Pancreatic Cysts are Diverse

- Non-Mucinous
  - Serous
  - Pseudocyst
  - Neuroendocrine
  - Adeno Ca
  - Pseudopapillary
  - Lymphoepithelial

- Mucinous
  - IPMN
  - MCA
Pancreatic Cysts are Diverse

Pancreatic Cyst

Non-Mucinous
- Serous
- Pseudocyst
- Neuroendocrine
- Adeno Ca
- Pseudopapillary
- Lymphoepithelial

Mucinous
- IPMN
- MCA

Pancreatic Cysts are Common

- Aging population
- More imaging

Number of ambulatory visits in US with MRI/CT/PET
Management seems simple

- Surveillance
- Surgery

Diagnosis is Difficult

- ERCP
- MRCP
- CT/MRI
- Symptoms
- Cyst Fluid Analysis
- Cytology
- Patient age
- Patient anxieties
- Patient comorbidities
- Serologic Tumor Markers

Symptoms

Cyst Fluid Analysis

ERCP

MRCP

CT/MRI

Cytology

Patient age

Patient anxieties

Patient comorbidities

Serologic Tumor Markers
Fukuoka Guidelines

- High risk stigmata - Surgery
  - Obstructive jaundice
  - Enhancing solid component
  - MPD > 10 mm

- Worrisome features - EUS
  - Cyst > 3 cm
  - Thickened/enhancing cyst wall
  - MPD 5 to 9 mm
  - Non enhancing mural nodule
  - Abrupt change in caliber of MPD with upstream atrophy

- No high risk stigmata or worrisome features - Surveillance

Tanaka M. Pancreatology 2012;12:183
How good are the Fukuoka Guidelines?

- 194 patients who had surgery for pancreatic cyst
- Fukuoka guidelines applied retrospectively
- 19% had invasive Ca or HGD
  - PPV 33%
  - NPV 88%
- No cancers missed but few patients with HGD not detected

But!!!

- All patients sent to surgery: no control group, selection bias
- Fukuoka guidelines accurately identify patients with advanced neoplasia (cancer/HGD)
- Surgery is recommended for many patients with no neoplasia

Kaimaklotis P. Clin Gastroenterol Hepatol 2015;13:1808

Most patients with IPMN day from other causes

- 725 patients with IPMN
  - 55% surgery
  - 45% observation
- Charlson comorbidity index (CACI)
- 78% of deaths not related to IPMN
- CACI was able to identify patients with high risk of death from non-IPMN causes

You cannot make asymptomatic patient feel better

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts

Santhi Swaroop Vege, Barry Ziring, Rajeev Jain, and Paul Moayyedi, and the Clinical Guidelines Committee

Vege SS. Gastroenterology 2015;148:819
The AGA Guidelines

• Only for asymptomatic cysts
• Only incidental cyst
• Only for patients with no FH of pancreatic Ca
• Excluded
  – Main duct IPMN
  – Mixed type IPMN
  – Cystic neuroendocrine tumors
  – Adeno Ca with cystic degeneration
  – Pseudopapilary tumors
  – Mucinous cyst adenomas

The AGA Guidelines

• Only for asymptomatic, incidentally found side branch IPMN
The Good the Bad and The Ugly

The Good

- Evidence based approach
- Exhaustive literature search
- Use of the GRADE system*
- Strength of the recommendation is provided

*Guyatt GH. BMJ 2008;336;924
The Bad

• The quality of the evidence is low
• 8/10 recommendations are “conditional:”
  – Strong: clinical decision should apply to most patients
  – Conditional: significant number of patients could have a different approach

*Guyatt GH. BMJ 2008;336;924

Strong Recommendations

1. The AGA recommends that before starting any pancreatic cyst surveillance program, patients should have a clear understanding of programmatic risks and benefits.

8. The AGA recommends that if surgery is considered for a pancreatic cyst, patients are referred to a center with demonstrated expertise in pancreatic surgery. (Strong recommendation, very low quality evidence)
Conditional Recommendations but Most of Us Will Agree

3. The AGA suggests that pancreatic cysts with at least 2 high-risk features, such as size ≥3 cm, a dilated main pancreatic duct, or the presence of an associated solid component, should be examined with EUS-FNA. (Conditional recommendation, Very low quality evidence)

5. The AGA suggests that significant changes in the characteristics of the cyst, including the development of a solid component, increasing size of the pancreatic duct, and/or diameter ≥3 cm, are indications for EUS-FNA. (Conditional recommendation, Very low quality evidence)

Arbitrary Recommendations

9. The AGA suggests that patients with invasive cancer or dysplasia in a cyst that has been surgically resected should undergo MRI surveillance of any remaining pancreas every 2 years. (Conditional recommendation, Very low quality evidence)

- Why MRI?
- Why every 2 years?
10. The AGA suggests against routine surveillance of pancreatic cysts without high-grade dysplasia or malignancy at surgical resection. (Conditional recommendation, Very low quality evidence)

- Very little data on the rate of recurrence or development metachronous lesions
- 4% recurrence in low and intermediate grade IPMN *


The Ugly

- EUS indicated only if 2 high risk features
- EUS not recommended at baseline and risk stratification is done exclusively by MRI
  - EUS imaging has higher resolution than MRI
  - EUS-FNA can detect more cancers than high risk stigmata
  - How can we exclude neuroendocrine, pseudopapillary, adeno Ca, mucinous cyst adenomas?
  - How about contrast enhanced EUS?
  - How about new available therapies – RFA or ETOH ablation?
  - How about new cyst fluid markers and new devices?
Available Markers

Kaplan Meier (n= 492 patients):

Al-Haddad MA. Endoscopy. 2015;47(2):136

New Markers

• 130 pts with resected pancreatic cyst: 12 serous cystadenomas, 10 solid pseudopapillary, 12 MCN, and 96 IPMN
• BRAF, CDKN2A, CTNNB1, GNAS, KRAS, NRAS, PIK3CA, RNF43, SMAD4, TP53, and VHL
• Molecular markers + clinical features that classified cyst type with 90%-100% sensitivity and 92%-98% specificity.
• 67 of the 74 patients correctly identified as not requiring surgery
• 91% reduction of the number of unnecessary operations

Springer S. Gastroenterology. 2015;149(6):1501
Available New Technology
EUS Micro-forceps

- 68 y/o male with one episode of acute abd pain (?kidney stone vs ?pancreatitis)
- CT 22 mm cyst in the body and mildly dilated MPD (5 mm): pseudocyst vs IPMN
- EUS with micro-forceps biopsy: mucinous cyst
- Surgery: IPMN with high grade dysplasia

The Ugly

2. The AGA suggests that patients with pancreatic cysts <3 cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics. (Conditional recommendation, Very low quality evidence)

- Should you follow with the same intensity 5 mm cyst and 25 mm cyst?
The Ugly

4. The AGA suggests that patients without concerning EUS-FNA results should undergo MRI surveillance after 1 year and then every 2 years to ensure no change in risk of malignancy. (Conditional recommendation, Very low quality evidence)

• Should you follow with the same intensity cyst with no high risk MRI features (guideline 2) and cyst with 2 high risk MRI features but negative EUS (guideline 4)?

The Ugly

6. The AGA suggests against continued surveillance of pancreatic cysts if there has been no significant change in the characteristics of the cyst after 5 years of surveillance or if the patient is no longer a surgical candidate. (Conditional recommendation, Very low quality evidence)

• How long does it take for cancer to develop?
• Patient specifics not factored in
  – Old patients: Prevalent cancer
  – Young patients: Incident cancer
Key Principles behind the AGA Guidelines

• Evidenced based
• Cyst are common
• Cancer is rare
• Cost of surveillance is high
• Surgery has high complications rates
• Cost cutting

Key Points of the AGA Guidelines

• Narrow focus: Side branch IPMN
• Baseline risk stratification based on MRI alone
• EUS-FNA indicated only if 2 high risk features
• Less frequent surveillance
  • Same surveillance interval
    – Cyst with no high risk features
    – Cyst with 1 high risk feature
    – Cyst with 2 high risk features and negative EUS-FNA
• Stop surveillance after 5 years if no change
• Higher threshold for surgery: 2 high risk features AND “concerning” EUS-FNA
Pancreatic Cysts: The AGA Guidelines

Low quality evidence = Expert opinion


... Another point to emphasize is that this guideline is primarily for the practicing community gastroenterologist and their patients, and not for the tertiary and quaternary centers that deal with more complex problems related to pancreatic cysts.
Fukuoka Guidelines

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