EXPERT REVIEWS

Management of serous cystic neoplasms of the pancreas

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Pancreatic serous cystadenomas are uncommon benign tumours that are often found incidentally on routine imaging examinations. Radiological imaging techniques alone have proven to be suboptimal to fully characterize cystic pancreatic lesions. Endoscopic ultrasound, with the addition of fine-needle aspiration in difficult cases, has showed greater diagnostic accuracy than conventional imaging techniques. The best management strategy of these neoplasms is still debated. Surgery should be limited only to symptomatic and highly selected cases and most of the patients should only be strictly monitored. In the current paper, we provide an updated overview on pancreatic serous cystadenomas, focusing our attention on epidemiology, clinical characteristics and diagnostic evaluation; finally, we also discuss different management strategies and areas for future research.

KEYWORDS: confocal laser endomicroscopy • endoscopic ultrasound • fine-needle aspiration • metabolomic analysis • mucinous cystic neoplasms • pancreatic cysts • serous cystadenocarcinoma • serous cystadenoma • surgery

The prevalence of pancreatic cysts in subjects without a history of pancreatic disease, based on imaging techniques, amounts to about 2.5% and tends to substantially increase with age, rising to 8% in the elderly [1,2]. Pancreatic cysts include both neoplastic and non-neoplastic lesions and, according to the most recent WHO classification [3], serous cystic neoplasms belong to pancreatic cystic neoplasms, together with mucinous cystic neoplasms, intraductal papillary mucinous neoplasms (IPMNs) and solid pseudopapillary neoplasms. Serous cystic neoplasms are almost exclusively constituted by serous cystadenomas (SCAs), with only sporadic cases of malignancy reported [4,5]. SCAs being benign lesions, a correct diagnosis is mandatory to avoid unnecessary pancreatic surgery and exclude malignant disease. Although in most cases clinical and radiological characteristics allow to correctly differentiate SCAs from other lesions, several common traits with other types of potentially malignant cystic lesions can induce misleading diagnosis.

We provide an updated overview on pancreatic serous cystic neoplasms, focusing our attention on epidemiology, clinical characteristics and diagnostic evaluation; furthermore, we will discuss management strategies and areas for future research.

Definition & epidemiology

First described by Compagno and Oertel in 1978 [6], serous cystic neoplasms are epithelial tumors of unknown origin, sharing some morphologic and immunohistochemical features with centroacinar and ductular cells of the pancreas. Small cuboidal cells with clear cytoplasm, producing a watery fluid similar to serum, line the cystic wall (FIGURES 1 & 2). This epithelium is glycogen-rich and does not express mucin production. Serous cystic neoplasms are uncommon tumors that comprise about 16% of all resected cystic tumors of the pancreas, based on large surgical series [7]. Approximately 60–75% of SCAs affect women [8–12], while the mean age of patients who underwent pancreatic surgery for SCAs was 56 years in European series [11], 58 years in Asian series [8] and 62 years in USA series [10].

Serous cystic neoplasms may generate in any portion of the pancreas but predominantly in the head of the gland (40–50%). In rare cases, serous cystic neoplasms can spread over the entire pancreas. The diameter of the tumor ranges from a few centimeters to more than 20 cm, with mean size of 4–5 cm on surgical series [8,10,11].

Nowadays, about 30 cases of the malignant variant, the so-called serous cystadenocarcinoma, have been reported in literature since

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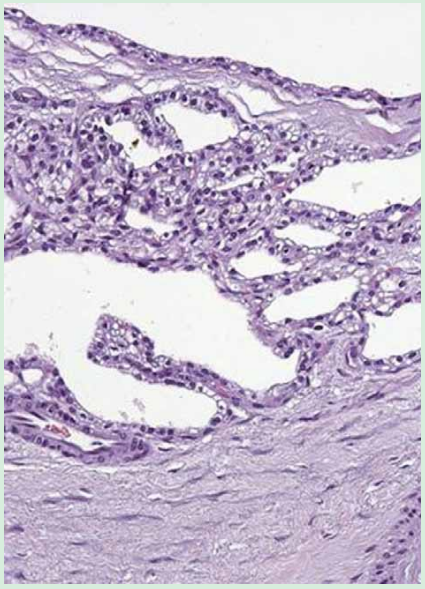

Figure 1. At high-power cuboidal cells, with monomorphic nuclei and clear cytoplasm, lining the cyst (H&E, 100X).

the first described case in 1989 [13]. Serous cystadenocarcinoma is defined by the WHO as a SCA that presents metastases or invasion of adjacent organs [3]. Several characteristics such as predominance with female gender (60%), older age of patients when first detected and larger mean diameter (usually >10 cm) suggest that this variant can acquire malignant potential while growing [14,15].

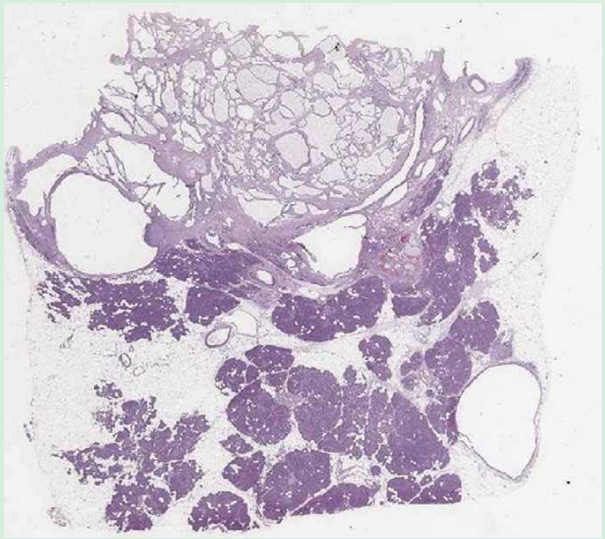

Figure 2. Whole-mount microphotograph showing a lesion composed of multiple cysts of various sizes and surrounded by unremarkable pancreatic parenchyma (H&E, 20X, whole-mount).

Clinical presentation

About half of SCAs are asymptomatic and are found incidentally on radiologic examinations performed for other unrelated reasons [16]. When symptoms do occur, they are not specific and usually related to mass effect or, in case of malignancy, to infiltration of adjacent structures [12,17]. Abdominal pain or discomfort, palpable mass and weight loss are the most common manifestations [12]. Jaundice, due to bile duct compression, is infrequent [18]. A recently published multinational, retrospective study including 598 patients with a diagnosis of SCA showed that nonspecific abdominal pain was reported in 29% of cases, diabetes mellitus in 7% of patients and, finally, bilio-pancreatic symptoms, including typical pancreatic pain, acute pancreatitis, jaundice and steatorrhoea in 7% of cases [19]. Tumor rupture, hemoperitoneum and acute surgical abdomen have also been described [20,21].

Conversely, all cases of serous cystadenocarcinoma showed clear symptoms, generally due to the local invasion of adjacent organs (spleen, stomach, small intestine, adrenal gland, vascular and neural tissues), and metastases (liver, bone marrow, lung and lymph nodes) [4].

Von Hippel–Lindau disease & serous cystic lesions

Von Hippel–Lindau (VHL) disease is an autosomic genetic disease, inherited in a dominant manner with a high penetrance with new mutations accounting for 20% of cases [22]. VHL disease is caused by genetic mutation of the *VHL* tumor suppressor gene located in the short arm of chromosome 3, and its alteration results in the impairment of hypoxia-inducible factor degradation; therefore, angiogenic and growth factors are overexpressed. VHL is characterized by the development of several tumors, primarily hemangioblastoma of the central nervous system, retinal hemangioblastomas, renal cell carcinoma, adrenal pheochromocytoma and also pancreatic tumors, mainly represented by pancreatic endocrine tumors and cystic tumors [23].

The frequency of pancreatic involvement in VHL patients varied from 17 to 77.2% and SCAs were overall reported in about 2.7–9.5% of patients with VHL [24,25]. The cysts found in VHL syndrome are virtually identical to sporadic SCAs, apart from their diffuse distribution in the pancreas instead of a single well-defined lesion. SCAs are generally diagnosed at a young age (25 years) and have a benign course, as do simple cysts, since only 2.5% of SCAs tend to become symptomatic over the years [24]. There are at least two ways in which *VHL* mutations might stimulate SCA formation. First, the development of a rich capillary network within SCAs could alter local hemodynamics, thus inducing the production of cyst fluid [26]. A second way involves the stabilization of microtubules and the absence of primary cilia [27–29]. Notably, all the sporadic cases of SCA had intra-genic mutations of *VHL* or loss of heterozygosity in or adjacent to *VHL* gene, thus strongly suggesting a pivotal role of this gene in the pathogenesis of SCA [30].

Diagnostic evaluation

The most common diagnostic examinations used for evaluating pancreatic cystic lesions include computed tomography (CT), MRI and endoscopic ultrasound (EUS). Despite the advances in imaging techniques, the accuracy of the preoperative diagnosis of pancreatic cystic tumor is still low, reaching about 60% even in tertiary referral centers for pancreatic surgery [31]. Several imaging features are helpful for the differential diagnosis of pancreatic cystic lesions: presence of septa (unilocular, multilocular), dimension of internal cysts (microcystic if <2 cm, or macrocystic), aspect of the wall (thin if <2 mm, or thick) and margins (smooth or lobulated) [32,33]. Typically, SCA appeared as an isolated, lobulated, well-marginated, multilocular, microcystic lesion (Figures 3–5). These features define the 'honeycomb' or 'sponge' aspect, characterized by the presence of numerous (usually >6) small cystic spaces (2–3 mm of diameter) separated by a thin septa [32,34,35]. In less than 20% of cases, the septa may centrally coalesce into a characteristic 'stellate scar' with or without calcification itself, which is considered to be pathognomonic for SCA (Figure 6). In 10–30% of cases, calcifications within the septa are also seen. Differently from IPMNs, serous cystic neoplasms are characterized by the lack of any connection to the pancreatic ductal system.

In addition to the microcystic typical aspect, other three morphologic variants have been described: the macrocystic or oligocystic type, characterized by fewer and larger cysts (>2 cm) or even by one single cyst (unilocular) (Figures 7 & 8); the mixed micro-macrocystic type (Figure 9) and, finally, the solid type, consisting in very small cysts with multiple, thick fibrous septa (Figure 10) [28,32,36]. The oligo-macrocystic pattern is observed in about 10% of patients with serous cystic lesions and is more difficult to differentiate from other cystic lesions, mainly mucinous cystic neoplasms and pseudocysts [36,37]. In contrast to mucinous cystic neoplasms, a macrocystic SCA typically presents a thin wall and lobulated contours and can be found in the head of the pancreas [37,38]. Moreover, the cysts observed in SCAs usually display a clear fluid with rare examples of heterogeneous content, which is otherwise typical of pseudocysts [32].

EUS & fine needle aspiration

When morphologic features reported by radiological imaging techniques (CT and/or MRI) are insufficient to differentiate cystic lesions, EUS can provide further, additional and useful information (Figures 6–10) [39]. Indeed, EUS provides high-resolution images over a short distance to the pancreas, accurately showing every cystic element, such as wall, margins and internal structures, as well as detailed images of the parenchyma [34]. EUS can be useful to identify the presence of a communication between the cyst and the pancreatic duct, thus leading to a more reliable diagnosis of side-branch IPMN rather than SCA. In addition, EUS-guided fine-needle aspiration (FNA) allows cytological and biochemical analyses of the cystic fluid (Figure 8). It has been recently showed, in a cohort of 154 patients, that EUS with or without FNA was superior to CT alone in accurately classifying a cyst as neoplastic (76 vs 48%; $p < 0.0001$); similarly, it was also more likely to be correct than MRI alone for prediction of neoplasia (76 vs 34%; $p < 0.0001$) [39]. Overall, the increase in diagnostic yield of EUS and fluid analysis over CT and MRI for prediction of a neoplastic cyst was 36 and 54%, respectively [39]. In 2004, O'Toole *et al.* compared the EUS characteristics of mucinous cystadenoma and macrocystic SCA [40]. The comparison revealed that a thickened cyst wall (≥3 mm) and a cystic echo pattern suggesting thick content were significantly associated with the mucinous cystadenoma, while microcysts, located either peripherally or internally along intracystic septations, were more frequently observed in macrocystic SCAs [40].

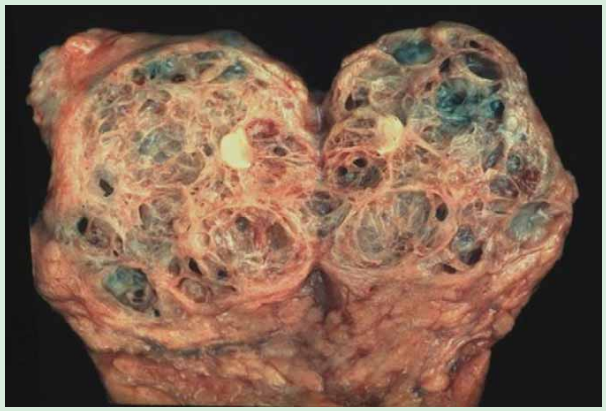

Figure 3. Gross photograph of the pancreatic tail which shows, on sectioning, a multicystic lesion with a central calcification.

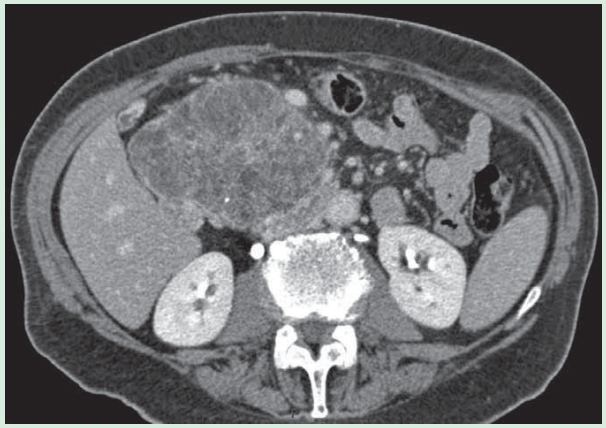

Figure 4. Microcystic serous cystic neoplasm in a 78-year-old woman with right upper-quadrant pain.
Contrast-enhanced computed tomography image demonstrated a multiseptaded lobulated cystic lesion in the pancreatic head and uncinate process.

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Figure 5. Microcystic serous cystic neoplasm in a 76-year-old asymptomatic woman. Magnetic resonance colangiopancreatographic image demonstrated a multicystic lesion in the pancreatic head without communication with the main pancreatic duct.

Recent evolution of transducers and ultrasound equipment has allowed the harmonics contrast-enhanced assessment. A retrospective study of the preliminary experience with contrast-enhanced EUS found a correlation between the color-enhanced pattern and the pancreatic pathology [41]. Indeed, all of the cases of SCA presented the color signals filling microcystic regions; unfortunately the small sample did not allow any definitive conclusion [41]. To date, comparative studies that evaluated the clinical utility of contrast-enhanced EUS in the differential diagnosis of pancreatic cystic lesions are lacking; however, the role of this technique seems of limited value.

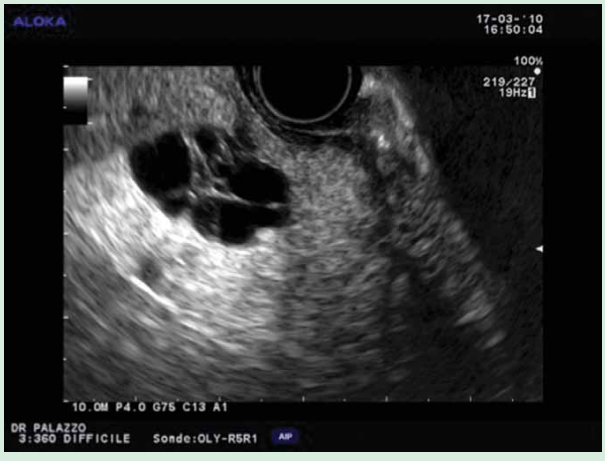

Figure 6. Typical aspect of serous cystadenoma at endoscopic ultrasound with 'central star' and microcysts within the star and the septa.

When morphological features alone are unhelpful to fully characterize the cyst, FNA should be performed at the time of EUS and cyst fluid aspiration analyzed. Fluid aspirated from SCAs is usually watery; conversely in mucinous cystic neoplasms it is typically viscous and muddy-brown in pseudocysts. Otherwise when the EUS-based morphology is highly suggestive of SCA, FNA and cystic fluid analyses are not recommended.

Cyst fluid analyses

In 2005, a pooled analysis of 12 studies, including 450 patients, investigated the value of cyst fluid analysis in the differential diagnosis of benign (SCA and pseudocyst) versus premalignant or malignant (mucinous cystadenoma and mucinous cystadenocarcinoma) lesions [42]. Level of amylase <250 U/l allowed to virtually exclude pseudocyst and suggested a diagnosis of SCA, mucinous cystadenoma or mucinous cystadenocarcinoma, with a sensitivity of 44%, a specificity of 98% and an overall accuracy of 65% [42].

Carcinoembryonic antigen (CEA) is the most accurate test available to differentiate pancreatic cystic lesions. Indeed, the positive and negative predictive values of SCA or pseudocyst when the cut-off value is set at CEA <5 ng/ml are 94 and 56%, respectively, with an accuracy of 70%. A cut-off value set at a higher level (>800 ng/ml) allows to distinguish mucinous cystadenoma and mucinous cystoadenocarcinoma from benign lesions, with a 98% positive predictive, 77% negative predictive and an overall accuracy of 81% [42]. In the Co-operative Pancreatic Cyst Study, Brugge *et al.* [43] evaluated 341 patients and found that a cut-off value for CEA of 192 ng/ml had the highest accuracy (79%) for differentiating between mucinous and non-mucinous cysts, with moderate sensitivity (73%) and specificity (84%). Furthermore, the diagnostic accuracy of CEA analysis was significantly greater than the accuracy of EUS morphology alone (51%) [43]. Conversely, CA 19-9 has showed discouraging results; in the pooled analysis of van der Waaij *et al.* [42], CA 19-9 below the cut-off value of 37 U/ml allowed the distinction between mucinous and non-mucinous cysts with an overall low diagnostic accuracy (46%) and an unsatisfactory sensitivity (14%).

Despite the wide use of EUS-FNA of pancreatic cystic lesions, the results of cytological analysis are somewhat disappointing [44,45]. Small amounts of cells in the aspirated fluid, patchy epithelial lining of cysts, variable levels of expertise among cytopathologists, contaminating gastrointestinal epithelium all contribute to reduce the accuracy of this procedure [46–48]. One of the largest series of SCAs of the pancreas subjected exclusively to EUS-FNA and surgical resection confirmation showed that almost all of the cases presented hypocellular aspirate smears, with some degree of cellularity with bland cuboidal epithelial cells and granular debris [49]. Cell-blocks are rarely helpful, since in almost all of the cases they do not contain cells of interest [49]. A definite diagnosis of SCA can be suspected on the presence of characteristic

glycogen-rich cuboidal cells, but this finding is described in less than 20% of cases. Therefore, cytological examination of the cyst fluid is often non-diagnostic [49]. A recently published meta-analysis, including a total of 18 retrospective and prospective studies, evaluated the accuracy of EUS-FNA for the diagnosis of pancreatic cystic neoplasms and found that cytology has a moderate pooled sensitivity of 54% and a high pooled specificity of 93% [50]. Notably, in all reported cases of serous cystadenocarcinoma, a preoperative diagnosis was never made, except for the very recently published case of Wasel *et al.* [51], in which a diagnosis was achieved before surgery, but only after performing percutaneous biopsies of the pancreatic and liver lesions, thus confirming that the differential diagnosis between benign and malignant lesions is frequently challenging.

Major focus of the research groups is the identification of novel cyst fluid biomarkers, and the metabolomic approach has provided interesting findings on this issue. Based on a preliminary experience, Park and co-workers have found that two metabolites, glucose and kynurenine, were differentially abundant in SCAs [52]. In particular, when cyst glucose levels of SCAs were compared with those of lesions that were not SCAs (pseudocysts, IPMNs, mucinous cystic neoplasms and cancer), the median cyst glucose level was significantly elevated, with an receiver operator characteristic curve of 0.93 (95% CI: 0.86–1.0). The highest diagnostic accuracy was obtained at a cut-off of 66 mg/dl, with a sensitivity and specificity for differentiating SCAs from lesions that were not SCAs of 88 and 89%, respectively. Similarly, SCA lesions had significant kynurenine abundance, and the area under the receiver operator characteristic curve was 0.85 (95% CI: 0.66–1.0) [52]. The finding of glucose abundance in pancreatic cysts is clinically meaningful, not only because of the high diagnostic accuracy but also because its determination requires a very small amount of fluid and is generally performed in almost all hospital laboratories. Similarly, optimistic results have been recently reported with the determination of α-inhibin level within the cyst fluid obtained by EUS-FNA [53]. Although further, larger, confirmatory studies are needed before translating the determination of these metabolites in the clinical practice, metabolomic profiling approach has clearly showed to represent an interesting and fascinating area of future research.

Genetic testing

Molecular analyses have been proposed to increase the accuracy of cystic fluid assays. *K-ras* mutation analysis in cystic lesions may provide useful information, but published data suggest that it cannot be recommended as the only test, but should always be considered in addition to other genetic analyses (i.e., loss of heterozygosity) and diagnostic modalities (i.e., CEA measurement). The prevalence of *K-ras* gene mutations in benign cystic lesions has been reported to range from 0 to 42% and from 20 to 53% in malignant lesions [54–58]. The role of *K-ras* testing in the differential diagnosis between mucinous and non-mucinous, malignant and benign cystic

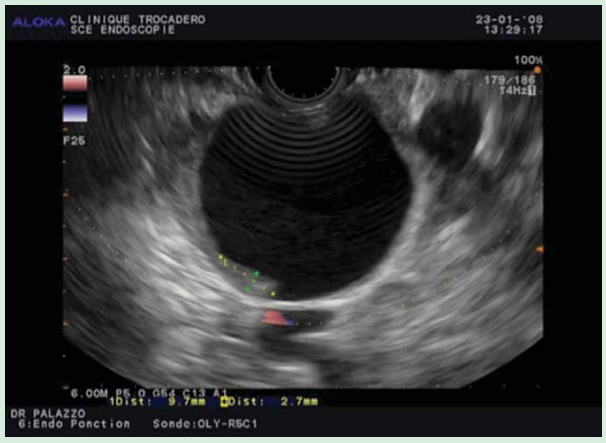

Figure 7. Macrocystic serous cystadenoma with pseudo-mural nodule at endoscopic ultrasound; the finding was not distinguishable from a mucinous cyst and a fine-needle aspiration was needed to provide additional information.

neoplasms is still unclear. In the Pancreatic Cyst DNA Analysis Study, the largest multicentre trial performed to evaluate molecular analysis of pancreatic cyst fluid in the diagnosis of pancreatic cysts, Khalid and co-workers reported that the presence of *K-ras* mutation presented a high specificity (96%) but a low sensitivity (45%) for mucinous differentiation [56]. Furthermore, the combination of *K-ras* testing and CEA analysis improved the sensitivity from 64 to 82% while maintaining the specificity at 83% [56]. Similar results were reported in a recent 6-year study that included 618 pancreatic cyst fluids obtained by EUS-FNA: *K-ras* mutations had a high specificity (100%), but a poor sensitivity (54%) for mucinous cysts [59].

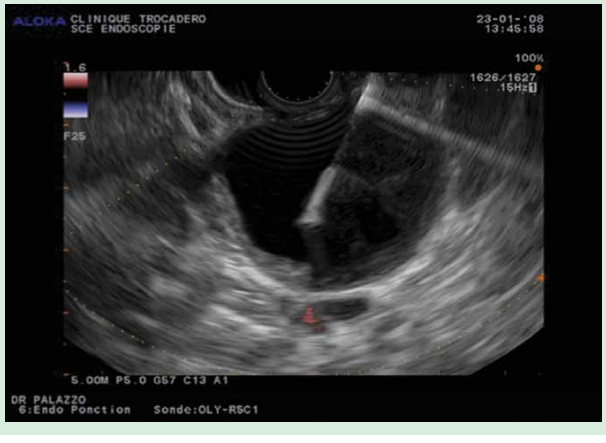

Figure 8. Endoscopic ultrasound-guided fine-needle aspiration demonstrating the diagnosis of serous cystadenoma: carcinoembryonic antigen < 5 ng/ml; amylase < 2500 UI and the histological analysis on cell-block concluded for serous cystadenoma.

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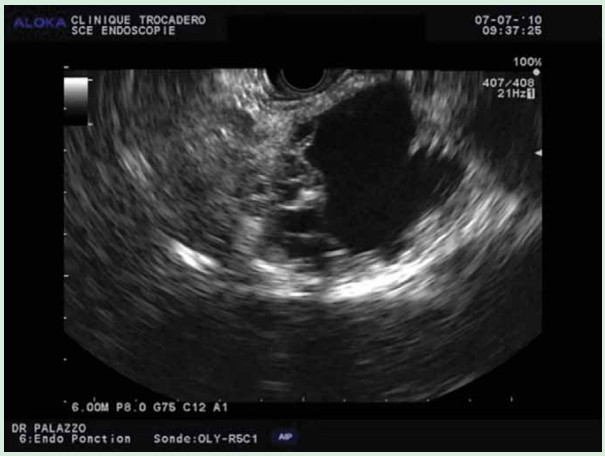

Figure 9. Macrocystic and microcystic (mixed) serous cystadenoma with calcification within the microcystic part.

Similarly, the combination strategy of both assays, *K-ras* testing and CEA, increased the sensitivity to 83% while maintaining a high specificity of 85% [59]. Identification of recurrent and specific genetic mutations in neoplastic cysts will be the subject of future research.

As previously mentioned, *VHL* gene mutations have been identified in all cases of sporadic SCAs; more interestingly, point mutations of *VHL* gene were also detected in cyst fluid analysis in about half of the cases [30]. In the same study, the application of a panel of five genes (*VHL, RNF43, KRAS, GNAS, CTNNB1*) allowed correctly distinguishing mucinous from non-mucinous cysts [30]. Although the clinical utility of these findings has not yet been investigated, genetic analysis of cyst fluid and of the epithelial wall will definitively have a major role in the near future.

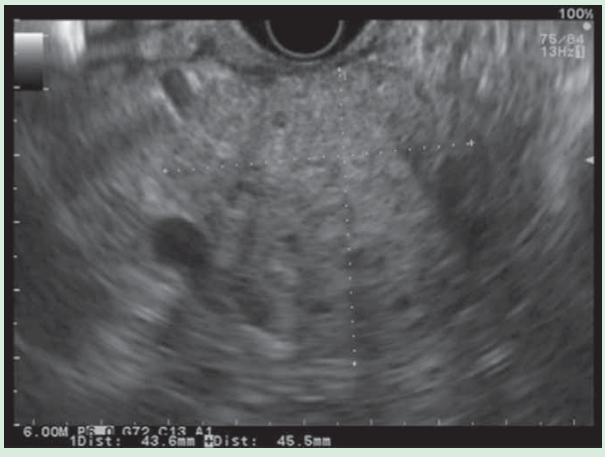

Figure 10. Solid type of serous cystadenoma at endoscopic ultrasound, consisting in very small cysts with multiple, thick fibrous septa.

Confocal laser endomicroscopy

Needle-based confocal laser endomicroscopy (nCLE) during EUS-FNA procedure is another fascinating methodology in the diagnosis of pancreatic cysts. nCLE utilizes a sub-millimeter probe compatible with a 19-Gauge needle and enables real-time imaging with microscopic details of pancreatic cystic lesions (Figure 11 and Video). A prospective multicentre French study (CONTACT) has recently assessed the performance of nCLE for the diagnosis of pancreatic cysts [60]. This study found that the detection of a superficial vascular network is a histological feature of SCA, which can be highlighted by nCLE. In a preliminary series of 18 cases, nCLE achieved an overall good accuracy of 83%, with a sensitivity of 62.5% and a specificity of 100% for the diagnosis of SCA, with an excellent intra-observer and a good inter-observer agreement [60]. A larger, prospective study is ongoing to validate this finding and confirm the role of nCLE for the diagnosis of pancreatic cystic lesions.

Prognosis, treatment & follow-up strategies

Unlike other cystic neoplasms, SCAs almost invariably have a benign course with a very low risk of malignancy (0–3%) [10,14,61]. However, the lack of clear histopathological features evidences of malignancy, and the fact that no patient died for reasons specifically related to serous cystadenocarcinoma, even in cases showing metastatic disease, has raised several doubts on the correctness of the diagnosis [62]. To this day, there is no unanimous consensus regarding the optimal treatment of serous cystic neoplasms. Because accurate differentiation between benign versus malignant cystic tumor is attainable only with pathological examination of the resected lesion, some authors recommended resection for all pancreatic cystic lesions [63]. This approach could be justified by the fact that pancreatic surgery, if performed in tertiary, large volume, referral centers, has become safer than in the past, with decreased morbidity and mortality. In addition, the so-called 'locally aggressive behavior', which means the extension of the neoplasm into adjacent organs or local invasion of surrounding blood vessels, has been claimed as a possible justification for surgical resection [64]. However, these local complications are very rare, and prophylactic surgery does not seem to be appropriate [61]. Of note, only pancreatic head location and a large tumor size (>6 cm) have been detected as independent risk factors for this aggressive behavior; therefore, in this subgroup of patients, the preventive surgical approach might be justified [10]. It should be stressed that the approach of resecting all pancreatic cystic lesions does not reflect the current standard of management of SCA. Indeed, SCA-related mortality is nil, whereas operative mortality is not. A multinational, retrospective study involving 58 centers in 18 countries showed that the post-operative mortality reported in patients that underwent pancreatic surgery for SCA was 0.8%, while the SCA related mortality was 0% in patients with a median follow-up period of 3.1 years [19]. Therefore, this latter strategy is highly recommended, and surgery should

only be considered in a subset of patients with clear indications.

Serous cystic neoplasm is characterized by a slow but progressive growth, which may progress from an initially asymptomatic lesion to a larger and symptomatic one, needing a more complex surgical intervention [65]. Recent evidences indicate that the size at presentation is the cornerstone for treatment approach. In particular, it has been demonstrated that tumors larger than 4 cm are more frequently symptomatic (72% if ≥4 cm vs 22% if <4 cm) and faster growing (0.12 vs 1.98 cm/year) than lesions smaller than 4 cm [21]. Hwang *et al.* confirmed these findings and suggested to consider minimally invasive pancreatectomy in tumors larger than 3 cm regardless of symptoms [65]. However, two more recent studies [12,66] documented a significantly lower mean growth rate of serous cystic neoplasms (0.28–0.29 cm/year) than previously reported. Malleo *et al.* followed a large cohort of patients every year with MRI and observed a very slow rate of tumor growth for the first 7 years (0.1 cm/year), while it substantially accelerated thereafter (0.6 cm/year) [66]. In addition, the oligocystic/macrocystic type and a history of non-pancreatic malignancies were found to be significant predictors of tumor growth, with a mean rate of growth of 0.34 cm/year. Notably, tumor diameter at the time of diagnosis was not a predictive factor of growth; therefore, the use of this parameter in decision-making has been discouraged [66–68].

Management of serous cystic neoplasms should mainly follow a conservative approach, keeping track of asymptomatic small lesions (<4 cm) and monitoring if any modification in size and appearance or onset of symptoms do occur. Surgical resection should be reserved for symptomatic patients or when a potentially malignant tumor cannot be excluded [14,66,68,69]. In order to avoid the risk of misdiagnosed malignant lesion, it must be remembered that all cases of serous cystoadenocarcinomas reported in literature were symptomatic. It is unclear whether large tumor size has any impact on malignant potential, but it would intuitively increase the probability of developing symptoms on the long term [64]. Decisions in large serous cystic neoplasms should be made on a case-by-case basis, considering the patient's age as well as comorbidities and tumor location. A young subject fit for surgery with a potentially growing lesion located in the body/tail of the pancreas is a candidate for a long and expensive follow-up; in this case, a function-preserving, minimally invasive, laparoscopic or robotic surgical resection, should be discussed with the patient. Otherwise, large serous cystic neoplasms can be strictly observed and surgery proposed should any modification in size or symptoms occur. The risk for occult malignancy and the development of symptoms due to mass effect in yet asymptomatic subjects must be weighed against the risk of pancreatic surgery that, despite growing experience and most recent surgical techniques, is associated with a perioperative morbidity of 15–30% and a mortality rate of 1–2%, even in tertiary referral centers [10,65,70].

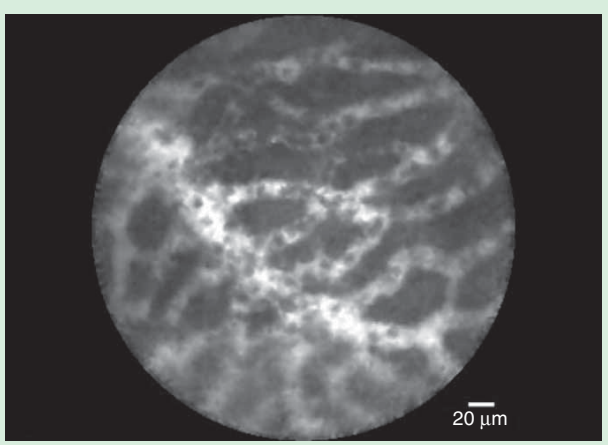

Figure 11. Needle-based confocal laser endomicroscopy allows highlighting the superficial vascular network of the wall of the cyst that represents a histological feature of serous cystadenoma.

Since almost all serous cystic neoplasms have a non-invasive behavior, surgery should be as limited as possible depending on the anatomic region involved. If the tumor is located in the head of the pancreas, duodenum-preserving head resection should be performed. For lesions at the body/neck and body/tail, central pancreatectomy and spleen-preserving distal pancreatectomy should be carried out, respectively. Enucleation of the tumor has been successfully performed, even if some authors reported greater morbidity and mortality [20]. Lymphadenectomy is generally not required in the absence of malignancy. The advantage of preserving surgical excision includes more favorable outcomes in terms of functional preservation and quality of life [71]. In case of serous cystoadenocarcinoma, surgical resection both of primary tumor and eventual metastases is generally successful.

In the last decade, alternative EUS-guided treatments have been explored, especially for patients unfit for surgery. Pancreatic cyst ablation with the injection of ethanol possibly followed by a second ablative agent, paclitaxel, is considered a promising technique [72]. However, at present, the results have been almost disappointing, with complete resolution rates around 30% [73] with ethanol lavage, rising to 60% when paclitaxel is added to the procedure [74]. Furthermore, based on the surgical resection specimens, imaging-based resolution may not correlate with histologic ablation, and it should be pointed out that long-term follow-up data are still missing; therefore close monitoring is strongly advised even after complete resolution [74]. A recently published prospective study evaluated changes in pancreatic cyst fluid DNA following EUS-guided pancreatic cyst ablation with a combination of ethanol and paclitaxel, in 22 patients with suspected benign cysts [75]. The study provided three interesting findings: almost all mutant DNA appeared to be eliminated in cysts after ablation; a partial or complete image-defined

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resolution was observed in 75% of treated cases; moderate and severe adverse events were not so infrequent as previously believed. Indeed, previous reports showed that most adverse events are mild and self-limited (i.e., abdominal pain) and the risk of post-procedural pancreatitis is low (2%), although cases of venous thrombosis have been reported [76]. At opposite, in a prospective study by DeWitt and co-workers, which included 22 patients that underwent a total of 31 procedures, adverse events were classified as moderately severe in four patients (13%), in particular three cases of pancreatitis (10%) and one case of chemical peritonitis and ileus (3%) were described; furthermore, 13% of patients experienced abdominal pain and a gastric wall cyst developed in one patient. Therefore, concerns on the safety profile of this procedure still exist. Most importantly, there are also some concerns about ablation of benign cysts, such as SCA, which can be easily monitored with imaging techniques. It has been suggested that cyst ablation may be considered for macrocystic SCAs showing a progressive size increase during follow-up [77]; however, it should be pointed out that this procedure remains an investigational treatment to be performed only within the settings of well-designed clinical trials.

To this day, the best follow-up strategy has not been standardized yet. Once SCA is clearly diagnosed, an imaging surveillance every 2 years has been proposed, and it seems a reasonable strategy in patients with a small lesion (<4 cm) [20,61,78]. Otherwise, larger tumors should be observed yearly to decide whether resection could be indicated [10]. Recent consensus statements recommended follow-up imaging initially repeated after 3–6 months from the diagnosis and then individualized depending on the growing rate [67].

Surgery is considered curative. Given the absence of documented recurrence after complete surgical resection, post-surgery follow-up is unnecessary. Very rare cases of late onset of liver metastases, with consequently change of diagnosis from benign SCA in cystadenocarcinoma, have been successfully treated with the sole surgery; chemotherapy is not necessary in any case.

Conclusion

SCAs are uncommon benign tumors that comprise about 16% of all resected cystic tumors of the pancreas. About half of SCAs are asymptomatic and found incidentally on radiologic examinations performed for other, unrelated reasons. CT and MRI morphology alone have proven to be suboptimal to fully characterize cystic pancreatic lesions, in particular to differentiate macrocystic SCAs and mucinous cystic neoplasms. EUS, with the addition of FNA in difficult cases, has showed greater diagnostic accuracy than conventional imaging techniques. CEA is the most accurate test available to differentiate pancreatic cystic lesions. However, a non-negligible portion of pancreatic cysts remains indeterminate, even after extensive evaluation. The role of metabolomic and genetic testing as well as confocal endomicroscopy in clinical practice is under investigation and definitively represents an area of future research. To this day, there is no unanimous consensus regarding the optimal treatment of serous cystic neoplasms. Surgery should be limited only to symptomatic and highly selected cases, and the majority of patients should be strictly monitored to observe whether any modification in size or onset of symptoms does occur. EUS-guided pancreatic cyst ablation has been proposed as a possible alternative to surgery; however, results are still disappointing. Further studies should investigate the best follow-up strategy; in the meanwhile, imaging on a bi-annual basis for small lesions (<4 cm) and on annual basis for larger cysts is advisable.

Expert commentary

Pancreatic cystic lesions are increasingly been detected because of the availability of high-quality imaging techniques. Despite extensive evaluations, a non-negligible portion of pancreatic cysts remains indeterminate. EUS morphology and EUS-FNA, with CEA dosage on cystic fluid, represent very important diagnostic tools and can be useful in correctly distinguishing mucinous from non-mucinous cysts. The best management strategy of these neoplasms is still debated. Because SCAs have a benign course with a very low risk of malignancy, surgical resection should be reserved for symptomatic patients or when a malignant tumor cannot be excluded.

Five-year view

In the near future, all the potentialities of EUS with the addition of fine-needle aspiration will be investigated; in particular, metabolomics and genetic analyses will be further explored, due to the enthusiastic results already observed. Furthermore, the possibility to thrust a needle into a cystic lesion will allow carrying within the lesion other devices, with both diagnostic and therapeutic purposes.

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Key issues

- Pancreatic cystic lesions are being increasingly detected with the more widespread use of diagnostic techniques and improvements in imaging technology.
- Unlike mucinous cystic neoplasms, serous cystadenomas (SCAs) of the pancreas are considered benign tumors. Therefore, a correct diagnosis is mandatory to avoid unnecessary pancreatic surgery and ensure patients excluding a malignant disease.
- Radiological imaging techniques alone have proven to be suboptimal to fully characterize cystic pancreatic lesions.
- Endoscopic ultrasound, allowing for cytological and biochemical analyses of the cystic fluid obtained by fine-needle aspiration, has showed greater diagnostic accuracy than conventional imaging techniques.
- Carcinoembryonic antigen dosage on cystic fluid is the most accurate test available to differentiate pancreatic cystic lesions.
- The role of genetic testing, metabolomic analysis and needle-based confocal laser endomicroscopy during endoscopic ultrasound-fine-needle aspiration procedure is under investigation and definitively represents an area of future research in the diagnosis of pancreatic cystic lesions.
- Serous neoplasms of the pancreas present an extremely small risk of malignancy; therefore, the vast majority of them should not undergo surgical resection.
- Surgery should be limited only to symptomatic and highly selected cases of SCAs and the majority of patients should be strictly monitored to observe whether any modification in size or onset of symptoms does occur.
- The best follow-up strategy of SCAs is still debated; however, imaging on an annual or even bi-annual basis is advisable.

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