CONFLICT OF INTEREST

NOTHING TO DISCLOSE
(unfortunately)
“Well, Dr. Warshaw, I have never seen the pancreas but I certainly believe in it”
695 Resected Cystic Neoplasms of the Pancreas
Massachusetts General Hospital 1990-2009

- 25% Main-duct IPMN
- 19% Branch-duct IPMN
- 14% MCN
- 24% Serous Cystadenoma
- 4% Solid Pseudopapillary Tumor
- 5% Indeterminate mucinous lesions
- 5% Cystic Islet Cell Tumor
- 4% Other
The clinical challenges

Differential diagnosis
  • 10-30% mistaken for pseudocyst

Determination of malignancy
  • Biopsy unreliable: variation, denudation

Appropriate treatment
  • observation
  • resection
  • drainage - NO!

All but SCN have malignant potential, but are
the most curable cancers of the pancreas
Pancreatic Adenocarcinomas

PanIN → ductal carcinoma-in-situ

IPMN-adenoma → IPMN with high-grade dysplasia

MCN-adenoma → MCN with high-grade dysplasia

Invasive adenocarcinoma that may be histologically identical
Three Pancreatic Adenocarcinomas

Same histologic appearance
Same aggressive lethality

But
Different origin
Different rate of development

Why? Clues for treatment?
Serous cystadenoma (SCN)

3:1 F/M, 7th decade, average 4.9 cm (1-30), body/tail
Glycogen-rich cuboidal epithelium
Ductal immunoprofile (centroacinar?)
Microcystic, macrocystic, (solid)
Other new subtypes?
Do not express CEA (CEA low in cyst fluid)
Slow growing, very rarely malignant (<10 proven)
Associated pancreatic cancers
Serous Cystadenoma: MGH experience

- 106 patients; 75% female; age 61.5 ± 13
- 47% asymptomatic; 25% abdominal pain; 10% mass; 7% jaundice; 1% pancreatitis
- Even distribution throughout pancreas; mean diameter 4.9 ± 3 cm; direct correlation between size and symptoms
- 7% macrocystic
- No cases of malignant SCA found

Tseng et al, Ann Surg 2005
Growth Rate of Serous Cystadenomas

Tseng et al, Ann Surg 2005

Plot elements:
- median = line within box
- 25th & 75th percentiles = vertical borders of box
- 5th and 95th percentiles = ends of whiskers

Time of observation ranges from 3-162 months.

Tumor size at presentation

<4 cm (n=15)

≥4 cm (n=9)

\[ P=0.0002 \]
Treatment of serous cystic neoplasms

- Observation – if small, asymptomatic, Dx definite
  - growth rate uncertain
  - 26 pts observed 38 mos: no operations

- Resection – if large, symptomatic, obstructing, documented growth, pancreatitis
  (high fistula rate after enucleation)
# Cystic Pancreatic Endocrine Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>Cystic-29</th>
<th>Solid-141</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sizes (mm)</td>
<td>49±26</td>
<td>23±30</td>
<td>0.006</td>
</tr>
<tr>
<td>MEN-1 (%)</td>
<td>21</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>73</td>
<td>45</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-functional</td>
<td>80</td>
<td>50</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Bordeianou et al JACS, 2008*
Mucinous Cystic Neoplasm
Mucinous Cystic Neoplasms

Histopathologic criteria for MCN diagnosis:

- Presence of ovarian-like stroma layer
- Lack of communication with the main pancreatic duct
Mucinous Cystic Neoplasms

- Adenoma 72%
- Invasive carcinoma 12%
- Carcinoma in situ 5.5%
- Borderline 10.5%

Mean of 16 slides examined per patient (range: 3 – 94)

Mucinous Cystic Neoplasms

- 11-year difference in age between patients with noninvasive and invasive MCNs (tumor progression)
- Larger size, and nodularity are strongly associated with malignancy
- No cancer in asymptomatic patients with size < 4 cm and without nodules
- No LN metastases
- 57% cure of invasive MCN cancers; 100% if non-invasive

Mucinous Cystic Neoplasms

5-year Disease-Specific Survival

- MCNs adenoma, borderline or CIS (n = 135) = 100%
- Invasive cancer (n = 28) = 57%
- Overall 5 and 10 year actuarial survival: 93% and 84%

Mucinous Cystic Neoplasms
Tumor Recurrence

• No recurrence in noninvasive MCNs
• Seven patients (4.5%) comprising 37% of invasive MCNs developed tumor recurrence; of these
  – 4 patients had extracapsular infiltration
  – 3 patients had diffuse intracapsular infiltration
  – none had intracapsular, focally invasive carcinoma

• Recurrence site
  – Peritoneum in two patients
  – Liver in five

All patients with recurrence died after a mean of 6.5 months

Mucinous Cystic Neoplasms
Recommendations

• Given the young age of patients with MCNs, and the possibility of tumor-progression, resection remains the treatment of choice

• In small MCNs without nodules, parenchyma/spleen-preserving and minimally invasive procedures should be performed
INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS

• The “new kid in the block” is now an established settler (Has he been here all along?)

• One of the most common indications for pancreatic resection at MGH

• Clear differences in the presentation and implications of Main Duct vs Branch Duct IPMN (? Different biology)

• True incidence of this disease (many asymptomatic Br IPMN)
Main-Duct Intraductal Papillary Mucinous Neoplasms (IPMN)

Men > women, head > tail, age 68
Pain/pancreatitis, exocrine insufficiency
(if chronic pancreatitis)
Increasing numbers reported
(incidence or recognition?)
Long indolent phase (probable) in progression to invasive cancer
Serum Ca 19-9 ↑ with advanced cancer
Association with other GI tumors (colon, stomach)
Intraductal Papillary Mucinous Neoplasms
Main-duct IPMN

- 60% of resectable main-duct IPMN contain cancer, in situ or invasive
- Malignant IPMN occur in older patients and are more likely to present with jaundice or new-onset diabetes
- More than 25% of IPMN are asymptomatic (benign or malignant)
- Resection for cure is highly probable (benign including in situ cancer – 100%; invasive malignant – 60%)
- Recurrence in a pancreatic remnant is uncommon (5-7%)
- Re-resection of remnant recurrence is possible and beneficial
10-year Disease-specific survival (adenoma-borderline-in-situ carcinoma) vs. invasive carcinoma in main-duct IPMN

Salvia, Ann Surg 2004
Symptomatic Vs. Incidentally Discovered Pancreatic Resections for Branch Duct IPMN (2002-2005)

Count

2002  2003  2004  2005

Symptomatic
- Yes
- No

Rodriguez et al, Gastroenterol 2007
Multifocal side-branch IPMN
Histologic Diagnosis in 145 Patients with Resected Br-IPMN

- Adenoma: 46%
- Borderline: 32%
- Carcinoma In Situ: 11%
- Invasive Carcinoma: 11%

Rodriguez et al, Gastroenterol 2007
Presence of Nodules in Resected Specimens as a Function of Histologic Subtype of Br-IPMN

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>% Specimens with Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma (0/66)</td>
<td>0</td>
</tr>
<tr>
<td>Borderline (4/47)</td>
<td>8.5</td>
</tr>
<tr>
<td>Carcinoma in situ (7/16)</td>
<td>43.8</td>
</tr>
<tr>
<td>Invasive Carcinoma (12/16)</td>
<td>75</td>
</tr>
</tbody>
</table>

Rodriguez et al, Gastroenterol 2007
### Mucin Types Predict High Risk in IPMN

<table>
<thead>
<tr>
<th>Cyst fluid:</th>
<th>High risk ng/ml</th>
<th>Low risk ng/ml</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated MUC2</td>
<td>10±3</td>
<td>4.4±1.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Elevated MUC4</td>
<td>20.6±10.6</td>
<td>4.5±1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum:</td>
<td>MUC5</td>
<td>19.9±9.3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Maher et al, Ann Surg Oncol 2011*
Branch-duct IPMN Pathology

• Of patients with invasive cancer (n=16):
  – 19% (n = 3) had positive lymph nodes
  – Mean tumor size = 50mm ± 24
  – Only 3 patients had diameter of ≤ 30mm
    • Of these 2 had only small foci of invasive carcinoma
    • All of these had also nodules or symptoms

Rodriguez et al, Gastroenterol 2007
Branch-duct IPMN Recurrence

- **N = 10 patients (6.9%)**
  - **Local (n=4):**
    - All had IPMA w/ **negative** margin (mean 34.7 months)
    - Asymptomatic
    - Managed w/ observation
  - **Distant/Local (n=6):**
    - IPMIC
    - All liver/lung (mean 26.6 months)
    - 2 had lymph node involvement
    - All expired from disease

Rodriguez et al, Gastroenterol 2007
Branch-duct IPMN
10-year Disease-Specific Survival

- Br-IPMN adenoma, borderline or CIS (n = 129) = 100%
- Invasive cancer (n = 16) = 60%

Rodriguez, Gastroenterol 2007
Lymph Node Ratio (LNR) as a Predictor of survival with Invasive Intraductal Papillary Carcinoma

Patients with positive lymph nodes – 44/104 (42%)
Recurrence disease – 47%
5-year disease-specific survival (DSS) – 60%

<table>
<thead>
<tr>
<th>LNR</th>
<th>5-year DSS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>86.5</td>
</tr>
<tr>
<td>&gt;0 to 0.2</td>
<td>34.4</td>
</tr>
<tr>
<td>&gt;0.2</td>
<td>11.1</td>
</tr>
</tbody>
</table>

P < 0.0001

Partelli et al, Ann Surg 2010
Subtypes of IPMN Epithelium

Precursor Epithelium Types

- Intestinal, gastric, pancreatobiliary, oncocytic

Adenocarcinoma Pattern

- Invasive Ca from non-intestinal types (i.e. gastric) give rise to tubular pattern with more lymphnode metastases, aggressive spread and 5-year survival of 20% (p=0.67 vs. PDAC)
- Invasive Ca from intestinal type gives rise to colloid pattern, expresses MUC 5AC, MUC2, COX2 (tumor suppressor activity), and has a 5-year survival of 67% (p=0.001 vs. PDAC)

Sadakari, Surgery 2010
Subtypes of invasive IPMN Adenocarcinoma have Different Prognosis

Types of Invasive IPMN

Colloid

Tubular

Overall survival

\[ P < 0.001 \]
Origin of IPMN Epithelial Subtypes

- Colloid and oncocytic carcinomas arise primarily from intestinal and oncocytic-type epithelium, mainly originate in main-duct IPMNs, and have a favorable prognosis (median survival 89 mos.).
- Tubular carcinomas arise primarily from gastric-type epithelium, mainly originate in side-branch IPMNs, and have an unfavorable prognosis comparable with PDAC (median survival 35 mos).
- Side-branch IPMNs progress to invasive cancer less frequently than main-duct IPMNs, but are more aggressive when they become invasive (median survival 18 vs. 58 mos).

Mino-Kenudson, Gut (in press)
Improved Prognosis: Early Detection vs. Better Biology

- IPMC
  - Early T stage
  - Low LN metastasis (35% vs. 66%)
  - Perineural invasion (47% vs. 70%)
  - Vascular invasion (19% vs. 34%)
  - Margin involvement (22% vs. 36%)

Mari Mino-Kenudson et al.

PDAC (n=579) vs. IPMC (n=69)

Median Survival 54 vs. 18 months

\[ P < 0.00001 \]

Node positive PDAC vs. IPMC

PDAC n=381 vs. IPMC INV (n=17)

\[ P = 0.3353 \]

Node Negative PDAC vs. IPMC

pN0

PDAC (n=198) vs. IPMC INV (n=43)

\[ P < 0.001 \]
## Mucin-producing Pancreatic Neoplasms

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Invasion</th>
<th>LN(+)</th>
<th>5-yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCN</td>
<td>168</td>
<td>11%</td>
<td>0%</td>
<td>58%</td>
</tr>
<tr>
<td>IPMN branch</td>
<td>159</td>
<td>11%</td>
<td>24%</td>
<td>56%</td>
</tr>
<tr>
<td>IPMN (main)</td>
<td>81</td>
<td>48%</td>
<td>33%</td>
<td>51%</td>
</tr>
<tr>
<td>IPMN (combined)</td>
<td>149</td>
<td>42%</td>
<td>49%</td>
<td>64%</td>
</tr>
</tbody>
</table>

(p=0.001)

Crippa, Clin Gastroent Hepatol 2010
Adjuvant Therapy for Invasive IPMN-Carcinoma
N=44

**LN (+)**
Overall DSS survival (mo) 18

**LN(-)**
not reached

<table>
<thead>
<tr>
<th></th>
<th>Untreated</th>
<th>Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS LN(+) (mo)</td>
<td>3.5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

Alexander et al, Gastroint Cancer Res 2011
Ductal Adenocarcinoma Arising in MCN or IPMN

- High cure rate when resectable
- Rapidly lethal (6-9 months) when unresectable, recurrent, or metastatic
- Indolent phase → aggressive phase
  - Accumulation of genetic mutations?
**Multistep progression of PDAC**

**Most prevalent Mutations**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Freq (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kras</td>
<td>95</td>
</tr>
<tr>
<td>Ink4a</td>
<td>90</td>
</tr>
<tr>
<td>P53</td>
<td>75</td>
</tr>
<tr>
<td>Smad4</td>
<td>50-75</td>
</tr>
<tr>
<td>Lkb1</td>
<td>5</td>
</tr>
</tbody>
</table>

*Hezel, Bardees, et al., Genes Dev 2006*

*Bardeesy, DePinho, Nat Rev Gen, 2003*
Gene Expression Profiles in both IPMN and PDAC

Most highly upregulated genes (cDNA microarray analysis)

Trefoil peptide family (TFF1, TFF2, TFF3)
Lipocalin 2
Galactin 3

These genes may be involved at any early common stage of pancreatic carcinogenesis in these alternative routes of epithelial progression to full malignancy

Terris, Am J Pathol 2002
Histologic Effects of Anti-Shh Treatment in Xenografts

Effects of anti-Shh Therapy on PDACs

Effects of anti-Shh Therapy on IPMNs

Fritz et al, Pancreas 2010
## Genetic Differences: PDAC vs IPMN

<table>
<thead>
<tr>
<th>Genetic Aberration</th>
<th>Prevalence in IPMNs</th>
<th>Prevalence in PDAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS mutations</strong></td>
<td>40-60%</td>
<td>95-100%</td>
</tr>
<tr>
<td><strong>p53 mutations</strong></td>
<td>8%</td>
<td>75%</td>
</tr>
<tr>
<td>Decreased SMAD4 expression</td>
<td>16%</td>
<td>50%</td>
</tr>
</tbody>
</table>

IPMN-Ca vs. PDAC

Chromosome sites of common allelic loss

**IPMN** (High-grade dysplasia and invasive cancer) 5q, 6q, 11q

**PDAC** 9p, 17p, 18q

**K-ras Mutation**

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPMN (gastric)</td>
<td>70%</td>
<td>0.02</td>
</tr>
<tr>
<td>IPMN (other)</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>PDAC</td>
<td>90-100%</td>
<td></td>
</tr>
</tbody>
</table>

## Expression of DPC-4 Protein

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Expression</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPMN (79)</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Invasive IPMN-Ca (29)</td>
<td>-</td>
<td>97%</td>
</tr>
<tr>
<td>Pan-IN, grade 3</td>
<td>-</td>
<td>70%</td>
</tr>
<tr>
<td>PDAC</td>
<td>-</td>
<td>44%</td>
</tr>
</tbody>
</table>

A fundamental genetic difference in tumorigenesis?

966 Cystic Neoplasms of the Pancreas
(695 Resected + 271 under observation)
Massachusetts General Hospital 1990-2009

- 4% Cystic Islet Cell Tumor
- 3% Solid Pseudopapillary Tumor
- 18% Serous Cystadenoma
- 3% Indeterminate mucinous lesions
- 10% MCN
- 19% Main-duct IPMN
- 40% Branch-duct IPMN
Incidental Pancreatic Cystic Neoplasms

Asymptomatic cysts (40% of all cases)

17% had in situ or invasive cancer; 42% had premalignant neoplasia

- Cysts < 2cm: 1/28 (3.5%) had cancer (50% MCN, IPMN)
- Cysts > 2cm: 13/50 (26%) had cancer (66% MCN or IPMN) \( (p=0.04, \text{ cysts } < 2 \text{ cm vs. } > 2 \text{ cm}) \)
- Small side-branch IPMNs can be watched (may be multiple)

Pancreatic cyst fluid analysis

• Accessible by FNA (percutaneous)
  – No evidence for tumor dissemination
• Cuboidal or mucinous epithelial cells diagnostic (±Ca)
  – Absence (50%) does not exclude neoplasm
• Normal or low amylase excludes (99%) pseudocyst
• High CEA excludes serous cystadenoma
• High CEA probably indicates MCN or IPMN
Cyst Fluid CEA in Diagnosis of Pancreatic Mucinous Cysts

- 267 patients at Memorial-Sloan Kettering
- Cyst fluid aspirated at EUS
- Diagnosis of mucinous cyst by CEA > 192 ng/ml
  - Sensitivity 73%
  - Specificity 65%
- Cyst fluid CEA level not associated with malignancy
- CEA level not associated with radiographic progression

Nagula, J Gastrointest Surg 2010
Incidental Pancreatic Cysts: What are we watching?

330 asymptomatic patients with pancreatic cysts
- 59% discovered by CT, 41% by MRI, US, EUS
Mean cyst size – 26 mm
Multiple cysts – 18%
136 resections: correct diagnosis by CT/MRI – 63%,
plus EUS/FNA – 69%
Missed: main duct IPMNs (10), NET (3), SPN (2),
acinar cell cancer (1)

How safe is surveillance?

Correa-Gallego et al, Pancreatolegy 2010
Rationale for Resection of (most) Pancreatic Cystic Neoplasms

- Uncertainty of diagnosis
- Potential for malignancy
- Symptoms
- Growth
- Cost of surveillance
- Peace of mind
Additional Reasons to Resect all Pancreatic Cystic Neoplasms

• It helps the bottom line
• Residents need the experience
• It’s what I do

(“If you are a hammer, all the world looks like a nail.”)
Surgical Resection is recommended for
  • All MCNs
  • All main-duct IPMNs
  • All branch-duct IPMNs with either
    – Symptoms
    – Size >3 cm
    – Mural nodules
Observation is appropriate for smaller IPMNs without symptoms or mural nodules
Pancreatic Cancer

For patients who undergo curative resection, their prognosis appears to be determined by the biology of the tumor rather than factors involved in the resection.

Geer and Brennan, Am J Surg 1993; 165:68