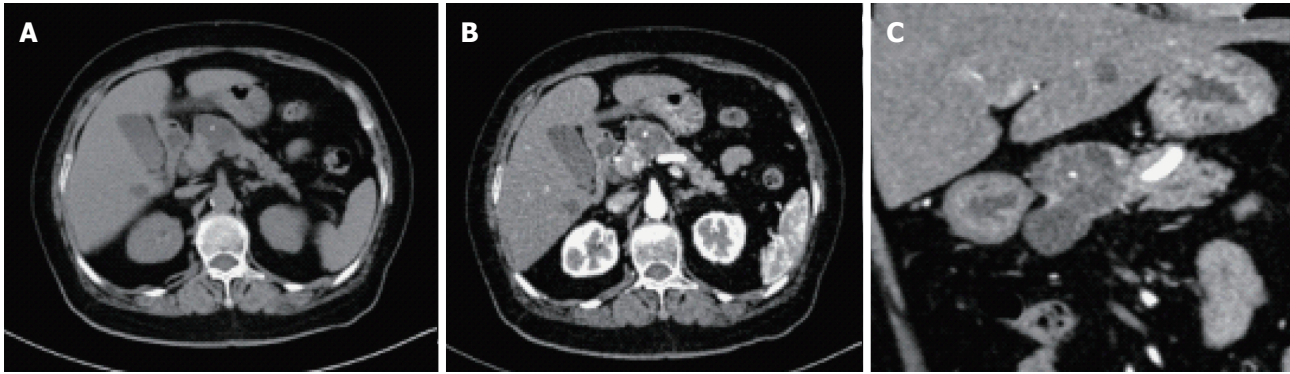


Figure 6 Central calcifications were found by computed tomography with and without enhancement (A and B), and also shown after three dimensional reconstruction (C).

is no universal consensus on the best management strategy, but it is widely accepted that not every single case should be surgically resected, regardless of how advanced surgical technology has been developed, and symptomatic, local invasive or potential malignant SCNs should be resected<sup>[37,54,78]</sup>. It is also advised that resection should be considered for large (> 4 cm), rapidly growing SCNs, given that such SCNs are more likely to cause symptoms<sup>[4,33]</sup>. However, it is difficult for a clinician to predict whether and when an incidentally found asymptomatic SCN will grow to cause symptoms. One older study claimed that a more rapid growth rate of approximately 1.98 cm/year was observed in cysts > 4 cm, whereas the growth rate was approximately 0.12 cm/year in cysts < 4 cm<sup>[4]</sup>. A more recent multicenter study failed to confirm those results. In that same study, a rate of growth of 6.2% per year or a doubling time of 12 years was calculated for the nonresected SCNs, while resected SCNs grew faster (17% per year for a doubling time of 4.5 years)<sup>[18]</sup>. In addition, there is also a paucity of knowledge about the relationship between growth rate and potential malignancy<sup>[7]</sup>. Obviously, symptoms do occur when fast-growing SCNs are left unresected<sup>[79]</sup>. It is tempting to conclude that initial size is neither associated with malignant transformation, nor proportionally related to developing symptoms. However, growth rate is more powerful to predict if and when the symptoms occur. Thus, the growth rate should be weighed when considering if an SCN should be subjected to surgical intervention. One multinational study stated that, in patients followed beyond 1 year ( $n = 1271$ ), size increased in 37% (growth rate: 4 mm/year), was stable in 57%, and decreased in 6%, hence, surgical treatment should be proposed only in cases in which diagnosis remains uncertain after complete work-up<sup>[20]</sup>.

Surgery is considered curative. Despite increasing experience and advanced surgical techniques, pancreatic surgery holds a perioperative morbidity of 15%-30% and a mortality rate of 1%-2%, even in high-volume centers<sup>[3]</sup>. The indications for surgical intervention are as follows: (1) presence of symptoms; (2) Uncertain diagnosis. MCNs and IPMNs can mimic SCNs

on radiology scans, especially macrocytic SCNs. When premalignant MCNs and IPMNs cannot be excluded, the lesions can be managed as IPMNs when the cysts are < 4 cm<sup>[80]</sup> and are advised to be surgically removed accordingly following the International consensus in 2012 and the European consensus in 2013<sup>[81,82]</sup>, and (3) growth rate of the neoplasm. As discussed above, large SCNs are not correlated with an increased risk of malignancy. Also, growth rate is not linked with initial size. The notion that any cyst > 4 cm or even > 5 cm be resected should be abandoned. In this regard, clinicians need to remain cautious when neoplasms grow rapidly, and make decisions on a case-by-case basis, including patient's age, comorbidity and tumor location. Large SCNs can always be closely observed first and then sent for surgery once they grow faster and cause unrelieved symptoms.

From an anatomical point of view, surgical resection of an SCN largely depends on the location of the lesion. As a result of the benign nature of SCN, as a general rule, it is recommended that pancreatic functions are protected and preserved as much as possible for better outcome and quality of life. If SCNs are localized in the pancreatic head, pylorus-preserving pancreatoduodenectomy or Begar procedure is often carried out. If SCNs are located in the body or tail of the pancreas, spleen-preserving distal pancreatectomy should be the first choice. For patients whose SCNs are located in the neck of the pancreas, central segmental pancreatectomy is an alternative procedure, preserving islet cell mass and reducing the risk of iatrogenic insulin-dependent diabetes. Enucleation is not recommended because greater morbidity (up to 35%) and associated complications such as pancreatic fistula<sup>[83]</sup> have been reported.

As mentioned above, clinicians are encouraged to manage SCNs in a conservative manner, which means that, initially, these lesions do not require surgery but serial follow-up when radiological diagnosis is certain and symptoms are absent. However, to date, the best follow-up strategy has not been standardized. Some advocate follow-up imaging every 12 mo, while others suggest biennial surveillance<sup>[84,85]</sup>. The European con-

sensus in 2013 suggests that asymptomatic nonresected patients should enter a follow-up program, initially repeated after 3-6 mo, and then individualized depending on growth rate<sup>[81]</sup>. Once SCNs are resected, no further surveillance imaging is needed.

## CONCLUSION AND FUTURE DIRECTIONS

Comprising about 16% of all resected PCNs, SCNs are uncommon benign lesions that are asymptomatic and found incidentally. Despite overall low risk of malignancy, the presence of these pancreatic cysts still generates anxiety, leading to extensive medical investigation with considerable financial cost to health care systems. CT and MRI alone are not powerful enough to characterize cystic pancreatic lesions fully, and more specifically, to differentiate macrocystic SCNs from MCNs. However, EUS, with or without addition of FNA, adds more diagnostic value to conventional imaging techniques. CEA, although not perfect, plays a role in differentiating pancreatic cystic lesions. New cystic fluid markers from chemical and molecular analyses are just beginning to emerge, paving a new way to future research. As for treatment and management strategy, surgery should be limited only to symptomatic SCNs and lesions that show aggressive behavior, while the majority of patients should be strictly monitored and followed up by serial imaging. Further investigations on best follow-up strategy are warranted. Patients would benefit from multidisciplinary management and receive precise medical advice once gastroenterology, surgery, pathology and radiology are all involved in individual patient care as a team. As such, patient care based on a multidisciplinary team is encouraged if applicable.

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