Surgical management of cystic pancreatic neoplasms

Csaba Gajdos, MD
Survey Question # 1

- 33 yo female with h/o pancreatitis
- 3.3 cm cystic lesion in the pancreas
- Previous attempted endoscopic drainage over 1 yr ago
- Constant abdominal pain (4-5/10)
- EUS reveals mucin and papillary epithelial cells
Survey Question # 2

- 61 yo female with 2 months h/o new onset epigastric pain
- CT A/P reveals 1.3cm cystic lesion in the body and 0.5 cm lesion in the head of pancreas
- EUS finds mucin in first lesion
- Her symptoms are gone after “cleaning her bowels”
Survey Question # 2
Pancreatic Cystic Lesions

- Cystic neoplasms represent about 10% of pancreatic neoplasms
- The proportion of pancreatic resections nearly doubled (from 16% to 30%) in certain tertiary care hospitals in the last 15 years
Pancreatic Cystic Lesions

**FIGURE 1.** The number of patients evaluated (A), mean cyst diameter (B), and percentage of patients with symptomatic lesions (C) over the 10-year time period of the study.

Pancreatic Cystic Lesions

• Increasingly recognized
  – Widespread use and improved cross sectional imaging
• Spectrum of benign to malignant lesions
  – Pseudocysts
  – Serous cystadenomas
  – Mucinous cystadenomas
  – Intraductal papillary mucinous neoplasm (IPMN)
Pancreatic Cystic Lesions

History

• Symptoms related to lesion?
  – Pain
  – Obstructive jaundice
  – Weight loss

• Pancreatitis—past or present?
Pancreatic Cystic Lesions
Decision Points

• Differential diagnosis of the cyst
  – Neoplastic vs. Non-neoplastic
  – Risk of malignancy
• Likelihood of harm
  – With and without testing
  – With and without treatment
• Particularly relevant for asymptomatic patient
Can imaging techniques reliably distinguish mucin-containing lesions (potentially malignant) from other cystic lesions?

- Cyst fluid analysis – amylase, tumor markers, genomics / proteomics
Challenges in Management

22 months later
Challenges in Management

• “Neither randomized control trials or systematic reviews of RCTs (level 1 evidence) nor cohort studies or reviews of cohort studies (level 2 evidence) have been published. Only one report fit the criteria for level 3 evidence (case control study)”

• After additional review and analysis, we considered only six reports to be “cornerstone papers” of merit for the final review”

_Bassi C et al. J Gastrointest Surg 2008_
Differential Diagnosis
Pseudocyst

Clinical
• Gender
• Age
• Ethanol abuse
• Pancreatitis history
• Malignant potential
• Location

Imaging studies
• Septae
• Locularity
• Calcifications

• Male
• Variable
• Yes
• common
• No
• Variable

Differential Diagnosis
Serous Cystadenoma

Clinical
• Gender
• Age
• Ethanol abuse
• Pancreatitis history
• Malignant potential
• Location

Imaging studies
• Septae
• Locularity
• Calcifications

• Female (2-3:1)
• 60’s
• No association
• Uncommon
• No (rare)
• Evenly distributed

• Yes
• Multiple small (usually)
• Yes (central sunburst or stellate)

SEROUS CYSTADENOMA
SEROUS CYSTADENOMA
Figure 51.1
Microcystic type of cystic neoplasm in the pancreas. Numerous small cysts, most of which measure no more than several millimeters, form the microcystic pattern. Serous cystadenoma (microcystic, glycogen-rich adenoma) shown here is the prototypical and almost the sole example of microcystic neoplasia in the pancreas. This well-circumscribed appearance, along with spongelike microcystic pattern and stellate scar, is pathognomonic for serous cystadenoma.
Histology

**Figure 1.** Serous cystadenoma. (A) Hematoxylin and eosin stain of a surgical specimen demonstrating microcysts lined by cuboidal epithelium with clear cytoplasm (original magnification ×20). (B) Periodic acid-Schiff stain (without digestion) demonstrates characteristic intracytoplasmic glycogen granules (arrows) (original magnification ×100).
Differential Diagnosis
Mucinous cystadenoma

Clinical
- Gender
- Age
- Ethanol abuse
- Pancreatitis history
- Malignant potential
- Location

Imaging studies
- Septae
- Locularity
- Calcifications

- Female
- Adenoma (50-60’s) Ca (60-70)
- No association
- Uncommon
- Yes
- Variable

- Yes
- Multilocular (usually)
- Yes (peripheral, curvilinear)

Figure 51.2
Megacystic (oligocystic) pattern. In contrast to the microcystic pattern, the loculi in this mucinous cystic neoplasm are fewer in number and larger in size, most measuring in the order of centimeters. It is difficult to predict the grade of this mucinous cystic neoplasm from the macroscopic findings alone. Although this lesion is of moderate complexity and devoid of papillary nodules, extensive sampling and thorough microscopic examination would be necessary to determine whether in situ or invasive carcinoma is present.
Histology

Figure 4. Photomicrograph of a surgically resected mucinous cystic neoplasm (MCN) demonstrating ovarian-type stroma lined by mucinous, columnar epithelium with low-grade epithelial dysplasia (original magnification ×40). These are defining features for MCN.
Mucinous Cystadenocarcinoma
Mucinous Cystadenocarcinoma
Differential Diagnosis
Intraductal Papillary Mucinous Neoplasm

Clinical
- Gender
- Age
- Ethanol abuse
- Pancreatitis history
- Malignant potential
- Location

Imaging studies
- Septae
- Locularity
- Calcifications

- Male (3-4:1)
- 60’s
- No association
- Uncommon
- Yes
- Variable

- No
- Multiocular (usually)
- No

Histology

Figure 7. Characteristic microscopic features of intraductal papillary mucinous neoplasm with well-formed, finger-like papillae, and an absence of ovarian-type stroma (original magnification $\times 40$).
Curved reformat - IPMT - Main Duct Type
IPMT - SIDE BRANCH TYPE
IPMN vs. MCN

• Can we distinguish them preoperatively?
  – Ovarian stroma
    • Risk of malignancy 6-36% (less if stroma)

• Criteria for resection of IPMN
  – Main duct: MPD<15mm, mural nodules
  – Branch duct: >3cm, mural nodules
  – Mixed types

Tanaka et al. Pancreatology 2006;6:17-32
IPMN: Branch Duct vs Main Duct

• Prevalence of cancer:
  – Main duct: invasive 43% (70% if CIS included)
  – Branch duct 15% (25% if CIS included)

• May be difficult to differentiate MCN from side branch IPMN
  – Similar low malignancy risk?
  – Different risk of multifocality and need for surveillance

Tanaka et al. Pancreatology 2006;6:17-32
International Consensus Guideline on IPMN Management

Size < 1 cm

MR or thin slice CT
In 1 year

Size 1-3 cm

EUS and MRCP or ERCP

High-risk stigmata:
Mural nodules
Dilated main duct
Positive cytology

No

Size > 3 cm

Resection

Yes

MR or CT
1-2 cm every 6-12 mo*
2-3 cm every 3-6 mo

No

Sumptomatic, size >3 cm or positive high-risk stigmata

*The interval of follow-up can be lengthened after 2 years of no change

Tanaka et al. Pancreatology 2006;6:17-32
SOLID PSEUDOPAPILLARY TUMOR
Figure 9. (A) Pancreaticoduodenectomy specimen demonstrating focal hemorrhage and cystic degeneration consistent with a diagnosis of solid pseudopapillary tumor (SPPT). (B) A 4.5-cm solid and cystic lesion with coarse internal calcification, consistent with SPPT (arrow), found incidentally on a CT scan performed for workup of nephrolithiasis. The patient was originally referred with a presumed diagnosis of neuroendocrine tumor of the pancreas.
# Diagnostic Features of Pancreatic Cystic Lesions

## Table 1. Clinical Features of Cystic Neoplasms of the Pancreas and Comparison with Pseudocysts

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Inflammatory pseudocyst</th>
<th>SCA</th>
<th>MCN</th>
<th>IPMN</th>
<th>SPPT</th>
<th>Lympho-epithelial cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>1:1</td>
<td>1:3–4</td>
<td>1:9</td>
<td>1:2–1</td>
<td>1:10</td>
<td>4:1</td>
</tr>
<tr>
<td>Age (y), range</td>
<td>40–70</td>
<td>60–80</td>
<td>30–50</td>
<td>60–80</td>
<td>20–40</td>
<td>60–80</td>
</tr>
<tr>
<td>History</td>
<td>Pancreatitis</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### Cross-sectional imaging

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Evenly distributed</th>
<th>Head &lt; body/tail</th>
<th>Head &lt;&lt; body/tail</th>
<th>Head &gt; body/tail</th>
<th>Evenly distributed</th>
<th>Evenly distributed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Uni- or multiloculated macrocyst, findings of chronic pancreatitis</td>
<td>Multiple, small diameter microcysts; rarely seen is a macrocystic SCA</td>
<td>Unilocular or multiloculated macrocyst with smooth contour</td>
<td>Irregular, polycystic mass with dilation of main and/or branch ducts</td>
<td>Large, well encapsulated, solid/cystic mass</td>
<td>Well-encapsulated, uni- or multiloculated cyst protruding from the gland</td>
</tr>
</tbody>
</table>

### Findings suggestive of malignancy

| Findings suggestive of malignancy | --- | Metastatic disease (very rare, reports are anecdotal) | Larger size (>3 cm), eggshell calcification, solid component or mural nodule | Main duct dilation >10 mm, branch duct lesion >3 cm, solid component, mural nodules, calcification | Metastatic disease (rare and usually present at diagnosis; metachronous metastasis much less common) | --- |

### Cyst fluid assessment

<table>
<thead>
<tr>
<th>Mucin</th>
<th>Low</th>
<th>Low</th>
<th>High</th>
<th>High</th>
<th>NA</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Low (&lt;5 ng/mL)</td>
<td>Low (&lt;5 ng/mL)</td>
<td>High (&gt;5 ng/mL)</td>
<td>High (&gt;5 ng/mL)</td>
<td>NA</td>
<td>ID</td>
</tr>
<tr>
<td>Amylase</td>
<td>High (&gt;250 U/L)</td>
<td>Low (&lt;250 U/L)</td>
<td>Low (&lt;250 U/L)</td>
<td>Low (&lt;250 U/L)</td>
<td>NA</td>
<td>ID</td>
</tr>
</tbody>
</table>

Definitive diagnosis and classification of a pancreatic cyst might require synthesis of data from a number of diagnostic sources; clinical decisions should not be based on one data point in isolation.

ID, insufficient data exists about assessment of tumor markers in cyst fluid; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; NA, not applicable as FNA and cyst aspiration are rarely performed as part of the diagnostic workup for SPPT; SCA, serous cystadenoma; SPTT, solid pseudopapillary tumor.
Pancreatic Cystic Lesions
Potential Management Strategies

• Additional Imaging Studies
  – CT
  – MRI (MRCP may show ductal communication with IPMN)
  – EUS +/- FNA

• Cyst fluid Characterization

• Risk/Benefit assessment of surgical resection

• Watchful Waiting
Pancreatic Cyst

H + P

Rule out pseudocyst and other non-neoplastic cysts

Pancreas Protocol CT

SCA

> 4cm or symptomatic

Consider resection

< 4cm and asymptomatic

Close followup Serial CT

< 4cm branch duct and asymptomatic

Indeterminate

EUS FNA Fluid markers

< 3 cm branch duct and asymptomatic

Indeterminate

Consider resection

Indeterminate

Consider resection

IPMN

Main duct or branch duct > 3 cm or symptomatic

Close followup Serial CT

MCN

Consider resection
Table 1. Characteristics of Pancreatic Cystic Neoplasms with Low Risk of Malignancy as Described in The Published International Guidelines*

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>2.</td>
<td>Size &lt; 30 mm</td>
</tr>
<tr>
<td>3.</td>
<td>Main Pancreatic Duct Dilation &lt; 6mm</td>
</tr>
<tr>
<td>4.</td>
<td>No solid component within or associated with cyst on imaging</td>
</tr>
</tbody>
</table>

* Tanaka et al. Pancreatolog 2006;6:28
Pancreatic Cystic Lesions Does Size Matter?

- Retrospective study from MGH
- 86 pts with cysts 3 cm or smaller
- 48 operated; 38 monitored
- 75 benign; 8 borderline malignant, 3 carcinoma in situ (PPV 87% for size)
- Unilocular cysts PPV benign 97%
- Septations poor for prediction of malignancy PPV 20%

Pancreatic Cystic Lesions
Role of EUS

- Endosonographic architecture
  - Not sufficient for accurate classification
  - Solid mass and invasive tumor – malignant

- EUS appearance
  - Serous: numerous small cysts with thin septae
  - Mucinous: macrocystic-- uni- or multilocular
  - IPMN: mural nodules may show invasive features and target for FNA
Pancreatic Cystic Lesions
Cyst fluid Characterization

• EUS FNA: safe and well tolerated <1% complication rate
  – Technique: limit passes, antibiotics

• Fluid analysis
  – Cytology: insensitive
  – Amylase/Lipase: confusing
  – Tumor Markers: CEA most useful
Pancreatic Cystic Lesions: The Cooperative Pancreatic Cyst Study

- 341 patients EUS + FNA
- 112 surgical resection (68 mucinous, 7 serous, 27 inflammatory, 5 endocrine, 5 other)
- ROC analysis: cyst fluid CEA > 192 ng/ml – differentiate mucinous vs. non-mucinous (AUC .79)
- CEA better than EUS morphology or cytology (50-60%)
- Cyst fluid CEA most accurate test to identify mucinous lesion

Brugge et al. Gastroenterology 2004;126:1330-1336
Pancreatic Cyst Identified

Symptomatic

Surgical Candidate

Yes

Resection

EUS +/- FNA to support benign etiology (pseudocyst)

NO/Borderline

CT diagnostic for serous lesion

Yes

Monitor

EUS

“Diagnostic” for serous lesion

Yes

Monitor

FNA

Mucinous

Surgery

Non-Mucinous

Monitor
Pancreatic Cystic Lesions

• Diagnostic Testing should influence management
  – Does EUS +/- FNA change surgical decision-making?
  – Costs and risks
• Collaborative approach with endoscopist, radiologist, pancreaticobiliary surgeon and GI pathologist
  – Frozen sections for IPMN margins problematic
• Patient must be actively involved in understanding risks and uncertainties
• Critical need for prospective, controlled data to provide evidence based diagnostic and therapeutic strategies
Pancreatic Cystic Lesions
What the future holds

• Improved diagnosis
  – Cyst fluid molecular analysis
    • Gene markers
    • Mutational analysis
    • Telomerase (Mishra G et al. GIE 2006;63:648-54)
  – Trucut biopsy
  – Ethanol Lavage
Absolute criteria for who should/should not undergo surgical resection for a cystic pancreatic neoplasm do not currently exist

Rational approach:
- All symptomatic patients who are reasonable operative risks should undergo surgical resection (in one a study malignant lesion was found in 40% of symptomatic pts compared to 17% of asymptomatic counterparts)

- Asymptomatic patients:
  - much less clear
  - things that push towards resection:
    - any solid component in the cyst
    - CEA in cyst fluid elevated (79% specific for mucin-producing tumor (MCN or IPMT))
  - good operative risk
Must balance risk of operation with risk of developing malignancy in tumor (numbers from operative series- so may not represent truly asymptomatic lesions)

Risk of malignancy:

- **Serous cystadenomas** (no malignant risk)

- **Mucinous cystic neoplasms (MCN):** about 8-30% have an invasive component; risk of malignant degeneration unknown-can occur even up to 15-20 years after diagnosis

- **Intraductal mucinous papillary neoplasms (IPMN):** about 1/3 have an invasive component; risk of malignant degeneration unknown; also can occur many years after presentation
Surgical Approaches to Cystic Neoplasms

- Lesion in head/neck/uncinate process: pancreaticoduodenectomy
- Lesion in body/tail: distal pancreatectomy and splenectomy
- Lesions diffusely involving the gland or involving the head and extending into the body: total pancreatectomy
Serous Cystadenoma

- Indications for Surgery
  - symptoms
  - large size*
  - inability to distinguish a serous cystic neoplasm from a mucinous lesion

- *Series of 106 pts (MGH)
  Rate of growth of lesion (24 pts had serial radiography)
  - < 4 cm: median growth of 0.12 cm per year
  - > 4 cm: median growth of 1.98 cm per year

Mucinous Cystic Neoplasms (MCN)

- Series of 163 pts. from MGH and University of Verona
- ovarian stroma required for diagnosis
- Median size 5 cm. Average age 45 yrs.
- 12% had invasive cancer.
- All invasive cancers > 3cm; 84% of these had a solid component
- Argued all MCNs should be surgically resected
  - avoid life-long monitoring
  - authors assume that all (or most) small MCN progress to cancer over time

- Surgical complication rate: 49% overall morbidity, with a 24% pancreatic fistula rate, and 10% of patients requiring an interventional radiology procedure or re-operation.

Main duct IPMN or Mixed Variant IPMN

• Risk of malignancy thought to approach 70%
• Current recommendations are for surgical resection regardless of presence of symptoms
Branch Duct IPMN

• Resect if:
  
  >3 cm in size
  
symptoms
  
mural nodules

In the absence of these 3 criteria, observation may be indicated
Pancreatoduodenectomy
(Whipple procedure)
Distal Pancreatectomy
Total Pancreatectomy
Decision to operate a balance between risk of surgery and risk of cancer

Complications from Pancreatic Surgery

Death rate
1) Whipple 1-3%
2) Distal pancreatectomy 0.5%
3) Total pancreatectomy 1-3%

Risk of diabetes
1) Whipple 8-10% (removing 50% of gland)
2) Distal pancreatectomy (can remove up to 70% and not get diabetes if remainder of gland is normal)
3) Total pancreatectomy 100%
Surgical Resection

1) Serous cystadenoma
   no follow-up needed
2) Non-invasive MCN
   no follow up needed
3) Invasive MCN (adenocarcinoma)
   treat like pancreatic adenocarcinoma
Surgical Resection- IPMN

- Two main types
  - main duct
  - side branch
Goal is complete resection with negative surgical margin
We rely on intraoperative frozen section in operating room
IPMN

- Need to decide how you will approach a positive margin in the operating room and discuss possible scenarios with the patient
- Frozen section margin status
  - Negative: operation complete
  - Positive for non-invasive IPMN (adenoma): proceed with further resection, and total pancreatectomy if indicated, or consider surveillance program*
  - Positive for carcinoma in situ or invasive IPMN: proceed with further resection, and total pancreatectomy if indicated*
    (factors such as patient age, compliance, co-morbidities come into play)
IPMN

- Both main duct and side branch type IPMN’s can recur: all patients need to be enrolled in a surveillance program (CT or EUS)

- recurrence with negative margin: 7-10%
Thanks to Dr. Diane Simeone for mentoring me in pancreas surgery and for sharing her slides