Mucinous Cystic and Intraductal Neoplasms of the Pancreatobiliary Tract: Recent Advances

PRESENTED BY
David S. Klimstra, MD
Disclosure of Relevant Financial Relationships

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David Klimstra reported no relevant financial relationships
Mucinous Cystic and Intraductal Neoplasms of the Pancreatobiliary Tract: Outline

- Mucinous cystic neoplasms of the pancreas (and bile ducts)
- Intraductal neoplasms of the pancreas
  - Intraductal papillary mucinous neoplasms (IPMNs)
  - Intraductal oncocytiic papillary neoplasms (IOPNs)
  - Intraductal tubulopapillary neoplasms (ITPNs)
- Intraductal neoplasms of the bile ducts
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 neuroendocrine tumor 2%
  - Others 2%
Mucinous Cystic Neoplasms

- **Anatomic sites**
  - Most common in the pancreas
  - Hepatic counterpart (formerly, “hepatobiliary cystadenoma”)
  - Exceedingly rare in bile ducts and gallbladder
  - Peritoneal primaries

- **Characteristic presentation**
  - Mean age = 45 years
  - Female >>> male (20-40:1)
  - Tail / body >>> head
  - Mean size = 8.5 cm (up to 36 cm)
Mucinous cystic neoplasm
Mucinous cystic neoplasm
Mucinous cystic neoplasm:
Cellular stroma

Estrogen receptor

Inhibin
Mucinous Cystic Neoplasms: Recent Advances

- Variant morphologies
  - Variations in epithelium
  - Stromal extension
- Two-tiered grading
  - “Baltimore consensus meeting”
  - Applies to all preinvasive neoplasms of the pancreas
- Update on associated carcinomas
  - Subtypes
  - Outcomes
Mucinous cystic neoplasm:
Non-mucinous epithelium

Mucinous cystic neoplasm of the liver and bile ducts
Mucinous cystic neoplasm: stromal extension into pancreas
Fetal pancreas at 24 weeks: cellular periductal mesenchyme
Mucinous cystic neoplasm: grading dysplasia
Mucinous Cystic Neoplasms: Terminology Recommendations from the Baltimore Consensus

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>MCN with low grade dysplasia</td>
<td>MCN, low-grade</td>
</tr>
<tr>
<td>MCN with intermediate grade dysplasia</td>
<td>MCN, low-grade</td>
</tr>
<tr>
<td>MCN with high grade dysplasia</td>
<td>MCN, high-grade</td>
</tr>
</tbody>
</table>

➢ “High-grade” to be used ONLY for the most dysplastic third of the spectrum

Mucinous Cystic Neoplasms: Invasive Carcinoma and Prognosis


- **41 patients:**
  - Alive and Well: 20
  - Alive with disease: 1
  - Dead of disease: 12
- **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
Mucinous Cystic Neoplasms: Invasive Carcinoma and Prognosis


- **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: Invasive Carcinoma and Prognosis

- 29 invasive carcinomas (16%)
- 24 tubular, 4 undifferentiated, 1 papillary, 0 colloid
- 3-year survival, 44%; 5-year survival, 26%
- Three patients with invasive carcinoma <0.5 cm died
Mucinous Cystic Neoplasms: Summary of Prognosis

- Overall indolent; less than 10% mortality
- Invasive carcinoma can be minimal
- Sampling issue paramount
- Recognize clear-cut malignancy when present
- Exercise caution when absent
Pancreas: Intraductal Papillary Mucinous Neoplasm
Intraductal papillary mucinous neoplasm
Intraductal papillary mucinous neoplasm
Papilla Types in IPMNss (WHO 2010)

Gastric  Intestinal  Pancreatobiliary  Oncocytic
# Immunoprofile of Intraductal Papillary Mucinous Neoplasms of Pancreas

<table>
<thead>
<tr>
<th>Subtype</th>
<th>MUC1</th>
<th>MUC2</th>
<th>MUC5AC</th>
<th>MUC6</th>
<th>CK7</th>
<th>CK20</th>
<th>CDX2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Gastric</strong></td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Intestinal</strong></td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>PB</strong></td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
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Intraductal Papillary Mucinous Neoplasms: Terminology Recommendations from the Baltimore Consensus

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</tr>
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➢“High-grade” to be used ONLY for the most dysplastic third of the spectrum

IPMN: Invasive Carcinoma and Survival

Genetic Features of Intraductal Papillary Mucinous Neoplasm

<table>
<thead>
<tr>
<th></th>
<th>KRAS</th>
<th>TP53</th>
<th>SMAD4</th>
<th>CDKN2A</th>
<th>GNAS</th>
<th>RNF43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ductal Adenocarcinoma</td>
<td>&gt;95%</td>
<td>50-70%</td>
<td>40-60%</td>
<td>95%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>early</td>
<td>late</td>
<td>late</td>
<td>mid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraductal Papillary</td>
<td>80%</td>
<td>25-65%</td>
<td>5%</td>
<td>50%</td>
<td>60%</td>
<td>75%</td>
</tr>
<tr>
<td>Mucinous Neoplasm</td>
<td>early</td>
<td>late</td>
<td>late</td>
<td>mid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wu et al., *Sci Transl Med* 2011;3:92ra66
Wu et al., *PNAS* 2011;108:21188
Distribution of Common Mutations by IPMN Subtype

- **Mutations by Papilla Type**
- **Mutations by Invasive Carcinoma Type**

* * p = n.s.

- Blue = Colloid
- Red = Tubular

Multilocular IPMNs

- 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: Recurrence after Resection

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” (?)
“Simple Mucinous Cyst”
Simple Mucinous Cysts

- Definition: >1 cm; simple mucinous lining; no papillae; no HG dysplasia; no cellular stroma
- Supports neoplastic nature
- Not identical to gastric type IPMN (*KRAS* - 80%, *GNAS* - 50%, *RNF43* - 10%)

Attiyeh, et al., *under review*
WHO 2019: Intraductal Oncocytic Papillary Neoplasm

Intraductal Oncocytic Papillary Neoplasm

Intraductal Oncocytic Papillary Neoplasm: Solid Pattern
### Intraductal Oncocytic Papillary Neoplasm

<table>
<thead>
<tr>
<th>Features</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range) (y)</td>
<td>59 (36-74)</td>
</tr>
<tr>
<td>Female/Male</td>
<td>15/9</td>
</tr>
<tr>
<td>Preoperative diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Mucinous cystic neoplasm</td>
<td>3/12 (25)</td>
</tr>
<tr>
<td>Intraductal papillary mucinous neoplasm</td>
<td>3/12 (25)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>14/21 (67)*</td>
</tr>
<tr>
<td>Body/tail</td>
<td>6/21 (28)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>1/21 (5)</td>
</tr>
<tr>
<td>Median tumor size (range)</td>
<td>4.5 (1-14)</td>
</tr>
<tr>
<td>Invasion</td>
<td>7/24 (29)</td>
</tr>
<tr>
<td>LVI</td>
<td>2/15 (13)</td>
</tr>
<tr>
<td>PNI</td>
<td>1/15 (7)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>1/17 (6)</td>
</tr>
<tr>
<td>Positive margin</td>
<td>4/17 (24)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Median follow-up (range) (y)</td>
<td>6.8 (0.1-18.5)</td>
</tr>
<tr>
<td>Died of postoperative complications or other causes</td>
<td>5/18 (28)</td>
</tr>
<tr>
<td>Died of disease</td>
<td>0/18 (0)</td>
</tr>
<tr>
<td>Alive with disease</td>
<td>0/18 (0)</td>
</tr>
<tr>
<td>No evidence of disease</td>
<td>13/18 (72)</td>
</tr>
</tbody>
</table>

Intraductal Oncocytic Papillary Neoplasm: Invasive Carcinoma

Intraductal Oncocytic Papillary Neoplasm: Immunophenotype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>MUC1 %</th>
<th>MUC2 %</th>
<th>MUC5AC %</th>
<th>MUC6 %</th>
<th>CK7 %</th>
<th>CK20 %</th>
<th>CDX2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intestinal</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
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<td>-</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>-/+</td>
<td>-/+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>F</td>
<td>F</td>
</tr>
</tbody>
</table>

* in goblet cells

MUC1 50%
MUC2 29%*
MUC5AC 100%
MUC6 89%
CDX2 9%*
HepPar-1 61%

Basturk et al., Virchows Arch 2016; 469: 523-32.
Abnormal β-catenin 1/21 (5%)
Mesothelin 21 (87.5%)
Claudin-4 2/23 (9%)
MUC1 12 (50%)
MUC2 7 (29%)
MUC1+, MUC2+ 3 (12.5%)
MUC1-, MUC2- 8 (33%)
MUC1+, MUC2- 9 (37.5%)
MUC1-, MUC2+ 4 (17%)
MUC5AC 22/22 (100)
MUC6 8/9 (89%)
CDX2 2/22 (9%)
HepPar-1 14/23 (61%)

Intraductal Oncocytic Papillary Neoplasm: Genomic Features

<table>
<thead>
<tr>
<th>Genes</th>
<th>KRAS</th>
<th>TP53</th>
<th>DPC4</th>
<th>CDKN2A</th>
<th>GNAS</th>
<th>RNF43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraductal Oncocytic Papillary Neoplasm</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>Intraductal Papillary Mucinous Neoplasm</td>
<td>80%</td>
<td>25-65%</td>
<td>5%</td>
<td>50%</td>
<td>60%</td>
<td>75%</td>
</tr>
</tbody>
</table>

- Recurrent mutations in *ARHGAP26, ASXL1, EPHA8, ERBB4*
- Focal oncocytic features in IPMN: conventional IPMN genomic alterations

Basturk et al., *Mod Pathol* 2016;29:1058
Basturk et al., *Virchows Arch* 2016;469:523
Intraductal Oncocytic Papillary Neoplasm: Gene Fusions

- Recurrent fusions involve *DNAJB1, ATP1B1, PRKACA, PRKACB*
  - *ATP1B1-PRKACB (45%); DNAJB1-PRKACA (38%); ATP1B1-PRKACA (17%)*
- IOPNs and IPMNs with oncocytic features, and associated invasive carcinomas
- Absent in other IPMNs and pancreatobiliary neoplasms

Vyas et al., *Mod Pathol* 2019; Nov. 1 [Epub ahead of print].
Intraductal Oncocytic Papillary Neoplasm: Gene Fusions

Vyas et al., *Mod Pathol* 2019; Nov. 1 [Epub ahead of print].


**PRKACA break-apart FISH**

![Gene Fusions Diagram](image-url)
Fibrolamellar Hepatocellular Carcinoma

- Young patients
- No cirrhosis
- Normal AFP
- (?) better prognosis
- \textit{DNAJB1-PRKACA} fusion
Hepatocyte Differentiation in IOPN

HepPar1

Albumin ISH
Intraductal Tubulopapillary Neoplasm of the Pancreas

- Also reported as “Intraductal Tubular Neoplasm”
- Approximately 50 cases reported
- Mean age = 55 yrs (range = 25-79); F > M
- Symptoms: chronic pancreatitis
- Location: head > tail; 30% diffuse involvement

Intraductal Tubulopapillary Neoplasm
Intraductal Tubulopapillary Neoplasm
Intraductal Tubulopapillary Neoplasm
Intraductal Tubulopapillary Neoplasm: Invasive Carcinoma
Intraductal Tubulopapillary Neoplasm: Invasive Carcinoma
### Intraductal Neoplasms of Pancreas: Immunophenotype

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</tr>
<tr>
<td>Intestinal</td>
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<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>PB</td>
<td>++</td>
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<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>-/+</td>
<td>-/+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ITPN</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Positive or Normal (%)

| Keratins  | Cam 5.2 | 12/12 (100) | CK 7 | 16/16 (100) | CK 19 | 16/18 (89) | CK 20 | 3/16 (19)* |
| Glycoproteins | B72.3 | 2/7 (29) | CA125 | 2/14 (14)* | CA19.9 | 13/14 (93) | mCEA | 6/12 (50) |
|            | MUC1    | 15/17 (88) | MUC2 | 0/17 (0) | MUC5AC | 1/24 (4)* | MUC6 | 17/25 (68) |
| Lineage markers | CDX2 | 1/14 (7)* | HepPar-1 | 1/6 (17)* | Chromogranin | 1/27 (4)* | Synaptophysin | 1/27 (4)* |
|            | Chymotrypsin | 0/24 (0) | Trypsin | 0/26 (0) | Molecular markers | β-Catenin | 14/15 (93), membranous | E-Cadherin | 16/16 (100), membranous |
|            | p16 | 4/12 (33) | Nuclear p53 | 4/15 (27) | SMAD4 | 16/16 (100) |
## Genetic Features of Intraductal Tubulopapillary Neoplasm

<table>
<thead>
<tr>
<th>Gene</th>
<th>Intraductal Tubulo-papillary Neoplasm</th>
<th>Intraductal Papillary Mucinous Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>0%</td>
<td>80%</td>
</tr>
<tr>
<td>TP53</td>
<td>5%</td>
<td>25-65%</td>
</tr>
<tr>
<td>DPC4</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td>GNAS</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>RNF43</td>
<td>0%</td>
<td>75%</td>
</tr>
</tbody>
</table>

- 32% chromatin remodeling genes (MLL1, MLL2, MLL3, BAP1, PBRM1, EED, ATRX)
- 27% PI3K pathway genes (PIK3CA, PIK3CB, INNPP4A, PTEN)
- 40% MCL1 amplification
- 18% FGFR2 fusions
- 10% no mutations

Basturk et al., *Mod Pathol* 2017;30:1760
Intraductal Tubulopapillary Neoplasm of the Pancreas: Outcome

- Invasive component in ~70%; predominant in 10%
- Alive and free of tumor: 32% (mean F/U, 19 mos)
- Alive with recurrence: 55% (mean F/U, 61 mos)
- Died of tumor: 9% (mean, 32 mos)
- Died of other causes: 5%
- 1-, 3-, 5-year survival
  - With invasive carcinoma: 100%, 91%, 71%
  - Without invasive carcinoma: 100%

Basturk et al., *Am J Surg Pathol* 2017;41:313
Intraductal Neoplasms of the Pancreas: 2019 WHO Classification

- **Terminology**
  - Intraductal papillary mucinous neoplasm
    - Gastric type
    - Intestinal type
    - Pancreatobiliary type
  - Intraductal oncocytic papillary neoplasm
  - Intraductal tubulopapillary neoplasm

- **Dysplasia grading**
  - 2-tiered system
    - Low grade vs. high grade
Preinvasive, Mass-forming Neoplasms of the Bile Ducts: Intraductal Papillary Neoplasms

- Uncommon
- May be multicentric ("papillomatosis")
- Asian vs. Western cohort differences
- Usually have high grade dysplasia
- Often have invasive carcinoma component
- Pancreatobiliary >> intestinal morphology
- Favorable prognosis
# Intraductal Papillary Neoplasms of the Bile Ducts

<table>
<thead>
<tr>
<th>Clinicopathologic Features</th>
<th>n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>69 (42-81)</td>
</tr>
<tr>
<td>Male:Female</td>
<td>58:42</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td><em>Intrahepatic</em></td>
<td>36%</td>
</tr>
<tr>
<td><em>Hilar</em></td>
<td>31%</td>
</tr>
<tr>
<td><em>Distal</em></td>
<td>33%</td>
</tr>
<tr>
<td>Mean overall tumor size (cm)</td>
<td>5 (1.5 – 11.4)</td>
</tr>
<tr>
<td>Invasive Component</td>
<td></td>
</tr>
<tr>
<td><em>Present</em></td>
<td>72%</td>
</tr>
<tr>
<td><em>Absent</em></td>
<td>28%</td>
</tr>
</tbody>
</table>
Intraductal Papillary Neoplasms of the Bile Ducts
Intraductal Papillary Neoplasm of Proximal Bile Ducts
Intraductal Papillary Neoplasm of Distal Common Bile Duct
Intraductal Papillary Neoplasms of Bile Ducts
Intraductal Papillary Neoplasm of Bile Ducts: Dysplasia Grading

<table>
<thead>
<tr>
<th>Former terminology (2010 WHO)</th>
<th>Revised terminology (2019 WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPN with low grade dysplasia</td>
<td>IPN, low-grade</td>
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<td>IPN, high-grade</td>
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➢ “High-grade” to be used ONLY for the most dysplastic third of the spectrum
Bile Duct: Intestinal Type Intraductal Papillary Neoplasm
Intraductal Oncocytic Papillary Neoplasm of Bile Ducts

Martin et al. *Cancer* 2002; 95: 2180-7
Intraductal Tubulopapillary Neoplasms of Bile Ducts

Intraductal Tubulopapillary Neoplasm of the Bile Duct

1997 Hilar Bile Ducts

2001 Intrapancreatic Common Bile Duct
Pancreatic IPMNs vs. Intraductal Papillary Neoplasms of Bile Ducts

- Some histologic similarities
- Many differences in frequencies
  - Mucin hypersecretion
  - Intestinal type papillae
  - Oncocytic variant
  - Colloid carcinoma
  - Prevalence of high grade dysplasia
- “Biliary IPMN”
Spectrum of Cell Lineages of IPNB

- Pancreatobiliary: 70%
- Oncocytic: 15%
- Gastric: 10%
- Intestinal: 5%

Rocha et al. Hepatology 2012; 56:1352-60
# Immunoprofile of Intraductal Papillary Neoplasms of Bile Ducts

Wang et al. USCAP Pancreas Platform Presentation, March 19, 2018

<table>
<thead>
<tr>
<th>Subtype</th>
<th>MUC1 %</th>
<th>MUC2 %</th>
<th>MUC5AC %</th>
<th>MUC6 %</th>
<th>CK7 %</th>
<th>CK20 %</th>
<th>CDX2 %</th>
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<tr>
<td>Intestinal</td>
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<td>PB</td>
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<td>ITPN</td>
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</table>
Genomic Profile of Intraductal Papillary Neoplasms of Bile Ducts

Targeted NGS (468 genes) of **intraductal component**

Wang et al. USCAP Pancreas Platform Presentation, March 19, 2018
Genomic Profile of IPN of Bile Ducts

Genes Altered By Histologic Subtype

<table>
<thead>
<tr>
<th>Gene</th>
<th>% affected</th>
<th>p-value</th>
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<tr>
<td>TP53</td>
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<td>0.042</td>
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<td>ARID2</td>
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<td>CDKN2A</td>
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<tr>
<td>APC</td>
<td>55.6</td>
<td>0.014</td>
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<tr>
<td>KRAS</td>
<td>44.4</td>
<td>0.015</td>
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<tr>
<td>SMAD4</td>
<td>60.0</td>
<td>0.017</td>
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<tr>
<td>HIST2H3C/D</td>
<td>33.3</td>
<td>0.15</td>
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<tr>
<td>ATM</td>
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<td>0.15</td>
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<tr>
<td>BLM</td>
<td>28.6</td>
<td>0.026</td>
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</tbody>
</table>

Wang et al. USCAP Pancreas Platform Presentation, March 19, 2018
Intraductal Papillary Neoplasm with Invasive Adenocarcinoma (75%)
Intestinal IPN of Bile Duct with Invasive Colloid Carcinoma
Invasive Adenocarcinoma Arising in IPN of Bile Ducts

- Survival correlates with
  - Presence of invasion
  - Depth of invasion (5mm cutoff)

- Favorable prognosis after complete resection

Rocha et al. *Hepatology* 2012; 56:1352-60
THANK YOU!