

Cystic pancreatic neoplasms: Observe

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Outline

- Background of cystic neoplasms
- Diagnosing cystic neoplasms
 - CT
 - EUS
 - Cyst fluid analysis
- Natural history of cystic neoplasms
- Risk of operative resection

Background

- Many patients with pancreatic cystic lesions are asymptomatic, making it difficult to determine the incidence and prevalence.
- Cystic lesions of the pancreas are found in about 1% of the population based on CT.
- Up to 24% of patients have pancreatic cysts at autopsy.
- About 10-15% of pancreatic cysts are estimated to be due to primary neoplasms and the remainder due to pseudocysts.
- Up to 75% of cystic lesions are incidental findings, causing no symptoms and 80% of those resected are benign.

Typical characteristics

Cyst type	Pseudocyst	SCA	MCN	IPMN	SPN
Age	Variable	Middle-aged	Middle-aged	Elderly	Young
Sex	M > F	F > M	Female	M > F	Female
Pancreatitis history ¹	Yes	No	No	Yes ²	No
Location	Evenly	Evenly	Body/tail	Head	Evenly
Malignant potential	None	Rarely	Moderate to high	Low to high	Low
Biliary obstruction	Yes, Uncommon	No	No	Yes, Uncommon	No

Imaging-CT and EUS

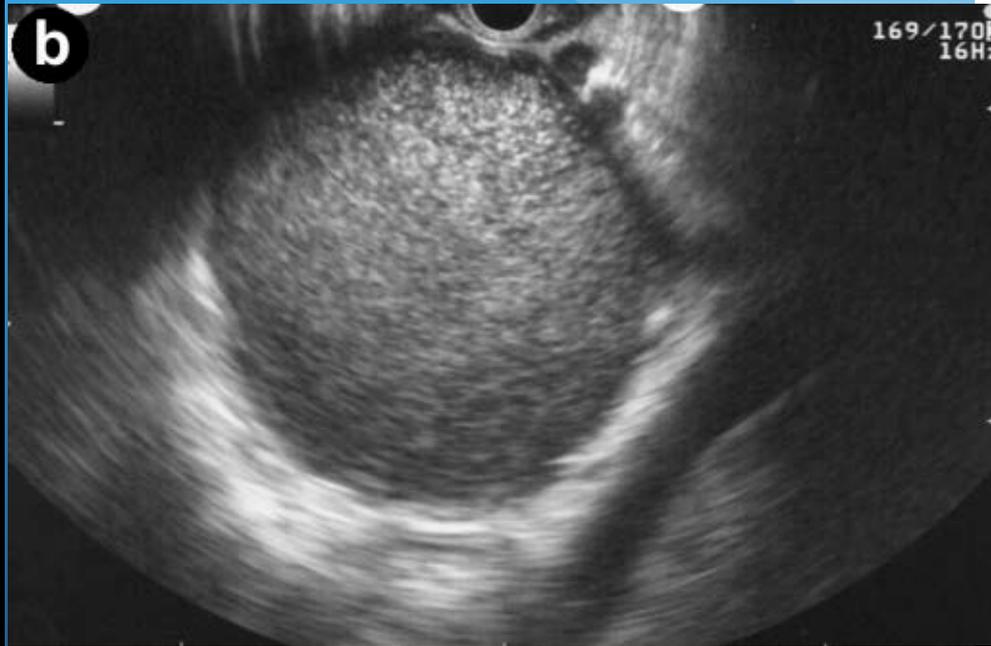
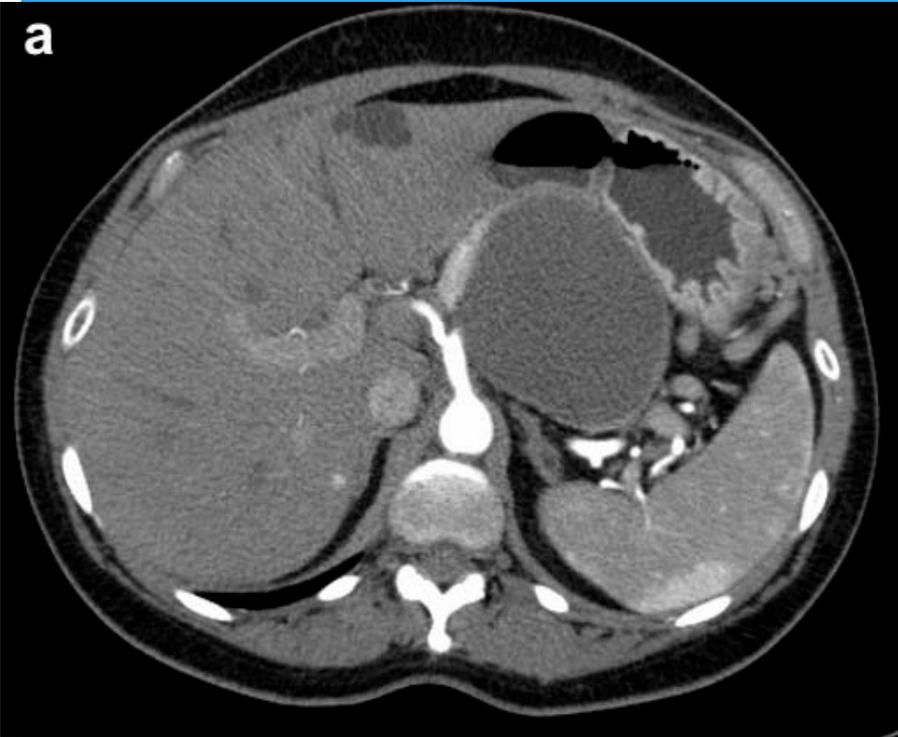
- CT characterizes the mass via size, uni- vs multi-loculated, pancreatic duct communication and/or dilation, presence of mass or mural nodule.
 - Enhanced characterization with pancreas protocol.
- EUS provides detailed information about septations, adjacent masses, wall characteristics.
 - Advantages: simultaneous FNA and sampling cystic fluid for analysis.
 - Accuracy of EUS alone of malignant or premalignant 51-95%.
 - EUS morphology risk factors for malignancy: thick wall, septations, intramural nodules, masses, and wall calcifications.

CT and EUS: Serous cystadenoma



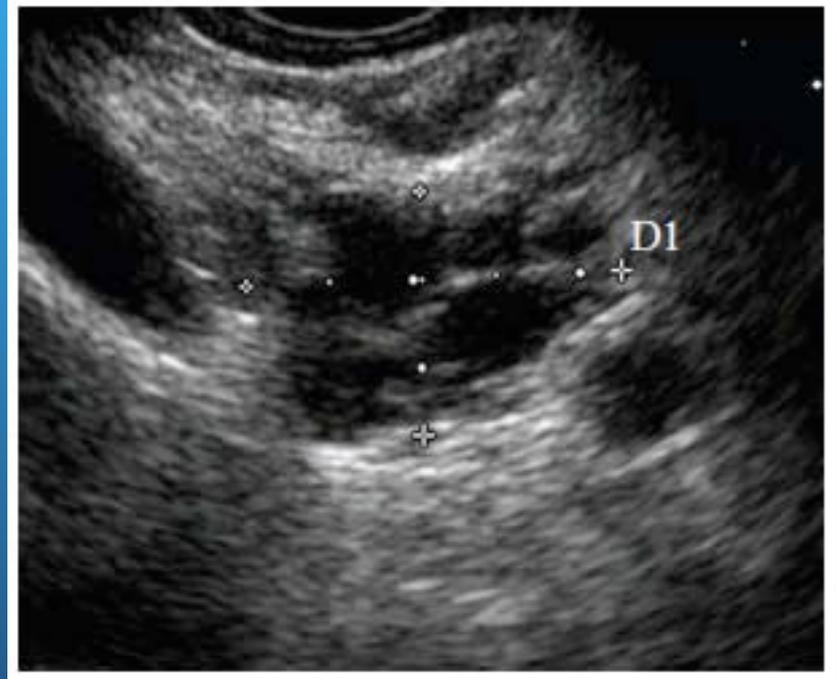
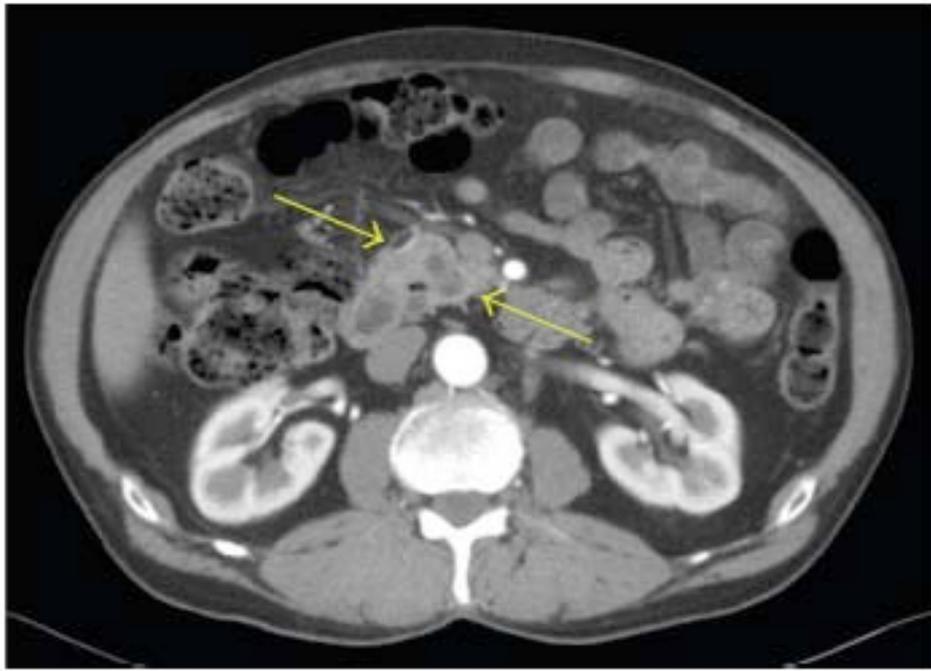
Typically <2 cm, multi-loculated with honeycomb appearance. May have a central stellate scar (pathognomonic). Rare to have pancreatic duct communication or dilation.

CT and EUS: Mucinous Cystic Neoplasm



Typically >2 cm, uni or multi-locular with “orange fruit” appearance. Uncommon for pancreatic duct communication or dilation. May have peripheral calcification.

CT and EUS: Intraductal Papillary Mucinous Neoplasm



Typically see ductal dilation, possibly duct communication.
Mural nodules often seen.

CT and EUS: Pseudocyst



Usually uni-locular with no internal septa. Can have thick or thin wall. May have calcifications.

Cystic fluid analysis

Cyst Type	Location	Fluid color and viscosity	Cytology	CEA	Amylase
Mucinous cystadenoma	Body/tail more than head	Colorless, thick fluid	Extracellular mucin. Mucinous epithelial cells in a background of ovarian stroma may be seen	Moderate to highly elevated	Variable
Intraductal papillary mucinous neoplasm	Main duct or side branch; head more than body and tail	Colorless, thick fluid	Extracellular mucin. Mucinous epithelial cells with papillary projections and variable atypia may be seen	Moderate to highly elevated	Elevated
Serous cystadenoma	Body/tail more than head	Colorless, frequently blood contaminated	Typically acellular. Small glycogen staining cuboidal cells may be seen in the background	Undetectable to low	Low
Pseudocyst	Anywhere	Yellow to brown thin fluid	Macrophages with no mucin. Mixed inflammatory infiltrate	Low to minimally increased	Elevated

Cooperative Pancreatic Cyst Study

- Multicenter study of 341 patients with prospectively collected results of EUS morphology, fluid cytology and cyst fluid analysis.
- 112 patients underwent surgical resection with histology for comparison.
- CEA was the most accurate tumor marker in differentiating mucinous and non-mucinous lesions.
- The optimal cutoff was >192 ng/ml with sensitivity of 73% and specificity of 84%.
- 60% (68) of the lesions resected were mucinous; 76% (52/68) were MCN; 56% (29/52) were malignant.
- 36% (40/112) of those resected were malignant or borderline malignant.

Comparison of EUS, Cytology and CEA in differentiating between mucinous and non-mucinous cysts

	EUS morphology	Cytology	CEA
Sensitivity	32/57 (56.1%)	19/55 (34.5%)	42/56 (75%)
Specificity	25/55 (45.4%)	45/54 (83.3%)	46/55 (83.6%)
Accuracy	57/112 (50.9%)	64/109 (58.7%) ^a	88/111 (79.2%) ^{b,c}

^aThree patients did not have cytology result.

^bOne patient did not have a CEA result.

^c $P < 0.05$ vs cytology, EUS morphology.

Combination diagnosis

	EUS morphology or cytology	EUS morphology or cytology or CEA	Cytology or CEA
Sensitivity ^a	70	91	82
Specificity	38	31	71
Accuracy	54	62	77 ^b
Area under ROC curve	0.5418 ^c	0.6107 ^c	0.7668

^aThe values reported were compared with regression analysis using area under ROC curves and are more accurately termed *areas* rather than percentage.

^b $P < 0.05$ vs. EUS morphology-cytology, EUS morphology-cytology-CEA.

^cArea less than CEA alone, $P < 0.0001$; see Table 3 for CEA alone ROC area.

PANDA study

- 391 patients from 7 institutions who underwent EUS evaluation for pancreatic cysts were enrolled. 91 were excluded due to no cyst on EUS, solid mass on EUS, or inadequate cystic fluid.
- 124 of 299 had pathologic diagnoses based on surgical resection or malignant EUS-FNA findings.
- Differentiating between mucinous and non-mucinous cysts:

	Sensitivity	Specificity
CEA level >148 ng/ml	67%	67%
<i>k-ras</i> mutation	45%	96%
CEA >148 ng/ml and <i>k-ras</i> mutation	84%	67%
CEA >192ng/ml and <i>k-ras</i> mutation	82%	83%

Natural history

- Prospective study of patients who were evaluated for pancreatic cysts at the Cleveland Clinic over 4 years.
- Of the 221 patients evaluated, 80 underwent surgical resection.
- Of the 141 patients observed, 98 were followed for more than 12 mos.
- 79% (78) underwent EUS cyst aspiration. 76% were unilocular. All except 4 had CEA < 200 ng/ml. All except 7 were negative for mucin.

Radiologic follow-up

<i>Radiographic change</i>	<i>Number</i>	<i>Mean % diameter change, cm</i>
Decrease (%)	20 (23%)	—
Complete resolution	10	—
Partial resolution	10	23
Increase (%)	16 (19%)	21

- 84/98 were followed up with imaging for a mean of 24 months.
- Of the 22 patients with lesions ≥ 4 cm and negative aspirates, 10 remained unchanged, 5 decreased in size or resolved, 1 increased in size, 3 were resected, and 3 refused resection or imaging.
- A total of 4 patients underwent resection during the surveillance period. Pathology was mucinous cystadenoma, lymphoepithelial cyst, pseudocyst, serous cystadenoma.
- Asymptomatic patients with CEA < 200 ng/ml and negative mucin stain are unlikely to have a mucinous neoplasm that requires resection in mean of 24 months.

Natural history by EUS

- Prospective cohort over 10 years that included patients who underwent EUS and cyst aspiration and were asymptomatic from incidentally discovered pancreatic cysts.
- Of the 317 who underwent EUS, 93 patients with asymptomatic incidental pancreatic cysts were enrolled in the study.
- 22 underwent resection due to size >3cm and/or concerning EUS features. 9% had adenocarcinoma, 60% had premalignant lesions.
- 71 had lesions < 3cm with benign features and no operation.
- All 33 patients that underwent FNA had cytology negative for malignant cells.

Follow-up

- 69 (97%) were alive and free of symptoms of pancreatic disease.
- 2 were determined to have died of unrelated causes.
- Mean follow up was 28 months (range 4-120 months).
- 45/71 had follow-up imaging with CT or EUS. There was no progression of any of the lesions. 4 patients had complete resolution of the cyst.
- Asymptomatic pancreatic cysts with benign features on imaging may be followed clinically and radiographically.

Natural history

- 15 year prospective cohort of 1,424 patients diagnosed with a pancreatic cyst.
- Initial management: 422 (37%) - operative resection; 719 (63%) - non-operative management.
- Mean follow-up of non-operative group was 28 months. Changes that led to operative treatment occurred in 47 patients (6.5%).
- Of the 719 managed non-operatively, invasive malignancy was seen in 12 (1.7%).
- Of the 422 managed with initial resection, 23% had carcinoma or high grade dysplasia.
- Operative mortality 0.7%. Complications \geq Grade III occurred in 36%.

Risk of malignancy if $\leq 3\text{cm}$

- Retrospective review of all pancreatic resections for cystic neoplasms at 5 institutions over 8 years.
- There were 166 resections of neoplasms $\leq 3\text{cm}$. 135 were pathologically benign and 31 were malignant.
- Patients with malignant tumors were older, more likely to be symptomatic and have malignant features on imaging such as dilated pancreatic/bile ducts, adenopathy, and a solid component.
- CEA $> 192\text{ng/ml}$ was 55% sensitive and 89% specific for differentiating between mucinous and non-mucinous cysts.
- Fluid cytology was 79% sensitive and 90% specific for determining malignancy.
- Only 1 in 30 (3.3%) asymptomatic patients with no radiologic features for malignancy that were resected was found to have occult cancer on resection.

Risk of surgery vs. potential for malignancy

- Using the Nationwide Inpatient Sample database, Kotwall et al. determined the national overall rate of mortality for all hospitals for the Whipple procedure is 14%.
- A retrospective series of cystic lesions of the pancreas by Allen et al. showed one postoperative death (1.5%) and 19 (29%) postoperative complication of the 65 that were resected. There was a 3% risk the lesion was malignant.
- Crippa et al. retrospectively analyzed 163 resected MCNs at University of Verona and Mass General and found no operative mortality and 49% operative morbidity. Only 17.5% (28) had cancer.
- Gaujoux et al. found the operative mortality to be 0.7% and complications \geq Grade III to be 36%. There was a 1.7% chance of developing pancreatic malignancy.

Conclusions

- CT, EUS, fluid cytology, and cyst fluid analysis of CEA and *k-ras* can determine the potential for malignancy with increasing accuracy.
- Cystic lesions without malignant features on EUS or cytology and CEA < 200 ng/ml are not likely to progress to malignancy.
- Cystic lesions can be observed with radiologic follow-up with many lesions resolving or decreasing in size.
- Risk of surgery with high morbidity outweighs the low potential that a lesion harbors malignancy.

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Thank you!
Questions/Comments?