Chapter 8
Cystic Lesions of the Pancreas

Omer Basar and William R. Brugge

Abbreviations

BD-IPMN	Branch-duct intraductal papillary mucinous neoplasm
CEA	Serum carcinoembryonic antigen
CLE	Confocal laser endomicroscopy
CPEN	Cystic pancreatic endocrine neoplasms
CT	Computed tomography
ERCP	Endoscopic retrograde cholangiopancreatography
EUS	Endoscopic ultrasonography
EUS-FNA	Endoscopic ultrasound guided fine needle aspiration
FNA	Fine-needle aspiration

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IPMN	Intraductal papillary mucinous neoplasm
MCN	Mucinous cystic neoplasm
MDCT	Multidetector CT
MD-IPMN	Main-duct intraductal papillary mucinous neoplasm
MR	Magnetic resonance
MRCP	Magnetic resonance cholangiopancreatography
PCL	Pancreatic cystic lesions
PCN	Pancreatic cystic neoplasms
RFA	Radiofrequency ablation
SCN	Serous cystic neoplasm
SPN	Solid pseudopapillary neoplasm
US	Ultrasonography
VHL	von Hippel–Lindau disease

Question 1: I Was Told that I Have a Cyst in My Pancreas. Is It Cancer? How Did I Get It?

With increasing use of high resolution imaging techniques, pancreatic cysts are now being discovered with increasing frequency. It is important to determine whether a pancreatic cyst is benign (usually no treatment is needed) or pre-neoplastic (benign cyst having a potential to become cancerous) or neoplastic (must be resected). Non-neoplastic cysts of the pancreas account for 80 % of all pancreatic cysts and the most common is the pancreatic pseudocyst, which is mostly a local complication of acute pancreatitis. The prevalence of neoplastic cysts increases with age and can be associated with genetic abnormalities. Neoplastic cysts usually include a serous or mucinous epithelium, which shows its neoplastic potential: serous cysts are typically benign and mucinous have at least some malignant potential.

Question 2: Can My Cyst Be Treated Without Surgery?

The most common non-neoplastic cyst, pseudocysts, mostly resolves over time without any treatment. In cases that cysts cause symptoms or become infected drainage, is required.

Today, endoscopic drainage is the preferred technique for treatment and surgery is reserved for those who failed endoscopic approach.

The most common mucinous neoplastic cyst is IPMN and all IPMNs have a potential for malignancy progression over time. For the subtype main duct-IPMN, international consensus guidelines recommend resection for all patients, since the incidence of invasive carcinoma is high and its 5-year survival rates are low. For the subtype branch duct IPMN, given the low risk of low malignant progression, most of the BD-IPMN patients without symptoms or risk factors should be followed up. An alternative treatment is EUS-guided cyst ablation and ethanol and/or paclitaxel injection. Radio-frequency ablation is still under investigation.

MCNs are the other group of mucinous cyst and current consensus guidelines recommend surgical resection. For patients refusing surgery, EUS-guided cyst ablation therapies may be considered.

Serous cystic neoplasm has an excellent prognosis; surgery is recommended only for patients with symptoms.

Question 3: What If I Don't Do Anything; Will the Cyst Become a Cancer?

Pseudocyts will not become a cancer.

The mean frequency of developing malignancy in MD-IPMN is 61.6 %. The prognosis of SCN is excellent and these patients are commonly managed conservatively.

Introduction

Pancreatic cystic lesions (PCL) are relatively rare and in recent years they are being increasingly recognized with the improvement and widespread use of cross-sectional imaging tools [1, 2]. The vast majority of PCL are recognized incidentally in asymptomatic patients and the others are discovered in patients with symptoms such as abdominal pain and jaundice.

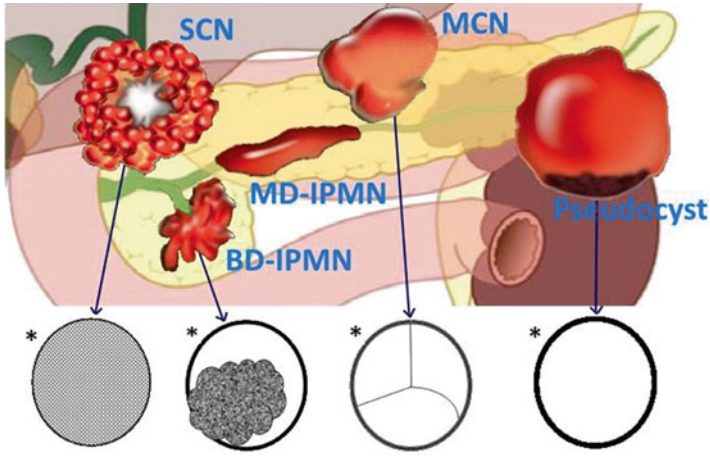

Fig. 8.1 Illustrations of the common pancreatic cysts. (*) The schematization of the morphology of cysts

In the past, most of the pancreatic cysts were believed to be pseudocysts, and the others were believed to be extremely rare. However, PCL are now recognized to be an extensive group of pancreatic tumors showing different histological, demographical, morphological, and clinical characteristics. The prevalence of pancreatic cystic lesions is reported to be ranging from 1.2 to 19 % in image-based studies (Fig. 8.1), [1–4]. A study evaluated 24,039 CT or MRI scans and reported that 290 patients (1.2 %) had pancreatic cysts, and a majority of the patients had no history of pancreatitis [5]. In an autopsy series on 300 patients, cystic lesions were found in 73 cases (24.3 %) [6]. The prevalence of cysts increases with age [3].

A number of systems have been used to classify pancreatic cysts. PCL may be broadly categorized as either non-neoplastic or neoplastic cysts (Table 8.1). Today, neoplastic cysts of pancreas are defined more commonly as pancreatic cystic neoplasms (PCN). PCN are frequently found to have a mucinous or serous epithelial lining. Serous cystic neoplasms are considered typically benign and cause symptoms

Table 8.1 Pancreatic cystic lesions

Non-neoplastic cysts
• *Epithelial*
Lymphoepithelial cyst
Mucinous non-neoplastic cysts
Squamoid cysts
Enterogenous cysts
Endometrial cyst
Para-ampullary duodenal wall cyst
• *Non-epithelial*
Pseudocyst
Infection-related cyst
Simple cyst
Retention cyst
Neoplastic cysts (pancreatic cystic neoplasms)
• *Mucinous cystic lesions*
Intraductal papillary mucinous neoplasm
Mucinous cystic neoplasm
• *Non-mucinous cystic lesions*
Serous cystic neoplasm
Solid pseudopapillary neoplasm
Cystic pancreatic endocrine neoplasm
Acinar-cell cystic neoplasm
• *Other neoplastic cystic lesions*
Ductal adenocarcinoma with cystic degeneration

secondary to space occupying mass effect. Mucinous cysts, including mucinous cystic neoplasm and intraductal papillary mucinous neoplasm, have a malignant potential. Thus, it is important to distinguish a non-neoplastic cyst from neoplastic or non-mucinous from mucinous cyst because the latter are considered being premalignant lesions. Non-neoplastic cysts of pancreas account up to 80 % of all PCL, however, the prevalence of PCN increase with age [1, 2, 5]. Because many

of these lesions are indistinguishable from each other preoperatively, many of them were resected unknowingly. In recent years, diagnostic methods, management algorithms and treatment options of PCL have been gradually changed. Accurate diagnosis is mandatory for PCL to choose the optimal management, which includes either follow-up conservatively or resect surgically. In this chapter, the major types of PCL are reviewed based on the recent advances in the diagnosis and management of these lesions.

Non-neoplastic Cysts

Non-neoplastic cysts of pancreas are benign lesions, which can be further classified as epithelial and non-epithelial cysts. Epithelial, non-neoplastic cysts of pancreas are categorized as lymphoepithelial cyst, mucinous non-neoplastic cysts, squamoid cysts, enterogenous cysts, endometrial cysts and para-ampullary duodenal wall cyst [7–9]. These lesions can be either congenital or acquired. Imaging studies are not usually sufficient enough to distinguish epithelial cysts from their mucinous complements. Although these entities are benign, because they often mimic mucinous neoplastic cysts, definite diagnosis is usually challenging until they are resected. Non-epithelial, non-neoplastic pancreatic cysts include pancreatitis-associated pseudocysts, the most common cyst of the pancreas, retention cysts, and infection related cysts including parasitic cysts [10]. On the other hand, cystic transformation of pancreas is observed in autosomal dominant polycystic renal disease [11], medullary cystic kidneys [12], congenital syndromes and cystic fibrosis [13].

Lymphoepithelial cysts are often thought to arise from the pancreas but they are characteristically round and well-bordered peri-pancreatic cysts. On cross-sectional imaging, they appear classically cystic and endoscopic ultrasonography (EUS) reveals a solid appearing cystic lesion filled with uniform, homogenous, hypo-echoic material. Pathological examination of a resected cyst shows an outer border of

benign lymphoid tissue with an inner lining of squamous epithelium ("lympho"+"epithelial"). Aspirated fluid with EUS guided fine needle aspiration (EUS-FNA) is a viscous, thick, pasty material. Cytology of the aspirated fluid reveals anucleated squamous cells, keratinaceous debris, lymphocytes, and histiocytes. Since lymphoepithelial cysts are benign, surgical resection is only advised for patients with symptoms due to mass affect.

Although there is an uncertainty whether congenital, simple, benign cysts occur in pancreas, these cysts are generally classified as a subgroup of non-neoplastic cysts. Non-solid simple cysts are seen in patients with cystic fibrosis within a diffusely atrophic fatty parenchyma. Simple cysts, which are of no clinical significance, are also demonstrated in patients with polycystic renal disease.

Pancreatic Pseudocysts

Pancreatic pseudocysts are the most common cystic lesions of pancreas and are inflammatory fluid collections associated with pancreatitis. These lesions mainly effect adult men and are local complications of acute pancreatitis due to different etiologies such as chronic alcoholism, biliary or traumatic pancreatitis [14]. The most common local complication of acute and chronic pancreatitis is peri-pancreatic and sometimes

Table 8.2 Fluid collections of acute pancreatitis

Type of pancreatitis	Fluid collection	Time
Interstitial edematous pancreatitis	Acute pancreatic fluid collection	<4 weeks after onset
Interstitial edematous pancreatitis	Pancreatic **Pseudocyst**	>4 weeks after onset
Necrotizing pancreatitis	Acute necrotic collection	<4 weeks after onset
Necrotizing pancreatitis	Walled-off necrosis	>4 weeks after onset

intra-pancreatic fluid collections. According to the revised Atlanta classification, local complications of acute pancreatitis are acute peri-pancreatic fluid collections, pancreatic pseudocyst, acute necrotic collections and walled-off necrosis [15]. Considering the absence or presence of pancreatic necrosis, acute fluid collections within 4 weeks from onset of acute pancreatitis, are named acute pancreatic fluid collection and acute necrotic collection. After the development of an enhancing capsule, a persistent acute pancreatic fluid collection is further termed a pancreatic pseudocyst and an acute necrotic collection is referred to as a walled-off necrosis. All of these entities can be either infected or sterile (Table 8.2). Pseudocyst occurs in 10–20 % of acute pancreatitis [16]. The definition "pseudocyst" applies to a peri-pancreatic cystic lesion, which has no epithelial lining and therefore is not a true cyst [17]. The development of a well-defined wall composed of granulation or fibrous tissue distinguishes a pseudocyst from an acute fluid collection. Pancreatic pseudocysts are thought to arise from disruption of main pancreatic duct or its branches in the absence of identifiable pancreatic necrosis [15]. Without an antecedent episode of acute pancreatitis, pseudocyst may also arise insidiously in patients with chronic pancreatitis [18]. Rarely, pseudocysts may also arise in acute necrotizing pancreatitis patients, which is called "disconnected duct syndrome". In this syndrome, a still viable distal pancreatic remnant is separated by parenchymal necrosis of the neck and body of pancreas [19]. Additionally, after surgical necrosectomy, a pseudocyst may develop due to necrosis and subsequent leakage of pancreatic secretions from disconnected ducts into necrosectomy cavity [19]. Pseudocysts are round or oval, well circumscribed homogenous fluid collections, with a well-defined enhancing wall, which essentially contain no solid material inside. Rarely, pseudocysts may be multilocular and irregular in shape. Pseudocysts are usually single but may be multiple in 10 % of cases. Pseudocysts contain fluid, which is usually rich in amylase and lipase due to the constant communication with pancreatic ducts, and pseudocysts are usually sterile [17].

In contrast, small pancreatic pseudocysts are usually surrounded by a thin wall and are usually closely associated with the pancreas. Pseudocysts may sometimes be large, which occupy spaces adjacent to the stomach and pancreas or remote areas, including the chest. Pseudocysts can be localized in the liver, usually in the left lobe [20, 21], in the spleen [22, 23], and rarely in the kidney [24]. Histologically, the walls of pseudocysts consist of fibrosis and inflammatory tissue without epithelial lining, and are similar in all types of pseudocysts. The size of pseudocysts varies from 2 to 20 cm [14, 17, 18].

Clinical manifestations of pseudocysts are related with a local mass effect. The common symptoms associated with chronic pancreatic pseudocysts are usually mild recurrent abdominal pain, nausea and vomiting, early satiety, and weight loss. Generally, the size and the duration of cysts are the most important predictors for symptoms related to a pseudocyst [25]. Physical examination is rarely diagnostic for pseudocysts; a palpable, smooth, firm, non-tender mass in epigastric region, usually moving with breathing, may be a physical finding of large pseudocysts. Weight loss, which is observed in 20 % of patients due to gastric compression, results in poor intake as well as maldigestion. Jaundice is noted in 10 % of patients, who usually progresses slowly, and arises as a result of bile duct compression by the pseudocyst or the inflamed pancreas itself. Fever and chills are unusual in chronic, uncomplicated pseudocysts and presence of fever in these patients should raise the suspicion of pseudocyst infection [26].

Diagnosis

A pancreatic pseudocyst is clinically suspected when the episode of acute pancreatitis does not resolve, in the presence of continuous abdominal pain after clinical resolution of acute pancreatitis, persistent high levels of amylase and an onset of a palpable epigastric mass after an episode of acute pancreatitis. In some cases the episode of acute pancreatitis may not

be clinically overt or patients might have had mild pancreatitis. Transabdominal ultrasonography (US) is usually the initial diagnostic procedure for a pseudocyst. An echoic structure associated with distal acoustic enhancement is the usual appearance on US. Abdominal computed tomography (CT) is superior to US with a sensitivity of 90–100 % to detect a pseudocyst. A patient with a history of pancreatitis and abdominal CT revealing a round or oval well circumscribed fluid filled lesion surrounded by a thick, dense wall adjacent to pancreas is almost diagnostic for a pancreatic pseudocyst [14] (Fig. 8.2). CT may also show clues of acute or chronic pancreatitis, when evaluating the adjacent pancreatic tissue. Big pseudocysts may be seen in the mediastinum, pelvis or may involve the mesentery, as well. Although pseudocysts are

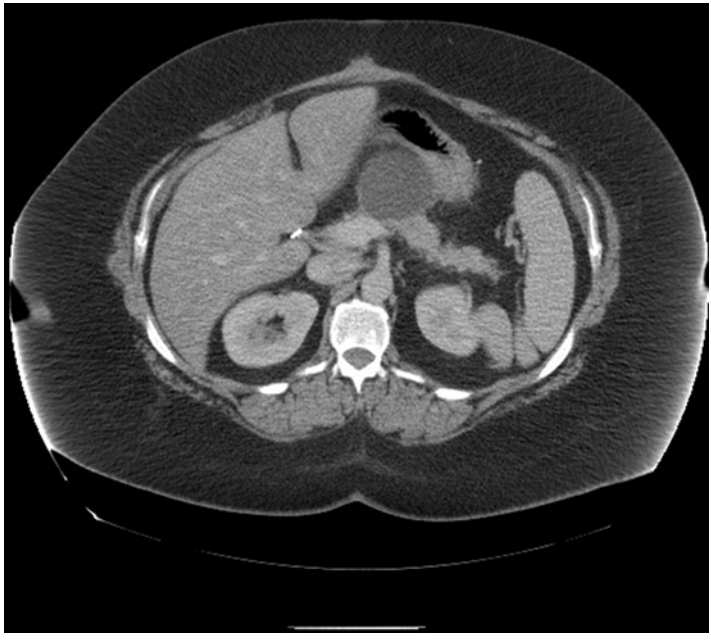

Fig. 8.2 CT showing a 3 cm pseudocyst in the body of pancreas indenting the stomach

most commonly unilocular, fibrotic strands within the cavity may cause multiple septations, which is frequently encountered in patients with post-pancreatitis complex fluid collections. Since pancreatic mucinous cysts can also be septated, it may be difficult to distinguish pseudocysts from pancreatic mucinous cysts without analyzing the cystic fluid. A pseudocyst may also contain debris, blood, or it may sometimes be infected, which is observed as high-attenuation areas within the fluid-filled cavity. When a pseudocyst is infected, the liquid becomes purulent, but does not contain solid material. CT scans can also provide more detailed information regarding the surrounding anatomy and can demonstrate additional pathologies. Persistent communication of a pseudocyst with pancreatic duct can be shown by contrast enhanced CT, which may help determine the management of the disease. On the other hand, magnetic resonance cholangiography (CP) is superior to CT in demonstrating this communication [27, 28], but usually magnetic resonance imaging (MRI) and MRCP do not add any extra information over CT [29]. Although CT is more popular, MRI may be more helpful before therapeutic interventions of complex fluid collection [30]. ERCP is not essential for diagnosis of pseudocysts but it can be helpful for treatment in some cases.

To further evaluate a pancreatic cysts EUS can be used, which is superior to distinguishing pseudocysts from other PCL [31]. In the EUS examination pseudocysts are seen as anechoic, fluid-filled lesions adjacent to the upper GI tract and pancreas (Fig. 8.3). A thick, hyperechoic rim often surrounds pseudocysts. Calcifications in a cyst wall are highly suggestive of a mucinous cystadenoma, rather than a pseudocyst. Debris may be observed in the cystic cavity and may represent blood, infection, or necrotic material. Color Doppler of the wall will often reveal multiple, prominent vessels, including para-gastric varices.

In cases where CT demonstrates gas within the pseudocyst, an infected pseudocyst should be suspected. In the absence of gas, fine-needle aspiration (FNA) with Gram staining and culture for bacteria may help diagnose the infection.

EUS guided FNA, including cystic fluid analysis, discriminates pseudocysts from neoplastic cysts in more than 90 % of the patients [26]. A high amylase activity in the aspirated cyst is a strong predictor of a communication with the pancreatic duct, which helps confirm the diagnosis of a pseudocyst. On the other hand, relatively low levels of CEA in the cystic fluid may distinguish a pseudocyst from Intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) [32]. Cytological analysis of a pseudocyst for histiocytes, inflammatory cells and degenerative debris and more importantly, to rule out a mucinous lesion is also needed. Epithelial cells should raise the suspicion of a cystic neoplasm rather than a pseudocyst [32]; presence of granulocytes suggests an acute infection.

Treatment

Spontaneous resolution is observed in the majority of acute peri-pancreatic fluid collections. A small percentage of fluid

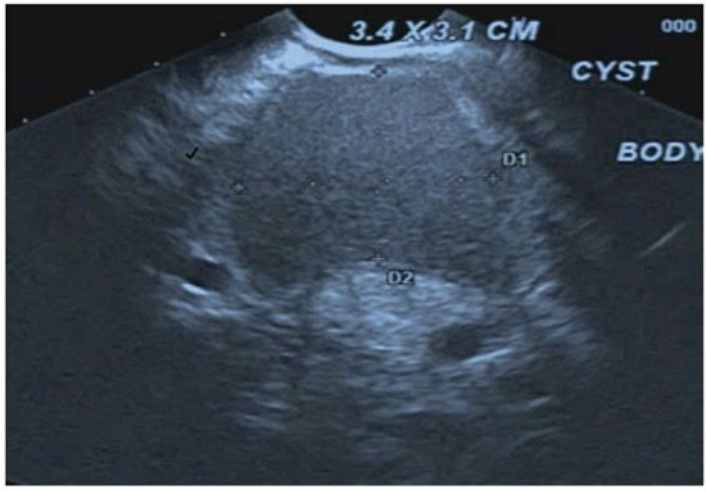

Fig. 8.3 EUS revealing a pseudocyst 3.4 × 3.1 cm in diameter in the body of pancreas

collections mature into pseudocysts. Most of these pseudocysts also resolve over time without any treatment. Small pseudocysts, which are less than 4 cm in diameter, often disappear without any complications; however, bigger pseudocysts are more likely to cause symptoms or complications. Approximately 25 % of pseudocysts cause symptoms, or become infected and require drainage, less than 10 % of cases experience a complication [30, 33]. Spontaneous resolution of pseudocysts takes place through fistulation into the GI tract or the pancreatic duct. The indications for interventions to drain are symptomatic persistent pseudocyst or cysts with complications such as bleeding, infection, biliary obstruction or gastric outlet syndrome. Forty percent of pseudocysts that are smaller than 6 cm in diameter requires drainage [34]. For large or symptomatic cysts, after excluding infection or necrotic material, drainage is usually satisfactory. In cases when CT demonstrates gas inside the fluid collection, infection is clinically suspected, but FNA is usually required to rule out the infection. Surgical drainage is not the first preferred method for infected pseudocyst today.

Several types of procedures may be used for draining a pseudocyst [35]. Under the guidance of US/CT, percutaneous drainage with percutaneous catheter placement is a simple way. This simple percutaneous drainage procedure has a high short term success, but high risk of complications with significant discomfort to the patient exits [14]. Percutaneous drainage with retroperitoneal approach through the lateral flank, which avoids perforation of bowel and solid organs, is generally more preferable than anterior approach through the peritoneal cavity [36]. The overall success rate of surgical drainage performed by providing a large anastomosis between the pseudocyst cavity and the stomach or small bowel is very high; however, this invasive technique has high complication rates. Surgery should be reserved for those who cannot tolerate or failed endoscopic drainage [37].

Presently, endoscopic drainage is the preferred technique for the treatment of pancreatic pseudocysts [38]. Endoscopic retrograde cholangiopancreatography (ERCP) guided

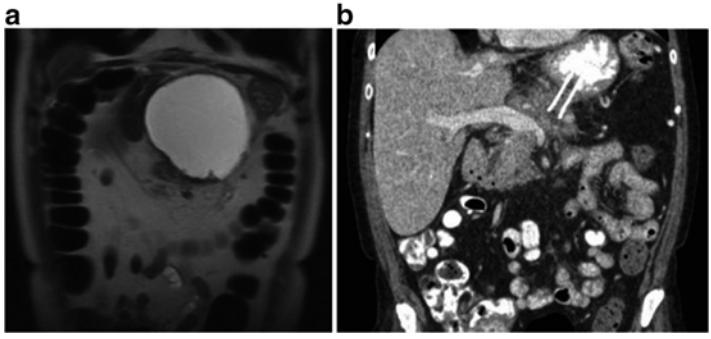

FIG. 8.4 (**a**) MRI showing a large pseudocyst in a patient with alcoholic pancreatitis. EUS guided cystogastrostomy was performed and two metallic stents were placed. (**b**) CT showing almost complete resolution of the pseudocyst

drainage through ampulla of Vater should be preferred when a communication between pancreatic duct and pseudocyst is suspected. The trans-papillary approach of drainage has also been found to be useful when pseudocysts are associated with strictures or are as a result of leakage from the main pancreatic duct [39].

Trans-gastric or trans-duodenal approaches are preferred for pseudocysts that are in proximity to gastroduodenal wall (Fig. 8.4). EUS is helpful to determine the size, location, and thickness of the pseudocyst wall. Endoscopic drainage is relatively contraindicated in cysts having a wall thickness greater than 1 cm or when large intervening vessels or varices are evident with EUS. In the absence of a visible bulge in the stomach, EUS guidance is required for drainage. Furthermore, necrotic pancreatic tissue can be removed through an endoscopic cystogastrostomy or duodenostomy via balloon dilation of the fistula tract. Overall, endoscopic drainage is successful in more than 90 % of the cases, with a complication rate of 13 %, and recurrence rates of less than 10 % [26].

Pancreatic Cystic Neoplasms

IPMN, MCN, serous cystic neoplasm (SCN), solid pseudopapillary neoplasm (SPN), and Cystic pancreatic endocrine neoplasms (CPEN) are the main types of PCN (Table 8.1). Population based studies showed that SCN account for 32–39 %, MCN for 10–45 %, IPMN for 21–33 %, and SPN for less than 10 % of all PCN in Western Hemisphere. A nationwide survey from Korea reported that IPMN account for 41 %, MCN for 25.2 %, SPN for 18.3 %, SCN for 15.2 %, and others for 0.3 % of PCN [1, 40]. Since the diagnosis and management varies in each type of PCN, differentiating one from another is important.

Intraductal Papillary Mucinous Neoplasms

IPMNs were first described in 1982 and they were initially thought as rare neoplasms. Prior to The World Health Organization classification of IPMN in 1996, they were named as papillary carcinoma, mucinous ductal ectasia or villous adenoma and many of these mucinous lesions were misclassified. IPMNs have become a major clinical focus in recent years because of the increased use of cross-sectional imaging in clinical practice and increased identification of asymptomatic PCLs.

IPMNs originate from pancreatic ductal cells and may involve pancreatic ducts diffusely or in a multifocal manner. IPMNs are mucinous cystic lesions of the pancreas characterized by mucin-secreting, papillary projections from the pancreatic ductal surface [41]. Hence IPMN is an intraductal proliferation of neoplastic mucin-producing columnar epithelium rising from the main pancreatic duct or its side branches. Intraluminal growth causes dilatation of the involved duct and its proximal segment. The most common site of involvement is the head of the pancreas as a solitary cystic lesion, but may be multifocal in 20–30 % of the cases.

Although the exact incidence of IPMNs is unknown, it is believed that 20–50 % of all PCNs are IPMNs [1, 41, 42]. In a recent surgical series IPMNs accounted up to 36 % of all resected cysts of pancreas [43]. Radiographically and histopathologically, based on the involvement of pancreatic ductal system, IPMN are classified into either main-duct IPMN (MD-IPMN) or branch-duct (BD-IPMN) or mixed-IPMN (both dilation of the main and side branch ducts). The main pancreatic duct is segmentally or diffusely involved in MD-IPMN and is usually >10 mm in diameter. In 5–10 % of cases, the main pancreatic duct is diffusely involved [41, 42]. Carcinoma-in-situ is observed in up to 60 % and invasive adenocarcinoma in up to 45 % of cases. Hence patients with MD-IPMN in general should undergo resection [44–47]. A non-dilated main duct communicates with one or more side branch ducts in BD-IPMN and multifocal involvement is seen in up to 40 % of cases [48, 49]. In patients with BD-IPMN who had undergone resection, 40 % malignancy is reported [45, 46, 48, 49]. When side branch dilation is associated with main duct dilation, it is called mixed-IPMN and malignancy rate is reported to be in between those of MD-IPMN and BD-IPMN, who had undergone resection.

Currently, most of the investigators and clinicians believe that IPMNs represents a field defect [50]. IPMN covers a spectrum of precursor lesions from adenoma to intraductal carcinoma to invasive cancer. Recent reports state that IPMN, as a dysplastic premalignant lesion, has a potential to progress from low-grade dysplasia to invasive carcinoma [51, 52]. According to degree of dysplasia WHO classified IPMNs into subgroups; (1) IPMNs with low- or intermediate-grade dysplasia, (2) IPMNs with high-grade dysplasia (carcinoma in situ), and (3) IPMNs with an associated invasive carcinoma. Currently, dysplasia is classified as low, moderate or high by most histopathological assessments. Detailed histological studies further classified IPMN into subtypes including gastric foveolar type, intestinal, pancreatobiliary, and intraductal oncocytic papillary subtype. Gastric foveolar type epithelium is predominantly seen in BD-IPMN, which are usually

low-grade lesions [53]. On the other hand, intestinal type is mostly present in MD-IPMN and has an intermediate to high-grade dysplasia. Colloid type adenocarcinoma usually develops in association with intestinal type IPMN and it indicates better prognosis [54]. Invasive cancers developing from pancreatobiliary IPMN are usually tubular-type adenocarcinoma, which tend to have worse prognosis than colloid adenocarcinoma. Intraductal oncocytic papillary cancers are very rare and cancers developing from them show different oncocytic cytology and they are suggested to be identical with ductal adenocarcinoma [55, 56]. Patients with gastric-type IPMN have the best prognosis, whereas those with intestinal and pancreatobiliary type have worse prognosis. The types of mucin expressed by subtypes of IPMN are summarized in Table 8.3.

Diagnosis

IPMNs are usually detected in asymptomatic patients incidentally discovered on cross-sectional imaging performed for another reasons. Some patients may present with recurrent non-specific symptoms including abdominal pain and discomfort, malaise, nausea and vomiting [41]. Patients with an associated invasive carcinoma may present with jaundice, weight loss and diabetes mellitus. IPMNs presents predominantly in men with a mean age of 65. Laboratory tests including complete blood count, liver enzymes, pancreatic enzymes, are usually within normal limits. Serum carcinoembryonic antigen (CEA) and CA 19-9 are generally not of diagnostic

Table 8.3 Types of mucin expressed by different subtypes of IPMN

Subtype	Mucin
Gastric foveolar type	Overexpression of MUC5AC, MUC6
Intestinal type	Overexpression of MUC5AC, MUC2 and weak expression of MUC6
Pancreatobiliary type	MUC1, MUC5AC

Table 8.4 Genetics of IPMN

Genetic abnormality	Frequency
KRAS mutation	38–100 % [57, 58]
Loss of p16	78 % [59]
p53 mutation	50 % [60]
SMAD4/DPC4 expression	In almost all of noninvasive IPMN [59]
Loss of SMAD4/DPC4 expression	10 % of colloid cancer [59]
PIK3CA mutation	11 % [61]
GNAS mutation	66 % [62]
STK11/LKB1 gene inactivation	25 % [63]

value [1]. Genetic abnormalities in IPMNs are summarized in Table 8.4.

The diagnosis of IPMN is classically established by imaging [64]. The aim of imaging studies in patients with IPMN includes detecting and differentiating them from the other types of PCL, differentiating the type of IPMN (MD-IPMN or BD-IPMN) and evaluating it for resectability.

Although it was a standard procedure in the past, endoscopy and ERCP have a limited role for the evaluation of IPMN today [64]. The finding of a dilated main pancreatic duct (usually >10 mm) with filling defects, in the absence of imaging features of acute pancreatitis and obstructing lesions is highly suggestive of MD-IPMN. In some cases, during endoscopy or ERCP, the pancreatic orifice is patulous, and mucin that is emanating from the ampulla can be visualized ("fish-mouth" papilla). However, absence of this endoscopic feature in no way excludes the diagnosis. In the absence of pancreatitis features, cystic dilations of side branch ducts (multiple parenchymal cysts on imaging), especially if these are communicating with the main pancreatic duct, are generally considered indicative of BD-IPMN. The other types of PCN are very rarely multifocal and it should be kept in mind that multiple benign cysts may be seen in cystic fibrosis and polycystic renal disease. Moreover, in some occasions, due to

mucus plugging, the cystic side branch ducts cannot be filled with contrast. Since ERCP is an invasive procedure with complications, one of the limited usages of ERCP is that ERCP identifies the intraductal papillary outgrowths of IPMN and may also identify a communication with a cyst and the main pancreatic duct. In addition, visualization of the entire pancreatic ductal system is not always possible due to copious amount of mucin during ERCP.

In clinical practice, most of the PCL are usually discovered by conventional imaging modalities (US, CT and MRI) which are usually performed for other reasons [65, 66]. Conventional imaging differentiates the types of PCL by evaluating the location, number, size, calcification, septations and pancreatic duct dilation. High quality cross sectional imaging is crucial for assessing PCL. Currently, multidetector CT (MDCT), which allows pancreatic thin sections, has become the most common method for evaluating PCL. Besides providing excellent visualization of mural nodules, calcifications and septations, MDCT also evaluates the pancreatic parenchyma. MDCT predicts the malignant features of pancreatic cyst with an accuracy of 56–85 % [67] and, the presence of thick septations, mural nodules and cyst wall thickness are signs of high-grade dysplasia and invasive carcinoma. When discriminating an aggressive type IPMN from non-aggressive IPMN, MRI with MRCP can be similar to MDCT in their diagnostic yield [68, 69] (Fig. 8.5). The sensitivity of MRCP may be better in showing a communication between the main duct and the cystic lesion [69]. On the other hand, it is reported that a combination of MDCT with MRI may be more helpful to obtain a specific diagnosis rather than either tool alone. In addition, both CT and MRI are accurate enough to detect metastasis in cases with IPMN associated invasive carcinoma.

EUS has become the more valuable procedure for the diagnosis of IPMNs as it has high resolution capacity and better imaging characteristics compared with cross-sectional imaging [70]. Moderate to marked dilation of the main pancreatic duct (either segmentally or diffusely) is the main EUS finding of IPMN. Pancreatic duct dilation is often associated

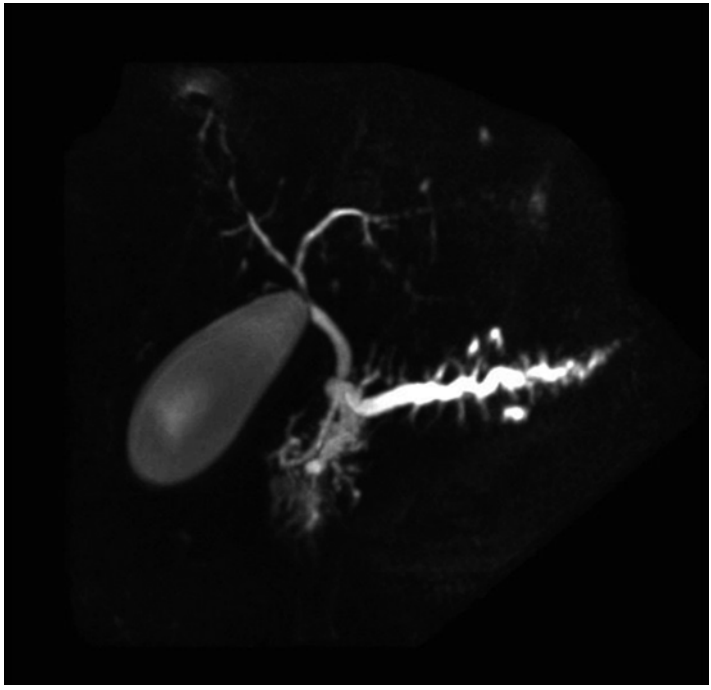

Fig. 8.5 MRCP revealing a diffusely dilated main pancreatic duct with its side branches consisted with a MD-IPMN

with intraductal mural nodules in patients with MD-IPMN. On the other hand, main pancreatic duct obstruction with mucus may result in parenchymal changes, which are similar with changes in pancreatitis. These parenchymal changes are enlargement of the pancreas or parenchymal atrophy, which makes it difficult to distinguish IPMN from chronic pancreatitis. The main duct is normal sized or mildly dilated in patients with BD-IPMN and the presence of multiple cysts, ranging from 5 to 20 mm in diameter reveals an appearance of a "cluster of grapes" (Fig. 8.6). Excellent visualization of internal septations, cyst wall thickening, debris in the cyst, mural nodule and papillary projections can be provided by

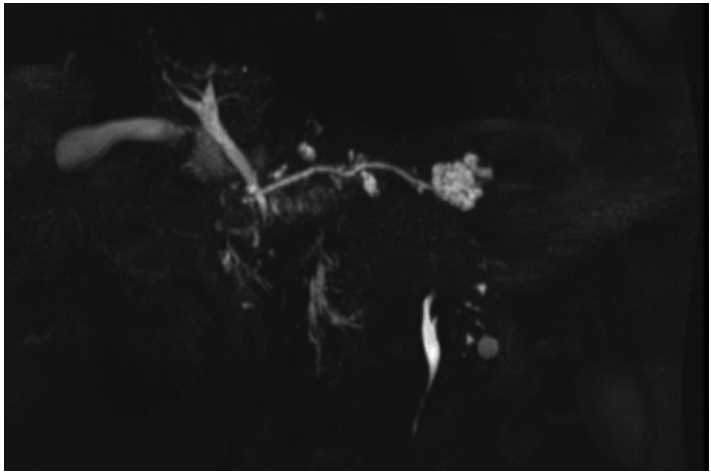

Fig. 8.6 Complex septated cystic lesion in the tail of pancreas consisted with cluster of grapes appearance of BD-IPMN on MRCP

EUS. EUS also allows visualization of lymph node metastases and vascular invasion [1, 31, 41, 70].

EUS criteria for malignancy in patients with MD-IPMN include marked dilatation of the main pancreatic duct (>10 mm), and large tumors (>40 mm) with irregular septa in patients with BD-IPMN. A mural nodule greater than 10 mm in size is a feature of malignancy in both MD-IPMN and BD-IPMN [71]. The accuracy of EUS to differentiate a benign cyst from malignant IPMN varies from 40 to 90 % in several studies which is superior to US, ERCP and cross-sectional imaging tools [72]. In contrast, EUS has a low accuracy in differentiating malignancy from areas of focal parenchymal inflammation, which mimic malignancy.

EUS guided FNA can be performed and the aspirated fluid sent for biochemical, cytological and DNA analysis [73, 74] (Fig. 8.7). Macroscopically observed highly viscous, gelatinous fluid is suggestive of either IPMN or MCN. High levels of CEA in cystic fluid, which is detected both in patients with IPMN and MCN, reflects the presence of a mucinous epithelium.

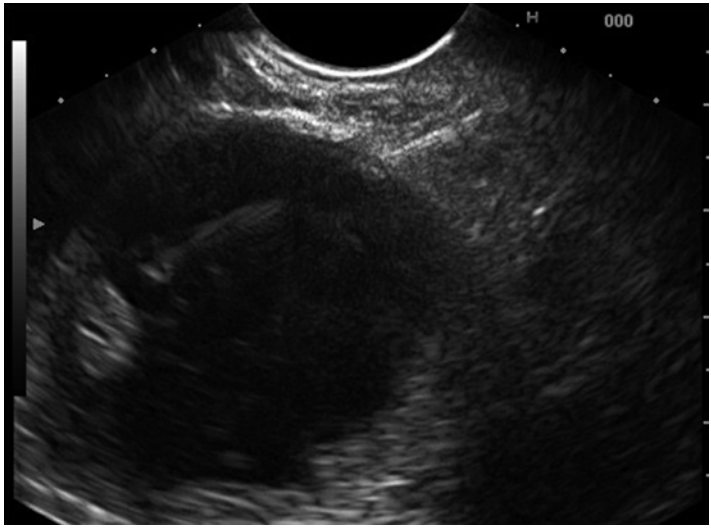

Fig. 8.7 EUS-FNA of a BD-IPMN with a mural nodule

Rather than predicting IPMN associated invasive cancer or differentiating IPMN from MCN, cystic fluid CEA levels better distinguishes non-mucinous cyst from mucinous ones. In a prospective study of patients with PCL, a cut-off CEA level of 192 ng/mL was found to be the best predictor of a mucinous cyst with a sensitivity of 73 %, specificity of 84 %, and accuracy of 79 % [75]. When compared with CA19.9, CA125, CA72-4 and CA15-3, CEA provided the best accuracy for the diagnosis of cystic mucinous neoplasms. IPMN may also have elevated cyst fluid amylase levels since it usually communicates with main pancreatic duct as against MCN and SCN [32, 76].

In a recent study, the amounts for glucose and kynurenine were significantly lower in mucinous cysts compared with non-mucinous cysts, however, neither of them could discriminate a malignant cyst from a premalignant one [77]. The clinical utility of these biomarkers needs to be further studied. Aspirated pancreatic cyst fluid involves exfoliated

epithelial cells to be analyzed for cytology, whether the cyst is mucinous or non-mucinous. Unfortunately, cytology of the aspirated material is usually non-diagnostic because of the low cellularity and limited volume. A positive cytology is typically 100 % specific for detecting malignancy in patients with mucinous cysts [78]. Additionally, the accuracy of cyst fluid analysis for detecting high-grade dysplasia is 80 % to predict malignancy [79].

Finally, markers of dysplasia including KRAS mutation, p53 mutation and loss of p16 and SMAD4 were investigated. In the initial studies, KRAS mutation alone was found to be highly specific for mucinous neoplasms. Further studies demonstrated KRAS mutation followed by allelic loss could be a predictor for malignant cysts. However, the sensitivity of KRAS mutation for detecting mucinous cysts was very low [80]. Although, KRAS being an early oncogenic mutation in adenoma-carcinoma sequence, it does not differentiate benign cysts from malignant ones. Additional studies reported that the assessment for GNAS mutations might help differentiate IPMN from mucinous cyst, but it cannot predict malignancy [81]. The detection of GNAS mutations seems to be specific for IPMN.

Confocal laser endomicroscopy (CLE), which uses low power laser, is a novel imaging technology. It shows in vivo histology of the gastrointestinal mucosa and a recent CLE miniprobe has been developed to to visualize the cyst wall and epithelium directly by passing it through a 19-gauge FNA needle during EUS-FNA., which is able. Preliminary studies reported that CLE has 59 % sensitivity and 100 % specificity to show the epithelial villous structures associated with IPMN [82].

Management

The mean frequency of malignancy in MD-IPMN is 61.6 % and that of invasive caner, 43.1 %. Studies revealed that patients with non-invasive IPMN tend to be 5 years older than those with invasive IPMN [69, 76]. The finding of

low-grade dysplasia and invasive carcinoma coexisting in the same cyst suggests that all IPMNs have a potential for progression to malignancy over time. Since the incidence of invasive carcinoma is high and its 5-year survival rates are low (31–54 %), international consensus guidelines recommend resection for all patients with MD-IPMN. In cases when surgical margin is positive for high-grade dysplasia, additional resection should be tried to obtain at least moderate-grade dysplastic margin. In the same guideline, 5–9 mm dilation of main pancreatic duct is considered as a "worrisome feature", and the patients are recommended for follow-up but not immediate resection. Worrisome features for IPMN include a cyst size greater than 3 cm, thickened/enhancing cyst walls, presence of lymphadenopathies, non-enhancing mural nodule, main pancreatic duct size of 5–9 mm and sudden change in caliber of pancreatic duct with distal pancreatic atrophy. Besides, high-risk stigmata include obstructive jaundice in a patient with cystic lesion at the head of pancreas, enhancing solid component within the cyst and main pancreatic duct size greater than 10 mm in diameter [71].

The mean frequency of malignancy in resected BD-IPMN is 25.5 % and the mean frequency of invasive cancer is 17.7 %. BD-IPMN mostly occurs in the elderly patients. Patients with non-invasive BD-IPMN have similar ages with invasive BD-IPMN [83]. The annual malignancy rate is only 2–3 %. At the time of initial diagnosis, given the low risk to malignant progression, most of the BD-IPMN patients without symptoms should be followed up [69]. Risk factors suggesting progression to malignancy are rapidly increasing cyst size, mural nodule and cytology showing high-grade dysplasia. Size, however by itself, does not appear to correlate with risk of malignancy and data is not enough for immediate resection in patients with BD-IPMN >3 cm in the absence of "high-risk stigmata" and "worrisome features" [71].

The need for long-term follow-up of patients with BD-IPMN who are younger (<65 years) increases the cumulative risk of malignancy and cost of management is the

main challenge. Some patients may refuse surgery or surgery may be contraindicated in some high-risk patients. As an alternative treatment, EUS-guided cyst ablation has been tried [84]. During this procedure, ablation of the cyst epithelium is achieved with injecting cytotoxic agents such as ethanol and saline. For complete ablation, ethanol lavage was found superior to saline. Better results were obtained with the combination of paclitaxel injection and ethanol lavage. Combining ethanol with paclitaxel eliminated cysts in 62 % of patients with a median follow-up period of 21.7 months [84, 85]. In a pilot study, six patients with PCN underwent radiofrequency ablation (RFA) and the patients were followed up for 3–6 months. Complete resolution was observed in two of them [86].

The recurrence after surgical resection vary from 7 to 30 %. Annual monitoring with either CT or MRI for noninvasive IPMN and monitoring every 6 months for invasive IPMN is recommended [71]. For patients with BD-IPMN who did not undergo surgery and have cysts > 2 cm without "worrisome features", performing EUS for every 3–6 months is recommended. MRI is also recommended as an alternative of EUS. Annual monitoring with cross-sectional modalities are suggested for BD-IPMN that are 2–3 cm in diameter, and 2–3 years intervals are suggested for BD-IPMN that are below 1 cm. Detecting malignant transformation of a benign cyst are the goal of follow-up in these patients [87].

Mucinous Cystic Neoplasms

MCN are reported to account for 23 % of all resected PCN [88]. They are more common in females, the mean age at diagnosis is younger, most commonly located in the pancreatic body or tail and are almost always solitary. The typical presentation is a female in her 50s with a solitary cyst in the tail of pancreas. In contrast, patients with IPMN usually present in an elderly male with a multifocal cysts identified in the head of pancreas.

MCN is defined as cyst-forming epithelial neoplasm that compromises a mucin-producing columnar ductal epithelium with an underlying ovarian-type stroma, not communicating with the main pancreatic duct [1, 89]. A thick layer of spindle cells containing receptors for progesterone and estrogen surrounds the MCN. This pathognomonic densely cellular "ovarian like tissue" simulates an ovarian hamartoma; even a sarcoma. The histological characteristics of the stroma and its tendency for luteinization suggest that the ovarian tissue possibly derivate the stromal component of MCN. It has been hypothesized that, during embryogenesis, the ectopic ovarian stroma in pancreas may release hormones and growth factors which results in proliferation of the nearby epithelium to proliferate and to form cystic tumors. The ovarian type mucosa of MCN stain variably for progesterone and estrogen receptors and human chorionic gonadotropin may help differentiate MCN from BD-IPMN. Interestingly, this stroma is also observed in postmenopausal females and even in male patients and it is crucial for diagnosis. Furthermore, mucinous transitional epithelium is the source of almost all MCN associated malignancies. MCN are classified as (1) mucinous cystadenoma (benign), (2) mucinous cystic tumor (borderline), and (3) mucinous cystadenocarcinoma (malignant) [90, 91].

The frequencies of KRAS mutations are reported to increase as the stage of dysplasia increase. In contrast, p53 mutations are frequently found only in cases with severe dysplasia or cancer [92, 93].

MCN is a single spherical cyst containing a thick mucin or a compound of mucin, blood and necrotic material; and it may be unilocular or multilocular. Except for a fistula formation, MCN do not communicate with pancreatic duct. On the other hand, a multicenter study from Japan reported a communication rate of 18 % in patients with MCN [94].

Up to one-third of MCN are reported to harbor an invasive carcinoma and risk factors for malignancy include large cyst size, advanced age, mural nodules and an associated mass. Lesions may be asymptomatic in 30 % of patients or

may present with abdominal pain, discomfort, dyspepsia, anorexia, weight loss, fatigue, jaundice or palpable mass [95]. Routine laboratory tests are usually nonspecific, however in cases when the bile duct is obstructed, serum levels of cholestatic liver enzymes and bilirubin are elevated [45].

CT findings of MCN include a macrocyst with thin septae, which is best shown after intravenous contrast administration. Peripheral calcifications may be seen, which are named, "eggshell calcifications". They are lamellated and they contrast the central stellate calcifications of SCN. The cysts are seen bright (high signal intensity) on T2-weighted images on MRI. The wall of the cyst and septa are better shown on T1-weighted images after intravenous gadolinium administration. The presence of wall thickening, peripheral calcification, and thick septations can be suggestive of a malignant mucinous cystic neoplasm. In a study of 52 patients with MCN, the presence of these three findings predicted a 95 % risk of malignancy [96] (Fig. 8.8).

EUS findings of MCN include large, septated, thin-walled, fluid-filled cyst [4]. Usually, a communication with ductal system cannot be demonstrated. Thickening and irregularity of cyst wall, large size and visualization of intracystic solid components or adjacent solid mass are suggestive of malignancy. CEA levels in the aspirated fluid are elevated and generally amylase level is low. Cyst fluid cytology does not help distinguish MCN from IPMN. ERCP is not indicated, since MCN rarely communicate with pancreatic duct.

Because MCN can progress to cancer, current consensus guideline recommend surgical resection of all MCN [71]. Because of their location, MCN < 4 cm without mural nodules are recommended for laparoscopic resection (distal pancreatectomy) with splenic preservation. Patients with noninvasive MCN have excellent outcomes [97] and do not require follow-up after surgery since they are not at risk of recurrence and there is no cancer risk in the pancreatic remnant. In contrast, patients with invasive MCN are at risk of distant recurrences, and after resection the 2-year survival is 67 % and 5-year survival 50 % [1]. For patients who are not a good

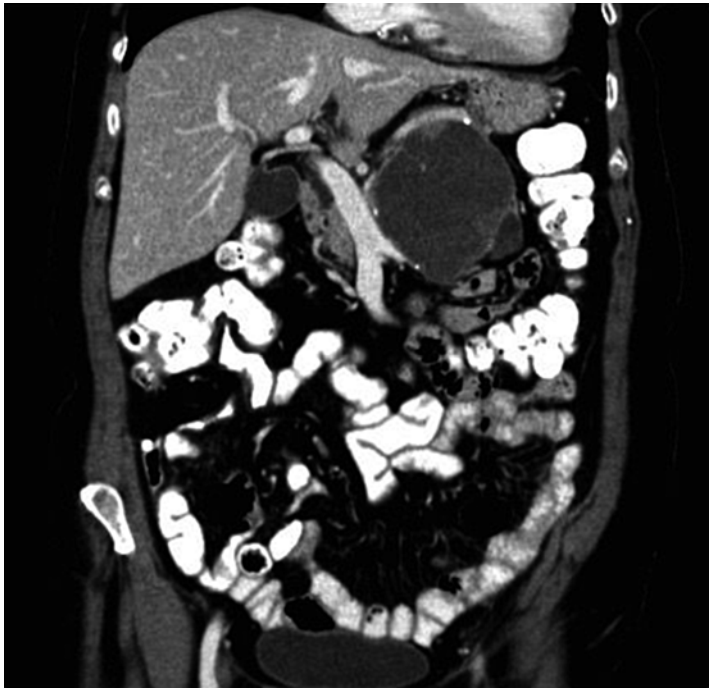

Fig. 8.8 Malignant MCN rising from the body of pancreas on CT

candidate for surgery or who refuse surgery, EUS-guided cyst ablation therapies may be considered. Patients having small lesions without a solid component may be followed up.

Serous Cystic Neoplasms

SCN are cystic neoplasms that arise from centroacinar cells and are thin walled cystic collections lined by a cuboidal epithelium. This cuboidal epithelium is typically PAS positive on staining (stain with glycogen) and the cyst typically consists of serous fluid. They are classified according to the degree of dysplasia as either serous cystadenoma or serous

cystadenocarcinoma. More than 80 % of SCN occur in women at mean age of late 50s or early 60s. The most common site of involvement is pancreatic body or tail, SCN are mostly considered as benign lesions and tend to grow slowly and may achieve large diameters [98].

SCN is reported to develop in 90 % of patients with von Hippel–Lindau (VHL) syndrome, and a mutation in the VHL gene is seen in 70 % of serous cystadenoma patients [99]. KRAS mutations are rare in patients with SCN. SCN are characteristically benign lesions; to date only 25 malignant cases have been reported in the literature [1]. SCN are usually single, round lesions, which are sometimes >20 cm in diameter. The usual appearance of SCN is a cluster of numerous tiny microcysts, surrounding a more solid spongiform central core, which is termed a scar. The scar is usually stellate shaped and is usually located in the center of the lesion. A single layer of cuboidal epithelial cells lines SCN and they do not communicate with the pancreatic duct. The lesions are rich in vascular epithelial growth factor receptors, and a complex vascular structure supports the lesion. Four variants of serous cystadenoma are described: (1) macrocystic serous cystadenoma, which compromise previous serous oligocystic and ill-demarcated serous adenoma, (2) solid serous adenoma, which are well-circumscribed solid lesions that share the similar immune-histological and cytological features of classic SCN, (3) VHL-associated SCN that occur in patients with VHL syndrome having multiple serous cystadenomas and macrocystic variants, and (4) mixed serous neuroendocrine neoplasm. SCN typically involve the pancreas diffusely or in a patchy fashion in patients with VHL [100]. The rare entity, mixed serous neuroendocrine neoplasm is associated with pancreatic neuroendocrine neoplasms and is highly suggestive of VHL syndrome.

Most of these cysts are discovered incidentally during imaging studies. Patients are usually free of symptoms. Symptomatic patients with SCN present with abdominal pain, anorexia, palpable mass, fatigue, malaise, and weight loss. SCN may lead to biliary or pancreatic duct obstruction

and may cause GI bleeding in cases when they erode into the adjacent bowel [91].

The classical appearance of SCN on CT and MRI is microcystic or less commonly oligocystic appearance. Multiple small cysts with a central fibrous scar are pathognomonic for microcystic-type lesions. A solid component, which is because of dense fibrous feature of this lesion, often appears on CT (Fig. 8.9).

The oligocystic (unilocular) SCN is often difficult to differentiate from BD-IPMN and MCN on CT/MRI, which have similar morphology [101]. SCN should be suspected in patients when a lobulated, unilocular cystic lesion without wall enhancement located in the pancreatic head [91]. The cystic fluid reveals lower signal intensity on T1-weighted fat-suppressed MRI when compared with fibrous matrix. In contrast, the fluid becomes bright on T2-weighted images. The classical findings of SCN on EUS are multiple small, anechoic cysts with thin septa. EUS with Doppler or contrast enhanced imaging tools may demonstrate the central region, which are typically hypervascular. The hypervascular nature can result in a bloody aspirate during EUS-FNA and show hemosiderin-laden macrophages. Low amylase levels, low CEA concentrations (usually <0.5 ng/mL) and rarely, the finding of PAS-positive stained cuboidal cells are the typical characteristics of the aspirated fluid [102]. Eighteen cases with SCN were included in a recent study and a superficial vascular network sign, which corresponds to the dense subepithelial capillary vascularization, was demonstrated by nCLE with 63 % sensitivity and 100 % specificity.

The prognosis of SCN is excellent. They are most commonly managed conservatively, reserving surgery for the rare symptomatic patients. Instead, some institutions prefer surgical resection. Studies suggest long-term survival after resection, even in rare cases with cystadenocarcinoma. Currently; the universally recommended indications for surgery are presence of symptoms, cyst size >4 cm and when the diagnosis is uncertain. Although increase in size is not a predictor of malignant transformation, large SCN are reported to grow faster and they are more likely to cause symptoms [98, 100].

FIG. 8.9 Macrocystic lesion in the neck of pancreas consisted with SCN on MRCP

Solid Pseudopapillary Neoplasms

SPN were previously referred to solid and cystic pseudopapillary tumors or solid and cystic tumors. SPN are low-grade malignant neoplasms that consist of epithelial cells forming solid and pseudopapillary structures. Microscopically, they have solid (solid pseudopapillary) and cystic (hemorrhagic-necrotic pseudocystic) components. Poorly cohesive monomorphic cells and myxoid stromal bands having thin-walled blood vessels form the solid part. Eventually, the poorly cohesive neoplastic cells migrate and form a pseudopapilla with the residual neoplastic cells. Mucin is lacking, and glycogen is not conspicuous. SPN are single, large, well demarcated, round and often fluctuant masses. SPN commonly undergo hemorrhagic cystic degeneration [103].

SPN are classified as low-grade malignant neoplasms because they do not represent the histologic criteria of malignant behavior including vessel and perineural invasion, or parenchymal infiltration and metastasis [104]. SPN probably accounts for 5 % of PCN and predominantly found in young

women at her 20s or 30s at diagnosis. Symptoms are usually related with mass effect such as pain, anorexia, nausea, vomiting, jaundice, and weight loss. SPN might also be an incidental finding.

CT reveals SPN as a well-circumscribed, encapsulated mass with varying areas of soft tissue and necrotic foci without septa. The capsule of SPN is frequently thick and enhancing and in one third of the patients, peripheral calcifications is visualized. SPN are well-defined lesions on MRI (Fig. 8.10). On T1-weighted images, high signal intensity reflects areas filled with blood and on T2-weighted images, these areas show low or inhomogeneous signal intensity [105].

On EUS, SPN demonstrates well-defined, hypoechoic mass, which include solid and cystic areas. In some patients, internal calcifications can be seen. Based on cytology and immunohistochemistry, the reported diagnostic accuracy of EUS-FNA for SPN is 65 %. Aspirated cyst fluid is typically highly cellular, sometimes may display necrotic debris. CEA

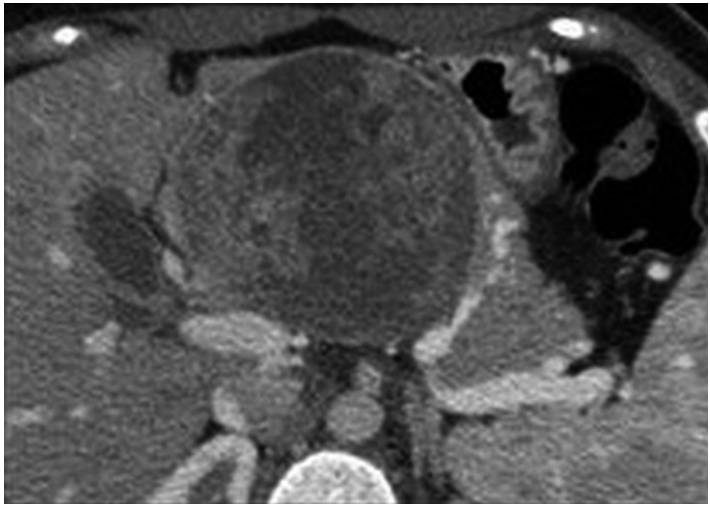

Fig. 8.10 MRI showing a large complex cystic SPN

levels of the cyst fluid are low, reflecting a nonmucinous epithelium [106].

Surgical resection is the main therapy. It is curative and recurrence after surgery is rare [1]. Long-term survival have been documented even in cases with local invasion, recurrences, or metastases [107]. To date, no definite biological or morphologic predictors of outcome have been documented. Older age of onset and SPN with an aneuploidy DNA content, are the suggested indicators of poor outcome.

Table 8.5 summarizes the general features of common pancreatic cysts.

Cystic Pancreatic Endocrine Neoplasms

CPEN are very rare and macroscopically they have an irregularly thickened wall. In the presence of a significant solid compartment, CT shows a mural enhancement, diagnostic feature of CPEN. FNA of the fluid is usually hemorrhagic and after aspiration, the residual lesion resembles a typical solid pancreatic endocrine neoplasm, which is a well-bordered hypoechoic mass (Fig. 8.11). Fine needle aspiration of the remnant cystic fluid shows cells with round, uniform nuclei that are stained with chromogranin and synaptophysin. CPENs are usually asymptomatic, incidentally diagnosed and hormonal related symptoms are very rare. Although current literature does not definitely describe the malignant behavior of CPEN, surgical resection is often suggested. Patients with comorbidities and elderly patients should be followed up with cross-sectional imaging.

General Approach to Diagnosis and Management

Various associations and multidisciplinary physician groups have recommended algorithms for the management of PCL (Fig. 8.12) [34, 108]. The aims of these guidelines are to estimate the behavior of PCL and the risk of missing a chance to treat an early malignancy, and to evaluate the risks of surgical

Table 8.5 Common features of some pancreatic cysts

Parameters	Pseudocyst	IPMN (MD and BD)	MCN	SCN
Demographics	Variable aged (adult) men, history of alcoholic, biliary or traumatic pancreatitis	Men in his 60s–70s	Women in her 40s–50s	Women in her 60s–80s
Gross features	Often in pancreatic tail, solitary small to very large size, fibrous-thick walled capsule	Often in head of pancreas, may be incidental and multifocal, multilocular	Often in body and tail, incidental, single, large, thick-walled	Entire pancreas, Numerous of small cysts or oligo/ macrocystic
Microscopic features	Absence of epithelial lining, degenerative debris, inflammatory cells, histiocytes,	Mucin producing epithelium with papilla ± atypia, colloid-like mucin, positive mucin staining	Tall columnar mucin producing epithelium ± atypia, colloid-like mucin, positive mucin staining 'ovarian-like mucosa'	Often acellular and non-diagnostic, small cluster of cells with bland cuboidal morphology, positive glycogen staining, negative mucin staining
CT/MRI	Usually unilocular cyst, often pancreatic parenchymal inflammatory findings	MD; diffuse or limited involvement of MPD, BD; single cyst or cluster of cysts, communication to pancreatic duct, may be multifocal	Macrocysts with thick septa, peripheral eggshell calcification, wall thickening	Microcystic, multiple small cysts, central fibrous scar with calcification, occasionally oligocystic

EUS	Thick-walled, anechoic, unilocular cystic lesion, Findings of chronic pancreatitis	MD; dilated MPD, hyperechoic nodules arising from ductal wall. BD; small-cluster of grape-like dilations of BD, mural nodules	Large cystic lesion, few septa, no ductal dilation, occasionally focal, peripheral calcifications, atypical papillary projections	Multiple, anechoic, small, cystic areas, 'honeycomb' appearance, sometimes central fibrosis or calcifications
Cystic fluid characteristics	Low viscosity, clear or colored in brown to green, non-mucinous, sometimes hemorrhagic CEA ↓↓, amylase ↑, lipase ↑	High viscosity, viscous mucus, CEA usually ↑, Amylase ↑ (%60) KRAS mutation (+) (%80)	High viscosity, viscous mucus, CEA usually ↑, KRAS mutation (+) (%14) GNAS mutation (−)	Low viscosity, clear fluid, sometimes hemorrhagic, CEA ↓↓, amylase ↓↓
Confocal endomicroscopy	Not described	Epithelial villous structures, no vascular networking	Epithelial villous structures, no vascular networking	Thickened cyst wall, unilocular vascular networking, fibrous bands

MPD main pancreatic duct, *MD* main duct, *BD* branch duct

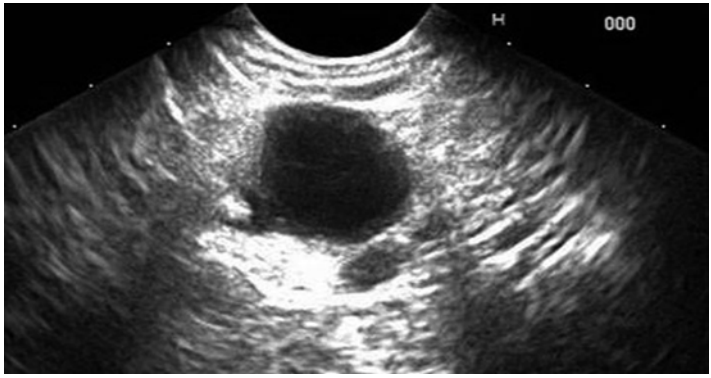

FIG. 8.11 EUS showing an anechoic 19×20 mm cystic lesion in the body of pancreas. The outer wall was irregular and thick with calcifications. After distal pancreatectomy, pathology revealed well-differentiated CPEN

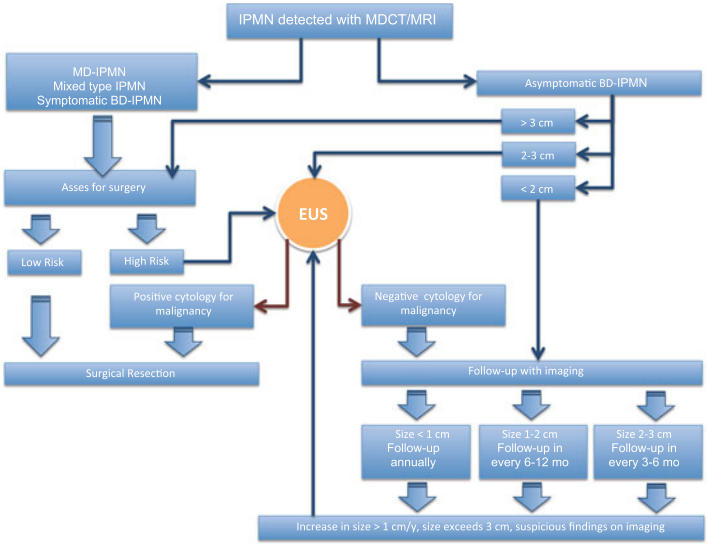

FIG. 8.12 A suggestive algorithm in patients with IPMN

resection or alternative therapies. Most of these guidelines highlight the size and morphology of the cyst as the most important issues. In general, the first step is to differentiate a pseudocyst from a PCN. The diagnosis of pseudocysts is mainly based on a pancreatitis history, biochemical and imaging findings. However, some patients with a pseudocyst may have mild pancreatitis or may not have a clinically recognized pancreatitis. On the other hand, some patients with PCN may present with pancreatitis. After excluding the diagnosis of a pseudocyst, the main goal is to differentiate a mucinous cyst from a serous cyst. If the diagnosis is a mucinous cyst, patients with MD-IPMN, combined-type IPMN, and MCN should be considered for surgical resection. Patients with BD-IPMN should be managed according to the guidelines. SCN should be followed, except for symptomatic ones or when they are larger than 4 cm.

EUS-FNA indications of PCL are not well defined in the guidelines. EUS-FNA is not generally recommended for all cystic lesions of pancreas when cross sectional imaging clearly diagnose it. In cases with an IPMN measuring more than 2 cm, and when the imaging shows benign features, the lesion should be aspirated. To make more certain, aspirated cystic fluid should be sent for CEA, *KRAS*, and GNAS evaluation. Evaluating the aspirated fluid for DNA mutations, especially when the aspirated cystic fluid is in a small amount, may enhance the results of cytology.

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