Management of Asymptomatic Pancreatic Cysts

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Why Asymptomatic pancreatic cysts are important for us?

- High prevalence
  1% of patients undergoing abdominal CT scan have a cystic lesion in the pancreas

- Clinical dilemma
  Mucinous vs Non-mucinous
  Benign vs Premalignant or Malignant
**Classification**

<table>
<thead>
<tr>
<th>No epithelium</th>
<th>Serous epithelium</th>
<th>Degenerative change in solid tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>Serous cystic neoplasm</td>
<td>Cystic ductal adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Squamous epithelium</td>
<td>Cystic neuroendocrine tumor</td>
</tr>
<tr>
<td>Mucinous epithelium</td>
<td>Lymphoepithelial cyst</td>
<td>Cystic acinar cell carcinoma</td>
</tr>
</tbody>
</table>

**Serous Cystic Neoplasm (SCN)**

- **Sex**: F>M
- **Age**: 6th decade
- **Location**: Anywhere
- **Morphology/imaging**: Multicystic/honeycomb appearance. Central scar and calcification.
- **Histopathology**: Glycogen-rich cuboidal cells lining cystic spaces and amorphous stroma. PAS stain (+)
- **Malignancy potential**: Generally Benign

Varieties of SCN

<table>
<thead>
<tr>
<th>Microcystic SCN</th>
<th>Oligocystic SCN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

Sex
- F (95%) >> M

Age
- 4th, 5th decade

Location
- Body (tail)

Morphology/imaging
- Unilocular or septated cyst +/- wall calcifications,
- MPD communication (-)

Histopathology
- Variable cellular atypia and secretes mucin with ovarian-like stroma.

Malignancy potential
- Yes

Varieties of MCN

Intraductal Papillary Mucinous Neoplasms (IPMN)

- Sex: M (70%) > F
- Age: 6th and 7th decade
- Location: Head
- Morphology/imaging:
  - Dilated main duct or pancreatic duct branches.
  - Solid component (+) → malignancy?
- Malignancy potential: Yes
Intraductal Papillary Mucinous Neoplasms (IPMN)

Mucinous secretion

Fish-mouth appearance

MAIN DUCT IPMN

IPMN

Risk factors for malignancy

- Older age
- Presence of symptoms
- Involvement of main pancreatic duct
- Dilation of main pancreatic duct
- Mural nodule
- Size >30mm (side branch type)
**IPMN**

*Differentiation of sub-type is important*

- **Side Branch IPMN**
  - Prevalence of Cancer
  - Low (6~46%)

- **Main duct IPMN**
  - Prevalence of Cancer
  - High (57~92%)

**IPMN**

- **Side Branch IPMN**
  - Mucinous cyst
  - Communicating with PD
  - Without MPD dilation
**IPMN**

**Main duct IPMN**

- Mucinous cyst
- Dilation of PD (>10mm)

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**Mucinous cystic neoplasms**

*Differentiation is important for management*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCN</th>
<th>Branch duct IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>&gt;95%</td>
<td>~30%</td>
</tr>
<tr>
<td>Age (decade)</td>
<td>4th and 5th</td>
<td>6th and 7th</td>
</tr>
<tr>
<td>Location (% body/tail)</td>
<td>95%</td>
<td>~30%</td>
</tr>
<tr>
<td>Common capsule</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Calcification</td>
<td>Rare, curvilinear, in the wall of cyst</td>
<td>No</td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Orange-like</td>
<td>Grape-like</td>
</tr>
<tr>
<td>Internal structure</td>
<td>Cyst in cyst</td>
<td>Cyst by cyst</td>
</tr>
<tr>
<td>Pancreatic duct communication</td>
<td>Infrequent</td>
<td>Yes</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>Normal or deviated</td>
<td>Normal</td>
</tr>
<tr>
<td>Ovarian-type stroma</td>
<td>Positive (76%)</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Imaging diagnosis

- Computed Tomography (CT)
- Magnetic Resonance Image (MRI)
- Endoscopic Ultrasound (EUS)

Typical characterization on CT scan

<table>
<thead>
<tr>
<th>Unilocular</th>
<th>Macrolocular</th>
<th>Microlocular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>IPMN, MCN</td>
<td>SCA</td>
</tr>
</tbody>
</table>

Imaging diagnosis

-MRI-

- Communication with pancreatic duct: IPMN
- Presence of central scar: SCN

*MRI may be a feasible tool for surveillance without radiation exposure.*

Imaging diagnosis

- Specific diagnosis
  - CT: Accuracy 61.9 to 76.2%
  - MRI: Accuracy 55.6% to 76.2%
  - CT+MRI: Accuracy 73.0% to 77.8%

Imaging diagnosis
-EUS imaging-

*High-resolution images*

- Thick wall type
- Tumor protruding type
- Thick septal type
- Micro cystic type
- Thin septal type
- Simple type


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EUS classification

- Thick wall type
- Tumor protruding type
- Thick septal type
- Micro cystic type
- Thin septa type
- Simple type

Imaging diagnosis
-EUS imaging-

- Benign vs Malignant
  - Thick wall
  - Septation
  - Intramural nodule/Mass
  
  Accuracy 40% to 93%

- Mucinous vs Non-Mucinous
  
  Accuracy 51%

EUS Imaging without FNA not enough as an independent predictor.

Cystic fluid analysis with EUS-FNA

- Cytology
- Viscosity
- Biochemistry
- Tumor markers
- DNA and others

Asymptomatic 79 year-old female with 30mm cyst in the body of pancreas.
Cystic fluid analysis
-Cytology-

- Mucinous versus non-mucinous

Accuracy 59%

- Mucinous vs Non-Mucinous

Sensitivity 63%, Specificity 88%

Cystic fluid analysis
-Viscosity-

- Indirect measurement of mucin, glycoprotein, DNA contents
Brugge WR, et al. Gastroenterology 2004

- Viscosity $\geq 1.6$ is highly suggestive for mucinous lesion

<table>
<thead>
<tr>
<th>Predicted cyst</th>
<th>Cyst fluid analysis formula</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC</td>
<td>VIS&lt;1.6 or lipase UL&gt;6000 and CEA ng/ml</td>
<td>91.3</td>
<td>100</td>
<td>97.2</td>
</tr>
<tr>
<td>SCyA</td>
<td>VIS&lt;1.6 and lipase UL&lt;6000</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>MCyA</td>
<td>VIS$\geq$1.6 and CEA ng/ml &lt;6000</td>
<td>85.7</td>
<td>100</td>
<td>97.2</td>
</tr>
<tr>
<td>MCyA-CA</td>
<td>VIS$\geq$1.6 and CEA ng/ml $\geq$6000</td>
<td>100</td>
<td>92</td>
<td>94.3</td>
</tr>
</tbody>
</table>
Cystic fluid analysis
-Viscosity-

■ String sign:

Non-mucinous 0 mm vs Mucinous 3.5 mm (median)


Cystic fluid analysis
-CEA-

CPC Study
(Cooperative Pancreatic Cyst Study)

■ Prospectively enrolled 371 patients
■ Histopathology was gold standard
■ EUS, cytology and various fluid tumor markers were evaluated.
Cystic fluid analysis

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CPC Study

Mucinous vs Non-Mucinous

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst fluid CEA</td>
<td>73%</td>
<td>84%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Cyst fluid analysis

-CEA-

- Pooled analysis of 12 studies, 450 patients.
- Cysts with an amylase concentration <250 U/L were SCA, MCA, or MCAC (sensitivity 44%, specificity 98%) and, thus, virtually excluded PC.
- A carcinoembryonic antigen (CEA) <5 ng/mL suggested a SCA or PC (sensitivity 50%, specificity 95%).
- CEA >800 ng/mL strongly suggested MCA or MCAC (sensitivity 48%, specificity 98%).

Cystic fluid analysis
-DNA Quantification and Allelic Loss-

**PANDA Study**

- Prospective, multicenter trial
- 391 patients (Final cohort was 113)
- Mucinous vs Non-Mucinous
- Malignant vs Pre-malignant


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**PANDA STUDY**

- The study cohort consisted of 113 patients with 40 malignant, 48 premalignant, and 25 benign cysts.
- Cyst fluid k-ras mutation was helpful in the diagnosis of mucinous cysts (odds ratio 20.9, specificity 96%).
- Components of DNA analysis detecting malignant cysts included allelic loss amplitude over 82% (AUC 0.9) and high DNA amount (optical density ratio >10, AUC 0.79). The criteria of a high amplitude k-ras mutation followed by allelic loss showed maximum specificity (96%) for malignancy.
- All malignant cysts with negative cytologic evaluation (10/40) could be diagnosed as malignant by using DNA analysis.
Cystic fluid analysis
-DNA Quantification and Allelic Loss-

**DNA analysis to the rescue!**

<table>
<thead>
<tr>
<th>Pathological findings</th>
<th>ALA% if &gt;82%</th>
<th>OD if &gt;10</th>
<th>Cycle threshold value if &lt;25</th>
<th>K-ras followed by allelic loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 IPMC-NI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 MCAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Liver met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 IPMC-I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5 IPMC-NI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6 IPMC-NI</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>7 IPMC-NI</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 IPMC-NI</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 IPMC-NI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10 IPMC-I</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Adapted from Ref. 24)

**ACG Guidelines**

*The most important clinical tools are*

- Cross sectional imaging
- Endoscopic ultrasound
- Cystic fluid analysis

*The most important differential is*

Mucinous or Non-Mucinous

Management

Cost effectiveness for asymptomatic pancreatic cyst

- Strategy 1: no specific intervention
- Strategy 2: an aggressive surgical intervention
- Strategy 3: EUS-guided FNA with cystic fluid analysis

Compared them in Markov-based clinical model


A strategy based on risk stratification of malignant potential by EUS-guided FNA and cyst fluid analysis is the most cost-effective strategy.

Surgery

<table>
<thead>
<tr>
<th>SCN</th>
<th>MCN</th>
<th>IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Malignant potential?</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Malignancy: 17.5% \(^9,^{28}\)

The prognosis is excellent if resected before invasion.

Resection is recommended

Main duct IPMN

©

Side-branch IPMN

Surgery -IPMN-

Prevalence of cancer

57% to 92%

Good surgical candidate should be offered surgical resection.


Main duct IPMN

©

Side-branch IPMN

Surgery -IPMN-

Prevalence of cancer

6% to 46%

Lower prevalence of malignancy
Treatment should be individualized

Surgery
-For IPMN-

International consensus guideline

- Symptoms attributable to the cyst (e.g., pancreatitis)
- Dilation of the main pancreatic duct (≥10 mm)
- Cyst size ≥30 mm
- Presence of intramural nodules
- Cyst fluid cytology suspicious/positive for malignancy


Management of asymptomatic cysts

Cyst size

<1cm

- EUS
- Monitor

High risk stigmata

Yes
- EUS+FNA

No
- Monitor
Management of asymptomatic cysts

<table>
<thead>
<tr>
<th>Cyst size</th>
<th>1 to 3cm</th>
<th>&gt;3cm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUS+FNA</strong></td>
<td><strong>Consistent with mucinous</strong></td>
<td><strong>Consistent with mucinous</strong></td>
</tr>
<tr>
<td>No</td>
<td>?</td>
<td>No</td>
</tr>
<tr>
<td>Yes</td>
<td>High risk stigmata Positive cytology</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Monitor</td>
<td>Yes</td>
</tr>
<tr>
<td>Monitor</td>
<td></td>
<td>Monitor</td>
</tr>
</tbody>
</table>

Pancreatic cysts—Injection of alcohol

**Gan et al, GIE 2005**
- EUS guided ethanol lavage for ablation of pancreatic cystic lesions. 23/25 patients with complete follow-up, 8 patients (35%) had complete resolution of their cysts on follow-up imaging.

**Dimaio et al, Pancreas 2011**
- Two sessions of EUS guided lavage versus only one session.
- 38% had complete resolution after two sessions of ethanol lavage.

**Dewitt et al, GIE 2009**
- EUS-guided ethanol lavage results in a greater decrease in pancreatic cyst size compared with saline solution lavage with a similar safety profile. Overall CT-defined complete pancreatic cyst ablation was 33.3%.
Panc.cysts-EUS guided Chemo.

- EUS guided ethanol lavage with Paclitaxel injection in 14 pts. - cystic pancreatic tumors. Oh, GIE, 2008
- Complete resolution in 11/14 patients (78%)

Alcohol injection or alcohol with paclitaxel are promising but not ready for prime time routine clinical application.

28 months follow up

- Size <3 cm
- Solitary cyst
- No septation
- No solid component
- Normal PD caliber
- CEA < 192 ng/ml

Follow up

What is the optimal interval of surveillance?

2 year follow up from the baseline study for cyst size <3cm, no intracystic growth
Das et al, Am J Gastro 2008

My current practice:
MRI may be better test for follow up than CT
First follow up may be at 12 months with MRI and if no change repeat another MRI in one year.

Take home message

■ There are variety of pancreatic cystic lesions. Mucinous vs Non- mucinous. Malignant vs Non-malignant.

■ A strategy based on risk stratification of malignant potential by EUS-guided FNA and cyst fluid analysis is the most cost-effective strategy.
The End

Thank you for your attention