Current Management of Pancreatic Cysts (IPMNs)

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Sea Pines General Surgery Update
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January 2006: 68 yo male with CLL, incidental cysts
Triphasic CT and EUS performed
EUS: No solid component, cyst fluid CEA 350 ng/ml

Pathology: IPMN, with 1 cm invasive tubular cancer, node negative.
Cystic lesions pancreas

Introduction

- Radiographic finding with a broad histologic differential:

  - Benign
    - Pseudocyst
    - Serous cystadenoma
    - Retention cyst
    - Lymphangioma
    - Acinar cell cystadenoma
  
  - “Pre-Malignant”
    - IPMN
  
  - Malignant
    - Mucinous Cystic Neoplasm
    - Adenocarcinoma
    - Neuroendocrine
    - Solid pseudopapillary
    - Lymphoma

  Observe → Resect
Introduction

• Controversy: Arguments favoring routine resection focused on inability to determine diagnosis without operation (cannot miss a cancer)

1995: “Given the current low morbidity and mortality of pancreatic resection in specialized centers, it is our policy to resect all cystic tumors unless invasion of neighboring structures or the general condition of the patient precludes it.”

2002:
*Society for Surgery of the Alimentary Tract:*
“The majority of patients with pancreatic cystic neoplasm referred to me are those with IPMN. These are all premalignant and should be resected.”
Cystic lesions pancreas

Overview

• Clinical significance of cystic lesions of the pancreas
• Accuracy of non-operative diagnosis
  • Serous cystadenoma
  • Mucinous cystic neoplasm
  • Intraductal papillary mucinous neoplasms (IPMN)
• IPMN (the wheat)
  • Histopathologic sub-types
    Genetic pathways
  • Current management recommendations
    Defining high-risk lesions
• Patient Outcomes
Clinical significance:

- de Jong et al.:
  - 2803 consecutive MRI (abdomen), mean age 51 yrs
  - 66 patients (2.4%) with cystic lesion pancreas
  - 4/66 lesions (6%) larger than 2cm

U.S.
Population: 317 million
Mean age: 40 years
Number of cystic lesions of the Pancreas:

\[ 317 \times 0.018 = 5.7 \text{ million} \]

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Cystic lesions pancreas

Clinical significance:

- Increasing identification and evaluation:
  MSKCC, 1995 – 2013: 2,245 patients in registry evaluated (GI or surgery) for a cystic lesion of the pancreas (577.2).

>2,400 clinic visits (577.2) in GI and surgery in 2013

Clinical significance:


![Graph showing increasing number of resections for Carcinoma and Non-carcinoma over years from 1995 to 2012. The graph has a y-axis labeled '# resected' ranging from 0 to 200, and an x-axis labeled 'Year' ranging from 1995 to 2013. The data points are color-coded with red for Carcinoma (n=1474) and yellow for Non-carcinoma (n=1093).]
Cystic lesions pancreas

Non-operative diagnosis

- Radiographic, endoscopic, and cytologic discrimination.

<table>
<thead>
<tr>
<th>Test</th>
<th>Accuracy (mucinous vs. non-mucinous)</th>
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</thead>
<tbody>
<tr>
<td>CT imaging</td>
<td>45% - 65%</td>
</tr>
<tr>
<td>EUS morphology</td>
<td>51%</td>
</tr>
<tr>
<td>Cytology</td>
<td>59%</td>
</tr>
<tr>
<td>Cyst fluid CEA</td>
<td>70% - 80%</td>
</tr>
</tbody>
</table>

Cystic lesions pancreas

Non-operative diagnosis

- Cyst fluid biomarkers

<table>
<thead>
<tr>
<th>Tumor Marker</th>
<th>Serous Cystadenoma</th>
<th>Mucinous Cystic Neoplasm</th>
<th>Intraductal Papillary Mucinous Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>CA 72-4</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>CA 19-9</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>CA 125</td>
<td>Low</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td>CA 15-3</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Amylase</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

CEA>200ng/ml: positive predictive value of 80 - 94%

Cystic lesions pancreas

Non-operative diagnosis: Serous cystadenoma

Radiographic appearance:
- Microcystic “honeycomb”
- Central Calcification
- “Solid component”

Endoscopic findings
- Cyst fluid CEA – low

Natural history
- Not metastatic
Cystic lesions pancreas

Non-operative diagnosis: Mucinous cystadenoma

Radiographic appearance
- Macrocystic
- Unique to women (ovarian stroma)
- No communication with duct

Endoscopic findings
- Cyst fluid CEA elevated (>200ng/ml)

Natural history
- “pre-malignant”
Non-operative diagnosis: IPMN

- Radiographic appearance
  - Branch duct
  - Main duct

- Endoscopic findings
  - Bulging ampulla with mucin
  - Elevated fluid CEA

- Natural history
  - Pre-malignant
  - Field defect: “Whole gland” process
Cystic lesions pancreas

Non-operative diagnosis: how good are we?

- MSKCC: 719 patients selected for radiographic surveillance with >1 year radiographic follow-up:

  5-year risk of death from pancreatic cancer: 3%
  Approximates mortality risk from pancreaticoduodenectomy

Introduction

• Intraductal papillary mucinous neoplasms of the pancreas first classified in 1996 by the World Health Organization.

• Interest has increased:
  • Increased use of cross-sectional imaging has resulted in increased identification.
  • Only identifiable precursor lesion of pancreatic cancer!
  • Management controversy as frequency, site, and rate of progression to invasive disease unknown.

Kloppel et al. WHO International Classification of Tumors, 1996.
IPMN

Histopathologic sub-types

- IPMN progression pathways to carcinoma:

Adapted from J Hepatobiliary Pancreat Surg (2007) 14:217
Management recommendations

- Operative resection recommended when presumed risk of high-grade dysplasia or invasive disease (high-risk lesion)

- Increased risk of high-risk disease when main duct is involved.

Johns Hopkins, 136 patients resected for IPMN
HGD/Invasive disease

- Main Duct: 60%
- Combined: 40%
- Branch Duct: 20%


Management recommendations

- **Main duct IPMN:** Operative resection recommended
- **Branch duct IPMN:**
  - Selective approach generally utilized
  - “Consensus” guidelines:
    Non-operative approach reasonable for incidentally discovered BD IPMN <3 cm in diameter and without solid component.
  - Size and solid component: two factors most frequently associated with high grade dysplasia or invasive disease

IPMN

Management recommendations

• Need for improved markers of high-risk disease

• Increased risk of high-grade dysplasia or carcinoma when main duct is involved.

Johns Hopkins, 136 patients resected for IPMN

HGD/Invasive disease

Main Duct 60%
Combined 40%
Branch Duct 20%

IPMN – Current Directions

Improved identification of high-risk disease

- Clinical and radiographic markers of high-grade dysplasia or invasive disease.

IPMN

Outcome

Resection
Histopathologic review

Partial pancreatectomy

Invasive

OUTCOME

Non-invasive

OUTCOME

Surveillance
Cyst fluid CEA>200ng/ml

OUTCOME

Clinical, radiographic, endoscopic assessment
IPMN

Outcome following resection of invasive disease

- Initial reports suggested improved survival for invasive IPMN in comparison to patients with resected pancreatic carcinoma.

Outcome following resection of invasive disease

- Direct comparison: Invasive IPMN, Ductal carcinoma

Earlier stage at diagnosis
- T-stage
- N-stage
- Differentiation
- Vascular invasion
- Perineural

Histopathologic sub-type
- Colloid
- Tubular

T1 lesions:
- 29% of resected IPMN
- 5% of conventional ductal cancers

Outcome following resection of invasive disease

- Histopathologic sub-type and outcome (n=59):

Overall survival:
5-year: 68%

Overall survival (5yr):
Colloid: 87%
Tubular: 55%

Outcome following resection of invasive disease

- IPMN compared to nomogram matched conventional pancreatic carcinoma:

  Similar survival between invasive tubular and matched conventional pancreatic cancer.

  Significantly improved survival in patients with invasive colloid lesions.

IPMN

Outcome following resection of non-invasive disease

- Following partial pancreatectomy for non-invasive IPMN there should be no risk of distant recurrence from the resected lesion.

- Risk: recurrent IPMN (invasive and non-invasive) developing in the remnant gland (field defect).

- Risk approximately 5% - 10% in studies with median follow-up of approximately three years.
### Outcome following resection of non-invasive disease

- **Risk of gland recurrence:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>%non-invasive</th>
<th>Gland recurrence</th>
<th>Median f/u (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo</td>
<td>2002</td>
<td>113</td>
<td>65</td>
<td>11%</td>
<td>36</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2004</td>
<td>62</td>
<td>52</td>
<td>7%</td>
<td>38</td>
</tr>
<tr>
<td>JHMC</td>
<td>2004</td>
<td>136</td>
<td>62</td>
<td>4%</td>
<td>24</td>
</tr>
<tr>
<td>MGH/Verona</td>
<td>2004</td>
<td>140</td>
<td>59</td>
<td>7%</td>
<td>31</td>
</tr>
<tr>
<td>Virginia Mason</td>
<td>2005</td>
<td>100</td>
<td>75</td>
<td>2%</td>
<td>31</td>
</tr>
<tr>
<td>MDACC</td>
<td>2006</td>
<td>35</td>
<td>63</td>
<td>3%</td>
<td>30</td>
</tr>
<tr>
<td>MSKCC</td>
<td>2006</td>
<td>78</td>
<td>100</td>
<td>8%</td>
<td>40</td>
</tr>
<tr>
<td>Columbia</td>
<td>2013</td>
<td>183</td>
<td>85</td>
<td>13%</td>
<td>32</td>
</tr>
</tbody>
</table>
Outcomes for IPMN

Patients undergoing initial surveillance

56 yo, female, incidental, EUS cyst fluid CEA 400

January 2010

June 2010
Outcomes for IPMN

Patients undergoing initial surveillance: Clinic 2/14/2014

56 yo, female, incidental, EUS cyst fluid CEA 400

60 yo male, with new onset diabetes and slightly increased serum CA 19.9: 72.
Outcomes for IPMN

Summary

- Cystic lesions of the pancreas occur in 2.5% of the population (increasing prevalence with age)
- Many of these lesions will represent pre-cancerous lesions: IPMN and MCN
- IPMN represents a whole gland process with several genetic pathways to distinct forms of invasive cancer
- Resection should be recommended when there is concern for high-grade dysplasia
  - Main duct IPMN
  - Large branch duct lesions with mural nodules