Classification of pancreatic cysts

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INTRODUCTION

Pancreatic cysts are diagnosed with increasing frequency because of the widespread use of cross-sectional imaging. Pancreatic cysts may be detected in 40 to 50 percent of patients who undergo abdominal magnetic resonance imaging for unrelated reasons. The frequency increases with age [1,2].

Pancreatic cysts can either be neoplastic (eg, intraductal papillary mucinous neoplasms) or non-neoplastic. Accurate cyst categorization is important, since non-neoplastic cysts require treatment only if symptomatic, whereas some of the pancreatic cystic neoplasms have significant malignant potential and should be resected.

This topic will review the classification of pancreatic cysts. An overview of pancreatic cystic neoplasms and issues related to pancreatic inflammatory fluid collections and intraductal papillary mucinous neoplasms of the pancreas are discussed separately:

- (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management".)
- (See "Approach to walled-off pancreatic fluid collections in adults".)
- (See "Endoscopic interventions for walled-off pancreatic fluid collections".)
- (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations".)
- (See "Clinical manifestations and diagnosis of acute pancreatitis", section on 'Local complications'.)

TYPES OF PANCREATIC CYSTS

Cystic lesions of the pancreas can be divided pathologically into inflammatory fluid collections, non-neoplastic pancreatic cysts, and pancreatic cystic neoplasms (PCNs). Rarely, solid pancreatic tumors may also present as a pancreatic cyst (eg, pancreatic neuroendocrine tumor). Most pancreatic cysts are detected incidentally when abdominal imaging is performed for some other indication [1,2]. PCNs account for more than half of pancreatic cysts, even in patients with a history of pancreatitis [3].

Pancreatic cystic lesions can be an isolated finding, or they can be associated with an underlying disorder such as von Hippel-Lindau disease or polycystic kidney disease. In a study of 158 consecutive patients with von Hippel-Lindau disease, 77 percent had a pancreatic abnormality, including 70 percent with cysts, 9 percent with serous cystadenomas, and 9 percent with neuroendocrine tumors [4]. (See "Clinical features, diagnosis, and management of von Hippel-Lindau disease".)

Pancreatic cysts are seen in 7 to 10 percent of patients with autosomal dominant polycystic kidney disease. (See "Autosomal dominant polycystic kidney disease (ADPKD): Extrarenal manifestations", section on 'Pancreatic cysts'.)

Inflammatory fluid collections — These are not true epithelial cysts and typically represent local complications of acute pancreatitis. Inflammatory fluid collections were previously grouped together under the heading of pancreatic pseudocysts. In 2013, a revision of the Atlanta classification of acute pancreatitis was published that updated the terminology used to describe pancreatic fluid collections to better reflect the underlying pathophysiology [5]. According to the revised Atlanta classification, inflammatory fluid collections include acute peripancreatic fluid collections, pseudocysts, acute necrotic collections, and walled-off pancreatic necrosis [5]:

- Acute peripancreatic fluid collections occur in the setting of acute interstitial pancreatitis within four weeks of the onset of pancreatitis. They are typically extra-pancreatic and do not have a definable wall. The fluid contains no solid material, and there is no pancreatic necrosis present.

- Pseudocysts represent more mature fluid collections that are usually outside the pancreas (though they may be intrapancreatic). They typically develop at least four weeks after acute pancreatitis. They have a well-defined wall, and as is the case with acute peripancreatic fluid collections, there should be no solid material or pancreatic necrosis present. Pseudocysts may also develop following pancreatic trauma.

- Acute necrotic collections occur in the setting of necrotizing pancreatitis, may be adjacent to or involve the pancreas, have no definable wall, and may contain both liquid and solid material.

- Walled-off pancreatic necrosis is a mature (typically developing at least four weeks after acute pancreatitis), encapsulated collection of pancreatic necrosis that may contain liquid and solid elements (with or without loculation). They may be intra- or extra-pancreatic.

It is important to remember that PCNs can sometimes cause acute pancreatitis, or patients presenting with acute pancreatitis may harbor an incidental PCN. As such, all cysts discovered at the time of acute pancreatitis cannot be assumed to be inflammatory. Review of prior imaging if available, clinical presentation and radiological features, and follow-up are important to make this distinction.

NON-NEOPLASTIC PANCREATIC CYSTS

Non-neoplastic pancreatic cysts (NNPCs) include a variety of very rare cysts that are often asymptomatic and do not require resection. These include true cysts, acinar cystic transformation of the pancreas, retention cysts, mucinous non-neoplastic cysts, and lymphoepithelial cysts. They are typically diagnosed after surgical resection of a lesion that was thought to be a pancreatic cystic neoplasm (PCN) preoperatively.

True cysts — There are only a few cases reported of true cysts or "benign epithelial cysts" of the pancreas. These cystic lesions with a cuboidal epithelial lining have an unclear natural history.

Acinar cystic transformation of the pancreas — Also known as acinar cell cystadenomas, these are exceedingly rare lesions. These are believed to be non-neoplastic lesions lined by benign acinar and ductal epithelium that may occur anywhere in the pancreas, but usually in the pancreatic head in females. Usually incidentally discovered, these may grow and lead to symptoms due to space occupation. Usually confused for other cystic lesions, the diagnosis is only made after resection [6,7].

Retention cysts — Retention cysts are small dilated pancreatic duct side branches arising due to obstruction (eg, from pancreatic intraepithelial neoplasia or from inspissated protein debris seen in association with chronic pancreatitis or cystic fibrosis).

Mucinous non-neoplastic cysts — Mucinous non-neoplastic cysts are exceedingly difficult to differentiate from PCNs. Like PCNs, mucinous non-neoplastic cysts are lined with a mucinous lining, but they lack any neoplastic features (eg, atypia) or ductal communication [8]. These lesions have an unclear natural history.

Lymphoepithelial cysts — Lymphoepithelial cysts (LEC) are rare, benign, and usually asymptomatic cystic lesions. Often described as peripancreatic, these lesions are lined by mature keratinizing squamous epithelium surrounded by a distinct layer of lymphoid tissue [9]. Endoscopic ultrasound with fine needle aspiration (EUS-FNA) may be required to differentiate an LEC from a PCN. FNA cytology usually reveals characteristic epithelial cells and small, mature lymphocytes in a background of keratinaceous debris, anucleate squamous cells, and multinucleated histiocytes [10]. Resection is recommended in symptomatic cases, but not for asymptomatic patients.

PANCREATIC CYSTIC NEOPLASMS

Identifying pancreatic cystic neoplasms (PCNs) is important, since some have malignant potential. PCNs are categorized using the WHO histological classification [11].

There are six subtypes of PCNs:

- Serous neoplasms
- Mucinous cystic neoplasms (MCNs)
- Intraductal papillary mucinous neoplasms (IPMNs)
- Intraductal oncocytic papillary neoplasms (IOPNs)
- Intraductal tubulopapillary neoplasms (ITPNs)
- Solid pseudopapillary neoplasms (SPNs)

The key demographic and clinical features of PCNs are summarized in the table (table 1). Each of the subtypes has benign and malignant forms.

The relative frequencies of the different PCNs were examined in a retrospective series of 851 patients undergoing surgical resection for a cystic neoplasm of the pancreas between 1978 and 2011 [12]. Intraductal papillary mucinous neoplasms accounted for 38 percent of lesions, mucinous cystic neoplasms for 23 percent, serous cystic tumors for 16 percent, and solid pseudopapillary neoplasms for 3 percent. When only the 376 patients who had surgery between 2005 and 2011 were considered, 49 percent had intraductal papillary mucinous neoplasms, 16 percent had mucinous cystic neoplasms, 12 percent had serous cystic tumors, and 5 percent had solid pseudopapillary neoplasms. However, this series is subject to sampling bias, as it only evaluated resected PCNs. Most branch duct IPMNs and serous cystadenomas do not require resection; thus, the relative frequency of these lesions may have been underestimated.

Serous neoplasms — Most serous neoplasms are serous cystadenomas, which are benign neoplasms lined by glycogen-rich cuboidal cells that originate from pancreatic centro-acinar cells

(image 1 and picture 1). These lesions can arise anywhere in the pancreas and are most commonly diagnosed in women over the age 60 years [13-15].

The WHO classifies serous neoplasms of the pancreas as microcystic serous cystadenoma, macrocystic (oligocystic) serous cystadenoma, solid serous adenoma, von Hippel-Lindau syndrome-associated serous cystic neoplasm, and mixed serous-neuroendocrine neoplasm [11]. For clinical purposes and in the non-*VHL* population, the most commonly encountered are microcystic serous cystadenomas, which are composed of multiple small cystic spaces (picture 2A-C), and oligocystic serous cystadenomas, which are composed of fewer, larger cysts [16-18]. The oligocystic variant can be difficult to distinguish from an MCN or branch duct IPMN, which can have a similar appearance. Unless symptomatic, these can be followed conservatively since malignant degeneration is exceedingly rare. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Management'.)

Mucinous cystic neoplasms — Mucinous cystic neoplasms (MCNs) (picture 3A-B) occur almost exclusively in women and are most commonly discovered after the age of 40 years [19]. MCNs exhibit variable cellular atypia and secrete mucin similar to IPMNs [20,21]. In contrast to IPMNs, MCNs demonstrate ovarian-like stroma [22], typically arise in the pancreatic tail or body (picture 4) [21], and do not communicate with the pancreatic duct. (See 'Intraductal papillary mucinous neoplasms' below.)

Due to the risk of malignancy developing, resection is recommended in appropriate candidates. However, in the absence of mural nodules, malignancy is rarely found in cysts <4 cm in size [22-24]. Thus, the patient's age and health status need to be considered when making management decisions. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Management'.)

Intraductal papillary mucinous neoplasms — Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing papillary neoplasms of the pancreatic ductal system that exhibit variable cellular atypia and cause dilation of the pancreatic ducts [25]. IPMNs have an equal sex distribution, with incidence peaking over the age of 50 years [26]. They are the most commonly encountered cystic neoplasm.

IPMNs may involve the main pancreatic duct (main duct IPMN) (image 2), its side branches (branch duct IPMN), or both (mixed-type IPMN) (image 3). They are often multifocal or diffuse, and can extend microscopically from the clinically apparent lesions.

The characteristic pathologic features include the diffuse or segmental dilation of the pancreatic duct without stricturing, the intraductal expansion of mucin-producing ductal cells (which may be

flat or project into the lumen), and the dilation of either one or both pancreatic orifices, through which there is a copious secretion of mucus (picture 5).

Histologically, the columnar mucin-producing cells can be hyperplastic or dysplastic. They can be further classified based upon the degree of dysplasia exhibited by the epithelial cells as low-grade dysplasia, high-grade dysplasia, or invasive cancer [11].

Intraductal oncocytic papillary neoplasms — Intraductal oncocytic papillary neoplasms (IOPNs) are rare, representing approximately 5 percent of all intraductal neoplasms, and occur more commonly in females. The majority occur in the head of the pancreas, and involve the main pancreatic duct, although they can also involve the branch ducts [27]

These tumors form branching papillae composed of cuboidal to columnar cells, with a fibrovascular core. Most IOPNs harbor high-grade dysplasia, but rarely progress to invasive cancer. The overall survival rate is excellent [28,29].

Intraductal tubulopapillary neoplasms — Intraductal tubulopapillary neoplasms are even more rare than IOPN, accounting for approximately 3 percent of intraductal neoplasms, and are slightly more common in females. These neoplasms tend to form fleshy nodular lesions composed of tubular glands in cribriform architecture. They grow in dilated ducts, with resultant duct occlusion. There is typically no mucinous fluid production and less cystic formation. Even if invasive cancer is present, prognosis is significantly better than that of ductal adenocarcinoma [29-31]. Management involves a combination of surveillance and resection depending upon the risk of malignancy and patient-related factors [32]. IOPN and ITPN are newer pathologic classifications, however, from a clinical standpoint, they are managed similarly to IPMN. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Management'.)

Solid pseudopapillary neoplasms — Solid pseudopapillary neoplasms (SPNs) of the pancreas are rare neoplasms that typically occur in young women less than 35 years of age. They have also been called solid and papillary epithelial neoplasms, papillary cystic tumors of the pancreas, and solid and cystic tumors.

SPNs are most commonly found in the body or tail of the pancreas and may contain both solid and cystic components and occasional calcifications (image 4 and picture 6) [33,34]. Due to malignant risk, it is recommended that SPNs be resected. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'Management'.)

Malignant potential — The malignant potential of pancreatic cystic neoplasms is discussed elsewhere. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and

management", section on 'Management' and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Prognosis'.)

CYSTIC DEGENERATION IN SOLID PANCREATIC TUMORS

Cystic degeneration has been described in most solid pancreatic tumors, including endocrine tumors, ductal carcinoma, and acinar cell carcinoma. These lesions are managed similarly to the malignancies from which they arise. (See appropriate topic reviews).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cysts".)

SUMMARY AND RECOMMENDATIONS

- Cystic lesions of the pancreas may be divided pathologically into inflammatory fluid collections, non-neoplastic pancreatic cysts, and pancreatic cystic neoplasms (PCNs). In addition, solid tumors may develop cystic degeneration. (See 'Types of pancreatic cysts' above.)

- There are six subtypes of PCNs with varying degrees of malignant potential (table 2 and table 1):

  - Serous neoplasms
  - Mucinous cystic neoplasms (MCNs)
  - Intraductal papillary mucinous neoplasms (IPMNs)
  - Intraductal oncocytic papillary neoplasms (IOPNs)
  - Intraductal tubulopapillary neoplasms (ITPNs)
  - Solid pseudopapillary neoplasms (SPNs)

- Differentiating PCNs from other cystic lesion, as well as determining the subtype of PCN, is important for assessing malignant potential. While serous cystadenomas have almost no malignant potential, the mucin producing PCNs (MCNs and intraductal neoplasms) and SPNs do. (See 'Non-neoplastic pancreatic cysts' above and 'Pancreatic cystic neoplasms' above.)

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Topic 5637 Version 26.0

GRAPHICS

Key demographic and clinical features of patients with pancreatic cystic neoplasms[1-4]

	Serous cystic tumor	Mucinous neoplasm	Main-duct intraductal papillary mucinous neoplasm	Branch-duct intraductal papillary mucinous neoplasm	S pseud nec
Age of presentation	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Variable, usually 5th to 7th decade	Usually decade
Gender distribution	Females >males	Almost exclusively females	Females = males	Females = males	Females
Typical clinical presentation	Incidental or abdominal pain or mass effect	Incidental or abdominal pain or malignancy related	Incidental or pancreatitis or pancreatic insufficiency or malignancy related	Incidental or pancreatitis or malignancy related	Incident abdomi mass ef
Typical imaging characteristics	Microcystic/honeycomb appearance Oligocystic appearance less common	Unilocular or septated cyst ± wall calcifications Solid component, if present, may suggest malignancy	Dilated main pancreatic duct ± parenchymal atrophy Solid component, if present, may suggest malignancy	Dilated pancreatic duct branch or branches Solid component, if present, may suggest malignancy	Solid an mass ± calcifica
Typical aspirate characteristic	Thin, often bloody	Viscous	Viscous	Viscous or thin	Bloody
Typical cytology findings	Cuboidal cells that stain positive for glycogen; yield <50%	Columnar cells with variable atypia Stains positive for mucin;	Columnar cells with variable atypia Stains positive for mucin;	Columnar cells with variable atypia Stains positive for mucin;	Charact branchi with my High yie solid co

		yield <50% High yield from solid component for malignancy	yield <50% High yield from solid component for malignancy	yield <50% High yield from solid component for malignancy	
Typical carcinoembryonic antigen (CEA) level	<5 to 20 ng/mL in majority of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	>200 ng/mL in approximately 75% of lesions	Insuffici
Typical glucose level	>50 mg/dL in majority	<50 mg/dL in majority	<50 mg/dL (limited data)	<50 mg/dL in majority	Insuffici
Typical DNA analysis	Allelic loss affecting chromosome 3p and VHL mutation specific	K-ras mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	K-ras and GNAS mutation specific (>90%), not sensitive (<50%) TP53, PTEN, PIK3CA, high DNA amount or high-amplitude allelic loss seen in malignancy	CTNNB1 specific
Relative malignant potential	Negligible	Moderate	High	Low to moderate	Modera
Treatment	Resect if symptomatic	Resection	Resection and post-resection surveillance	Closely monitor or resect Post-resection surveillance required	Resectic

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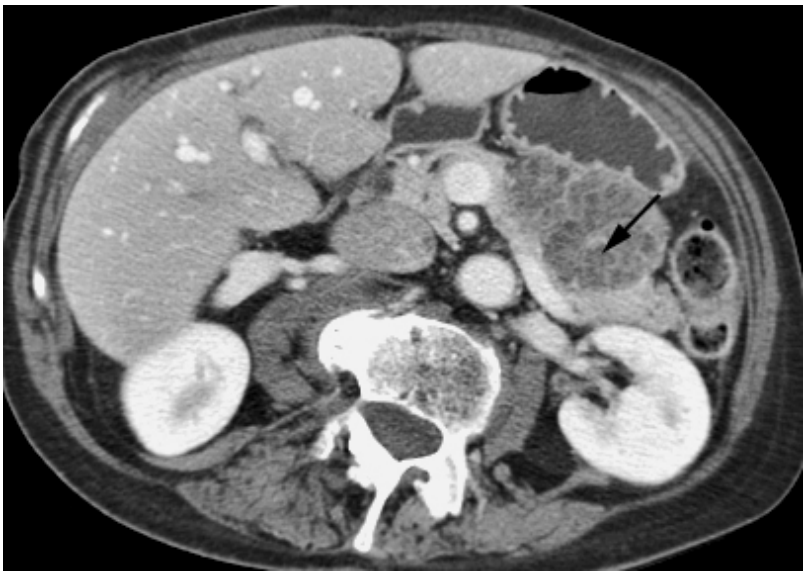
Graphic 57759 Version 9.0

Pancreatic serous cystadenoma



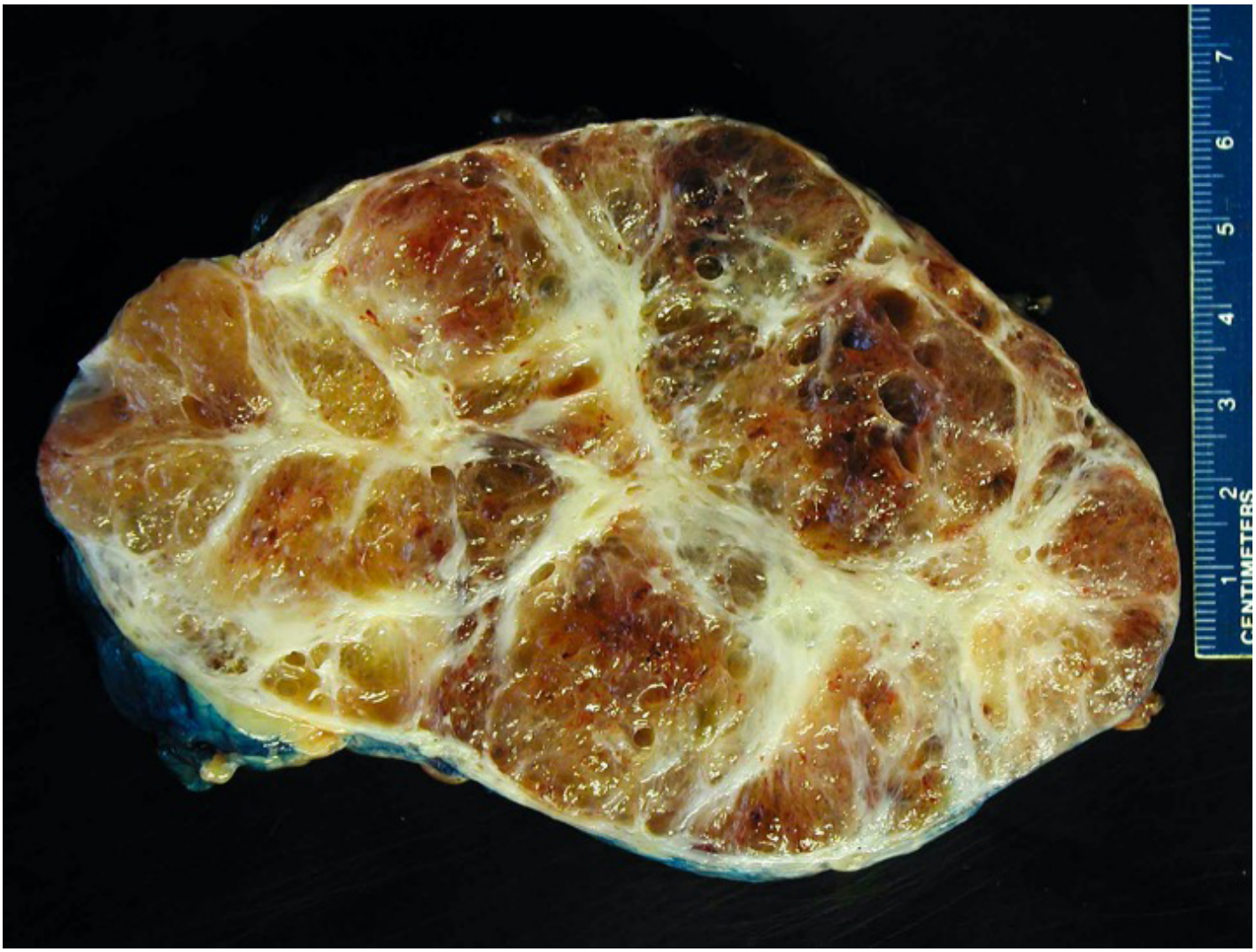
CT showing a serous cystadenoma of the pancreas. Note central calcification of stellate scar (arrow).

CT: computed tomography.

Courtesy of Kevin McGrath, MD.

Graphic 66608 Version 5.0

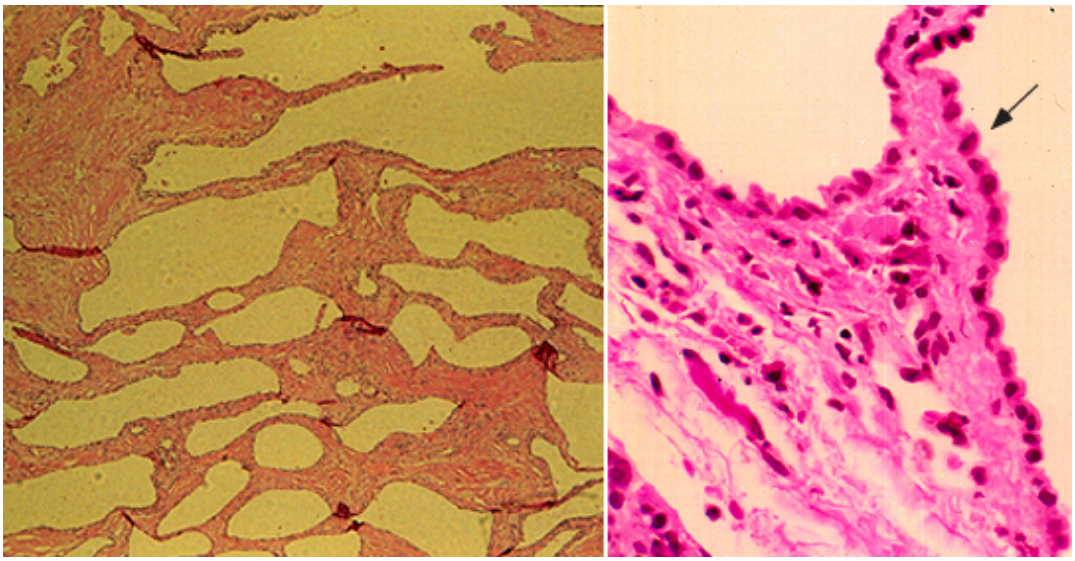
Gross appearance of a resected pancreatic serous cystadenoma



Gross appearance of a resected pancreatic serous cystadenoma. Note the white central scar, with emanating fibrous septa.

Graphic 61511 Version 4.0

Serous cystadenoma of the pancreas



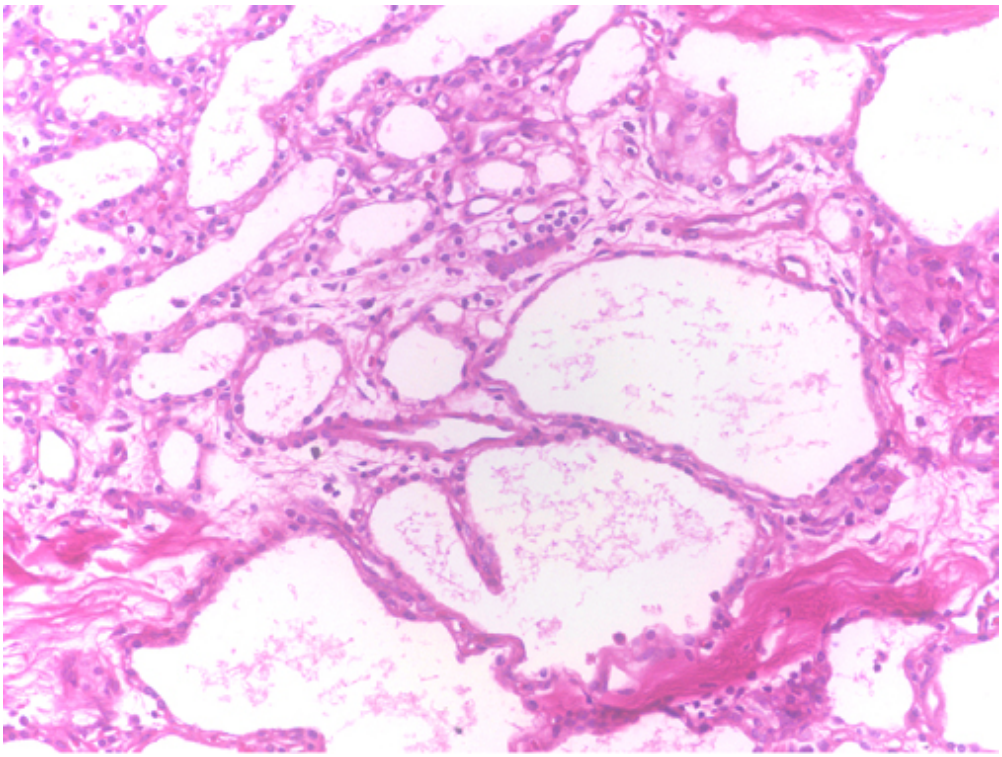
Low- and high-power light micrographs of a serous cystadenoma of the pancreas.

Left panel: Low power reveals multiple microcystic spaces within the lesion. Right panel: High power shows that the lining of the cystadenoma is comprised of flat cuboidal glycogen-rich cells (arrow).

Courtesy of Robert Odze, MD and Michael L Steer, MD.

Graphic 73288 Version 2.0

Pancreatic serous cystadenoma

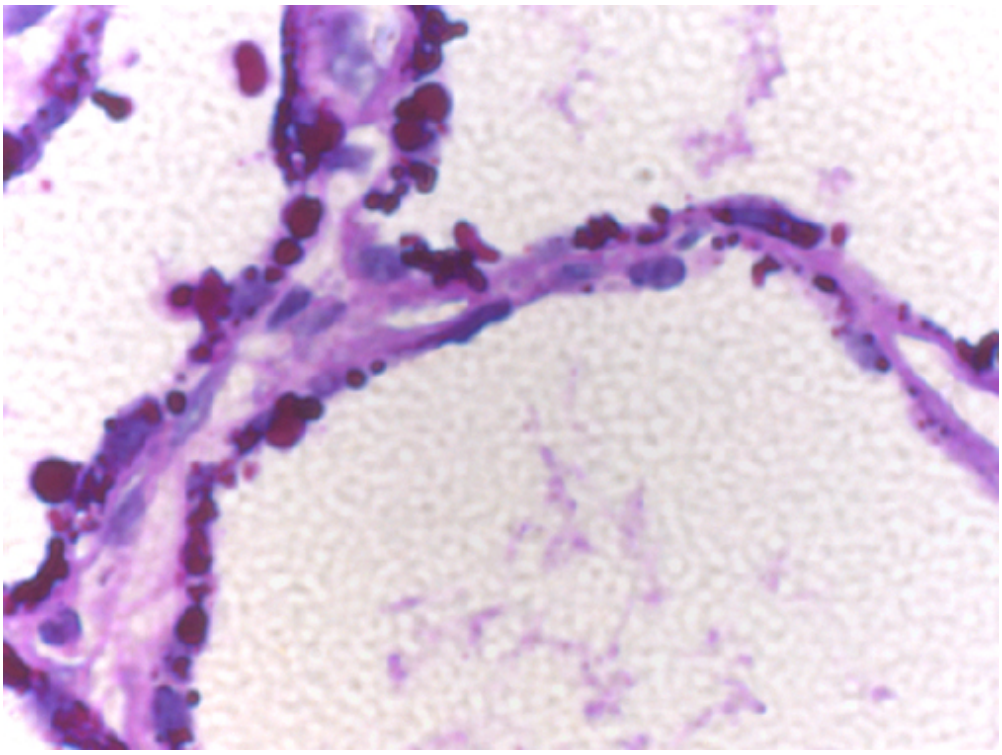


Light microscopic appearance of a pancreatic serous cystadenoma (H&E stain). Note cuboidal cells lining cystic spaces and amorphous stroma.

Courtesy of Michael L Steer, MD.

Graphic 82546 Version 2.0

Pancreatic serous cystadenoma

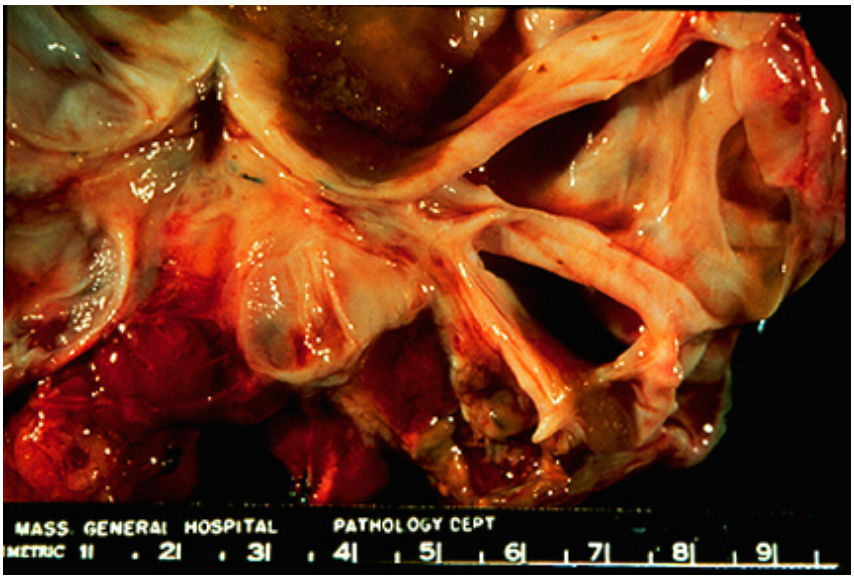


Periodic Acid Schiff (PAS) staining of pancreatic serous cystadenoma. Note positive staining identifying glycogen-rich cells lining cystic spaces.

Courtesy of Mike Steer, MD.

Graphic 71673 Version 2.0

Pancreatic mucinous cystic neoplasm

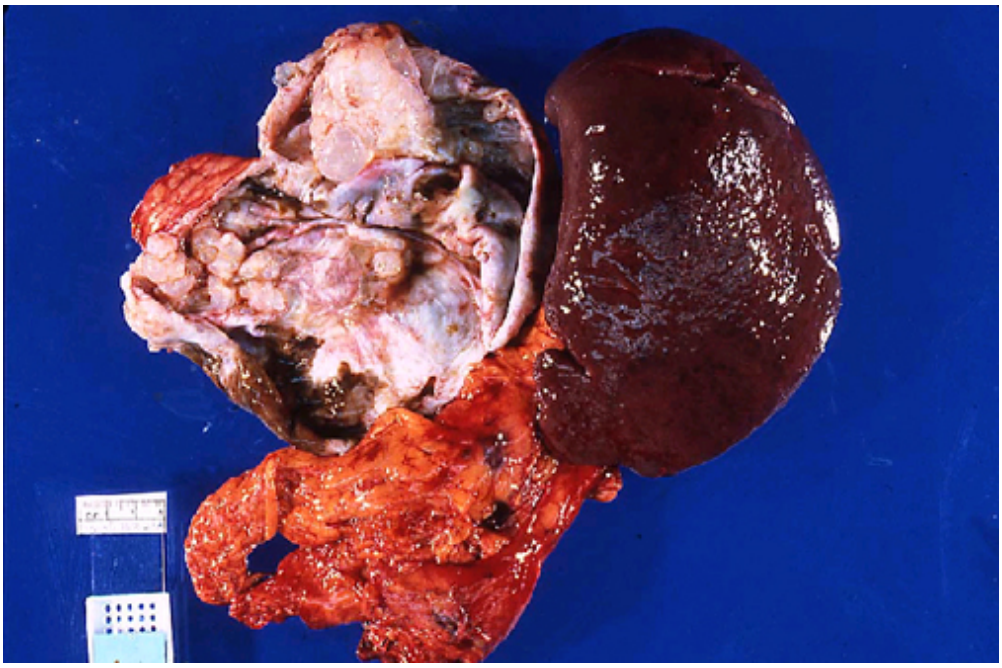


Surgical specimen of a mucinous cystic neoplasm consisting of multiple cystic spaces.

Courtesy of Robert Odze, MD.

Graphic 58137 Version 2.0

Pancreatic mucinous cystic neoplasm

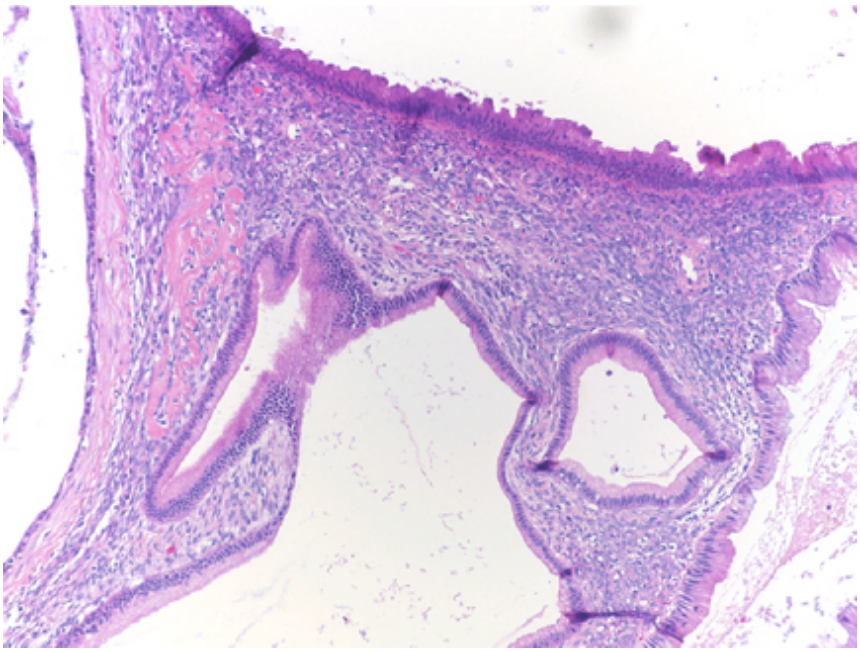


Gross appearance of a mucinous cystadenoma of the pancreas and attached spleen.

Courtesy of Michael L Steer, MD.

Graphic 66804 Version 3.0

Pancreatic mucinous cystic neoplasm

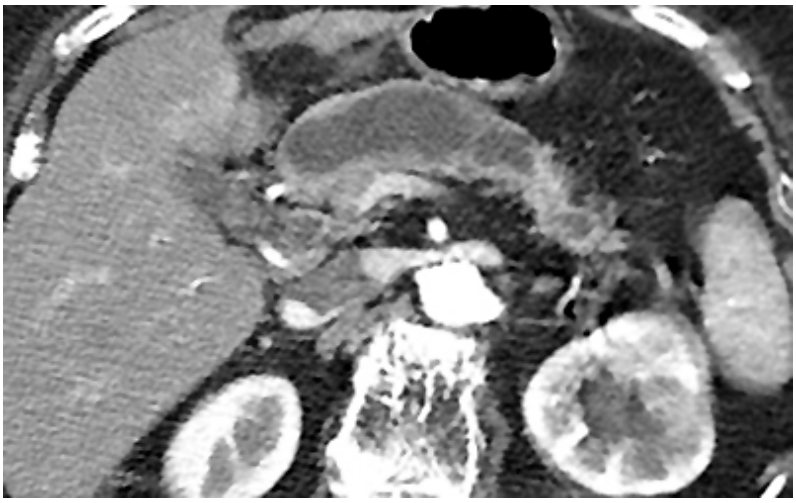


Microscopic appearance of a mucinous pancreatic cystadenoma. Note cystic spaces lined with columnar goblet cells and stroma, which has "ovarian-like" appearance.

Courtesy of Michael L Steer, MD.

Graphic 52386 Version 3.0

Computed tomography of intraductal papillary mucinous neoplasm with parenchymal atrophy



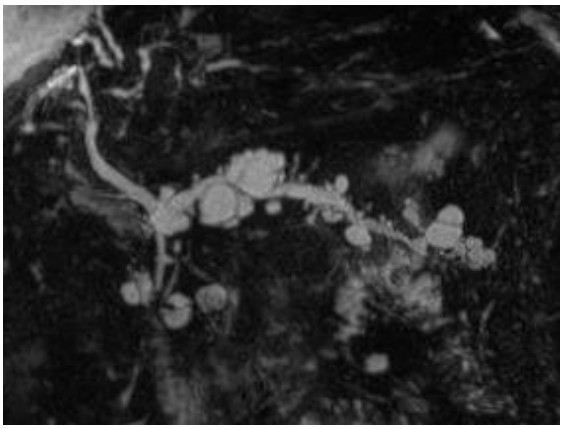
CT scan of main duct intraductal papillary mucinous neoplasm, revealing a markedly dilated pancreatic duct with parenchymal atrophy.

CT: computed tomography.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 51921 Version 4.0

Mixed-type intraductal papillary mucinous neoplasm of the pancreas

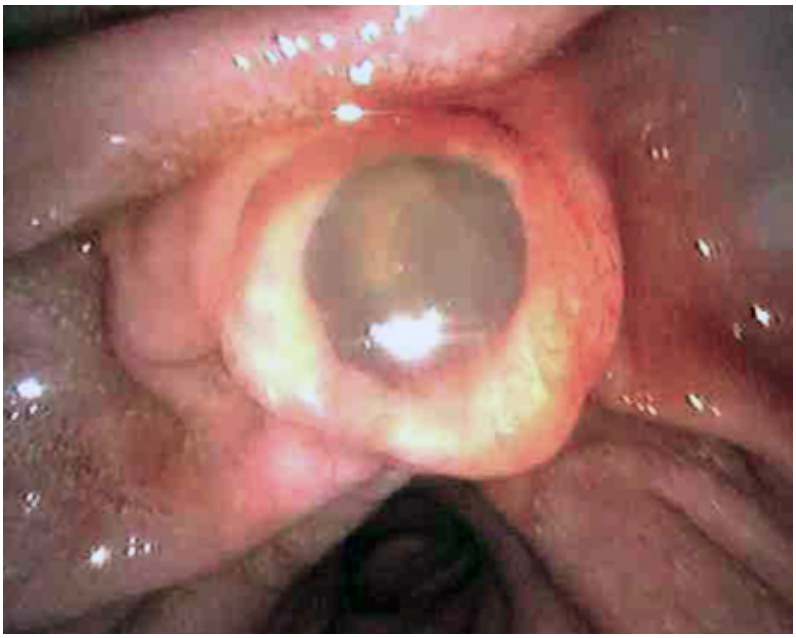


Magnetic resonance cholangiopancreatography revealing mixed-type intraductal papillary mucinous neoplasm. There are multiple dilated branch ducts and a moderately dilated main pancreatic duct in the pancreatic body region.

Courtesy of Kevin McGrath, MD.

Graphic 101892 Version 1.0

Papilla extruding mucus in a patient with IPMN

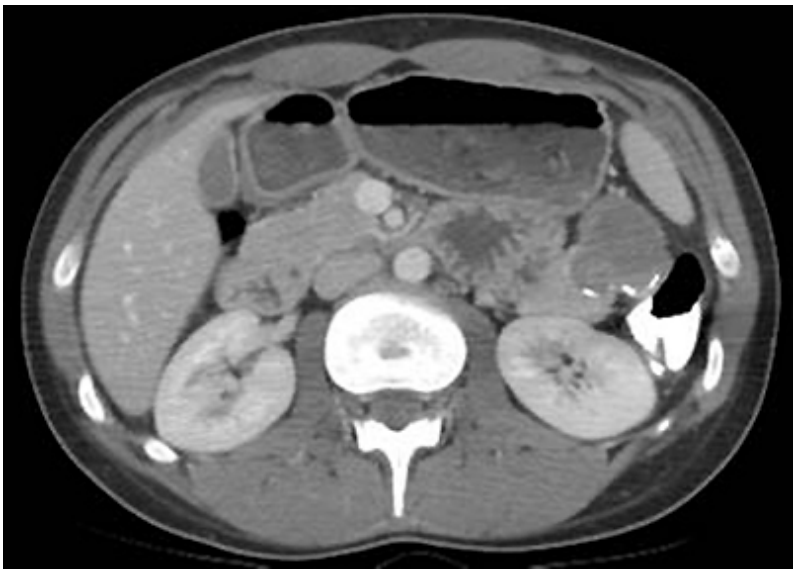


A gaping papilla extruding mucus, pathognomonic of main-duct intraductal papillary mucinous neoplasm.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 52643 Version 1.0

Solid pseudopapillary neoplasm of the pancreas

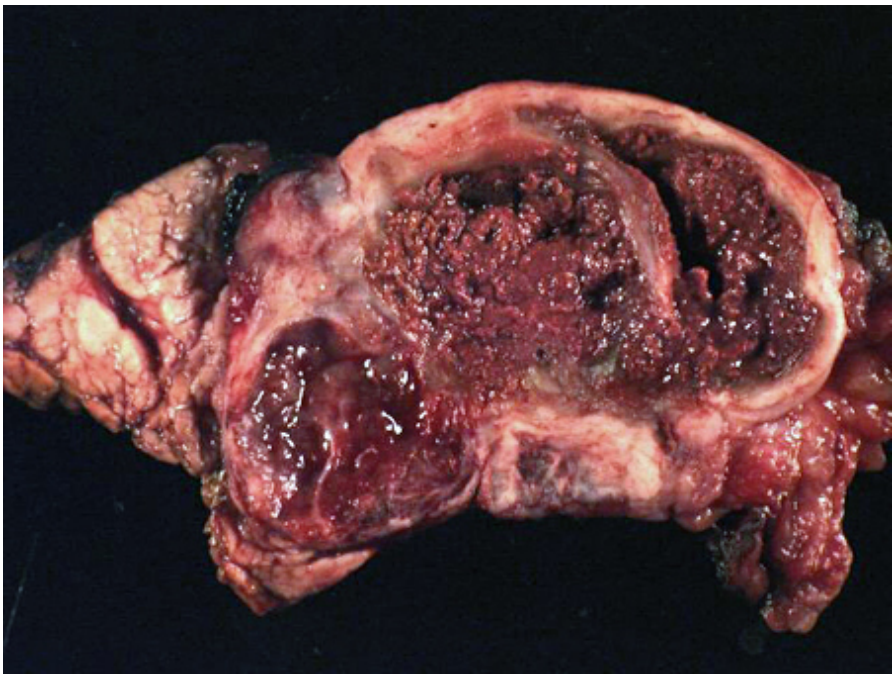


Incidental finding of a 4 cm solid pseudopapillary neoplasm with peripheral calcification in the pancreatic tail of a young woman.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 76413 Version 3.0

Gross image of pseudopapillary neoplasm of the pancreas



Corresponding gross image of the solid pseudopapillary neoplasm depicted in Radiograph 5.

Courtesy of Kevin McGrath, MD, and Asif Khalid, MD.

Graphic 63887 Version 2.0

World Health Organization classification of pancreatic cystic neoplasms

Serous neoplasms
Serous cystadenoma
Microcystic serous cystadenoma
Macrocystic (oligocystic) serous cystadenoma
Solid serous adenoma
Von Hippel-Lindau syndrome-associated serous cystic neoplasm
Mixed serous-neuroendocrine neoplasm
Serous cystadenocarcinoma
Mucinous cystic neoplasm
Mucinous cystic neoplasm with low-grade dysplasia
Mucinous cystic neoplasm with high-grade dysplasia
Mucinous cystic neoplasm with associated invasive carcinoma
Intraductal papillary mucinous neoplasm
Intraductal papillary mucinous neoplasm with low-grade dysplasia
Intraductal papillary mucinous neoplasm with high-grade dysplasia
Intraductal papillary mucinous neoplasm with associated invasive carcinoma
Solid pseudopapillary neoplasm
Solid pseudopapillary neoplasm
Solid pseudopapillary neoplasm with high-grade carcinoma

Data from: Zamboni G, Kloeppel G, Hruban RH, et al. Mucinous cystic neoplasms. Tumours of the pancreas. In: World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Digestive System, 5th ed, Aaltonen LA, Hamilton SR (Eds), IARC Press, Lyon 2019.

Graphic 69594 Version 4.0

Contributor Disclosures

Asif Khalid, MD No relevant financial relationship(s) with ineligible companies to disclose. **Kevin McGrath, MD** No relevant financial relationship(s) with ineligible companies to disclose. **John R Saltzman, MD, FACP, FACG, FASGE, AGAF** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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