



CYSTIC NEOPLASMS OF THE PANCREAS

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Objectives

- ▣ List the differential diagnosis for pancreatic cysts
- ▣ Review the epidemiology
- ▣ Illustrate the types of cysts through case discussions
- ▣ Discuss radiographic and endoscopic imaging techniques
- ▣ Present guidelines for management

Differential Diagnosis of Pancreatic Cysts

- ▣ Pseudocyst
- ▣ Inclusion cyst (reactive)
- ▣ Serous cystadenoma (SCA)
- ▣ Mucinous cystic neoplasm (MCN)
- ▣ Intraductal papillary mucinous neoplasm (IPMN)
- ▣ Solid pseudopapillary tumor (SPT)
- ▣ Lymphoepithelial cyst
- ▣ Cystic endocrine neoplasm
- ▣ Cystic degeneration of solid tumors

Cystic Neoplasms of the Pancreas

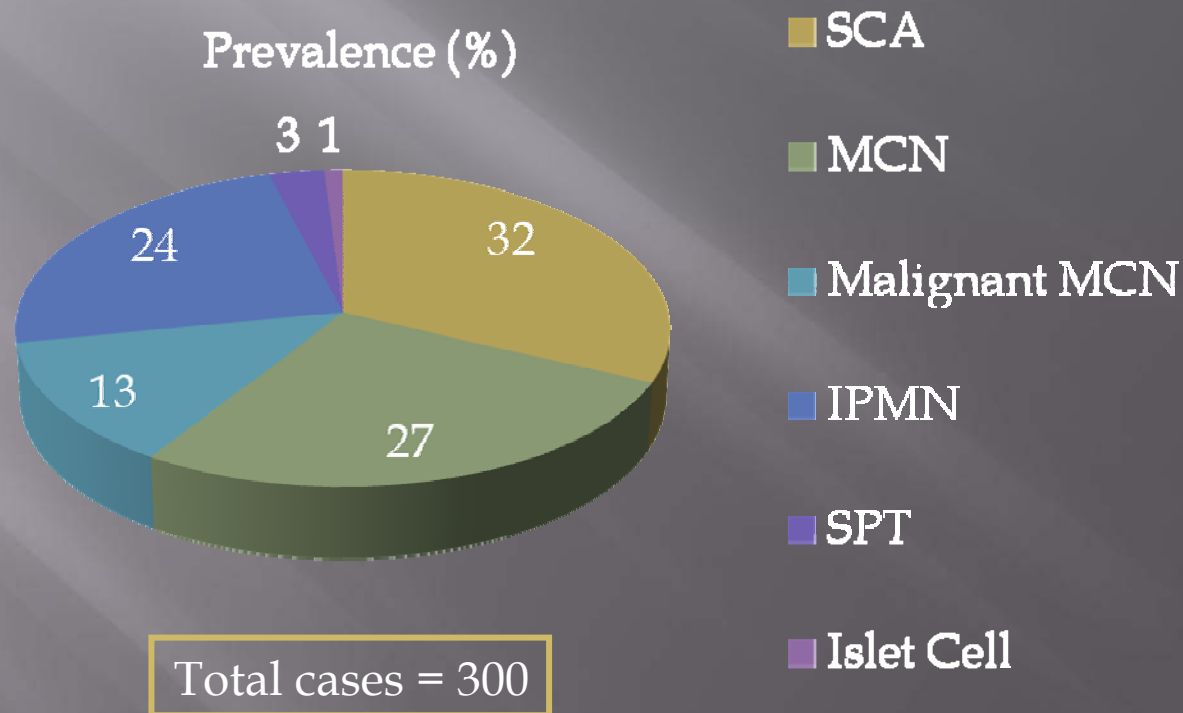
- ▣ Female predominance 4:1
- ▣ Mean age of diagnosis is 54 years
- ▣ The prevalence of pancreatic cysts is 1.2%
 - 10% of cysts are neoplastic
- ▣ One percent of pancreatic neoplasms are cystic
- ▣ They are typically asymptomatic and found incidentally on diagnostic imaging for other indications

Spinelli KS, et al. *Ann Surg* 2004; 239:651.

Fernandez-del Castillo C, et al. *Surg Clin North Am* 1995; 75:1001.

Warshaw AL, et al. *Ann Surg* 1990; 212:432

Cystic Neoplasms of the Pancreas: Massachusetts General Hospital Series



Does the Cyst Have Malignant Potential?

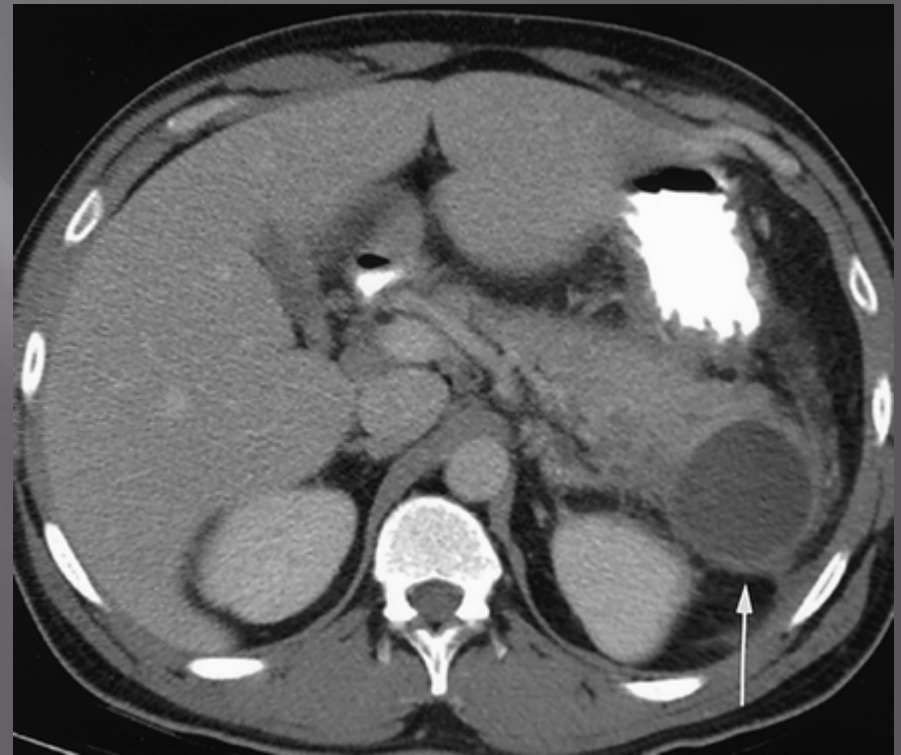
- ▣ The initial evaluation focuses on differentiating cysts with malignant potential from those without
- ▣ Pseudocysts, inclusion cysts and SCA's are considered benign
- ▣ MCNs, IPMNs, SPT's, and solid tumors have malignant potential

Pseudocysts

- ▣ A pseudocyst represents a collection of pancreatic juices that has extravasated from the ductal system due to inflammation or obstruction
 - Lack an epithelial lining (hence the term “pseudo”)
 - Extravasation is due to inflammation and/or obstruction
- ▣ Clues that favor pseudocysts include history of acute or chronic pancreatitis or previous abdominal trauma

Imaging Characteristics That Suggest Pseudocyst

- ▣ No septa, loculations, solid components, or wall calcifications
- ▣ Hypovascularity
- ▣ Cyst communicates with the ductal system (also characteristic of IPMN)



EUS:

Recognizing Non-mucinous Cysts

▣ Pseudocyst:

- Anechoic, thick walled, rare septations, regional inflammatory nodes
- Parenchymal abnormalities suggestive of chronic pancreatitis
- Sensitivity 94%, Specificity 85%

▣ SCA:

- Multiple microcysts (<3mm) within a cystic lesion
- Accuracy 92% - 96%

Diagnostic Imaging

- ▣ Helical CT with IV contrast (pancreas protocol)
- ▣ PET/CT
- ▣ MRCP
- ▣ ERCP
- ▣ Pancreatoscopy
- ▣ EUS with fine-needle aspiration

Goal of Evaluation

- ▣ The critical decision is deciding which neoplasms need resection and which don't
- ▣ In general, cystic neoplasms are more indolent than pancreatic adenocarcinoma and resection can potentially cure

CASE 1

60 y.o. female with nephrolithiasis found to have
an incidental pancreatic lesion on CT



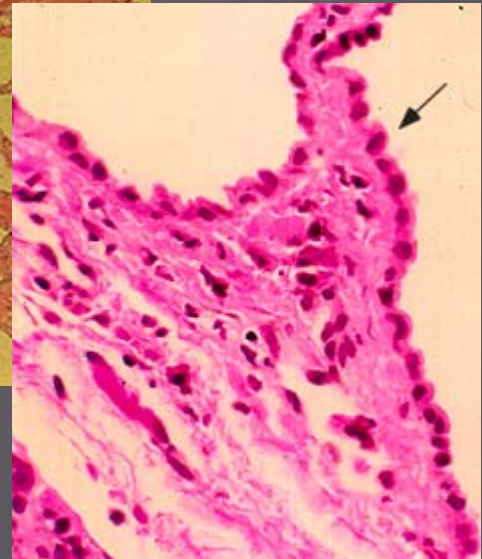
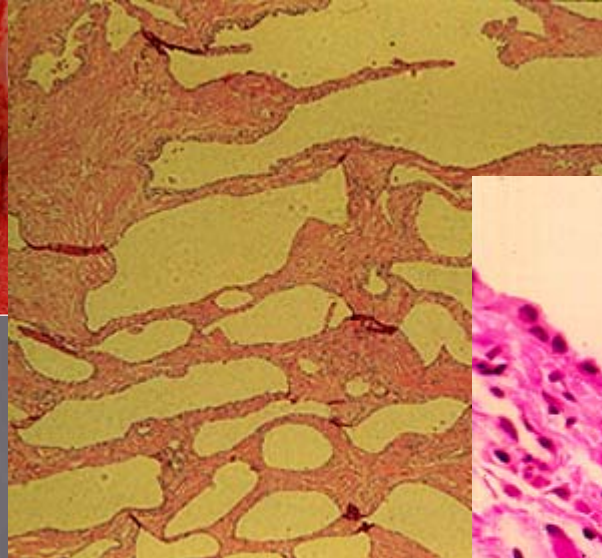
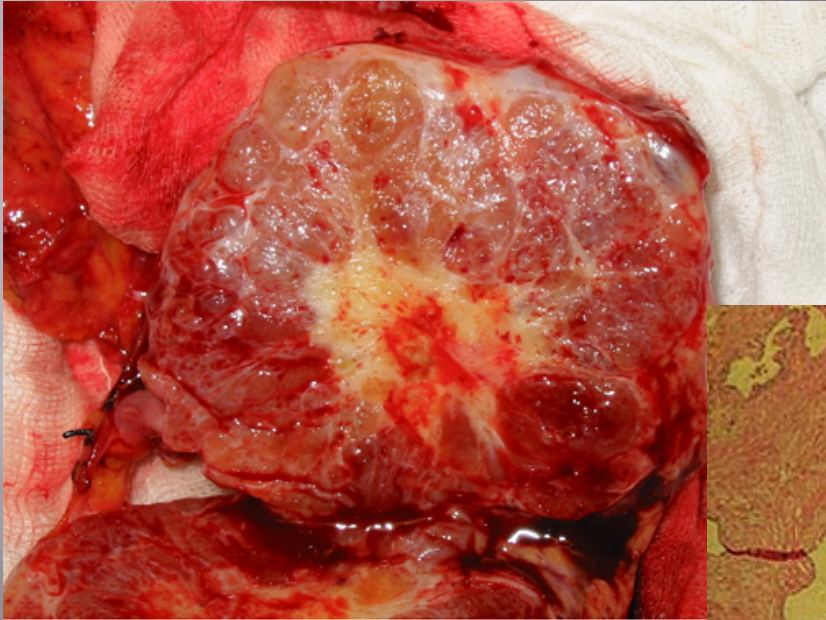
CASE 1



Serous Cystadenoma (SCA)

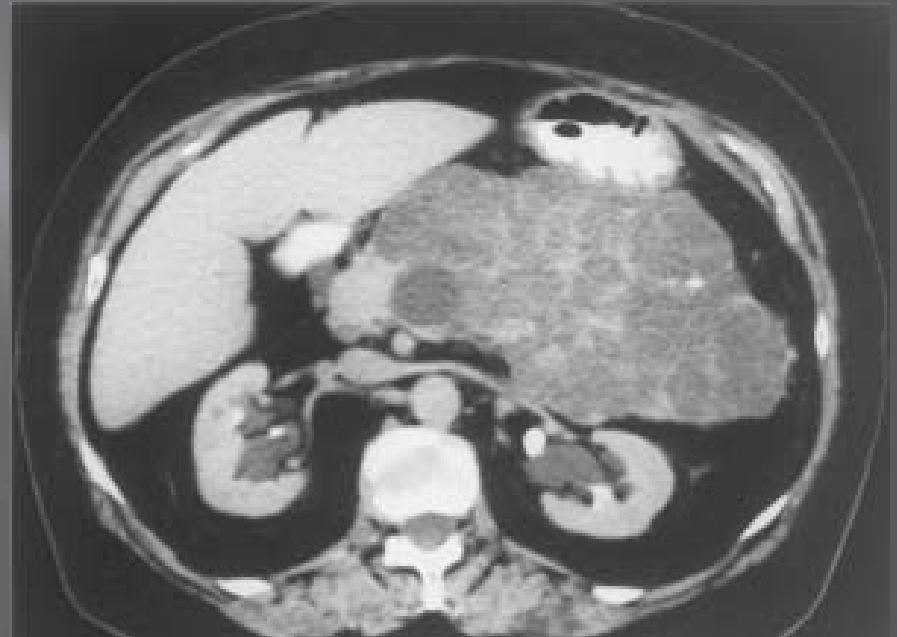
- ▣ “Microcystic adenoma”
- ▣ Women (80%), mean age 62 years
- ▣ Most occur in the body or tail (50% – 70%)
- ▣ Associated with von Hippel-Lindau disease
- ▣ Composed of multiple thin-walled cysts lending to a “honeycomb” appearance
- ▣ Contains a simple, glycogen-rich cuboidal epithelium with a fibrotic or calcified central scar

SCA



SCA

- ▣ Can be diagnosed by CT in 30% of cases; diagnostic criteria include:
 - Spongy mass with a central “sunburst” calcification (10-20%)
 - Microcysts enhance after contrast injection
 - Larger cysts are seen on the periphery



SCA

- ▣ Cystic fluid analysis
 - Non-viscous
 - Low CEA (<5 ng/ml)
 - Yield <50%
- ▣ Considered benign
- ▣ Serous cystadenocARCINOMAS have been described but evidence is on the level of case reports and they constitute less than 1% of known cases

SCA

- ▣ Symptomatic lesions may be resected, but observation is safe in asymptomatic individuals
- ▣ Risks of watchful waiting include:
 - Hemorrhage
 - Obstructive jaundice
 - Pancreatic insufficiency
 - Gastric outlet obstruction
- ▣ Some experts at high-volume centers recommend resection of ALL serous cystadenomas in medically fit patients

CASE 1

- ▣ Cystic fluid revealed CEA 3 ng/mL
- ▣ No further imaging needed
- ▣ FNA is not required if the diagnosis is firm
- ▣ The patient elected to forgo surgery unless symptoms develop

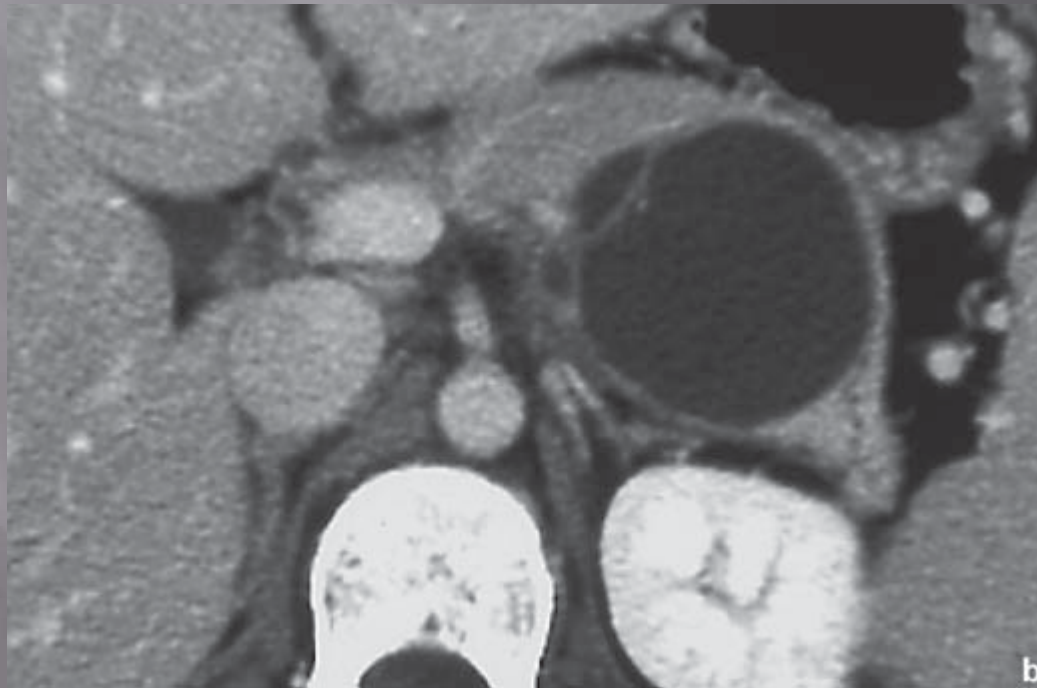
Risk of EUS-FNA

Adverse Event	Complication Rate (%)
Pancreatitis	0.5-4
Hemorrhage within the Cyst	<1
Retroperitoneal bleeding	<0.01
Infection	<1



CASE 2

62 y.o. otherwise healthy female who paid out-of-pocket for a “Full Body CT Scan”



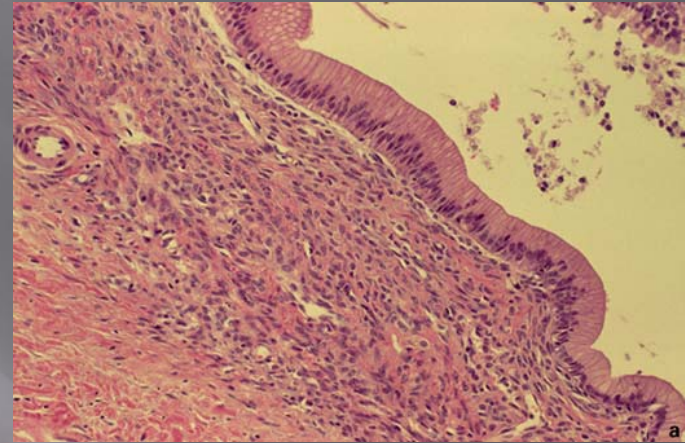
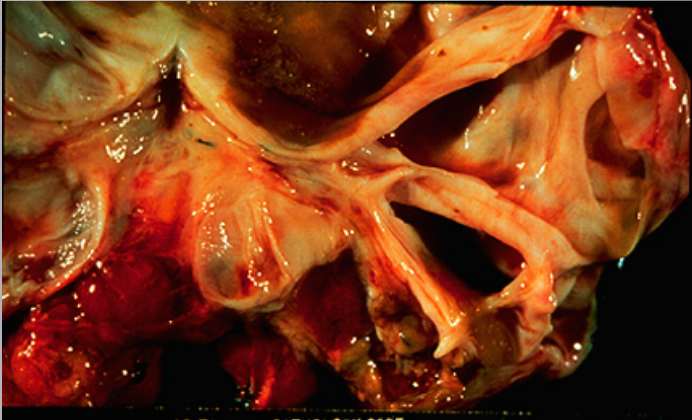
CASE 2



Mucinous Cystic Neoplasm (MCN)

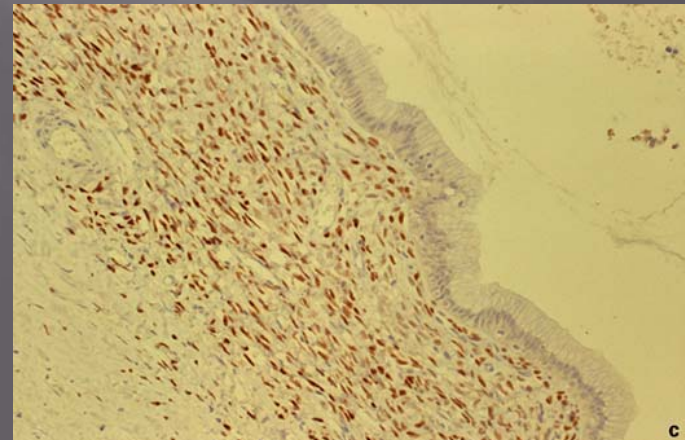
- ▣ Accounts for 44-49% of cystic neoplasms of the pancreas
- ▣ > 80% are in women, mean age 55 years
- ▣ May be 2 – 26 cm in maximum diameter
- ▣ Often located in the body or tail (66%)
- ▣ No communication with the pancreatic duct
- ▣ Composed of large compartments with thin septa that may contain an eccentric solid component

MCN



Mucin-producing
columnar epithelium

Highly cellular
ovarian stroma



MCN

Fluid Analysis

- ▣ 341 patients with pancreatic cystic lesions underwent EUS-FNA
- ▣ CEA, CA 72-4, CA 125 CA 19-9, and CA 15-3 were analyzed
- ▣ 112 patients underwent surgical resection
 - 68 MCN, 7 Serous, 27 inflammatory, 5 endocrine, 5 other

MCN

Fluid Analysis

- ▣ Conclusion:
 - CEA of 192 ng/mL was the most accurate for differentiating mucinous from non-MCN
 - ▣ Sensitivity 73%, Specificity 84%
 - No combination of tests was more accurate than CEA alone

Note: Study did not differentiate MCN from IPMN

Tumor Markers in Pancreatic Cyst Fluid Analysis

	Pseudocyst	Serous Cystadenoma	Mucinous Cystadenoma	IPMN
CEA	Low/Variable	Low	High	High
CA 19-9	High/Variable	Variable	Variable	Variable
CA 72-4	Low/Variable	Low	High	High
CA 15-3	Low	Low	High	Low/Variable
Amylase	High	Low/Variable	Low Variable	High
Cytology	Neutrophils and macrophages	PAS+ cuboidal epithelium with glycogen	Mucin+ Columnar cells with variable atypia	Mucin+ Columnar cells with variable atypia

Cytologic accuracy is around 50% and even less in smaller cysts

Cystic Fluid Analysis

- ▣ Pseudocysts are virtually excluded with amylase <250 and CEA >800
- ▣ Mucinous cysts can be excluded with a CEA <5 and CA 19-9 <37
- ▣ Fluid analysis cannot differentiate MCN from IPMN

Fluid analysis

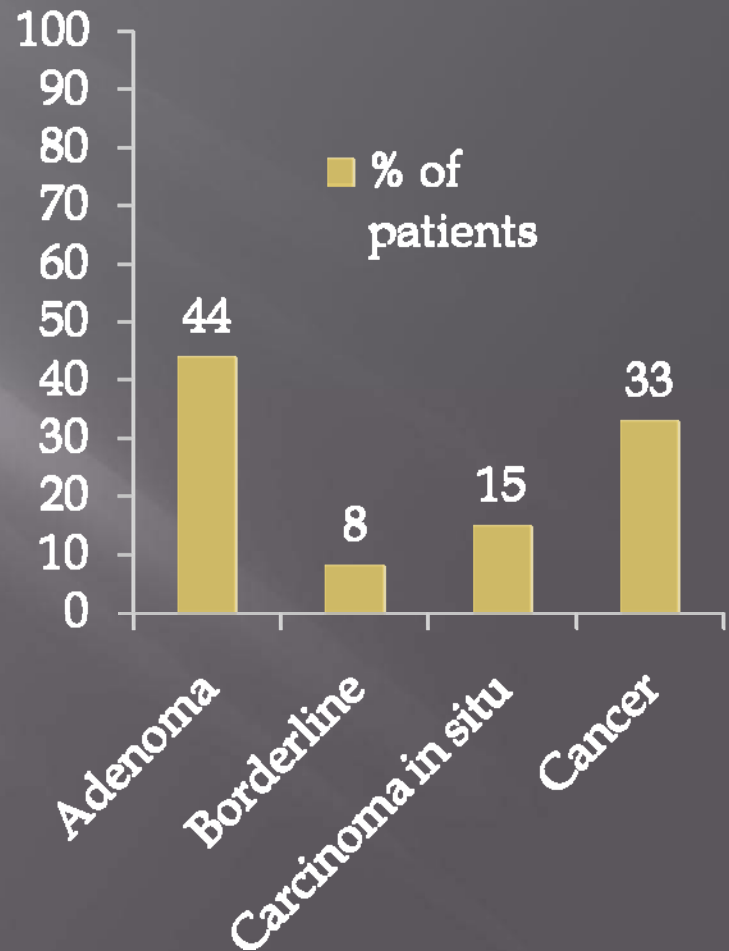
- ▣ Cystic fluid DNA
 - Molecular studies have shown the presence of K-ras, tumor suppressor gene mutations, and telomerase activity in mucinous cystic lesions

Khalid A, et al. *Gastroenterol Hepatol* 2005, 967-973.

MCN:

Pathology Results After Resection

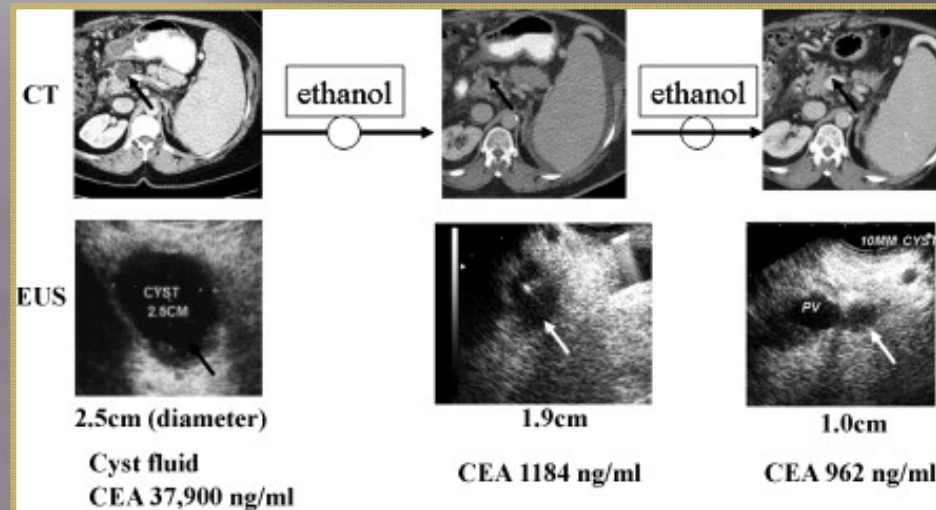
- ▣ Case series of 61 patients with MCN
- ▣ Final histopathologic diagnosis



MCN

- ▣ Management of surgical candidates:
 - Head lesion – pancreaticoduodenectomy
 - Body/tail lesion – distal pancreatectomy + splenectomy

EUS-guided Ethanol Ablation



5 year follow up of a mucinous cystic lesion

CASE 2

- ▣ FNA showed cystic CEA of 812 ng/mL
- ▣ Cytology showed mucin “+” columnar cells, no malignant cells
- ▣ Patient underwent distal pancreatectomy with a good surgical outcome

CASE 3

75 y.o. male with recurrent acute pancreatitis and multiple medical problems referred for EUS



Intraductal Papillary Mucinous Neoplasm (IPMN)

- ▣ Synonyms:
 - Mucinous ductal ectasia
 - Intraductal mucin-producing tumor
 - Intraductal cystadenoma
 - Pancreatic duct villous adenoma
 - Intraductal papillary neoplasm
- ▣ The term IPMN was officially adopted in 1996 by the World Health Organization and the Armed Forces Institute of Pathology

IPMN

- ▣ Found in male > female during the 6th to 7th decade
- ▣ Seventy-five percent of patients are symptomatic
 - Weight loss, abdominal pain, acute/chronic pancreatitis, nausea/vomiting, fever, diarrhea, diabetes, steatorrhea, jaundice
- ▣ Located more often in the head of the pancreas residing in the main duct or its side branches

IPMN

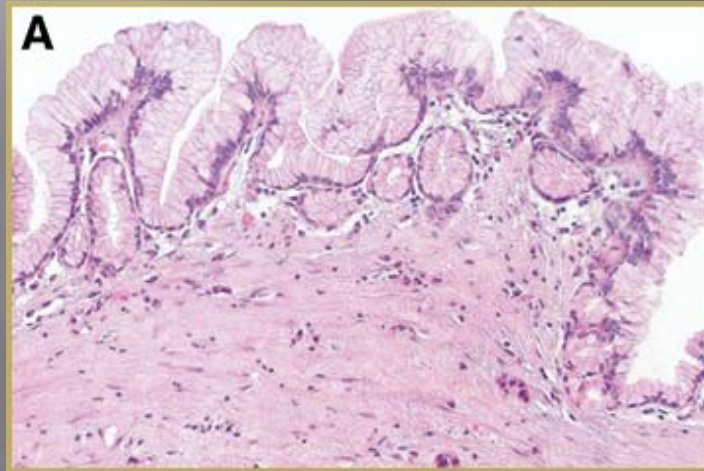
- ▣ Premalignant lesions characterized by proliferation of mucinous epithelium with ductal and cystic dilation
- ▣ Often exhibit papillary growth with mucin production
- ▣ Lack ovarian-type stroma that characterizes mucinous cystic neoplasms
- ▣ Invasive neoplasm is discovered in 20%-50% of IPMNs at the time of surgery

Hruban RH, et al. Am J Surg Path 2004;28:977-87.

Lim JH, et al. Radiographics 2001;21:323-340.

Sohn TA, et al. Ann Surg 2004;239:788-99.

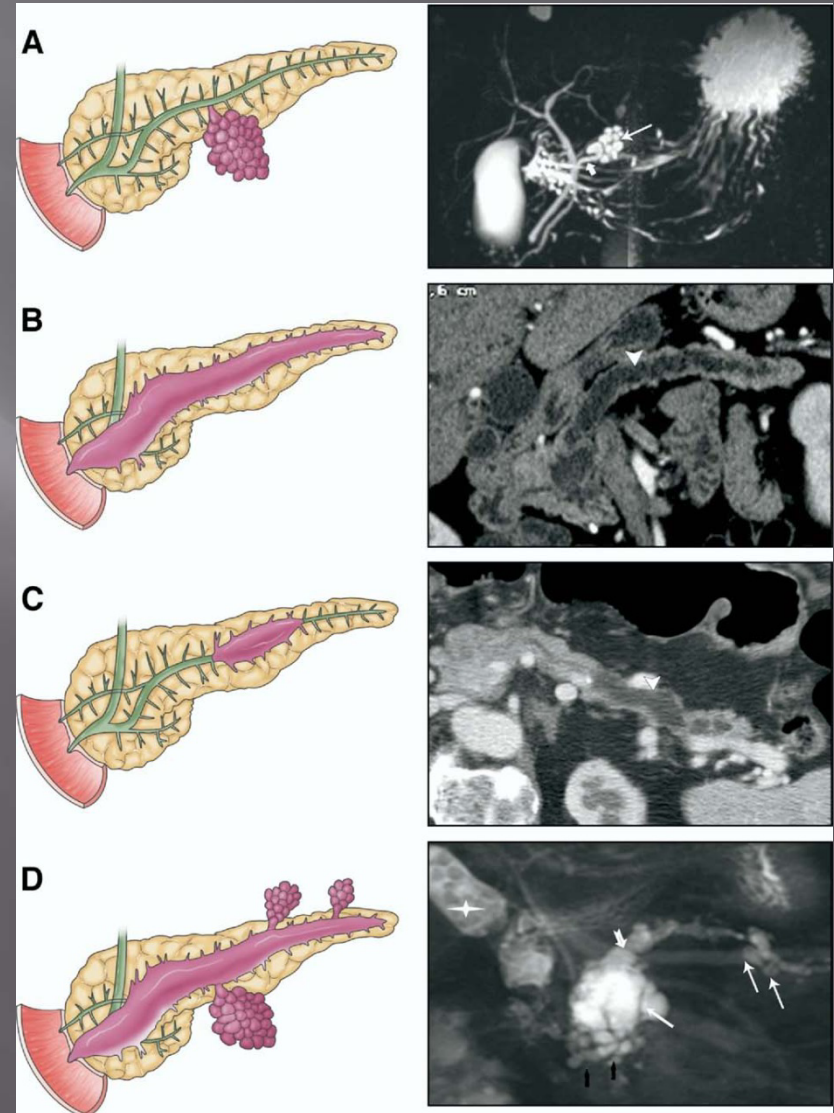
IPMN



Mucinous epithelium that lacks ovarian-stroma

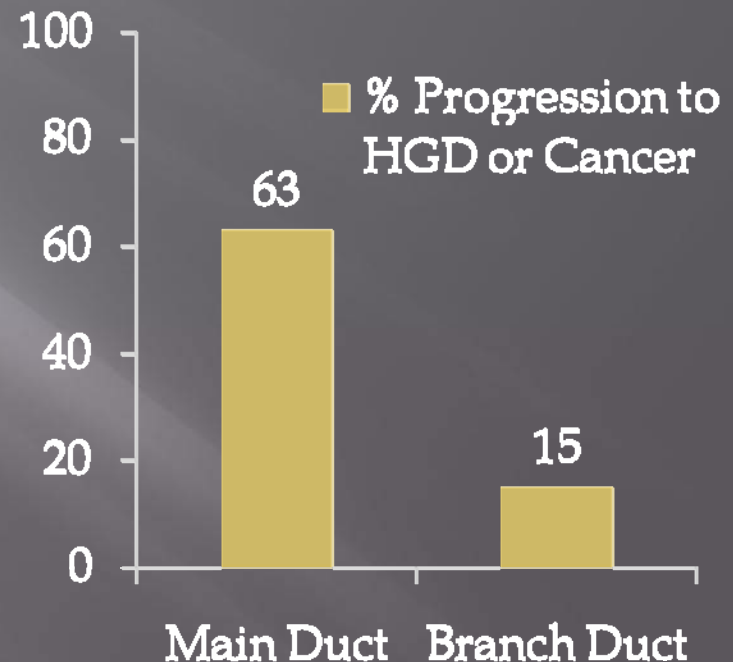
Morphologic Classification

- A. Branch duct IPMN
- B. Diffuse main duct IPMN
- C. Segmental main duct IPMN
- D. Mixed IPMN



Natural History of IPMN

- ▣ 106 patients (76 proven) (30 probable)
- ▣ MD = 53, BD = 53
- ▣ Median follow-up 21 months

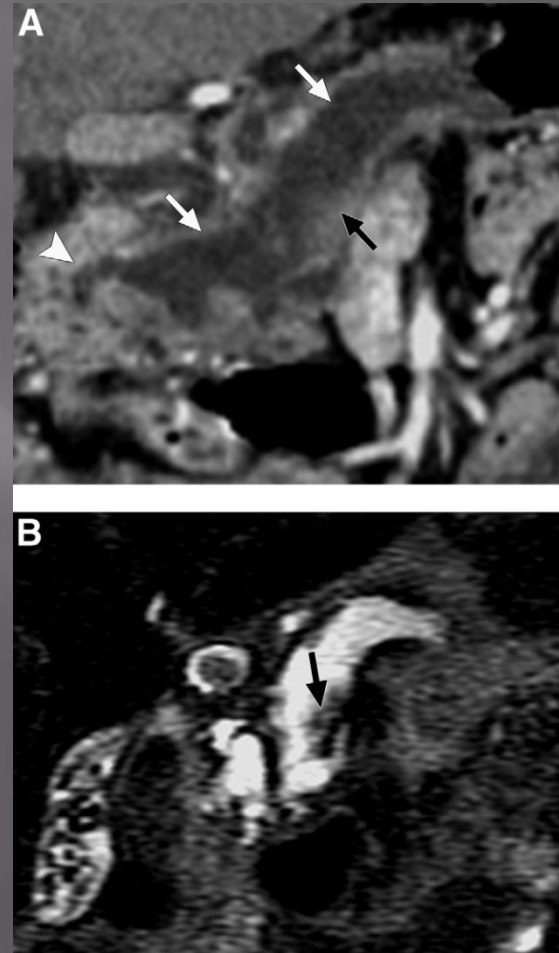


IPMN: Multi-detector CT and MRCP

- ▣ Requires a dedicated pancreatic protocol technique
- ▣ Communication between branch duct lesions and main PD can often be seen, but lack of communication does not rule out IPMN
- ▣ Involvement of the main pancreatic duct often shows dilation of the duct and atrophy in the body/tail region

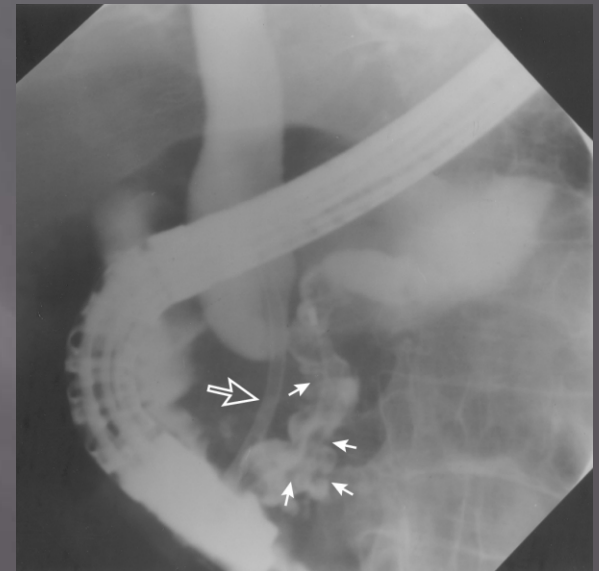
IPMN: Multi-detector CT vs. MRCP

- ▣ MRCP is better for small lesions (<3 cm) in showing ductal communication
- ▣ For main duct lesions, MRCP is better for showing small mural nodules

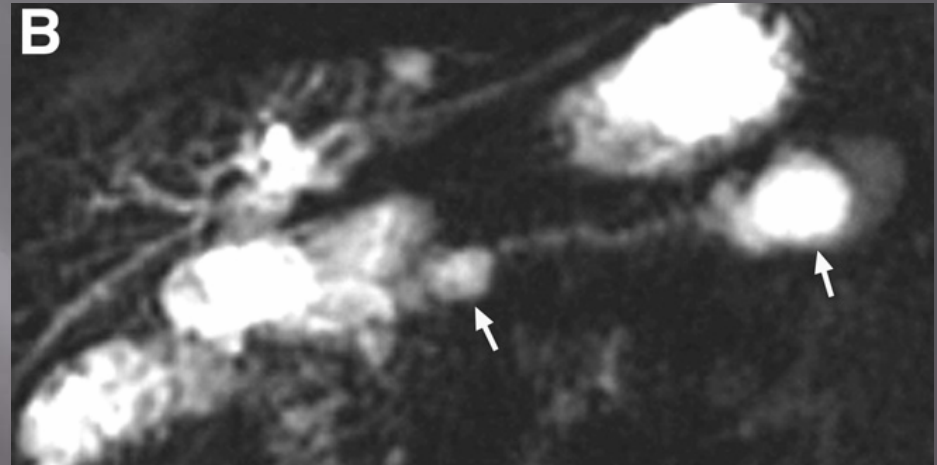
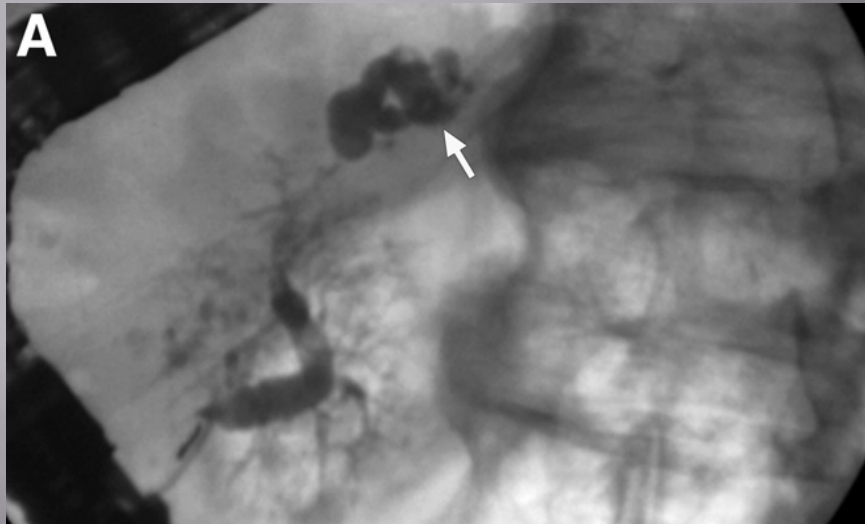


IPMN: ERCP

- ▣ Patulous ampulla of Vater extruding mucus (20% – 50%)
- ▣ Main Duct IMPN may show diffuse main duct dilation, mucinous filling defects, and a papillary tumor in main duct
- ▣ Branch duct lesions appear as a cluster of grapes that communicate with the main duct



IPMN: ERCP vs. MRCP



Limitations of ERCP vs. MRCP

- Malignant duct obstruction
- Differentiating mucin globules vs. mural nodules
- Risks of the procedure

IPMN: Pancreatoscopy



Direct visualization and biopsy

IPMN: EUS



Good at showing internal septa, mural nodules, solid masses, vascular invasion, and lymph node metastases

IPMN: EUS Features of Malignancy

- ▣ Thick walls
- ▣ Thick septations
- ▣ Prominent mural nodules
- ▣ Lymph node and vascular invasion
- ▣ With EUS alone, it is very difficult to distinguish benign from malignant neoplasms in the absence of advanced disease

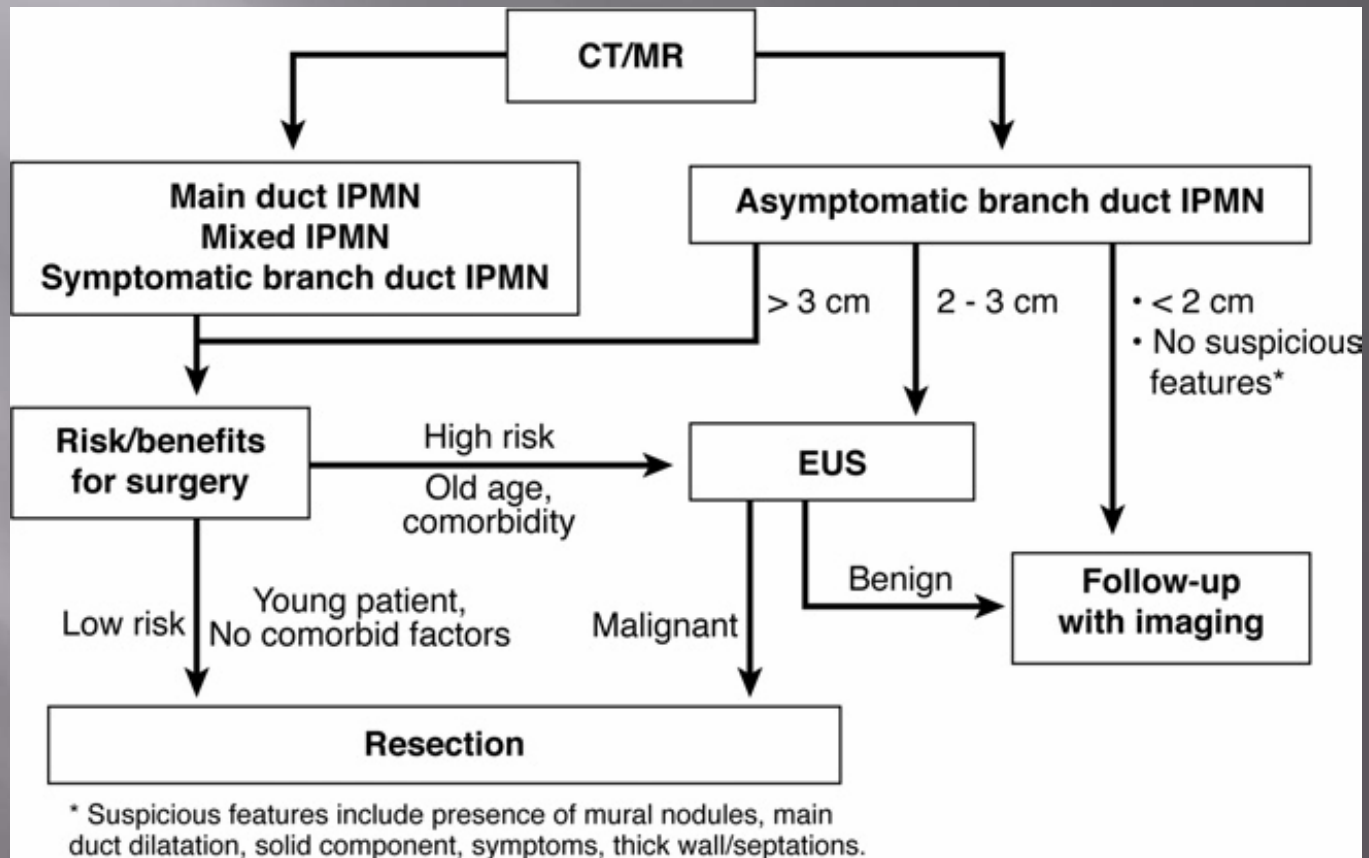
IPMN: EUS with FNA

- ▣ Limited yield in lesions smaller than 3 cm
- ▣ CEA and CA 72-4 cannot differentiate between types of mucinous lesions or presence of malignancy
- ▣ Five to 20% of mucinous lesions including adenocarcinomas do not contain elevated CEA levels

IAP (Sendai) Consensus Guidelines

- ▣ Proposed criteria for pancreatic resection in IPMN (1 or more of the following)
 1. Symptoms attributable to the cyst (e.g., pancreatitis)
 2. Dilation of the main pancreatic duct
 3. Cyst size >3 cm
 4. Presence of intramural nodules
 5. Cystic fluid cytology suspicious or positive for malignancy

Approach to IPMN



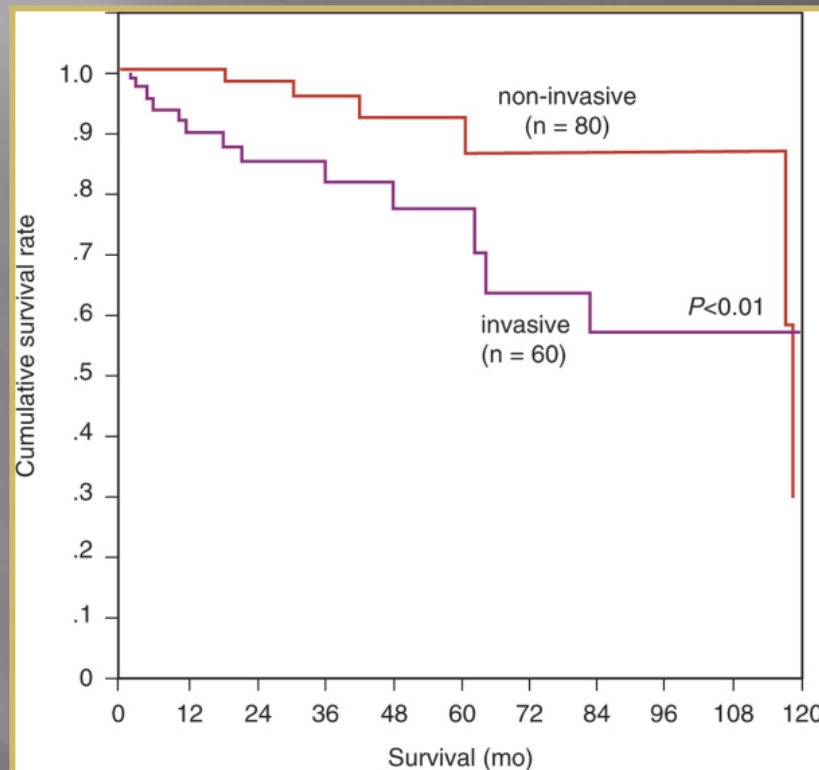
IPMN: Recurrence and Surveillance

- ▣ Recurrence is rare after resection of noninvasive tumors
- ▣ Three year recurrence rates for invasive tumors ranged from 12% - 65%
- ▣ Patients with recurrent disease localized to the pancreas benefit from complete pancreatectomy

Salvia R, et al. *Clinical Ann Surg* 2004; 239:678.

D'Angelica M, et al. *Ann Surg* 2004; 239:400.

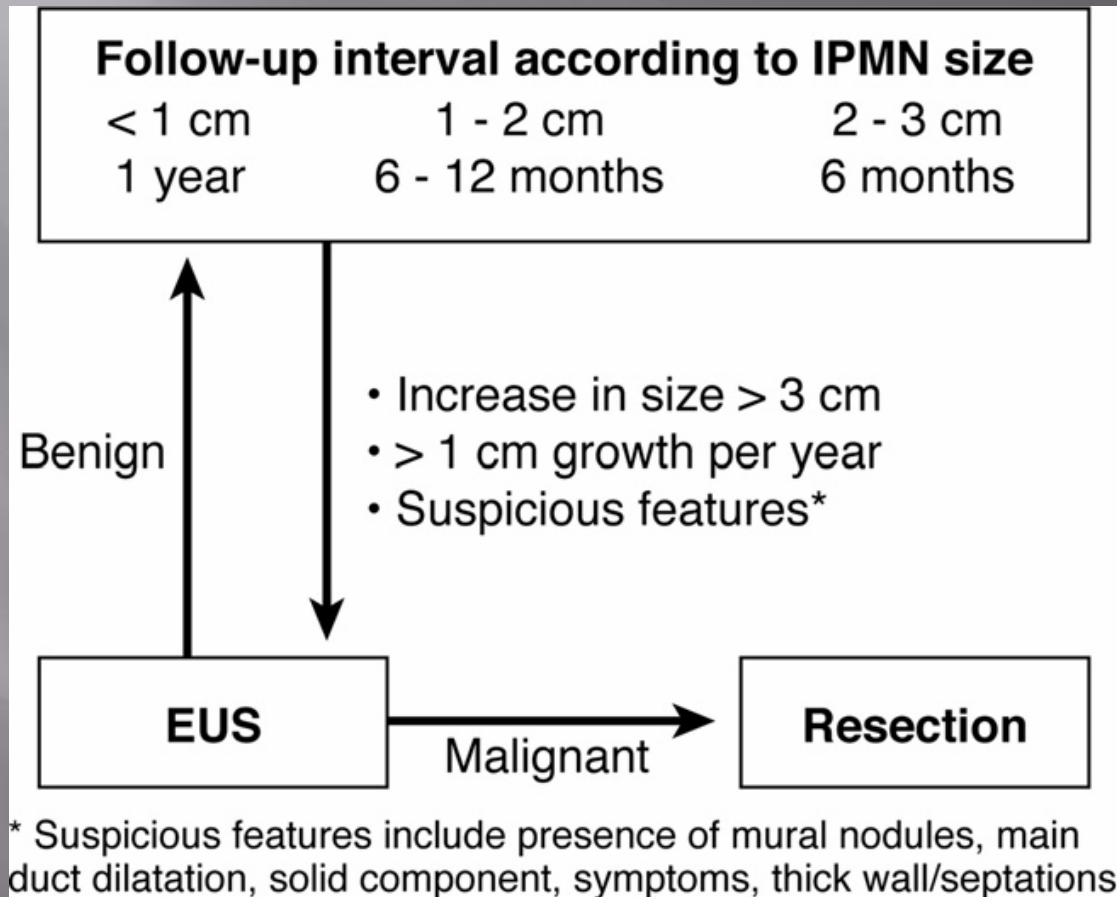
“Nothin’ Heals Like Cold Hard Steel”



Actuarial survival in patients with invasive and noninvasive IPMN

Salvia R, et al. Ann Surg 239:678, 2004.)

IPMN Surveillance



CASE 3

- ▣ The patient had main duct involvement with mural nodules that would require total pancreatectomy
- ▣ Given his poor health status and the risk of the procedure, he elected for palliative care referral

Solid Pseudopapillary Tumor

- ▣ Synonym: papillary cystic neoplasm
- ▣ Least common of pancreatic cystic neoplasms
- ▣ Women in 2nd – 3rd decade located in pancreatic body and tail
- ▣ Fluid is often bloody and necrotic

Solid Pseudopapillary Tumor

- ▣ Cytology shows branching papillae with myxoid stroma
 - Stains positive for vimentin and α -1-antitrypsin
- ▣ Locally aggressive invading adjacent structures
- ▣ Treatment: Surgical resection if possible

Lymphoepithelial Cyst

- ▣ Rare
- ▣ Mostly men, any age, asymptomatic
- ▣ Contain keratinizing squamous epithelium surround by lymphoid tissue
- ▣ T2-weighted MRI – intracystic keratin

Lymphoepithelial Cyst

- ▣ EUS – heterogeneous, hyperechoic cyst
- ▣ FNA – epithelial cells, lymphocytes, keratin debris, anucleate squamous cells, and multinucleated histiocytes

Cystic Endocrine Neoplasm

- ▣ May exhibit clinical features of solid endocrine tumors
- ▣ Unilocular cyst
- ▣ Fluid is thin and clear
- ▣ Cytology shows monomorphic endocrine tumor cells
 - Stains positive for chromogranin and synaptophysin
- ▣ Potentially malignant

Cystic Degeneration

- ▣ Solid pancreatic tumors may undergo cystic degeneration including:
 - Islet cell tumors
 - Ductal carcinoma
 - Acinar cell cancer
- ▣ Islet cell tumors may be indistinguishable from MCN or side branch IPMN
- ▣ Cytology may be helpful to differentiate

Final Pearls

- ▣ Small cysts can be malignant
 - A series of sub-2 cm cysts
 - ▣ 20% malignant
 - ▣ 45% had malignant potential
- ▣ CEA is not predictive of malignancy

Summary

- ▣ Recognition of pancreatic cystic neoplasms is on the rise
- ▣ Diagnostic evaluation focuses on determining the malignant potential of cysts
- ▣ Management is driven by symptoms, the certainty of the diagnosis and the surgical fitness of the patient

THANKS

Fluid Analysis: CEA

Author	# cases	CEA ng/mL Cyst	Sensitivity %	Specificity %
Hammel 1995	50	<5 for SCA	100	86
Hammel 1997	65	>20 for MCN from SCA	82	100
		>300 for MCN from pseudocyst	56	100
Hammel 1998	91	>400 for MCN	57	100
		<4 for SCA	100	93
Brugge 2004	112	>192 for MCN	73	84

Adapted from ACG Practic Guidelines. AJG 2007;2339-2349