Management of Pancreatic Cystic Disease

Ann Marie Joyce, M.D.

GASTRO HEALTH

Disclosure

Consultant for Boston Scientific

Outline

- Discuss the different types of pancreatic cysts
- Discuss the diagnosis and management of Cystic Neoplasms of the Pancreas

Cystic Structures of the Pancreas

- Benign
  - Pseudocyst
  - Congenital
  - Lymphoepithelial
  - Duplication cysts
  - Other mesenteric cysts
- Neoplastic
  - *Serous cystadenoma*
  - *Mucinous cystadenoma (MCN)*
  - *Intraductal papillary mucinous neoplasm (IPMN)*
  - Neuroendocrine tumor
  - Solid pseudopapillary neoplasm
  - Ductal Adenocarcinoma

Cystic Neoplasms of Pancreas

Cystic Neoplasms of Pancreas

- Incidental finding on 15% of MRIs and 3% of CT.
- Incidence increases with age (25% in pts over 70 yrs)
- 5-8% malignant transformation over 5-10 years.
  - Risk of malignant transformation is 0.24% per year with branch duct IPMN

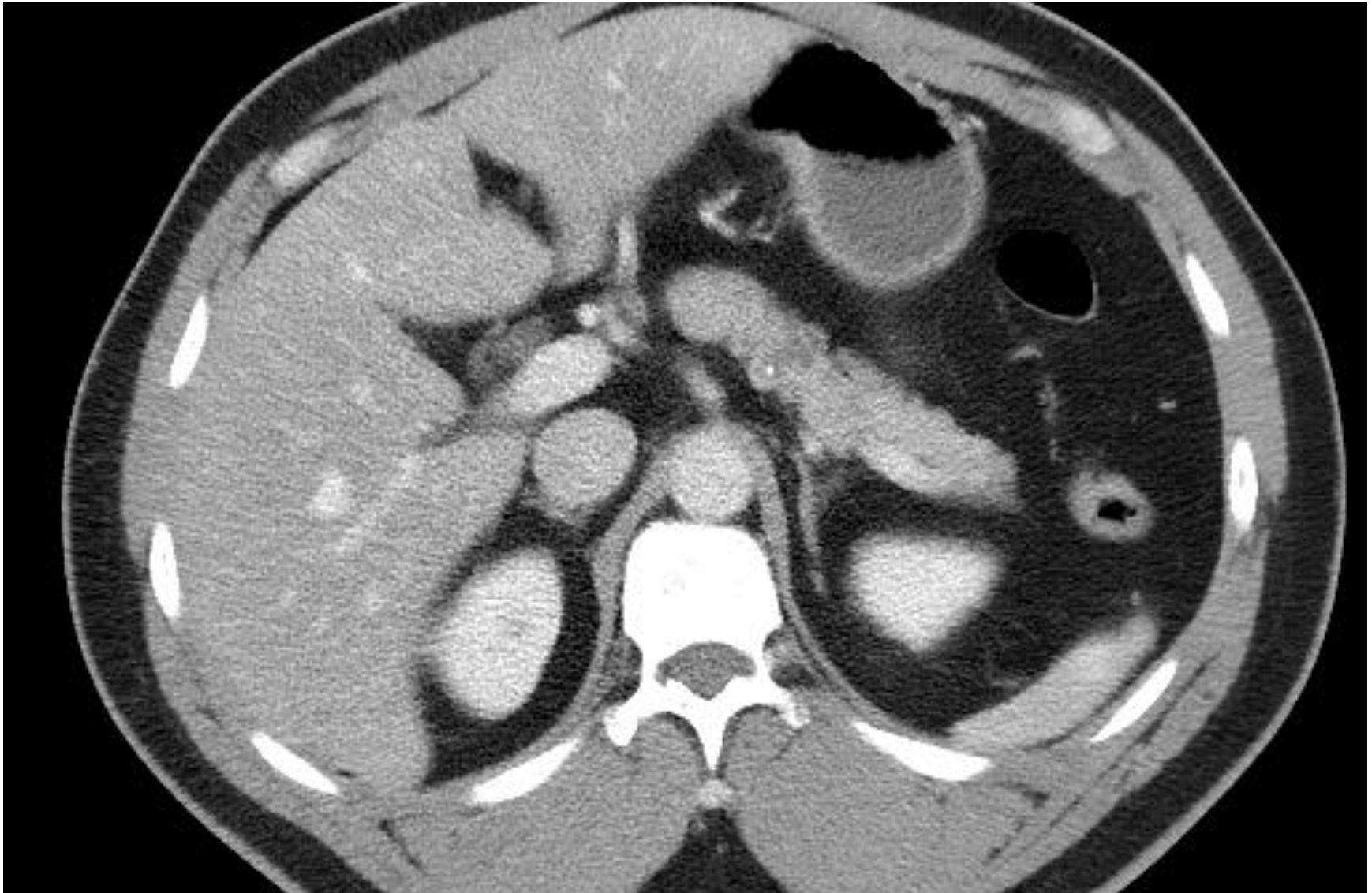
Lee, AmJGastro, 2010
deJong, Gastro Res Prac 2012
Scheiman, Gastro, 2015
Munigala, GIE, 2016

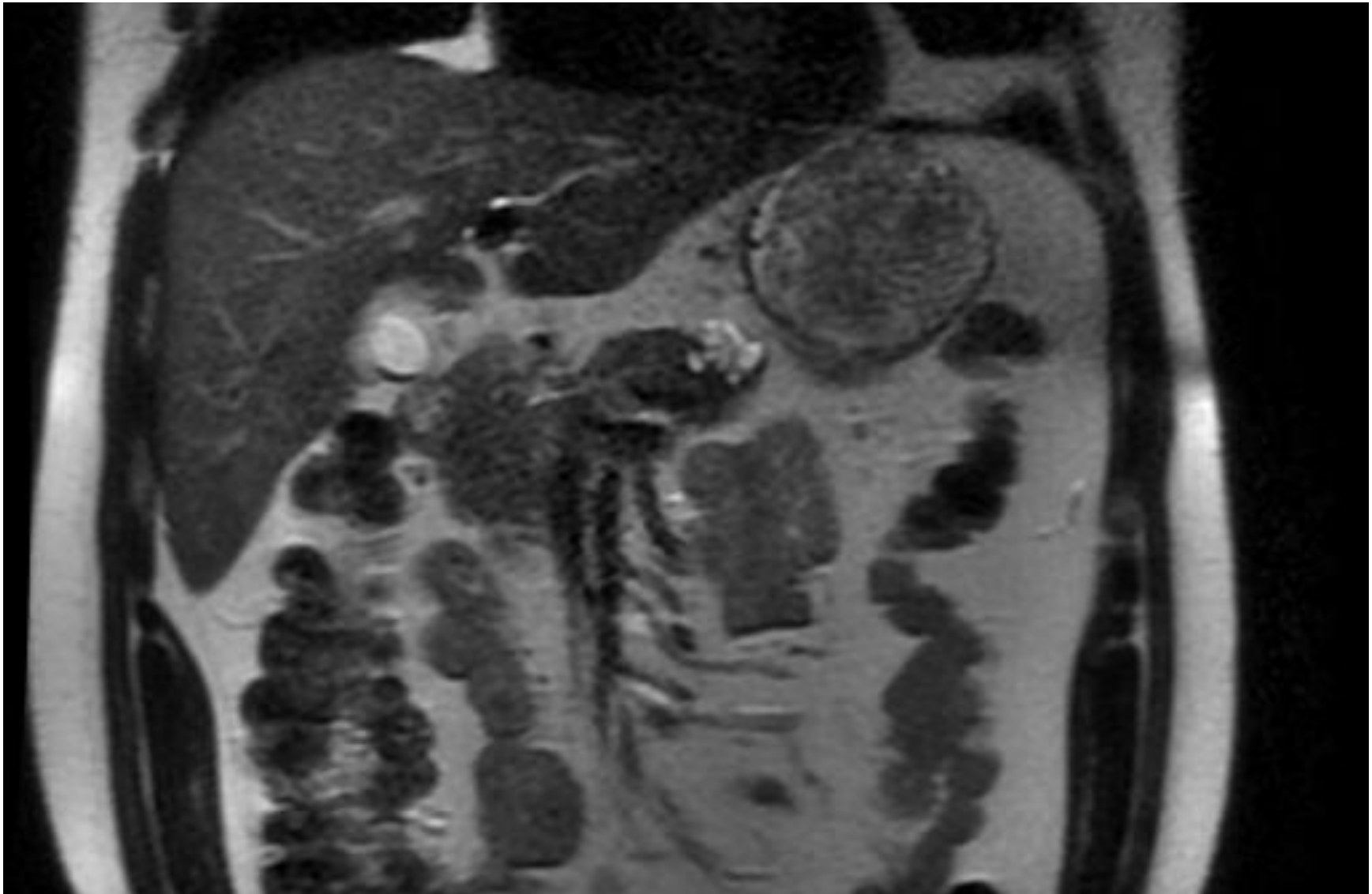
Risk Factors for Pancreatic Cancer

- There are about 40,000 (review) cases per year.
- Poor prognosis
- Majority cases of pancreatic adenocarcinoma are sporadic.
- Risk factors:
  - Family history (2 or more FDR)
  - Genetic abnormalities: BRCA, ATM, Lynch syndrome, Peutz Jegher, FAMM, Li Fraumani syndrome
  - Tobacco
  - Alcohol
  - Chronic pancreatitis
  - Diabetes
  - Pancreatic cysts

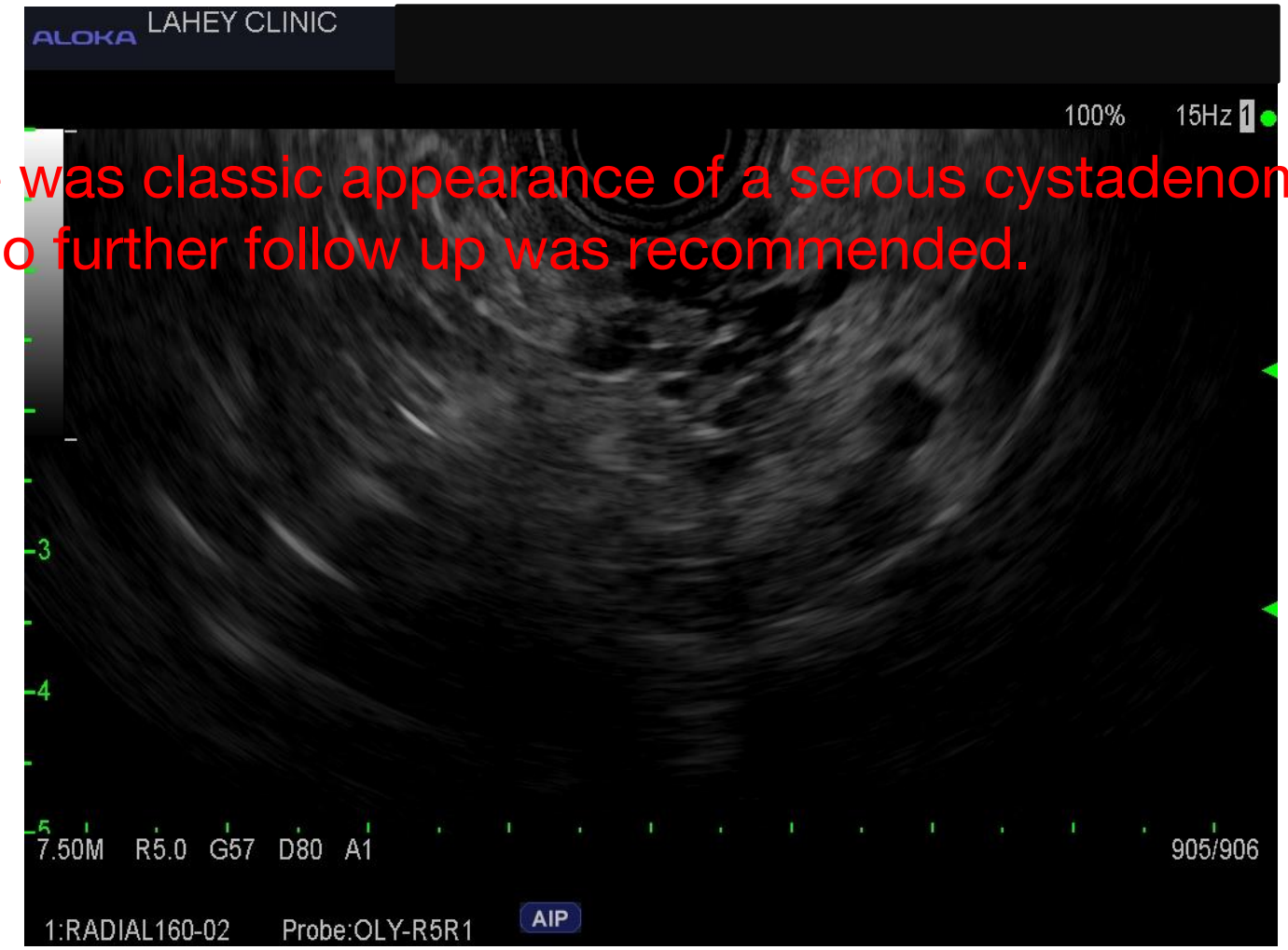
Case #1

- 63 year old female with no other significant medical problems presented to the ER with hematuria.
- She had no GI symptoms
- She denied any family history of pancreatitis or pancreatic cancer.
- She had a CT scan performed.
  - She was noted to have a 2cm cystic lesion in her pancreas.
- She was referred for EUS.





Back to our case



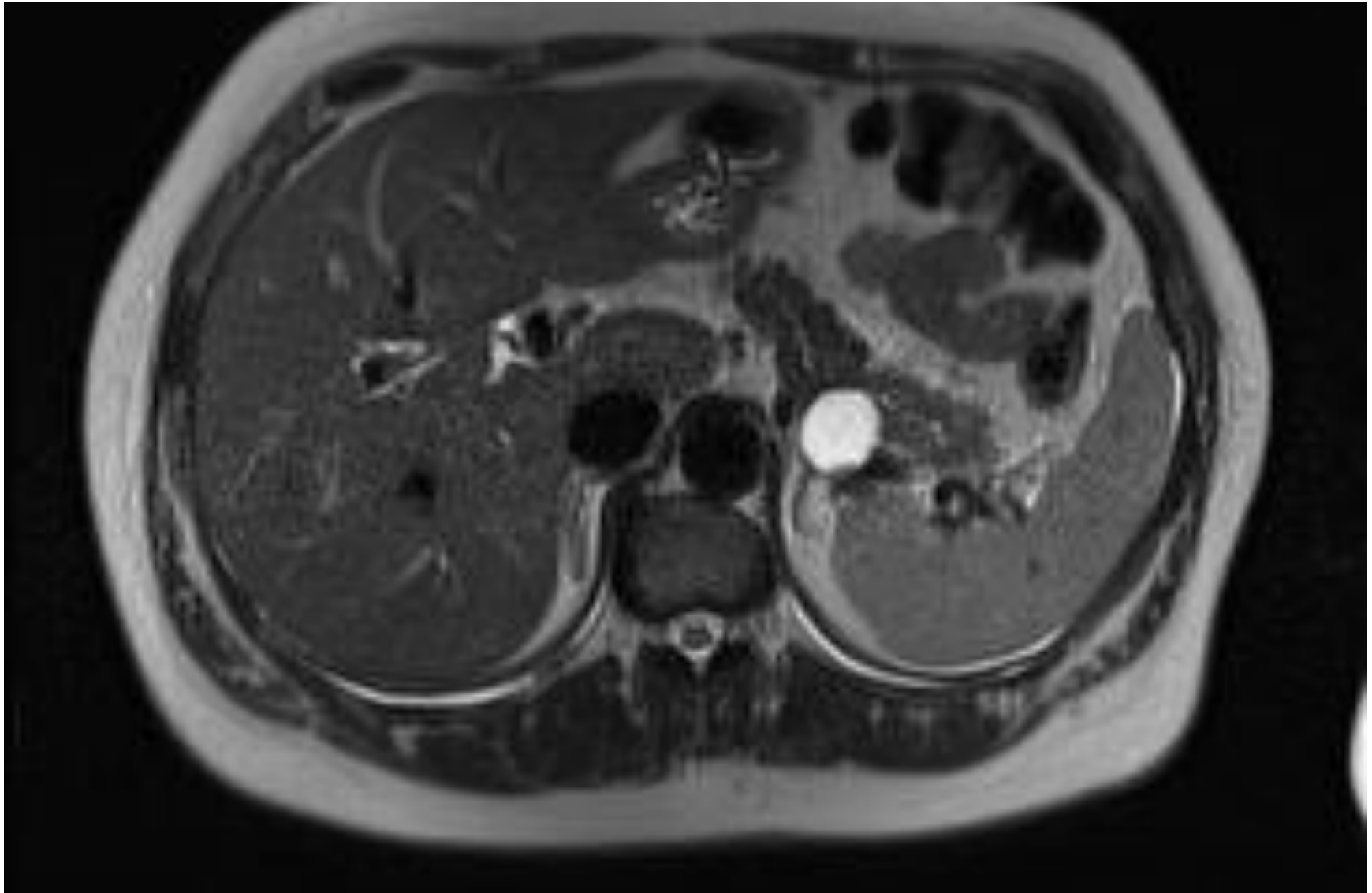
- There was classic appearance of a serous cystadenoma and no further follow up was recommended.

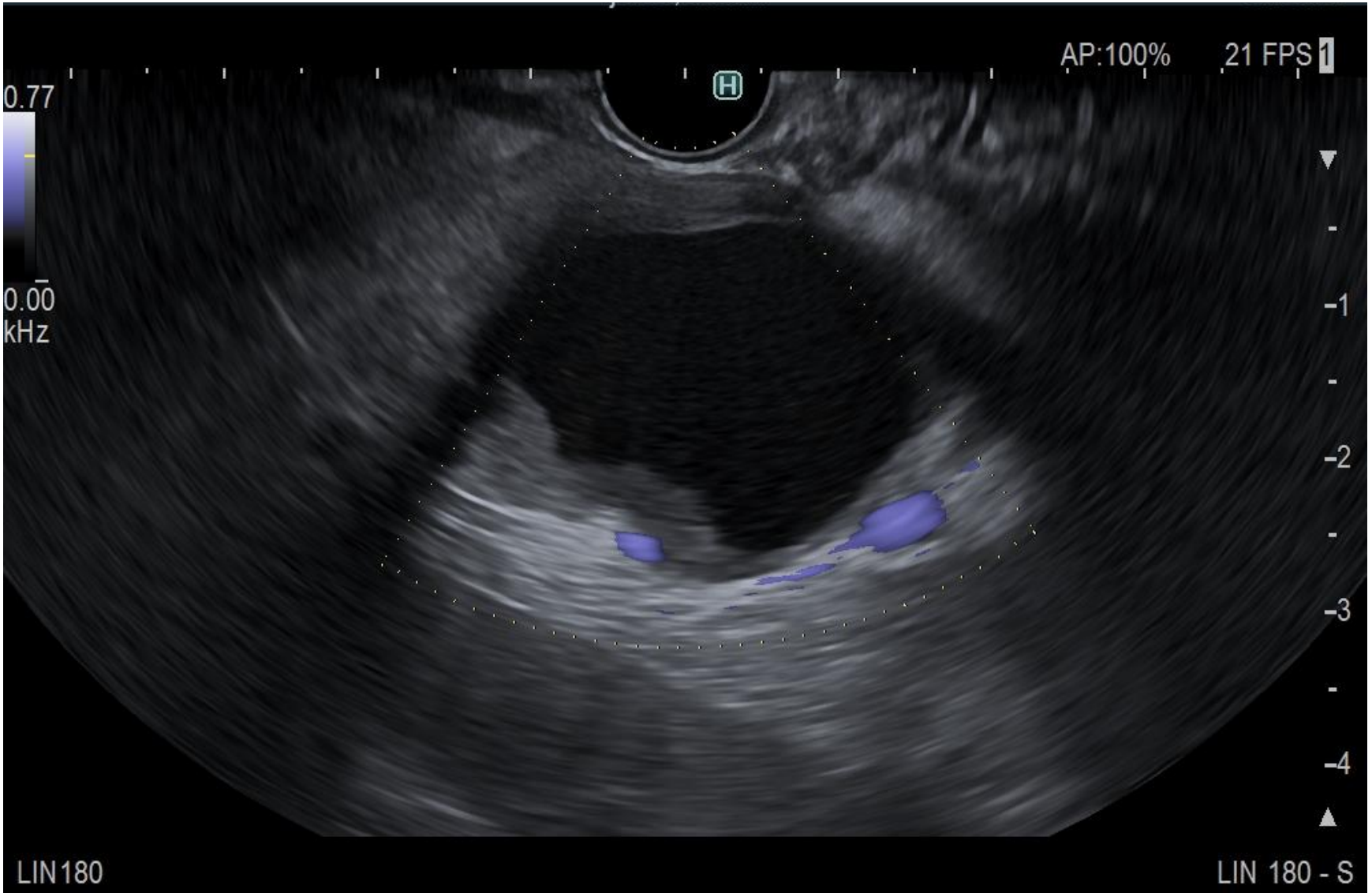
Serous Cystadenoma

- 10-15% of definitely diagnosed pancreatic cystic neoplasms
- Collection of multiple small (<2cm) thin-walled cysts
- Occur in female patients in their 50s
- Honey-comb appearance on imaging
- Central calcification present in 30%
- Associated with Von Hippel Lindau syndrome.
- Pathology: Cuboidal epithelial cells that stain positive for glycogen
- Risk of cancer is extremely low (less than 0.1%)
- Surveillance not recommended

Case #2

- 42 year old female who presented with intermittent LUQ pain.
- No documented evidence of pancreatitis.
- She was otherwise healthy.

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Mucinous cystic neoplasms

- Account for 15% of pancreatic cystic neoplasms
- Occur predominantly in females in 40s-50s
- Asymptomatic or abdominal pain
- Located in body or tail

Mucinous cystic neoplasms

- Characterized by a thick fibrous capsule that encircles the cystic spaces.
- Spindle cell stroma containing epithelioid cells similar to ovarian stroma
- Multicystic or single macrocystic lesion with columnar, mucin-containing epithelium
- May contain peripheral eccentric calcifications (15%)

Mucinous cystic neoplasms

- 10-15% resected MCNs contain HGD/CA
- Less than 0.4% of MCNs <3cm may have HGD/CA.
- Increased suspicion for malignancy if…..
  - Cyst greater than 4cm
  - Thickened wall
  - Mural nodule
  - Thickened septations
  - Peripheral calcification
- Three-year survival after curative resection approaches 59%.

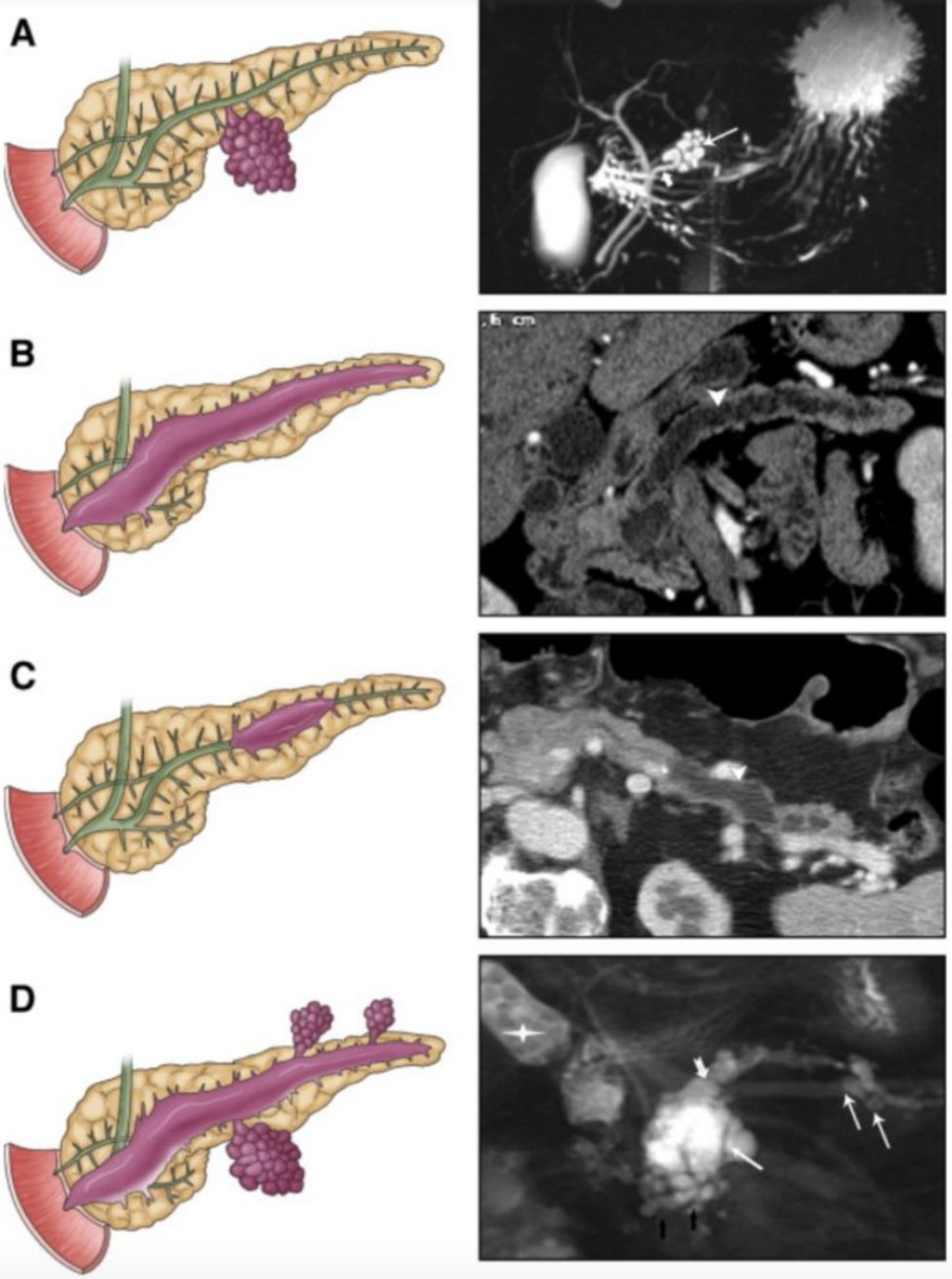
Servin-Rojas M Surgery 2023
Postlewait LM Jama 2017

Back to our case

- The patient had an EUS/FNA.
- There was an elevated CEA of 3702.
- The amylase was low at 63.
- The cytology was negative.
- She was referred for surgical resection.
- The pathology showed a mucinous cystadenoma.
- No further follow up needed.

Case #3

- 57 year old male presented to the ER with epigastric pain radiating to the back with nausea and vomiting.
- His LFTs were normal.
- His Lipase was 7525.
- He was noted to have pancreatitis.
- His initial CT scan in the ER showed evidence of fat stranding around the head of the pancreas. There was a question of a cystic lesion in the HOP.
- He was admitted, given a few boluses of LR and kept NPO.
- He recovered from his pancreatitis.
- He had a follow up MRCP.



Side branch IPMN*

Main duct IPMN**

Segmental IPMN

Mixed duct IPMN

Sahani DV Clin Gastro Hep 2009

Branched IPMN

- Most common pancreatic cyst.
- Solitary or multifocal lesions
- Pancreatic duct is not dilated

- Pathology: Dilated pancreatic ductal segments lined by intraductal dysplastic epithelium with mucous-secreting cells

- Occur in men in their 60s.

- 50% occur in the head.

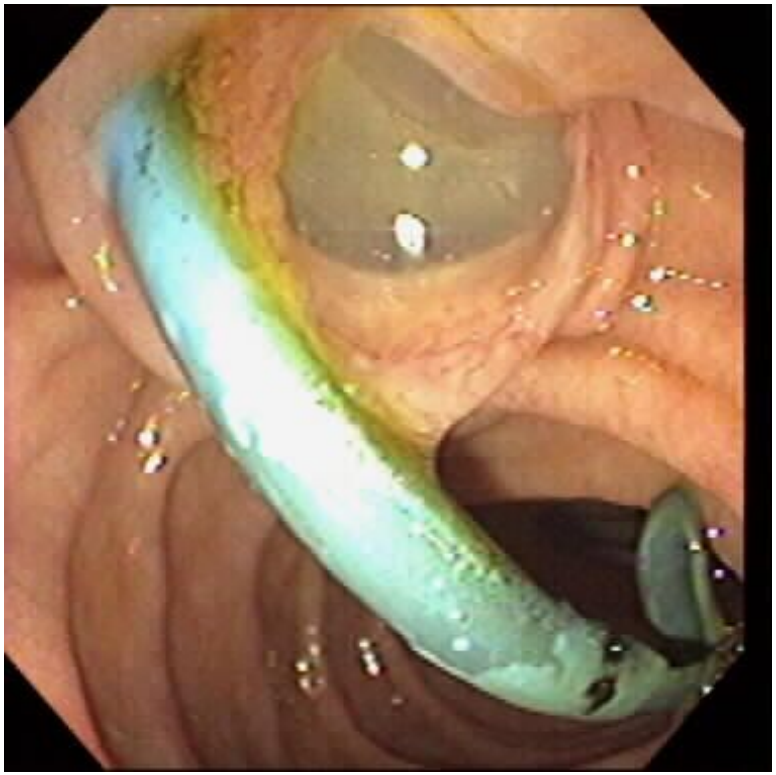
- Patients may present with idiopathic recurrent pancreatitis due to thick mucin occluding the pancreatic duct orifice.

Side Branch - IPMN

- Typically seen as multiple small cysts throughout the pancreas with a normal pancreatic duct.
- Follow a more indolent course as compared with main duct and mixed type.
- Rate of malignancy at 10 years is 6%.
- Ok to follow with MRI vs EUS
- If stable for 5 years then consider no further follow.

Han Y et al J Hepatobiliary Panc 2021

Main Duct IPMN



Pancreatoscopy

Main Duct - IPMN

- Dilated PD (>5mm) without a cystic component.
- About 30-40% of patients have invasive carcinoma at the time of diagnosis.
- Majority of patients are symptomatic.
- Definitive treatment is resection with clear margins.
- Have a 80% malignancy rate by 10 years.

Tanaka Pancreas 2018
Han J Hepatobiliary Panc 2021

IPMN

- Increased suspicion for malignancy:

Moderate Risk	High Risk
Cyst >3cm	
Main PD 5-9mm	Main PD >10mm
Non-enhancing nodule	Enhancing nodule
Cytology: Atypical cells	Cytology: HGD/CA
Pancreatitis	Jaundice

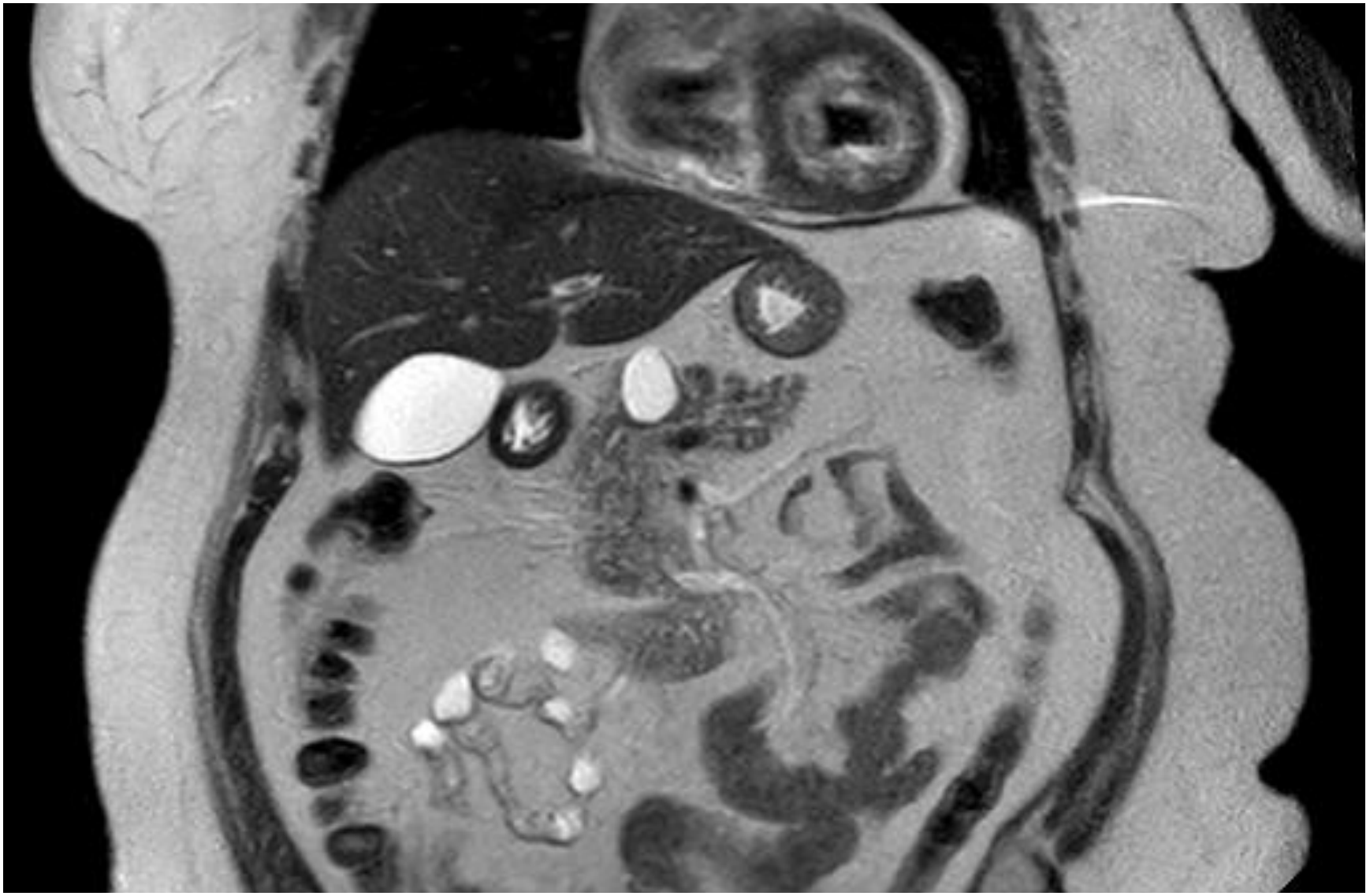
Back to our patient

- He recovered from his pancreatitis.
- He eventually underwent surgical resection of the side branch IPMN as a cause for his pancreatitis.

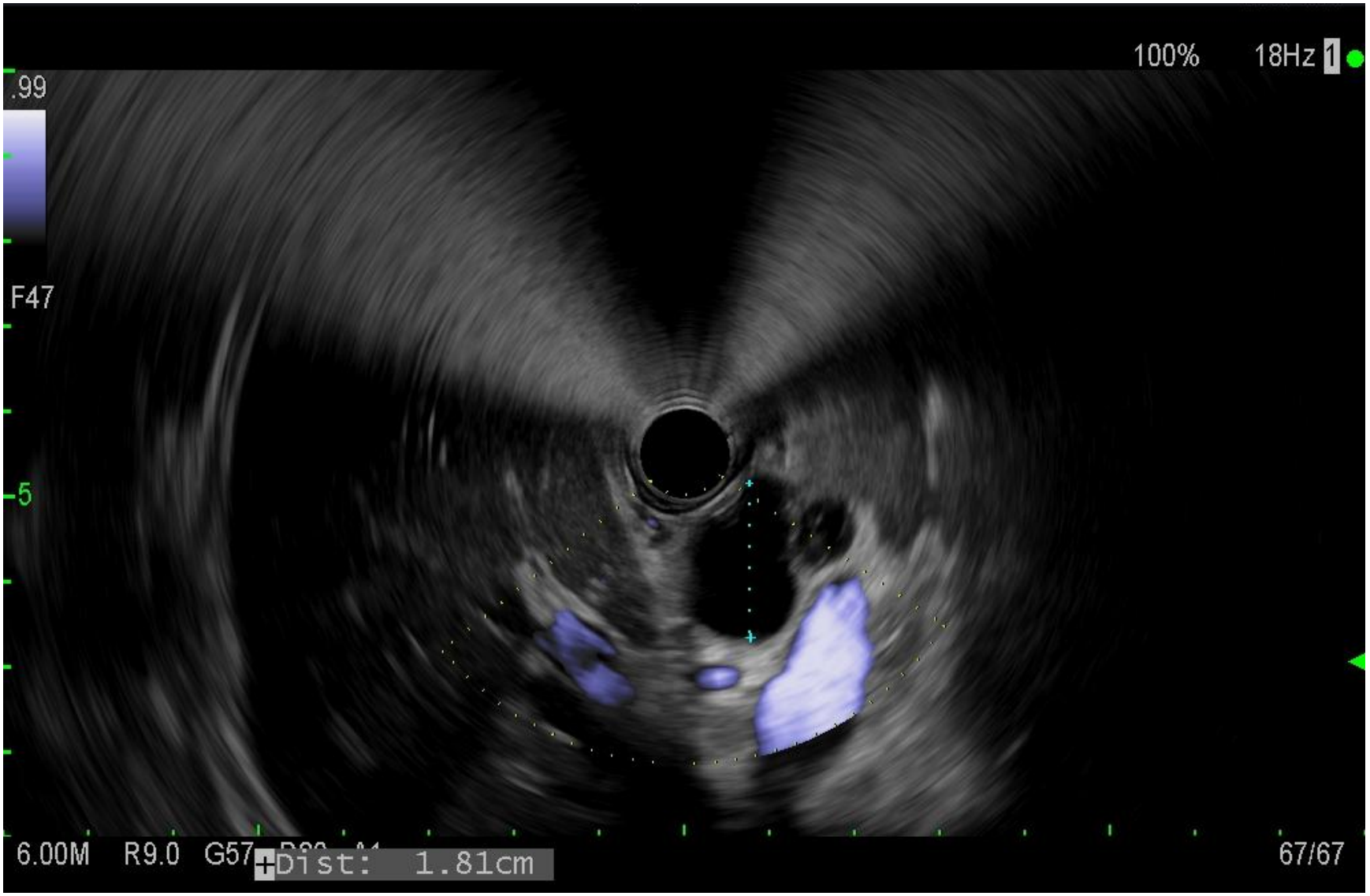
Case #5

- 52 year old female with a history of CAD presented to the ER with chest pain.
- She was ruled out for an MI and had a CT scan of her chest.
- The CT scan of the chest revealed a cystic lesion in the pancreas.
- She denied a history of pancreatitis.
- Her amylase and lipase were normal at the time of this presentation.

MRI



EUS



FNA performed

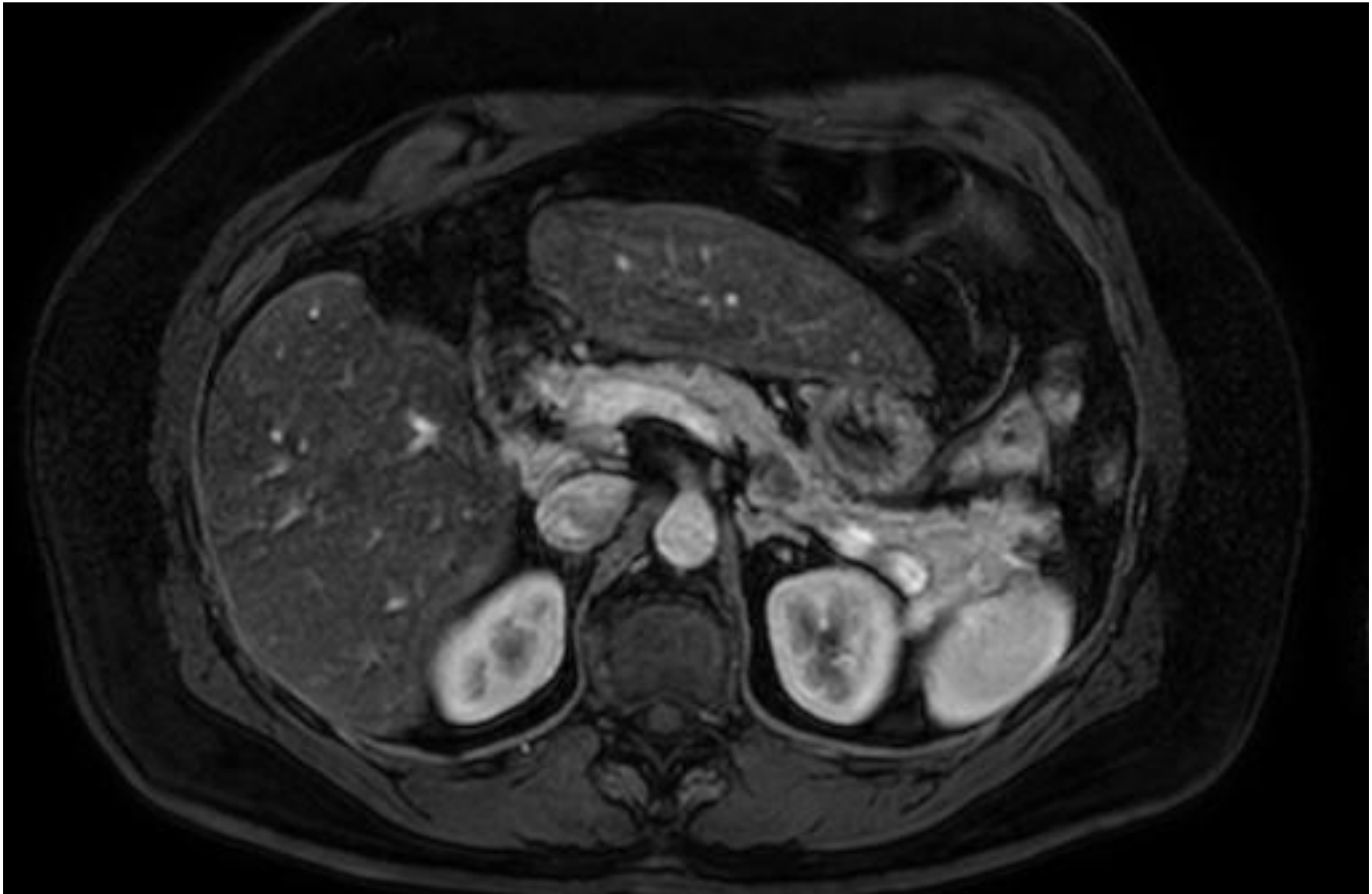
- CEA 2.6
- Amylase 56
- Cytology revealed a neuroendocrine tumor of the pancreas.
- She had a cyst enucleation.
- 2 year follow up: No recurrence

Cystic pancreatic neuroendocrine tumors

- Rare, account for 8% of cystic neoplasms
- About 10% of PENs are cystic
- May be symptomatic through hormone production.
- Irregularly, thickened wall
- Fluid is bland hemorrhagic fluid
- Target solid component

Case

- 56 year old female who has had intermittent RUQ pain for about one year.
- The pain has progressively gotten worse.
- Not related to eating.
- No weight loss.
- No family history of pancreatic cancer.
- She had a CCY in 2018.



Solid Pseudopapillary tumors

- Account for about 5% of cystic neoplasms
- Female predominant in their 30s.
- CT: cystic lesion
- EUS: solid and cystic
- FNA: Highly cellular with branching papillary structures and staining for vimentin and central myxoid stroma
- 15% are malignant.
- Surgical resection.

Evaluation of Pancreatic Cysts

Diagnostic Work Up

- High resolution CT scan with IV contrast vs MRI/MRCP
  - Location and size of cyst
  - Overview of other intra-abd organs
  - MRCP determine communication with duct
  - MRI preferred over CT

- EUS
  - Minimally invasive endoscopic procedure
  - Ability to evaluate the pancreas and other areas in the upper abdomen
  - Further define the cyst
  - Perform a FNA

Indications for EUS

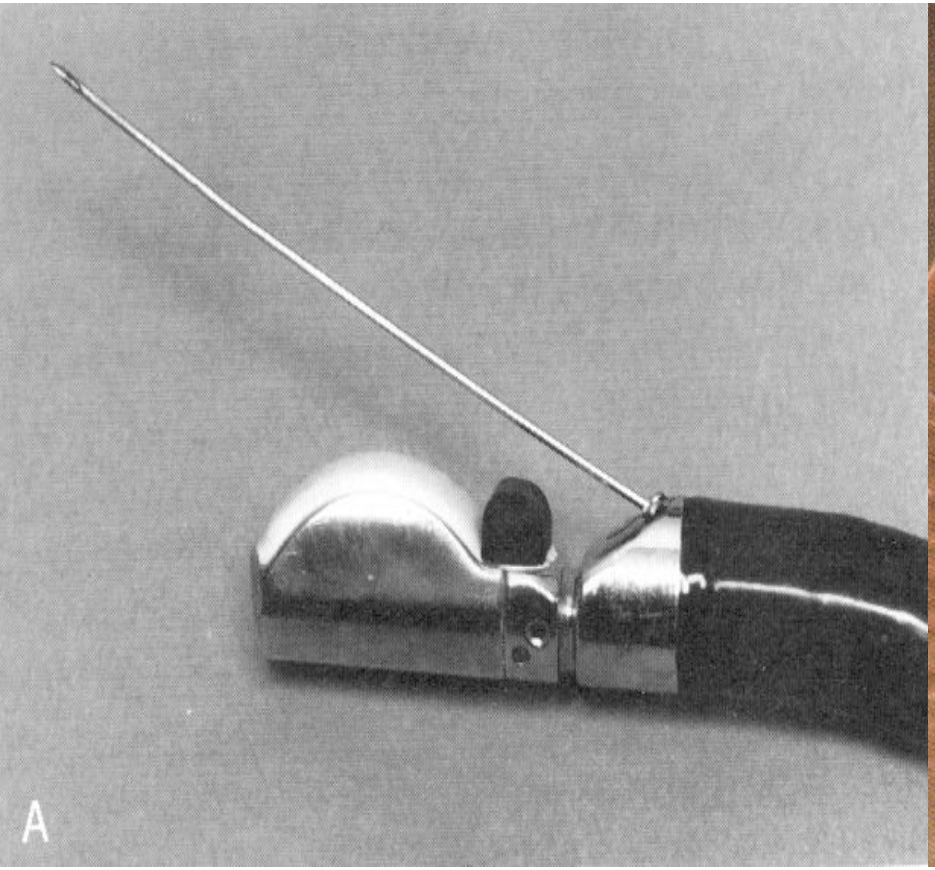
- Worrisome features on MRI.
- Pancreatic cysts with new onset or worsening DM
- Rapid increase in the size of the cyst (>3mm/yr)
- Jaundice secondary to the cyst
- Acute pancreatitis
- Significantly elevated CA 19-9

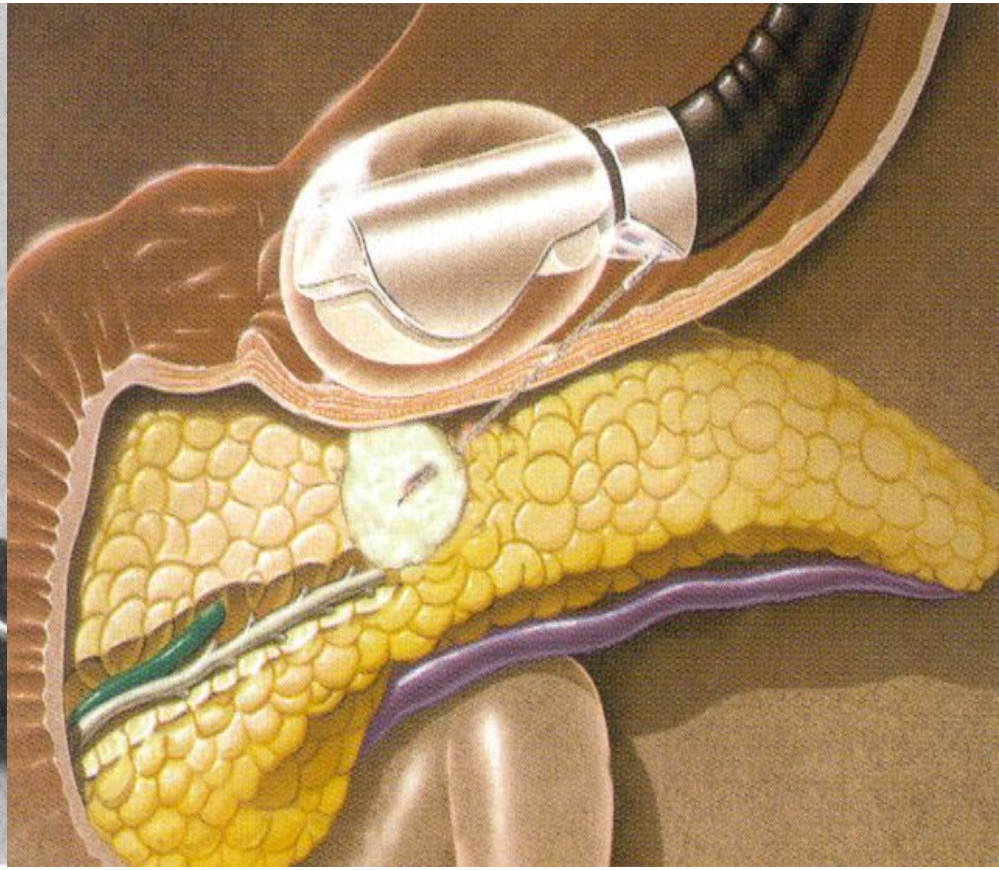
Role of EUS in differentiating malignant and benign pancreatic cystic lesions

- Conflicting results of the accuracy of morphology using EUS alone.
- No single set of defining features
- Marginal accuracy and interobserver agreement
  - accuracy 40-93%
- Operator dependent
- Clinical history is important

Ahmad AJG 2001
Ahmad GIE 2003
Sedlack GIE 2002

Fine Needle Aspiration





Analysis of Cystic Fluid

	Cytology	Amylase	CEA	Viscosity	Mucin
Serous cystadenomas	Glycogen-rich	↓	↓	↓	Negative
Mucinous cystic neoplasms	Mucinous	↓	↑↑	↑	Positive
Pseudocysts	Inflammatory	↑↑↑	↓	↓	Negative
IPMN	Mucinous	↑↑↑	↑	↑	Positive

FNA and Cyst Fluid Analysis

- CEA cut off 192 ng/ml, 79% accuracy for mucinous vs. non-mucinous
- Cytology alone only 59%
  - Increased when solid component present
- Evacuate cyst fluid contents
- Target solid component when present
- Safe, 2% complication rate
-
- Routine use of prophylactic antibiotics remains controversial

Cooperative Pancreatic Cyst Study

Glucose

- Similar sensitivity and specificity as CEA.
- Cutoff of <50 mg/dl suggests a mucinous cyst with a sensitivity ranging from 89-92% and specificity 75-86%.
- A pseudocyst may have a low glucose as well.
- Readily available
  - Glucometer vs lab

Different Techniques

- Standard: Drain fluid

- Other options include:

  - Brushings of the wall of the cyst
  - FNA of the wall of the cyst
  - Biopsy of the wall
  - Needle confocal microscopy

DNA Analysis

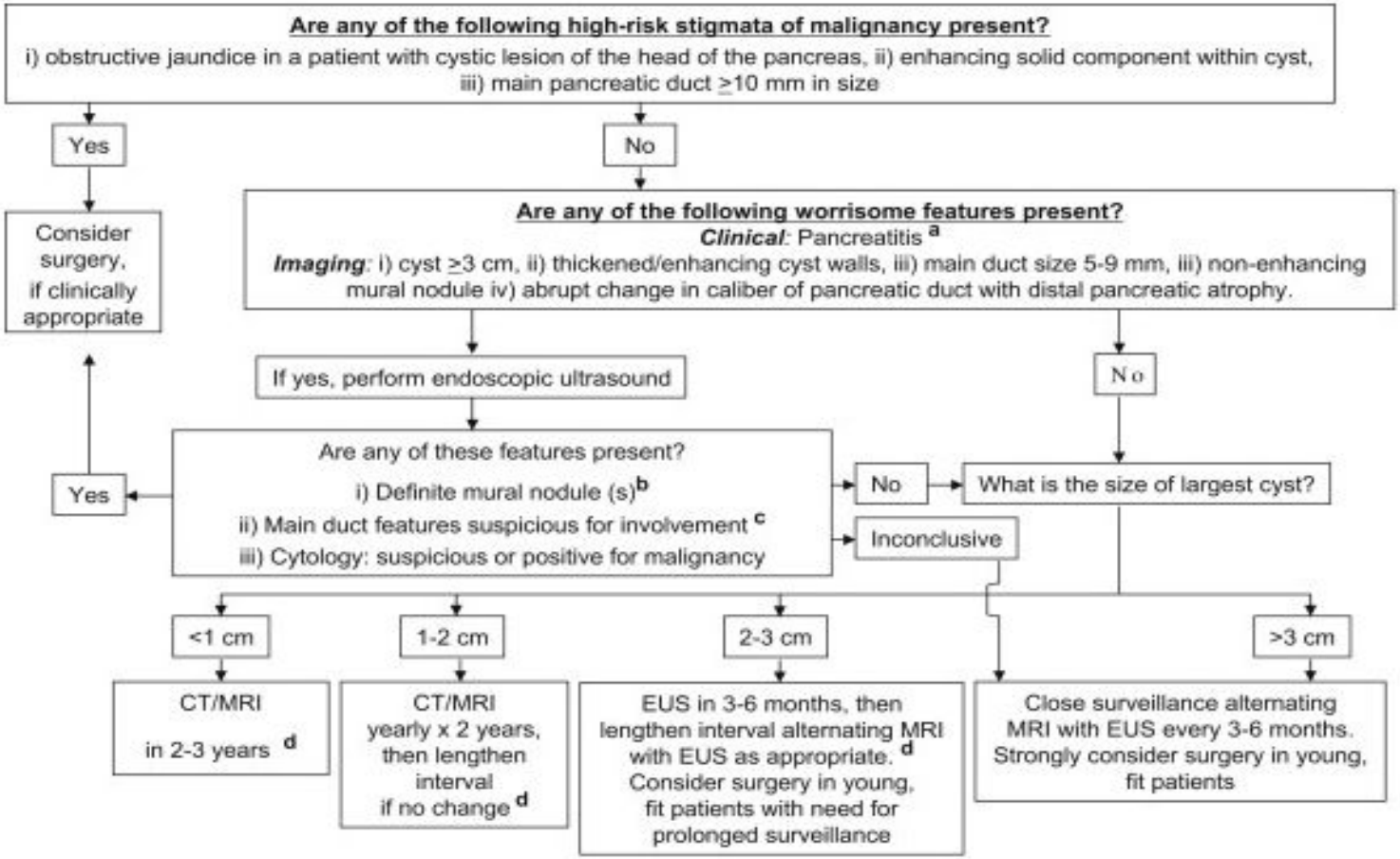
- Prospective, multicenter trial of 113 patients
- Requires only a few drops of fluid
- Predictors of mucinous cysts:
  - Presence of k-ras mutation
  - Higher number of microsatellite loss
  - Higher mutational amplitude
- Specificity of 96%
- May be useful where the diagnosis is unclear.

Khalid, GIE, 2009

Molecular Genetic Testing with Next-Generation Sequencing

- KRAS, GNAS and BRAF associated with a mucinous cyst that are a precursor to CA
- TP53, SMAD4, PIK3CA, CDKN2A, PTEN predict that progression to advanced lesions
- Retrospective review of 440 patients with cysts with NGS.
- Sensitivity 75%
- Specificity 95.6%
- Cysts without worrisome features and high risk mutation, shortened surveillance interval.
- Cysts with worrisome features and high risk mutation, consider surgery.

Jones, DDW 2023



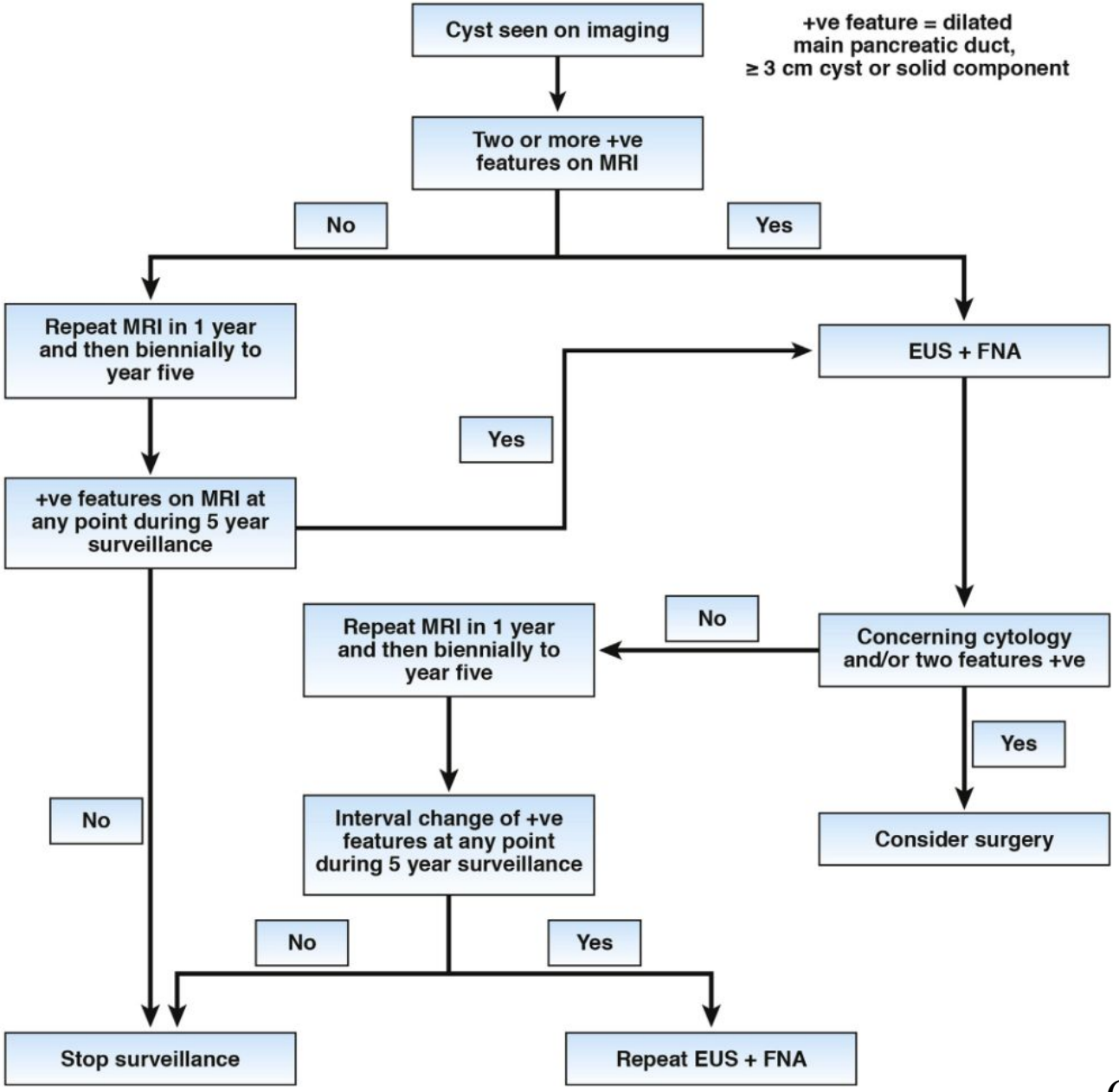
a. Pancreatitis may be an indication for surgery for relief of symptoms.
b. Differential diagnosis includes mucin. Mucin can move with change in patient position, may be dislodged on cyst lavage and does not have Doppler flow. Features of true tumor nodule include lack of mobility, presence of Doppler flow and FNA of nodule showing tumor tissue
c. Presence of any one of thickened walls, intraductal mucin or mural nodules is suggestive of main duct involvement. In their absence main duct involvement is incolclusive.
d. Studies from Japan suggest that on follow-up of subjects with suspected BD-IPMN there is increased incidence of pancreatic ductal adenocarcinoma unrelated to malignant transformation of the BD-IPMN(s) being followed. However, it is unclear if imaging surveillance can detect early ductal adenocarcinoma, and, if so, at what interval surveillance imaging should be performed.

Fig. 2. Algorithm for the management of suspected BD-IPMN.

Updated Sendai guidelines

Management of Asymptomatic Neoplastic Pancreatic Cysts

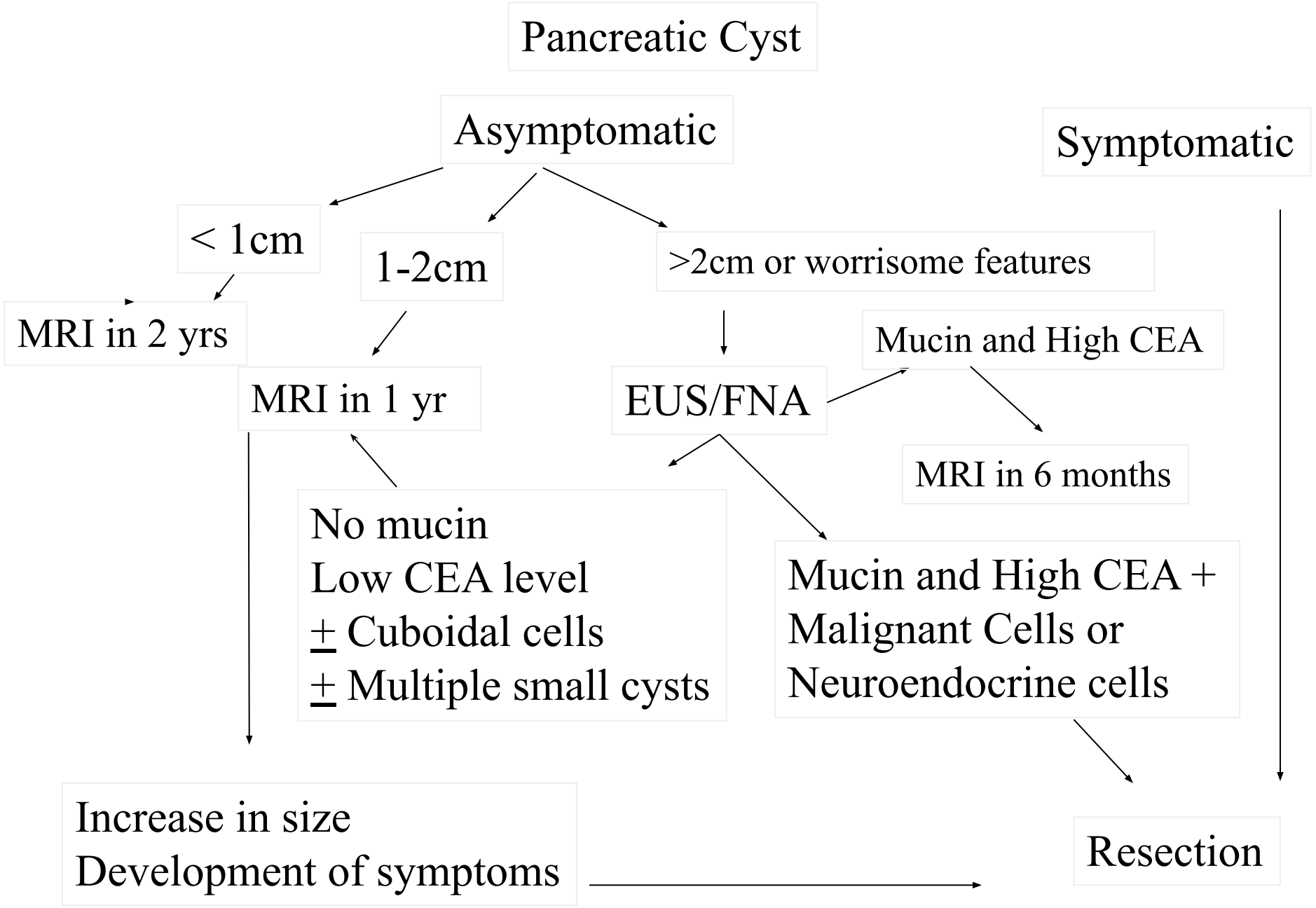
Clinical Decision Support Tool



Gastro 4/2015

General Principles of Management

- Not a surgical candidate ⇨ Discontinue surveillance
- High risk stigmata/Symptoms ⇨ Surgery
- Worrisome features ⇨ EUS


Pancreatic Cyst
Asymptomatic
Symptomatic
< 1cm
1-2cm
>2cm or worrisome features
MRI in 2 yrs
MRI in 1 yr
EUS/FNA
Mucin and High CEA
MRI in 6 months
No mucin
Low CEA level
± Cuboidal cells
± Multiple small cysts
Mucin and High CEA +
Malignant Cells or
Neuroendocrine cells
Increase in size
Development of symptoms
Resection

Ethanol Ablation

- Increasing number of studies have demonstrated a role of ethanol ablation of cysts.
- Unilocular or a cyst with few cavities
- 2-5cm in size
- Poor surgical candidate or refusing surgery
- The cyst cavity is lavaged with 80% ethanol.
- Follow up of 9 patients in a median of 26 months revealed no evidence of cyst recurrence.
- Larger studies showed that ⅓ resolved.
- Significant risk of pancreatitis

DeWitt, GIE, 2010
Canakis GIE 2020

CHARM Trial

- Prospective, randomized, double blind trial
- 22 patients with mucinous cystic neoplasms from 1-5cm
- One grp ethanol with paclitaxel and gemcitabine and second grp no ethanol
- 6 months 90 vs 91% volume reduction
- 60% ablation at 6 months
- 75% ablation at one year
- One patient developed pancreatitis
- A larger NIH trial is underway to determine the correct formula.

Moyer, DDW, 2015

Future

- Improved predictors of malignancy:
  - Molecular analysis
    - Next generation sequencing
  - Direct cystoscopy
  - Confocal laser endomicroscopy

- Tailoring surveillance to high risk patients

- Endoscopic treatment:
  - Injection of chemotherapy

Summary

- Cystic neoplasms are now the most common cystic lesions of the pancreas.
- Overall low rate of malignancy
- Management based on clinical presentation, comorbidities and EUS/FNA findings.

References

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