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Management of Pancreatic Cystic Lesions

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Abstract

Objectives: In the last several decades, the knowledge of the cystic neoplasms has enlarged and the management has changed. The wide adoption in the diagnostic procedures of routine and advanced imaging has become the cornerstone of the diagnosis.

Methods: Pancreatic cystic tumors comprise neoplasms with a wide range of malignant potential. The most common include serous cystic neoplasm, mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), solid pseudopapillary neoplasms (SPPNs), and cystic pancreatic endocrine neoplasms (CPENs). Other cystic lesions are acute postnecrotic pseudocysts and chronic pseudocysts. Finally, the indeterminate cystic lesions have been presented.

Results: The epidemiology, pathological features, imaging characteristics, clinical evolution, and therapeutic choices of the most frequent lesions as well as less frequent forms are described. This study can be completed with the presentation of some cases of cystic pancreatic neoplasms treated in our service.

Conclusion: The improvement of imaging, endoscopic modalities, and cyst fluid studies allows now accurate and reliable diagnosis of pancreatic cystic lesions. Moreover, the enlarged knowledge of valuable pathological studies established the potential for malignant transformation of these lesions identifying higher-risk neoplasms. Finally, the management options should be based on the assessment of each type of cystic neoplasms and the distinction of pancreatic cystic neoplasms (PCNs) from other cystic lesions.

Keywords: cystic pancreatic lesions, pancreas, pseudocysts, pancreatitis, indeterminate pancreatic cystic lesions
1. Introduction

Cystic lesions of the pancreas are less frequent in relation to solid neoplasies. These lesions have attracted new and great interest. In the last several decades, the knowledge of the cystic neoplasms has enlarged and the management has changed dramatically. The wide adoption in the diagnostic procedures of routine and advanced imaging such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS) has become the cornerstone of the diagnosis.

EUS-guided fine needle aspiration (FNA) can allow the assessment of tumor markers, chemistries, cytology, and DNA analysis. Also pathological study has played a very important role.

2. Classifications and epidemiology

The recent WHO classification 2010 of all pancreatic tumors is more extensively used. This classification encompasses epithelial tumors (benign, premalignant lesions, malignant lesions, and neuroendocrine neoplasms), mesenchymal tumors, lymphomas, and secondary tumors [1].

Based on pathological, clinical and radiologic assessments, some not recent but valuable [2], several classifications of cystic pancreatic neoplasms and lesions have been proposed. We believe interesting to note the proposed classification that fully includes all cystic lesions of the pancreas [3]. This classification includes the following cystic lesions: neoplastic epithelial (benign, borderline, and malignant), non-neoplastic epithelial, neoplastic non-epithelial (very rare), and non-epithelial non-neoplastic (very rare).

The frequency of each cystic lesions is not defined with precision, may be for observers diversity (surgeons, radiologists, and pathologists) and for the assessment of different developmental stages of lesions.

Pancreatic cystic tumors comprise a variety of neoplasms with a wide range of malignant potential: benign, borderline, and malignant. The classification proposed by Kosmahl encompasses the majority of the recently now described lesions (Table 1).

Many cystic neoplasms listed in the classifications are infrequent or rare pathological varieties, with minimal and not evident clinical characterization [4]. The simplified classification can be proposed that comprises two groups of lesions:

- Non-mucinous cystic lesions: inflammatory pseudocysts without a true epithelial lining (in the setting of acute and chronic pancreatitis), serous cystic neoplasms (SCNs), solid pseudopapillary neoplasms (SPPNs), and cystic pancreatic endocrine neoplasms (CPENs).
- Mucinous cystic lesions (epithelial lining produces mucinous cyst fluid): intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs).
Cystic epithelial tumors | Non-neoplastic epithelial cysts
--- | ---
**Benign**
Intraductal papillary mucinous adenoma | Congenital cyst
Mucinous cystic adenoma | Lymphoepithelial cyst
Serous microcystic adenoma | Retention cyst
Serous oligocystic ill-demarcated adenoma | von Hippel-Lindau-associated cystic neoplasm
von Hippel-Lindau-associated cystic neoplasm | Benign cystic neuroendocrine tumors
Acinar cell cystadenoma | Cystic teratoma (dermoid cyst)
Cystic teratoma (dermoid cyst) | Borderline
Intraductal papillary mucinous neoplasm borderline | Non-neoplastic non-epithelial cysts
Mucinous cystic neoplasm borderline | Pancreatitis-associated pseudocysts
Solid pseudopapillary neoplasm | Parasitic cysts
Malignant
Intraductal papillary mucinous carcinoma | 
Mucinous cystic carcinoma | 
Ductal cystic adenocarcinoma | 
Serous cystadenocarcinoma | 
**Cystic non-epithelial tumors**
Lymphangioma | 
Sarcomas | 

Table 1. Classification of cystic neoplasms and lesions of pancreas [3].

This classification highlights as criterion of differentiation the presence of mucinous epithelium characterized by malignant potential.

Another criterion of classification of cystic lesions of pancreas is based on the epithelium lining of the cyst (Table 2).

In summary, the most common neoplasms include: serous cystic neoplasms (SCNs)/serous cystadenoma, mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), solid pseudopapillary neoplasms (SPPNs), and cystic pancreatic endocrine neoplasms (CPENs). There are others rare or very rare tumors: acinar cells cystadenoma, cystadenocarcinoma, cystic teratoma (dermoid cyst), and cystic pancreaticblastoma. Pancreatic cystic tumors are rare and less frequent than others pancreatic tumors. Image-based studies show prevalence of pancreatic cystic lesions ranging from 1.2 to 19% [6, 7].
No lining → Pseudocysts (pancreatitis associated)

Lining

Mucinous epithelium
- MCNs
- IPMNs

Serous epithelium
- SCNs
- VHL-associated pancreatic cysts

Squamous epithelium
- Lymphoepithelial cysts

Acinar cells
- Acinar cell cystadenocarcinomas

Endothelial lined cysts
- Lymphangiomas

Degenerative necrotic changes in a neoplasm
- SPPNs
- CPENs
- Cystic ductal adenocarcinomas

Table 2. Classification of cystic lesions of the pancreas [5].

In the autopsy series, the prevalence reaches 24% [8]. All cystic tumors of the pancreas reach about 10–15% of all cystic pancreatic lesions [7]. The exact prevalence of cystic pancreatic tumors is not defined. Autopsy study shows a prevalence of 24.3%; however, imaging studies have found the prevalence of 1.2–2.4%. On the other hand, pseudocystic lesions reach 90% of all pancreatic cystic lesions but only 45% of these patients had previous pancreatitis [6]. The economic impact that is necessary to follow these patients by imaging studies should be evaluated.

The epidemiologic and demographic features are different in the several types of cystic tumors, and they will be presented in specific sections.

3. Diagnostic perspectives and management options

The current use of imaging modalities has allowed some important results in the nosographic study: certain distinction between postnecrotic acute or chronic pseudocysts and cystic tumors; among the cystic neoplasms, the identification of clinical pathological features that allow recognizing some kinds of cystic tumors with several perspective of neoplastic evolution.
Cystic and intraductal mucinous neoplasms are pancreatic tumors of ductal origin and are characterized by cysts lined by mucinous epithelium.

Cystic tumors of the pancreas have the characteristic of precursor: they may be associated with or progress to invasive carcinoma. They are the preinvasive neoplasms, as the pancreatic intraepithelial neoplasms, but these tumors form clinically detectable masses, usually before they become invasive, as the gastrointestinal adenoma. From these data, we take the therapeutic decision. A rough and summary monitoring of this setting clearly shows that cystic lesions are becoming increasingly more common, particularly among resection specimens. The reasons for this increase in frequency are various: important improvement in imaging techniques allows increased detection of clinically silent neoplasms; the majority of the cystic tumors are surgically removable because they are non-infiltrative in their evolution, and finally great decrease in postoperative complications and mortality rate of pancreatic surgery. The increased imaging and pathological studies and confirmation of all pancreatic cystic lesions result in better knowledge of these lesions.

A rough estimate of relative frequency of the pancreatic cystic lesions from the published data in the literature has been reported [5, 9]: pseudocysts (pancreatitis associated), 30%; IPMNs, 20%; MCNs, 10%; SCNs, 20%; acinar cell cystadenocarcinomas, lymphoepithelial cysts and lymphangiomas, <5%; SPPNs, <5%; cystic ductal adenomas, <5%; CPENs and metastasis, <5%.

The more simple classification of pancreatic cystic lesions subdivides two main classes: non-neoplastic cysts with pseudocysts non-lining and simple or congenital cysts, retention cysts that reach 80% of cases; neoplastic cysts or lining lesions that set up 20% of cases and can be defined pancreatic cystic neoplasms (PCNs) [7]. The main problem in the management of these lesions is the sure distinction between non-neoplastic cysts (pseudocysts, retention, and simple cysts) and pancreatic cystic neoplasms. Moreover, in the latter group, we need to distinguish non-mucinous from mucinous cysts that are considered being premalignant lesions. The therapeutic choices can be very different from simple follow-up to surgical resection. The WHO [1, 10] histological classification of tumors of exocrine pancreas and classification of pancreatic cystic lesions, integrated and updated by Kosmahl et al. [3] should be valuable references in the development of this subject. The specific epidemiology, histological features, imaging characteristics, clinical evolution, and therapeutic choices of the most frequent lesions as well as rare forms are described in each specific section.

4. Serous cystic neoplasms (SCNs)

SCNs can be divided into serous cystadenoma and serous cystadenocarcinoma. Serous cystadenoma is a benign neoplasm consisting of uniform glycogen-rich epithelial cells that give rise innumerable small cysts containing serous fluid. These lesions arise from centroacinar cell-intercalated duct system [11, 12], producing MUC6.

Histological and immunohistochemical data characterize the morphology and pathological evolution of serous cystadenoma. The cells lining the small cysts have clear cytoplasm with
well-defined border and round uniform nuclei. They are negative for mucin stains; in these, lesions are not present the molecular genetic alterations, specific of mucinous-type ductal pancreatic neoplasia such as mutation in the K-ras, SMADH4/DPC4, TP53, and p16 genes [13]. In the pathogenesis of serous cystadenomas, the alterations of von Hippel-Lindau (VHL) gene have been demonstrated in 40% of cases [3]; therefore, serous cystadenomas are associated with von Hippel-Lindau syndrome, an autosomal dominant disorder, characterized by hemangioblastoma of central nervous system and retina, renal cysts and neoplasms, and phaeochromocytomas. The pancreatic cystic lesions in VHL syndrome usually develop earlier than central nervous system lesions.

The relative frequency of serous lesions into cystic pancreatic neoplasms ranges from 20 to 30%.

The SCNs occur predominantly in female patients (female/male ratio 3:1) of sixth–seventh decade. Almost 70% of SCNs occur in the body or tail of the pancreas and 30–40% of the patients are asymptomatic, and the lesions are detected incidentally. Symptomatic patients can present some trouble caused by size of the neoplasm such as abdominal pain, discomfort, malaise, anorexia, or objective signs as palpable mass, jaundice, and weight loss.

On imaging studies (CT or MRI), SCNs may present with two main morphologies: the more frequent, classic microcystic appearance and the less common oligocystic appearance.

Microcystic-type lesions present multiple small cysts, in one-third of cases with a central fibrous scar and calcification creating a sponge-like appearance, which can be considered pathognomonic. The size of the mass, much variable, ranges from few centimeters to 20–25 cm.

There are rare cases of oligocystic-type pattern (megacystic and macrocystic). This type consists of fewer and larger loculi, with lobulated contour without wall enhancement and usually is located in the pancreatic head [14]. The epithelial lining of these cysts may become denuded and can be difficult to distinguish from mucinous neoplasms. In this case, it can be useful to identify the characteristic glycogen-rich clear cells [15].

On EUS, the SCNs show multiple, small, anechoic cysts and thin septations. There is a vascular network on cyst wall. The aspirated cyst-fluid from EUS-FNA is low in CEA concentration, and the result of cytology is poor.

For SCNs, the risk of malignancy is <1%. SCNs with certain clinical diagnosis, little in size, from 2–2.5 to 4–5 cm, asymptomatic can be observed. The criteria of the control are based on increase of the size lesion and increase of the tumor markers (CEA). Beside the benign serous cystadenomas that are the majority of cases, there are also few malignant lesions, serous cystadenocarcinomas [16]. The structural histological findings are overlappable between serous cystadenoma and cystadenocarcinoma, and often only the metastatic potential should distinguish the malignant variants.

In the SCNs, the certainty of the preoperative diagnosis is most important for the therapeutic choice between non-operative management with follow-up and surgical treatment. Three
criteria should be evaluated for surgery: likelihood of malignant evolution, symptoms caused by increase of the size of the tumor, and age of the patient.

Malignant SCNs constitute <3% of all SCNs [17], but within these cases, there are also serous cystadenocarcinomas not as evolution of benign tumors. Therefore, the global risk of malignancy of SCNs is <1% [18, 19].

A lot of the patients are asymptomatic at the diagnosis (incidental diagnosis). The likelihood of symptoms increases with the size of tumor. In fact, 22% of the patients is symptomatic with tumor <4 cm in diameter, but for tumor more than 4 cm, 77% of the patients becomes symptomatic [19].

The average age at the diagnosis frequently is 65 years or more.

The choice of treatment of SCNs can be summarized. We can consider several cases:

• old patients (>65 years), asymptomatic, size tumor <4 cm with pathognomonic imaging appearance should be observed;
• young patients (<65 years), asymptomatic, size tumor <4 cm with pathognomonic imaging appearance also should be observed;
• patients asymptomatic, size tumor >4 cm with pathognomonic imaging appearance could be observed (but the surgery can be discussed);
• patients symptomatic, size tumor >4 cm with pathognomonic imaging appearance should be proposed for surgery;
• cases with not complete diagnostic appearance or uncertain diagnosis should be proposed for surgical treatment.

In summary, surgical indications for SCNs with certain diagnosis (imaging, fluid cyst evaluation, etc.) are based on serious symptoms, great size tumors, or great increase of the size tumor in patient diagnosed and followed over time and increase of tumor marker (CEA) in fluid cyst [20].

5. Mucinous cystic neoplasms (MCNs)

These are the most frequent cystic pancreatic neoplasms. They amount for 20–40% of all cystic tumors with the prevalence of 25–30% for mucinous cystadenoma and 15% for mucinous cystadenocarcinoma.

There are two types of MCNs, both not communicate with the pancreatic duct. The cysts are lined by columnar, mucin-producing ductal epithelium and sometimes papillary epithelium. In the first type, ovarian-type stroma is located under the epithelial layer; the ovarian-type stroma is positive to estrogen and progesterone receptors [6]. Ectopic ovarian stroma can be included in the pancreas during embryogenesis and this can cause, by releasing hormones, the proliferation of epithelium and then the cystic neoplasm. This hypothesis that connects the
stromal component of MCNs and ovarian tissue should be supported by morphological resemblance. This type is present almost exclusively in women of fifth–sixth decade and predominantly is located in body and tail of pancreas.

There is another type of MCNs, more common, without ovarian stroma that can be located anywhere in the pancreas and occurs in both sexes. The malignant potential is very high in MCNs based on the possible evolution of mucinous transitional epithelium. Consequently, MCNs may be classified based on the degree of dysplasia: MCNs with low-intermediate grade dysplasia, with high-grade dysplasia, and finally with associated invasive carcinoma [14]. Histological heterogeneity of MCNs is in evidence with coexistence of benign appearance and malignant epithelia. Malignancy, \textit{in situ} or invasive, is found in 35–45\% of cases [21].

The macroscopic appearance of MCNs is cystic mass, unicocular or multilocular, containing thick mucine or sometimes mixed with hemorrhagic materials. The cystic wall is well defined, fibrous, and sometimes (10\%) calcified.

Clinical appearance in the symptomatic patients presents abdominal pain, palpable mass, anorexia, fatigue, weight loss, and in some cases pancreatitis. The results of routine laboratory examinations are generally non-specific. One-third of patient can be asymptomatic [22]. Imaging examinations (CT and MR) of MCNs show large cysts with septae and in some cases peripheral thin calcification of the walls. In some experiences, the presence of peripheral calcification, wall thickening, and thick septation has been highlighted as important for malignant evolution of MCNs [23]. Overlappable data can be detected by EUS: mass formed from fluid-filled cysts with thin walls, septae, and diameter 1–2 cm without duct communication. Malignancy suspicious can be based on wall thickening, irregularity, intracystic solid mass, and increased size of all lesion.

EUS-FNA can allow the evaluation of fluid content of cysts: CEA levels are high and can be useful in the diagnosis [6]. Pathological and evolutionary characteristic of MCNs affect treatment decisions. Malignant potential of these neoplasms is the cornerstone of the therapy. Relevant is the increase in the frequency of K-ras and p53 mutations as in sequence adenoma–carcinoma of colon cancer. Consequently, there is high likelihood of evolution into cancer if untreated. In fact, there is age difference of 10 years longer between patients with cystadenoma–carcinoma and patients with cystadenoma [24, 25]. Based on the pathological characteristics of histologic heterogeneity, extensive histologic sampling is necessary for certainty of diagnosis (from adenoma to carcinoma). The current and unanimous guidelines propose the surgical treatment for all MCNs. The contraindications for intervention are related to the patient’s conditions. The pancreatic resection is connected with the location of lesion: head, body, and tail. Duodenopancreatectomy, middle pancreatectomy, and distal pancreatectomy with or without splenectomy should be performed. Less extensive resections, such as enucleations are not recommended also because usually followed by high complications rate. Laparoscopic approaches are becoming more common and fully justified.

Cure rate of surgical resection for non-invasive MCNs (carcinoma \textit{in situ}) is 100\%. The 5-year survival rate for resected patients with invasive lesions is 40–50\%; whereas the 2-year survival rate is 60–70\%. Surveillance after surgery in these patients is required.
6. Intraductal papillary mucinous neoplasms (IPMNs)

The incidence of IPMNs is not well defined. In the recent years, their detection is increased based on the technical improvement of imaging examinations and the better knowledge of pathological features. Some data from the literature report that incidence range from 20 to 50% of all pancreatic cystic neoplasms [6, 26, 27]. Tumor arises from epithelium of the main pancreatic duct or its side branches. The lesions are lined by the intraductal proliferations of ducal columnar mucin-secreting epithelium with papillary projections that cause obstruction and dilatation of the duct. Tumors localized in the main pancreatic duct can spread in the rest of the duct. Men and women are equally affected. The neoplasm can be located anywhere in the pancreas. The most frequent localization of lesion is in the head of the gland and in 20–30% of cases can be multifocal. In 5–10% of cases, the pancreas can be diffusely interested [26, 27]. There are two varieties of this neoplasm, following its localization: main duct type (MD-IPMNs), most frequent (57–92%), and side branches type (BD-IPMNs), localized in the side branches of ducal system, less frequent (6–46%) [28]. In the combined type of IPMNs, main and branch ducts are both involved. IPMNs encompass epithelial changes from adenoma as premalignant lesions to carcinoma in situ, based on the progression of dysplasia, and finally invasive carcinoma. The degree of dysplasia allows the classification of IPMNs: IPMNs with low- or intermediate-grade dysplasia, IPMNs with high grade, and IPMNs with invasive carcinoma.

The characteristic behavior of IPMNs progresses toward malignancy. There is, in the observational studies, an age difference, 6 years longer, between patients with malignant tumors and patients with mucinous adenoma [29]. The communication with pancreatic duct system is characteristic. According to histological features (architecture and cytology), four types of IPMNs, such as gastric, intestinal, pancreatobiliary, and oncocystic, have been described. Gastric-type epithelium is frequent in side branches type with better prognosis (malignant potential 28%); intestinal-type and pancreatobiliary-type epithelia are more frequent in main duct type with bad prognosis (malignant potential 60%) [30]. Several patients can be symptomatic with non-specific symptoms. Clinical appearances can be usually abdominal discomfort or pain, malaise, nausea, and vomiting. Frequently, first clinical appearance is acute pancreatitis generally with benign evolution, due to mucous obstruction of the pancreatic ducts. Acute pancreatitis can be recurrent in 20% of cases. In most cases, IPMNs are asymptomatic. IPMNs with invasive carcinoma should be associated with more evident clinical data such as weight loss, jaundice, and diabetes.

IPMNs usually are diagnosed in elderly (sixth decade). Because high likelihood of malignant evolution of these lesions, there is an age difference, 6 years longer, between patients with malignant or benign lesions [29]. The results of blood examinations, as liver function tests, lipase, amylase, serum CA 19-9, and CEA, and routine tests are non-specific for these pancreatic cystic neoplasms.

Imaging examinations are decisive for diagnosis. They can be less invasive such as US, CT, MRI, and more invasive such as EUS, endoscopic retrograde cholangiopancreatography (ERCP).
Transabdominal US has limited diagnostic role. This examination can show dilatation of the main duct with cystic images around the ducts and thick mucinous content. Sometimes, US can detect the duct communications. CT and MRI are currently employed in the diagnostic assessment of IPMNs. These examinations can detect morphological features of the lesions: size and location, calcification, pancreatic duct dilatation, appearance of the cysts with septae, and thickening of wall. These morphological appearance detected by imaging examinations can identify IPMNs excluding other cystic pancreatic lesions and can distinguish the MD-IPMNs from BD-IPMNs. MRI and CT can also demonstrate the communication between the duct and cyst.

In the past years, endoscopic retrograde cholangiopancreatography (ERCP) was crucial imaging examination in the diagnosis of IPMNs. ERCP may detect dilated main pancreatic duct with mucinous filling and/or intraductal proliferations. These features are characteristic of MD-IPMNs. Whereas in the BD-IPMNs, the examination shows cystic lesions due to dilatation of affected branch ducts that communicate with main pancreatic duct.

In some cases, the imaging studies show a dilated pancreatic duct but not the intraductal tumor. Moreover, the dilatation can be proximal and distal to the tumor, because of overproduction of mucous. Classically, the endoscopic observation of open Vater’s papilla and mucin extrusion has been reported.

Unfortunately, ERCP is invasive procedure and its diagnostic use has been limited. In the recent years, EUS plays an important role in the diagnostic program of pancreatic diseases. EUS should be useful in the differentiation of types of IPMNs. EUS findings in MD-IPMNs can be a characteristic of morphological changes of these lesions such as various extension and degree of duct dilatation and, in some cases, the presence of intraductal tumor. The recurrent acute pancreatitis can show several parenchymal damages such as edema and enlargement of the gland or signs of parenchymal atrophy. Characteristics of BD-IPMNs are the lesions formed by multiple little cysts (few millimeters) with internal septation, mucous, wall nodule, or thickening, intracystic papillary projections. The Wirsung’s duct should be moderately dilated [31].

Based on EUS findings, some criteria of malignancy in IPMNs were defined: great dilatation (>10 mm) of the main pancreatic duct and evident, large intraductal tumor (>10 mm) in MD-IPMNs; large cystic lesions (>40 mm) with thick, irregular septation, wall thickening, mural nodule in BD-IPMNs. We can also add to these criteria of malignancy the vascular invasion and lymph node metastases. The accuracy of EUS malignancy criteria ranges from 40 to 90% [32, 33]. Fine needle aspiration biopsy (FNAB) during EUS allows taking samples for biochemical, cytological, and DNA analyses. The first macroscopic finding is the mucinous fluid characteristic of MCNs and IPMNs. High concentration of CEA should be characteristic of mucinous lesions, such as high level of amylase because duct system communication. Brugge has emphasized the cutoff CEA level for differentiating mucinous from non-mucinous pancreatic cystic lesions: the CEA level of 192 ng/ml has the sensitivity of 73% and specificity of 84% [34]. Unfortunately, this analysis not distinguish MCNs from IPMNs and benign from malignant lesions. Cytological study should be useful for the diagnosis of mucinous lesions with the presence of epithelial cells (different from glycogen-rich clear cells of serous cysta-
denoma). Moreover, the presence of high-grade cytological atypia relevant to malignancy can be detected [35]. DNA analysis of pancreatic cyst fluid shows K-ras mutation, characteristic for mucinous lesions, and GNAS mutation more present in IPMNs. The latter can differentiate IPMNs from MCNs [36].

The planned interventions for treatment of IPMNs are duodenopancreatectomy or distal/middle pancreatectomy based on location of lesions. We need to take into account that the tumors localized in the main pancreatic duct can spread in the rest of the duct. Consequently, the surgical planification can have changes with possible extension of pancreatic resection to allow negative or low-grade dysplasia at surgical margins. In fact, intraoperative frozen section diagnosis of the transection margin shows positive results in 20–50% of cases [28]. Surgical indications for IPMNs are based on risk of malignancy that is different for MD-IPMNs and for BD-IPMNs. The frequency of malignant potential in MD-IPMNs is 61.6% and the frequency of invasive IPMNs is 43.1% [32]. The malignant potential in BD-IPMNs reaches 28% and the frequency of the invasive lesions is 18%. Therefore, the indication for pancreatic resection is justified and recommended in the majority of the patients with MD-IPMNs by international consensus guidelines [32]. On the contrary, surgical indications in the patients with BD-IPMNs are more debatable. IPMNs, with some not negligible differences between main duct type and branch duct type, encompass epithelial changes from adenoma, carcinoma in situ, and invasive carcinoma. The lesions benign at the beginning progress toward malignancy. This characteristic of biological evolutivity makes difficult and complex the surgical indications or the timing of intervention after a possible observation period. Beside the positive and specific diagnosis of each type of cystic pancreatic neoplasm as IPMNs or MCNs, SCNs are crucial for the next diagnostic step, recognizing the malignancy of the neoplasm. In the difficult diagnosis of IPMN, the criteria based on CT imaging suggested by international consensus guidelines should be useful [32]. These criteria have been subdivided as “high-risk stigmata” and “worrisome features.” The first are obstructive jaundice in a patient with cystic lesion of the head of the pancreas, enhancing solid component within cyst, main pancreatic duct size of 5–9 mm, or main pancreatic duct >10 mm in size. The “worrisome features” are cyst size >3 cm, thickened/enhancing cyst walls, non-enhancing mural nodule, and lymphadenopathy [32]. Ablation therapies of cystic neoplasms have been proposed: EUS-guided injection of cytotoxic agents (e.g., paclitaxel, ethanol) and radiofrequency ablation. These procedures are not widely employed and their results are not defined and can be evaluated with difficulty, also because these ablation therapies have been used for various PCNs [37–39]. The results of surgical treatment for non-invasive disease are very positive with 5-year overall survival of 100%; for invasive disease, 5-year overall survival drops to 50–60% [28]. Recurrence rate of IPMNs can be evaluated after surgical resection. The mean recurrence rate is 15% in the remnant pancreas (ranges from 7 to 30%). The recurrence of IPMNs as invasive disease ranges from 3.4 to 44% [40, 41]. The differential diagnosis between IPMNs and chronic pancreatitis can be difficult in some cases. Usually, alcohol abuse is frequent in chronic pancreatitis. Several clinical and morphological features are common to both diseases: main duct and branch duct dilatation, intracystic and intraductal calcifications, and recurrent episodes of pancreatitis. Moderate and segmental dilatation of main pancreatic duct with intraductal lithiasic obstruction, moderate dilatation of the branch ducts communicating with main duct, and finally the widespread of
the pancreatic ductal system are characteristic of chronic pancreatitis. On the contrary, segmental and marked dilatations of the branch ducts with little calcifications are characteristics of IPMNs.

7. Solid pseudopapillary neoplasms (SPPNs)

SPPNs represent 9% of all cystic pancreatic tumors and have the major incidence in young female patients (second–third decade). SPPNs are a neoplasm of unknown, not well-defined origin: in fact, in the past, various descriptive names were employed. The macroscopic appearances of SPPNs are large solid masses (8–10 cm in size) and well encapsulated, and often the cut section shows areas of hemorrhage, cystic degeneration, and solid areas. The microscopic features are polygonal epithelioid cells that form solid pseudopapillary structures alternated hemorrhagic necrotic pseudocyst. There is also evident extensive vascular network, often with infiltrative growth pattern. Alterations in the antigen-presenting cell/beta-catenin pathway [42] and vimentine positive can be present. The histologic picture may resemble closely to pancreatic endocrine neoplasms (PEN) but chromogranin is negative. In some cases, histologic criteria of malignancy such as high nuclear grade, venous invasion, and atypical cells may be observed; the metastatic spread is possible (10–15% of cases). SPPNs can be located in all side of the pancreas. Clinical appearances are abdominal pain, palpable mass, nausea/vomiting, jaundice, and weight loss. The imaging examinations (CT, MRI, and EUS) show a solid and cystic masses with a well-defined and thick capsule with sometimes peripheral calcifications without septations. EUS-FNA provides little information. SPPNs can be considered lesions with low malignity and rare occurrence of metastasis, usually hepatic (10–15%). The recommended treatment is surgery and the complete resection is often possible (94%); the cure rate reaches 85–95% of patients [6, 44]. The pancreatic resection is based on the location of neoplasm in the gland [43, 44].

8. Cystic pancreatic endocrine neoplasms (CPENs)

CPENs encompass 8% of all pancreatic cystic tumors and about 15% of pancreatic neuroendocrine tumors [45, 46]. The majority of CPENs are non-functioning and asymptomatic. These neoplasms usually are diagnosed in elderly patients (sixth–seventh decades) without sex prevalence. They can be associated with multiple endocrine neoplasia types. The diagnosis, generally incidental, is based on imaging examinations (US, MRI, and CT). Cystic mass is usually with hypervascular rim, and in several cases, there is septation or a solid component [45]. The lesions are generally well circumscribed with regular wall around areas of cystic degeneration.

EUS-guided FNA can reveal low levels of CEA. Immunohistochemical staining for chromogranine and synaptophysin is present. Malignant potential of CPENs is not clearly defined because it is difficult to detect malignancy on biopsy. The lesions are considered premalignant,
and surgical treatment is indicated especially for lesions plus than 2 cm in size. The resective surgery presents excellent results with very long survival (plus than 85% of patient treated) [46]. Observational strategy has been proposed [47] for CPENs based on the similar experience with non-functioning pancreatic endocrine neoplasms (PENs) [48]. The results of non-operative choice are not defined.

9. Acute postnecrotic pseudocysts

Pancreatic pseudocysts are inflammatory lesions. They are evolutions and complications of chronic and acute pancreatitis. The etiologies of pancreatitis are various: alcoholic, biliary, or traumatic. The pseudocysts represent about 80% of all cystic lesions of the pancreas. The pseudocyst wall has no epithelial lining unlike the true cysts [49]. Histologically, the pseudocyst wall consists of fibrosis and inflammatory tissue. Moderate and severe acute pancreatitis are characterized by fluid necrotic collections in or near the pancreas at the beginning without wall. With the flogistic evolution, the fluid necrotic collections are surrounded by granulation and fibrous tissue [50]. Acute postnecrotic pseudocysts are the final evolution of necrotizing pancreatic gatherings, characterized by complete separation of the tissues, with liquid content and a fibrous wall [51]. The incidence of acute pseudocysts is low, at 5–16%. Several clinical imaging and chemistries features can be useful for differential diagnosis between pseudocysts and cystic pancreatic tumors. In the history, there is usually previous pancreatitis; the cystic walls are regular and thin, without calcification: in the 65–70% of cases, there is the communication with Wirsung’s duct; in the intracystic fluid, CEA, CA19-9, and mucous cells, on the contrary increased amylase and lipase, are absent. The evolution of a lesion with a fibrous wall and the formation of a pseudocyst can be completed in several weeks and in some cases in a longer period (12–16 weeks). Small cysts (<5–6 cm) can develop for many months without clinical appearance. In some cases, spontaneous improvement until the resolution of the pseudocysts can occur [52].

Diagnosis of acute postnecrotic pseudocysts is greatly facilitated by the history of previous episodes of acute pancreatitis. The imaging examinations (transabdominal US, CT, MRI, and MRCP) are crucial for positive diagnosis (sensitivity of CT is very high 90–100%) [49]. Characteristic picture on CT is roundish cyst, fluid filled, without septations, and surrounded by a thick wall around the pancreas. EUS can be used for further evaluation but usually do not add other information on CT. EUS-guided FNA and cyst fluid analysis can demonstrate high amylase concentration.

The size of pseudocysts (plus than 6–7 cm) and the clinical presentation and evolution (lesions symptomatic and/or persistent over many months) can direct the treatment [53].

The choice of therapeutic procedure should be based on the very frequent connection of the acute pseudocysts with pancreatic ducts [53]. The percutaneous US/CT-guided drainage is usually complicated by pancreatic fistula with persistent leakage from the drain, infection, and repeated changes of the drain [53, 54]. Therefore, the intervention of choice must provide persistent drainage of pancreatic secretion by a cystodigestive anastomosis or fistulas [53].
Another pathological characteristic of acute pseudocysts is the close connections with various adjacent intestinal organs (stomach, duodenum, and small intestine) according to the anatomical site where the pseudocyst develops [53].

Drainage of the pseudocysts by endoscopic technique has been proposed [55, 56]: this is performed by creating a small opening between the cyst and the stomach. The disadvantage of this technique is incomplete drainage with recurrence of pseudocysts and infections because the communication can be small and in site not declive [53, 57]. The surgical cysto-gastro-duodenal anastomosis can employ the more adjacent intestinal organ (stomach or duodenum or small intestine) and can perform cystogastrostomy or cystojejunostomy or cystalternostomy [52, 53].

For cysts located in the body or tail of pancreas, the cystojejunostomy or cystogastrostomy is performed depending on the development of the cyst above or under the mesocolon. For pseudocysts located on the head of the pancreas, cystalternostomy is usually performed. The same surgical procedures can be performed with a laparoscopic approach with the advantage of the minimal invasiveness [53].

10. Chronic pseudocysts

In the chronic pancreatitis parenchymal fibrosis and ducts, dilatation can cause chronic pseudocysts [53]. Chronic pancreatitis encompasses various complications. Most frequent are pseudocyst formation, mechanical obstruction of the duodenum, or common bile duct. Pseudocysts occur in about 10% of patients with chronic pancreatitis. There are great pathological differences from acute and chronic pseudocysts. The first usually develop from peripancreatic fluid accumulations that cause the pseudocysts formation in the setting of acute pancreatitis. On the contrary, chronic pseudocysts develop as a result of ductal disruptions [53]. Pseudocysts may be single or multiple, various in size. In fact, the pancreatic pseudocysts generally are caused and long maintained by some leaks from the pancreatic ducts that give the constant filling by pancreatic secretions [50]. A long history and clinical evolution of chronic pancreatitis can give usually a clear diagnostic direction. Chronic recurrent abdominal pain characterizes the clinical appearance of the disease. The other common symptoms are nausea and vomiting, early satiety. Jaundice can occur in 10% of patients with a slow start due to bile duct compression by the pseudocyst or the pancreatic flogosis. The imaging examinations, particularly EUS, allow, beside the cystic lesion, to detect the characteristic parenchymal features of chronic pancreatitis: the damage of the pancreatic duct system, parenchymal fibrosis, and calcifications [53]. The Rosemont classification [58] of chronic pancreatitis, based on EUS findings, identifies major criteria such as main pancreatic duct calculi and lobularity and minor criteria with cysts, dilated ducts >3.5 mm, irregular pancreatic duct contour, and dilated side branches >1 mm.

The surgical treatment of chronic pancreatitis should be based on the clinical and pathological scenario: two types of surgical procedures with the aim of improving or eliminating ductal hypertension by intestinal anastomotic drainage can be performed [53]. Resectional proce-
dures allow eliminating the areas of chronic inflammation frequently in the head of the pancreas. A late complication of chronic pancreatitis encompasses evident ductal dilatation. The incidence of these chronic pseudocysts is high: 20–40% [59]. The pseudocysts can be connected with adjacent organs such as stomach or duodenum. Consequently, endoscopic approach can be performed with mini-invasive intent, cystogastrostomy, or duodenocystostomy [60]. The morbidity of this procedure is 3–11%, without mortality. The treatment of chronic pseudocysts by drainage through the duodenal papilla and ductal system also has been proposed by endoscopy. This procedure with ERCP allows putting in place the transpapillary endoprotesis as drainage. In addition, the transluminal stones removal and/or lithotripsy can be possible, if intraductal stones are present [60–62]. The surgical management has shown good results in the treatment of chronic pseudocysts, pancreatic duct dilatation with stenosis, and stones. The Puestow procedure and its modifications of Partington and Rochelle [63, 64] are the standard surgical drainage methods in chronic pancreatitis with pseudocyst and/or dilated ducts. These interventions involve the anastomosis between dilated main duct and pseudocystic wall with a Roux-en-Y loop of jejunum. The results show low morbidity (<10%) and low mortality (<1%) with relief from abdominal pain in 85–90% of the patients [65–67]. Sometimes, with a dilated pancreatic duct, a fibrotic inflammatory mass may be present in the pancreas. In these cases, the interventions that couple drainage and resective procedures defined “hybrid” can be chosen: Beger, Frey interventions, and some variants [67–69].

11. Indeterminate pancreatic cystic lesions

Cystic lesions of the pancreas today are an important diagnostic challenge. In each case the specific diagnosis must be defined: pseudocysts, SCNs, MCNs, IPMNs, and SPPNs are the most common lesions. Perhaps more important is to establish the malignant potential and the objective data of a neoplastic degeneration. The diagnostic procedures to choose should be geared toward minimally invasiveness. Imaging examinations are at the first line: CT, MRI, MRCP, and PET are minimally invasive and have shown various degrees of sensitivity and specificity. ERCP and EUS–FNA are invasive and can give some useful information. If imaging findings allow the certain diagnosis of specific lesion of which is well known the malignant potential and the characteristic features of malignant evolution, the therapeutic choices (surgery or observation) are enough defined. Moreover, clinical symptomatic picture adds further certainty to the treatment program. There are also, among cystic pancreatic neoplasms, some well-defined diagnoses characterized by imaging and clinical data for which the management is uncertain and debatable. In summary, there are two problems in the management of cystic pancreatic lesions. Firstly, the difficulty in the diagnostic definition and/or in the detection of malignancy; moreover, also, in some cases, the positive diagnosis of the lesions is characterized by particular pathological and clinical features that cause uncertainty in the choice of treatment between surgery, observation program, and for how many times the control can be prolonged.

All clinical, pathological, and imaging findings with also analysis of cyst fluid examination by EUS-FNA have been reported above in the detailed report of each cystic lesions of the pancreas.
This knowledge crucial for the diagnosis and management should be integrated by the classification that separates pancreatic cystic lesions in two categories. There are pancreatic cysts benign, not premalignant, such as SCNs, pseudocysts, lymphoepithelial cysts, and lymphangioma, and pancreatic cysts premalignant and malignant such as MCNs, IPMNs, SPPNs, and CPENs [70]. Roughly, the first conclusion can be the indication of surgical resection for premalignant lesions and observation for benign or indolent lesions. The indeterminate cystic lesions can be located between the cysts frankly benign such as pseudocysts or serous cystadenoma or lymphangioma and, on the other hand, the cystic lesions frankly malignant or with clear findings of malignant evolution such as MD-IPMNs, IPMNs associated with invasive carcinoma, MCNs with increased size, cyst-wall irregularity, and intracystic solid regions. In the indeterminate cystic lesions, the management choices can be debatable and uncertain. In this group, small cysts with not certain diagnosis, small BD-IPMNs, or MCNs can be considered. Characteristic in this setting is the asymptomatic pancreatic cyst incidentally detected on abdominal CT. The improvement of an unclear diagnosis can be achieved with MRI and MRCP. If the data obtained with these examinations are not conclusive (e.g., main duct <1 cm; thick cyst wall size >2 cm), the diagnostic process can continue with invasive procedure such as EUS-FNA. The detection of nodule or solid mass or main duct >1 cm and cytology positive for malignancy is crucial for the surgical resection. In the patients without these diagnostic data, the conservative option marked by periodic controls with CT or MRI or EUS (repeat the control test in 6 months) can be evaluated [70]. In the patients with clear diagnosis (CT, MRI, EUS, and clinical data), serous cystadenoma asymptomatic can be followed with periodic imaging control with MRI or CT (repeat the test in 1 year); if symptomatic, overall in young patient (<65 years), surgery should be considered. Patients with MD-IPMNs, mixed-type IPMNs, SPPNs, and MCNs should be proposed for surgical resection. BD-IPMNs characterized by main pancreatic duct >1 cm, cystic lesion in the head of pancreas, jaundice, solid component, main duct with thickened wall, and mural nodule, which are features concerning malignancy, can undergo surgical resection, if, without these findings, CT, MRI, and EUS (repeat the control test in 6 months) may be followed conservatively.

There is almost unanimously consensus [32, 71] for surgical indications in patients with MCNs, SPPNs, MD-IPMNs, and mixed-type IPMNs. Patients with serous cystadenoma should be directed to conservative management. Surgery can be proposed only in symptomatic patients or if the diagnosis is uncertain. Patients with BD-IPMN can be observed also if the size lesion is more than 3 cm unless there are features concerning for potential malignancy.

12. Clinical cases

This chapter can be completed with the presentation of some cases of cystic pancreatic neoplasms treated in our Service. These detailed examinations can contribute to clarify several clinical pathological features.

• **First case study**: female, 35 years old. Anamnestic data: non-specific vague upper abdominal pain and postprandial fullness since 4 months. The diagnosis is incidental by US and CT.
The multislice CT shows cystic mass located in the tail of the pancreas, size 8.5 cm, unilocular, fluid content, and wall well defined, with contact but not infiltration of posterior gastric wall and splenic vessels. The cystic pancreatic lesion, with this radiologic features, may be also a postnecrotic pseudocyst.

Differential diagnosis, for a cystic pancreatic lesion with these imaging features, may be discussed between MCNs and postnecrotic pseudocysts (Figure 1).

Figure 1. MCN of the tail of the pancreas (arrow).

The first question is whether other examinations for preoperative diagnosis can be useful. In these cases, the anamnestic data are most important: this patient had not in the past acute pancreatitis that can explain pseudocyst. Consequently in our opinion, other abdominal imaging cannot add other information. The preoperative diagnosis is MCN with the surgical indication: distal pancreatectomy and splenectomy.

The second question regards the method of treatment of proximal pancreatic stump. The transection (pancreatic body and splenic vein) with linear stapler and tubular drainage can be suggested. The splenic artery is treated separately.

The third question regards the incidence of pancreatic fistula in distal pancreatectomy. The most important and frequent complication of distal pancreatectomy is the pancreatic fistula. The incidence of pancreatic fistula ranges from 5 to 30% [72–75]. This variability is explained because there are no the standard definition of the fistula: there are a little gatherings or a few drainage in the postoperative period that are not diagnosed as fistula. The criteria for grading pancreatic fistula have been proposed by ISGPF [76, 77] based on drain and amylase level, persistent drainage (>3 weeks), signs of infections, sepsis, clinical conditions, and need for reoperation. The fistula can be classified, with increase of severity, as grades A, B, and C. The grade A and B usually can be treated with non-invasive approach: parenteral nutrition, somatostatine, etc. CT control can be useful. Pathological feature shows cystic lesion, size 8.5 cm, mucoid content with smooth surfaces, and thickened, glistening wall. Histological diagnosis was mucinous cystadenoma. Lymph node is negative.
The fourth question is whether surgical treatment with laparoscopic approach can be proposed. A laparoscopic approach is possible for small or medium size mucinous cystic tumors located in the body or tail of the pancreas. The laparoscopic duodenopancreatectomy is a very complex procedure not yet worldwide performed. But there are two important considerations: not to break the cyst during the intervention because the spillage of mucoid material could lead to tumor spread; moreover, the cyst should be removed intact because the pathologist can do an appropriate examination of the complete wall of the cyst.

- **Second case study**: male, 80 years old. Anamnestic data: recurrent episodes of pancreatitis with upper abdominal pain, hyperamilasemia, diabetes, mild alteration of cholestasis tests, and no alcohol consumption since 10 months. The imaging examinations (US and CT) show cystic lesions of the head of the pancreas, its size is 7 cm, mild dilation of main pancreatic duct, and choledocal duct. The MRCP confirms the same lesion and no stones or sludge in the bile duct (Figure 2).

**Figure 2.** MD-IPMN of the head of pancreas (arrow).

Preoperative diagnosis: Because of previous episodes of acute pancreatitis and no biliary stones and alcohol consumption, the proposed diagnosis may be cystic neoplasm. In addition, in this case, we have had the pathognomonic sign: mucus extrusion through a bulging papilla at endoscopy. The diagnosis was intraductal papillary mucinous neoplasm. There are clear surgical indications: duodenopancreatectomy has been proposed.

Pathological description: head of the pancreas, increased in size \((7.5 \times 5.3 \times 4.5 \text{ cm})\), and dystrophic with cystic lesions with mucus. Histology: IPMN not invasive in the pancreatic ductal ectasia with squamous metaplasia of epithelium. There is no neoplastic invasion in the lymph nodes.
In the surgical management, how to regulate the extension of pancreatic resection in IPMN is very important. First consideration: IPMNs encompass a spectrum of epithelial changes from adenoma to invasive adenocarcinoma; in addition, there is the propensity of the tumor to spread microscopically along the pancreatic ducts. Because of these histopathological features, the most simple therapeutic choice is the intraoperative control (by frozen section) to rule out the presence of the tumor in the transection margin (over the all on main duct). In this perspective, the extension of pancreatic resection is possible once or twice, but is corrected to make a total pancreatectomy? The standard choices are difficult. In the experience of Massachusetts, General Hospital has performed 63% duodenopancreatectomy, 17% distal pancreatectomy, and 19% total pancreatectomy [28]. The positive frozen-section intraoperative examination ranges from 23 to 52%. If recurrence occurs in the pancreas after first intervention, a second resection may be possible.

- **Third case study**: male, 78 years old. Anamnestic data: the patient has been operated for lung cancer 3 years ago.

In the follow-up, US of abdomen shows cystic lesion of the pancreatic head. As the most patients with serous cystadenoma, our patient was asymptomatic and the diagnosis incidental. CT and MRI confirm cystic tumor (size 1.5 cm) in the head of pancreas, well circumscribed and multinodular. There are also mild dilation of main bile duct and Wirsung. Our conclusion was for SCN (Figure 3).

![Figure 3. SCN of the head of the pancreas (arrow).](image-url)

In this patient, the diagnosis may be serous cystadenoma and the therapeutic choice is the organized controls. At present, we have made three controls (by imaging) every 6 months: There is no clinical or morphological modification of the lesion.

The first question is in which patients, the prolonged observation of the cystic tumor of the pancreas may be reasonable? Serous cystadenomas are indolent, slow-growing tumors, with
a very low incidence of malignancy (3%) [17]. These lesions become symptomatic with the increase in size. The reasonable therapeutic organization for serous tumors may be the following: first to take the certainty of the clinical diagnosis (serous cystic neoplasm).

Patient with little lesion (<4 cm) asymptomatic (in addition take in mind the great incidence of this tumors in sixth–seventh decade) with certain diagnosis can be undergone to non-operative treatment and followed up. Patient with the lesion bigger in size (>4 cm) symptomatic, in particular if younger, may be undergone to surgical treatment with pancreatic resection.

13. Conclusions

The improvement of imaging, endoscopic modalities, and cyst fluid studies allow now accurate and reliable diagnosis of pancreatic cystic lesions.

Moreover, the enlarged knowledge of valuable pathological studies established the potential for malignant transformation of these lesions identifying higher-risk lesions. Finally, the management options should be based on the assessment of each type of cystic neoplasms and the distinction of pancreatic cystic neoplasms from other pancreatic cystic lesions.

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