Diagnosis of Cystic and Intraductal Tumors of the Pancreas

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Classification of Pancreatic Neoplasms

ACINAR CELL NEOPLASMS
- Acinar cell cystadenoma
- Acinar cell carcinoma
- Acinar cell cystadenocarcinoma

PANCREATOBlastoma

SOLID-PSEUDOPAPILLARY NEOPLASM

NEUROENDOCRINE NEOPLASMS
- Neuroendocrine microadenoma
- Well differentiated pancreatic neuroendocrine tumor
  - Functioning: Insulinoma
  - Glucagonoma
  - Somatostatinoma
  - Gastrinoma
  - VIPoma
  - PPoma
- Non-functioning: Poorly differentiated neuroendocrine carcinoma
- Small cell carcinoma
- Large cell neuroendocrine carcinoma

NEOPLASMS WITH MIXED DIFFERENTIATION
- Mixed acinar-neuroendocrine carcinoma
- Mixed acinar-ductal carcinoma
- Mixed ductal-neuroendocrine carcinoma
- Mixed acinar-neuroendocrine-ductal carcinoma

SEROUS CYSTIC NEOPLASMS
- Microcystic serous cystadenoma
- Macrocystic serous cystadenoma
- Solid serous adenoma
- Serous cystadenocarcinoma

MUCINOUS CYSTIC NEOPLASMS
- Mucinous cystic neoplasm with low grade dysplasia
- Mucinous cystic neoplasm with moderate dysplasia
- Mucinous cystic neoplasm with high grade dysplasia
- Mucinous cystic neoplasm with invasive carcinoma

INTRADUCTAL NEOPLASMS
- Intraductal papillary-mucinous neoplasms
- Intraductal tubulopapillary neoplasms

INVASIVE DUCTAL ADENOCARCINOMA
- Tubular adenocarcinoma
- Adenosquamous carcinoma
- Columnar (mucinous neoplastic) adenocarcinoma
- Signet ring cell carcinoma
- Undifferentiated carcinoma
- Anaplastic carcinoma
- Sarcomatoid carcinoma
- Carcinosarcoma
- Undifferentiated carcinoma with osteoclast-like giant cells

Classification of Pancreatic Neoplasms: Ductal Neoplasms

SEROUS CYSTIC NEOPLASMS
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- Macrocystic serous cystadenoma
- Solid serous adenoma
- Serous cystadenocarcinoma

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- Mucinous cystic neoplasm with low grade dysplasia
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INTRADUCTAL NEOPLASMS
- Intraductal papillary-mucinous neoplasms
- Intraductal tubulopapillary neoplasms

Classification of Pancreatic Neoplasms

Cystic Pancreatic Neoplasms

- Fundamentally cystic neoplasms
  - Serous cystic neoplasms
  - Mucinous cystic neoplasms

- Secondarily cystic neoplasms
  - Solid pseudopapillary neoplasm
  - Most other primarily solid neoplasms

- Intraductal neoplasms
  - Intraductal papillary mucinous neoplasm
  - Intraductal oncocytopapillary neoplasm
Cystic Pancreatic Neoplasms

- Intraductal papillary mucinous neoplasms: 40%
- Serous cystic neoplasms: 30%
- Solid pseudopapillary neoplasm: 12%
- Mucinous cystic neoplasms: 10%
- Cystic ductal adenocarcinoma: 4%
- Cystic pancreatic endocrine neoplasm: 2%
- Others: 2%

Ductal Adenocarcinoma: Genetic Features

- K-ras mutations (95%)
- p16 abnormalities (90%)
- p53 mutations (60%)
- DPC4 / Smad4 mutations (55%)
- Her2/neu overexpression (95%)
- BRCA2 mutations (5%)
- STK11/LKB1 mutations (5%)
- hMLH-1, hMSH-2 mutations (5%)
- Promotor methylation of numerous genes
**Ductal Adenocarcinoma: Genetic Features**

- K-\textit{ras} mutations (95%)
- p16 abnormalities (90%)
- p53 mutations (60%)
- DPC4 / Smad4 mutations (55%)
  - Her2/neu overexpression (95%)
  - BRCA2 mutations (5%)
  - STK11/LKB1 mutations (5%)
  - hMLH-1, hMSH-2 mutations (5%)

**Precursors to Invasive Ductal Adenocarcinoma**

- Pancreatic Intraepithelial Neoplasia (PanIN)
- Intraductal Papillary Mucinous Neoplasms
- Mucinous Cystic Neoplasms
Pancreatic Intraepithelial Neoplasia: Background

- Metaplastic and proliferative lesions long recognized
- Some common, age-related, often incidental
- Others more associated with invasive ductal adenocarcinomas
- Spectrum of intraepithelial lesions
  - Morphologic progression: metaplasia->hyperplasia->dysplasia
  - Accumulation of genetic abnormalities
- “PanIN” terminology proposed, 1994
- Target for earlier detection of pancreatic carcinoma

PanINs in Autopsy Studies

<table>
<thead>
<tr>
<th>Kozuka*</th>
<th>Mukada**</th>
</tr>
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<tbody>
<tr>
<td>1979</td>
<td>1982</td>
</tr>
<tr>
<td>n</td>
<td>1174</td>
</tr>
<tr>
<td>Invasive carcinoma</td>
<td>24 (2.0%)</td>
</tr>
<tr>
<td>Simple hyperplasia</td>
<td>213 (18.1%)</td>
</tr>
<tr>
<td>Papillary hyperplasia</td>
<td>78 (6.6%)</td>
</tr>
<tr>
<td>Atypical hyperplasia</td>
<td>13 (1.1%)</td>
</tr>
</tbody>
</table>

Molecular Alterations in PanINs

<table>
<thead>
<tr>
<th>PanIN 1A</th>
<th>PanIN 1B</th>
<th>PanIN 2</th>
<th>PanIN 3</th>
<th>Invasive Carcinoma</th>
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</thead>
<tbody>
<tr>
<td>K-ras</td>
<td>35%</td>
<td>45%</td>
<td>65%</td>
<td>85%</td>
</tr>
<tr>
<td>p53</td>
<td>0%</td>
<td>0%</td>
<td>&lt;5%</td>
<td>20%</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>82%</td>
<td>86%</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>p16</td>
<td>24%</td>
<td>19%</td>
<td>55%</td>
<td>71%</td>
</tr>
<tr>
<td>DPC-4</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>31%</td>
</tr>
</tbody>
</table>

* Cancer 1979; 43:1418-1428

Pancreatic Intraepithelial Neoplasia (PanIN)

Progression of Intraductal Neoplasia to Invasive Carcinoma

- THREE cases reported
- All had documented CIS (PanIN 3) in resection specimens with involvement of margins
  - Associated with invasive carcinoma: new carcinoma after 9 yrs
  - Associated with pancreatitis and pseudocyst: carcinoma after 10 yrs
  - Associated with pancreatitis: carcinoma found 17 months later
- Evidence of progression
- Difficulty of temporal follow-up of intraductal lesions

PanINs: Translation to the Surgical Pathology Report

- **PanIN Neoplasm**
  - Reflects clonal nature and expression of cancer associated genes
  - Does not mean “requires clinical treatment”
- **PanINs 1 and 2**
  - Common incidental findings
  - Generally not reported
- **PanIN 3**
  - Strongly suspected to be significant
  - However, “the clinical significance and therefore appropriate management have not been established” (yet)

Issues Regarding PanINs

- Molecular phenotype emerging
- Natural history largely unknown
- Identification at clinical level difficult

- Need measurable markers of late stage preinvasive neoplasia (PanIN 3)
- Need clinically detectable model for preinvasive neoplasia
Intraductal Papillary-Mucinous Neoplasms

- Uncommon tumors of pancreatic ducts with papilla formation and mucin hypersecretion
- Clinically detectable
- Often lack invasive carcinoma (65-75%)
- Histologic similarities with PanINs
- (?) Same molecular pathway as PanINs and conventional ductal adenocarcinoma
Intraductal Papillary-Mucinous Neoplasms: Intraductal Ultrasound

Hara et al. Gastroenterology 2002; 122: 34
Intraductal papillary mucinous neoplasm with invasive colloid carcinoma
Intraductal papillary mucinous neoplasm with invasive tubular adenocarcinoma

Development of Carcinoma in IPMNs

Intestinal type papillae
Pancreatobiliary type papillae
Colloid carcinoma
Tubular carcinoma

Intraductal papillary mucinous IPMNs:

Classification

WHO 2000
Intraductal papillary mucinous adenoma
Intraductal papillary mucinous neoplasm, borderline
Intraductal papillary mucinous carcinoma in situ
Papillary mucinous carcinoma

AFIP Fascicle
IPMN with low grade dysplasia
IPMN with moderate dysplasia
IPMN with high grade dysplasia
IPMN with an associated invasive carcinoma (specify type)

IPMN: Survival

Cumulative Survival

Time (months)

n = 32
p = 0.01

n = 30

n = 13
p = 0.008

n = 17

n = 17

p = 0.008

Cumulative Survival

Time (months)

non-invasive (——)
invasive (-----)
invasive colloid carcinoma (-----)
invasive tubular carcinoma (-----)
### Intraductal Papillary Mucinous Neoplasms: Classification

**WHO 2010**
- IPMN with low grade dysplasia
- IPMN with intermediate grade dysplasia
- IPMN with high grade dysplasia
- IPMN with an associated invasive carcinoma

**AFIP Fascicle**
- IPMN with low grade dysplasia
- IPMN with moderate dysplasia
- IPMN with high grade dysplasia
- IPMN with an associated invasive carcinoma

### Intraductal Papillary-Mucinous Neoplasms: Main vs. Secondary Ducts

- 70% involve main duct, 30% confined to secondary (branch) ducts
- Secondary duct type confined to head/neck
- Secondary duct type in younger patients
- Secondary duct type less aggressive
  - Main duct type: 20% CIS, 37% invasive carcinoma
  - Secondary type: 15% CIS, 0% invasive carcinoma

Intraductal Tubulopapillary Neoplasm of the Pancreas

- Also reported as “Intraductal Tubular Carcinoma”
- Approximately 35 cases reported
- Mean age = 54 yrs (range = 25-72); F > M
- Symptoms: chronic pancreatitis
- Location: head > tail; 30% diffuse involvement
- Favorable outcome

Intraductal Neoplasms: Immunohistochemistry

Keratins
- Cam5.2: 100
- AE1:AE3: 95
- CK7: 70
- CK19: 85
- CK20: 30

Glycoproteins
- CEA (m): 85
- CA19-9: 90
- B72.3: 50

Lineage Markers
- Chromogranin (35)
- Synaptophysin (35)
- Trypsin: 0
- Chymotrypsin: 0

Mucin Expression in Pancreatic Ductal Neoplasia

- Mucinous change common in neoplasia
- Increase in normal mucins
  - CA19-9
- Expression of tumor-associated glycoproteins
  - CEA, B72.3, CA125, CA72-4, CA15-3
- Mucins are secreted
MUC Proteins

- Numerous (>20) species identified
- Variety of functions
- Membrane bound vs. secreted
- MUCs 1-7 studied in the pancreas
- MUC1, MUC5B, MUC6 mRNA present in normal pancreas; protein expression less consistent
- MUC2, MUC3A, MUC4, MUC5AC, MUC7 absent
- Aberrant expression in intraductal and invasive pancreatic neoplasia
  - MUC1, MUC4, MUC5AC, MUC6 in infiltrating ductal adenocarcinoma

MUCs in Pancreatic Neoplasia

**MUC1**
- Mammary type mucin
- Maintenance of lumen formation
- Inhibitory role in cell-cell, cell-stroma interaction
- Inhibits cytotoxic immunity against tumor cells
- Activation of tumorigenesis pathways
- Considered as a marker of “aggressive phenotype”

**MUC2**
- Intestinal (goblet) type mucin
- Protective function
- Gel formation
- Tumor suppressor activity
- Considered as a marker of “indolent phenotype” in pancreas ca.

Morphologic Subtypes of IPMNs:
- **Pancreatobiliary Type**
  - MUC1: 90% of cases
  - MUC2: 1% of cases

- **Colloid (mucinous non-cystic) ca.**
  - MUC1: 0% of cases
  - MUC2: 100% of cases
Morphologic Subtypes of IPMNs:
Intestinal (Villous) Type

MUC1
MUC5AC
MUC2

Morphologic Subtypes of IPMNs:
Gastric Foveolar Type

MUC1
MUC2
MUC5AC

MUC Expression in Pancreatic Neoplasia

<table>
<thead>
<tr>
<th>Tubular Ca</th>
<th>Colloid Ca</th>
<th>IPMN Int.</th>
<th>IPMN PB</th>
<th>IPMN Gastric</th>
<th>PanIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC1</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>MUC2</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

CDX2 in Pre-invasive Neoplasia
- IPMN
  - Gastric: 0/17 (0%)
  - Intestinal: 12/13 (95%)
  - Pancreatobiliary: 0/9 (0%)
  - Oncocytic: 0/2 (0%)
- PanIN
  - All: 2/23 (9%)

p = 0.000001
**CDX2 in Invasive carcinomas**

- Colloid Carcinoma: 10/11 (90%)
  - The only negative colloid ca. arose in association with a PB type IPMN
- Tubular Carcinoma: 12/74 (16%)
  - Usually focal

\[ p = 0.0001 \]

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**Pancreatic carcinogenesis**

- IPMAdenoma
- IPMC-non invasive
- Colloid ca.
- Tubular inv.
- MUC1 + - PANCREATOBILIARY-AGGRESSIVE
- MUC1 - INTESINAL-INDOLENT
- PanIN  I-II
- PanIN  III (CIS)
- Tubular inv.

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**Genetic Features of Intraductal Papillary Mucinous Neoplasms**

<table>
<thead>
<tr>
<th></th>
<th>K-ras</th>
<th>p53</th>
<th>DPC4</th>
<th>p16</th>
<th>STK11/LKB1</th>
<th>PIK3CA</th>
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<tbody>
<tr>
<td>Ductal Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>early</td>
<td>&gt;95%</td>
<td>50-70%</td>
<td>40-60%</td>
<td>95%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>late</td>
<td>5-20%</td>
<td>5-20%</td>
<td>5-20%</td>
<td>5%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

|                  |       |     |      |     |            |        |
| Intraductal Papillary Mucinous Neoplasms |       |     |      |     |            |        |
| early            | 80%   | 25-65% | 5%  | 5%  | 50%** | 25%     |
| late             | 20%   | 25-65% | 5%  | 50%** |        | 10%     |

**promoter methylation**

**Normal Expression of DPC4/Smad4**
IPMN: Exome Sequencing

- KRAS (codon 12) and GNAS (codon 201) mutations in 80% and 60%, respectively
  - GNAS encodes for Gαs, one of the guanine nucleotide-binding proteins (G-proteins); role in cellular signal transduction
  - GNAS mutants maintain a permanent association with GTP and induce continuous constitutive adenylate cyclase activation with cyclic AMP formation
- RNF43 mutated in 75%
  - The protein encoded by RNF43 has been shown to have intrinsic E3 ubiquitin ligase activity
- Mutations in APC in 25%

Wu et al., Sci Transl Med 2011;3:92ra66
Wu et al., PNAS 2011;108:21188

Multilocal IPMN

- Each locule monoclonal
- Some different locules from the same case harbor different mutations
- Two adjacent locules more likely to contain the same KRAS or GNAS mutation than two topographically separate locules

IPMNs vs. PanINs: Similarities

- Both are inherently intraductal
- Both are composed predominantly of columnar, mucin-producing cells
- Both may be either flat or papillary
- Both exhibit a range of cytoarchitectural atypia
- Both are recognized precursors to invasive adenocarcinoma
- Both sequentially accumulate similar genetic alterations with increasing cytoarchitectural atypia
- PanINs may involve large ducts and IPMNs may involve small ducts

**IPMN vs. PanIN: Differences**

- Clinical presentation
- Size of involved ducts
- Abundance of papillae
- Special papilla subtypes
- CK20, MUC2, CDX2 = intestinal type IPMN
- Molecular phenotypes overlap

**Guidelines**

- “PanINs usually involve ducts < 5 mm in diameter”
- “IPMNs usually produce a lesion greater than 1 cm in diameter”

**Pancreatic Intraepithelial Neoplasia (PanIN) vs Intraductal Papillary Mucinous Neoplasm (IPMN)**

**6 mm, incidental lesion**

**Mega-PanIN vs Micro-IPMN Guidelines**

- Review radiologic findings for features of IPMN
- Review gross findings for papillae and/or cysts
- Get step sections to verify the size of the ducts and investigate for (1) tall papillae, (2) abundant luminal mucin, and (3) MUC2 immunoexpression, any of which, if present, point towards an IPMN
IPMN with coexisting PanINs
vs IPMN with extension to small ducts

It can be difficult (if not impossible) to distinguish between IPMNs and PanINs affecting the same pancreas.

IPMN vs Retention cyst

- Retention cysts occur secondary to pancreatic ductal obstruction
- Minimal or no atypia
- Unilocular
- Low cuboidal or flat epithelium
- “PanIN can occur” (?)

Mucinous Cystic Neoplasms

- Mean age = 45 yrs
- Female >>>> male (20-40:1)
- Tail / Body >>>> Head
- Mean size = 8.5 cm (up to 36 cm)
### Mucinous Cystic Neoplasms: Classification

<table>
<thead>
<tr>
<th>W.H.O.</th>
<th>AFIP Fascicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous cystadenoma</td>
<td>MCN with low grade dysplasia</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm, borderline</td>
<td>MCN with moderate dysplasia</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma in situ</td>
<td>MCN with high grade dysplasia</td>
</tr>
<tr>
<td>Invasive mucinous cystadenocarcinoma</td>
<td>MCN with associated invasive carcinoma</td>
</tr>
</tbody>
</table>
Mucinous Cystic Neoplasms:

Classification (WHO 2010)

- MCN with low grade dysplasia
- MCN with intermediate grade dysplasia
- MCN with high grade dysplasia
- MCN with associated invasive carcinoma
  ("mucinous cystadenocarcinoma")

Mucinous Cystic Neoplasms:

Behavior

- 41 patients:
  - Alive and Well: 20
  - Alive with tumor: 1
  - Dead of tumor: 12
  - Operative deaths: 1
  - Unrelated deaths: 7
- Mean survival of those dying of tumor = 30 months
- Of those alive and well,
  - Definitive carcinoma: 5
  - Atypical epithelium: 8
  - Apparently benign: 4
- Of those dying of tumor,
  - Definitive carcinoma: 9
  - Atypical epithelium: 2
  - Apparently benign: 1


Malignant Potential in
Mucinous Cystic Neoplasms

- 56 Cases:
  - 22 adenomas (F/U median 42.5 mos, range 4-114 mos)
  - 12 borderline tumors (F/U median 69.5 mos, range 9-180 mos)
  - 22 carcinomas (F/U median 23 mos, range 2-134 mos)
    - 6 non-invasive (F/U median 76 mos)
    - 3 intratumoral
    - 5 within the tumor wall
    - 8 extrapancreatic tissues
- All alive and well except those with invasion of tumor wall or extrapancreatic tissues (8/13 DOD, mean survival 11 mos)


Mucinous Cystic Neoplasms:

Clinical Behavior

- Overall indolent; less than 10% mortality
- Sampling issue paramount
- Recognize clear-cut malignancy when present
- Exercise caution when absent
Genetic Features of Mucinous Cystic Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>K-ras</th>
<th>p53</th>
<th>DPC4</th>
<th>p16</th>
<th>GNAS</th>
<th>RNF43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal Adenocarcinoma</td>
<td>&gt;95% early</td>
<td>50-70% late</td>
<td>40-60% late</td>
<td>95% mid</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mucinous Cystic Neoplasms</td>
<td>70-85% Early</td>
<td>35-50% Late</td>
<td>50% Late</td>
<td>15%* mid</td>
<td>0%</td>
<td>50%</td>
</tr>
</tbody>
</table>

** promoter methylation

Mucinous Cystic Neoplasms:

Differential Diagnosis

- **Radiographic / Gross**
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Macrocystic serous cystadenoma
  - Solid pseudopapillary neoplasm
    - Pseudocyst
- **Microscopic**
  - IPMN
  - Ductal adenocarcinoma with mucinous glands
    - Pseudocyst

Mucinous Cystic Neoplasm vs. Pseudocyst

Serous Neoplasms

- Microcystic serous cystadenoma
  - Microcystic adenoma
  - Glycogen-rich adenoma
- Macrocystic serous cystadenoma
  - Oligolocular ill-demarcated adenoma
- Solid serous adenoma
- Serous cystadenocarcinoma
Serous Cystic Neoplasms

- Mean age = 65 yrs
- Female > male (7:3)
- Associated with von Hippel Lindau syndrome
- Head = Body / Tail
- Mean size = 6 cm (up to 30 cm)
Macrocystic serous cystadenoma

Solid serous adenoma

PAS
dPAS
Serous Cystic Neoplasms: Differential Diagnosis

- Radiographic / Gross
  - Microcystic
    - Large: ???
    - Small: any macrocystic lesion
  - Macrocytic
    - Branch duct IPMN
    - Mucinous cystic neoplasm
    - Retention cyst

- Microscopic
  - Microcystic
  - Lymphangiomatosa
  - Renal cell carcinoma
  - Macrocystic
  - Lymphangiomatosa

Pancreatic Neoplasms with Degenerative Cystic Change

- Pancreatic endocrine neoplasm
- Acinar cell carcinoma

- Ductal adenocarcinoma
Solid Pseudopapillary Neoplasm

- Many synonyms
  - “Solid and cystic tumor”, “solid and papillary epithelial neoplasm”, “papillary-cystic carcinoma”, “Hamoudi tumor”, “Frantz’s tumor”, ad nauseam
- 2-5% of pancreatic neoplasms
- Tumor of young females
  - F:M = 9:1; Mean age ~ 28 yrs
- Symptoms usually related to presence of mass
  - Detected during pregnancy, after trauma, incidentally
### Solid Pseudopapillary Neoplasm: Staining Results

<table>
<thead>
<tr>
<th>Stain</th>
<th>% Positive</th>
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<tbody>
<tr>
<td>Trypsin</td>
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</tr>
<tr>
<td>Chymotrypsin</td>
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<td>Lipase</td>
<td>0</td>
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<tr>
<td>Chromogranin</td>
<td>0</td>
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<tr>
<td>Synaptophysin</td>
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<tr>
<td>Neuron Specific Enolase</td>
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<tr>
<td>CD56</td>
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<td>CEA</td>
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<td>Keratin</td>
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<td>Vimentin</td>
<td>100</td>
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<tr>
<td>α-1-antitrypsin</td>
<td>84</td>
</tr>
<tr>
<td>CD10</td>
<td>75</td>
</tr>
<tr>
<td>CD117</td>
<td>50</td>
</tr>
<tr>
<td>β-catenin (nuclear)</td>
<td>90</td>
</tr>
<tr>
<td>Progesterone receptors</td>
<td>75</td>
</tr>
</tbody>
</table>

### Solid Pseudopapillary Neoplasm: “Hyaline Globules”

### Solid Pseudopapillary Neoplasm: Genetic Features

- APC / β-catenin pathway (90%)
  - β-catenin mutations
  - Overexpression of cyclin D1
- No abnormalities in “ductal adenocarcinoma genes”
  - K-ras
  - p53
  - DPC4
Solid Pseudopapillary Neoplasm:
Prognosis

- Very low grade malignant neoplasm
- Complete resection usually curative
- Metastases
  - 10-15% of patients
  - Liver and peritoneum (NOT lymph nodes)
  - Long-term survival possible
- High grade malignant transformation
  - Two cases reported
  - Diffuse sheets of cells, pleomorphism, mitoses
  - Rapid dissemination and death

Diagnostic Issues in Pancreatic Cysts

- Preoperative Diagnosis
  - Radiology
  - Cytology
  - Cyst fluid biochemical analysis
  - Cyst fluid proteomic analysis
  - Cyst fluid molecular analysis
  - Cyst fluid miRNA detection

Preoperative Diagnosis of Pancreatic Cysts

- Distinguish Mucinous from Non-mucinous Lesions
  - Pseudocyst
  - Serous cystic neoplasm
  - Cystic neuroendocrine neoplasm
- Distinguish Low Grade Dysplasia from High Grade Dysplasia and Invasive Carcinoma
  - Resection vs. follow-up
  - Optimum test: positive = high grade; negative = low grade
  - Acceptable test: negative = low grade

Preoperative Diagnosis of IPMNs: Radiographic Criteria

- Main duct involved
- > 3 cm.
- Solid mural nodule
- Growth during F/U

Allen et al. J Gastrointest Surg 2003; 7: 970
Cyst Fluid Analysis for Diagnosis of Cystic Lesions

- Measure viscosity, amylase, glycoproteins (CEA, CA72-4, CA125, CA19-9, CA15-3)
- High amylase, low viscosity, low glycoproteins in pseudocyst
- Low amylase, low viscosity, low glycoproteins in serous cystadenoma
- High viscosity, high glycoproteins in mucinous neoplasms

MUC Measurement for Diagnosis of Cystic Lesions

- MUC1, MUC2, MUC4, and MUC5AC analyzed by ELISA
- Low risk (low grade / moderate dysplasia)
- High risk (high grade dysplasia / carcinoma)

Brugge et al. Gastroenterology 2004; 126: 1330
Pitman et al. Pancreatology 2008; 8: 277

Histologic Subtype Correlates with MUC Expression

MUCs are Elevated in High Risk IPMNs

<table>
<thead>
<tr>
<th>Degree of Dysplasia</th>
<th>Pancreatic Cyst Fluid Concentration (u/mL)</th>
<th>MUC 2</th>
<th>MUC 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma or High Grade Dysplasia</td>
<td></td>
<td>10</td>
<td>20.6</td>
</tr>
<tr>
<td>Low Grade or Moderate Dysplasia</td>
<td></td>
<td>4.4</td>
<td>4.6</td>
</tr>
</tbody>
</table>

* p<0.05

Molecular Diagnosis of Pancreatic Cystic Lesions

- Utilizes aspirated cyst fluid
- DNA quantification, K-ras mutation, mutational amplitude, LOH analysis
- More frequent K-ras mutation, LOH with greater degree of dysplasia
- Some low grade (+), some high grade (-)

Schoedel et al. Diagn Cytopathol 2006; 34: 605
Khalid et al. Gastroint Endosc 2009; 69: 1095

Wu et al., Sci Transl Med 2011;3:92ra66
Wu et al., PNAS 2011;108:21188
Cystic and Intraductal Neoplasms

- Mucinous changes are characteristic of precursor lesions
- PanINs, IPMNs, and MCNs are precursors to Ca
- Neoplastic progression (increasing dysplasia) occurs in these neoplasms
- Separate pathways of carcinogenesis occur in the pancreas
- Understanding of the alterations in mucins and genetic markers with tumor progression may guide diagnosis and therapy