Future Diagnosis of Pancreatic Cysts: Molecular and Confocal Analysis

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Professor of Medicine: Mayo Clinic Florida
Editor in Chief: GIE
Case 1

65 yr old female, otherwise healthy, intermittent pelvic pain. CT performed
Pancreatic duct

Pancreatic cystic mass
EUS-FNA

2cm simple cyst, no mural nodules
Small side branch connection to main PD
No Main PD dilation

Cytology: Mucinous epithelium, no dysplasia
Fluid CEA 257, Amylase 7563

Diagnosis: Side Branch IPMN, low grade
How Common Are Cysts/IPMN?

MRI done for non-pancreatic reason

Random sample of MRIs (50/year), all re-read by expert panc radiologist

Prevalence assess as function or year, MRI hardware (1-3T), software

41% had at least 1 cyst (median 4mm)
14% had IPMN (all low risk)
Clinical Dilemmas

- What is it?
  - Mucinous vs Serous vs Non-neoplastic?
- Is it malignant, likely to become malignant?
- Management
  - Resection vs Observation vs Ablation vs Nothing
- The patient is very worried (so are you)
  - Should you…
    - Reassure her that all if fine OR
    - Tell her we really don’t know what it is or the risk of cancer!
In the ancient past......

- CT scan: Cyst is large or small
- EUS: Mural nodule
- FNA: CEA, Amylase
- Sendai Guidelines
  - Big (3cm), mural nodule, Main Duct, symptoms → Surgery
  - Small → Observe
Japanese Multicenter Study of IPMN

- 1379 Cases
  - 1024 surgically resected
    - Invasive cancer: 44%
    - Borderline: 1.1%
    - Adenoma: 48%
    - Hyperplasia: 6%
  - 355 observed (median 40 months)

Suzuki: Pancreas, 2004;28:241-246
## Predictors of Invasive Cancer:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Benign</th>
<th>Cancer</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>35%</td>
<td>50%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Main Duct</td>
<td>40%</td>
<td>60%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Main+Branch</td>
<td>35%</td>
<td>65%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mural Nodule</td>
<td>28%</td>
<td>63%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cyst size</td>
<td>28 +/-14</td>
<td>35 +/-18</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Main duct size</td>
<td>9 +/- 5</td>
<td>13 +/- 10</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Suzuki: Pancreas, 2004;28:241-246
Natural History on Non-Resected IPMN

- 355 Patients
  - Follow up: 40 months (0-225)
  - Serial CT or MRI exams
  - 303 Branch duct: 31 Main duct
    - Increased in size: 11%
    - Decreased in size: 13%
    - No change in size: 77%
  - None developed cancer

Suzuki: Pancreas, 2004;28:241-246
# Cooperative Pancreatic Cyst Study

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sens</th>
<th>Spec</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA (192)</td>
<td>73%</td>
<td>84%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CA125</td>
<td>83%</td>
<td>37%</td>
<td>0.183</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>19%</td>
<td>94%</td>
<td>0.82</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>68%</td>
<td>62%</td>
<td>0.004</td>
</tr>
<tr>
<td>CA 72-4</td>
<td>80%</td>
<td>61%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

341 patients: 112 surgically resected
Accuracy for mucinous vs non mucinous

Brugge et al. Gastroenterology 2004;126:1300-06
ROC curve for cyst fluid CEA concentrations (ng/mL; log scale) for differentiating between mucinous and nonmucinous cystic lesions.

Brugge et al, Gastroenterology 2004
In 2012 We Got New Guidelines: Fukuoka
Size, mural nodule, EUS

Are any of the following high-risk stigmata of malignancy present?
- Obstructive jaundice in a patient with a pancreatic head cystic lesion
- Enhancing solid component within the cyst
- Dilated main pancreatic duct (≥10 mm)

Yes
Consider surgery if appropriate

No

Are any of the following worrisome features present?
- Clinical: Pancreatitis
- CT Imaging: ≥3 cm cyst, thickened/enhancing cyst wall, main duct size 5–9 mm, non-enhancing mural nodule, abrupt change in pancreatic duct caliber with distal atrophy, or lymphadenopathy

Yes
Yes, perform EUS-FNA

No

What is the size of the largest cyst?

<1 cm
- CT/MRI in 2 to 3 y

1 to 2 cm
- Annual CT/MRI for 2 y, then lengthen interval if no change

2 to 3 cm
- EUS in 3 to 6 mo, then lengthen interval with alternating MRI & EUS. In young fit patients, consider surgery

Inconclusive

>3 cm
- Alternating MRI & EUS every 3 to 6 mo. In young fit patients, consider surgery
In 2015 We Got Newer Guidelines: AGA
Less EUS, Less Surveillance

- Cyst seen on Imaging (referral for MRI)
- Two or more +ve features on MRI
  - No: Repeat MRI in 1 y & then biennially for 5 y
  - Yes: EUS-FNA
    - +ve features = dilated main pancreatic duct, ≥3 cm cyst or a solid component
      - Yes: Concerning cytology and/or 2 +ve features
        - Yes: Consider Surgery
        - No: Repeat EUS-FNA
      - No: Repeat EUS-FNA
    - No: +ve features on MRI during 5 y surveillance
      - No: Stop Surveillance
      - Yes: Repeat EUS-FNA
Assessing the Impact of Recent Guidelines

Lekkerkerker, et al.
GIE 2016;85:1025 - 1031

- Large academic center in Europe
- Evaluated 115 surgically resected panc cysts
  - Post-hoc assessed accuracy of each guideline

<table>
<thead>
<tr>
<th>Guideline</th>
<th>IAP</th>
<th>AGA</th>
<th>European</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of IPMN patients with HGD/Cancer where surgery was justified (“PPV”)</td>
<td>54%</td>
<td>59%</td>
<td>53%</td>
</tr>
<tr>
<td># of Missed Cancer/HGD if guideline applied</td>
<td>0</td>
<td>4 (12% of all HGD/Cancer)</td>
<td>0</td>
</tr>
</tbody>
</table>
Assessing the Impact of Recent Guidelines

Singhi, Aatur D. et al.  
GIE, 2016;83:1107 - 1117.e2

- UPMC cohort of 225 Cyst Patients, all with EUS FNA; 41 with confirmed path diagnosis
- Compared current AGA guideline and novel molecular testing of cyst fluid (KRAS, GNAS, VHL, TP53, PIK3CA, PTEN)

<table>
<thead>
<tr>
<th>Accuracy for HGD/Cancer</th>
<th>AGA</th>
<th>Molecular Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>62%</td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>79%</td>
<td>90%</td>
</tr>
<tr>
<td>PPV</td>
<td>57%</td>
<td>79%</td>
</tr>
<tr>
<td>NPV</td>
<td>82%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Pittsburgh Guideline: Molecular + Clinical

**MRI Evaluation**
- Cyst >1.5 cm
- Solid component within the cyst
- Dilated main pancreatic duct (>0.5 cm in size)
- Clinical symptoms related to the cyst
- Family history of pancreatic cancer

**EUS-FNA** (with cytology, molecular testing and chemical analysis)

- Criterion 1: Suspicious or positive for a malignant neoplasm by cytopathology
- Criterion 2: Mucinous cyst ≥3 cm with (a) main duct dilatation and/or (b) definitive mural nodule
- Criterion 3: Detection of KRAS and/or GNAS mutations with (a) TP53 and (b) PIK3CA or PTEN mutations by molecular testing.

**Yes**
- Consider surgery

**No**
- Continue with algorithm
Natural History of Low Risk IPMN: Impact of New Guidelines

International Intraductal Papillary Mucinous Neoplasms Registry
Long-Term Results Based on the New Guidelines

Maria Morris, MD,* Massimo Raimondo, MD,* Timothy A. Woodward, MD,* Verna J. Skinner, MS,† Paolo G. Arcidiacono, MD,‡ Maria C. Petrone, MD,§ Claudio De Angelis, MD,§ Selene Manfrè, MD,§ Silvia Carrara, MD,∥ Manol Jovani, MD,∥ Pietro Fisaroli, MD,∥∥ and Michael B. Wallace, MD, MPH*

• Mayo Florida International Registry (6 Centers US, Europe)
• Describes natural hx of low risk (by AGA guideline)
• 1180 pts with IPMN
  • Median fu 3 years (1-13)
  • Incidence of cancer/HGD 34.5/1000 pt years
• 431 low risk IPMN
  • 8/431 progressed to HGD/cancer, IR 4.9/1000 pt year
  • None progressed after 5th year (cohort 112 pts)

Kaplan Meier Curves: Does the “5 year rule” make sense?

All IPMN (n 1180)

Low Risk IPMN (n 431)

Instantaneous (by month) risk
Next-Generation Sequencing of Cyst Fluid

Key Findings

<table>
<thead>
<tr>
<th>KRAS or GNAS</th>
<th>Cyst Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS or GNAS</td>
<td>IPMN</td>
</tr>
<tr>
<td>TP53 or CDKN2A or SMAD4</td>
<td>Malignant</td>
</tr>
<tr>
<td>VHL</td>
<td>Serous</td>
</tr>
</tbody>
</table>

Jones, Brugge, Castillo, GIE 2016;83:140-48
Large Pacific IPMN Consortium

• Soon to merge
• Mayo-Columbia (1180+)
• Pacific-European (574+)
Summary of Current Data

• Current Guidelines (all available) have very limited accuracy when compared to surgery

• Surgical and EUS FNA series find up to 12% with “missed” cancer/hgd

• However natural hx studies suggest guideline identify a truly low risk group (Indolent HGD)
Thank you
Priorities for Research?

• Registries
• Biobanks
• Imaging repositories
• CAD tools for radiological images
Discussion Points: Knowledge Gaps

• What long term natural history studies are needed to define low risk and identify risk factors for progression?
  • What is primary outcome/endpoint?
  • Secondary endpoints
  • Required imaging data (CT, MRI, EUS) at baseline and follow up?
  • AGA vs IAP algorithm
Discussion Points: Knowledge Gaps

• Biomarkers (cyst fluid, secretin-juice, blood)
  • Biobank now or perform molecular profiling now?

• Optimal imaging methods (EUS, CE-EUS, FNA, CT, MRI, Confocal)
  • Defining true prevalence
  • CAD of radiological images?