Cystic pancreatic neoplasms: Observe

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Outline

- Background of cystic neoplasms
- Diagnosing cystic neoplasms
  - CT
  - EUS
  - Cyst fluid analysis
- Natural history of cystic neoplasms
- Risk of operative resection
Many patients with pancreatic cystic lesions are asymptomatic, making it difficult to determine the incidence and prevalence.

Cystic lesions of the pancreas are found in about 1% of the population based on CT.

Up to 24% of patients have pancreatic cysts at autopsy.

About 10-15% of pancreatic cysts are estimated to be due to primary neoplasms and the remainder due to pseudocysts.

Up to 75% of cystic lesions are incidental findings, causing no symptoms and 80% of those resected are benign.
### Typical characteristics

<table>
<thead>
<tr>
<th>Cyst type</th>
<th>Pseudocyst</th>
<th>SCA</th>
<th>MCN</th>
<th>IPMN</th>
<th>SPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Variable</td>
<td>Middle-aged</td>
<td>Middle-aged</td>
<td>Elderly</td>
<td>Young</td>
</tr>
<tr>
<td>Sex</td>
<td>M &gt; F</td>
<td>F &gt; M</td>
<td>Female</td>
<td>M &gt; F</td>
<td>Female</td>
</tr>
<tr>
<td>Pancreatitis history(^1)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes(^2)</td>
<td>No</td>
</tr>
<tr>
<td>Location</td>
<td>Evenly</td>
<td>Evenly</td>
<td>Body/tail</td>
<td>Head</td>
<td>Evenly</td>
</tr>
<tr>
<td>Malignant potential</td>
<td>None</td>
<td>Rarely</td>
<td>Moderate to high</td>
<td>Low to high</td>
<td>Low</td>
</tr>
<tr>
<td>Biliary obstruction</td>
<td>Yes, Uncommon</td>
<td>No</td>
<td>No</td>
<td>Yes, Uncommon</td>
<td>No</td>
</tr>
</tbody>
</table>

Hutchins, World J Gastroenterol, 2009
Imaging-CT and EUS

- CT characterizes the mass via size, uni- vs multi-loculated, pancreatic duct communication and/or dilation, presence of mass or mural nodule.
  - Enhanced characterization with pancreas protocol.

- EUS provides detailed information about septations, adjacent masses, wall characteristics.
  - Advantages: simultaneous FNA and sampling cystic fluid for analysis.
  - Accuracy of EUS alone of malignant or premalignant 51-95%.
  - EUS morphology risk factors for malignancy: thick wall, septations, intramural nodules, masses, and wall calcifications.
CT and EUS: Serous cystadenoma

Typically <2 cm, multi-loculated with honeycomb appearance. May have a central stellate scar (pathognomonic). Rare to have pancreatic duct communication or dilation.

Al-Haddad, J Pancreas, 2010
CT and EUS: Mucinous Cystic Neoplasm

Typically >2 cm, uni or multi-locular with “orange fruit” appearance. Uncommon for pancreatic duct communication or dilation. May have peripheral calcification.

Jani, Diagnostic and Therapeutic Endoscopy, 2011
CT and EUS: Intraductal Papillary Mucinous Neoplasm

Typically see ductal dilation, possibly duct communication. Mural nodules often seen.

Jani, Diagnostic and Therapeutic Endoscopy, 2011
CT and EUS: Pseudocyst

Usually uni-locular with no internal septa. Can have thick or thin wall. May have calcifications.

Jani, Diagnostic and Therapeutic Endoscopy, 2011
### Cystic fluid analysis

<table>
<thead>
<tr>
<th>Cyst Type</th>
<th>Location</th>
<th>Fluid color and viscosity</th>
<th>Cytology</th>
<th>CEA</th>
<th>Amylase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous cystadenoma</td>
<td>Body/tail more than head</td>
<td>Colorless, thick fluid</td>
<td>Extracellular mucin. Mucinous epithelial cells in a background of ovarian stroma may be seen</td>
<td>Moderate to highly elevated</td>
<td>Variable</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>Main duct or side branch; head more than body and tail</td>
<td>Colorless, thick fluid</td>
<td>Extracellular mucin. Mucinous epithelial cells with papillary projections and variable atypia may be seen</td>
<td>Moderate to highly elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>Body/tail more than head</td>
<td>Colorless, frequently blood contaminated</td>
<td>Typically acellular. Small glycogen staining cuboidal cells may be seen in the background</td>
<td>Undetectable to low</td>
<td>Low</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>Anywhere</td>
<td>Yellow to brown thin fluid</td>
<td>Macrophages with no mucin. Mixed inflammatory infiltrate</td>
<td>Low to minimally increased</td>
<td>Elevated</td>
</tr>
</tbody>
</table>
Cooperative Pancreatic Cyst Study

- Multicenter study of 341 patients with prospectively collected results of EUS morphology, fluid cytology and cyst fluid analysis.

- 112 patients underwent surgical resection with histology for comparison.

- CEA was the most accurate tumor marker in differentiating mucinous and non-mucinous lesions.

- The optimal cutoff was >192 ng/ml with sensitivity of 73% and specificity of 84%.

- 60% (68) of the lesions resected were mucinous; 76% (52/68) were MCN; 56% (29/52) were malignant.

- 36% (40/112) of those resected were malignant or borderline malignant.

Brugge, Gastroenterology, 2004
Comparison of EUS, Cytology and CEA in differentiating between mucinous and non-mucinous cysts

<table>
<thead>
<tr>
<th></th>
<th>EUS morphology</th>
<th>Cytology</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>32/57 (56.1%)</td>
<td>19/55 (34.5%)</td>
<td>42/56 (75%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>25/55 (45.4%)</td>
<td>45/54 (83.3%)</td>
<td>46/55 (83.6%)</td>
</tr>
<tr>
<td>Accuracy</td>
<td>57/112 (50.9%)</td>
<td>64/109 (58.7%)(^a)</td>
<td>88/111 (79.2%)(^b,c)</td>
</tr>
</tbody>
</table>

\(^a\)Three patients did not have cytology result.
\(^b\)One patient did not have a CEA result.
\(^c\)\(P < 0.05\) vs cytology, EUS morphology.
Combination diagnosis

<table>
<thead>
<tr>
<th></th>
<th>EUS morphology or cytology</th>
<th>EUS morphology or cytology or CEA</th>
<th>Cytology or CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity(^a)</td>
<td>70</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>Specificity</td>
<td>38</td>
<td>31</td>
<td>71</td>
</tr>
<tr>
<td>Accuracy</td>
<td>54</td>
<td>62</td>
<td>77(^b)</td>
</tr>
<tr>
<td>Area under ROC curve</td>
<td>0.5418(^c)</td>
<td>0.6107(^c)</td>
<td>0.7668</td>
</tr>
</tbody>
</table>

\(^a\)The values reported were compared with regression analysis using area under ROC curves and are more accurately termed areas rather than percentage.

\(^b\)P < 0.05 vs. EUS morphology-cytology, EUS morphology-cytology-CEA.

\(^c\)Area less than CEA alone, P < 0.0001; see Table 3 for CEA alone ROC area.
PANDA study

- 391 patients from 7 institutions who underwent EUS evaluation for pancreatic cysts were enrolled. 91 were excluded due to no cyst on EUS, solid mass on EUS, or inadequate cystic fluid.

- 124 of 299 had pathologic diagnoses based on surgical resection or malignant EUS-FNA findings.

- Differentiating between mucinous and non-mucinous cysts:

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA level &gt;148 ng/ml</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td><em>k-ras</em> mutation</td>
<td>45%</td>
<td>96%</td>
</tr>
<tr>
<td>CEA &gt;148 ng/ml and <em>k-ras</em> mutation</td>
<td>84%</td>
<td>67%</td>
</tr>
<tr>
<td>CEA &gt;192ng/ml and <em>k-ras</em> mutation</td>
<td>82%</td>
<td>83%</td>
</tr>
</tbody>
</table>

Khalid, Gastrointest Endosc, 2009
Natural history

• Prospective study of patients who were evaluated for pancreatic cysts at the Cleveland Clinic over 4 years.

• Of the 221 patients evaluated, 80 underwent surgical resection.

• Of the 141 patients observed, 98 were followed for more than 12 mos.

• 79% (78) underwent EUS cyst aspiration. 76% were unilocular. All except 4 had CEA< 200 ng/ml. All except 7 were negative for mucin.
Radiologic follow-up

- 84/98 were followed up with imaging for a mean of 24 months.
- Of the 22 patients with lesions > 4 cm and negative aspirates, 10 remained unchanged, 5 decreased in size or resolved, 1 increased in size, 3 were resected, and 3 refused resection or imaging.
- A total of 4 patients underwent resection during the surveillance period. Pathology was mucinous cystadenoma, lymphoepithelial cyst, pseudocyst, serous cystadenoma.
- Asymptomatic patients with CEA<200ng/ml and negative mucin stain are unlikely to have a mucinous neoplasm that requires resection in mean of 24 months.
Prospective cohort over 10 years that included patients who underwent EUS and cyst aspiration and were asymptomatic from incidentally discovered pancreatic cysts.

Of the 317 who underwent EUS, 93 patients with asymptomatic incidental pancreatic cysts were enrolled in the study.

22 underwent resection due to size >3 cm and/or concerning EUS features. 9% had adenocarcinoma, 60% had premalignant lesions.

71 had lesions < 3 cm with benign features and no operation.

All 33 patients that underwent FNA had cytology negative for malignant cells.
Follow-up

- 69 (97%) were alive and free of symptoms of pancreatic disease.
- 2 were determined to have died of unrelated causes.
- Mean follow up was 28 months (range 4-120 months).
- 45/71 had follow-up imaging with CT or EUS. There was no progression of any of the lesions. 4 patients had complete resolution of the cyst.
- Asymptomatic pancreatic cysts with benign features on imaging may be followed clinically and radiographically.
Natural history

- 15 year prospective cohort of 1,424 patients diagnosed with a pancreatic cyst.

- Initial management: 422 (37%) - operative resection; 719 (63%) - non-operative management.

- Mean follow-up of non-operative group was 28 months. Changes that led to operative treatment occurred in 47 patients (6.5%).

- Of the 719 managed non-operatively, invasive malignancy was seen in 12 (1.7%).

- Of the 422 managed with initial resection, 23% had carcinoma or high grade dysplasia.

- Operative mortality 0.7%. Complications > Grade III occurred in 36%.
Risk of malignancy if <=3cm

- Retrospective review of all pancreatic resections for cystic neoplasms at 5 institutions over 8 years.

- There were 166 resections of neoplasms ≤ 3cm. 135 were pathologically benign and 31 were malignant.

- Patients with malignant tumors were older, more likely to be symptomatic and have malignant features on imaging such as dilated pancreatic/bile ducts, adenopathy, and a solid component.

- CEA>192ng/ml was 55% sensitive and 89% specific for differentiating between mucinous and non-mucinous cysts.

- Fluid cytology was 79% sensitive and 90% specific for determining malignancy.

- Only 1 in 30 (3.3%) asymptomatic patients with no radiologic features for malignancy that were resected was found to have occult cancer on resection.

Lee, J Gastrointest Surg, 2008
Risk of surgery vs. potential for malignancy

- Using the Nationwide Inpatient Sample database, Kotwall et al. determined the national overall rate of mortality for all hospitals for the Whipple procedure is 14%.

- A retrospective series of cystic lesions of the pancreas by Allen et al. showed one postoperative death (1.5%) and 19 (29%) postoperative complication of the 65 that were resected. There was a 3% risk the lesion was malignant.

- Crippa et al. retrospectively analyzed 163 resected MCNs at University of Verona and Mass General and found no operative mortality and 49% operative morbidity. Only 17.5% (28) had cancer.

- Gaujoux et al. found the operative mortality to be 0.7% and complications ≥ Grade III to be 36%. There was a 1.7% chance of developing pancreatic malignancy.
Conclusions

- CT, EUS, fluid cytology, and cyst fluid analysis of CEA and \( k-ras \) can determine the potential for malignancy with increasing accuracy.

- Cystic lesions without malignant features on EUS or cytology and CEA<200 ng/ml are not likely to progress to malignancy.

- Cystic lesions can be observed with radiologic follow-up with many lesions resolving or decreasing in size.

- Risk of surgery with high morbidity outweighs the low potential that a lesion harbors malignancy.
References

16. Pitman MB, Michaels PJ, Deshpande V, Brugge WR, Bounds BC. Cytological and cyst fluid analysis of small (< or =3 cm) branch duct intraductal papillary mucinous neoplasms adds value to patient management decisions. Pancreatology 2008;8:277-84.
Thank you!
Questions/Comments?