

Cystic pancreatic tumors: should we resect all of them?

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Abstract. – OBJECTIVE: Pancreatic cystic tumors are relatively rare tumors and only 1% of them are malignant. They are often asymptomatic and detected as incidental findings through diagnostic imaging. Currently there are no universal guide lines for the correct clinical approach to pancreatic cystic lesions. Cross-sectional imaging demonstrates some typical morphological features that determine the pre-operative diagnosis of the pancreatic cystic lesions (serous or mucinous cystadenoma, intraductal papillary mucinous neoplasms). In addition, endoscopic ultrasonography permits the collection and analysis of the fluid content. The aim of this paper is to describe our case load in the management of pancreatic cystic neoplasms and propose some criteria for choosing between surgical or conservative approaches.

PATIENTS AND METHODS: 12 patients with pancreatic cystic neoplasms were retrospectively evaluated. They were studied using cross-sectional imaging modalities (computed tomography and magnetic resonance); endoscopic ultrasonography was performed in 7 patients.

RESULTS: In each patient a careful evaluation of several factors (age, comorbidity, imaging features, symptoms, life expectancy) conditioned our clinical decision. Among our 12 patients, surgical resection was performed in 7 cases.

DISCUSSION: The treatment of pancreatic cystic lesions is still a dilemma because even in the presence of malignant potential, pancreatic surgery remains very complicated and demolitive.

Many factors need to be considered in the management of cystic pancreatic tumors. The most important include histological type, location, size, age and clinical condition of the patient.

CONCLUSIONS: A correct multidisciplinary pre-operative diagnosis is mandatory. Surgery should only be performed in selected cases.

Key Words:

Pancreas, Pancreatic Neoplasma, Pancreatic Cyst, Disease Management, Magnetic Resonance Imaging.

Introduction

The first description of a pancreatic cystic neoplasm was reported by Becourt in 1824^{1,2}. However, the first nosological classification of these neoplasms was only introduced about thirty years ago³⁻⁶. In recent years, several works have been published on pancreatic cystic tumors, including several clinical entities with different biological behavior. These may be in fact benign, borderline or malignant⁷. The widespread use of cross-sectional imaging – such as Multidetector Computed Tomography (MDCT) and/or Magnetic Resonance (MR) – has markedly increased the number of cystic neoplasms, as imaging modalities accidentally detect cystic lesions in patients studied for different reasons⁸⁻¹⁰.

Cystic tumors are relatively rare, accounting for approximately 10% of all pancreatic neoplasms. Only 1% of all pancreatic cystic tumors are malignant neoplasms¹¹. Serous cystadenoma, mucinous cystadenoma, intraductal papillary mucinous neoplasm (IPMN) and solid-pseudopapillary tumor represent about 90% of all pancreatic primary cystic neoplasms.

They are often asymptomatic at the beginning, and develop mechanical symptoms with their progressive growth, compressing adjacent anatomical structures (portal vein, biliary duct, stomach, duodenum, nerves). Despite extensive literature regarding clinical and diagnostic features of cystic neoplasms, there are still some uncertainties about treatment. Currently, the diagnostic dilemma for surgeons of whether to opt for resection surgery or not still remains. Better diagnostic strategy for these patients is recommended, avoiding surgery for patients with non-malignant cystic tumors where resection is probably not necessary. On the other hand, imaging modalities are often not able

to clearly distinguish lesions that require surgery and lesions that do not require any surgical intervention. Some clinical features will be discussed in this paper, highlighting from our study, elements that clinicians should keep in mind when managing cystic pancreatic neoplasms.

Some authors propose surgical treatment for all these neoplasms, due to the excellent results obtained in pancreatic resections, especially in comparison with surgical results reported in the 80s, when mortality after pancreato-duodenectomy at a value of 20% was considered “normal”. Although mortality after pancreatic resection in high volume centers has decreased (less than 2%), in low-volume centers it is still high – about 15%. In addition, in high volume centers reported morbidity rates remain at approximately 40%^{10,12-14}.

The continually high values of morbidity along with non-trascurable mortality reported in previous studies would suggest adopting a patient-by-patient multidisciplinary approach. In addition, non-surgical approaches seem to be required due to the fact that approximately one third of cystic pancreatic neoplasms are accidentally discovered and are asymptomatic¹⁵.

Cross-Sectional Imaging Features of Cystic Pancreatic Neoplasms

As reported in previous works, in many cases the diagnosis of cystic neoplasms with imaging alone is still impossible, due to the considerable overlap among cystic lesions. As a consequence, in Sahani et al⁸, “a simple-imaging based classification” was proposed to help radiologists and clinicians in the management of cysts⁸.

Main imaging features currently adopted for the diagnosis of pancreatic cystic neoplasms include: location, pattern of intralesional cysts (unilocular, oligocystic, polycystic appearance), calcifications, communication with main pancreatic duct or side-branches ducts, thickness of septa, presence of internal debris or mural nodules.

Mucinous cystadenoma is generally encountered in the pancreatic body and tail, whereas serous cystadenoma is located in the head of the pancreas¹⁶.

Serous cystadenoma are typically encountered in the head of the pancreas and have three main morphologic patterns. In 70% of cases, serous cystadenomas are characterized by a polycystic pattern. The honeycomb pattern is seen in approximately 20% of patients, whereas the oligocystic appearance is uncommon, since it has been reported in less than 10% of patients^{8,17}. Nevertheless, these patterns could be associated with

other cystic neoplasms, and a certain degree of overlap is generally encountered. MRCP plays a very important role in the classification of the mentioned patterns thanks to its high contrast resolution; two-dimensional and three-dimensional sequences allow identifying the number of intralesional cysts, and their diameter¹⁸. The polycystic pattern consists of multiple small cysts, generally of a few millimeters.

IPMNs arising from side-branch ducts may have a polycystic pattern, and in these cases only clear communication enables a differential diagnosis from serous lesions. Nevertheless, the absence of communication with the main pancreatic duct does not allow for the exclusion of IPMN^{8,19}. Considering the oligocystic pattern, radiologists should include all three types of the most important pancreatic cystic lesions, serous cystadenoma, mucinous cystadenoma and IPMNs in the differential diagnosis. Again, a diagnostic tool for the differential diagnosis could be the presence of communication with the main pancreatic duct. A lobulated contour is more frequently associated with serous cystadenoma and IPMNs^{17,20}.

Calcifications are different between serous and mucinous lesions; a central calcified scar is in fact virtually pathognomonic for serous cystadenoma¹⁷, whereas peripheral calcifications are generally associated with mucinous cystadenoma¹⁶.

The thickness of septa represents another important morphological feature for the diagnosis of cystic pancreatic neoplasms because serous lesions have thin septa, whereas mucinous neoplasms may exhibit prominent septa inside the lesions¹⁶. Again, MR has higher sensibility and accuracy in the characterization of septa.

Morphologic studies suggestive of invasive carcinoma in an IPMN at CT and MR include involvement of main pancreatic duct, diffuse or multifocal involvement, main pancreatic duct dilatation, large mural nodule, large size of the mass and combined type of IPMN²¹. In addition, among pancreatic cystic neoplasms with internal solid components, radiologists a solid-pseudopapillary tumor need to be considered carefully^{22,23}. This tumor, in its typical MDCT and MR presentation, is generally a well-defined encapsulated mass composed of a mixture of cystic and solid components²⁴.

Finally, radiologists should be able to differentiate pancreatic cystic neoplasms from many other peripancreatic structures – such as arterial or vein aneurysms; these peripancreatic structures can simulate pancreatic cystic lesions, due to

choledocal and pancreatic compression with consequent “mechanical” symptoms^{25,26}.

The role of Endoscopic Ultrasonography (EUS) in the Pre-Operative Diagnosis of Cystic Pancreatic Neoplasms

Endoscopic UltraSonography (EUS) helps obtain many important details about cystic lesions, such as wall thickness, presence of septa and nodules. In addition, it provides measurement of the main pancreatic duct, identifying stenosis along its course, and shows the presence of enlarged lymph nodes²⁷⁻²⁹.

The great advantage of EUS is the possibility of collecting liquid from cystic lesion – performing a fine-needle aspiration⁴⁶. Here the fluid content is evaluated for the color (clear, amber, brown, hematic), viscosity and presence of mucin. The latter allows us to differentiate a mucinous cystic tumor from a serous cystadenoma. The diagnostic accuracy of fine-needle EUS is between 92-96%³⁰.

In cystic tumors less than 6 cm, but also in those less than 2 cm in diameter, the EUS accuracy ranges from 82 to 91%, much higher than those obtained by the use of CT and MRI³¹.

The dosages of CEA and CA 72.4 in the cystic fluid of the mucinous lesions are much higher (typically over 800 ng/ml) than those of non-mucinous ones. A level > 800 ng/ml is 98% specific for a mucinous cyst using a meta-analysis of pooled data from 12 studies at different institutions³². The CEA and CA72.4 levels reach higher values in malignant mucinous neoplasms³³⁻³⁷. In a previous work by Brugge et Al a level of 192 ng/ml had a diagnostic sensitivity of 75%, a specificity of 84% and an accuracy of 79% in differential diagnosis of mucinous and non-mucinous cysts³⁵.

Sometimes the collected fluid is analyzed for its cellular contents, although it is difficult to obtain an adequate amount of material and generally there is little presence of cellular material in the fluid.

Finally, an important diagnostic tool of FNA (Fine Needle Aspiration)-EUS is a selective biopsy of suspected areas which may have uncertain nodules or thick segments along the lesion’s walls.

The aim of this paper is to describe our experience in the management of pancreatic cystic neoplasms. The different behavior adopted in the treatment of these neoplasms is reported, highlighting the multidisciplinary approach adopted in our series of pancreatic cystic neoplasms. In addition, we focused on clinical (age, general conditions), radiological (size, shape, calcifications, septa) and morphological features (histopathological features) that influence the choice of treatment.

Materials and Methods

12 patients (7 females, range 58-85 years) with pancreatic cystic neoplasms were retrospectively evaluated. They were studied by cross-sectional imaging modalities, MDCT, MRI and MR-CP. CT examinations were also performed with intravenous administration of iodinate contrast medium, collecting unenhanced and enhanced images. Dynamic acquisitions (arterial, portal and venous equilibrium phases) were obtained using the smart prep system.

MR and MRCP exams were performed using a 1.5 Tesla Magnetic Resonance with an eight-channel phased-array coil used for image acquisition. The synchronization with patients’ breath was achieved by placing a “respiratory” belt around their abdomen.

In our study, protocol, biliary and pancreatic systems were studied performing two-dimensional (2D) single-shot fast spin-echo (SSFSE) sequences and three dimensional (3D) fast recovery fast spin-echo sequences (FRFSE). Dynamic enhanced images after gadolinium injection were acquired using T1-weighted three-dimensional (3D) FSPGR sequences. The dynamic multiphase hepatic acquisition - including arterial, portal and delayed phases - was carried out using the smart prep system. The contrast medium was administered by a double testis injector with contrast injection rate of 1-2 ml/sec. In all patients an immediate bolus of physiological solution was injected after the contrast agent.

Endoscopic ultrasonography was performed in 7 patients using a linear echoendoscope. Fine-needle aspiration was collected in 3 cases only.

Results

Our case load includes 12 patients with pancreatic cystic neoplasms, observed from 2007 to 2013. For each patient, a different clinical approach based on various criteria: age, comorbidity, imaging features, symptoms, life expectancy was adopted. Surgical treatment in seven cases was chosen while in the remaining five cases a more conservative approach was preferred.

Surgical resection was performed in 7 patients (6 females and 1 male), among which the pre-operative diagnosis was: four serous cystadenomas, two IPMNs and one mucinous cystadenoma.

In three of the four serous cystadenomas, surgery was mandatory because the patients were

symptomatic. Infact, the neoplasms appeared as giant cephalo-pancreatic masses (diameters of 6, 8 and 11 cm respectively) that caused choledocal compression and consequent “mechanical” symptoms, such as subittero and/or pain (Figure 1).

In all cases the imaging features led to the hypothesis of a serous tumor. Only in one case the pre-operative diagnosis was almost certainly due to the collection of a serous fluid obtained by a FNA-EUS.

In the fourth patient the cystic pancreatic lesion was a chance finding during a CT exam performed for the staging of colonic cancer. The CT abdominal images showed a small-size cystic lesion (2 cm) in the tail of the pancreas and the possibility of a serous pancreatic neoplasm was clearly suggested by many morphological features (unilocular cyst without peripheral calcification and thickened septa). Considering the small-size and the absence of symptoms, this patient should have been scheduled for a follow-up program. However, the location in the pancreatic tail, the clinical suspicion of a non-serous neoplasm, and above all the need for surgical treatment of the colonic malignancy, necessitated the removal of the pancreatic lesion. Therefore, a distal pancreatectomy was performed simultaneously with left hemicolectomy. The histological result confirmed the serous type of the lesion.

In 2 patients (1 female, 1 male) the pre-operative diagnosis was IPMN.

The woman, who was 58 years old, required a cephalic pancreatic cyst. It had been previously reported in a CT scan performed 6 months before, during a previous hospitalization for acute pancreatitis. The patient revealed no history of choledocolithiasis or alcohol abuse, and was scheduled for a MRCP exam. The images (Figure 2) clearly depicted a giant cystic lesion centered along the course of the main pancreatic duct and radiology suggested the possibility of primary IPMN. It was pre-operatively already labeled as mucinous after the removal of intra cystic material during an echo-endoscopy. Therefore, it was decided to perform a pancreato-duodenectomy and the successive histological result deposed a borderline IPMN.

In the male patient, who suffered pancreatitis-like symptoms, CT exam (Figure 3) clearly depicted a cystic dilatation involving the entire course of main pancreatic duct that measured up to 2 cm in diameter. The patient underwent a total pancreatectomy, and the final histological examination revealed “adenocarcinoma arising on IPMN”.

The seventh patient presented a giant cystic lesion located on the pancreatic tail. The absence of previous pancreatitis history and the macrocystic appearance suggested a mucinous lesion. Considering the age (< 60 years old) and good health of the patient, in addition to the large-size of the cystic mass, surgery was deemed appropri-

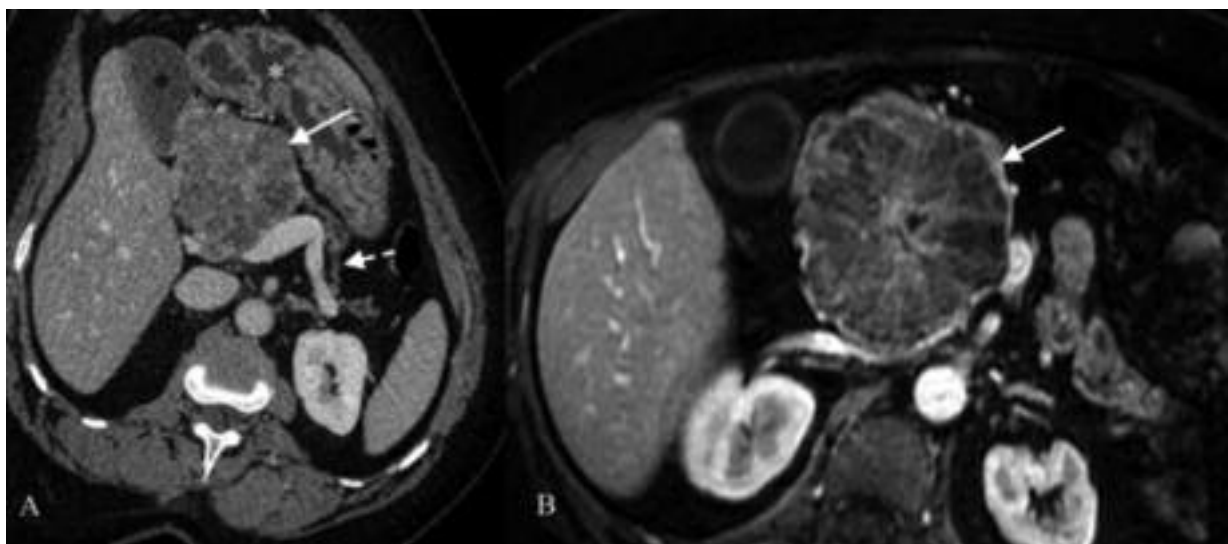


Figure 1. A serous cystadenoma in a 66 year-old female patient. Axial post-contrast CT image (**A**) and axial enhanced T1-weighted acquisition (**B**) show a large mass in the cephalic region of the pancreas (white arrows) with spongiform appearance. Note also, the atrophgia of the remaining pancreatic parenchyma (white dashed arrow); gastric antrum (white asterisk), duodenum, choledocal duct, gallbladder (black asterisk) and portal vein were compressed without infiltration. These mechanical symptoms required surgery.

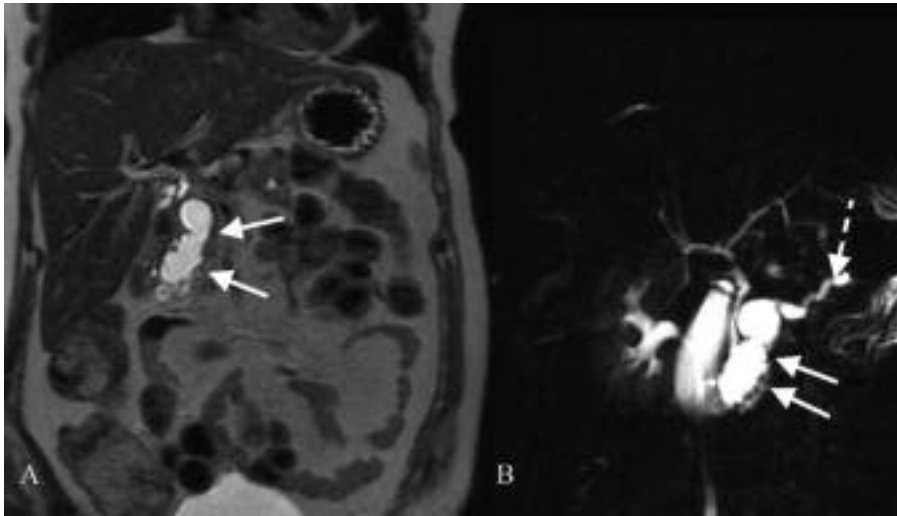


Figure 2. IPMN of the main pancreatic duct. Coronal T2-weighted (A) and MRCP (B) images show the cystic lesion of the main pancreatic duct (arrows). The dashed arrow in B indicates the dilatation of the duct in the pancreatic body and tail. It was decided to perform a pancreato-duodenectomy and the successive histological result deposited a borderline IPMN.

ate. The lesion was successfully removed by performing a distal pancreatectomy. The final diagnosis was mucinous cystadenoma.

In summary, surgical treatment included 4 pancreato-duodenectomies, 2 distal pancreatectomies and 1 total pancreatectomy. The post-operative mortality rate in the population was equal to zero and no pancreatic fistulas were observed in the patients.

Only in one case a surgical revision was needed. The patient with a cephalic IPMN treated with a pancreato-duodenectomy developed stenosis of the gastrojejunostomy that could not be resolved with an endoscopic dilatation and required a surgical remaking of the anastomosis (3 months after the first surgical procedure).



Figure 3. Adenocarcinoma arising on IPMN. Axial contrast-enhanced CT image shows a cystic dilatation with a diameter of 2 cm involving the entire course of the main pancreatic duct (arrows); it is associated with a completed atrophy of the pancreatic parenchyma. The patient underwent a total pancreatectomy.

The patient treated with total pancreatectomy died 4 months after surgery of metabolic complications related to the difficulty of controlling diabetes. The remaining 6 patients were scheduled for clinical and radiological follow-ups.

In 5 patients a conservative approach was adopted. In all cases that did not undergo surgical treatment, the pancreatic lesions, 4 located in the pancreatic head and 1 recognizable in the pancreatic tail, were small in size (< 3 cm). In three patients, other additional criteria for a non-interventional choice were the age (older than 75 years) and the typical appearance of serous tumor without mechanic symptoms. The last two patients (72 and 63 years-old) had very small lesions classified as secondary IPMNs, located respectively in the head (Figure 4) and in the tail of the pancreas. In view of their radiological appearance (secondary IPMNs), the lesions were initially scheduled for a follow-up program but the MR examinations have shown no modifications to-date.

Discussion

After pre-operative diagnosis, surgeons should carefully revise all cystic neoplasm features and patient condition, in order to establish the correct treatment. The main diagnostic dilemma still seems to be whether to perform surgical resection or not. Currently, there are no well-defined guidelines in this regard³⁸.

Many factors need to be considered in the management of cystic pancreatic tumors; the most important include histological type, location, size, age and clinical condition of the patient³⁹⁻⁴¹.



Figure 4. Secondary IPMN in a 65 year-old male patient. Coronal MRCP image shows a small polilobular cystic lesion in the uncinus process (*arrow*). The morphological appearance and the apparent continuity with the main pancreatic duct suggest the diagnosis of secondary duct IPMN; the patient was scheduled for a follow-up program. Focal ectatic pancreatic branch ducts are also recognizable in the pancreatic head body (*dashed arrows*).

Small-sized lesions are generally asymptomatic and cross-sectional imaging modalities – performed by an experienced and dedicated radiologist – are able to classify these small lesions as benign. A dimension of less than or equal to 3 cm has been considered an important factor in the management of pancreatic cysts. The positive predictive value (PPV) for benignity is about 87% in cases of lesions smaller than 3 cm, while the PPV increases at 97% if these lesions are unilocular in appearance⁴².

For IPMN, imaging modalities should identify imaging features reported as “high-risk stigmata” or “worrisome features” in the evaluation of pancreatic cysts. “High-risk stigmata” include essentially main pancreatic duct dilatation ≥ 10 mm and the presence of solid component showing enhancement after contrast administration⁴³.

In addition to cyst size, some authors recommend considering other features such as CEA levels race and age. In a previous work, Buscaglia et al⁴⁴ reported white race, age > 50 , cyst size larger than 1.5 cm and high CEA level as significant factors in increased risk of malignancy. Among clinical symptoms, jaundice and diabetes have been significantly associated with malignancy⁴⁵.

In our surgically-treated IPMNs, the large size (> 3 cm) detected on MRCP images, the echoendoscopy reports and the clinical symptoms suggested aggressive treatment, in accordance with literature criteria.

The great advantage of EUS, as previously mentioned in this paper, is the possibility of col-

lecting liquid from cystic lesion by performing a fine-needle aspiration⁴⁶. Cyst fluid can be analyzed for tumor markers, cytology, mucins, DNA analysis, viscosity and chemistries⁴⁷. These fluid contents may be helpful in the diagnosis of mucinous lesions. In the pre-operative assessment, the presence of a mucine-rich fluid helped to correctly classify one of the two IPMNs surgically removed as a mucinous lesion.

Among our serous cystadenomas, surgical intervention was necessary for the mechanical symptoms observed, with biliary dilatation caused by a giant lesion (> 6 cm). The large size of the lesions may in fact require an aggressive approach even in the case of a benign nature. In a recent paper, it was stated that serous cystadenomas exceeding 4 cm, given their propensity for growth and developing symptoms, should be resected in appropriate surgical candidates⁴⁸. A sign which could be considered strongly suspicious, thus requiring surgical treatment, is the increase in size of the lesion. Nevertheless, serous cystadenomas can reach a considerable size even maintaining their benign nature, requiring resection if they begin to be symptomatic.

Conclusions

In order to establish a selective surgical approach, clinicians should clearly distinguish between serous and mucinous neoplasms. In case of serous cystic tumours, the patients may be scheduled for a follow-up program, and surgery is required only in presence of “mechanical” symptoms. Mucinous cystadenomas should always be proposed for the resection after careful assessment of the patient’s general condition.

IPMNs arising from main pancreatic duct should be resected bearing in mind the general condition of the patient and the presence of “high-risk stigmata” or “worrisome features”⁴⁹. IPMNs developing from secondary branches could be scheduled for a follow-up program, especially for lesions that do not exhibit intracystic solid components and do not exceed 3 cm in size.

In some kind of patients i.e. HIV-positive and elderly patients the radiologic imaging could be difficult to clarify the difference between benign and malignant lesion⁵⁰⁻⁵³.

In summary, it is no longer possible to argue that we should resect all pancreatic cystic tumors. Surgery can be proposed:

- For symptomatic patients
- For lesions of at least 3 cm in diameter,

- For lesions with some suspicious characteristics: solid components, septa, main pancreatic duct dilatation, suspicious cells in intracystic fluid, markers rising.

It is also important to keep in mind that lesions a multidisciplinary approach - including gastroenterologists, radiologists and surgeons - should be adopted in order to perform a correct management⁵⁴.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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