Multidisciplinary and Multimodal Approach To the Pre-Operative Diagnosis of Pancreatic Cysts

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Boston, MA

Pancreatic Cysts

- 1.2% of the general population
- 7-8% of the elderly
- 10% of pancreatic neoplasms
- Benign, premalignant and malignant
- Most patients are asymptomatic
- Management conundrum
- Accurate diagnosis requires a multidisciplinary and multimodal team approach

- Differential Diagnosis
  - Pseudocyst
  - Lymphoepithelial cyst
  - Serous cyst
  - Mucinous cyst
    - (MCN and IPMN)
  - Cystic degeneration of typically solid tumors
    - PanNET
    - SPN
    - other
  - Other more rare cysts
Management Options

• Surgical
  – Distal pancreatectomy
  – Middle pancreatectomy
  – Pancreatoduodenectomy (Whipple)

• Medical
  – Drain
  – Ablate

• Observation

Surgical procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Whipple</th>
<th>Middle pancreatectomy</th>
<th>Distal pancreatectomy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>368 (43.2%)</td>
<td>63 (7.4%)</td>
<td>373 (43.8%)</td>
<td>47 (5.5%)</td>
</tr>
<tr>
<td>Complications (%)</td>
<td>49%</td>
<td>49.3%</td>
<td>36.4%</td>
<td>32.4%</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>12.5%</td>
<td>35.5%</td>
<td>18.2%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>6.5%</td>
<td>0%</td>
<td>0.3%</td>
<td>0%</td>
</tr>
<tr>
<td>Other major complication</td>
<td>12.9%</td>
<td>12.7%</td>
<td>12.6%</td>
<td>11.8%</td>
</tr>
<tr>
<td>Median length of stay, days</td>
<td>8 days</td>
<td>6 days</td>
<td>6 days</td>
<td>8 days</td>
</tr>
<tr>
<td>Operative mortality, n</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Procedure</th>
<th>MCN</th>
<th>MD IPMN</th>
<th>BD IPMN</th>
<th>SCA</th>
<th>CNET</th>
<th>SPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>199</td>
<td>180</td>
<td>146</td>
<td>137</td>
<td>62</td>
<td>29</td>
</tr>
<tr>
<td>Malignant (%)</td>
<td>10.3%</td>
<td>33.7%</td>
<td>13.7%</td>
<td>0.0%</td>
<td>10.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year survival (%)</td>
<td>94.0%</td>
<td>83.0%</td>
<td>88.0%</td>
<td>97.0%</td>
<td>98.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>5-year survival (%)</td>
<td>90.0%</td>
<td>78.0%</td>
<td>80.0%</td>
<td>90.0%</td>
<td>98.0%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>
International Consensus Guidelines for Management of IPMN and MCN
(Tanaka, et.al. Pancreatology. 2006; 6:17)

The International Consensus Guidelines 2012 for the Management of IPMN and MCN of the Pancreas

• **High Risk Stigmata** — Surgery if clinically feasible
  - Obstructive jaundice in a patient with a cyst in the pancreatic head
  - Enhancing solid component of the cyst
  - Main pancreatic duct dilatation ≥10mm

• **Worrisome Features** — EUS-FNA
  - Cyst ≥3cm
  - Thickened/enhancing cyst walls
  - Main duct 5-9mm
  - Non-enhancing mural nodule
  - Abrupt change in MPD size with distal pancreatic atrophy

• **EUS-FNA** — Susp/Pos cytology — Surgery

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**Current Recommendations**

- **Surgery-recommended**
  - MCN, all grades
  - IPMN-HGD
  - IPMN-invasive
  - Cystic PanNET
  - SPN
  - Cystic Acinar Cell Ca.
  - Cystic PDAC

- **Surgery-optional**
  - PCT
  - LEC
  - SCA
  - IPMN-LGD
  - IPMN-IGD??

Cytology is a critical test in cyst classification for management. Decision to operate is based on surgical risk versus malignancy risk.
### Pancreatic Cysts: CT

<table>
<thead>
<tr>
<th>No.</th>
<th>Type</th>
<th>Imaging Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unilocular</td>
<td>Benign imaging</td>
</tr>
<tr>
<td>2</td>
<td>multilocular</td>
<td>Benign to worrisome imaging</td>
</tr>
<tr>
<td>3</td>
<td>complex</td>
<td>Worrisome to high-risk imaging</td>
</tr>
</tbody>
</table>

### Challenges in Cyst Characterization: Morphologic Overlap

- MCN
- Pseudocyst
- IPMN

Cohen-Scali F et al. Radiology 2003
Khurana B et al. AJR 2003
Kim S et al. AJR 2006

### EUS Recommended (2012 guidelines)

- Worrisome Imaging
  - Cyst > 3cm
  - Thickened/enhanced cyst walls
  - MPD 5-9 mm
  - Nonenhancing mural nodule
  - Abrupt change in caliber of MPD with distal atrophy
Nonspecific EUS Imaging

- Broad differential diagnosis:
  - Mucinous
    - BD-IPMN
    - MCN
  - Nonmucinous
    - Macrocystic SCA
    - Lymphangioma
  - Benign
  - Malignant (≥HGD)

Small Cysts with “Benign” Imaging are not all low-grade


EUS-guided FNA

- Technique of choice
- Controversial
- Not used in Japan and much of Korea
- Requires significant experience for quality aspiration and interpretation
FNA

- Only way to look inside the cyst
- Procures cyst fluid for analysis
- May produce sufficient cells for CB
- Requires training for both the endoscopist performing the FNA and the pathologist interpreting the sample
- EUS-FNA is safe

Peritoneal Seeding in Intraductal Papillary Mucinous Neoplasm of the Pancreas Patients Who Underwent Endoscopic Ultrasound-Guided Fine-Needle Aspiration: The PIPE Study


**Table 1. Characteristics of patients with IPMN with pre-operative EUS-FNA (EUS-FNA Group) and patients with no pre-operative tissue sampling (No Sampling Group).**

<table>
<thead>
<tr>
<th></th>
<th>EUS-FNA Group</th>
<th>No Sampling Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>61</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Sex (male: female)</td>
<td>32:29</td>
<td>32:36</td>
<td>0.540*</td>
</tr>
<tr>
<td>Age at surgery, y</td>
<td>68 (39-83)</td>
<td>66 (37-89)</td>
<td>0.790†</td>
</tr>
<tr>
<td>Follow-up period, mo</td>
<td>66.7 (6.0-161.4)</td>
<td>58.6 (7.6-155.2)</td>
<td>0.621‡</td>
</tr>
<tr>
<td>Pancreatic head involvement, no. (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive IPMN, no. (%)</td>
<td>11 (18.0)</td>
<td>19 (27.9)</td>
<td>0.184*</td>
</tr>
<tr>
<td>Peritoneal seeding, no. (%)</td>
<td>1 (1.6)</td>
<td>3 (4.4)</td>
<td>0.621§</td>
</tr>
</tbody>
</table>

Quality FNA

- Quality specimen: Specimen representative of the lesion
- Proper tissue triage and preparation

Quality interpretation: Knowledge of pancreatic pathology
- Experience of interpreter
- Team approach to diagnosis
Two basic questions for Cyst analysis

1) Is the cyst mucinous or non-mucinous?

2) Is the cyst low-grade or high-grade?

Cytological Preparations

No-ROSE

- Cysts
  - Direct smears
    - If fluid thick enough
  - Fresh undiluted cyst fluid
    - CEA; Amylase
    - Molecular
    - Cytology
      - Cytospin
      - Cellblock
Pancreatic Cyst Fluid Triage

CFA cut-off levels lab and study dependent

CEA by cyst fluid analysis

<table>
<thead>
<tr>
<th>CEA &gt;800ng/ml</th>
<th>Neoplastic mucinous cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA &lt;5ng/ml</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>Amylase &lt;250 U/L</td>
<td>Not a pseudocyst</td>
</tr>
</tbody>
</table>

Serous Inflammatory Mucinous Borderline Malignant
CEA and Amylase: Key Points

- Elevated CEA (≥ 192 ng/ml) supports a mucinous cyst
  - Does not distinguish IPMN from MCN
  - Level does not correlate with malignancy
  - Rare FP: PCT, GI duplication cyst, LEC
- Amylase levels
  - Elevated in the 1000's for most PCT
  - Low amylase level tends to exclude a PCT
  - Level does not distinguish IPMN from MCN

Molecular Tests

- KRAS
  - Mutation(s) support a neoplastic mucinous cyst
  - Does not distinguish IPMN and MCN
  - Does not correlate with grade
- GNAS
  - Mutation supports IPMN over MCN
  - Does not correlate with grade
- RNF41
  - Mutation supports a mucinous cyst
  - Does not distinguish IPMN and MCN
- 3p deletions
  - 3p25, VHL gene, supports SCA
  - Other 3p deletions also noted in SCA
- CTNNB1 (beta-catenin) deletion
  - Mutation(s) support SPC
- TP53, CDKN2A loss SMAD4 loss support a HR cyst

Impact of Next-Generation Sequencing on the Clinical Impression of Pancreatic Cysts

- NGS supported the imaging impression in 78% but changed it in 12%
- NGS defined a cyst as mucinous in 48% of cysts with a non-elevated CEA
- KRAS and/or GNAS mutations supported a diagnosis of IPMN in 71% of cases without an elevated CEA
- KRAS mutation reclassified 19% of cysts non-neoplastic by imaging and with low CEA
Cytology Interpretation

• Multimodal Approach
  – Clinical Information
    • Patient age and gender
    • Symptoms
    • Past medical history
  – Radiological Information
    • Location of mass in the pancreas (and thus organ traversed for EUS)
    • Mass characteristics
      » Solid or cystic
        » Size, contours, invasion
        » Cyst structure: uni- or multilocular, thick/thin wall, Ca++, nodule/leak in the wall
        » Gross cyst contents: thick, viscous, thin, water, clear, brown
    – Ancillary tests: CEA, amylase, molecular analysis

Communication within the Care Team is Critical to Success

EUS-FNA Requisition Form
Recommended Standardized Reporting Terminology

- Nondiagnostic
- Negative
  - AP, CP, AIP, LEC, PCT, Splenule
- Atypical
- Suspicious
- Neoplastic
  - Benign: SCA
  - Other: MCN, IPMN, PanNET SPN
- Positive/Malignant
  - PDAC, ACC, PBL, lymphomas, metastases


Complex Cysts (solid and cystic)

High-Risk Imaging

Secondarily Cystic Solid Neoplasms: SPN

- Clinical
  - Rare but may represent up to 6% of all pancreatic neoplasms and 24% of resected cysts
  - 89% in young women, mean age ~ 28 years
  - 1/3 in head, 1/3 in body and 1/3 in tail
- Radiology
  - Shows large solid and cystic neoplasm

Image: AFIP Fawroz Saad SB 2017
Classic Cytology

SPN

- Papillary branching
- Myxoid stroma
- Clinging cells and single cells
- Euchromatin
- Oval, indented, grooved nuclei
- Perinuclear vacuoles/globules

Cytohistology: CB

SPN

Beta-catenin

Secondarily Cystic Solid Neoplasms: cPanNET
Cystic PanNETs

- ~10% of PanNETs
- Half are completely cystic and half are solid and cystic
- Most are nonfunctioning
- If clinically suspected, serum chromogranin A (CgA) levels may support the diagnosis when elevated (sensitivity ~70%)
  - False positive CgA levels have been reported in patients taking proton pump inhibitors, renal or liver failure and untreated hypertension.
  - Elevated serum pancreatic polypeptide increases sensitivity to 93%

Imaging Features

- Thick cyst wall is a clue
- Pseudocysts also have a thick wall, but almost all of these patients have a history of pancreatitis
- MCN have a thick wall, but these cysts are septated and almost all are in women
- SPN are solid and cystic, but these tumors are almost always in young women
- IPMNs and MCNs can be solid and cystic when malignant

| TABLE 2. Accuracy of Cytology and EUS for the Diagnosis of Cystic Pancreatic Neuroendocrine |
|-----------------------------------------------|----------------|--------|--------|----------------|
| N     | Diagnostic | Suspicious | HR | Benign or indeterminate |
| Cytology | 35     | 71%        | 77% | 86% | 5%             |
| EUS    | 34     | 38%        | 47% | 50% | 15%            |

Key: EUS, endoscopic ultrasound; HR, high-risk
Table 3. Comparison of CPanNet patients and mucinous cyst patients

<table>
<thead>
<tr>
<th></th>
<th>CPanNet (n=15)</th>
<th>Mucinous cyst (n=15)</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male : female)</td>
<td>9 : 6</td>
<td>9 : 6</td>
<td>1.000</td>
</tr>
<tr>
<td>Age, y, median (range)</td>
<td>57 (34–80)</td>
<td>57 (33–79)</td>
<td>0.950</td>
</tr>
<tr>
<td>Cyst diameter, mm, median (range)</td>
<td>29 (16–70)</td>
<td>23 (8–90)</td>
<td>0.110</td>
</tr>
<tr>
<td>Wall thickness (thick : thin)</td>
<td>10 : 5</td>
<td>2 : 13</td>
<td>0.003</td>
</tr>
<tr>
<td>Septation (yes : no)</td>
<td>6 : 9</td>
<td>9 : 6</td>
<td>0.273</td>
</tr>
<tr>
<td>Associated mass lesions (yes : no)</td>
<td>8 : 7</td>
<td>4 : 11</td>
<td>0.136</td>
</tr>
<tr>
<td>Cyst fluid CEA level, ng/mL, median (range)</td>
<td>1.1 (0.3 – 500)</td>
<td>400 (2.8 – 6661)</td>
<td>&lt;0.001 ∥</td>
</tr>
<tr>
<td>Diagnostic cytology (n, %)</td>
<td>11 (73.3) #</td>
<td>3 (20.0) **</td>
<td>0.003 §</td>
</tr>
</tbody>
</table>

Cystic PanNETs

- Imaging Nonspecific
  - Thick cyst wall
  - Solid and cystic
- Cytology is THE diagnostic test
  - CEA low
  - Amylase low
  - KRAS/GNAS negative
- Cells usually diagnostic when present

PanNET Cytohistology: CB
Grading GEP NETs
(Who, ENETS)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitoses</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 2</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>2</td>
<td>2-20</td>
<td>3-20%</td>
</tr>
<tr>
<td>3</td>
<td>&gt;20</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

Multilocular Cyst

Serous Cystadenoma

- Clinical
  - Benign, slow growing neoplasm
  - Women > men, mean age 7th decade
  - Associated with VHL with deletion of 3p25 in most cases
  - Often asymptomatic, but can hemorrhage and cause pain
- Radiology
  - Circumscribed, multi-lobulated
    - Microcystic with fibrous septae, central scar, calcifications in ~30-40%
- Histology
  - "Glycogen-rich"
  - dPAS+ cuboidal epithelium
Serous Cystadenoma: Variants

Unilocular and Macrocystic

- Cuboidal non-mucinous epithelial cells
- Hemosiderin-laden macrophages in a clean or bloody, non-pseudocyst like background
- CEA and amylase low
- NO KRAS/GNAS
- 3p deletions support diagnosis

SCA
Cytohistology: CB SCA

Neoplastic Mucinous Cysts

MCN IPMN

Non-Complex Cyst
Pancreatic Pseudocyst

Clinical
Associated with pancreatitis, trauma, surgery (almost always)

Radiology
Unilocular, non-septated
Thick walled
No mural nodule

Histology
Cyst lining of histiocytes and inflammatory cells

Pancreatic Pseudocyst cytology
• cyst debris with blood, proteinaceous material and yellow hematoxylin-like pigment
• variable inflammation
• NO cyst lining epithelium (beware of contamination, mucin and epithelium)
• CEA low; amylase usually in the 1000’s; no KRAS or GNAS

Mucinous Cystic Neoplasm
• Clinical
  • F:M=20:1
  • Most are benign
  • Prognosis excellent for non-invasive completely resected tumors
  • Resection recommended despite grade
• Radiology
  • Body and tail (90%)
  • Do not communicate with the pancreatic ductal system
  • Thick walled (Ca++ in 20%)
  • Thin or thick septa
Mucinous Cystic Neoplasm

- Not associated with the pancreatic ducts
- Lined by mucinous, generally non-papillary epithelium
- Subepithelial "ovarian-like stroma" required
- Atypia may be very heterogeneous; invasion may be very focal, so the entire cyst should be submitted for histology


- Collaborative study between MGH and University of Verona
- 163 patients with MCN, strictly defined

Mucinous Cystic Neoplasm

- Difficult to distinguish from IPMN on cytology alone
- Ovarian-type stroma typically not seen
- Cyst lining denudation produces cyst aspirate resembling PCT
- CEA ↑↓
- Amylase ↓↑
- KRAS +/GNAS-
Intraductal Papillary Mucinous Neoplasm

**Main duct type**
- Diagnosed clinically
  - Dilated main pancreatic duct (definition varies, but >5mm)
  - Pancreatic head mostly, but occur all through the pancreas
  - Intestinal type lining most common
  - 60% have HGD
  - 45% have invasive carcinoma
  - Symptoms common but 25% asymptomatic
  - Treatment: resection

**Branch Duct Type**
- Most often in head/uncinate
- 1/3 with multiple cysts
  - Supports clinical dx
- Most patients asymptomatic
- Imaging: “bunch of grapes”; single cyst may not be diagnostic for BD-IPMN unless visualized connection to the MPD
- Most lined by gastric type epithelium
- Most low grade
- Treatment: depends….
IPMN

• Variously papillary mucinous epithelium of variable cell type and heterogeneous atypia
• No association with ovarian-like stroma under the epithelium

AFIP 4th Series Fascicle

Gastric (null) Type Cells: Most BD-IPMN
Usually LGD
MUC 5AC+, MUC 6+, MUC1-, MUC2-, CDX2-

AFIP 4th Series Fascicle

Intestinal Type Cells: Most Main Duct-IPMN
Moderate/Intermediate-grade dysplasia
MUC 5AC+, MUC 6 weak, MUC1-, MUC2+, CDX2+
Pancreatobiliary Type: Less common type
High grade dysplasia
MUC 5AC+, MUC 6 focal,
MUC1+, MUC2-, CDX2-

Oncocytic Type: Uncommon type
High grade dysplasia
MUC 5AC goblet cells+, MUC1-, MUC2
MUC 6 + , CDX2-

Intraductal Papillary Mucinous Neoplasm of the Pancreas:
Cytologic Analysis and Correlation with Histologic Grade

Low grade dysplasia  Moderate dysplasia  HGD/Carcinoma
Two basic questions for Cyst analysis

1) Is the cyst mucinous or non-mucinous?
   1) Gross examination
   2) CEA (best test)
   3) Cytology
   4) Molecular mutations

2) Is the cyst low-grade or high-grade?
   1) Cytology!!

Gross Cyst Fluid

Mucinous cyst fluid
Non-mucinous cyst fluid

Acellular thick, colloid-like mucin is NOT non-diagnostic!
Mucinous Epithelium

Ancillary Tests for Mucinous Etiology

- CEA ≥ 192 ng/ml
- Genetic mutations
  - KRAS (IPMN or MCN)
  - GNAS (IPMN)
Two basic questions for Cyst analysis

1) Is the cyst mucinous or non-mucinous?
   1) Gross examination
   2) CEA (best test)
   3) Cytology

2) Is the cyst low-grade or high-grade?
   1) Cytology!!

Diagnostic Morphology of Carcinoma

Already invasive - prognosis decreases ~50%

Ideal World- Recognize HGD

with accuracy
Atypical Epithelial Cells

Morphological Overlap with AEC

Histologically Confirmed LGD-IGD

Grading Epithelial Atypia in EUS-FNA of Intraductal Papillary Mucinous Neoplasms: An international interobserver concordance study
Martha B Pitman MD\textsuperscript{1}, Barbara A Centeno MD\textsuperscript{2}, Muriel Genevay MD\textsuperscript{3}, Ricardo Fonseca, MD\textsuperscript{4} and Mari Mino-Kenudson MD\textsuperscript{1},
Cancer Cytopathology 2013;121(12):729-736.

Table 3. Kappa Coefficient for Two-Tiered Cytological Grading of Branch-Duct IPMN Cyst Fluids

<table>
<thead>
<tr>
<th>Grade</th>
<th>Four Reviewers</th>
<th>Randolph's Multirater Kappa</th>
<th>Two Reviewers*</th>
<th>Cohen's Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2, 3-4</td>
<td>54%</td>
<td>0.45</td>
<td>87%</td>
<td>0.74</td>
</tr>
<tr>
<td>0-1, 2-4</td>
<td>52%</td>
<td>0.44</td>
<td>88%</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* Two most experienced reviewers
Cytological Criteria of High-Grade Epithelial Atypia in the Cyst Fluid of Pancreatic Intraductal Papillary Mucinous Neoplasms

Martha B. Pitman, MD, Barbara A. Centeno, MD, Ebubekir S. Daglilar, MD, William R. Brugge, MD, and Mari Mino-Kenadson, MD

Cancer Cytopathology 2014;122(1):40-47.

Low grade atypia on PCF cytology is associated with a high risk of chromatin pattern IPMN with HGD
Adenocarcinoma
MC without HGA
- Adenocarcinoma
NET
4
IPMN with HGD
Adenocarcinoma
IPMN with LGD
de Oliveira PB et al. Prevalence of incidental pancreatic cysts on 3 tesla magnetic...
Increased
MC with HGA
Background
Nuclear membrane irregularities
IPMN with HGA
MC without HGA
MC with HGA
IPMN with HGA
and Martha B Pitman
High
Adenocarcinoma
Adenocarcinoma
ratio
Non
This
Abnormal
Serous cystadenoma
Endometriotic cyst
Adenocarcinoma
Small cell size compared to 12µ enterocyte
IPMN with HGA
MCN, denuded
- IPMN with LGD
- Serous cystadenoma
cellular necrosis

OBJECTIVES
Evaluation of the risk of malignancy in PCF cytology with HGA

METHODS
FNA for a pancreatic cyst at Massachusetts General Hospital, Boston, MA, United States

RESULTS
Figure 1. Radiologic and cytologic findings of high risk cyst by radiology, which was later found to...

REFERENCES
Kenudson, MD

Conclusions
Malignant histologic features included wall, non duct caliber with distal pancreatic atrophy, enhanced, thickened cyst pancreatic duct size of 5 jaundice. Worrisome imaging features were cysts ≥3cm in size, main pancreatic duct dilatation ≥1cm, and were documented.

Benign/Low Grade Glandular Epithelium

High Grade Atypical Epithelial Cells in Pancreatic Mucinous Cysts are a More Accurate Predictor of Malignancy than “Positive” Cytology

Woodward Plante 2014;4:806

* Risk of Malignancy in Pancreatic Cysts with High Grade Atypical Cytology

Raza S Hoda
Department of Pathology

Martha Bishop Pitman M.D, et.al. (Cancer Cytopath 2010)

ORGANIZATION
MASSACHUSETTS GENERAL HOSPITAL

PHYSICIANS ORGANIZATION

Risk of Malignancy in Pancreatic Cysts with High Grade Atypical Cytology

Arica I Halder, Rehanf Ali, Matthew B. McHale, and Martha Bishop Pitman
Department of Pathology, Massachusetts General Hospital, Boston, MA, United States

Benign/Low Grade Glandular Epithelium

HGA is most accurately identified in mucinous cyst fluids by:
1. an increased N/C ratio,
2. an abnormal chromatin pattern
3. background necrosis

1. an increased N/C ratio,
2. an abnormal chromatin pattern
3. background necrosis

Table 1. Cytological Criteria of High-Grade Epithelial Atypia in Pancreatic Mucinous Cysts

<table>
<thead>
<tr>
<th>Reference duodenal enterocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
</tr>
<tr>
<td>High-grade</td>
</tr>
</tbody>
</table>

Table 2. Pancreatic Cysts with Histologic Follow-up

<table>
<thead>
<tr>
<th>Classification</th>
<th>Benign/Low Grade Glandular Epithelium</th>
<th>Malignant Pancreatic Cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Malignancy</td>
<td>89%</td>
<td>81%</td>
</tr>
<tr>
<td>Risk of Positive Cytology</td>
<td>100%</td>
<td>89%</td>
</tr>
</tbody>
</table>

CONCLUSIONS
Risk of malignancy in pancreatic cysts with high grade atypia (HGA) are most accurately identified in mucinous cyst fluids by: an increased N/C ratio, an abnormal chromatin pattern, and background necrosis.
High Grade Atypical Glandular Epithelium

High Grade Atypical Epithelial Cells in Pancreatic Mucinous Cysts are a More Accurate Predictor of Malignancy than "Positive" Cytology

Martha Bishop Pitman M.D, et.al. (*Cancer Cytopath* 2010)

Cytohistology: CB

Ancillary Tests: IPMN/MCN

- IHC insufficiently specific to be diagnostic of grade in premalignant cysts
- SMAD4 may be helpful for dx of PDAC-loss of nuclear staining
**Moray™ Micro-forceps biopsy**

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**Moray™ Micro Forceps Biopsy Improves the Diagnosis of Specific Pancreatic Cysts**

M. Lisa Zhang, Ronald N. Arpin, William R. Brugge, David Forcione, Osman Yuksel, Omer Basar, Martha B. Pitman

MGH, Harvard Medical School [in press, Cancer Cytopathology]

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Comparison of Pancreatic Cyst Fluid Analysis and Moray™ Micro Forceps Biopsy for the Diagnosis of Mucinous Cysts

<table>
<thead>
<tr>
<th></th>
<th>PCF (%)</th>
<th>MFB (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Yield</td>
<td>35 (72.9)</td>
<td>36 (75.0)</td>
<td>0.818</td>
</tr>
<tr>
<td>Mucinous Diagnosis</td>
<td>29 (61.8)</td>
<td>28 (58.8)</td>
<td>0.949</td>
</tr>
<tr>
<td>High-risk Detection</td>
<td>3 (6.3)</td>
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<td>0.670</td>
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<td>9 (18.8)</td>
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<td>&lt;0.001</td>
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<tr>
<th>Cytology</th>
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<tr>
<td>Extracellular mucin</td>
<td>13 (44.8)</td>
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<tr>
<td>Mucinous epithelium</td>
<td>20 (69.0)</td>
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<td>Both</td>
<td>8 (27.6)</td>
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<tr>
<th>CEA &gt; 192 ng/ml</th>
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**Note:**

- **PCF (%):** Pancreatic Cyst Fluid (%)
- **MFB (%):** Moray™ Micro Forceps Biopsy (%)
- **P:** Probability

---

**Comparison of Pancreatic Cyst Fluid Analysis and Moray™ Micro Forceps Biopsy for the Diagnosis of Mucinous Cysts**

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### Specific Cysts Diagnosed by Pancreatic Cyst Fluid Analysis and Moray™ Micro Forceps Biopsy

<table>
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<th>Cysts</th>
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<tr>
<td><strong>PCF</strong></td>
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<tr>
<td>IPMN with low-grade atypia (LGA)</td>
<td>6 (12.5)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>2 (4.2)</td>
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<tr>
<td><strong>MFB</strong></td>
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</tr>
<tr>
<td>IPMN with low-grade dysplasia (LGD)</td>
<td>18 (37.5)</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Acinar cell cystadenoma</td>
<td>1 (2.1)</td>
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1. All cases diagnosed by GNAS mutation (IPMN) and cytology (LGA).
2. Diagnosed by cytology alone.
3. One case diagnosed by cytology alone and one case diagnosed by 3p25 mutation.

---

**Nonmucinous epithelial cells with prominent nucleoli in acinar cell cystadenoma, Pap stain, 60x**

[Image of histology slide showing nonmucinous epithelial cells with prominent nucleoli in acinar cell cystadenoma]

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**Acinar cell cystadenoma (LGE)**

[Image of histology slide showing acinar cell cystadenoma (LGE)]

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**Acinar cell cystadenoma, Trypsin**

[Image of histology slide showing acinar cell cystadenoma stained with Trypsin]
**Example Case**

65 year old female with incidental pancreatic cyst

- CEA 357 ng/ml
- Amylase 11,203 U/L
- NGS pending

**Low-risk “Sendai negative”**

**High-grade epithelial atypia**

- Neoplastic:Other
- Mucinous cyst with HGA consistent with BD-IPMN with at least HGD

**Histology follow-up**

IPMN with HGD
Acknowledgements

• Dr. Carlos Fernandez-del Castillo
• Dr. Dushyant Sahani
• Dr. Bill Brugge
• Dr. Mari Mino-Kenudson
• Dr. Ralph Hruban
• Dr. David Klimstra
• Dr. Lester Layfield