**Diagnosis of Cystic and Intraductal Tumors of the Pancreas**

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**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 oncocytic papillary neoplasm

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**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%

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**Model of neoplastic progression**
**Ductal Adenocarcinoma of the Pancreas**

**Survival after Resection**

![Graph showing survival rates with different lymph node statuses](image)

- **MSKCC 10/15/1983 - 4/14/2002**
- **n = 674**
- **p = 0.0003**

- Negative Lymph Nodes (n = 263)
- Positive Lymph Nodes (n = 411)

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**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

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**Ductal Adenocarcinoma:**

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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* 1979</th>
<th>Mukada** 1982</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></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>
<tr>
<td></td>
<td>6 (2.9%)</td>
</tr>
</tbody>
</table>

* Cancer 1979; 43:1418-1428

Molecular Alterations in PanINs

<table>
<thead>
<tr>
<th>K-ras</th>
<th>p53</th>
<th>HER-2/neu</th>
<th>p16</th>
<th>DPC-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PanIN 1A</td>
<td>35%</td>
<td>0%</td>
<td>82%</td>
<td>24%</td>
</tr>
<tr>
<td>PanIN 1B</td>
<td>45%</td>
<td>0%</td>
<td>86%</td>
<td>19%</td>
</tr>
<tr>
<td>PanIN 2</td>
<td>65%</td>
<td>&lt;5%</td>
<td>92%</td>
<td>55%</td>
</tr>
<tr>
<td>PanIN 3</td>
<td>85%</td>
<td>20%</td>
<td>100%</td>
<td>71%</td>
</tr>
<tr>
<td>Invasive Carcinoma</td>
<td>90%</td>
<td>55%</td>
<td>69%</td>
<td>95%</td>
</tr>
</tbody>
</table>


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 neoplasm with invasive colloid carcinoma

Development of Carcinoma in IPMNs

Intestinal type papillae

Pancreatobiliary type papillae

Colloid carcinoma

Tubular carcinoma
IPMN: Survival

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

**IPMN: Survival**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Cumulative Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>0.8</td>
</tr>
<tr>
<td>48</td>
<td>0.6</td>
</tr>
<tr>
<td>72</td>
<td>0.4</td>
</tr>
<tr>
<td>96</td>
<td>0.2</td>
</tr>
<tr>
<td>120</td>
<td>0.0</td>
</tr>
</tbody>
</table>

n = 32
p = 0.01

n = 30

n = 13
p = 0.008

n = 17

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


Papilla Types in IPMNs

- Gastric
- Intestinal
- Pancreatobiliary
- Oncocytic
Intraductal Oncocytic Papillary Neoplasm

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

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

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

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

<table>
<thead>
<tr>
<th>Tubular (conventional ductal) ca.</th>
<th>Colloid (mucinous non-cystic) ca.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC1: 90% of cases MUC2: 1% of cases</td>
<td>MUC1: 0% of cases MUC2: 100% of cases</td>
</tr>
</tbody>
</table>
Morphologic Subtypes of IPMNs:
Intestinal (Villous) Type

Tubular      Colloid        IPMN         IPMN        IPMN        PanIN
Ca               Ca              Int.              PB          Gastric
MUC1              -               +++            -      +++
MUC2              -               +++            -      -
MUC5AC            -               -               -      -

Morphologic Subtypes of IPMNs:
Gastric Foveolar Type

MUC Expression in Pancreatic Neoplasia

<table>
<thead>
<tr>
<th>MUC1</th>
<th>MUC2</th>
<th>MUC5AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
</tbody>
</table>

CDX2 in Pre-invasive Neoplasia

- IPMN
  - Gastric: 0/17 (0%)
  - Intestinal: 12/13 (92%)
  - 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

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>
</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>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Intraductal Papillary Mucinous Neoplasms</td>
<td>80% early</td>
<td>25-45% late</td>
<td>5%</td>
<td>50%** mid</td>
<td>25%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**promoter methylation

Pancreatic carcinogenesis

IPMC - non invasive
IPMAdenoma
PanIN I-II
Colloid ca.
PanIN III (CIS)

MUC1 + - PANCREATOBILIARY, AGGRESSIVE
MUC2 - INTESTINAL, INDIFFERENT

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

- **KRAS** (codon 12) and **GNAS** (codon 201) mutations in 80% and 60%, respectively
  - **GNAS** encodes for Gsα, 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

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**Multilocular IPMN**

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

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**IPMNs vs. PanINs: Differences**

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

**Pancreatic Intraepithelial Neoplasia (PanIN)**

**Intraductal Papillary Mucinous Neoplasm (IPMN)**

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**IPMN vs PanIN Guidelines**

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

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**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

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**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.
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 neoplasm

Mucinous cystic neoplasm

Mucinous cystic neoplasm

Mucinous cystic neoplasm
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 56 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>Genes</th>
<th>K-ras</th>
<th>p53</th>
<th>DPC4</th>
<th>p16</th>
<th>GNAS</th>
<th>RNF43</th>
</tr>
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<td>50-70%</td>
<td>40-60%</td>
<td>95%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Mucinous Cyst Neoplasms</td>
<td>70-85%</td>
<td>35-50%</td>
<td>50%</td>
<td>15%**</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 (vHL gene mutations)
- Head = Body / Tail
- Mean size = 6 cm (up to 30 cm)
Serous Cystic Neoplasms:
Differential Diagnosis

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

- Microscopic
  - Microcystic
    - Lymphangioma
    - Renal cell carcinoma
  - Macrocytic
    - Lymphangioma

Pancreatic Neoplasms with
Degenerative Cystic Change

- Pancreatic endocrine neoplasm
- Acinar cell carcinoma
Pancreatic Neoplasms with Degenerative Cystic Change

- 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 nauseum

- 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>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsin</td>
<td>0</td>
</tr>
<tr>
<td>Chymotrypsin</td>
<td>0</td>
</tr>
<tr>
<td>Lipase</td>
<td>0</td>
</tr>
<tr>
<td>Lipase</td>
<td>0</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>30</td>
</tr>
<tr>
<td>Neuron Specific Enolase</td>
<td>80</td>
</tr>
<tr>
<td>CD56</td>
<td>95</td>
</tr>
<tr>
<td>Mucicarmine</td>
<td>0</td>
</tr>
<tr>
<td>CEA</td>
<td>5</td>
</tr>
<tr>
<td>Keratin</td>
<td>32</td>
</tr>
<tr>
<td>Vimentin</td>
<td>100</td>
</tr>
<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
  - Loss of membranous E-cadherin
- No abnormalities in “ductal adenocarcinoma genes”
  - KRAS
  - TP53
  - 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

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
Cyst Fluid Analysis for Diagnosis of Cystic Lesions

- CEA levels more sensitive than all other glycoproteins (even in combination)
- Fluid CEA of 192 ng/ml separates mucinous vs. nonmucinous cysts (79% accuracy)
  - Cytology accuracy = 59%
  - EUS appearance accuracy = 51%
- Less sensitive to distinguish low grade vs. high grade dysplasia (>2500 ng/ml = worrisome)
- Proteomic profiling: CEA, CA72.4 = mucinous

Molecular Diagnosis of Pancreatic Cystic Lesions

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

References:
- Brugge et al. Gastroenterology 2004; 126: 1330
- Pitman et al. Pancreatology 2008; 8: 277
- Wu et al., Sci Transl Med 2011;3:92ra66
- Wu et al., PNAS 2011;108:21188
- Schoedel et al. Diagn Cytopathol 2006; 34: 605
- Khalid et al. Gastrointest Endosc 2009; 69: 1095
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

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” (?)
Recurrence in IPMN

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Invasive</th>
<th>Local recurrence</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC(^1) (2004)</td>
<td>63</td>
<td>48%</td>
<td>4 (6%)</td>
<td>38 mos.</td>
</tr>
<tr>
<td>MGH/Verona(^3) (2004)</td>
<td>140</td>
<td>59%</td>
<td>8 (7%)</td>
<td>31 mos.</td>
</tr>
<tr>
<td>Virginia Mason(^4) (2005)</td>
<td>100</td>
<td>25%</td>
<td>2 (2%)</td>
<td>31 mos.</td>
</tr>
<tr>
<td>MDACC(^5) (2006)</td>
<td>35</td>
<td>37%</td>
<td>1 (3%)</td>
<td>30 mos.</td>
</tr>
<tr>
<td>Osaka(^6) (2006)</td>
<td>20</td>
<td>15%</td>
<td>0</td>
<td>68 mos.</td>
</tr>
</tbody>
</table>

\(^1\)D'Angelica et al., Ann Surg (2004) 239:400  

Margin Status: IPMN without Invasive Carcinoma

<table>
<thead>
<tr>
<th>Margin status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Negative&quot;</td>
<td></td>
</tr>
<tr>
<td>No proliferative lesions</td>
<td>32 (41%)</td>
</tr>
<tr>
<td>PanIN1/2</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>&quot;Positive&quot;</td>
<td></td>
</tr>
<tr>
<td>IPMN with low grade dysplasia</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>IPMN with moderate dysplasia</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>IPMN with high grade dysplasia</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
</tr>
</tbody>
</table>


Local Recurrence Rates

<table>
<thead>
<tr>
<th>Margin status</th>
<th>Total</th>
<th>n</th>
<th>Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No proliferative lesions</td>
<td>32</td>
<td>1 (3%)</td>
<td></td>
</tr>
<tr>
<td>PanIN1/2</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IPMN</td>
<td>23</td>
<td>4 (17%)</td>
<td></td>
</tr>
</tbody>
</table>


Local Recurrence-Free Survival

P<0.01

Intraductal Papillary-Mucinous Neoplasms:
Margin Assessment

- Resect grossly evident disease
- If normal (not denuded!) or PanIN1/2 done
- If IPMN with moderate or high grade dysplasia (or PanIN3) consider resecting more
- If IPMN with low grade dysplasia done?
- If cannot tell IPMN vs. PanIN grade the dysplasia
- When to do total pancreatectomy???

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)


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>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma or High Grade Dysplasia</td>
<td>MUC 2* 10</td>
</tr>
<tr>
<td>Low Grade or Moderate Dysplasia</td>
<td>4.4</td>
</tr>
</tbody>
</table>

* p<0.05