IPMN—
Controversies in the Diagnosis
and Management
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Disclosures

No conflicts of interest
Background

• Widespread use of cross-sectional imaging has increased the rate of discovery of small incidental pancreatic cysts
• Only 2% of cysts are malignant at diagnosis
• 0.4% risk of malignant transformation per year of surveillance

Intraductal Papillary Mucinous Neoplasm (IPMN)

- Papillary growths producing mucin involving main pancreatic duct or side branch
- Variable risk of malignancy
- Can cause recurrent pancreatitis
  - Main-duct IPMN 23-53%
  - Side-branch IPMN 34%

Ringold DA, Gastrointest Endosc 2009; 70: 488.
IPMN- types

Branch Duct

Main Duct

Mixed

Malignancy Risk

Main-Duct IPMN: 62%

Branch Duct IPMN: 26%

IPMN- Grades of Dysplasia

• Benign
  – Adenoma / low-grade dysplasia

• Borderline dysplasia

• Malignant
  – High-grade dysplasia
  – Invasive carcinoma
Controversies

- Making an accurate diagnosis
- Management - when to operate
- Main-duct IPMN
Diagnostic Accuracy

- **EUS Morphology**: 51%
- **Cytology**: 59%
- **CEA > 192**: 79%

Brugge WR, Gastroenterol 2004; 126: 1330.
CEA & Mucinous Cysts

- 761 pts, > 10 yrs
- EUS appearance: 47.9%
- Cytology: 57.7%
- CEA (> 110): 85.7%
  - Benign vs Malignant: No difference

Cytology was most useful for identifying malignant cysts

Cizginer S, Pancreas 2011; 40: 1024.
Fluid DNA Analysis

• Only requires 200 µL of fluid for analysis
• K-ras mutation
  – 96% specificity for mucinous cysts
  – Low sensitivity (11-45%)
  – High $$$

Khalid A. Gastrointest Endosc 2009; 69: 1095.
Targeted Cyst Wall FNA
Results

<table>
<thead>
<tr>
<th>Non-Dx</th>
<th>Mucinous Cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid</td>
<td>55.1%</td>
</tr>
<tr>
<td>Mucin. Cyst Wall</td>
<td>18.8%</td>
</tr>
<tr>
<td>Cyst Wall</td>
<td>36.2%</td>
</tr>
</tbody>
</table>

Hong S. Gastrointest Endosc 2012; 75: 775.
Management of IPMN
Review article

International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas

Masao Tanaka a,*, Carlos Fernández-del Castillo b, Volkan Adsay c, Suresh Chari d, Massimo Falconi e, Jin-Young Jang f, Wataru Kimura g, Philippe Levy h, Martha Bishop Pitman i, C. Max Schmidt j, Michio Shimizu k, Christopher L. Wolfgang l, Koji Yamaguchi m, Kenji Yamao n

Multifocal IPMN

- 25-41% of IPMN are multifocal
- There is no increased risk of malignancy
- Management strategies same as unifocal
High Risk Stigmata?
- Pancreatic cyst resulting in jaundice
  - Enhancing solid component
  - Main pancreatic duct diameter $> 10$ mm

Surgery

Worrisome Features
- Cyst size $> 3$ cm
- Thickened/enhancing cyst walls
- Main duct diameter $5-9$ mm
- Abrupt change in caliber of PD with distal atrophy

Yes, EUS
EUS-FNA

- Mural Nodule
- Malignant Cytology

YES

Surveillance with CT / MRI

NO

Surgery

Pancreatitis
<table>
<thead>
<tr>
<th></th>
<th>High Risk Group</th>
<th>Low Risk Group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst Resection</td>
<td>16%</td>
<td>3%</td>
<td>0.001</td>
</tr>
<tr>
<td>Pancreas CA development</td>
<td>23%</td>
<td>0.05%</td>
<td>0.0001</td>
</tr>
<tr>
<td>5-year survival</td>
<td>67%</td>
<td>83%</td>
<td>0.0001</td>
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</tbody>
</table>

# Sendai 2012 Validation Puerto Rico Data

<table>
<thead>
<tr>
<th>Table 3</th>
<th>High Risk (n = 14)</th>
<th>Low Risk (n = 70)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressed to Cancer</td>
<td>2 (14.3%)</td>
<td>1 (1.4%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Survival at 2 years</td>
<td>85.71%</td>
<td>100%</td>
<td>0.0014</td>
</tr>
<tr>
<td>Pancreatic Surgery</td>
<td>9 (64.3%)</td>
<td>3 (4.3%)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Fernandez M. ACP 2014
Results

Fig 5. Surgical Procedure Performed

- **High Risk**
  - Whipple Procedure: 56%
  - Distal Pancreatectomy: 44%

- **Low Risk**
  - Whipple Procedure: 33%
  - Distal Pancreatectomy: 66%

Fernandez M. ACP 2014
### Accuracy of Revised Sendai 2012 Without EUS

#### Premalignant/Malignant

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPMN</td>
<td>42</td>
</tr>
<tr>
<td>MCN</td>
<td>49</td>
</tr>
<tr>
<td>Solid Pseudopapillary Tumor</td>
<td>30</td>
</tr>
<tr>
<td>AdenoCA</td>
<td>28</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>19</td>
</tr>
<tr>
<td>GIST</td>
<td>6</td>
</tr>
<tr>
<td>Metastases</td>
<td>2</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>1</td>
</tr>
<tr>
<td>Retroperitoneal Sarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Serous Cystadenocarcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Benign

<table>
<thead>
<tr>
<th>Condition</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous Cystadenoma</td>
<td>80</td>
</tr>
<tr>
<td>Branch-duct IPMN</td>
<td>25</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>8</td>
</tr>
<tr>
<td>Non-neoplastic cyst</td>
<td>21</td>
</tr>
<tr>
<td>Lymphangioma</td>
<td>2</td>
</tr>
<tr>
<td>No lesion</td>
<td>2</td>
</tr>
</tbody>
</table>

Sendai 2012 Accuracy for Identifying Premalignant or Malignant Lesions

- **High Risk**
  - HOP lesion w jaundice
  - Solid nodule/component
  - Main PD ≥ 10 mm

- **Worrisome**
  - Presence of any of the above
  - Thickened, enhancing wall
  - Main PD 5 – 10 mm
  - Change in duct caliber w distal atrophy

- **Low-Risk**

  88% Premalignant/Malignant

  92.5% NPV
  *No Malignant IPMNs Missed*

The Problem with Sendai...

Too many patients undergo surgery for benign pancreatic disease
Mural Nodule or Mucin?

Mural Nodule or Mucin?

Rate of Cyst Growth and Risk of Malignancy in BD-IPMN

- 201 BD-IPMNs
- 17% operated
  - 8 Malignant cysts (23%)

- Cysts growing > 2 mm/yr had a 44% 5-yr risk of malignancy
- All malignant cysts had annual cyst growth > 4 mm/yr

Main-duct IPMN
IPMN- types

Branch Duct  Main Duct  Mixed

Malignancy Rate 36 – 100%
Do All Main-Duct IPMNs Need Surgery?

- Symptoms
  - Weight Loss (>5% in past 6 mts)
  - Steatorrhea
  - Jaundice
  - Abdominal Pain

69% Malignant IPMN

Asymptomatic main-duct IPMNs with MPD size ≤ 8 mm
9% Malignancy Risk

Deciding Extent of Resection
Endoscopic Tools

- EUS
- Intraductal ultrasound
- Pancreatoscopy
Incidental pancreatic cysts are being increasingly detected.

Management is based on risk of malignant progression.

Pancreatic cysts without high risk or worrisome features can be safely followed with periodic imaging (CT or MRI).
Summary

• Surgically-fit pts with main-duct or mixed type IPMNs should be considered for resection
• Sendai 2012 guidelines can accurately identify pts who can be observed
  – Limited in its ability to accurately identify malignant cysts
• Fluid DNA analysis is promising but further prospective studies are needed