Pancreatic Cystic Neoplasm

F Sukhum Kobdej

Advisor : Dr Paramin Muangkaew

30/5/2025

Introduction

- Imaging studies have shown a prevalence ranging from 2 to 15%
  - Autopsy data suggest a prevalence as high as 50%
- Most cysts are benign; only a subset has malignant potential
  - Overall risk of malignancy : 0.5 to 1.5%
  - Annual risk of progression : 0.5%
- Cystic lesions of the pancreas can be categorized
  - Neoplastic
    - Mucin-producing cyst : MCN, IPMN
    - Nonmucin producing : SCA, SPN
  - Nonneoplastic (pseudocysts)

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43
BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

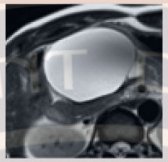
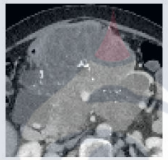
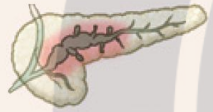
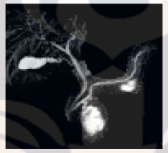
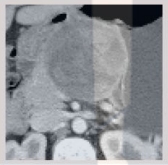
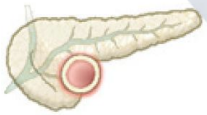
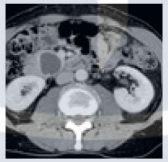
Cyst Type	Patient Characteristics and Clinical Presentation		Imaging Findings		Malignant Potential
Pseudocyst	Associated with antecedent acute or chronic pancreatitis		Unilocular or multilocular May be connected to MPD		0%
SCA	Predominantly in women (60% of cases) Occurs in 5th–7th decades of life Mostly asymptomatic		Microcystic or oligocystic Central scar No communication with pancreatic duct		0%
IPMN	Equal sex distribution Occurs in 5th–7th decades of life Mostly asymptomatic May cause pancreatitis	 Branch-duct IPMN  Main-duct IPMN	Communication with pancreatic duct Multiplicity MPD dilatation Fish-mouth papilla	 	1–38% 33–85%
MCN	Almost exclusively in women (90% of cases) Occurs in 4th–6th decades of life Mostly asymptomatic		Mostly pancreatic tail Unilocular or oligolocular Thickened wall Eggshell calcifications in 25%		10–34%
SPT	Almost exclusively in women (90% of cases) Occurs in 2nd or 3rd decade of life Mostly asymptomatic		Heterogeneous Eggshell calcifications		10–15%
CNET	Variable age and sex Mostly asymptomatic 10% Are functional		Enhancing, thickened wall		5–10%

Figure 1. Common Types of Pancreatic Cysts and Their Characteristics.

The clinical and imaging characteristics, as well as the risk of malignancy for each of the six most common pancreatic cyst types, are shown. The risk of metastatic disease is shown for SPT and CNET. SCA denotes serous cystadenoma, IPMN intraductal papillary mucinous neoplasm, MCN mucinous cystic neoplasm, SPT solid pseudopapillary tumor, and CNET cystic neuroendocrine tumor.

Pancreatic Cystic Neoplasm

- Benign cystic lesions
  - Pseudocyst
  - Serous cystadenoma
- Mucinous cysts -> 50% of incidentally found pancreatic cysts
  - MCN
  - IPMN
- Small cysts lacking distinctive features and cannot be characterized
  - Generally presumed to be mucinous
- Characterization of the cyst type
  - Crucial first step in the management and subsequent risk assessment
  - Imaging features and demographic data -> accurate classification of 70 to 80% of cysts
  - Equivocal diagnosis : endoscopic ultrasonography +/- fluid/FNA may be helpful

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

DEPARTMENT OF SURGERY RAMATHIBODI HOSPITAL

Investigation

- Imaging
  - CT with pancreatic protocol
    - Delineate and characterize the pancreatic parenchyma near a cystic lesion
    - Critical in assessing for a radiographically occult invasive cancer causing adjacent dilation of a pancreatic duct
    - Evaluation of septations, mural nodules, and calcifications
  - MRCP
    - Define cyst morphology
    - Better than CT for determining a connection with the pancreatic duct, presence of an enhancing mural nodule, or internal septations
    - Secretin-enhanced MRCP : improve the visualization of a connection between a pancreatic cyst and the main pancreatic duct

BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Investigation

- Endoscopy
  - Help to affirm the diagnosis of benign or low-risk cysts
  - VS MRI
    - Slightly higher accuracy for identifying ductal communication
    - Higher sensitivity for detecting small mural nodules
    - Identify the pathognomonic fish-mouth Papilla
  - Contrast-enhanced endoscopic ultrasonography
    - Confirm the presence of epithelial nodules -> the strongest predictive risk factor for malignant transformation, aside from main-duct dilatation
  - FNA can be performed for fluid analysis or intracystic biopsy of solid component

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

Investigation

- Cyst fluid analysis
  - Measurement of CEA, amylase, glucose -> help in establish diagnosis but not helpful in determining the grade of neoplasia
    - Elevated amylase : connection with pancreatic duct
    - Elevated CEA (>192 ng/ml) : mucinous cyst
    - Low level of glucose(<50-80 ng/ml) : mucinous
    - Yield for cytologic diagnosis is low
  - Detection of mutations associated with specific neoplasms
    - Helpful in small cyst with uncertain diagnosis
      - VHL mutation : nearly 100% specific for serous cystadenoma (sensitivity 25-50%)
      - KRAS mutation : >95% specific to mucinous cysts (sensitivity 60-70%)
      - GNAS mutation : specific for IPMNs (not MCN)
      - CTNNB1 mutation : Solid pseudopapillary tumor
      - MEN1 mutation : Cystic pancreatic neuroendocrine tumor

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

Table 1. Cyst-Fluid Characteristics and Genes Altered in Common Types of Pancreatic Cysts.*

Cyst Type	Macroscopic and Cytologic Features	CEA Level	Glucose Level	Amylase Level	Altered Genes	
					Associated with Cyst Type	Associated with Advanced Neoplasia
Pseudocyst	Macrophages and lymphocytes, debris	Variable	High	High	None	None
SCA	Proteinaceous debris and blood, glycogen-rich cuboidal epithelial cells	Very low	High	Low	*VHL*	None
IPMN	Thick mucinous fluid, mucinous epithelial cells, papillary structures†	High	Low	High	*KRAS*, *GNAS*	*TP53*, *CTNNB1*, *CDKN2A*, *SMAD4*, genes involved in mTOR pathway‡
MCN	Thick mucinous fluid, mucinous epithelial cells, ovarian-type stroma†	High	Low	Low	*KRAS*	*TP53*, *CDKN2A*, *CTNNB1*, *SMAD4*, genes involved in mTOR pathway‡
SPT	Hemorrhagic debris; monomorphic, discohesive small cells; hyaline globules and grooved nuclei	Variable	Normal	Low	*CTNNB1*	None
CNET	Uniform cells in loosely cohesive clusters; coarse, granular, chromatin-containing nuclei	Variable	Normal	Low	*MEN1*	None

* CEA denotes carcinoembryonic antigen, CNET cystic neuroendocrine tumor, SCA serous cystadenoma, and SPT solid pseudopapillary tumor.
† Ovarian stroma in mucinous cystic neoplasms (MCNs) and papillary structures in intraductal papillary mucinous neoplasms (IPMNs) are histologic findings that are observed only in rare cases in samples obtained by means of fine-needle aspiration or microforceps biopsy.
‡ Genes involved in the mammalian target of rapamycin (mTOR) pathway include *PIK3CA*, *PTEN*, and *AKT1*.

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

Investigation

- EUS guided needle-based confocal laser endomicroscopy
  - Real-time visualization of pancreatic cyst epithelium
    - Classify epithelial and vascular patterns
  - Intracystic endomicroscopy was performed via 19-gauge needle under EUS-guided

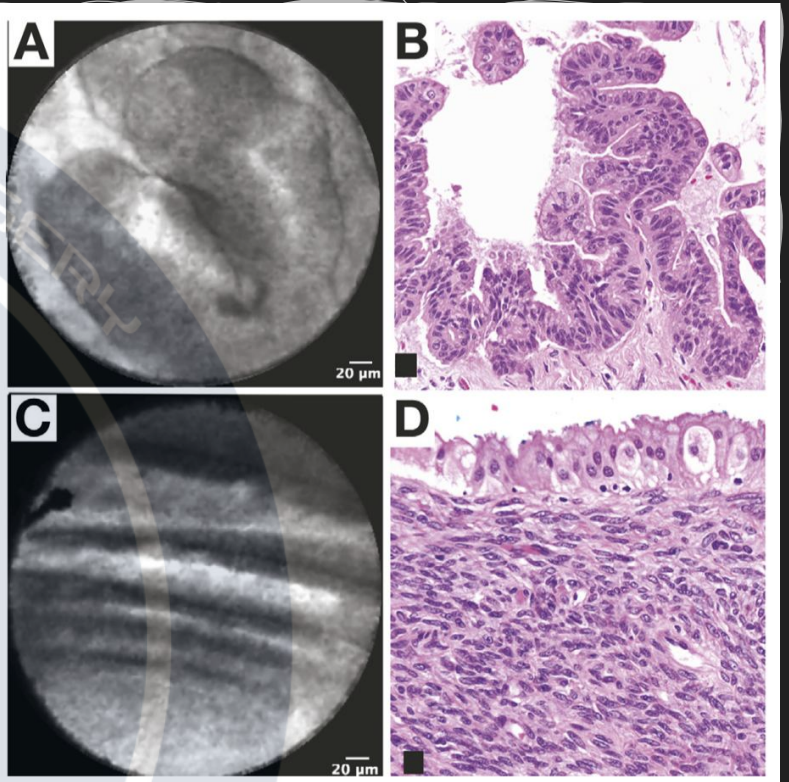
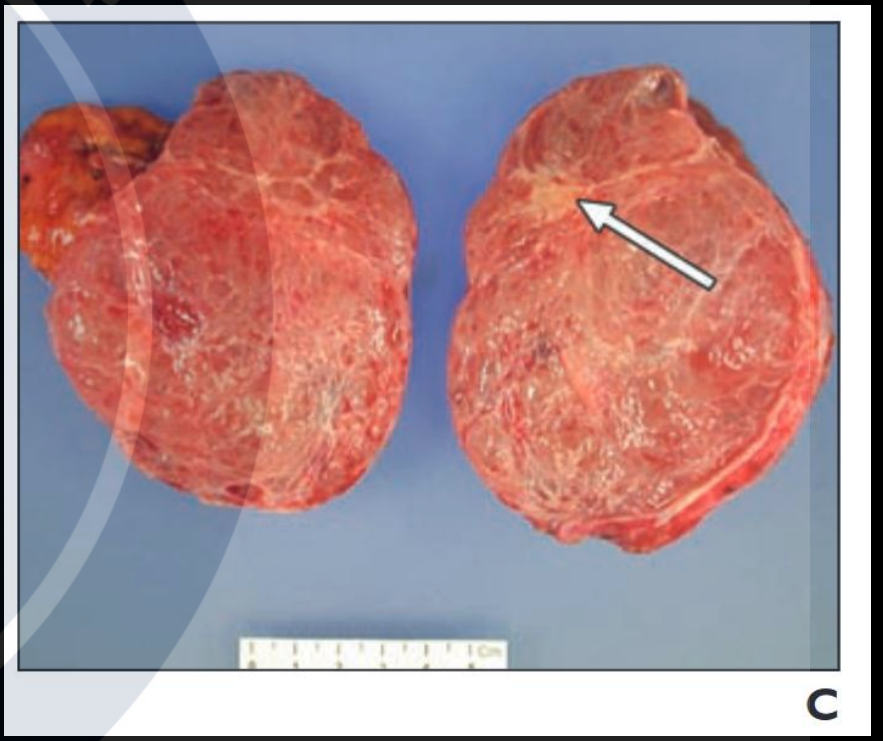


Figure 2. Correlation between confocal laser endomicroscopy (CLE) and histopathology in mucinous pancreatic cysts. (*A*) CLE image of intraductal papillary mucinous neoplasm (IPMN) showing finger-like papillary projections with an inner vascular core. (*B*) Histopathology of IPMN: this lesion shows a pancreatobiliary subtype with high-grade dysplasia (H&E; magnification, 400×). (*C*) CLE image of mucinous cystic neoplasm (MCN) showing horizon-type epithelial bands of variable thickness without papillary conformation. (*D*) Histopathology of MCN: this cyst consists of mucin-secreting columnar cells (low-grade dysplasia) overlying densely organized ovarian-type stroma (H&E; magnification, 400×).

Krishna et al. EUS-Guided Confocal Laser Endomicroscopy Increases Accuracy of Differentiation of Pancreatic Cystic Lesions. Clinical Gastroenterology and Hepatology 2020;18:432–440

Serous Cystadenoma

- Most common benign lesions, representing 16% of all pancreatic cysts
- Clear-cell adenomas rich in glycogen cytoplasm thought to arise from centroacinar cells
  - Microscopically described as having a rich capillary network that can help distinguish them from mucinous cysts
- Sporadic cases are common in patients with VHL syndrome (1/36,000 births)
  - Those without VHL also commonly found serous cystadenoma



Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.
Choi et al. Typical and Atypical Manifestationsof Serous Cystadenoma of thePancreas: Imaging Findings With Pathologic Correlation. AJR:193, July 2009

Serous Cystadenoma

- 60–75% of SCAs are found in women in the fifth to seventh decades
- A majority of SCAs arise from the body and tail of the pancreas, while 40% arise from the pancreatic head
- Low risk of malignancy (0.1% developed serous cystadenocarcinoma)
- Mostly asymptomatic(60%)
- Symptoms : non-specific abdominal pain, jaundice, DM

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Morphologic features
  - Microcystic type 58%
  - Macrocystic type 20%
  - Mixed type 16%
  - Solid type 3%

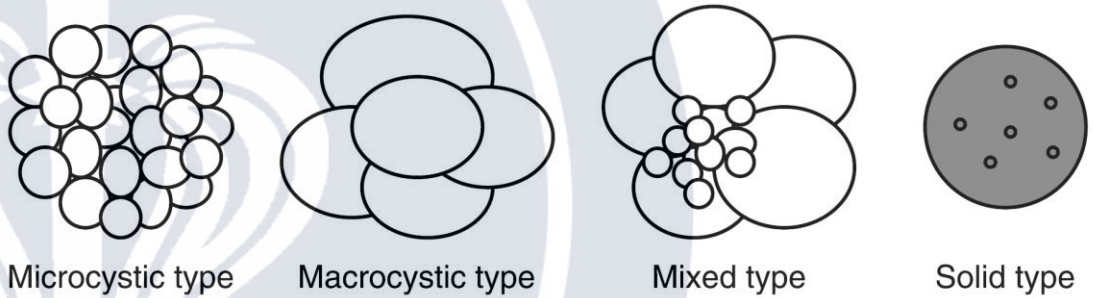


FIGURE 1. Schematic representation of serous cystic neoplasm subtype by gross appearance. Serous cystic neoplasms have 4 morphologic patterns: microcystic (honeycomb) type, macrocystic (oligocystic) type, mixed (polycystic) type, and solid type. Microcystic-type SCNs are characterized by a polycystic pattern of multiple cysts measuring 1 cm or smaller. The cystic spaces are separated by fibrous septa that can coalesce into a central scar that may calcify. Macrocystic-type SCNs are composed by some 1 cm or larger cysts. This pattern is similar to those of other cystic tumors such as intraductal mucinous papillary neoplasms or mucinous cyst neoplasms. Mixed-type SCNs exhibit multiple cysts measuring both smaller and larger than 1 cm. Solid type is rare variant that is a well-circumscribed tumor formed by simple cuboidal cells arranged in nests and trabeculae separated by thick fibrous bands. The distinction of solid-type SCN from islet cell tumors or hypervascular metastasis can be difficult preoperatively on cross-sectional imaging.

Kimura, et al. Multicenter Study of Serous Cystic Neoplasm of the Japan Pancreas Society. Pancreas. Volume 41, Number 3, April 2012
Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Single, well-circumscribed tumors
- Numerous small cysts with diameters smaller than 1 cm
- Arranged around a central stellate scar -> occasionally contained small calcifications

- Morphologic features
  - Microcystic type 58%
  - Macrocystic type 20%
  - Mixed type 16%
  - Solid type 3%

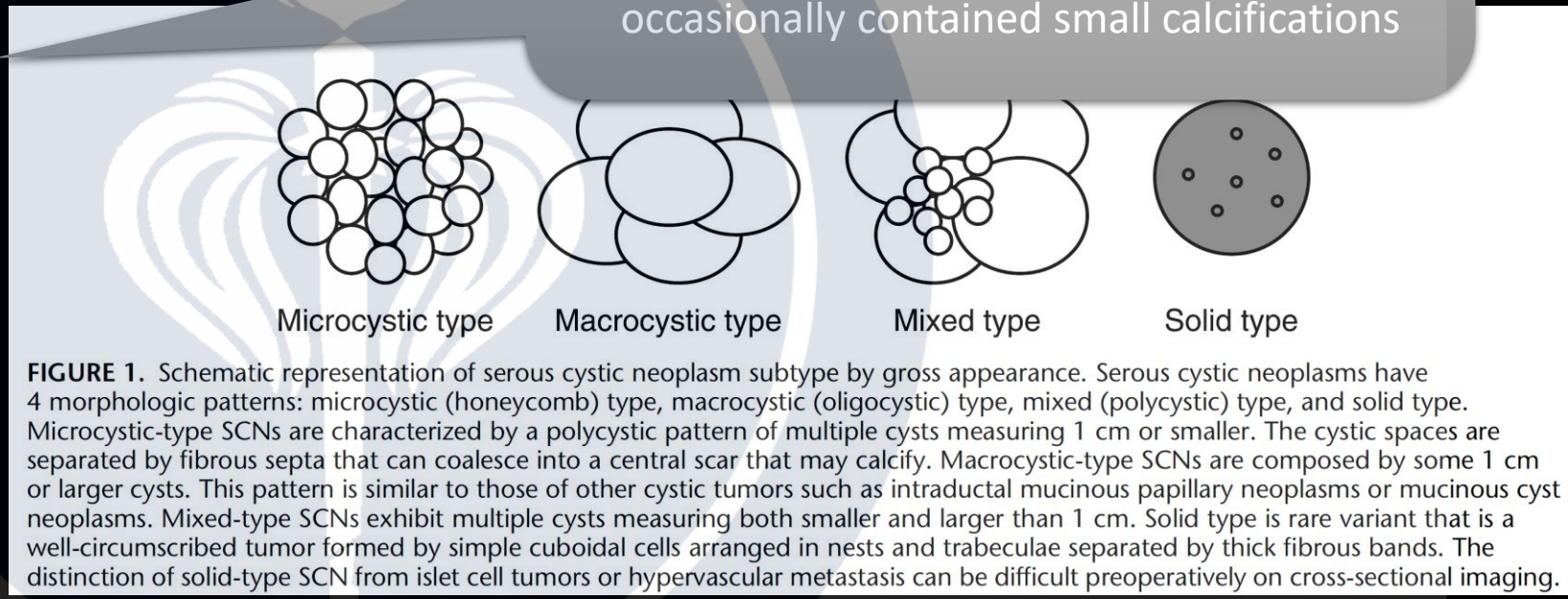


FIGURE 1. Schematic representation of serous cystic neoplasm subtype by gross appearance. Serous cystic neoplasms have 4 morphologic patterns: microcystic (honeycomb) type, macrocystic (oligocystic) type, mixed (polycystic) type, and solid type. Microcystic-type SCNs are characterized by a polycystic pattern of multiple cysts measuring 1 cm or smaller. The cystic spaces are separated by fibrous septa that can coalesce into a central scar that may calcify. Macrocystic-type SCNs are composed by some 1 cm or larger cysts. This pattern is similar to those of other cystic tumors such as intraductal mucinous papillary neoplasms or mucinous cyst neoplasms. Mixed-type SCNs exhibit multiple cysts measuring both smaller and larger than 1 cm. Solid type is rare variant that is a well-circumscribed tumor formed by simple cuboidal cells arranged in nests and trabeculae separated by thick fibrous bands. The distinction of solid-type SCN from islet cell tumors or hypervascular metastasis can be difficult preoperatively on cross-sectional imaging.

Kimura, et al. Multicenter Study of Serous Cystic Neoplasm of the Japan Pancreas Society. Pancreas. Volume 41, Number 3, April 2012
Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Few cysts larger than 1 cm in diameter
- Lack the central stellate scar and sharp demarcation
- This pattern is more likely found in the head and may cause symptoms
- By imaging : resembles MCN or branch duct IPMN

- Morphologic features
  - Microcystic type 58%
  - Macrocystic type 20%
  - Mixed type 16%
  - Solid type 3%

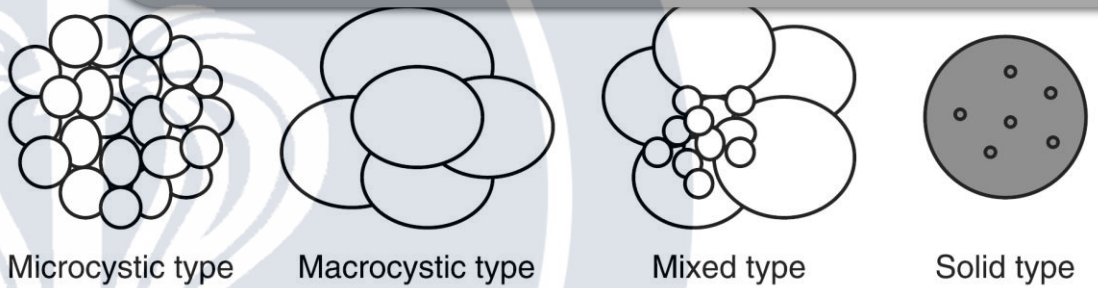


FIGURE 1. Schematic representation of serous cystic neoplasm subtype by gross appearance. Serous cystic neoplasms have 4 morphologic patterns: microcystic (honeycomb) type, macrocystic (oligocystic) type, mixed (polycystic) type, and solid type. Microcystic-type SCNs are characterized by a polycystic pattern of multiple cysts measuring 1 cm or smaller. The cystic spaces are separated by fibrous septa that can coalesce into a central scar that may calcify. Macrocystic-type SCNs are composed by some 1 cm or larger cysts. This pattern is similar to those of other cystic tumors such as intraductal mucinous papillary neoplasms or mucinous cyst neoplasms. Mixed-type SCNs exhibit multiple cysts measuring both smaller and larger than 1 cm. Solid type is rare variant that is a well-circumscribed tumor formed by simple cuboidal cells arranged in nests and trabeculae separated by thick fibrous bands. The distinction of solid-type SCN from islet cell tumors or hypervascular metastasis can be difficult preoperatively on cross-sectional imaging.

Kimura, et al. Multicenter Study of Serous Cystic Neoplasm of the Japan Pancreas Society. Pancreas. Volume 41, Number 3, April 2012
Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Morphologic features
  - Microcystic type 58%
  - Macrocystic type 20%
  - Mixed type 16%
  - Solid type 3%

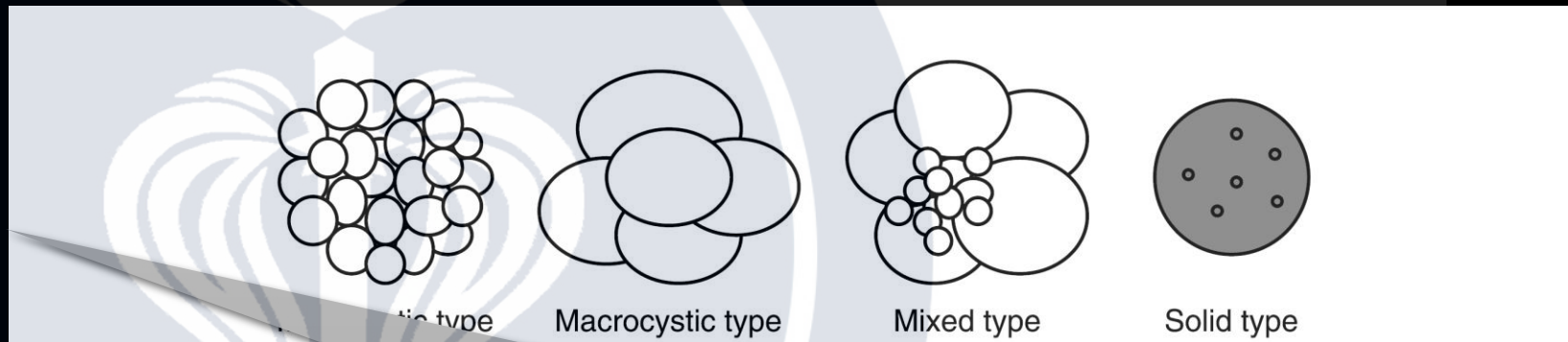


FIGURE 1. Schemati
4 morphologic pa
Microcystic-type
separated by fibr
or larger cysts. Th
neoplasms. Mixed
well-circumscribe
distinction of soli
us cystic neoplasms have
ystic) type, and solid type.
smaller. The cystic spaces are
Ns are composed by some 1 cm
illary neoplasms or mucinous cyst
lid type is rare variant that is a
by thick fibrous bands. The
atively on cross-sectional imaging.

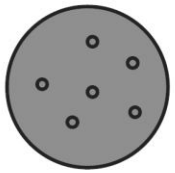
- Combination of cysts that are smaller than and larger than 1 cm
- Cysts larger than 1.5 cm comprised more than a third of the tumor and the remainder was microcystic

Kimura, et al. Multicenter Study of Serous Cystic Neoplasm of the Japan Pancreas Society. Pancreas. Volume 41, Number 3, April 2012
Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Morphologic features
  - Microcystic type 58%
  - Macrocystic type 20%
  - Mixed type 16%
  - Solid type 3%

- Solid hypervascular lesion with or without cystic lesions
  - Difficult to recognize a cystic structure by imaging studies or macroscopically
- Diagnosed solely by pathological findings
  - Difficult to distinguish from other solid tumors



Solid type

FIGURE 1. Schematic representation of serous cystic neoplasm subtype by gross appearance. Serous cystic neoplasms have 4 morphologic patterns: microcystic (honeycomb) type, macrocystic (oligocystic) type, mixed (polycystic) type, and solid type. Microcystic-type SCNs are characterized by a polycystic pattern of multiple cysts measuring 1 cm or smaller. The cystic spaces are separated by fibrous septa that can coalesce into a central scar that may calcify. Macrocystic-type SCNs are composed by some 1 cm or larger cysts. This pattern is similar to those of other cystic tumors such as intraductal mucinous papillary neoplasms or mucinous cyst neoplasms. Mixed-type SCNs exhibit multiple cysts measuring both smaller and larger than 1 cm. Solid type is rare variant that is a well-circumscribed tumor formed by simple cuboidal cells arranged in nests and trabeculae separated by thick fibrous bands. The distinction of solid-type SCN from islet cell tumors or hypervascular metastasis can be difficult preoperatively on cross-sectional imaging.

Kimura, et al. Multicenter Study of Serous Cystic Neoplasm of the Japan Pancreas Society. Pancreas. Volume 41, Number 3, April 2012
Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Cross-sectional imaging
  - CT and MRI scans can identify the typical characteristics distinguishing SCAs from other cysts
  - CT
    - Detect calcifications and hypervascularity
    - Insufficient soft tissue contrast and spatial resolution
      - Poor identification of the microcystic appearance and SCAs less than 2 cm
  - MRI
    - Identifying septations, the presence of a solid component, pancreatic ductal communication, and magnification of the macrocystic nature on T2-weighed images

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

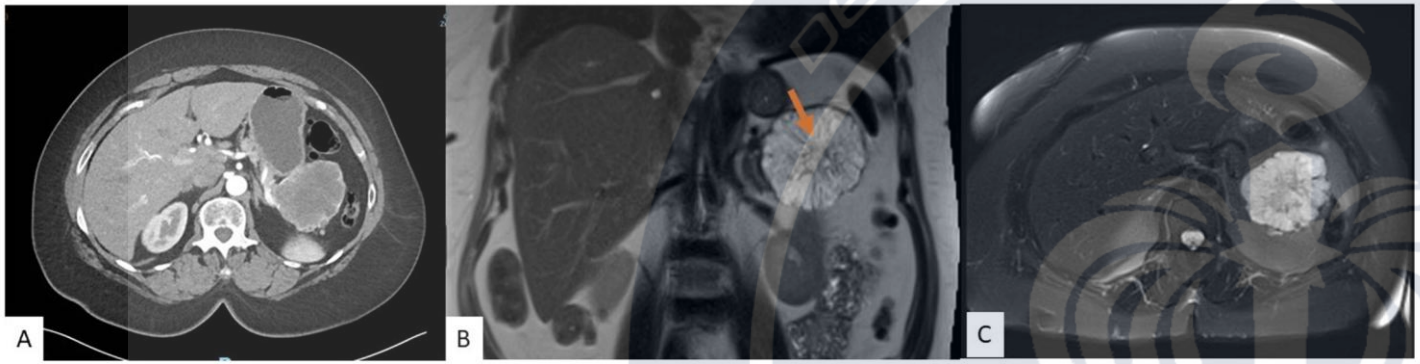


Figure 2. A 54-year-old female with an incidental pancreatic cyst. CT image showing a heterogeneously enhancing lesion with numerous small internal cysts in the tail of the pancreas measuring 6.4 cm × 7.3 cm × 5.4 cm (AP × TV × CC) (**A**). MRI coronal (**B**) and axial (**C**) views of a microcystic lesion in the tail of the pancreas with enhancing septations and central scar (arrow).

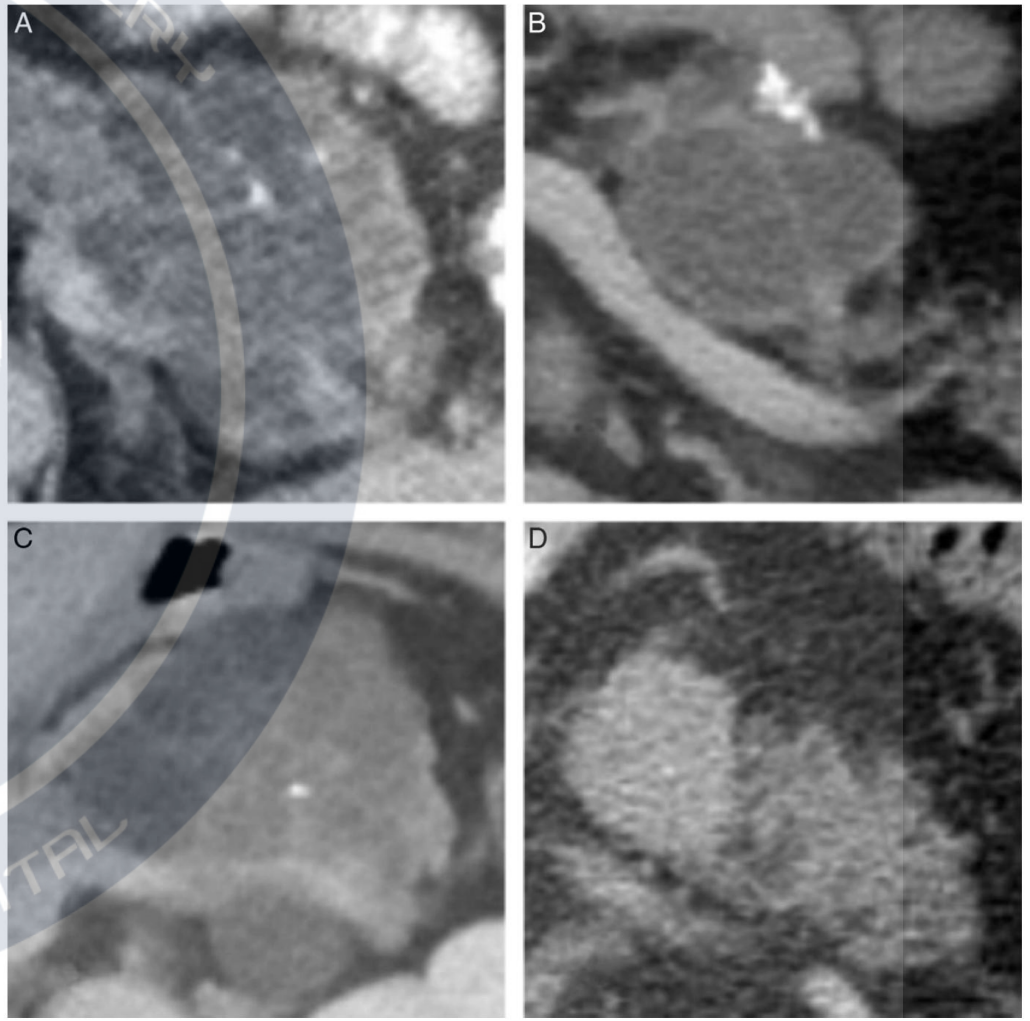


FIGURE 1. Morphological types of SCA. A, A classic microcystic type, (B) a macrocystic variant, (C) a mixed type, and (D) a solid type.

Assawasirisin et al. Pancreatic Serous Cystadenoma A Continuing Diagnostic Challenge. Annals of Surgery Volume 281, Number 3, March 2025

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Endoscopic ultrasonography
  - High-resolution imaging
    - Honeycomb feature of multiple small microcysts and multiple compartments
  - Operator dependent & not particularly helpful in distinguishing IPMN, MCN and macrocystic SCN
  - EUS c FNA : Higher sensitivity and specificity (97% and 100%, respectively)
- Cyst fluid analysis
  - Gross appearance : clear yellowish fluid with low viscosity
  - Low CEA, Low amylase
  - Molecular marker : VHL mutation

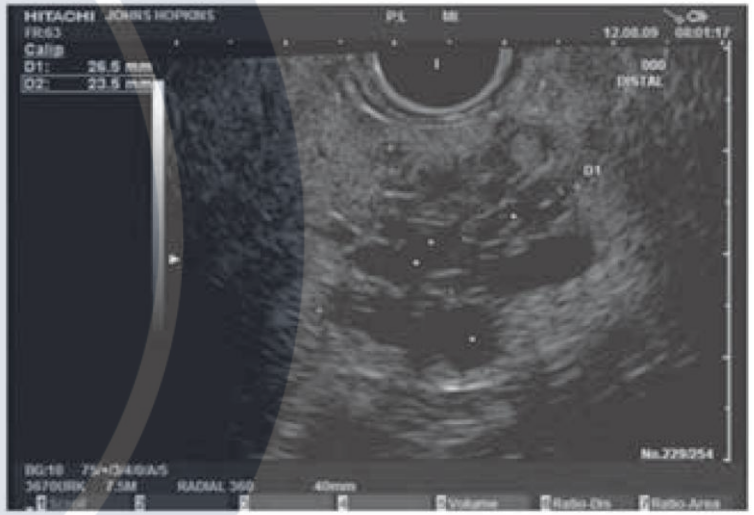
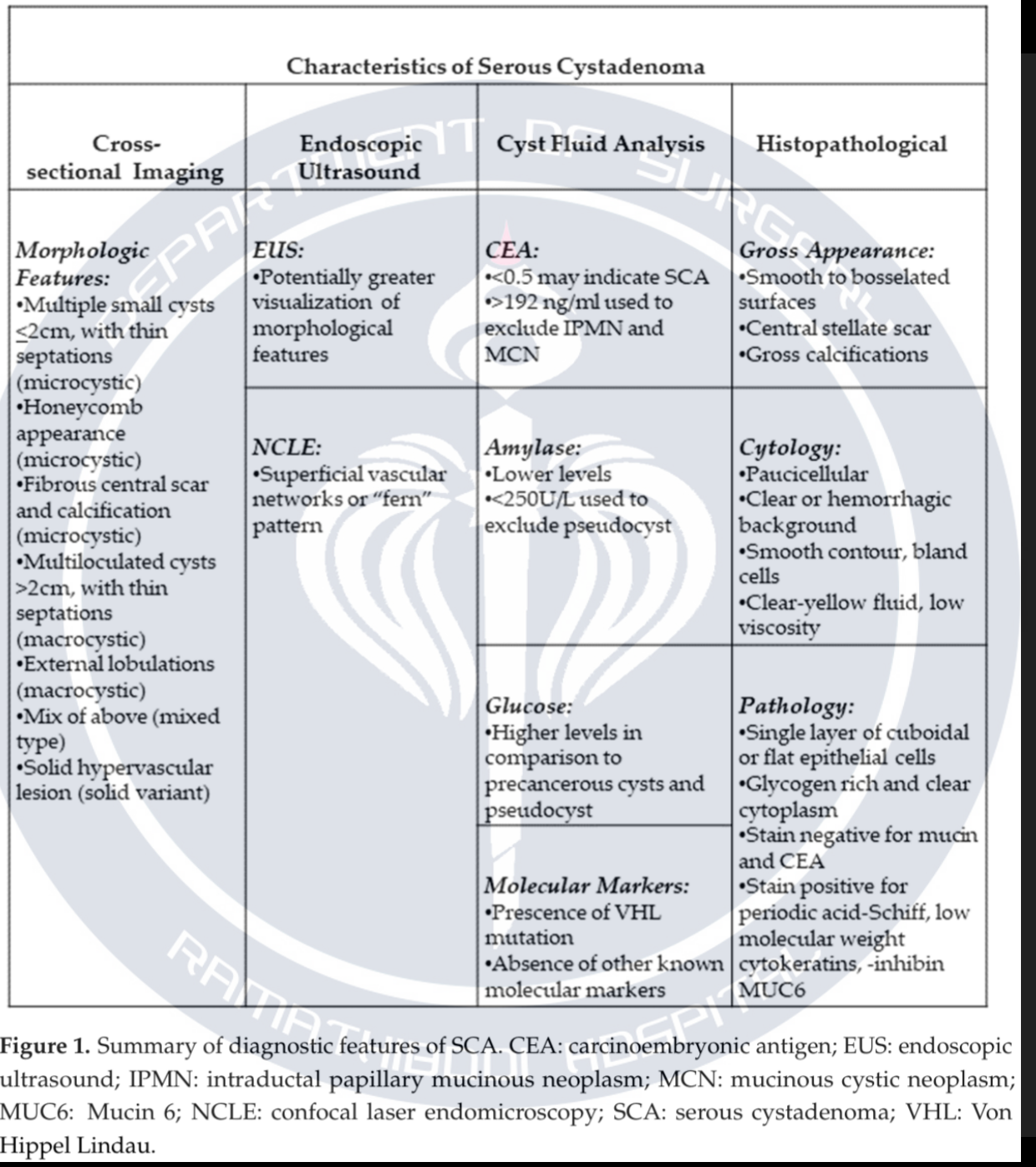


Figure 4. A typical pancreatic serous cystic neoplasm comprising multiple small microcysts.

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306

Khashab *et al.* Tumor Size and Location Correlate With Behavior of Pancreatic Serous Cystic Neoplasms. *Am J Gastroenterol* 2011; 106:1521–1526



Characteristics of Serous Cystadenoma

Cross-sectional Imaging	Endoscopic Ultrasound	Cyst Fluid Analysis	Histopathological
Morphologic Features: •Multiple small cysts ≤2cm, with thin septations (microcystic) •Honeycomb appearance (microcystic) •Fibrous central scar and calcification (microcystic) •Multiloculated cysts >2cm, with thin septations (macrocystic) •External lobulations (macrocystic) •Mix of above (mixed type) •Solid hypervascular lesion (solid variant)	*EUS:* •Potentially greater visualization of morphological features	*CEA:* •<0.5 may indicate SCA •>192 ng/ml used to exclude IPMN and MCN	*Gross Appearance:* •Smooth to bosselated surfaces •Central stellate scar •Gross calcifications
	NCLE: •Superficial vascular networks or "fern" pattern	*Amylase:* •Lower levels •<250U/L used to exclude pseudocyst	*Cytology:* •Paucicellular •Clear or hemorrhagic background •Smooth contour, bland cells •Clear-yellow fluid, low viscosity
		Glucose: •Higher levels in comparison to precancerous cysts and pseudocyst	*Pathology:* •Single layer of cuboidal or flat epithelial cells •Glycogen rich and clear cytoplasm •Stain negative for mucin and CEA •Stain positive for periodic acid-Schiff, low molecular weight cytokeratins, -inhibin MUC6
		Molecular Markers: •Prescence of VHL mutation •Absence of other known molecular markers	

Figure 1. Summary of diagnostic features of SCA. CEA: carcinoembryonic antigen; EUS: endoscopic ultrasound; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm; MUC6: Mucin 6; NCLE: confocal laser endomicroscopy; SCA: serous cystadenoma; VHL: Von Hippel Lindau.

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Serous Cystadenoma

- Management
  - SCN is a benign entity. Specific mortality is nearly zero
  - Symptomatic patients
    - Surgery in patients with symptoms related to the compression of adjacent organs (ie, bile duct, stomach, duodenum, portal vein)
    - The size of about 60% of SCN remains stable. An increase in cyst size is seen in 40% but the rate of growth is slow and new onset of symptoms is very rare
  - Asymptomatic patients
    - Consider surgery in size > 4 cm
    - Followed up for 1 year, After 1 year, symptom-based follow-up is recommended
    - Uncertain diagnosis : follow-up as for IPMN/MCN is required

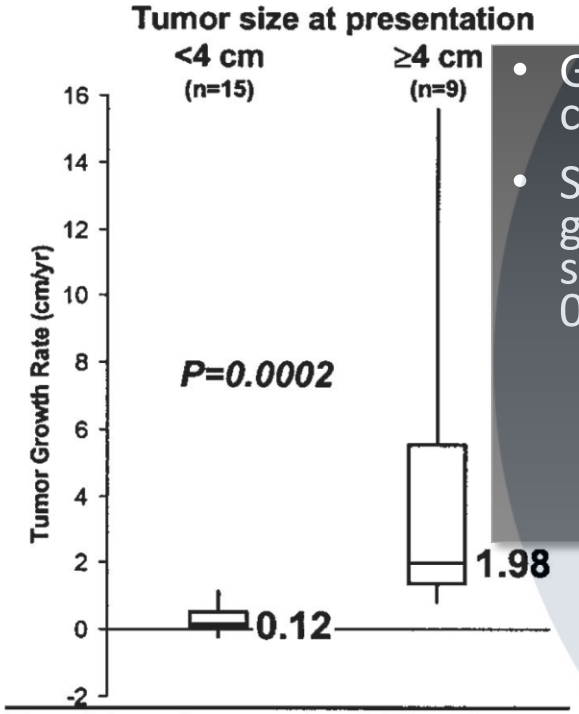
The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

Serous Cystadenoma of the Pancreas

Tumor Growth Rates and Recommendations for Treatment

Jennifer F. Tseng, MD, Andrew L. Warshaw, MD,* Dushyant V. Sahani, MD,† Gregory Y. Lauwers, MD,‡ David W. Rattner, MD,* and Carlos Fernandez-del Castillo, MD**

- Annals of Surgery, 2005
- 106 patients presenting with serous cystadenoma



Time of observation ranges from 3-162 months.
Plot elements:
median = line within box
25th & 75th percentiles = vertical borders of box
5th and 95th percentiles = ends of whiskers

FIGURE 3. Comparison of tumor growth for serous cystadenomas <4 and ≥4 cm in maximum diameter.

- Growth rate of serous cystadenoma : 0.6 cm/ yr
- Significant difference in tumor growth rate depending on the size at first presentation(*P* 0.0002)
  - Tumors < 4 cm (n =15), the rate was 0.12 cm/yr
  - Tumor > 4 cm (n 9), the rate was 1.98 cm/yr

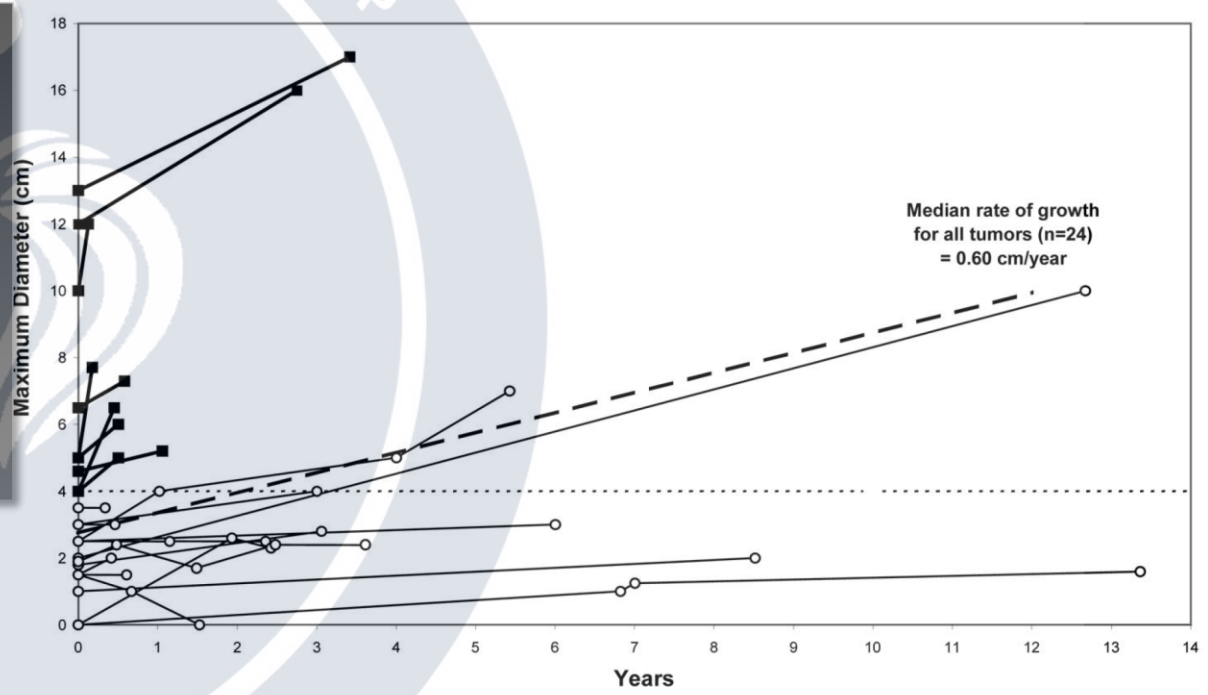


FIGURE 2. Serous cystadenoma tumor growth over time. Open circles represent tumors <4 cm at presentation, solid squares represent tumors ≥4 cm at presentation.

- Expectant management is reasonable in small asymptomatic tumors
- Recommend resection for large serous cystadenomas regardless of the presence or absence of symptoms

- Symptoms of Tumors < 4 cm vs > 4cm : 22 % vs 72 % P < 0.001

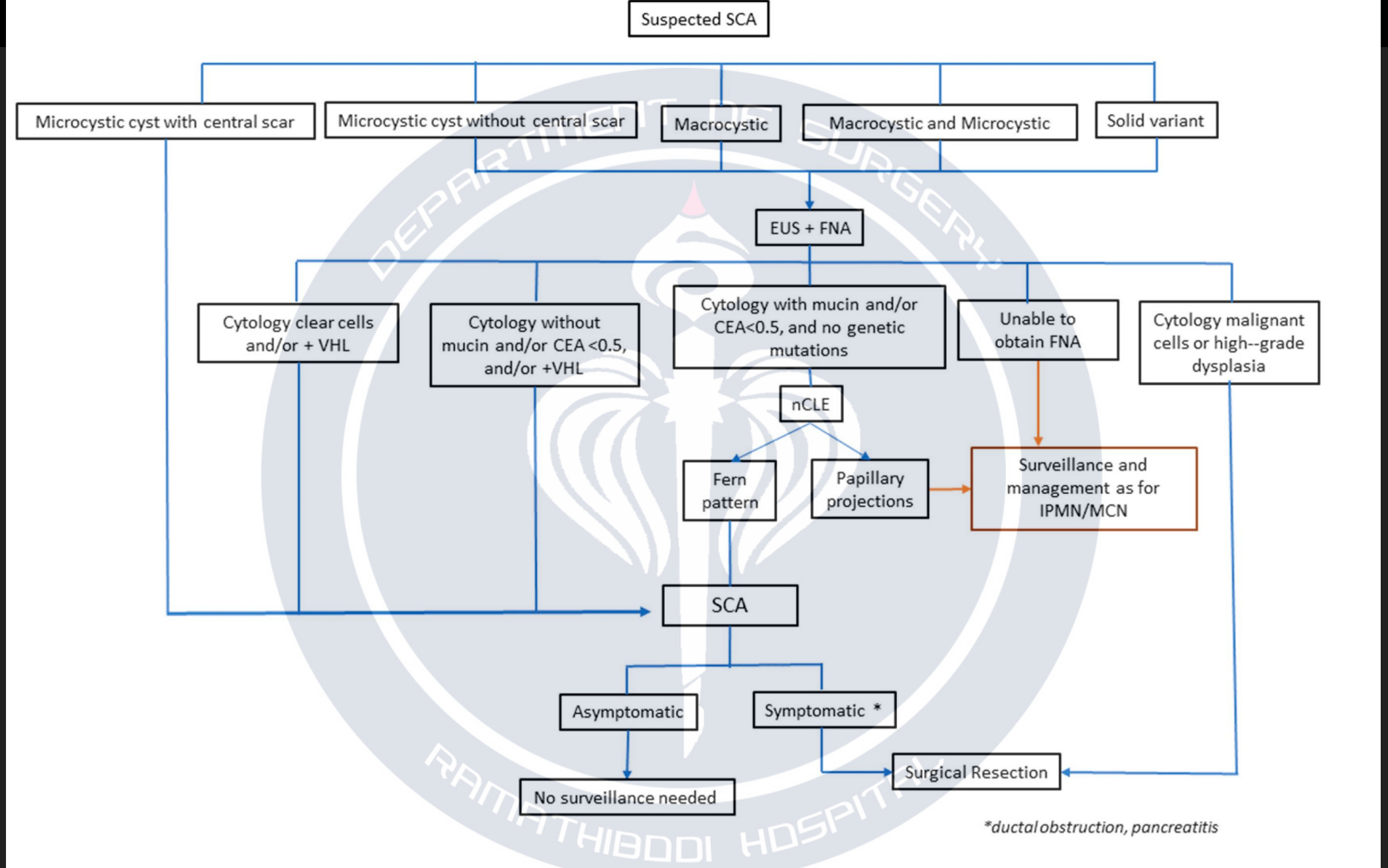


Figure 5. Proposed approach for diagnosis and management of suspected SCAs.

Kylie Ning, et al. Serous Cystadenoma: A Review on Diagnosis and Management. J. Clin. Med. 2023, 12, 7306.

Mucinous Cystic Neoplasm

- Cystic-forming, mucin-producing neoplasm of pancreas that lacks communication with the pancreatic ductal system
- 10% of pancreatic cystic lesions
  - Almost exclusively in women (male-to-female ratio, 1:9–20)
  - Age at diagnosis being 40 and 60 years
  - Mostly located in the pancreatic body and tail (93% – 95%)
- Known precursor lesion of pancreatic ductal adenocarcinoma (PDAC), with low-grade dysplasia or high-grade dysplasia
  - 15% of MCN will progress to invasive carcinoma

Xie et al. Update on mucinous cystic neoplasm of the pancreas: a narrative review. Journal of Pancreatology (2021) 4:3

Mucinous Cystic Neoplasm

- Unilocular or multilocular cystic tumor
- Vary in size, median dimension of the tumor ranging from 4.2 to 6 cm
- Cyst is walled by a thick fibrous capsule with focal hyalinization or calcification
  - Contains either thick mucus or a mixture of mucus and hemorrhagic necrotic material
- Papillary projections may be seen from the inner surface of the cyst
  - May contain foci of high-grade dysplasia and even invasive carcinoma

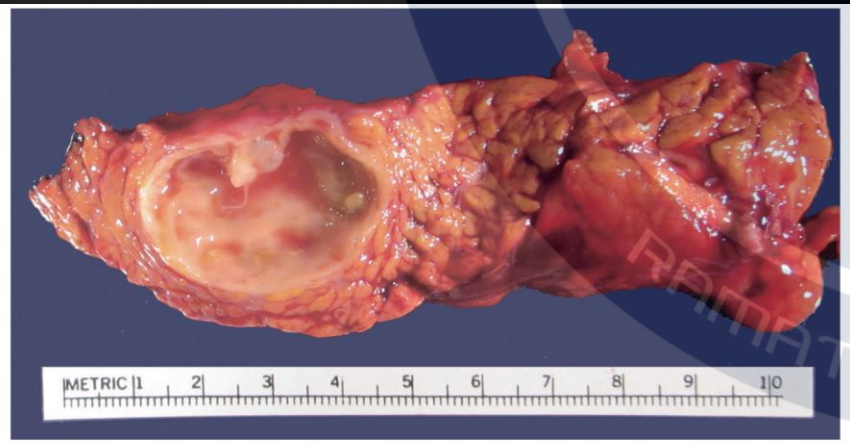


Figure 1. An example of MCN of the pancreas: a large, well-circumscribed unilocular cystic neoplasm is located in the pancreatic tail, with dense fibrous wall of 0.1 to 0.3 cm in thickness. Papillary excrescence can be seen on the inner surfaces. Unpublished data. MCN = mucinous cystic neoplasm.

- Ovarian-type stroma beneath the epithelium
  - Consists of spindle-shaped cells with round or elongated nuclei and sparse cytoplasm

Xie et al. Update on mucinous cystic neoplasm of the pancreas: a narrative review. Journal of Pancreatology (2021) 4:3

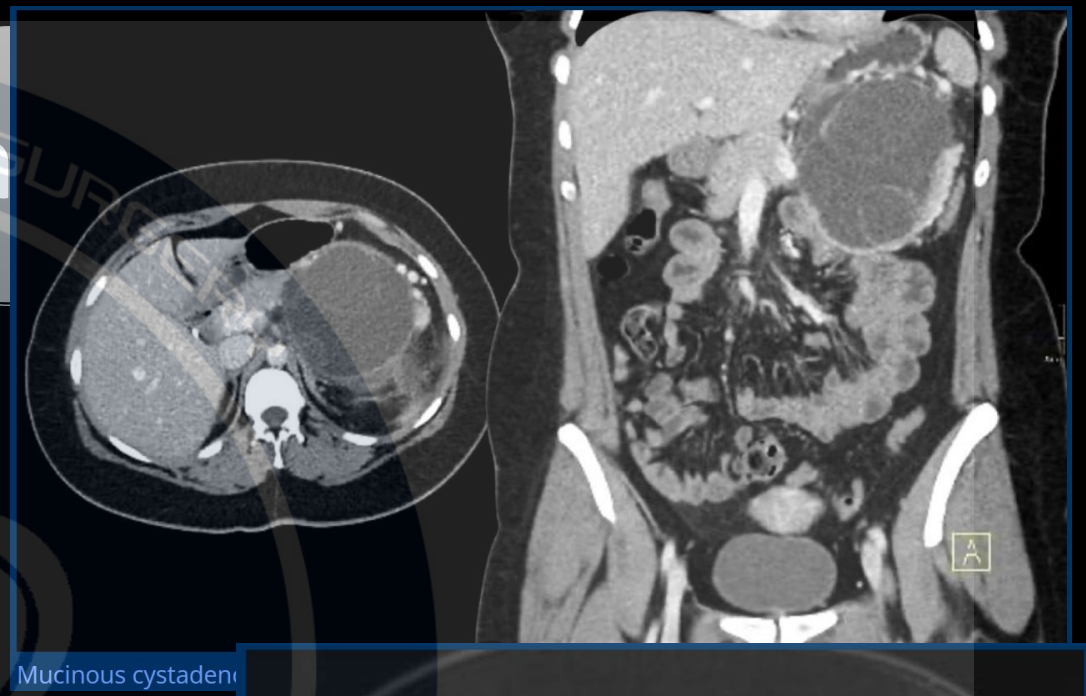
Mucinous Cystic Neoplasm

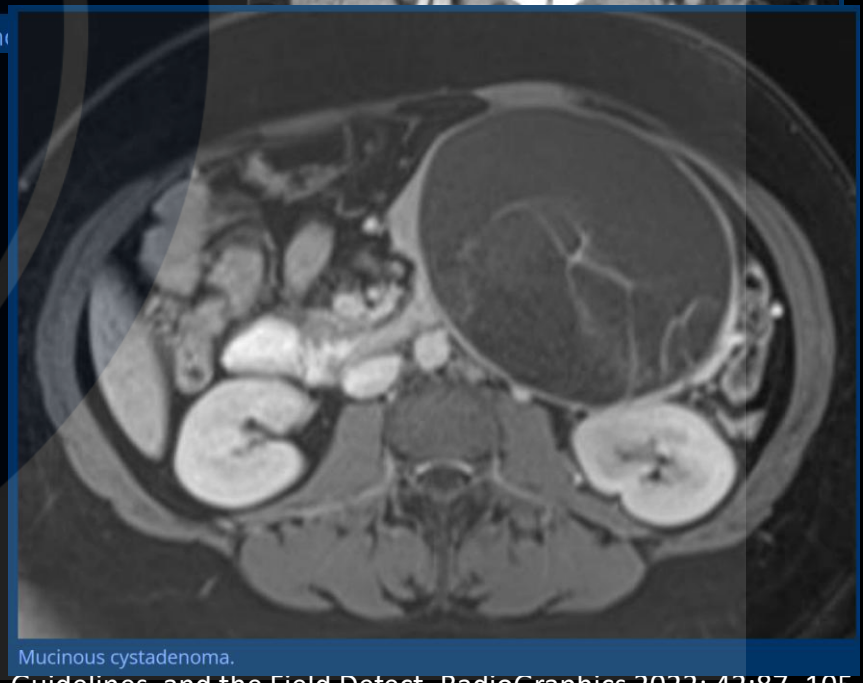
- Presentation
  - Often asymptomatic, typically detected during abdominal investigation from another reason
  - Symptoms : vague abdominal pain, abdominal fullness, abdominal mass, nausea-vomiting, back pain
- The prognosis of MCN without invasive carcinoma is excellent, with a 5-year survival of 96% to 100% after surgical resection
- Independent factors predictive of malignant transformation
  - Solid component or mural nodule
  - Larger tumor size *** highest odds ratio
  - Duct dilation

L.N. Nilsson et al. Nature and management of pancreatic mucinous cystic neoplasm (MCN): A systematic review of the literature. Pancreatology 16 (2016) 1028-1036
Xie et al. Update on mucinous cystic neoplasm of the pancreas: a narrative review. Journal of Pancreatology (2021) 4:3

Mucinous Cystic Neoplasm

- Cross-sectional imaging
  - Macrocystic with thick wall septations.
  - Peripheral calcifications seen in 25%
  - Location in the tail and body of the pancreas (95%)
- CT
  - Few cysts with occasional mural nodule and/or septa
  - Eggshell calcifications
- MRI
  - T1W: usually low SI
  - T2W: high SI; may have thick enhancing walls, septa, and/or nodules

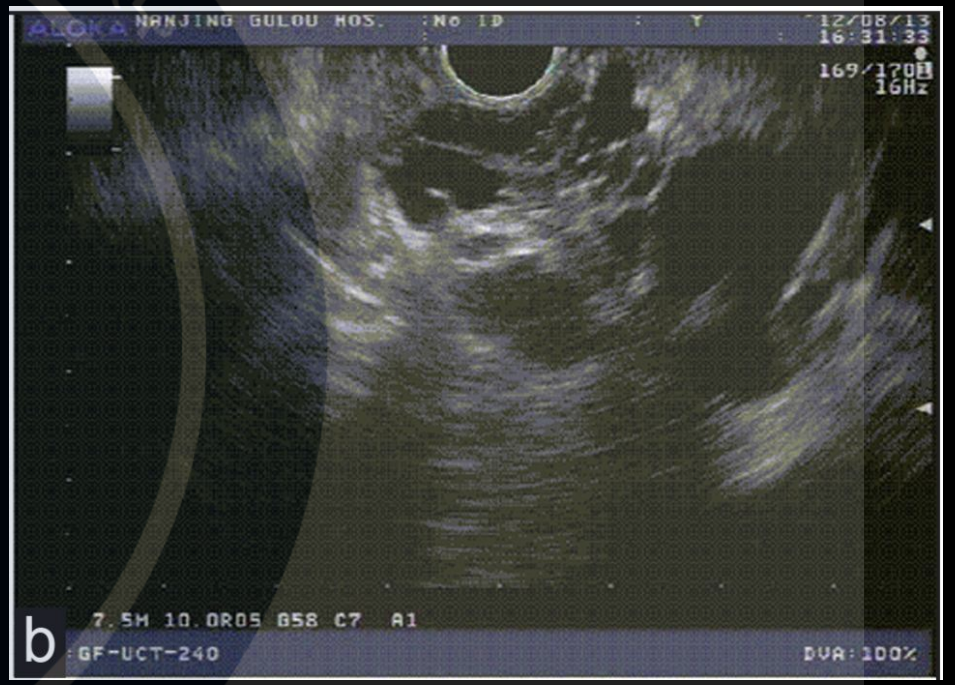



Mucinous cystadenoma.

Miller et al. Pancreatic Cystic Lesions and Malignancy: Assessment, Guidelines, and the Field Defect. RadioGraphics 2022; 42:87–105
Marc Engelbrecht et al. Pancreatic cystic Lesions Diagnosis and management. https://radiologyassistant.nl/abdomen/pancreas/pancreas-cystic-lesions

Mucinous Cystic Neoplasm

- Endoscopic ultrasound + FNA; cyst fluid analysis
  - EUS : thin-walled; septated cavities contain highly viscous clear fluid -> may be difficult to aspirate
  - EUS-FNA : Assess for the “string-sign” -> mucinous lesion
    - Positive if ≥ 1 cm string formed in cyst fluid and lasted for ≥ 1 second
  - Cyst fluid analysis : high CEA, low amylase
  - Molecular marker : KRAS mutation, no GNAS mutation



EUS image of a MCN in a 76-year-old male patient with presence of septations and approximately 3.7 × 2.8 cm in the head of the pancreas

L.N. Nilsson et al. Nature and management of pancreatic mucinous cystic neoplasm (MCN): A systematic review of the literature. Pancreatology 16 (2016) 1028-1036

Mucinous Cystic Neoplasm

- Management
  - Surgical resection
    - MCN size ≥40 mm
    - Symptomatic or have risk factors (ie, mural nodule) irrespective of their size
      - Imaging features indicating high-grade dysplasia or cancer -> Standard oncologic resection (distal pancreatectomy in 90-95% of MCNs) with lymph node dissection and splenectomy -> to avoid incomplete treatment of invasive carcinoma
  - MCN without suspect features with a low risk of malignancy
    - Non-oncological resection can be performed (distal pancreatectomy with splenic preservation with or without preservation of splenic vessels, or parenchymal sparing pancreatectomy)

The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

Mucinous Cystic Neoplasm

- Management
  - Surveillance : with MRI, EUS or a combination of both
    - MCN < 40 mm
    - Absence of risk features such as a suspicious mural nodule or symptoms
  - Every 6 months for the first year -> Then annually if no changes are observed
  - MCN measuring <40 mm and with no concerning features or symptoms
    - Lifelong surveillance as long as they are fit for surgery

The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 May 28; 29(20): 3119-3

DOI: 10.3748/wjg.v29.i20.3119

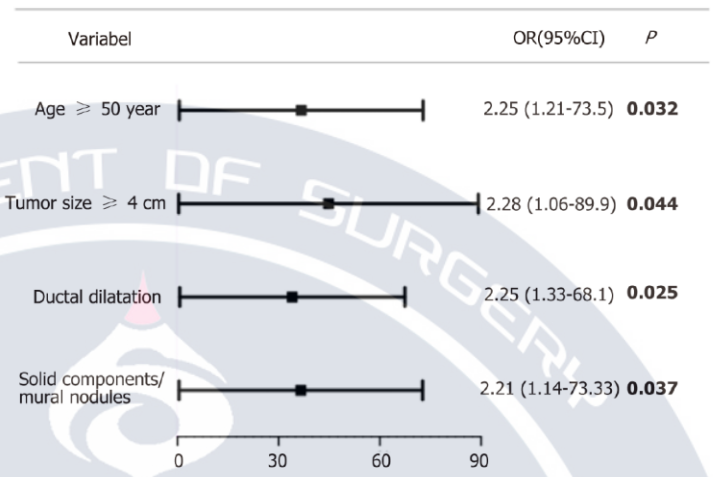
ISSN 1007-9327 (print) ISSN 2219-2840 (onli

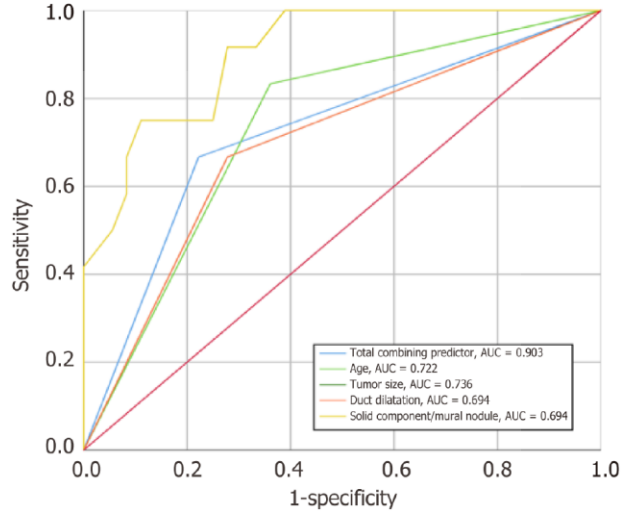
ORIGINAL ARTIC

Retrospective Study

Malignancy risk factors and prognostic variables of pancreatic mucinous cystic neoplasms in Chinese patients

Qing Xia, Fan Li, Rui Min, Shuai Sun, Yue-Xin Han, Zhen-Zhong Feng, Nan Li





DOI: 10.3748/wjg.v29.i20.3119 Copyright ©The Author(s) 2023.

Figure 3 Risk factors of malignant mucinous cystic neoplasm. A: Binary logistic regression analysis of preoperative risk factors for malignancy; B: Receiver operating characteristic curve analysis of the combined predictors and individual indicators. 95%CI: 95% confidence interval; AUC: Area under the curve.

< 4	23 (63.9)	2 (16.7)	
Location			0.348
Head and neck	8 (22.2)	5 (41.7)	
Body and tail	28 (77.8)	7 (58.3)	
Duct dilatation			**0.039**
Yes	10 (27.8)	8 (66.7)	
No	26 (72.2)	4 (33.3)	
Solid component/mural nodule			**0.039**
Yes	10 (27.8)	8 (66.7)	
No	26 (72.2)	4 (33.3)	
Septations			0.867
Yes	16 (44.4)	5 (41.7)	
No	20 (55.6)	7 (58.3)	
Calcification			0.851
Yes	9 (25)	4 (33.3)	
No	27 (75)	8 (66.7)	

Significant *P* in bold. Data presented in parentheses represent percentages. CA19-9: Carbohydrate antigen 19-9.

- Retrospective review, patients with resected MCN in single center
- Investigate high risk factors associated with malignant MCN
- Total 48 patients
  - Benign 36
  - Malignant 12
- Incidence of malignant MCNs was low, and the specific risk factors for malignancy were age, tumour size, presence of solid components or mural nodules, and duct dilatation

REVIEW ARTICLE

It is not necessary to resect all mucinous cystic neoplasms of the pancreas: current guidelines do not reflect the actual risk of malignancy

Tommaso Pollini[1,2], Giovanni Marchegiani[2], Antonio Facciorusso[3], Alberto Balduzzi[2], Marco Biancotto[2], Claudio Bassi[2], Ajay V. Maker[1,#] & Roberto Salvia[2#]

[1]Division of Surgical Oncology, Department of Surgery, University of California San Francisco, San Francisco, USA, [2]The Pancreas Institute, Department of General and Pancreatic Surgery, University of Verona, Verona, and [3]Gastroenterology Unit, Department of Surgical and Medical Sciences, University of Foggia, Foggia, Italy

- HPB 2023
- Systematic review of 40 studies, 3292 patients with resected MCNs
- Aim to determine the malignancy rate

- Pooled rate of malignant MCN was 16.1 %
- Considering the publication date of various guidelines
  - Significant reduction in the percent of malignant MCN resected after publication of the 2012 international guidelines and its revision in 2017 (21.0% vs 14.9%, $p < 0.001$ and 19.6% vs 14.0%, $p = 0.002$)
  - A similar increase in the number of non-malignant resected MCN was identified after the European guidelines in 2018

Before(21%) vs after(14.9%) guideline 2012

Before(19.6%) vs after(14%) guideline 2018

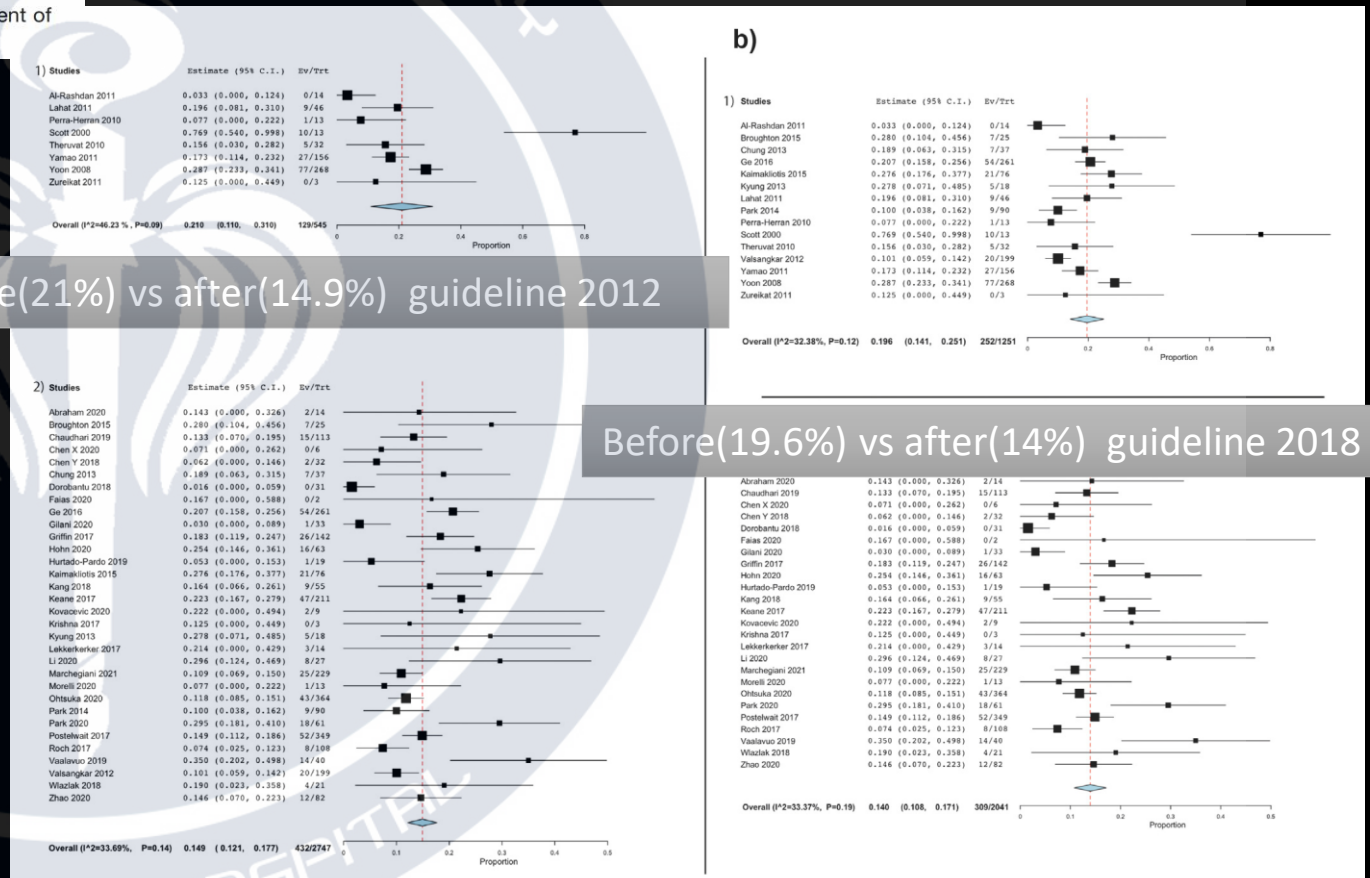
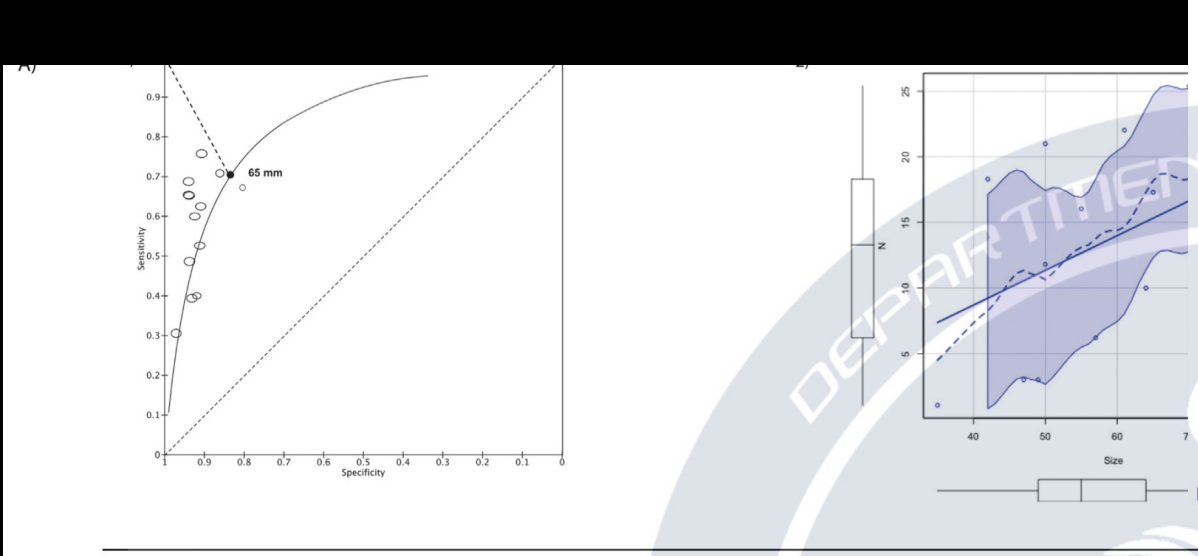


Figure 4 Sensitivity analysis reporting the pooled rate of malignant MCN according to year of publication. a) (1) forest plot reporting the incidence of malignant MCN in studies published before 2012 (21.0%, 95%CI 11.0–31.0%) and (2) after 2012 (14.9%, 95%CI 12.1–17.7%), $p < 0.001$. b) (1) forest plot of studies reporting the incidence of malignant MCN in studies published before 2017 (19.6%, 95%CI 14.1–25.1%) and (2) after 2017 (14.0%, 95%CI 10.8–17.1%), $p = 0.002$



Study or Subgroup	Malignant Events	Malignant Total	Benign Events	Benign Total	Weight	Odds Ratio M-H, Random, 95% CI
Abraham 2020	1	2	0	12	1.0%	25.00 [0.67, 934.44]
Griffin 2017	5	26	8	116	8.2%	3.21 [0.96, 10.79]
Keane 2017	12	47	20	164	16.2%	2.47 [1.10, 5.52]
Lekkerkerker 2017	2	3	0	11	1.1%	38.33 [1.18, 1245.02]
Marchegiani 2021	5	25	8	204	8.3%	6.13 [1.83, 20.51]
Ohtsuka 2020	18	43	28	321	19.1%	7.53 [3.67, 15.47]
Park 2014	3	9	3	81	4.0%	13.00 [2.14, 78.87]
Postelwait 2017	22	52	49	297	23.0%	3.71 [1.98, 6.97]
Roch 2017	2	8	19	100	4.6%	1.42 [0.27, 7.60]
Yamao 2011	14	27	28	129	14.5%	3.88 [1.64, 9.21]
Total (95% CI)		**242**		**1435**	**100.0%**	**4.34 [3.00, 6.29]**
Total events	84		163			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 10.57$, df = 9 (P = 0.31); $I^2 = 15\%$
Test for overall effect: Z = 7.78 (P < 0.00001)

Odds Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours Benign Favours Malignant

Figure 6 Association between mural nodules and malignancy in resected MCN

Association btw mural nodules and malignancy in resected MCN, OR 4.34(3.0,6.29)

B)

Study or Subgroup	Malignant Mean	Malignant SD	Malignant Total	Benign Mean	Benign SD	Benign Total	Weight	Mean Difference IV, Random, 95% CI
Griffin 2017	100	23.3	26	40	26	116	9.0%	60.00 [49.87, 70.13]
Hohn 2020	52.29	44.75	16	44.09	29.43	47	6.9%	8.20 [-15.29, 31.69]
Keane 2017	100	21.5	47	52	14	164	9.4%	48.00 [41.49, 54.51]
Kyung 2013	69	21.75	5	70	33.75	13	6.4%	-1.00 [-27.46, 25.46]
Lekkerkerker 2017	67	20	3	45	33.3	11	5.8%	22.00 [-7.99, 51.99]
Marchegiani 2021	97	38	25	63	32	204	8.2%	34.00 [18.47, 49.53]
Ohtsuka 2020	100	42.5	43	48	47.5	321	8.5%	52.00 [38.28, 65.72]
Park 2014	55	32	9	66	48	81	6.9%	-11.00 [-34.37, 12.37]
Postelwait 2017	72	56	52	46	37	297	8.2%	26.00 [10.21, 41.79]
Roch 2017	67	20	8	44	20	100	8.4%	23.00 [8.60, 37.40]
Scott 2000	70	42.5	10	110	30	3	4.1%	-40.00 [-82.97, 2.97]
Theruvat 2010	94	78	5	39	24	27	2.1%	55.00 [-13.97, 123.97]
Yamao 2011	90	46	27	60	38	129	7.7%	30.00 [11.45, 48.55]
Zhao 2020	58	20	12	35	24	70	8.6%	23.00 [10.36, 35.64]
Total (95% CI)			**288**			**1583**	**100.0%**	**25.96 [14.50, 37.43]**

Heterogeneity: $Tau^2 = 354.81$; $Chi^2 = 89.34$, df = 13 (P < 0.00001); $I^2 = 85\%$
Test for overall effect: Z = 4.44 (P < 0.00001)

Mean Difference IV, Random, 95% CI
-100 -50 0 50 100
Favours Benign Favours Malignant

Figure 5 Association between cyst size and malignancy in resected MCN. a) (1) Summary Receiver Operating Characteristic (SROC) curve (AUC 0.78 (95%CI 0.73–0.82). A threshold of 65 mm has been identified as the best to predict malignancy in resected MCN. (2) Meta regression of cyst size and malignancy. $R^2 = 0.28$, p = 0.02. b) Forest plot of the mean size difference between malignant and benign MCN. A random effect model was used

Association btw cyst size and malignancy in resected MCN
- From AUC : threshold of 65 mm
- Malignant MCNs were significantly larger than benign MCNs : mean difference 25.96 mm

- The pooled rate of malignancy in resected MCN is as low as 16%
  - Shows even a decreasing trend over time with an increasing denominator of resected lesions
- Size and mural nodules accurately predict the presence of overt malignancy
  - Absence of these features -> Surveillance of MCN can be proposed, particularly in younger individuals with cysts less than 6 cm

Intraductal Papillary Mucinous Neoplasm

- Cystic neoplasms originating from the epithelial cells of the pancreatic duct
  - Cell proliferation in the form of dysplastic papillary projections
  - Mucin secretion -> leads to cystic dilatation
- Incidence increase with age
  - 0 % in 20's and 0.2 % in 30's, and increased to 6.6 % in 70’s
- Morphological subtype
  - Gastric type — most often low-grade BD-IPMNs with the most favorable prognosis
  - Intestinal type
  - Pancreatobiliary type — highest risk of neoplastic progression

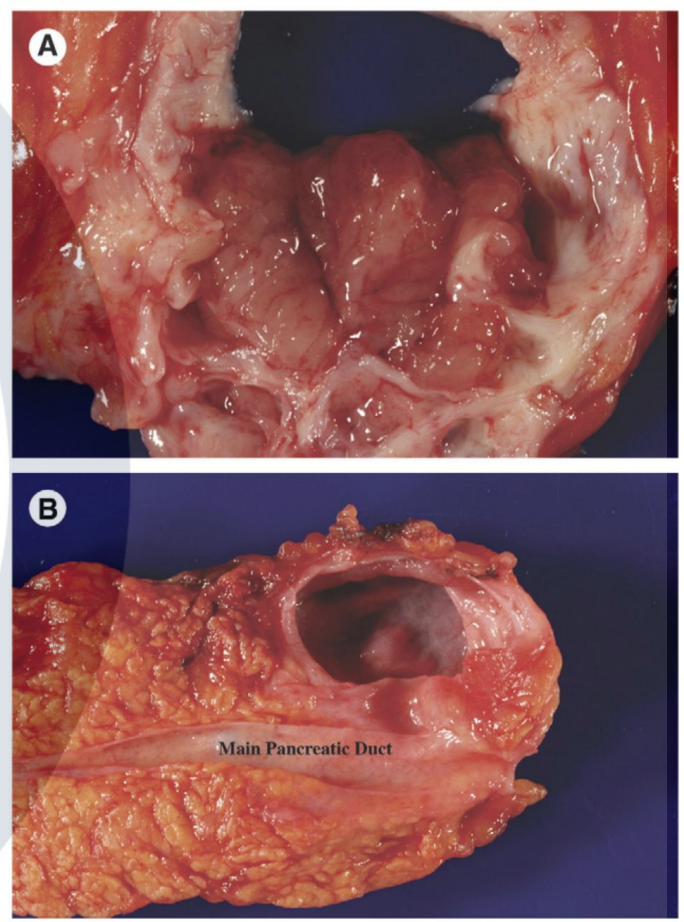


Fig. 1 Representative gross pictures of IPMN. A, MD-IPMN with markedly dilated main pancreatic duct and grossly visible intraductal papillary growth. B, BD-IPMN with a single cyst that does not involve the main duct.

T. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270
D. Moris et al. An Overview for Clinicians on Intraductal Papillary Mucinous Neoplasms (IPMNs) of the Pancreas. Cancers 2024, 16, 3825
C. Shi, R. H. Hruban. Intraductal papillary mucinous neoplasm. Human Pathology (2012) 43, 1–16

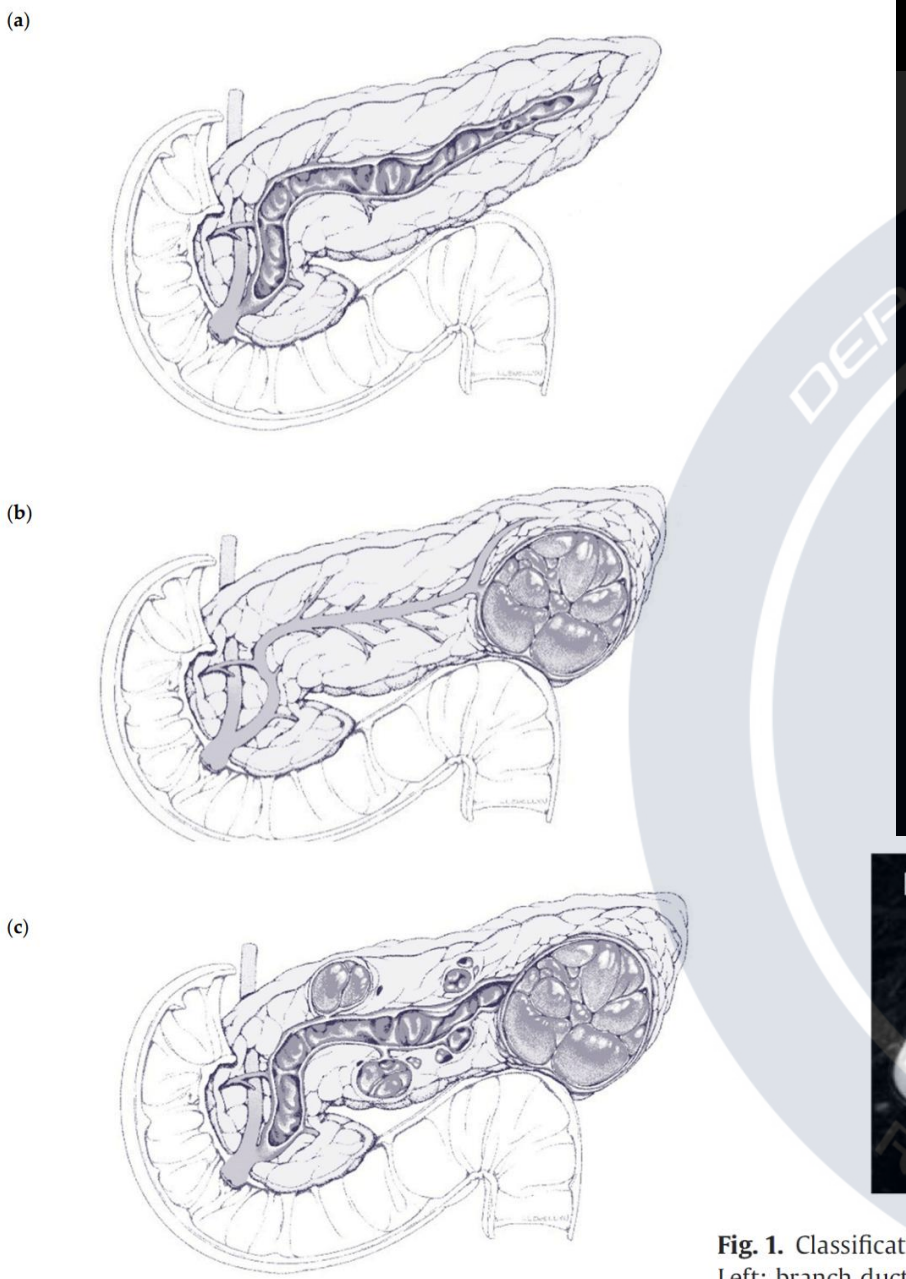


Figure 1. Anatomic subtypes of IPMN: (**a**) main duct dilatation, (**b**) side branch duct dilatation with mass, (**c**) mixed type—main duct dilatation with masses arising from side branches.

- Classification
  - Main duct IPMN : Risk of IC/HGD 62%
    - Segmental or diffuse dilation of the MPD of >5 mm without other causes of MPD obstruction
  - Branched duct IPMN : Risk of IC/ HGD 31 %
    - Pancreatic cyst of >5 mm in diameter that communicates with the main pancreatic duct
  - Mixed IPMN
    - Meets the criteria for both BD-IPMN and MD-IPMN

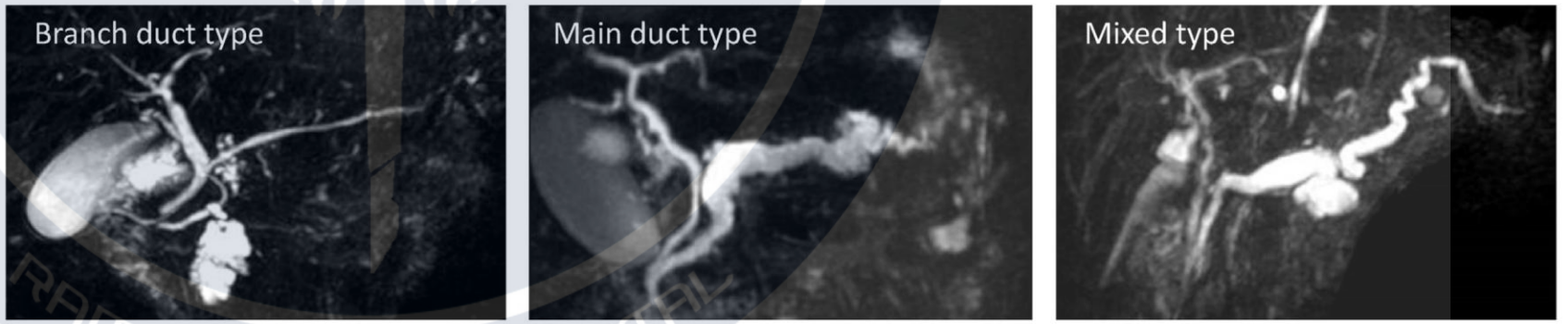


Fig. 1. Classification of IPMN on MRCP.
Left; branch duct type. Middle; main duct type. Right; mixed type. Reuse with permission from the Japanese Society of Gastroenterological Surgery [19].

T. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

D. Moris et al. An Overview for Clinicians on Intraductal Papillary Mucinous Neoplasms (IPMNs) of the Pancreas. Cancers 2024, 16, 3825

Intraductal Papillary Mucinous Neoplasm

- Presentation
  - Mostly asymptomatic in branch duct IPMN
  - Symptoms : Abdominal distention/pain, back pain (related to pancreatitis), jaundice
- Carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and hemoglobin A1c (HbA1c) should also be assessed
- Elevated levels of tumor markers and unexpected new onset or deterioration of diabetes mellitus (DM) often suggest the possible presence of IC

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Intraductal Papillary Mucinous Neoplasm

- Cross-sectional imaging
  - Main duct IPMN
    - Segmental of diffused pancreatic duct dilatation
    - Can appear to be cystic if only short segment of pancreatic duct is involved
    - Soft-tissue nodule representing the mucin-producing tumor may be difficult to identify because of its small size
  - Branch duct IPMN
    - Cluster of small cysts with lobulated margins and septa (grapelike lobulated appearance), or unilocular cysts on imaging studies
    - Usually locate at the uncinate process
    - Cyst communicate with pancreatic duct -> can be seen on CT but better visualized on MRI

Miller et al. Pancreatic Cystic Lesions and Malignancy: Assessment, Guidelines, and the Field Defect. RadioGraphics 2022; 42:87–105

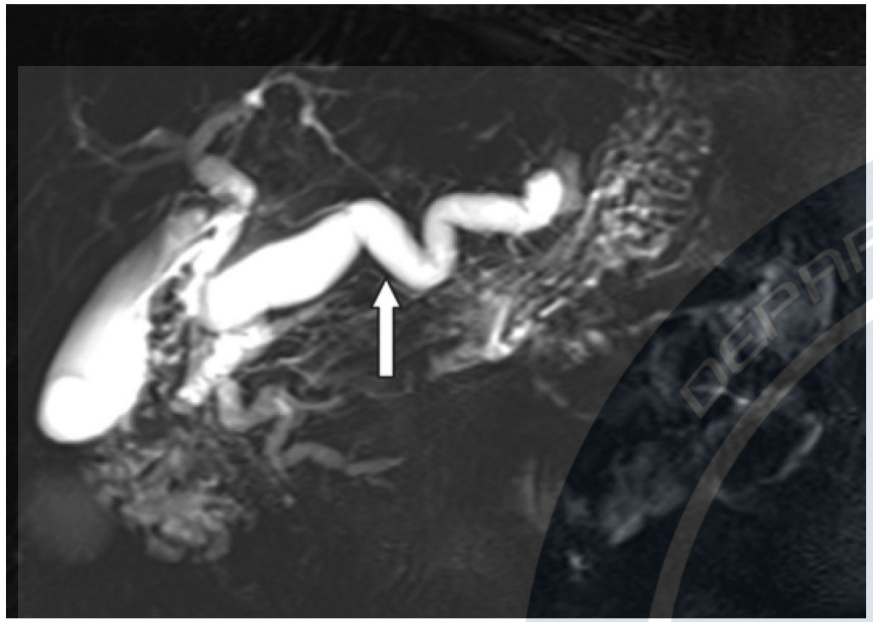


Figure 12. Main-duct IPMN in an 88-year-old woman. MRCP image shows a diffusely dilated 1.7-cm pancreatic duct (arrow) in the setting of main-duct IPMN.

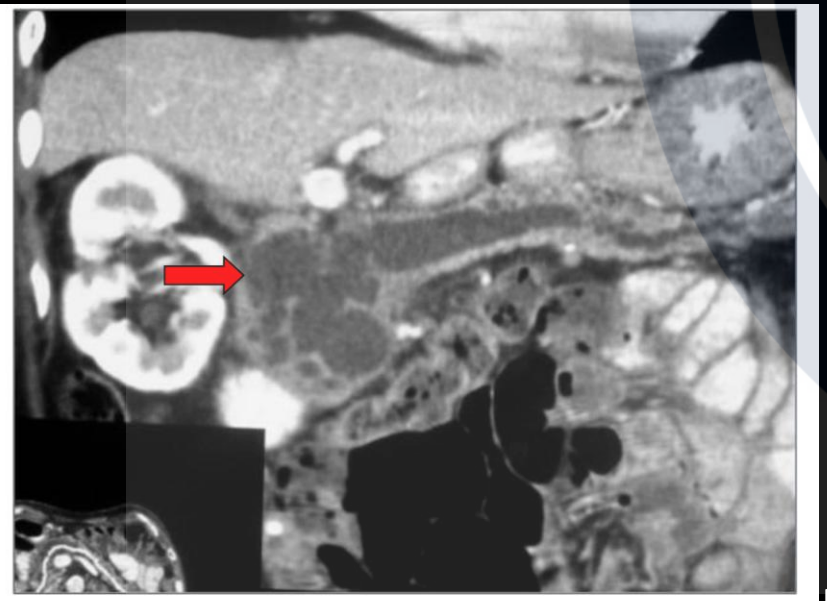


Figure 4. Curved reconstructed CT image in the course of the dilated pancreatic duct shows a typical case of main duct IPMN (arrow).

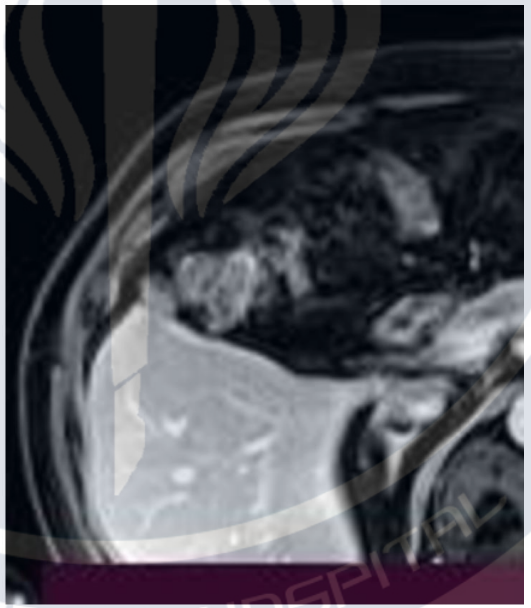
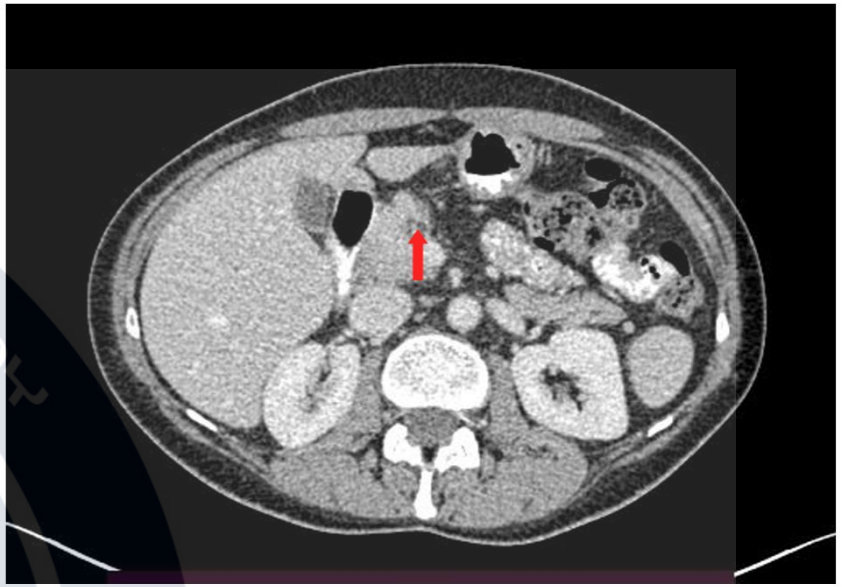
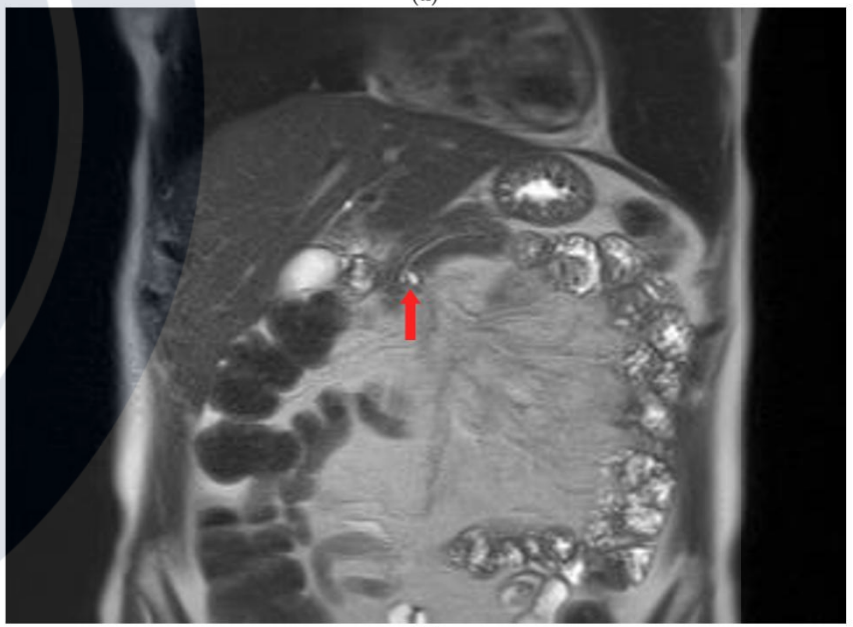


Figure 7. IPMN in the pancreatic tail, presenting image. Enhancing mural nodules are obvious (arr



(a)

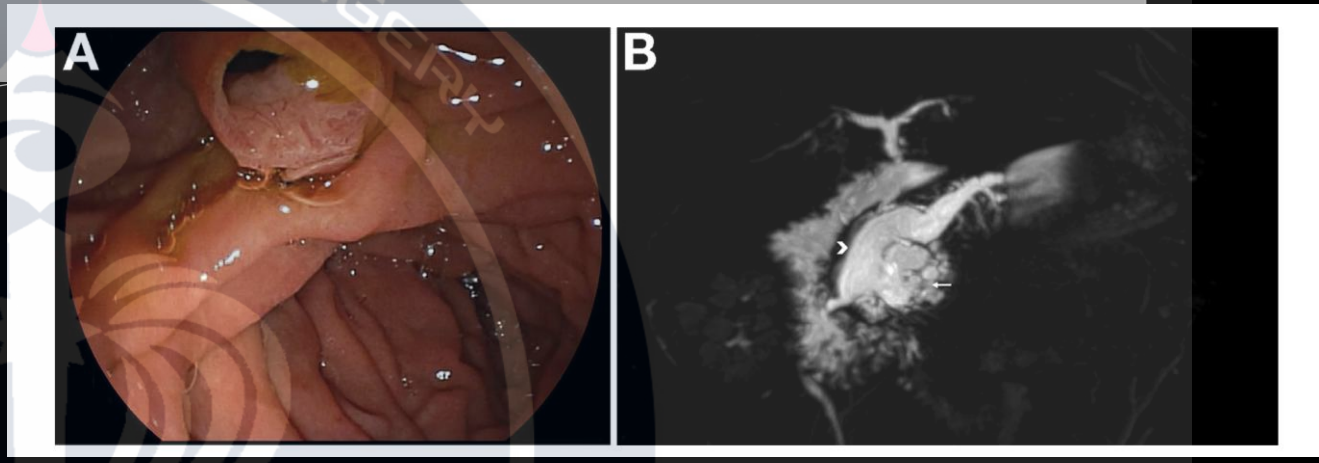


(b)

Figure 1. Contrast-enhanced CT image (**a**) and coronal T2-w MR image (**b**), show a small branch duct IPMN (arrow) communicating with the main duct. The IPMN is more easily seen on the MR image.

Miller et al. Pancreatic Cystic Lesions and Malignancy: Assessment, Guidelines, and the Field Defect. RadioGraphics 2022; 42:87–105
Triantopoulou, C. et al. Intraductal Papillary Mucinous Neoplasm of the Pancreas: AChallenging Diagnosis. Diagnostics 2023, 13, 2015

Intraductal Papillary Mucinous Neoplasm



- Endoscopic management/ workup
  - EUS/ EUS-FNA, cyst fluid analysis
    - Assessment of cystic fluid
      - High CEA (>192), high amylase
      - KRAS and GNAS mutation
    - Concern of peritoneal dissemination due to needle tract (incidence in systematic review 0.3%)
    - Should be performed if the result alter the further management
  - ERCP
    - Fish mouth appearance of papilla (prevalence 50%, specificity 91%)
    - Role is limited to biliary drainage in jaundice patients
    - Yield for pancreatic juice cytology is low and risk of post ERCP pancreatitis
    - Pancreatoscopy : Determine adequate resection line, skip lesion
      - Skip lesion : 6-42% of cases

T. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270
Ravishankar Asokkumar and Yung-Ka Chin. Fish-Mouth Papilla. Clinical Gastroenterology and Hepatology 2018;16:xxxiv
The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

Systematic review

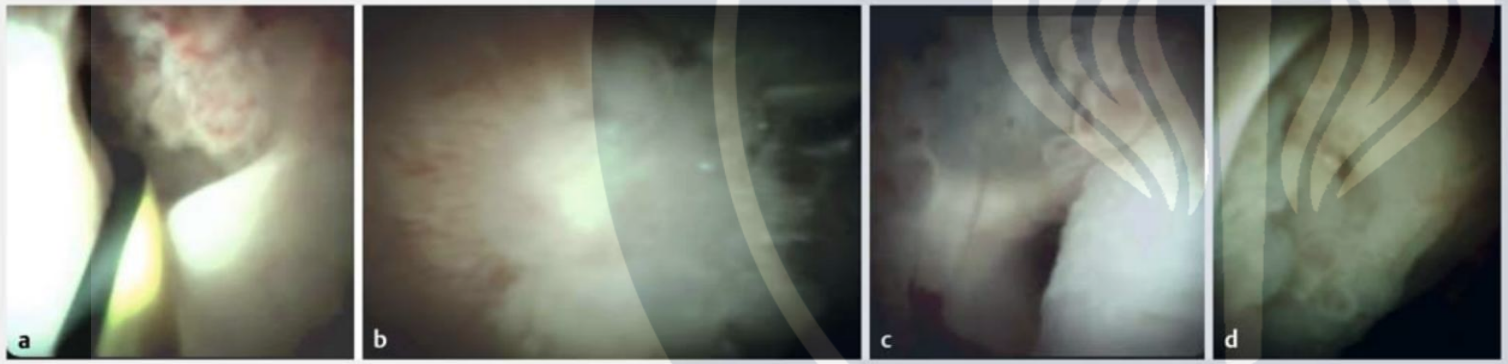
Thieme

The role of pancreatoscopy in the diagnostic work-up of intraductal papillary mucinous neoplasms: a systematic review and meta-analysis

OPEN ACCESS

Authors

David M. de Jong[1,*], Pauline M. C. Stassen[1,*], Bas Groot Koerkamp[2], Mark Ellrichmann[3], Petko I. Karagyozov[4], Andrea Anderloni[5], Leena Kylänpää[6], George J. M. Webster[7,8], Lydi M. J. W. van Driel[1], Marco J. Bruno[1], Pieter J. F. de Jonge[1], on behalf of the European Cholangioscopy study group



▶ **Fig. 3** Example images during peroral pancreatoscopy (POP) in four patients with intraductal papillary mucinous neoplasm (IPMN) showing: **a** a clear proximal margin of a main-duct IPMN (MD-IPMN) that was suspicious for malignancy, but was found to be a mixed-type IPMN without any malignancy on pancreatoduodenectomy (see also ▶ **Video 1**); **b** a clear image of a visible polypoid lesion in the setting of MD-IPMN, with biopsy revealing focal malignant transformation; **c** the clear fish-egg-like lesions in an MD-IPMN; **d** a very wide side branch in the body of the pancreas, with a nodular mass seen at the opening of the side branch, which showed mild dysplasia on POP-guided biopsy and later pancreatoduodenectomy.

- Endoscopy, 2022
- 25 studies of pancreatoscopy in IPMN

- Pancreatoscopic characteristic features of IPMN
  - Intraductal papillary or villous projections
  - Presence of mucus
  - Intraductal fish-egg-like lesions
    - Sometimes seen on a protruding lesion, and granular mucosa

de Jong David M et al. The role of … Endoscopy 2023; 55: 25–35

Systematic review

Thieme

The role of pancreatoscopy in the diagnostic work-up of intraductal papillary mucinous neoplasms: a systematic review and meta-analysis

OPEN ACCESS

Authors

David M. de Jong[1,*], Pauline M. C. Stassen[1,*], Bas Groot Koerkamp[2], Mark Ellrichmann[3], Petko I. Karagyozov[4], Andrea Anderloni[5], Leena Kylänpää[6], George J. M. Webster[7,8], Lydi M. J. W. van Driel[1], Marco J. Bruno[1], Pieter J. F. de Jonge[1], on behalf of the European Cholangioscopy study group

- Technical success ranged 86-100%
- After successful cannulation
  - Rate of adequate visualization of PD 60-100%
    - Inadequate clearance of mucus
    - Concomitant anatomical features : duct stricture
    - Non-dilated PD
- Adverse events rate : 12%
  - Most common : PEP (mostly mild-moderate severity)
- Determination of the extent of the lesion or identification of skip lesions by visualization or biopsy -> altered surgical approach in 13 %–62% of patients
  - More extensive surgical resection : 13%–31 % DP or PD -> Total pancreatectomy
  - Less extensive surgical resection : 6 %–31 % Total pancreatectomy -> DP or PD

de Jong David M et al. The role of … Endoscopy 2023; 55: 25–35

Intraductal Papillary Mucinous Neoplasm

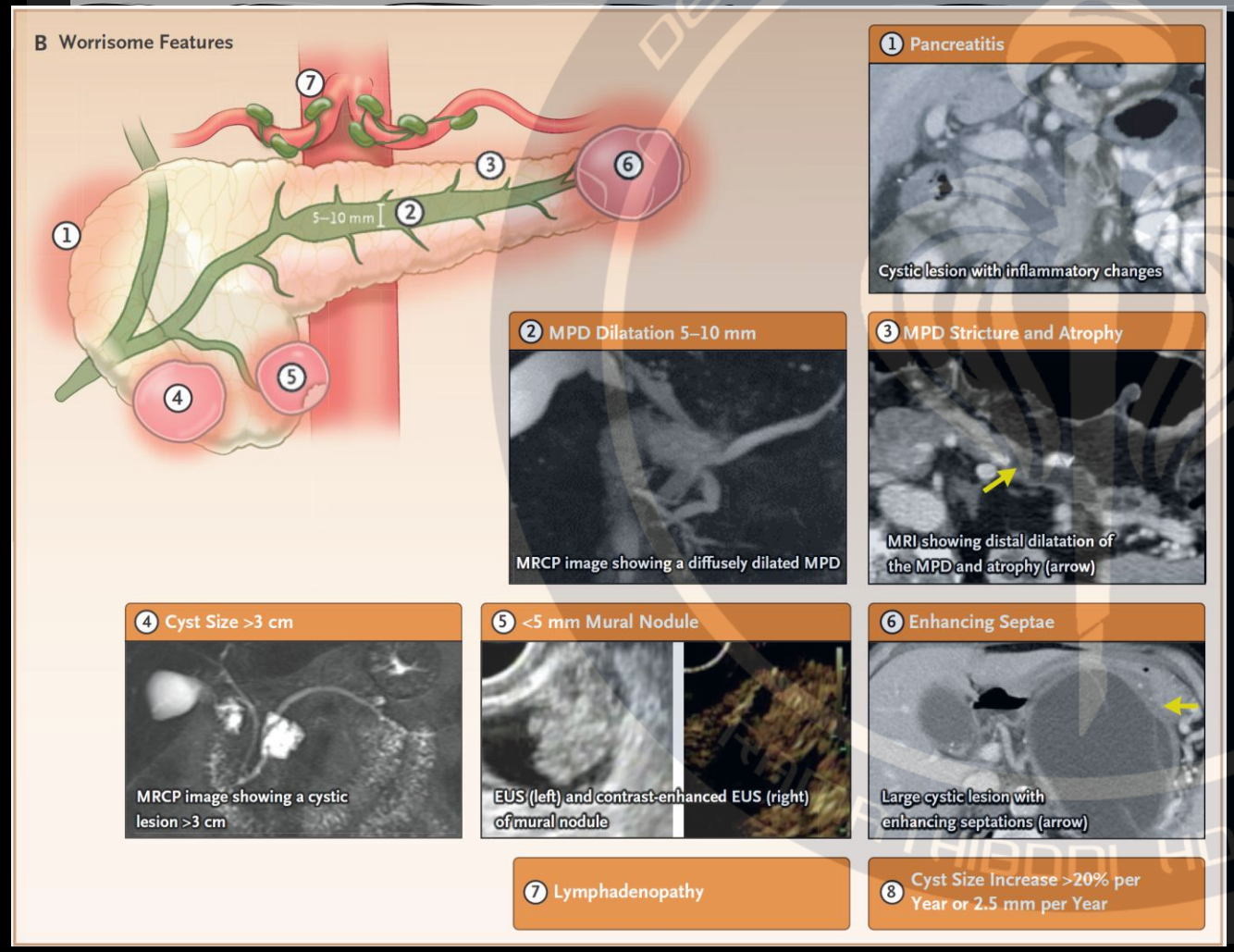
- Risk assessment
  - Factors predictive of HGD/IC in IPMN have been called HRS and WF
  - High risk stigmata : very strong predictors of HGD/IC but do not have perfect specificity

- High risk stigmata
  - Biliary obstruction
  - Main pancreatic duct dilatation $\geq$ 10 mm
  - Enhancing mural nodule $\geq$ 5 mm or solid component
  - Suspicious or positive results of cytology

T. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

Intraductal Papillary Mucinous Neoplasm



- Worrisome feature
  - Acute pancreatitis
  - Increased serum level of CA19- 9
  - New onset or acute exacerbation of DM within the past year
  - Cyst 30 mm
  - Enhancing mural nodule < 5 mm
  - Thickened/enhancing cyst walls ≥ 2.5 mm
  - MPD 5 mm and <10 mm
  - Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy
  - Lymphadenopathy
  - Cystic growth rate 2.5 mm/year

Tamas A. Gonda, et al. Pancreatic Cysts. N Engl J Med 2024;391:832-43

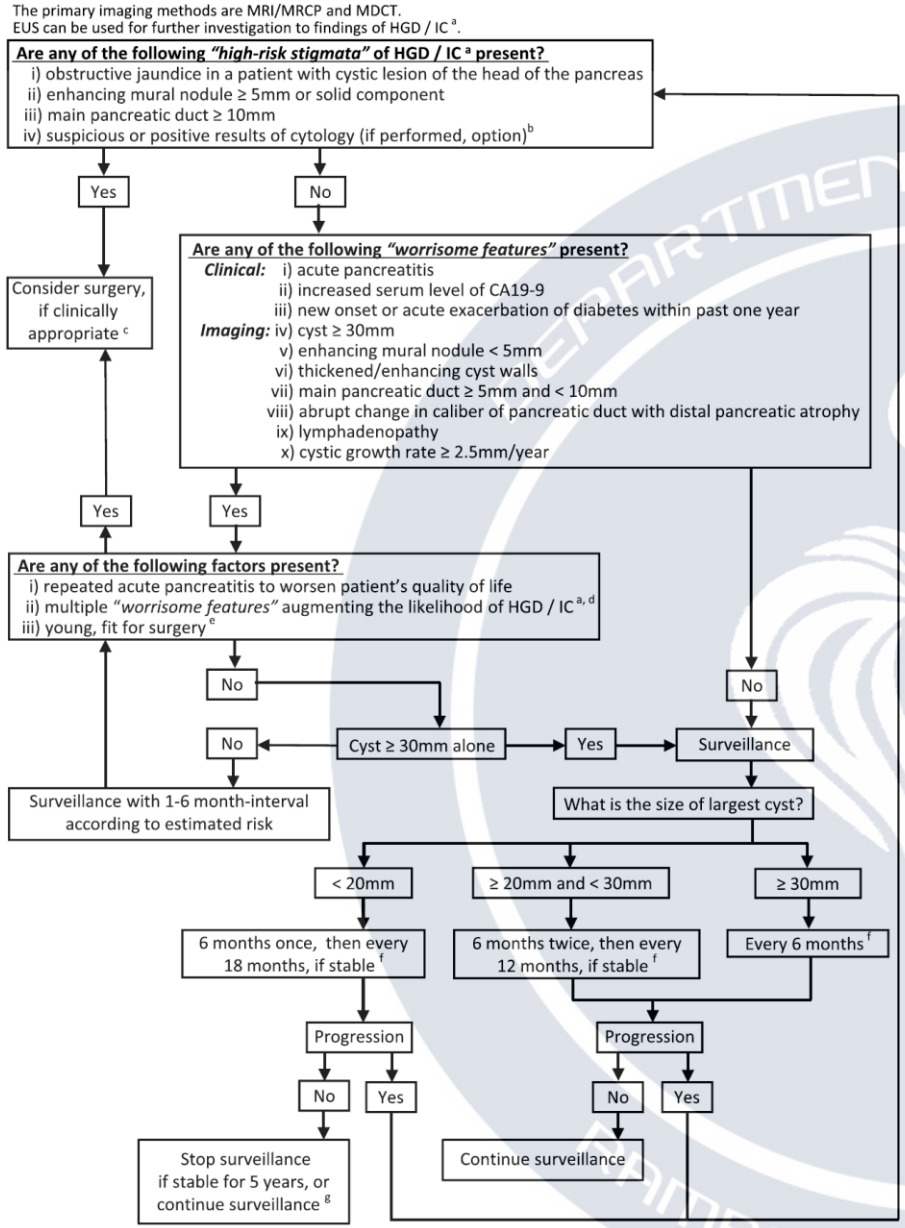


Fig. 3. Algorithm for the management of suspected BD-IPMN.
a. HGD; high-grade dysplasia, IC; invasive carcinoma. b. "Positive result" indicates "high-grade dysplasia" or "adenocarcinoma". c. See Fig. 5 showing operative principles and post operative surveillance. d. Nomogram can be referred. e. It is hard to define these ambiguous factors, and will be determined according to the physicians' viewpoints, patients' age, condition, life expectancy, and preference, cyst location, etc. f. Use combination of multi-detector computed tomography, magnetic resonance imaging/cholangiopancreatography, and endoscopic ultrasound, and blood examination including tumor marker/HbA1c, according to the institutional policy. g. Necessity of long-term surveillance remains unclear, and will be determined based on regional health economics, risk of concomitant ductal adenocarcinoma, and patients' age, condition, life expectancy, and preference, etc.

- Multiple worrisome feature
  - Presence of multiple WF has an additive effect on the risk of HGD/IC

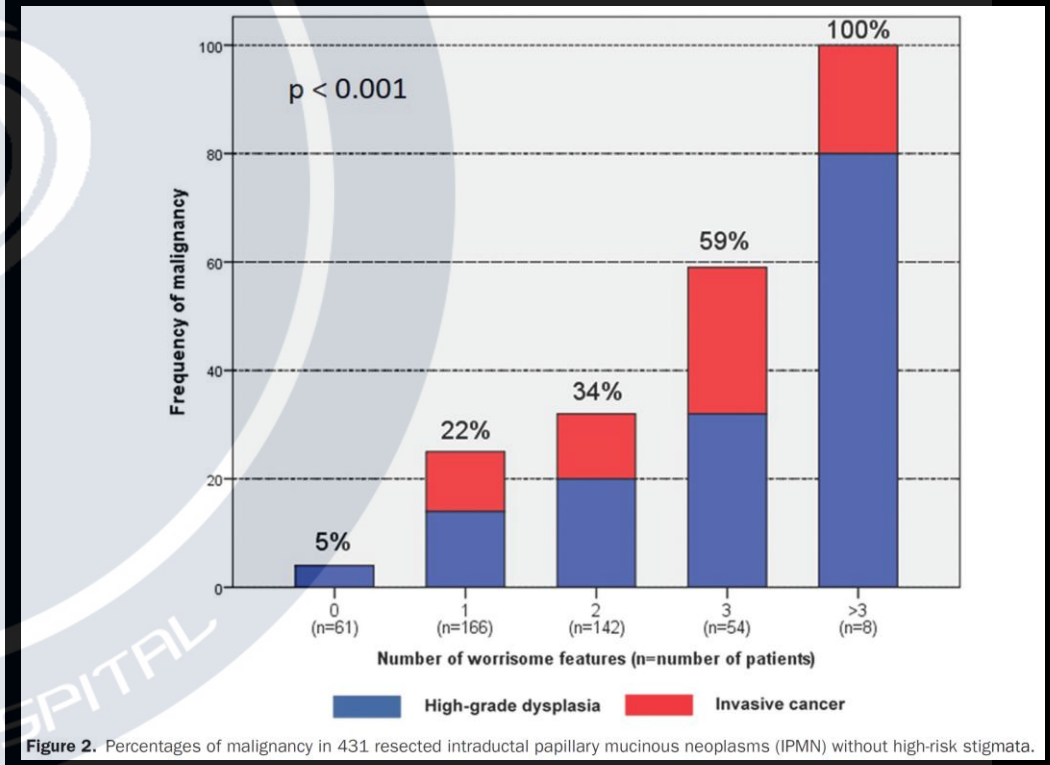


Figure 2. Percentages of malignancy in 431 resected intraductal papillary mucinous neoplasms (IPMN) without high-risk stigmata.

Zelga et al. Worrisome Features and Malignancy Risk in IPMN. J Am Coll Surg. Vol. 234, No. 6, June 2022

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Number of Worrisome Features and Risk of Malignancy in Intraductal Papillary Mucinous Neoplasm

Piotr Zelga, MD, PhD, Yasmin G Hernandez-Barco, MD, Motaz Qadan, MD, PhD, FACS, Cristina R Ferrone, MD, FACS, Avinash Kambadakone, MBBS, FSCBTMR, Nora Horick, MS, Asif Jah, MBBS, FRCS, Andrew L Warshaw, MD, FACS, Keith D Lillemoe, MD, FACS, Anita Balakrishnan MBBS, PhD, FRCS, Carlos Fernández-del Castillo, MD, FACS

- Journal of American College of Surgeon, 2022
- Retrospective studies
- 810 patients with IPMN who underwent pancreatic resection
- Determine the effect of multiple worrisome features

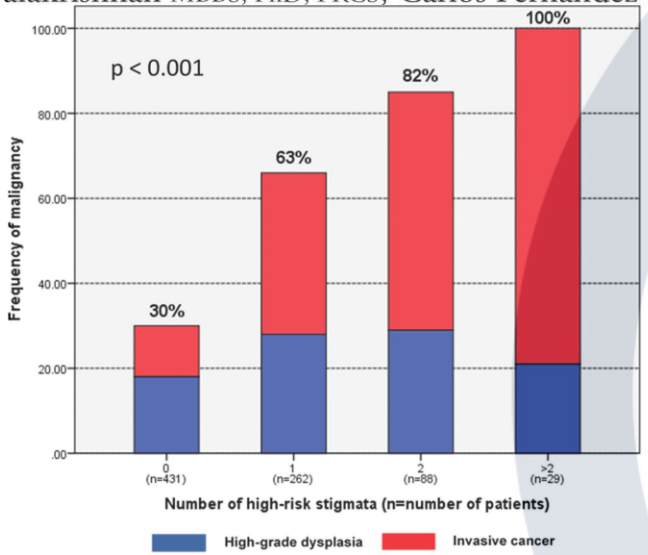
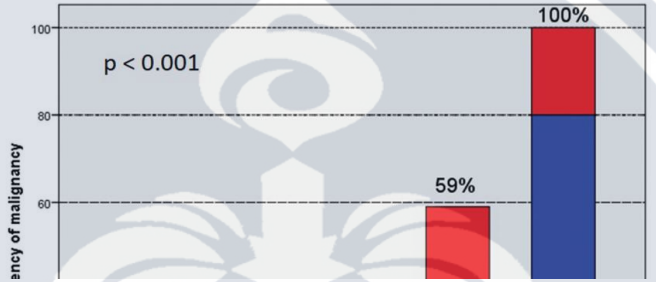


Figure 3. Percentages of malignancy according to the number of high-risk stigmata in 810 resected intraductal papillary mucinous neoplasms (IPMN).



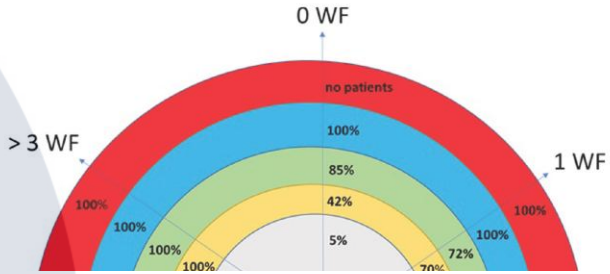


Table 3. Detailed Predictive Value for Each of High-Risk Stigmata and Worrisome Features from 2017 International Association of Pancreatology (IAP) Revised Guidelines

Factor	Number of patients	AUC	Sensitivity, %	Specificity, %	Relative risk, %	95% CI	PPV, %	NPV, %
High-risk stigmata								
Jaundice	93	0.578	19	96	1.84	1.63–2.07	83	54
Enhancing Mural Nodule ≥ 5 mm	119	0.588	23	94	1.78	1.57–2.01	80	55
MPD ≥ 10 mm	197	0.605	35	86	1.66	1.46–1.89	72	57
Worrisome feature								
Elevated serum CA 19-9	168	0.590	33	89	1.65	1.56–2.05	74	59
Lymphadenopathy	55	0.5340	11	97	1.64	1.40–1.92	79	52
Abrupt caliber change + distal atrophy	40	0.535	7	97	1.54	1.27–1.87	75	51
Enhancing thickened cyst wall	24	0.515	5	98	1.52	1.20–1.94	75	51
Enhancing mural nodule < 5 mm	35	0.516	6	97	1.39	1.10–1.77	69	51
MPD 5–9 mm	238	0.564	36	77	1.34	1.17–1.54	61	55
Acute pancreatitis	172	0.532	24	82	1.20	1.03–1.40	58	52
Cyst size ≥ 3cm	400	0.525	51	53	1.08	0.94–1.24	52	52
Cyst growth > 5mm/2years	81	0.509	9	89	0.90	0.71–1.16	46	50

AUC, area under curve; CA 19-9, cancer antigen 19-9; CI, confidence interval; MPD, main pancreatic duct; NPV, negative predictive value; PPV, positive predictive value.

- Presence of HRS in IPMN is associated with a very high likelihood of malignancy
- Additional WF increase this risk significantly
- When 3 or more are present, the risk is similar to that of HRS

Clinical Gastroenterology and Hepatology 2024;22:2413–2423

PANCREATOBILIARY

The Revised Kyoto Criteria and Risk of Malignancy Among Patients With Intraductal Papillary Mucinous Neoplasms

Tsuyoshi Hamada,[1,2,*] Hiroki Oyama,[1,*] Shuichi Tange,[1] Ryunosuke Hakuta,[1] Kazunaga Ishigaki,[1] Sachiko Kanai,[1,3] Yoshikuni Kawaguchi,[4] Kensaku Noguchi,[1] Tomotaka Saito,[1] Tatsuya Sato,[1] Tatsunori Suzuki,[1] Naminatsu Takahara,[1] Mariko Tanaka,[5] Kiyoshi Hasegawa,[4] Tetsuo Ushiku,[5] Yousuke Nakai,[1,3,§] and Mitsuhiro Fujishiro[1,§]

- 3336 patients diagnosed with IPMN
  - Examined short (< 6 mo) and long term risks of pancreatic carcinoma

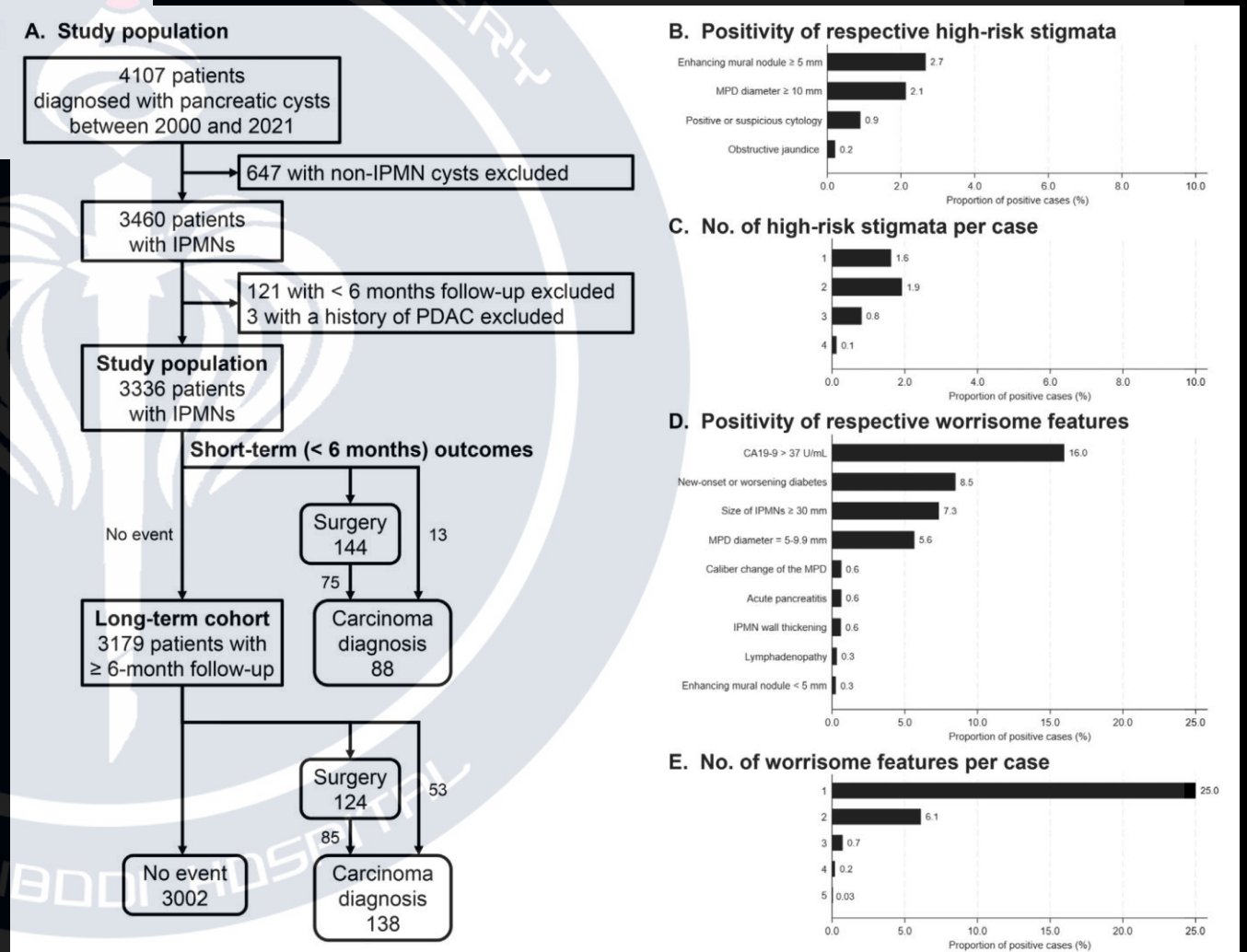


Figure 1. Study cohort of patients with IPMNs and risk profiles defined by the revised Kyoto criteria. (*A*) Flow diagram summarizing the selection of patients with IPMNs and clinical outcomes. (*B–E*) Distributions of high-risk stigmata and worrisome features in the whole cohort.

Table 2. Short-Term Risk of Pancreatic Carcinoma Overall by Baseline Risk Factors Defined by the Revised Kyoto Criteria (Analyses of Pancreatic Carcinoma Prevalence)

				OR (95% CI) for All Pancreatic Carcinoma	
		Patients	Events	Univariable	Multivariable[a]
Risk levels	None	2189	1 (0.05)	1 (reference)	1 (reference)
	WF	997	13 (1.3)	28.9 (3.78–221)	28.6 (3.73–219)
	HRS	150	74 (49)	2130 (292–15,500)	2269 (310–16,600)
HRS					
Mural nodule ≥5 mm	No	3247	42 (1.3)	1 (reference)	1 (reference)
	Yes	89	46 (52)	81.6 (48.8–137)	20.7 (10.9–39.4)
MPD diameter ≥10 mm	No	3265	56 (1.7)	1 (reference)	1 (reference)
	Yes	71	32 (45)	47.0 (27.5–80.4)	14.6 (6.94–30.6)
Positive or suspicious cytology[b]	No	145	16 (11)	1 (reference)	1 (reference)
	Yes	30	27 (90)	72.5 (19.8–266)	69.0 (17.0–280)
Obstructive jaundice	No	3329	81 (2.4)	1 (reference)	1 (reference)
	Yes	7	7 (100)	NA	NA
WFs					
CA19-9 >37 U/mL	No	2574	7 (0.3)	1 (reference)	1 (reference)
	Yes	489	7 (1.4)	5.33 (1.86–15.3)	6.90 (2.08–22.9)
MPD diameter = 5–9.9 mm	No	3006	4 (0.1)	1 (reference)	1 (reference)
	Yes	180	10 (5.6)	44.2 (13.7–142)	47.3 (14.2–158)
No. of positive features[c]	0	2081	1 (0.05)	1 (reference)	1 (reference)
	1	766	3 (0.4)	8.18 (0.85–78.7)	7.90 (0.82–76.1)
	2	187	4 (2.1)	45.5 (5.06–409)	39.4 (4.36–355)
	3–5	29	6 (21)	543 (62.8–4700)	413 (47.2–3620)
P_{trend}[d]				<.001	<.001

Values are n or n (%), unless otherwise indicated.

CA19-9, carbohydrate antigen 19-9; CI, confidence interval; HRS, high-risk stigma; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; NA, not available; OR, odds ratio; WF, worrisome feature.

[a]In addition to an exposure variable of interest, the multivariable model initially included the following variables except for the exposure variable or related variables: age (continuous), sex (female vs male), year of diagnosis (continuous), CA19-9 (continuous, log-transformed), CEACAM5 (carcinoembryonic antigen, continuous, log-transformed), the location of IPMNs (head vs body-tail vs multifocal), the size of IPMNs (continuous), the number of IPMNs (1 vs 2–5 vs ≥6), MPD diameter (continuous), and mural nodule (absent vs present). A backward elimination with the threshold *P* of .05 was conducted to select variables for the final model. The variables that remained in the final models were described in Supplementary Table 2.

[b]Cases with available cytology data were included.

[c]The IPMN growth rate was not considered.

[d]Calculated by entering the number of worrisome features (continuous, 0–5) in the model.

- Short term risk of pancreatic carcinoma
  - HRS : OR 2269
  - WF : 28.6

Table 3. Long-Term Risk of Pancreatic Carcinoma Overall by Baseline Worrisome Features Defined by the Revised Kyoto Criteria (Analyses of Pancreatic Carcinoma Incidence)

					SHR (95% CI) for All Pancreatic Carcinoma	
		Patients	Events	Person-Years	Univariable	Multivariable[a]
MPD diameter = 5–9.9 mm	No	2987	107 (3.6)	21,355	1 (reference)	1 (reference)
	Yes	158	24 (15)	856	5.15 (3.27–8.09)	3.46 (2.04–5.89)
Acute pancreatitis	No	3128	127 (4.1)	22,128	1 (reference)	1 (reference)
	Yes	17	4 (24)	82	6.56 (2.50–17.2)	5.65 (1.86–17.2)
IPMN growth ≥2.5 mm/y[b]	No	2195	69 (3.1)	17,210	1 (reference)	1 (reference)
	Yes	131	14 (11)	764	4.32 (2.43–7.66)	3.83 (2.14–6.86)
No. of positive features[c]	0	2077	63 (3.0)	15,292	1 (reference)	1 (reference)
	1	750	35 (4.7)	5001	1.61 (1.07–2.42)	1.43 (0.93–2.19)
	2	174	14 (8.1)	1087	2.87 (1.60–5.15)	2.17 (1.17–4.05)
	3–4	21	6 (29)	101	12.4 (5.14–29.7)	10.1 (4.20–24.5)
P_{trend}[d]					<.001	<.001

Values are n or n (%), unless otherwise indicated.
CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; SHR, subdistribution hazard ratio.
[a]In addition to an exposure variable of interest, the multivariable model initially included the following variables except for the exposure variable or related variables: age (continuous), sex (female vs male), year of diagnosis (continuous), carbohydrate antigen 19-9 (continuous, log-transformed), CEACAM5 (carcinoembryonic antigen, continuous, log-transformed), the location of IPMNs (head vs body-tail vs multifocal), the size of IPMNs (continuous), the number of IPMNs (1 vs 2–5 vs ≥6), MPD diameter (continuous), and mural nodule (absent vs present). A backward elimination with the threshold *P* of .05 was conducted to select variables for the final model. The variables that remained in the final models were described in Supplementary Table 9.
[b]Patients with available imaging studies at baseline and 1–3 years of follow-up were analyzed.
[c]The IPMN growth rate was not considered.
[d]Calculated by entering the number of worrisome features (continuous, 0–4) in the model.

- Long-term risk of pancreatic carcinoma
  - Increasing number of positive features was associated with a higher incidence of pancreatic carcinoma

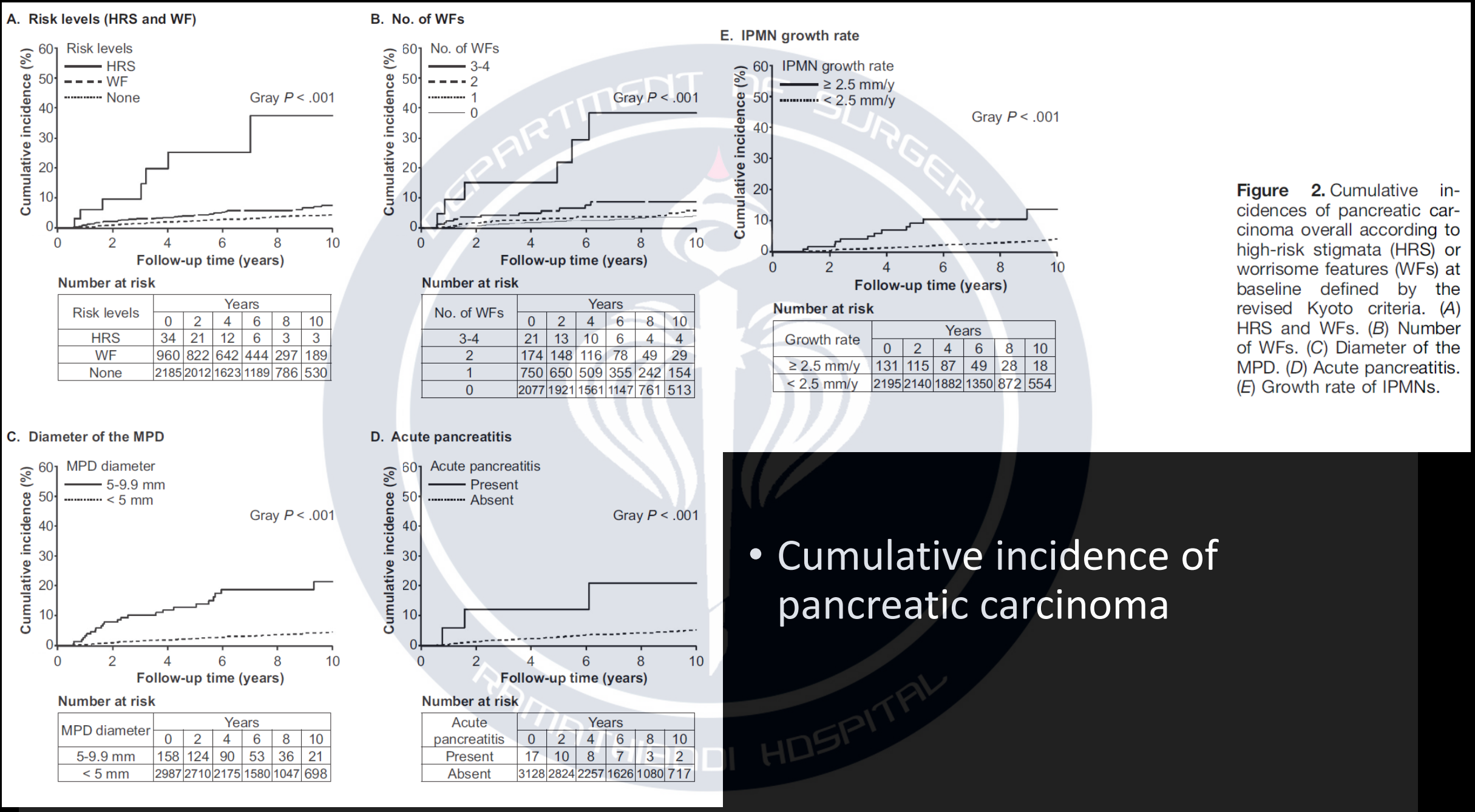


Figure 2. Cumulative incidences of pancreatic carcinoma overall according to high-risk stigmata (HRS) or worrisome features (WFs) at baseline defined by the revised Kyoto criteria. (*A*) HRS and WFs. (*B*) Number of WFs. (*C*) Diameter of the MPD. (*D*) Acute pancreatitis. (*E*) Growth rate of IPMNs.

- Cumulative incidence of pancreatic carcinoma

Intraductal Papillary Mucinous Neoplasm

- Multifocal IPMN
  - Incidence of multifocal BD-IPMNs : 20 - 40 %
  - Majority of these lesions arise independently based on the “field defect theory”
    - IPMNs may represent genomic instability of the entire pancreas
  - Multifocality does not increase the risk of HGD/IC of IPMNs
    - Management -> Determined by the highest risk lesions
  - Resection only of the high-risk lesion should be attempted, and others should be left untreated to avoid prophylactic total pancreatectomy

[1] T. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270v

Intraductal Papillary Mucinous Neoplasm

- Concomitant PDAC
  - Cumulative risk of concomitant PDAC increases year-by-year
    - Yearly incidence : 0.4 - 1.0 %
  - 3 to 5-fold higher than that of the age-matched population
    - IPMN : risk factor for PDAC, typically small branch duct IPMN

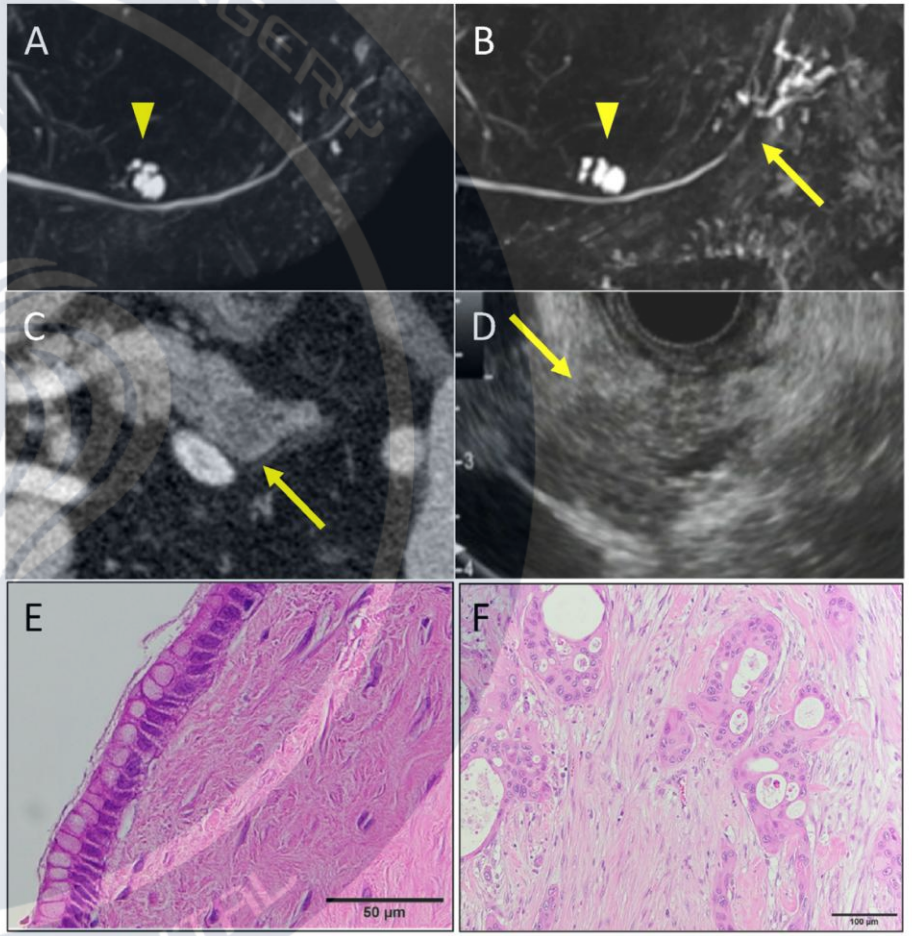


Fig. 6. Pancreatic ductal adenocarcinoma concomitant with BD-IPMN.
A. Magnetic resonance cholangiopancreatography (MRCP) shows 10 mm of BD-IPMN (arrow head) in the pancreas body. b. MRCP shows no change of BD-IPMN (arrow head) 14 months later, but stenosis of main pancreatic duct (MPD) (arrow) with distal dilation is noted. C. Computed tomography demonstrates a low-density solid lesion (arrow), 18 mm in diameter, in the pancreas tail. D. Endoscopic ultrasonography demonstrates a hypoechoic irregular solid lesion (arrow), 20 mm in diameter, in the pancreas tail. E. Distal pancreatectomy was performed. Pathological result of cystic lesion indicates low grade dysplasia of IPMN with gastric subtype. F. Pathological result of slid lesion indicates well to moderately differentiated tubular adenocarcinoma. There is neither topological communication nor transition area between cystic and solid lesions, and therefore, solid lesion is considered as pancreatic ductal adenocarcinoma concomitant with BD-IPMN.

[1] I. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270v

Intraductal Papillary Mucinous Neoplasm

- Extrapancreatic neoplasm
  - Incidence range from 20 to 30 %
    - 80 % : Found during initial assessment of or during surveillance after resection of extra-pancreatic neoplasms
    - 20 % : Diagnosed during surveillance of IPMN
  - The distribution of the involved extra-pancreatic organs differs among races and counties
    - Skin, breast, kidney, and prostate in western countries
    - Gastro-intestine in Asian
  - IPMN tends to develop in elderly patients -> Incidence of extra-pancreatic neoplasm in patients with IPMN is comparable to that of the population based incidence of each country
  - No additional screening for extra-pancreatic neoplasms is necessary for patients who have IPMN

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270v

Intraductal Papillary Mucinous Neoplasm

- Surgical management
  - BD-IPMN
    - Usually be completely removed by partial pancreatectomy
      - Can be selected when suspicion for IC is low (based on preoperative features and intraoperative findings)
    - Radical pancreatectomy with lymph node dissection
      - Performed when IC is suspected
  - Mixed and MD-IPMN
    - Indication for radical pancreatectomy or organ-preserving pancreatectomy is same with BD-IPMN based on the degree of suspicious of IC
    - Evaluation of extension of main pancreatic duct : goal of obtaining negative margin
      - Frozen section showed presence of IC/ HGD -> additional resection is recommended
      - Normal epithelium or LGD -> Additional resection is unneccessary

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

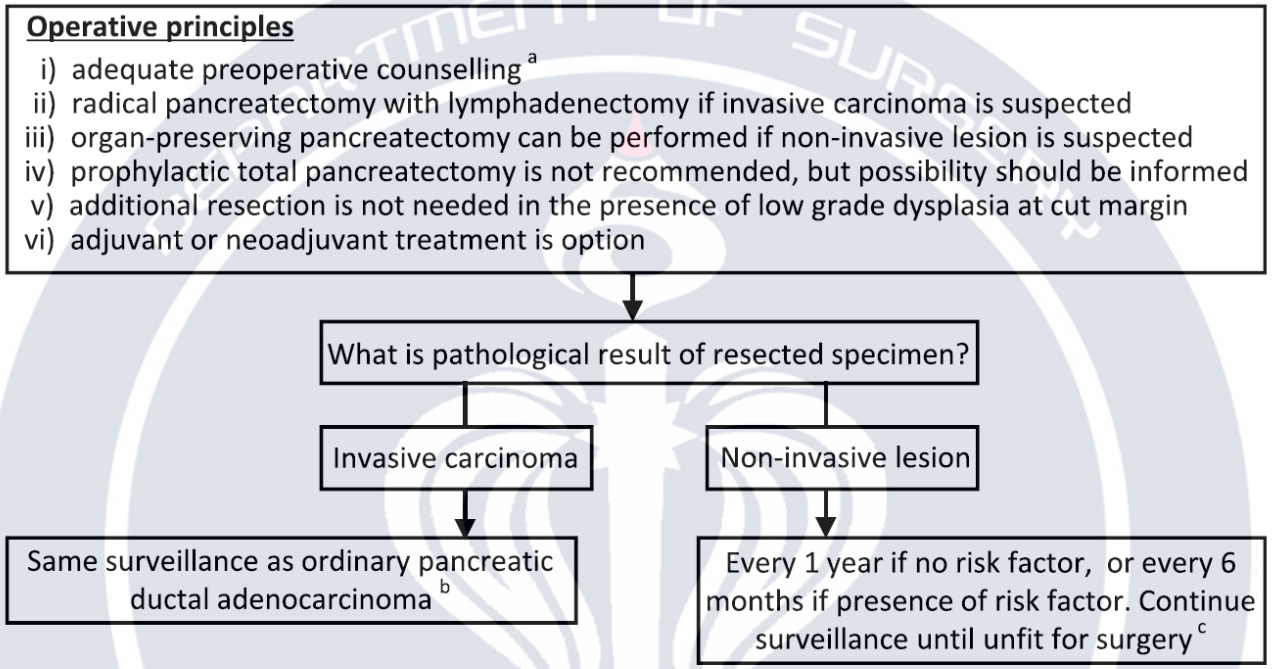


Fig. 5. Operative principles and postoperative surveillance for IPMN.
a. Following issues specific to IPMN should be informed to all patients at preoperative counselling in addition to usual perioperative events; (1) surgeons are usually going to make surgical choices in the operating room without knowing what the final diagnosis will be, (2) the resection might be extended up to the point of a total pancreatectomy if the operative findings show presence of high grade dysplasia/invasive cancer in the margins, (3) low grade dysplasia at cut margin or small indolent branch duct IPMN might be left in the remnant pancreas during partial pancreatectomy, and (4) long-term postoperative surveillance is needed even after partial pancreatectomy for low grade dysplasia with negative surgical margin because of unique characteristics of IPMN such as multifocality and skip progression. b. Follow the most fit protocol which is frequently used in each country/region. c. Pay attention to remnant pancreas for the possible development of clinically significant remnant pancreatic lesions, and risk factors for them are pathological result of high-grade dysplasia and the presence of family history of pancreatic cancer (**CQ3-4**). Use combination of physical examination, imaging study (multi-detector computed tomography, magnetic resonance imaging/cholangiopancreatography, and endoscopic ultrasound), and blood examination including tumor marker/HbA1c, according to the institutional policy. In patients undergoing total pancreatectomy for non-invasive lesion, IPMN-specific surveillance can be stopped if uneventful during 5-year postoperative surveillance.

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Risk of misdiagnosis and overtreatment in patients with main pancreatic duct dilatation and suspected combined/main-duct intraductal papillary mucinous neoplasms

Stefano Crippa, MD, PhD,[a] Ilaria Pergolini, MD,[a] Corrado Rubini, MD,[b] Paola Castelli,[c] Stefano Partelli, MD, PhD,[a] Claudio Zardini, MD,[d] Giorgia Marchesini, MD,[b] Giuseppe Zamboni, MD,[c,e] *and* Massimo Falconi, MD,[a] *Ancona, Negrar, and Verona, Italy*

- Surgery, 2016
- Retrospective analysis of 93 patients who were resected for combined/main duct IPMN
- Aim to evaluate the presence and extension of MPD involvement by tumor or OCP

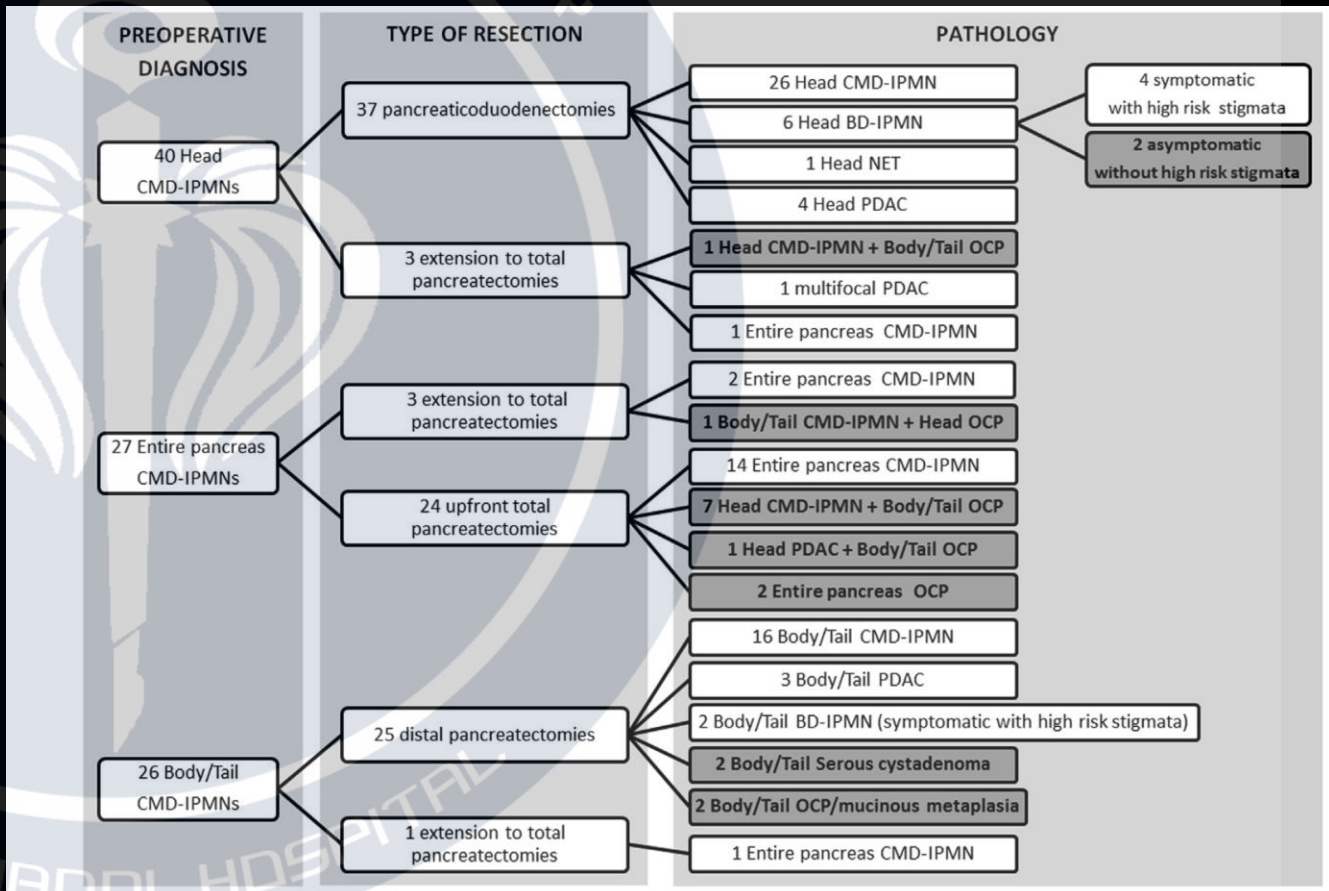


Fig 1. Course of 93 patients with suspected combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs) from the preoperative diagnosis to pathology. Cases of overtreatment are highlighted. *BD-IPMN*, Branch-duct intraductal papillary mucinous neoplasm; *NET*, G2 neuroendocrine tumor grading 2; *OCP*, obstructive chronic pancreatitis; *PDAC*, pancreatic ductal adenocarcinoma.

- Plan of resection -> according to location of tumor
- Extension of resection -> based on preop workup, frozen section of pancreatic margin
- Total pancreatectomy -> decision based on individualized pt age and comorbid

- Total cohort : over treatment in 18 cases (19%)

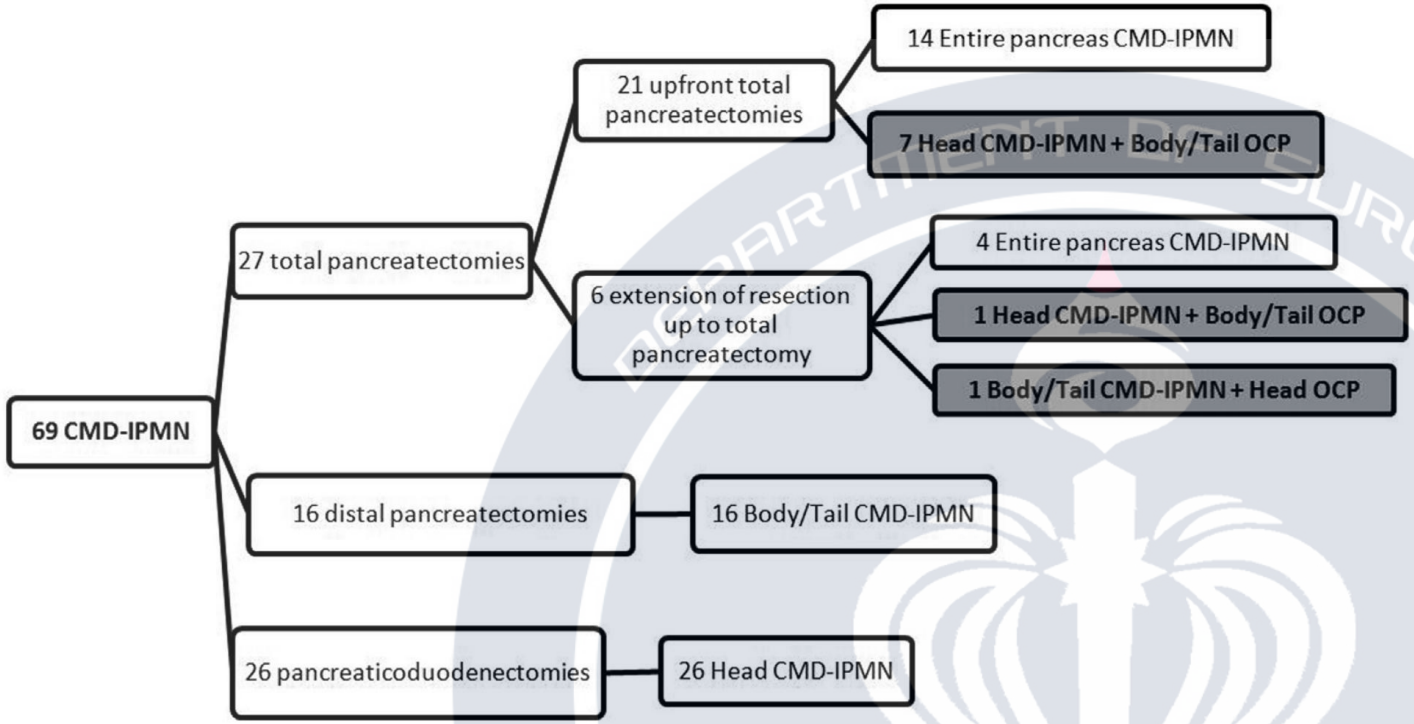


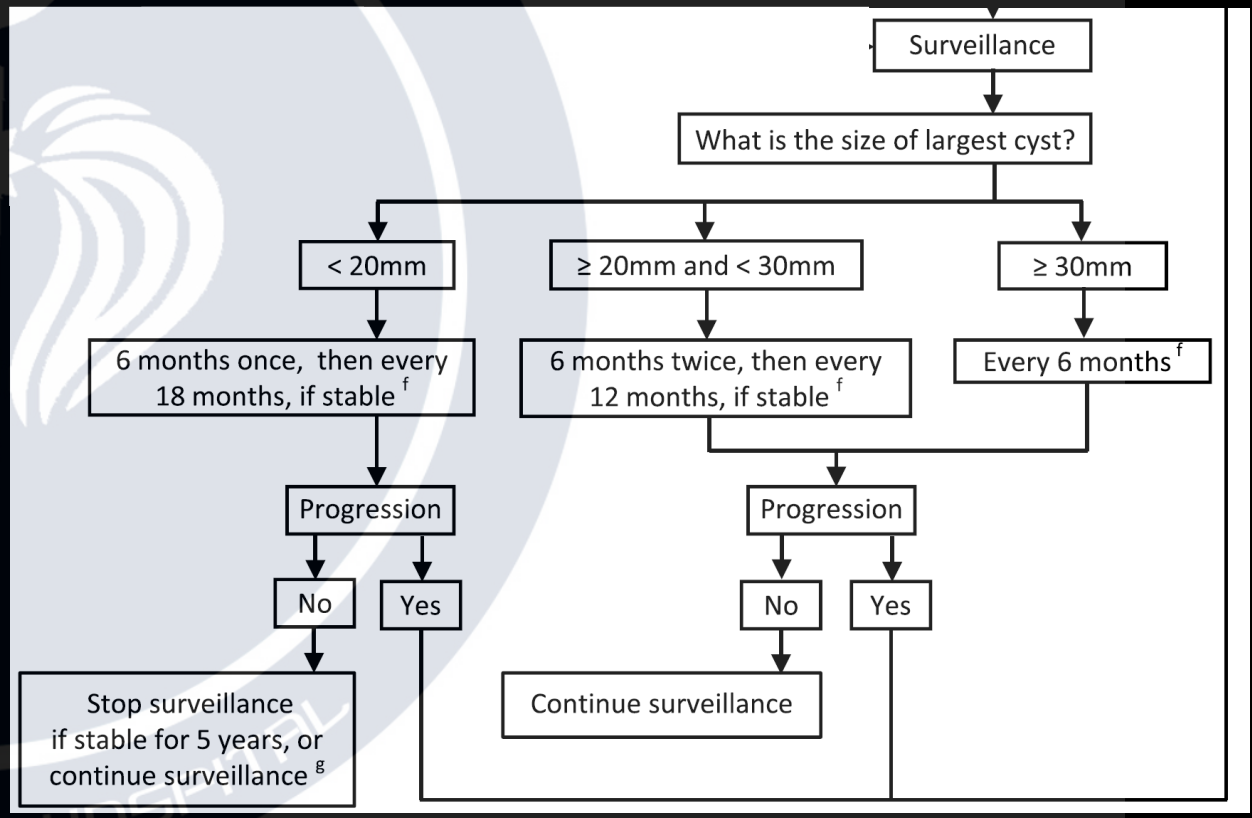
Fig 2. The flow chart of 69 pathologically confirmed combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs). Operative procedures and final pathology with localization of CMD-IPMN in the surgical specimen. Cases of too extensive resection are highlighted. *OCP*, Obstructive chronic pancreatitis.

- The median size of MPD in IPMN-involved areas was 12 mm
  - Compared with 7 mm in areas where only OCP was found, ($P < 0.05$)
- Asymptomatic patients with “worrisome” MPD dilatation (5–9 mm)
  - Radiologic observation

- Considerable risk of misdiagnosis and possible overtreatment in patients with preoperative diagnosis of CMD-IPMNs
- EUS with FNA -> Evaluate suspected multifocal disease and to find “worrisome features” and new diagnostic strategies should be considered
  - Advanced endoscopic techniques such as pancreatoscopy
- Partial pancreatectomy with frozen section should be performed instead of upfront total pancreatectomy

Intraductal Papillary Mucinous Neoplasm

- Surveillance
  - Non-resected IPMN
    - Incidence of transformation of indolent BDIPMN to HGD/IC increases year-by-year
      - 0.94-3.3 % by 5-years
      - 2.3-6.6 % by 10 years
      - 7.6-15.0 % at 15- years
    - Transformation occurs more frequently in IPMN with larger cyst size or larger MPD diameter at the time of the initial diagnosis



1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Intraductal

Mechanisms for development of lesions in the remnant pancreas

1. New development of multifocal IPMN or progression of multifocal untreated IPMN in the remnant pancreas
2. Recurrence of initially resected IPMN in the remnant pancreas
3. Development of PDAC concomitant with IPMN

- Surveillance
  - After resection
    - Median cumulative 5-year incidence of clinically significant remnant pancreatic lesions is 10 % (range, 0-21 %)
      - Risk continues to increase even after 5-years
      - Postoperative surveillance should be continued until the patient is surgically unfit
    - Risk factor : HGD at the initial pathology, Family history of PDAC
    - After total pancreatectomy for non-invasive lesion
      - IPMN-specific surveillance can be stopped if uneventful during 5-year postoperative surveillance
    - Imaging findings to predict the possible presence of clinically significant remnant pancreatic lesions are presence of solid mass, MPD dilation, and growth of the cyst

1. Ohtsuka et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology 24 (2024) 255-270

Intraductal Papillary Mucinous Neoplasm

- Pancreatic fistula from IPMN
  - Fistulas penetrating adjacent organs
    - Duodenum, stomach, and common bile duct
  - Pathogenesis
    - Direct invasion
    - Mechanical penetration
    - Autodigestion
  - MD-IPMN and mixed type IPMN accounted for majority of IPMN with fistula formation (82%)
  - Aggressive surgical strategies
    - Extended pancreatectomy and simultaneous resection of infiltrated organs

Table 1

Clinicopathological data of intraductal papillary mucinous neoplasm of the pancreas with fistula formation.

		Type		Malignant component			Invasion around fistula		
Affected organs	Case	MD/mixed	BD	Yes	No	N/A	Yes	No	N/A
Stomach	18	17	1	7	7	4	1	9	8
Duodenum	12	9	3	7	2	3	1	2	9
Bile duct	21	18	3	12	2	7	1	9	11
Small intestine	1	0	1	0	0	1	0	0	1
Colon	1	1	0	1	0	0	0	1	0
Portal vein	1	1	0	1	0	0	1	0	0
Stomach, duodenum	11	10	1	7	2	2	5	2	4
Stomach, bile duct	1	1	0	0	1	0	0	1	0
Stomach, colon	2	0	2	2	0	0	1	0	1
Stomach, spleen	1	1	0	1	0	0	0	1	0
Stomach, chest wall	1	1	0	1	0	0	1	0	0
Duodenum, bile Duct	5	2	3	2	0	3	1	0	4
Duodenum, colon	1	1	0	0	0	1	0	0	1
Duodenum, small intestine	1	1	0	1	0	0	0	1	0
Stomach, duodenum, bile duct	3	3	0	2	0	1	0	0	3
Stomach, duodenum, colon	1	0	1	1	0	0	1	0	0
Stomach, duodenum, small intestine	1	1	0	0	0	1	1	0	0
Stomach, duodenum, colon, spleen	1	1	0	1	0	0	0	0	1
Total number	83	68	15	46	14	23	14	26	43

BD = branch-duct, MD = main-duct, N/A = not applicable.

Shishido et al. Fistula formation into other organs secondary to intraductal papillary mucinous neoplasm of the pancreas A case report and literature review. Medicine (2023) 102:27

Intraductal Papillary Mucinous Neoplasm

- Pseudomyxoma peritonei arising from IPMN
  - Extremely rare
  - Arise from disseminated IPMN cells
    - Spontaneous rupture
    - Leakage of mucin during pancreatic resection
  - First-line treatment for PMP is reported to be CRS and HIPEC regardless of the primary lesion

Table 2
Summary of PMP derived from pancreatic IPMN.

Reference	Year	Age/ Sex	Site	Size (cm)	Morphology	Histological Invasiveness	Histological classification	Predominant differentiation	Surgery	Other treatment	Survival* (month)
Zanelli	1998	49/ M	N/D	N/D	N/D	N/D	N/D	N/D	1. PPPD 2. TP 3. RP mass debulking	None	A (>83)
Kurihara	2000	74/ M	Head	N/D	MD or Mixed	INV	Adeno (MPD) /Muc (stroma)	N/D	PD	None	D (62)
Mizuta	2005	53/ M	Tail	2	MD or Mixed	INV suspected	Muc	N/D	OMT/HIPEC	IP (CDDP)/SC (GEM) after OMT	A (>24)
Imaoka	2006	64/ M	Body/ Tail	N/D	Mixed	INV	Adeno (Body) /Muc (Tail)	N/D	DP	None	A (>6)
Lee	2007	55/ M	Body	8.5	BD	INV	Adeno	N/D	DP	SC (GEM, CDDP) after DP	A (>3)
Nepka	2009	82/ M	Head	2	MD	N/D	N/D	N/D	None	None	A (>12)
Imaoka	2012	74/F	Tail	4	MD	INV	N/D	N/D	1. DP 2. TP	None	D (42)
		56/ M	Head	N/D	MD	HGD	Adeno	N/D	1.PPPD 2. TP	None	A (>48)
Rosenberger	2012	75/ M	Body/ Tail	20	MD	LGD	N/D	N/D	DP	None	A (>48)
		75/ M	Head	3.5	MD	INV	Muc	N/D	PPPD	None	D (43)
Arjona-Sanchez	2014	63/F	Tail	N/D	MD	INV	Adeno	N/D	1. TP 2. CRS/HIPEC	SC (Cape) after CRS/HIPEC	A (>70)
Sugiura	2015	72/F	Body/ Tail	12	MD	INV	N/D	N/D	DP	SC (S-1) after DP	A (>12)
Hackeng	2019	62/ M	Body	N/D	MD	INV	Muc	N/D	TP	None	A (>4)
Sirisai	2019	69/ M	Tail	10	MD	INV	Muc	N/D	1. CRS/HIPEC 2. 2nd CRS/HIPEC	Proton beam radiation after 2nd CRS/HIPEC	D (93)
		54/ M	Tail	5	MD	INV	N/D	N/D	1. DP 2. ExRHC/OMT/PTN 3. CRS/HIPEC	1. SC (S-1) after DP 2. SC after ExRHC 3. SC (CPT-11, S-1) after CRS/HIPEC	A (50)
		69/ M	Tail	6	MD	INV	N/D	N/D	DP/SPL/RHC/TG/PTN	SC	A (7)
Present Case 1	2019	75/ M	Body/ Tail	10	MD	HGD/INV suspected	Muc suspected	Intestinal type suspected	OMT	None	D (3)
Present Case 2	2019	51/F	Body	N/D	Mixed	HGD	N/D	Intestinal type	1. Lap-DP 2. Lap-HIPEC 3. OMT/BSO 4. ExRHC/OMT/PTN	SC (GEM, nab-PTX) after lap-HIPEC	A (>33)

*: Survival time from first operation.
Abbreviations: A, alive; Adeno, ductal adenocarcinoma; BD, brunch duct type; BSO, bilateral salphingo-oophorectomy; Cape, capecitabine; CDDP, cisplatin; CPT-11, irinotecan; CRS, cytoreductive surgery; D, died; DP, distal pancreactomy; ExRHC, extended right hemicolectomy; GEM, Gemcitabine; HGD, IPMN with high-grade dysplasia; HIPEC, hyperthermic intraperitoneal chemotherapy; INV, IPMN with an associated invasive carcinoma; IP, intraperitoneal chemotherapy; Lap, laparoscopic; LGD, IPMN with low-grade dysplasia; MD, main duct type; Mixed, mixed type; MPD, main pancreatic duct; Muc, Mucinous adenocarcinoma; N/D, no data; nab-PTX, nab-Paclitaxel; OMT, omentectomy; PD, pancreatoduodenectomy; PPPD, pylorus preserving pancreatoduodenectomy; PTN, peritonectomy; RHC, right hemicolectomy; SC, systemic chemotherapy; SPL, splenectomy; S-1, Tegafur/gimeracil/oteracil; TG, total gastrectomy; TP, total pancreactomy; 5-FU, fluorouracil.

A. Kataoka et al. Immunohistochemical staining as supportive diagnostic tool for pseudomyxoma peritonei arising from intraductal papillary mucinous neoplasm: A report of two cases and literature review. Pancreatology 20 (2020) 1226-1233

Solid Pseudopapillary Neoplasm

- Approximately 0.9%-2.7% of all exocrine pancreatic neoplasms and 5% of cystic pancreatic neoplasms
  - Wide age range from 2 to 85 years , the mean age at presentation is 28.5 years
  - Predominantly in young women with a female-male ratio of 9.8:1
- May involve any portion of the pancreas but are slightly more common in the tail of the pancreas
- Rarely, can arise in extra pancreatic sites including the omentum, mesentery, retroperitoneum, ovary, stomach, and duodenum
- Distant metastases : 7.7% of cases
- Lymph node metastases : 1.6% of cases
  - Occasionally, directly infiltrate adjacent structures including the portal vein, duodenum, and spleen

Ayo O Omiyale. Solid pseudopapillary neoplasm of the pancreas. World J Hepatol 2021 August 27; 13(8): 896-903

Solid Pseudopapillary Neoplasm

- Gross appearance
  - Mostly round solitary masses with fibrous pseudocapsule
  - Large tumors ranging from 0.5 cm to 25 cm (mean, 10 cm)
  - Typically solid with varying proportion of cystic degeneration
  - Well-demarcated fleshy cut surface with hemorrhagic and necrotic areas
- Microscopic
  - Poorly cohesive epithelial cells forming solid and pseudopapillary structures
  - Differential Dx with other pancreatic tumors is challenging -> IHC

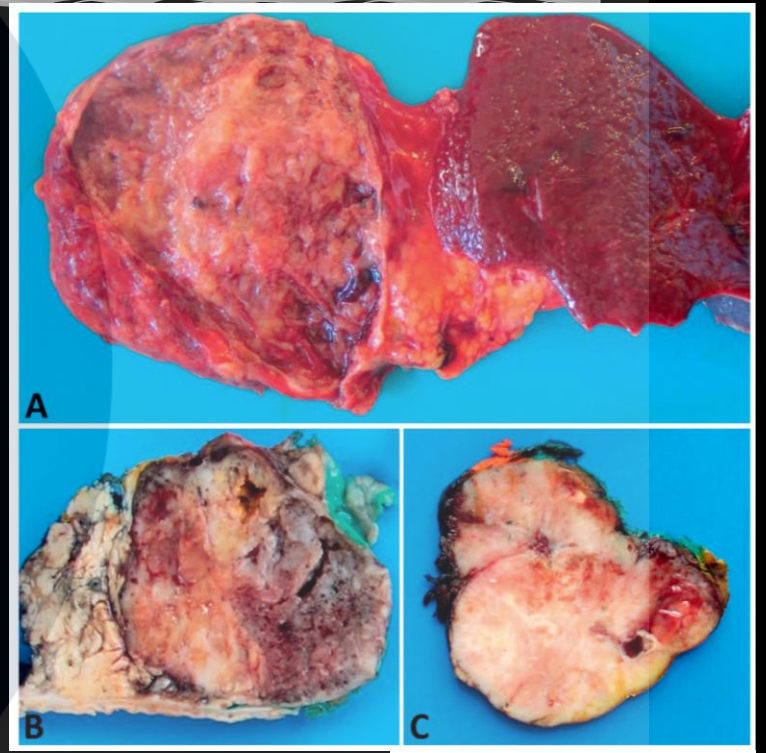


Figure 3. *Solid pseudopapillary neoplasms are round, well-demarcated neoplasms. Some cases are completely cystic, as shown in image A (on the left the spleen). Other cases can show a variable combination of solid, cystic, hemorrhagic, and necrotic areas (B), whereas more rarely SPNs can be predominantly solid (C). Courtesy of Prof Christine Sempoux, MD, PhD, Institute of Pathology, University Hospital of Lausanne, Lausanne, Switzerland.*

Table 3. Proposed Immunohistochemical Panel for the Diagnosis of Pancreatic Solid Pseudopapillary Neoplasm

Positive markers
β-catenin
CD99 (dotlike pattern)
Negative markers
Chromogranin
Trypsin
BCL10
E-cadherin (or nuclear)[a]

[a] The lack of, or nuclear immunoreactivity for, E-cadherin depends on the antibody used (see text).

Ayo O Omiyale. Solid pseudopapillary neoplasm of the pancreas. World J Hepatol 2021 August 27; 13(8): 896-903
La Rosa & Bongiovanni. Pancreatic Solid Pseudopapillary Neoplasm Key Pathologic and Genetic Features. Arch Pathol Lab Med—Vol 144, July 2020

Solid Pseudopapillary Neoplasm

- Presentation
  - Asymptomatic (38.1%)
  - Symptoms
    - Most common : Abdominal pain or discomfort
    - Other symptoms include abdominal mass, weight loss, jaundice, anorexia, fever, fatigue, abdominal discomfort, nausea, and vomiting
    - Rarely, may present with spontaneous or traumatic rupture of the tumor leading to hemoperitoneum

Ayo O Omiyale. Solid pseudopapillary neoplasm of the pancreas. World J Hepatol 2021 August 27; 13(8): 896-903

Solid Pseudopapillary Neoplasm

- Cross-sectional imaging
- CT
  - Well demarcated large heterogeneous masses with variably solid and cystic appearances
  - Enhancing solid areas are mostly peripheral, with cystic areas tending to be centrally located
    - Cystic component caused by hemorrhagic degeneration
  - Peripheral or central stippled calcifications may be identified in the tumor
- MRI
  - Well-defined mass with heterogeneous signal intensity on T1- and T2- weighted images indicative of the variably solid and cystic nature
  - High signal intensity on T1-weighted -> Areas of hemorrhagic necrosis or debris
  - The solid component of the tumor : Iso- to low signal intensity on T1-weighted images and slightly high signal intensity on T2-weighted images

Ayo O Omiyale. Solid pseudopapillary neoplasm of the pancreas. World J Hepatol 2021 August 27; 13(8): 896-903

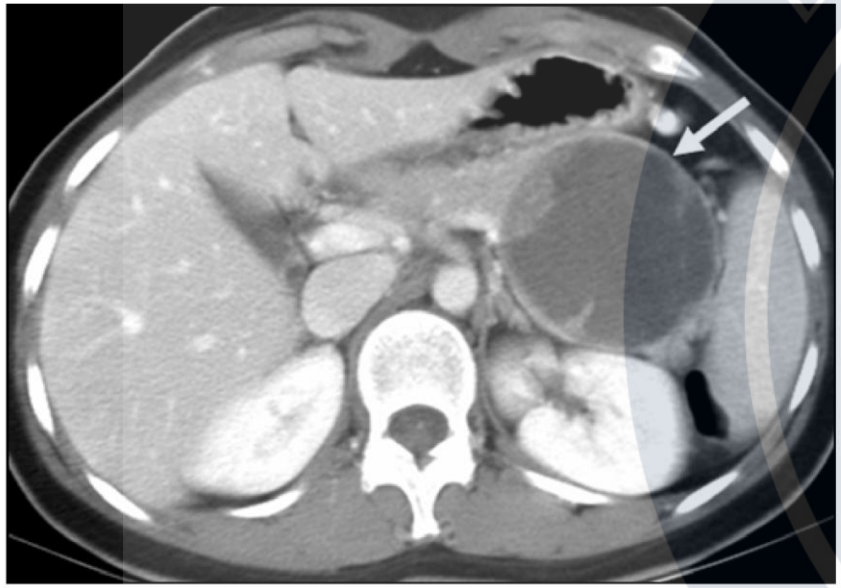


Fig. 1—19-year-old woman with palpable abdominal mass of solid pseudopapillary tumor. Contrast-enhanced CT scan shows well-encapsulated heterogeneous mass (*arrow*) in tail of pancreas.

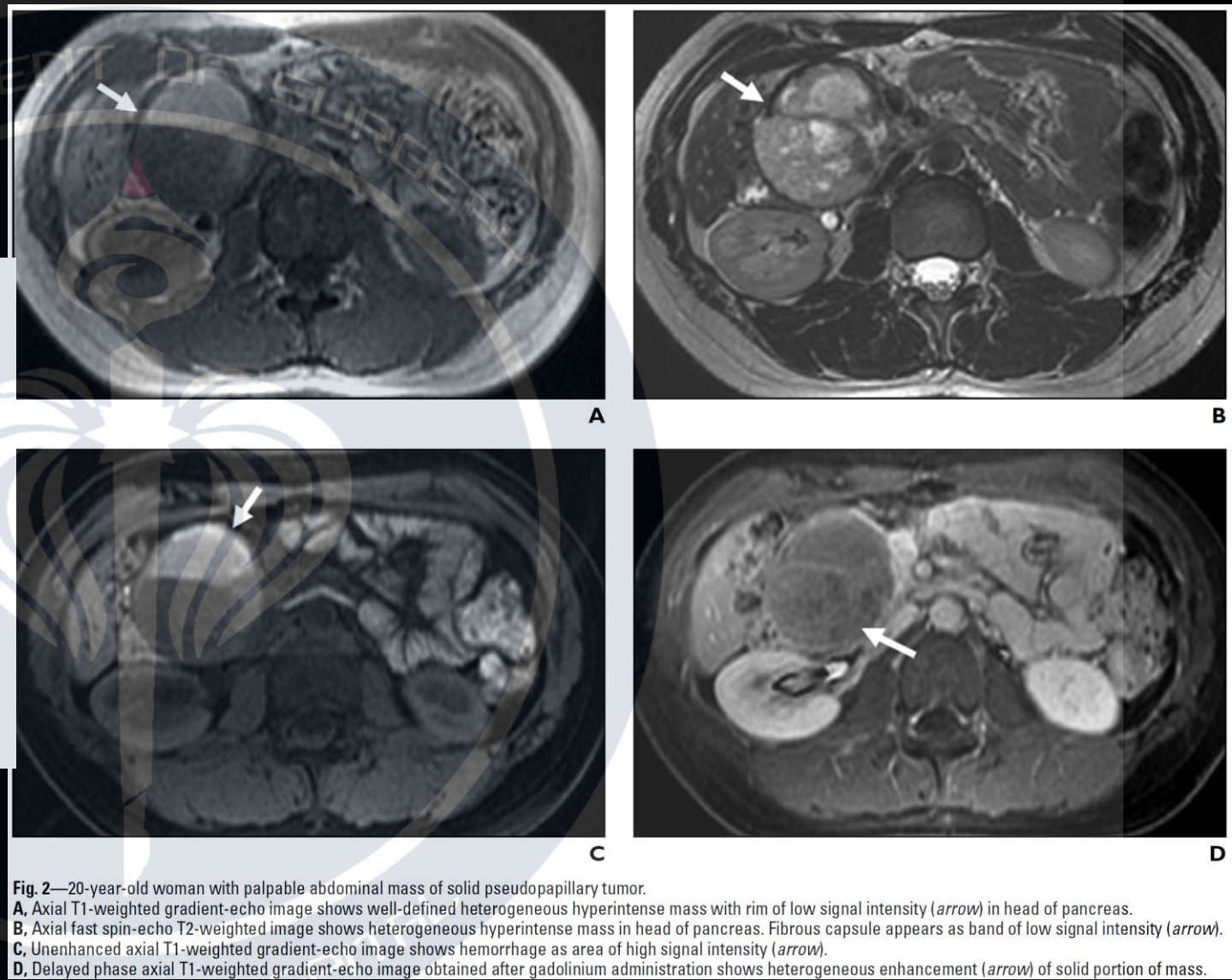
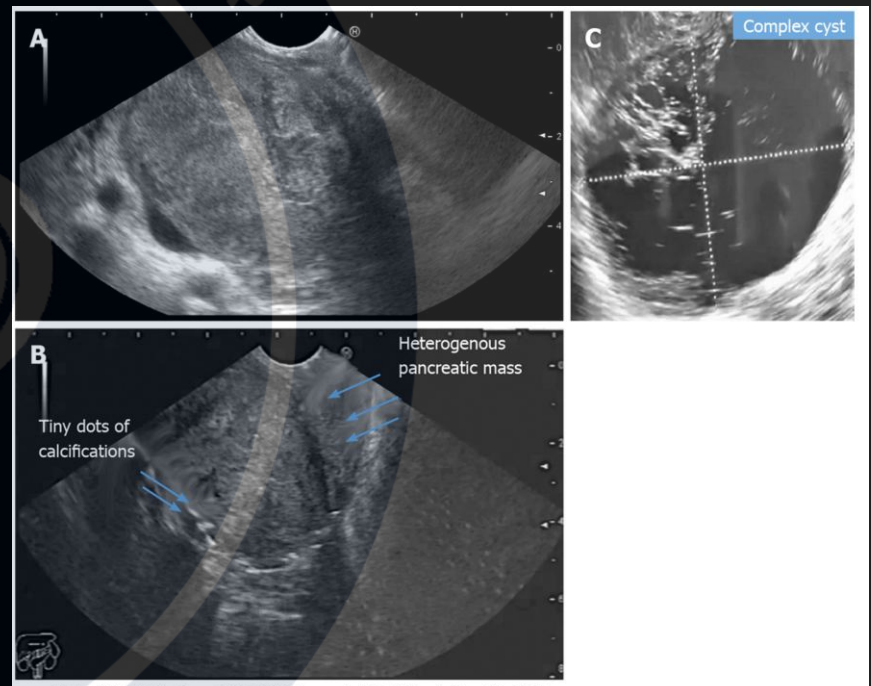


Fig. 2—20-year-old woman with palpable abdominal mass of solid pseudopapillary tumor.
A, Axial T1-weighted gradient-echo image shows well-defined heterogeneous hyperintense mass with rim of low signal intensity (*arrow*) in head of pancreas.
B, Axial fast spin-echo T2-weighted image shows heterogeneous hyperintense mass in head of pancreas. Fibrous capsule appears as band of low signal intensity (*arrow*).
C, Unenhanced axial T1-weighted gradient-echo image shows hemorrhage as area of high signal intensity (*arrow*).
D, Delayed phase axial T1-weighted gradient-echo image obtained after gadolinium administration shows heterogeneous enhancement (*arrow*) of solid portion of mass.

Choi et al. Solid Pseudopapillary Tumor of the Pancreas: Typical and Atypical Manifestations. AJR.187, August 2006

Solid Pseudopapillary Neoplasm

- EUS – FNA
  - EUS finding : can be solid, cystic or mixed characteristics
  - Well demarcated, regular border, no pathognomonic finding for SPN in EUS
  - EUS – FNA : The sensitivity for malignant cytology is 85% and the specificity is about 98%
  - Fluid analysis : low CEA, low amylase
  - Molecular marker : CTNNB1



DOI: 10.4253/wjge.v15.i4.273 Copyright ©The Author(s) 2023.

Figure 2 Endoscopic ultrasound. A: A large heterogeneous solid pseudopapillary neoplasm in the pancreatic head; B: A large heterogeneous solid pseudopapillary neoplasm with calcific spots in the pancreatic head; C: A cystic solid pseudopapillary neoplasm in the pancreatic body.

Pawlak KM et al. EUS in the characterization of SPN of the pancreas. World J Gastrointest Endosc 2023 April 16; 15(4): 273-284

Solid Pseudopapillary Neoplasm

- Management
  - Radical resection should be performed for all SPN
  - In cases of locally advanced, metastatic or recurrent SPNs, an aggressive surgical approach, with complete resection is indicated
  - Lymphadenectomy is not recommended due to low risk of lymph node metastasis
- Prognosis
  - Prognosis is excellent with a cure rate of > 95% following complete surgical resection

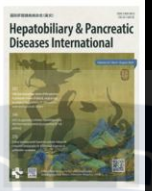
The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

HBPD International

Contents lists available at ScienceDirect

Hepatobiliary & Pancreatic Diseases International

journal homepage: www.elsevier.com/locate/hbpd



Review Article

Solid pseudopapillary tumor of the pancreas: A systematic review of clinical, surgical and oncological characteristics of 1384 patients underwent pancreatic surgery

Gennaro Mazzarella[a,b,*], Edoardo Maria Muttillo[a,c], Diego Coletta[d,e], Biagio Picardi[a], Stefano Rossi[a], Simone Rossi Del Monte[a], Vito Gomes[f], Irnerio Angelo Muttillo[a]

[a] Division of General and Emergency Surgery, San Filippo Neri Hospital, 00136 Rome, Italy
[b] Department of Surgery "Pietro Valdoni", Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy
[c] Surgical and Medical Department of Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, 00185 Rome, Italy
[d] Department of Surgical Sciences, Umberto I University Hospital, Sapienza University of Rome, 00136 Rome, Italy
[e] Department of General Surgery, Ospedali Riuniti Marche Nord, 61121 Pesaro, Italy
[f] Department of Pathology, San Filippo Neri Hospital, 00136 Rome, Italy

- Overall survival 98.1 %, recurrence 2.8 % in mean follow up 4.2 yr
- No consensus on validity of lymphadenectomy
  - Incidence of LN metastasis is rare -> routine lymphadenectomy is not indicated
- En-bloc resection with microscopic free margin is advocated
- No standard CMT regimen for SPN
- Incomplete resection, large tumor size, young patient age, tumor rupture and male are reported risk factors for recurrent disease

- Hepatobiliary & Pancreatic Diseases International 2024
- Systematic review of 28 studies, 1384 patients

Table 3
Oncological outcomes of pancreatic SPTs.

Studies	Overall survival	Recurrence	Mean follow-up (yr)
Torres et al. (2019) [22]	100%	0	3.6
Peng et al. (2006) [23]	100%	0	5
Coelho et al. (2018) [24]	95%	0	3.2
Lubezky et al. (2017) [25]	96.9%	9.4%	4.1
Wang et al. (2018) [26]	100%	0	4.5
Afridi et al. (2014) [27]	100%	0	0.9
Zhan et al. (2019) [28]	98.9%	1.1%	3.2
Wang et al. (2013) [29]	97.1%	0	2.2
Goh et al. (2007) [30]	100%	0	3.6
Cavallini et al. (2011) [31]	100%	0	3.9
Ansari et al. (2011) [32]	93.7%	0	5.2
Hanada et al. (2018) [33]	98%	2%	4.3
Dai et al. (2015) [34]	100%	2.2%	4.3
Tjaden et al. (2019) [35]	100%	10%	4.5
Marchegiani et al. (2016) [36]	98.4%	1.5%	5.2
Salvia et al. (2007) [37]	100%	0	4.8
Zampieri et al. (2011) [38]	100%	0	NS
Wright et al. (2020) [39]	98.7%	1.3%	3
Yagcı et al. (2013) [40]	80%	20%	7.9
Cai et al. (2014) [41]	98.3%	1.7%	4.8
Irtan et al. (2016) [42]	100%	9.8%	5.4
Matos et al. (2009) [43]	100%	0	5.6
McCluney et al. (2018) [44]	100%	0	2
Morikawa et al. (2013) [45]	100%	5.9%	4.2
Nakagohri et al. (2008) [46]	100%	0	3.8
Reddy et al. (2009) [47]	94%	2.7%	4.8
Kang et al. (2006) [48]	97%	3%	7
Speer et al. (2012) [49]	100%	9%	1.4
Total ($n = 28$)	98.1%	2.8%	4.2

SPTs: solid pseudopapillary tumors.

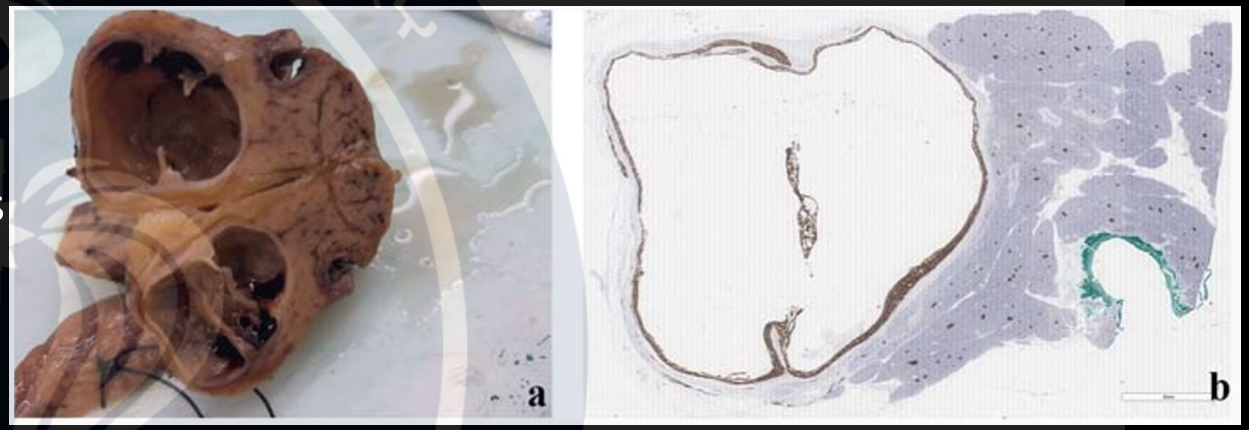
Cystic Neuroendocrine Tumor

- Reported proportions between 13% and 17% of pNETs
- Pancreatic neuroendocrine tumors
  - Manifest at any age, most often occur in the 4th to 6th decades of life
  - No sex predilection
  - Typically solitary, nonfunctional and were incidentally discovered
- Cystic PNETs
  - More frequently found in the tail of pancreas; contrast to solid PNETs
  - Lower pathologic stage and decreased Ki-67 proliferation index compared with solid counterpart
- Cause of cyst formation is controversial
  - Distinct biological entity or are formed by necrosis and degeneration variant

P. Caglia et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge International Journal of Surgery 21 (2015) S44-S49

Cystic Neuroendocrine Tumor

- Gross appearance
  - Variable size from small to large
  - No communication with the pancreatic ducts
  - Well circumscribed and surrounded by a thin to thick fibrous capsule



- Cytopathological features
  - Classic endocrine morphology of polygonal cells with plasmacytoid appearance, admixed with fragments of neoplastic cells
  - Uniformly sized round cell to slightly oval nuclei and coarse stippled chromatin
  - Cyst fluid is clear to straw-colored and thin in consistency
    - Larger lesions may be present hemorrhage within the cyst
- Localization and staging of the lesion is essential to appropriate therapy for pancreatic neuroendocrine tumors

P. Caglia et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge International Journal of Surgery 21 (2015) S44-S49
Pace M, et al. Cystic Pancreatic Neuroendocrine Tumor: A Challenging Diagnosis. World J Surg Surgical Res. 2022; 5: 1414

Cystic Neuroendocrine Tumor

- Cross-sectional imaging
- CT
  - Component of a large tumor with cystic degeneration or necrosis
    - Rarely obstruct the pancreatic duct
    - Smooth margins and peripheral enhancement usually on both arterial and portal phases (Rich blood supply)
- MRI
  - Typically low in T1- weighted sequences, and high in T2-weighted sequences
  - Hypervascular peripheral rim

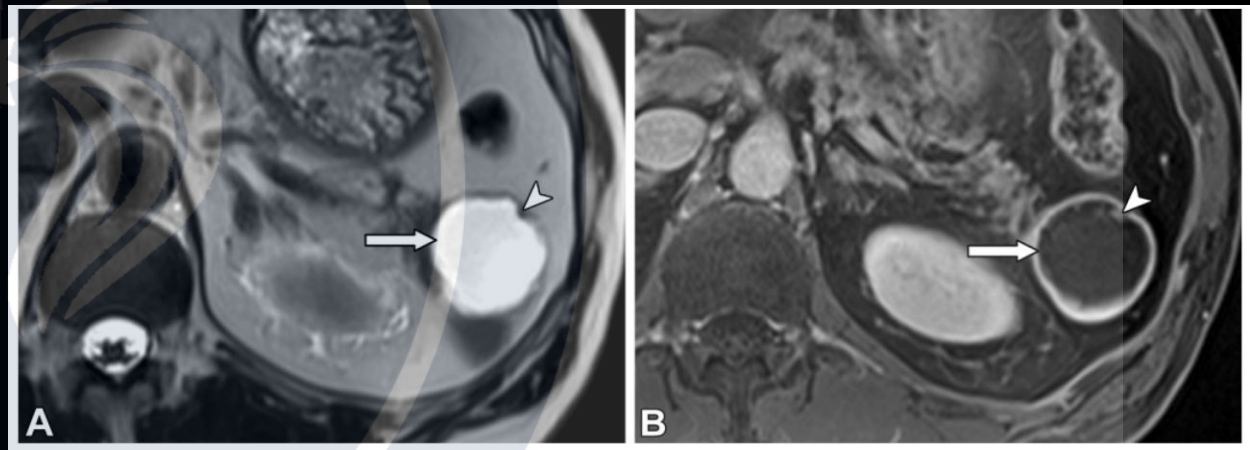


Figure 9. Cystic PNET in a 66-year-old man with a history of prostate cancer, and a pancreatic cyst seen at CT. **(A)** Axial T2-weighted MR image shows a 4.2-cm cystic lesion (arrow) in the pancreatic tail, with subtle nodularity (arrowhead) along the cyst wall. **(B)** Axial contrast-enhanced T1-weighted MR image shows a thick enhancing wall and nodularity (arrowhead) of the cystic lesion (arrow). Biopsy yielded World Health Organization grade 1 (carcinoid) neuroendocrine tumor.

P. Caglia et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge International Journal of Surgery 21 (2015) S44-S49
Miller et al. Pancreatic Cystic Lesions and Malignancy: Assessment, Guidelines, and the Field Defect. RadioGraphics 2022; 42:87–105

Pancreatic Neuroendocrine Tumor With Cystlike Changes: Evaluation With MDCT

Satomi Kawamoto[1]
Pamela T. Johnson[1]
Chanjuan Shi[2]
Aatur D. Singhi[3]
Ralph H. Hruban[3]
Christopher L. Wolfgang
Barish H. Edil[4]
Elliot K. Fishman[1]

- American Journal of Roentgenology, 2012
- Retrospective review of imaging of resected pancreatic NET
- Total 78 patients with resected pNET
- Determine the prevalence and CT appearance of cystlike changes of pNET

TABLE 1: Size of Pancreatic Neuroendocrine Tumors (NETs) and Prevalence of Cystic-Appearing Tumors on CT

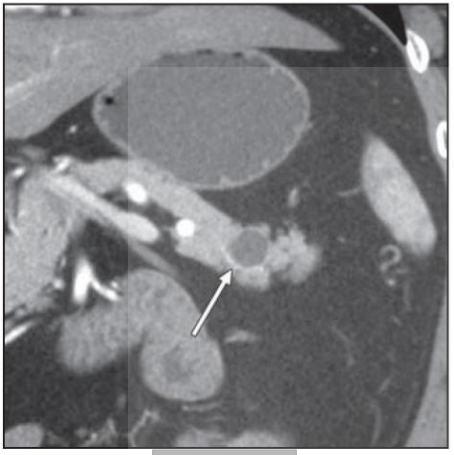
Characteristic	Pancreatic NETs		All Pancreatic NETs (*n* = 73)
	≤ 3 cm (*n* = 52)	> 3 cm (*n* = 21)	
Size (cm)			
Mean ± SD	1.7 ± 0.7	6.3 ± 2.7	3.0 ± 2.6
Range			0.7–13.1
Cystic appearance on CT, no. (%) of lesions			
≈ 100% Cystic appearance on CT	3 (4.1)	0	3 (4.1)
> 50% Cystic appearance on CT	7 (9.6)	3 (4.1)	10 (13.7)
≤ 50% Cystic appearance on CT	5 (6.8)	4 (5.5)	9 (12.3)
Solid appearance on CT	37 (50.7)	14 (19.2)	51 (69.9)

TABLE 2: Characteristics of Small (≤ 3 cm) Cystic Pancreatic Neuroendocrine Tumors (NETs)

Case No.	Cystic Change on CT	Size (cm)	Location	Peripheral Enhancement[a]			CT Diagnosis or Differential Diagnosis	Gross Pathology
				Arterial Phase[b]	Venous Phase[b]	CT Appearance (Internal Enhancing Structures)		
1[c]	≈ 100%	0.9	Head	–	–		Indeterminate, possible IPMN	Contained cystic component
2	≈ 100%	1.7	Tail	±	–	Equivocal, thin, smooth	Known pancreatic NET	Contained cystic component
3	≈ 100%	0.7	Tail	–	–		Indeterminate, possible IPMN	Contained cystic component
4	> 50%	2.4	Tail	++	+	Thin and thick, crescentic	Pancreatic NET, MCN	Contained cystic component
5	> 50%	1.4	Tail	+	±	Medium thickness, smooth	Pancreatic NET	Contained cystic component, focal necrotic component
6	> 50%	0.9	Body	+	–	Thin, smooth	Known pancreatic NET	Contained cystic component
7	> 50%	1.8	Tail	+	+	Medium thickness, irregular	Pancreatic NET, primary cystic neoplasm	Contained cystic component
8	> 50%	1.8	Neck	+	++	Medium thickness, smooth	Pancreatic NET	Contained cystic component
9	> 50%	1.5	Tail	+	±	Thin and medium thickness, smooth	IPMN, cystadenoma, pseudocyst	Contained cystic component, hemorrhagic component
10	> 50%	1.5	Tail	+	–	Medium thickness, smooth	Indeterminate, possible IPMN	Contained cystic component
11	≤ 50%	2.8	Head	+	++	Medium thickness, irregular (predominantly solid)	Pancreatic NET	Contained cystic component, hemorrhagic component
12[c]	≤ 50%	2.3	Tail	+	±	Thin and thick, smooth (predominantly solid)	Pancreatic NET	Contained cystic component
13	≤ 50%	3.0	Head	++	+	Thin and thick, smooth (predominantly solid)	Indeterminate cystic lesion	Solid
14	≤ 50%	1.4	Head	++	–	Thin and medium thickness, smooth (nodular)	Pancreatic NET, other neoplasm	Contained cystic component, hemorrhagic component
15	≤ 50%	2.5	Head	++	+++	Medium thickness and thick, irregular (predominantly solid)	Pancreatic NET	Contained cystic component

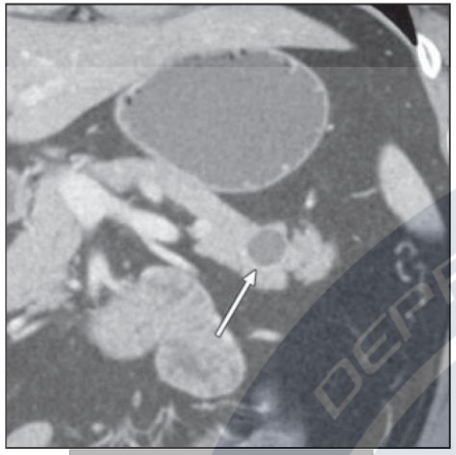
Note—IPMN = intraductal papillary mucinous neoplasm, MCN = mucinous cystic neoplasm.
[a]Peripheral enhancement was classified as smooth or irregular and as thin (≤ 3 mm), medium (> 3 and ≤ 6 mm), or thick (> 6 mm).
[b]Degree of peripheral enhancement was quantitatively graded by obtaining the difference of average attenuation of an enhancing component and of normal pancreatic parenchyma at the arterial phase and portal venous phase: – = ≤ 10 HU, ± = between 10 and ≤ 20 HU, + = between 20 and ≤ 40 HU, ++ = between 40 and ≤ 60 HU, or +++ = > 60 HU.
[c]Multiple endocrine neoplasia type 1.

- 13 of the 73 (17.8%) tumors were predominantly (> 50% or ≈ 100%) cystic
  - 10 of the 52 (19.2%) tumors 3 cm or smaller
  - 3 of the 21 (14.3%) tumors larger than 3 cm
- Peripheral contrast enhancement
  - 11 of the 13 (85%) predominantly cystic pancreatic NETs



A phase

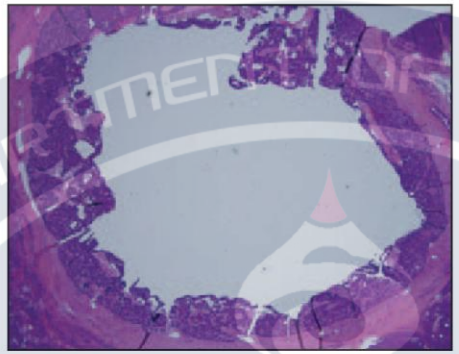
A



Portovenous phase

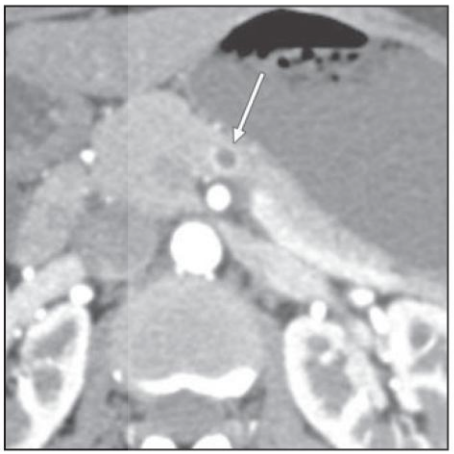
B

~100% cystic

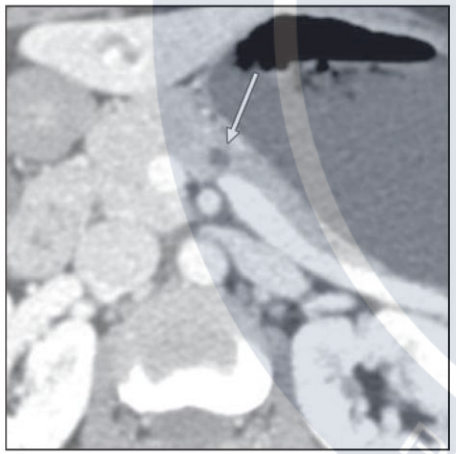


C

Fig. 2—Well-differentiated neuroendocrine tumor (NET), nonfunctioning, in 56-year-old man. Cystic mass was initially found on CT performed for abdominal pain; mass had increased in size during follow-up. Fine-needle aspiration performed at another institution revealed well-differentiated NET (case 2 in Table 2).
A, Coronal arterial phase multiplanar reformation (MPR) image shows purely cystic mass in tail of pancreas with equivocal minimal smooth rim of enhancement along inferior border (*arrow*).
B, Coronal venous phase MPR image shows purely cystic mass (*arrow*) without detectable peripheral enhancement.
C, Photomicrograph (H and E, 2×) shows there is unilocular cyst in center of tumor. Cyst is lined by neuroendocrine cells.

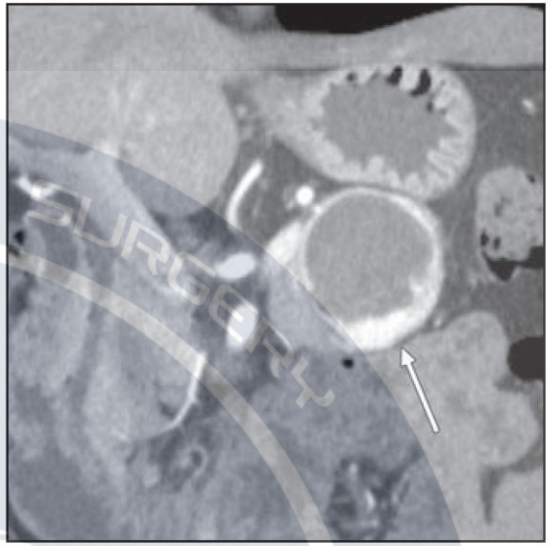


A

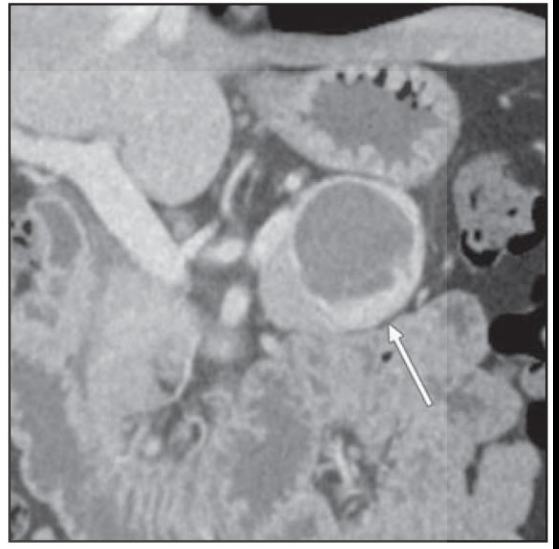


B

Fig. 3—Well-differentiated neuroendocrine tumor (NET), nonfunctioning, in 47-year-old woman. Small cystic lesion was incidentally found on CT performed for evaluation of hematuria. Endoscopic ultrasound and fine-needle aspiration revealed pancreatic NET (case 6 in Table 2).
A, Axial arterial phase image shows partially (> 50%) cystic mass with thin, smooth peripheral enhancement (*arrow*) greater than that of pancreatic parenchyma.
B, Axial venous phase image shows small cystic mass (*arrow*) with no detectable peripheral enhancement.

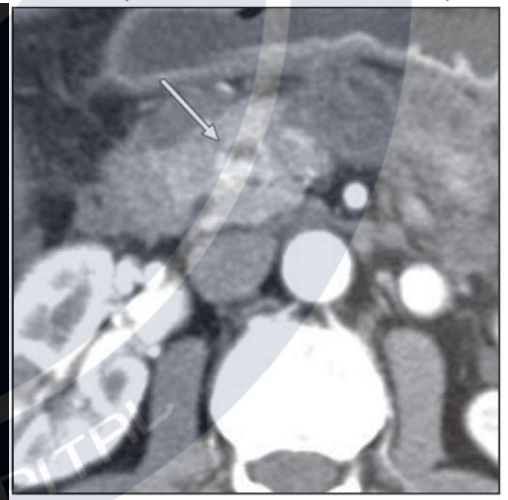


A

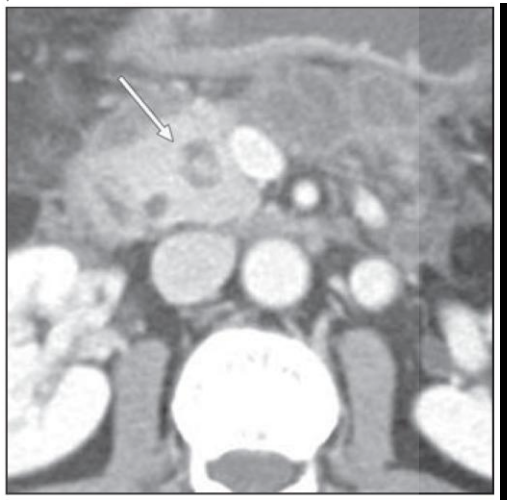


B

Fig. 4—Well-differentiated neuroendocrine tumor (NET), nonfunctioning, in 43-year-old man (case 16 in Table 3).
A and **B**, Arterial phase (**A**) and venous phase (**B**) coronal multiplanar reformation images show large partially (> 50%) cystic mass with thin-to-thick, smooth peripheral enhancement. Note focal crescentic thickening (*arrow*) along inferior border with intense contrast enhancement best seen on arterial phase. CT differential diagnosis included pancreatic NET and mucinous cystic neoplasm.



A



B

Fig. 5—Well-differentiated neuroendocrine tumor (NET), nonfunctioning, in 51-year-old woman. Pancreatic head mass was found on CT performed for evaluation of pancreatitis (case 14 in Table 2).
A and **B**, Arterial phase (**A**) and venous phase (**B**) axial images show partially (≤ 50%) cystic small mass in head of pancreas (*arrow*). Note that intense contrast enhancement of peripheral and internal nodular components is visible only on arterial phase. Peripancreatic inflammation and fluid collections are due to pancreatitis. CT differential diagnosis included pancreatic NET and other tumors.

S. Kawamoto et al. Pancreatic Neuroendocrine Tumor With Cystlike Changes: Evaluation With MDCT. AJR 2013; 200:W283-W290

Pancreatic Cystic Neoplasm

Cystic Neuroendocrine Tumor

- Somatostatin receptor scintigraphy
  - Radiolabeled somatostatin analogs -> Somatostatin receptors expressed by PNETs
    - Insulinomas -> not well visualized due to absent or low levels of somatostatin receptors
    - For other functional and non functional PNETs the ability of SRS to localize the tumor is good, with sensitivities ranging from 75 to 100%
    - SRS is also typically useful in evaluating the metastatic spread.
- Gallium 68–tetraazacyclododecane-tetraacetic acid-octreotate PET/CT
  - 68-Ga DOTATE PET/CT
  - Can help detect pNET with 93% sensitivity and 91% specificity
  - Stage pNET, detect recurrences, and assess tumor heterogeneity, especially that of grade 2 and grade 3 tumors

P. Caglia et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge International Journal of Surgery 21 (2015) S44-S49

Cystic Neuroendocrine Tumor

- Endoscopic ultrasound
  - EUS
    - Well-circumscribed lesions either completely cystic or with solid and cystic components -> Nonspecific morphology at EUS
    - Offers the additional benefit of obtaining biopsies and cyst fluid examination providing additional pathological findings
  - Cyst fluid analysis : Low CEA, Low amylase
  - Cytology
    - Diagnose malignant cystic lesions by demonstrating cells with high grade atypia or neoplastic in the cyst fluid
    - EUS has an 82% sensitivity and a 92% specificity in identifying PNETs

P. Caglia et al. Cystic pancreatic neuroendocrine tumors: To date a diagnostic challenge International Journal of Surgery 21 (2015) S44-S49

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

- Pancreatology, 2019
- Systematic review of 12 studies, 355 cystic pNET and 1530 solid pNET
- Explore differences between clinicopathological features

Cystic pancreatic neuroendocrine tumors: A distinctive subgroup with indolent biological behavior? A systematic review and meta-analysis

Jian-kang Zhu [a], Dong Wu [a], Jian-wei Xu [a], Xin Huang [a], Yuan-yuan Jiang [b], Barish H. Edil [c], Min Li [c, d], San-yuan Hu [a], Han-xiang Zhan [a, *]

[a] Department of General Surgery, Qilu Hospital, Shandong University, Jinan, Shandong Province, 250012, China
[b] Department of Pulmonary and Critical Care Medicine, Qilu Hospital Shandong University, Jinan, 250012, China
[c] Department of Surgery, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[d] Department of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

Table 2
Clinical features comparison between cystic and solid pNETs.

Clinical features	Included studies	Patients	Cystic pNETs n (%)	Solid pNETs n (%)	OR or WMD (95% CI)	P value
Gender	11	1824	Male: 197 (197/333, 59.2%) Female: 136 (136/333, 40.8%)	Male: 728 (728/1491, 48.8%) Female: 763 (763/1491, 51.2%)	1.56 (1.22–2.00)	0.0005
Age	11	1824	Estimate mean = 56.4 ± 12.6 y	Estimate mean = 55.6 ± 12.1 y	0.65 (−1.83–3.14)	0.61
Functional status	9	1567	Functional: 21 (21/298, 7.0%) Non-functional: 277 (277/298, 93.0%)	Functional: 272 (272/1269, 21.4%) Non-functional: 997 (997/1269, 78.6%)	0.31 (0.19–0.50)	<0.00001
Associated MEN-1	7	1332	Yes: 22 (22/224, 9.8%) No: 202 (202/224, 90.2%)	Yes: 47 (47/1108, 4.2%) No: 1061 (1061/1108, 95.8%)	2.71 (1.55–4.73)	0.0005
Unifocal	8	1494	Unifocal: 252 (252/273, 92.3%) Multifocal: 21 (21/273, 7.7%)	Unifocal: 1151 (1151/1221, 94.3%) Multifocal: 70 (70/1221, 5.7%)	0.63 (0.24–1.68)	0.36
Symptoms	6	920	Presence: 114 (114/224, 50.9%) Absence: 110 (110/224, 49.1%)	Presence: 401 (401/696, 57.6%) Absence: 295 (295/696, 42.4%)	0.80 (0.46–1.40)	0.43
Tumor location	11	1824	Head: 77 (77/333, 23.1%) Body & tail: 256 (256/333, 76.9%)	Head: 647 (647/1491, 43.4%) Body & tail: 844 (844/1491, 56.6%)	0.40 (0.30–0.54)	<0.00001
Tumor size	12	1885	Estimate mean = 31.8 ± 24.4 mm	Estimate mean = 32.4 ± 31.5 mm	2.62 (−1.84–7.08)	0.25

- Cystic pNETs were associated with male, MEN-1
- Tumors were more likely found in body-tail of pancreas and most of them are non-functional

Table 3
Pathological characteristics comparison between cystic and solid pNETs.

Pathological characteristics	Included studies	Patients	Cystic pNETs (%)	Solid pNETs n (%)	OR (95% CI)	P value
Synchronous distant metastasis	8	1566	Yes: 22 (22/302, 7.3%) No: 280 (280/302, 92.7%)	Yes: 211 (211/1264, 16.7%) No: 1053 (1053/1264, 83.3%)	0.48 (0.30–0.78)	0.003
Lymph node metastasis	8	1654	Yes: 51 (51/313, 16.3%) No: 262 (262/313, 83.7%)	Yes: 383 (383/1341, 28.6%) No: 958 (958/1341, 71.4%)	0.54 (0.39–0.75)	0.0003
Vascular invasion	7	1332	Yes: 30 (30/224, 13.4%) No: 194 (194/224, 86.6%)	Yes: 342 (342/1108, 30.9%) No: 766 (766/1108, 69.1%)	0.38 (0.19–0.77)	0.007
Perineural invasion	4	918	Yes: 12 (12/143, 8.4%) No: 131 (131/143, 91.6%)	Yes: 204 (204/775, 26.3%) No: 571 (571/775, 73.7.2%)	0.27 (0.15–0.51)	<0.0001
Tumor grading	8	1484	G1&G2: 252 (252/308, 81.8%) G3: 56 (56/308, 18.2%)	G1&G2: 941 (941/1176, 80.0%) G3: 235 (235/1176, 20.0%)	1.66 (1.09–2.52)	0.02
Tumor necrosis	3	743	Yes: 8 (8/89, 9.0%) No: 81 (81/89, 91.0%)	Yes: 95 (95/654, 14.5%) No: 559 (559/654, 85.5%)	1.29 (0.18–9.18)	0.80
TNM stage	4	1089	I&II: 154 (154/173, 89.0%) III&IV: 19 (19/173, 11.0%)	I&II: 703 (703/916, 76.7%) III&IV: 213 (213/916, 23.3%)	2.32 (1.36–3.95)	0.002
Ki-67 index	4	1141	<2%: 138 (138/211, 65.4%) >2%: 73 (73/211, 34.6%)	<2%: 459 (459/930, 49.4%) >2%: 471 (471/930, 50.6%)	2.52 (1.77–3.60)	<0.00001
Mitotic count	4	1065	<2%: 140 (140/196, 71.4%) >2%: 56 (56/196, 28.6%)	<2%: 537 (537/869, 61.8%) >2%: 332 (332/869, 38.2%)	2.75 (1.09–6.93)	0.03

- Cystic pNETs were less aggressive biological behavior compared to solid pNET

Table 4
Long-term survival comparison between cystic and solid pNETs.

Long-term outcome	Included studies	Patients	Cystic pNETs n (%)	Solid pNETs n (%)	OR(95% CI)	P value
5-year OS	4	689	Alive: 104 (104/111, 93.7%) Died: 7 (7/111, 6.3%)	Alive: 510 (510/578, 88.2%) Died: 68 (68/578, 11.8%)	1.82 (0.82–4.03)	0.14
5-year DFS	4	457	No recurrence: 106 (106/112, 94.6%) Recurrence: 6 (6/112, 5.4%)	No recurrence: 288 (288/345, 83.5%) Recurrence: 57 (57/345, 16.5%)	3.00 (1.28–7.04)	0.01
10-year OS	3	519	Alive: 65 (65/82, 79.3%) Died: 17 (17/82, 20.7%)	Alive: 360 (360/437, 82.4%) Died: 77 (77/437, 17.6%)	2.12 (0.12–37.33)	0.61
10-year DFS	3	519	No recurrence: 76 (76/82, 92.7%) Recurrence: 6 (6/82, 7.3%)	No recurrence: 278 (278/437, 63.6%) Recurrence: 159 (159/437, 36.4%)	5.92 (1.17–29.94)	0.03

- Overall survival was not significantly different
- 5-yr and 10-yr DFS were significant higher in cystic pNET

Cystic Neuroendocrine Tumor

- Management
  - Definitive diagnosis of a cystic PNET can be established only by histological examination
    - Preoperative diagnosis is often suspected based on particular features of cross-sectional imaging, and can be confirmed by EUS-guided cytology
  - For cystic PNET >20 mm
    - Surgery is recommended (pancreatoduodenectomy, distal pancreatectomy, or enucleation (including lymphadenectomy), according to tumor localization)
  - For asymptomatic cystic PNET ≤2 cm
    - In the absence of signs of malignant behavior, surveillance is recommended

The European Study Group on Cystic Tumours of the Pancreas. Gut 2018;**67**:789–804. doi:10.1136/gutjnl-2018-316027

TABLE 60.1 Characteristics of Common Cystic Neoplasms of Pancreas

	AGE OF PRESENTATION (DECADE)	GENDER DISTRIBUTION	IMAGING CHARACTERISTICS	MACROSCOPIC FEATURES	CONNECTION WITH MPD	INVASIVE OR HGD POTENTIAL	CYST FLUID ANALYSIS
IPMN-BD	5th to 7th	Equal	Macrocytic, grape-like cystic lesion, Unilocular or multilocular	Mucine producing epithelium with papillae	Yes	12%–30%	mucin, high CEA, GNAS frequently mutated, RNF43 mutated
IPMN-MD	5th to 7th	Equal	Segmental or diffuse dilation of main pancreatic duct	Mucine producing epithelium with papillae	Yes	36%–100%	mucin, high CEA, GNAS frequently mutated, RNF43 mutated
MCN	4th to 5th	Female > male	Macrocytic, unilocular body/tail location, peripheral calcification	Tall columnar mucin-producing epithelium Ovarian-type stroma	No	10%–50%	mucin, high CEA, GNAS wild, RNF43 mutated
SCA	5th to 7th	Female > male	Microcystic characteristic honeycomb pattern Stellate scar	Clear cytoplasm, well defined borders, uniform nuclei, glycogen-rich cells	No	Negligible	serous, very low CEA, VHL gene mutated, RNF43 wild
SPT	2nd to 3rd	Female > male	Macrocytic, Solid, and cystic, area of hemorrhage	Solid sheets of variable cells	No	10%–15%	Bloody, necrotic debris
Pseudocyst	4th to 5th	Equal	Unilocular associated with pancreatitis	No epithelial lining	common	0%	nonmucinous, high amylase, low viscosity, Dark, low CEA

BD, Branch duct; *CEA*, carcinoembryonic antigen; *HGD*, high-grade dysplasia; *IPMN*, intraductal papillary mucinous neoplasm; *MCN*, mucinous cystic neoplasm; *MD*, main duct; *MPD*, main pancreatic duct; *SCA*, serous cystadenoma; *SPT*, solid pseudopapillary tumor.

DEPARTMENT OF SURGERY RAMATHIBODI HOSPITAL

BLUMGART'S Surgery *of the* Liver, Biliary Tract and Pancreas. 7th ed. 2023

Thank You