



Differentiating Pancreatic Cystic Lesions

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Abstract

Pancreatic cystic lesions (PCLs) may represent malignant or premalignant neoplasms and require diagnostic evaluation. Patient's demographics and clinical presentation should be considered when diagnosing PCLs. Radiologically, location, ductal relation, external contour, wall, and septal enhancement give important clues for each type of lesion. Imaging features that suggest a high malignancy risk and warrant additional investigation are mural nodules, nearby mass, thick septa, and a dilated main pancreatic duct. Pseudocysts, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and serous cystadenoma are the most frequently encountered cystic lesions. Pseudocysts are most likely to follow a history of pancreatitis and have high amylase and lipase values. Intraductal papillary mucinous neoplasms are usually connected to the pancreatic duct and are associated with a *GNAS* mutation. Mucinous cystic neoplasms generally present as a solitary distal cystic pancreatic lesion in a middle-aged woman and lack ductal communication. Serous cystadenomas are associated with high vascular endothelial growth factor levels and a *VHL* mutation and have a cyst content rich in glycogen. This review describes performance of various imaging modalities and pathological markers for diagnosing and detecting malignant potential of PCLs and illustrates typical pathological and radiological features of the most common PCLs, including primary issues in the differential diagnosis of these lesions.

Highlights

- Patient demographics should be considered when diagnosing cystic lesions.
- Imaging is crucial for assessment of PCLs, by detecting the locularity, nodularity, external contour, and enhancement characteristics.
- EUS-FNA can aid in diagnosis of indeterminate cystic lesions on imaging.

Keywords: Intraductal papillary mucinous neoplasm; Mucinous cystic neoplasm; Pancreatic cystic lesions; Pancreatic pseudocyst; Serous cystadenoma

Introduction

PCLs represent a medical dilemma due to their heterogeneous disease processes and outcomes. Recently, these lesions have been increasingly detected incidentally due to advances in cross-sectional imaging. Disease prevalence ranges from 2.4% to 24.3%, with a positive correlation with age [1-6]. Approximately 1% to 3.5% of PCLs are malignant [7,8]. Treatment options vary greatly, from observation to radical surgery, and depend on the malignant potential of the detected lesion. Malignant potential relies on the histological subtype, with the highest risk in mucinous PCLs [9].

PCLs can be divided into three groups: (1) benign lesions, (2) cystic lesions with malignant potential, and (3) cystic malignant tumors [10]. The benign group includes pseudocysts, serous cystadenomas (SCAs), infectious cysts, retention cyst, Lymphoepithelial cysts, and congenital cysts [10,11]. Cystic lesions with malignant potential include intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), cystic pancreatic neuroendocrine neoplasms, and solid pseudopapillary neoplasms (SPN) [10,12]. Cystic malignant tumors are those tumors which are solid and undergo cystic degeneration such as cystic ductal adenocarcinoma and acinar cancers [10]. Among the various PCLs, pseudocysts, SCAs, MCNs, and IPMNs are the most frequently encountered [7,12,13]. To determine the PCL type, there is a need to integrate clinical, radiological, and pathologic assessments. In this review, we summarize performance of various imaging modalities and pathological markers in diagnosing and detecting malignant potential of PCLs and then discuss each of the most clinically encountered PCLs individually.

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The Imaging of PCLs

Radiologically, the lesion's location, ductal relation, internal content, external contour, wall, and septal enhancement provide important clues for its diagnosis. Imaging features that suggest a high malignancy risk and warrant additional investigations are mural nodules, associated mass, thick septa, and dilated main pancreatic duct [8,14].

CT is the most frequently used cross-sectional modality for PCL assessment despite having an accuracy ranging from 20% to 90% [15]. Studies have shown that while CT is less sensitive than MRI, there is no statistically significant difference between CT and MRI in characterizing PCL features [8]. Visser et al. [16] reported an accuracy of 57% for both CT and MRI in PCL-specific subtype categorization. When combined together, MDCT and MRI have the highest accuracy in PCLs characterization and 94.5% sensitivity in malignancy detection [17].

Endoscopic ultrasonography (EUS) provides excellent tissue resolution due to close proximity to the pancreas. Kim et al. [18] documented no statistically significant difference between EUS and MRI in characterizing features of PCLs, even though EUS was less sensitive and less accurate than MRI. Del Chiaro et al. [19] reported no statistical difference between EUS-FNA, CT, and MRI concerning errors in PCLs diagnosis. Adimoolam et al. [20] reported that EUS was superior at detecting PCL multifocality; the multifocality detection rate was 47% for EUS vs. 13% for CT ($P < 0.0001$) and 58% for EUS vs. 34% for MRI ($P = 0.0002$). EUS also has the advantage of offering interventional techniques, including cystic fluid sampling and drainage.

PET CT can be used to determine the malignant potential of PCLs. Kauhanen et al. [21] compared MRI and CT with PET CT, and PET CT showed a statistically significant higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in detecting malignant PCLs. With a SUV max cutoff of 3.6, PET CT had a sensitivity and specificity of 100% and 88% in detection of malignancy, respectively. Further, within a study population, PET CT changed the treatment plan in 5 patients [21]. In a meta-analysis, PET CT was found to have a sensitivity range of 57% to 94%, a specificity range of 65% to 97%, and an accuracy of 94% in malignant or premalignant PCL categorization. In comparison, the sensitivity and specificity range was 36.3% to 71.4% and 63.9% to 100%, respectively, for CT, and 91.4% to 100% and 89.7%, respectively for MRI [22].

Pathological Features

Multiple cystic fluid pathological parameters can be used to categorize the lesions, including fluid amylase, lipase, carcinoembryonic antigen (CEA), cancer antigen (CA)-125, mucin content, cytology, DNA content, and detection of genetic mutations. To date, CEA is the most reliable pathological marker in discriminating between mucinous and non mucinous PCLs. Brugge et al. [23] reported that a CEA value ≥ 192 ng/mL indicates a mucinous lesion [21]. CEA showed a sensitivity and specificity of 73% and 84%, respectively, in categorizing PCLs [23,24]. When combined with CEA, cystic fluid mucin (MUC) content analysis can add to the diagnostic accuracy [25]. Mucins are membrane bound or secretory glycoproteins. MUC1 is overexpressed in pancreatic adenocarcinoma, while MUC6 is characteristic of serous cysts [26-28]. Jabbar et al. [29] reported that cystic fluid mucin profiling performed better than both cytology and CEA in diagnosing PCLs. Proteomic mucin profiling

has a sensitivity, specificity, and accuracy of 97.3%, 97.6%, and 97.5%, respectively, in determining PCLs' malignant potential. Cysts with MUC5A, MUC2, and MUC1 overexpression have the highest risk of being premalignant or malignant [29].

Molecular analysis of the cystic fluid may provide a specific tool for detecting malignant cysts. Winner et al. [30] documented that the presence of the K-ras mutation and >2 loss of heterozygosity was 96.2% specific for malignant cysts. On the other hand, both of these parameters were less sensitive than CEA in discriminating between mucinous and non mucinous cysts. A combination of these parameters with CEA is better at differentiation [30]. Micro RNA expression is a promising tool for categorization of different PCLs. Micro RNAs-noncoding RNA molecules that control mRNA processing-are expressed differently in various PCLs [31].

Pancreatic Pseudocyst

Pancreatic pseudocysts are purely benign lesions [10,12,32-34] and are the most frequently encountered PCL in clinical practice. They are not true cysts, but a collection of inflammatory debris surrounded by a false wall of granulation tissue that develops 4 weeks after pancreatitis onset [35]. Pseudocyst represents a local complication of interstitial edematous pancreatitis [35]. After acute pancreatitis, 5% to 16% of patients are at risk of having a pancreatic pseudocyst, while 20% to 40% are at risk after chronic pancreatitis [36]. Clinically, patients with pseudocysts may be asymptomatic; may present with abdominal pain, early satiety, weight loss, may have complications of infection, rupture, biliary obstruction, or gastric outlet obstruction [33]. In most instances, pseudocysts are located in the peripancreatic region or within the pancreas, but rarely occur in other organs such as the liver, spleen, or mediastinum [12,35,37,38]. Microscopically, a pseudocyst is characterized by absent epithelial lining and hyper-cellularity in the surrounding stroma. Cyst content is variable according to cyst stage [39]. The fluid aspirate of pancreatic pseudocysts is characterized by high amylase and lipase and low CEA and CA 125 values [33].

Management strategies differ according to the pseudocyst's duration, size, location, and relation to the pancreatic duct. Pseudocysts <5 cm that do not persist for more than 6 weeks may resolve spontaneously. Pseudocysts which communicate with the main pancreatic duct and are located in the uncinate process, head, body, or neck of the pancreas are candidates for endoscopic transpapillary drainage by ERCP. If no ductal communication is present, pseudocysts can be managed by internal drainage, whether surgically or through an endoscopic transmural approach. The endoscopic transmural approach is feasible if the pseudocyst is <1 cm from or plugging through an adjacent gastrointestinal hollow organ. Pancreatic tail pseudocysts are the least accessible by ERCP; they are managed surgically or via transmural endoscopic internal drainage if they are <1 cm away from a hollow organ [36,40]. Percutaneous drainage can be done in immature or infected cysts [36].

On ultrasonography, a pseudocyst usually appears as a well-defined, unilocular, anechoic cyst with distal enhancement. Increased internal echogenicity is noted if the pseudocyst is detected early or is complicated with infection or hemorrhage [33]. On CT, the pseudocyst usually appears as a unilocular hypodense cystic lesion surrounded by a smooth dense wall that shows contrast enhancement (Figure 1 and 2). Cystic fluid may show areas of increased attenuation if complicated [13,32,36,41]. Usually, the pancreatic pseudocyst is

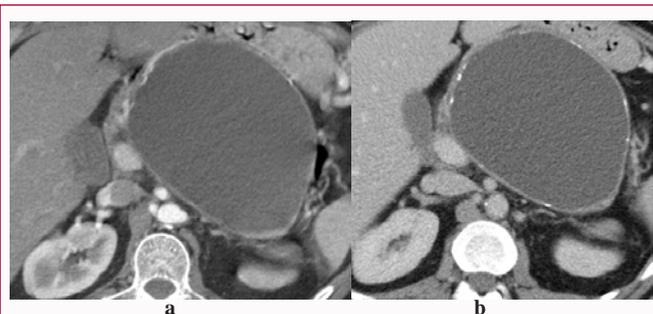


Figure 1: Pseudocyst. 40-year-old man who presented with intermittent epigastric pain, with moderate alcohol intake and no documented history of pancreatitis. Contrast-enhanced axial CT images of the abdomen on (a) arterial and (b) portal-venous phases show a cystic mass in the pancreatic tail with a thick wall and calcifications. This was proven to be a pseudocyst.

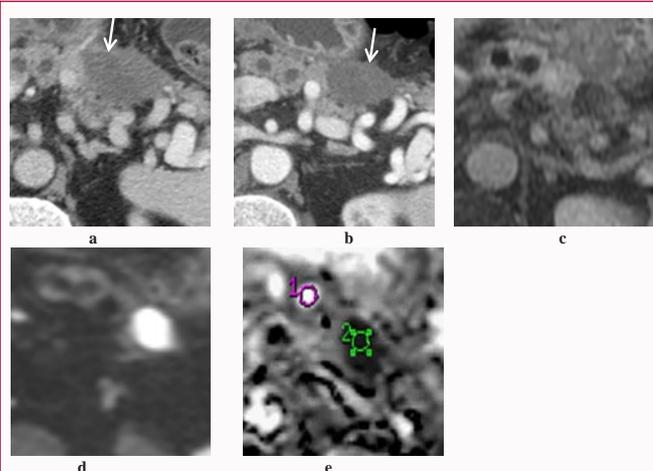


Figure 2: Pseudocyst. 60-year-old man with a history of main duct intraductal papillary mucinous neoplasm who developed pancreatitis following endoscopic ultrasonography for biopsy. Contrast-enhanced axial CT images of the pancreas obtained on follow-up; (a) 5 months, (b) 9 months after biopsy for the neoplasm showed an evolving pseudocyst (arrows). Gadolinium-enhanced axial MR images of the pancreas obtained 13-months after biopsy shows (c) a T1-hypointense non-enhancing lesion (d) with increased signal on DWI and (e) corresponding low signal intensity on the ADC map. Note the opposite signal characteristics of the nearby pancreatic duct.

associated with radiological evidence of chronic or acute pancreatitis, such as necrotic pancreas, duct dilatation, fibrotic parenchyma, ductal stone, or calcifications [13,14]. CT attenuation can differentiate between pancreatic pseudocyst and mucinous cystic lesions. Chalian et al. reported that pseudocyst has a higher attenuation than mucinous cystic lesions. 14.5 HU cutoff had a sensitivity and specificity of 74.4%, 71.9%, respectively in discriminating between both lesions [42]. On MRI T2-weighted images, it often appears as a hyperintense, unilocular cyst with a thick enhancing wall [43]. Presence of internal debris and absence of lobulated surface and calcification differentiate pseudocyst from other pancreatic cystic lesions [44]. Internal debris or clotting may resemble a mural nodule; post-contrast enhancement distinguishes mural nodules [12]. Location, ductal communication, and relation to other gastrointestinal organs should be reported, as they affect the management plan.

Intraductal Papillary Mucinous Neoplasm

IPMN is caused by hyperplasia of the mucinous epithelium lining the pancreatic ducts, forming papillae and cystic ductal dilatation [39]. IPMN is categorized as a main duct, branch duct, or mixed type.

Table 1: Expression of mucin glycoproteins in histological subtypes of intraductal papillary mucinous neoplasm.

Glycoprotein	Subtype			
	Gastric	Intestinal	Pancreatobiliary	Oncocytic
MUC5A	+	+	+	+
MUC1	-	-	+	+
MUC2	-	+	-	-
CDX2*	-	+	-	-

*CDX2 is a transcription factor characteristic of normal intestinal cells and intestinal metaplasia.

Malignancy risk is highest in the main duct group at 62.2%, compared with 57.4% for the mixed group and 24.4% for the branch duct group [45]. Based on degree of dysplasia, the World Health Organization classifies IPMN as low or intermediate-grade, high-grade, or associated with invasive carcinoma [32]. IPMN is the most common incidentally detected PCL (50%) [46,47].

Histologically, IPMN is classified as gastric (null cell-type), intestinal, pancreatobiliary, and oncocytic; the gastric and intestinal subtypes are the most frequently encountered [48-50]. Subtypes are differentiated not only morphologically, but also by expression of different types of mucin glycoproteins (Table 1). The gastric subtype, which is described as intraductal papillary mucinous adenoma, is negative for both MUC1 and MUC2 (null subtype). It is the least likely IPMN to develop invasive malignancy and usually has a smaller cyst diameter than other subtypes [48,51,52]. On the other hand, pancreatobiliary IPMN is usually MUC1 positive, which may explain its aggressive behavior, as MUC1 is linked to pancreatic ductal adenocarcinoma.

On progression to invasive malignancy, IPMN can give rise to colloid, tubular, or oncocytic carcinomas. Intestinal IPMNs are more likely to develop the less aggressive colloid carcinoma. The pancreatobiliary subtype frequently develops invasive tubular ductal adenocarcinoma. Despite being the most indolent IPMN, the gastric subtype usually gives rise to the most invasive tubular adenocarcinoma. Oncocytic carcinoma classically is preceded by oncocytic IPMN [46,53]. The prognosis and survival of IPMN associated with invasive carcinoma are generally better than those of pancreatic ductal adenocarcinoma. Mino-Kenudson et al. [55] reported a higher 5-year survival rate in IPMN associated with invasive carcinoma (47%) than in pancreatic ductal adenocarcinoma (34%) [48]. *DPC4* is a tumor suppressor gene that was found to be expressed in all IPMNs, even in IPMN associated with invasive carcinoma; but was downregulated in 55% of pancreatic ductal adenocarcinoma. Persistent expression of *DPC4* in IPMN associated with invasive carcinoma may explain its indolent biological behavior in comparison to pancreatic ductal adenocarcinoma [54].

Malignancy detection remains the challenging point in IPMN management. Histological subtype and relation to pancreatic duct can predict the IPMN's malignant potential. Gastric IPMN usually arises as branch duct type IPMN with benign behavior in most instances, while other types frequently affect the main pancreatic duct and have a higher incidence of malignancy. Even risk of malignant conversion is higher in intestinal IPMN than gastric IPMN when both are related to a branch duct [48,53]. Clinically, this pattern of biological behavior is reflected in disease outcome and prognosis. Hisaka et al. [48] documented 5-year survival rates of 91%, 75%, and 17% in gastric, intestinal, and pancreatobiliary IPMNs, respectively.

Table 2: Summary of clinical and pathological differences between the most frequently encountered PCLs.

	Pseudocyst	IPMN	MCN	SCA
Gender difference	No difference	M > F	F > M	F > M
History of pancreatitis	Yes	Maybe	No	No
Location	Evenly distributed	Head	Body, tail	Body, tail
CEA	<192 ng/dL	>192 ng/dL	>192 ng/dL	<192 ng/dL
VEGF-A	<8500 pg/mL	<8500 pg/mL	Usually <8500 pg/mL	>8500 pg/mL
VEGF-C	<200 pg/mL	<200 pg/mL	<200 pg/mL	>200 pg/mL
Amylase, lipase	High	May be high	Low	Low
Cyst content	Inflammatory debris	Mucin	Mucin	Rich in glycogen (PAS + ve)
Specific genetic mutations	None	GNAS	None	VHL
MUC glycoproteins	None	According to the histological subtype	MUC1 (malignant) MUC2 (benign)	Usually MUC6

CEA: Carcinoembryonic Antigen; IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm; MUC: Mucin; PAS + ve: Periodic Acid-Schiff Positive Stain; SCA: Serous Cystadenoma; VEGF: Vascular Endothelial Growth Factor

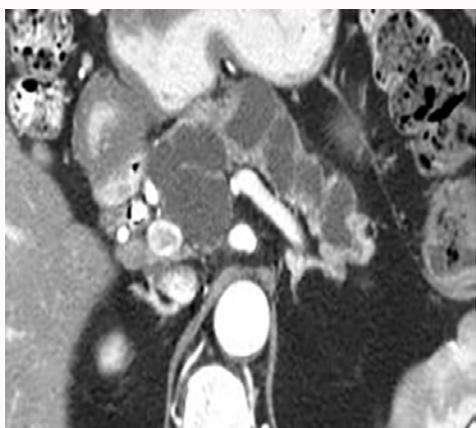


Figure 3: Main duct intraductal papillary mucinous neoplasm (MD-IPMN). 75-year-old woman presented with obstructive jaundice. Axial contrast enhanced CT shows dilated main pancreatic duct with no evident obstruction. This was proven to be malignant IPMN on pathological assessment.

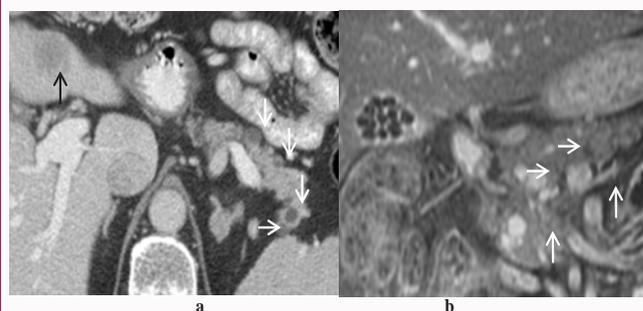


Figure 4: Branch duct intraductal papillary mucinous neoplasm (BD-IPMN). 75-year-old woman complaining of abdominal pain, was found to have multiple hypodense pancreatic lesion without ductal dilatation on (a) portal-venous axial contrast enhanced CT (white arrows) with a hypodense metastatic lesion in the left hepatic lobe (black arrow) from pancreatic adenocarcinoma associated with BD-IPMN. (b) Coronal FIESTA MRI shows multifocal hyperintense lesions (arrows). Her carcinoembryonic antigen level was 25 ng/dL.

As in all mucinous PCLs, IPMNs' cystic fluid usually shows a CEA >192 ng/dL (Table 2). Differences in CEA have been reported between different IPMN histological subtypes, with the highest mean in gastric IPMN and the lowest in the oncocytic subtype [55]. Fluid DNA analysis may give clues to malignant risk. K-ras and GNAS mutations have been associated with a higher malignancy incidence [56]. TP53 mutations are useful molecular marker for intermediate and high grade IPMN. TP53 mutations were reported in 17.8% and 38.1% of intermediate and high grade IPMNs respectively. In low grade IPMN no TP53 mutations were described [57]. Clinically, IPMN is more common in men than women, with a higher incidence in the sixth and seventh decades. Despite having a lower incidence rate than men, women are more prone to have the aggressive pancreatobiliary IPMN [49]. IPMN may be multifocal in 20% to 30% of patients [31,32].

Radiologically, ductal relation is a key radiographic feature for IPMN. Main duct IPMN is identified when there is segmental or diffuse main pancreatic duct dilation >5 mm without any obstruction (Figure 3) [13,58-60]. BD-IPMN typically presents as a unilocular or multilocular cystic mass connected to the pancreatic duct, although absent ductal communication does not exclude BD-IPMN [13,60]. MR cholangiopancreatography (MRCP) and secretin-enhanced MRCP showed better performance in detecting ductal relation [61]. BD-IPMN may be multifocal (Figure 4 and 5). Without ductal communication, multilocular BD-IPMN may be

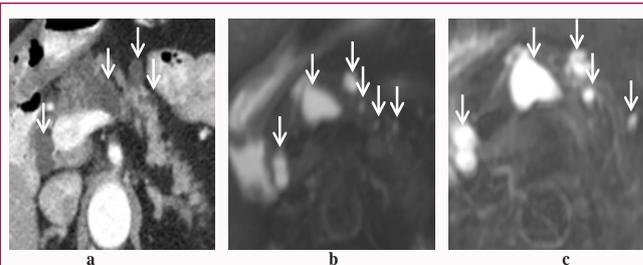


Figure 5: Branch duct intraductal papillary mucinous neoplasm (BD-IPMN). 59-year-old woman with incidentally discovered multifocal branch duct IPMN. (a) Contrast-enhanced axial CT of the abdomen shows multifocal hypodense lesions within the pancreas (arrows), which are more conspicuous on MRI, with a greater number of lesions seen (arrows) on (b) DWI, and (c) T2 sequences.

misinterpreted as serous cystadenoma (SCA) or MCN, especially in the absence of salient imaging features of those lesions (Table 3) [7]. Considering demographics, cystic fluid analysis, enhancement pattern, calcifications and tumor location (Table 2 and 3) may help to discriminate between multilocular BD-IPM, MCN, and SCA. Mixed IPMN carries features of both main duct and branch duct IPMNs [60]. On EUS mucin is seen extruding through the duodenal papilla and is considered as a characteristic feature of IPMN [12].

IPMN and MCN management is guided to a great extent by radiological interpretation. In 2012, international consensus

Table 3: Imaging features of most commonly encountered PCLs.

	Pseudocyst	IPMN		MCN	SCA
		MD-IPMN	BD-IPMN		
Iocularity	Usually unilocular	-	Usually unilocular	Uni/multilocular	Usually multilocular (honeycomb)
Ductal relation	May be connected	Main pancreatic duct dilation >5 mm	Often connected	Often not connected	Not connected
Enhancement pattern	Peripheral	Not enhancing	Not enhancing	Usually peripheral, septa may be enhanced	Usually septa are enhanced
Calcification	Pancreas present in pancreas itself	-	-	Usually peripheral	Usually central
Central scar	-	-	-	-	+
Outer surface	Smooth	-	-	Smooth	Lobulated

IPMN: Intraductal Papillary Mucinous Neoplasm; BD-IPMN: Branch Duct Intraductal Papillary Neoplasm; MD-IPMN: Main Duct Intraductal Papillary Neoplasm; MCN: Mucinous Cystic Neoplasm; SCA: Serous Cystadenoma

was reached for management of IPMN and MCN relying on risk stratification according to certain radiographical findings (cyst and main pancreatic duct diameter, associated mass, wall enhancement, and lymphadenopathy). According to the 2012 consensus guidelines, asymptomatic PCLs with a diameter <1 cm are less likely to harbor malignancy. A high-risk stigmata has been characterized for high-risk mucinous lesions consisting of a main pancreatic duct diameter >10 mm without obstruction, obstructive jaundice, and the presence of an enhancing solid mass. In the presence of these high-risk stigmata, surgical resection should be deemed without any further workup. Other worrisome features have been identified for further risk determination, including cyst diameter ≥ 3 cm, main duct diameter of 5 to 9mm, a non-enhancing mass, an enhancing wall, a sudden main duct diameter change with distal pancreatic atrophy, and lymphadenopathy. If any worrisome feature is detected, diagnostic EUS is the next step. Once the feature is confirmed, surgical resection is the best management modality. In the absence of high-risk stigmata and worrisome features, follow-up imaging is performed at certain intervals according to cyst size [45].

Mucinous Cystic Neoplasms

MCNs represent 10% of clinically encountered PCLs [20,62,63]. The classic presentation of MCN is a solitary distal cystic pancreatic lesion in a middle-aged woman. MCNs, unlike IPMNs, are solitary and usually lack ductal communication, especially branch duct IPMNs. Nevertheless, MCN ductal communication has been documented in 15% of MCN patients. Grossly, MCNs may be unilocular or multilocular cystic lesions surrounded by a fibrous capsule. Microscopically, they are differentiated from other PCLs by the presence of ovarian stroma. Also, MCNs have been found to express estrogen, progesterone, α -inhibin, and β -human chorionic gonadotropin receptors [64]. Multiple theories have been suggested for the pathogenesis of pancreatic MCN, including metaplasia and ectopic ovarian tissue implantation in the pancreas. These theories can be supported by finding the same lesions in other anatomical sites, such as the liver and retroperitoneum [62].

The malignant conversion risk for MCN is about 13.4% to 30.8%, with a higher incidence in older patients; most MCNs progress to tubular ductal adenocarcinoma. Malignant MCNs usually express MUC1 glycoprotein, while benign MCNs express MUC2 and CDX2 [65-67]. In two reports, MCN patients were found to have other tumors, especially breast carcinoma, with a prevalence of 6.5% in one study and 1.9% in another [68,69]. High cystic fluid CA19-9, CA 125, and CA 72-4 can be useful markers in discriminating between malignant and benign MCN [63,66]. Also, progesterone receptor

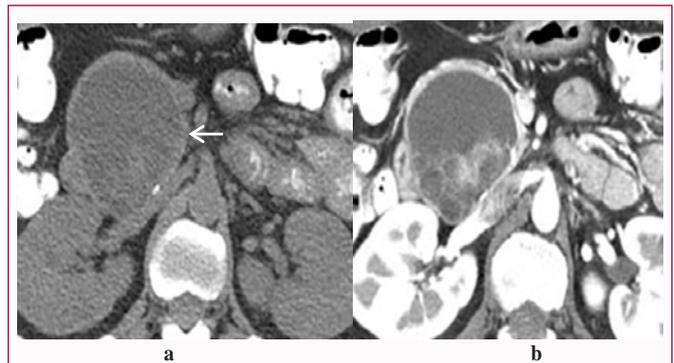


Figure 6: Mucinous cystic neoplasm (MCN). 44-year-old woman complained of postprandial epigastric pain. (a) Precontrast CT show a multilocular (white arrow) pancreatic head mass with (b) evident post contrast wall and septations enhancement and no evident ductal communication. Pathologically, the lesion was proven to be a low-grade mucinous cystic neoplasm.

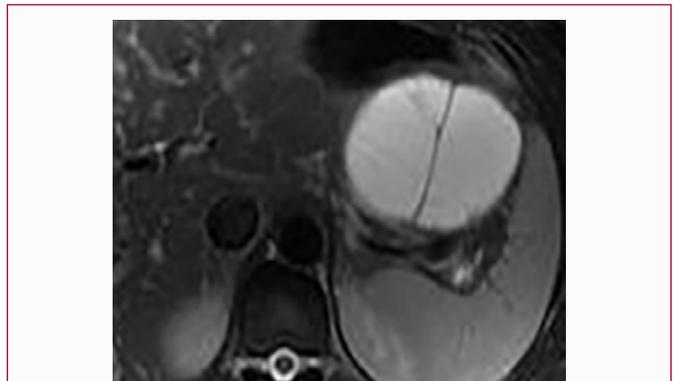


Figure 7: Mucinous cystic neoplasm (MCN). T2-weighted MRI of a 34-year-old woman with an incidentally discovered pancreatic tail cystic lesion showed a hyperintense multilocular pancreatic cystic lesion with evident septations. Pathologically, it was proven to be mucinous cystic neoplasm with intestinal metaplasia.

(PR) expression was found to be negatively correlated to MCN grade. The higher MCN grade, the lower is the PR expression [66].

Radiologically, MCN appears as a unilocular or multilocular mass in the distal pancreas with no ductal communication in most instances (Figure 6 and 7). On MRI, MCN has high signal intensity on T2 series (Figure 7) and usually low signal on T1. Nevertheless, MCN signal intensity may vary according to internal content (mucin, hemorrhage or debris) [12,32,70,71]. With contrast, MCN often shows peripheral enhancement (88%) and may exhibit septal enhancement (38%) [70]. MCN may display peripheral calcifications, mural or septal

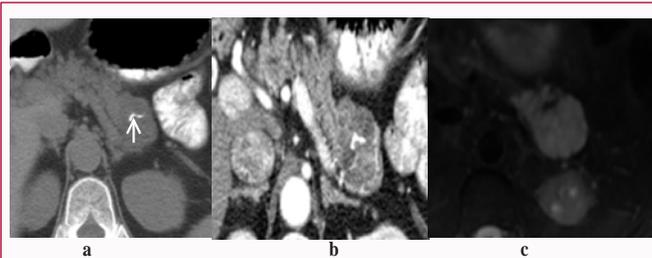


Figure 8: Serous cystadenoma (SCA). 65 year old woman with incidentally detected microcystic SCA. (a) Pre-contrast CT shows pancreatic tail cystic lesion with central scar (white arrow) which demonstrate (b) septal contrast enhancement, cyst size less than 1 cm, and has (c) a high signal intensity on T2 weighted MRI.

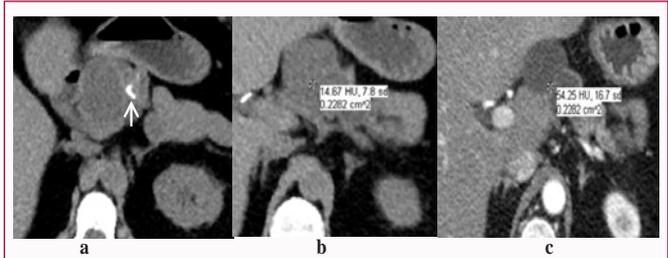


Figure 9: Serous cystadenoma (SCA). 68 year old woman with an incidentally detected macrocystic SCA. (a,b) pre-contrast axial CT shows multilocular cystic mass with central scar (white arrow) that showed evident septal enhancement on (c) contrast enhanced series. Note the difference in Hounsfield unit between (b) and (c) and large cyst size (>1 cm).

nodules or papillary projections [12,32,71]. Differentiation between MCN and pseudocyst, BD-IPMN, and macrocystic SCA is a tedious task (Table 3). A smooth outer surface, peripheral enhancement, and peripheral calcifications can help distinguish MCN from macrocystic SCA (lobulated outer surface, septal enhancement, and central calcification) [32,71]. When present with BD-IPMN, ductal communication distinguishes BD-IPMN from MCN. A history of pancreatitis is characteristic for pseudocyst [12,71]. Nevertheless, pathological assessment remains the last resort for discrimination between indeterminate lesions. Certain radiological findings have been found to predict a higher malignancy risk. Procacci et al. [67] reported that an MCN would be 95% likely to be malignant if there were thick septations, a thick wall, and mural or septal calcification. If only two of these features were found, the MCN would carry a malignancy risk of 56% to 74%. They also documented that patient age and lesion diameter did not correlate with malignancy. On the other hand, other reports documented that malignant potential of MCN correlates with cyst size and presence of mural nodules [66,69]. Le Baleur et al. [72] reported that a diameter cutoff of 4 cm is 100% sensitive and 54% specific in MCN malignancy risk identification. MCNs with a diameter >4 cm are more likely to be malignant [58]. In the same study, mural nodules were 100% sensitive and 98% specific for malignant MCN. Two other studies documented a statistically higher diameter mean in malignant vs. benign MCN [66,69]. Surgical resection of an MCN is recommended unless patients have comorbidities [45,63].

Serous Cystadenoma

SCA is a benign cystic lesion that affects women more than men (at a 3:1 ratio) and is more likely to affect the distal pancreas. Malignant conversion is extremely rare. Around 16% of PCLs are SCAs [73]. SCA is a clear cell tumor type that grossly presents as a large cystic lesion, formed of multiple small cysts with a central stellate scar. Microscopically, SCA is a glycogen-rich cyst lined with cuboidal cells that have a clear cytoplasm and round homogenous nuclei with a hypercapillarized stroma. Due to high glycogen content, SCA stains positive on Periodic acid-Schiff stain. In 40% of SCA cases, Von Hippel-Lindau (*VHL*) gene mutations have been described, which lead to overexpression of hypoxia-inducible factors. Increased hypoxia-inducible factors result in overproduction of VEGF and glucose transporter 1. SCA cystic fluid typically has a low CEA and CA19-9 and a high VEGF-A (>8500 pg/mL) and VEGF-C (>200 pg/mL). Elevated VEGF is 100% specific and 97% sensitive for SCA. *VHL*-associated SCA is usually multifocal. Despite being serous, MUC glycoproteins have been documented in SCA (MUC6, 70%;

MUC2, 34%; MUC1, 5%) [74-76].

Two variants of SCA have been identified: microcystic and macrocystic (oligocystic). Microcystic is the most common form (70%). It is a well-circumscribed lesion comprising multiple (>6) small cysts <2 cm in diameter, giving a honeycomb appearance (Figure 8). The macrocystic variant comprises larger cysts >2cm with less outlines demarcation than the microcystic variant and may be unicystic (Figure 9) [74,75]. On MRI, SCA appears hyperintense on T2 weighted images and usually hypointense on T1-WI and commonly shows post-contrast septal enhancement in 67% of lesions [70]. Typical imaging features of SCA that distinguish it from other PCL include; Microcystic morphology, surface lobulations, central scar, and dense septal enhancement (Table 3) [12,77]. Microcystic pattern presents in 70% of SCA and has a specificity of 97.8% alone for diagnosing SCA and 100% in presence of surface lobulations. Despite high specificity (100%) for SCA, central scar presents only in 30% of SCA. Central scar may show calcifications [77]. Macrocystic SCAs have large cysts and may be unilocular resembling MCN. The presence of surface lobulations, septal enhancement, central scar, and absence of peripheral enhancement favors diagnosis of SCA, but cystic fluid aspiration may be needed for definitive differentiation [12,70,78]. Wall thickness was documented to be larger in MCN compared to SCA. Manfredi et al reported a statistically significant difference in median wall thickness between MCN (4 mm) and SCA (2 mm) [70].

Management of SCA varies according to symptoms and size. Since most cases are benign, watchful follow-up is a good choice for management. For symptomatic lesions or those >4 cm, surgical resection might be considered [12,74].

Conclusion

PCLs are a heterogeneous group of diseases. Imaging is crucial for assessment of PCLs, by assessing the locularity, nodularity, ductal relation, calcification and enhancement characteristics. EUS-FNA can aid in diagnosis of indeterminate cystic lesions. To improve the accuracy of diagnosis, radiologists should give careful attention to patient history and cystic fluid pathology.

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