Pancreatic Cancer: Early Diagnosis and Treatment

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Disclosures

I have no financial relationships to disclose within the past 12 months relevant to my presentation

My presentation does not include discussion of off-label or investigational use products or devices
Outline

• Basic details on Pancreatic Cancer
• Hereditary forms of Pancreatic Cancer
• Discuss the role of imaging for the earlier diagnosis and staging of pancreas cancer and pancreatic cysts:
  – CT, MRI, PET, EUS
• Discuss the role of EUS FNA, cyst fluid analysis (cytology, CEA, amylase), molecular diagnostics
• Review IPMNs: Characteristics and International Pancreas Consensus guidelines for IPMNs
Outline

- Screening for Pancreatic Cancer
- Screening Algorithm for Patients with Hereditary Pancreatic Cancer Syndromes
- Approaches that can aid in the earlier diagnosis of pancreatic cancer and improve treatment & outcomes
Pancreatic Adenocarcinoma

- The fourth leading cause of cancer-related death in the U.S.
- Only 15% of patients are candidates for surgery
- Five-year survival following a Whipple is about 25% for node-negative and 10% for node-positive tumors

Ahmad et al. Long term survival after pancreatic resection for pancreatic adenocarcinoma. AJG 2001;96(9):2609-15
Pancreatic Cancer

More than 37,000 new cases of pancreatic cancer will be diagnosed this year. Patients have a very low survival rate compared with other cancer patients.

Pancreatic cancer
Liver cancer
Lung cancer
Esophageal cancer
Stomach cancer
Ovarian cancer
Colorectal cancer
Kidney cancer
Cervical cancer
Bladder cancer
Breast cancer
Prostate cancer

Pancreatic cancer estimates for 2007
NEW CASES
DEATHS
Men
Women

SURVIVAL RATE
Five years after diagnosis

5%
10.5
15
15.6
23.9
44.7
64.1
65.6
71.6
80.8
88.5
99.9

The New York Times
(08/07/07)
<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable Disease</td>
<td>12 to 20 months</td>
</tr>
<tr>
<td>Locally Advanced Disease</td>
<td>6 to 10 months</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td>3 to 6 months</td>
</tr>
</tbody>
</table>
Contributing Factors for the Poor Outcome in Pancreatic Cancer

• Late presentation, aggressive nature and lack of effective therapies all contribute to the poor prognosis

• Early detection is crucial to improve the overall prognosis

• Accurate Staging is vital for selecting out the subset of patients who have potentially resectable tumors
How can we improve the prognosis and outcomes in Pancreatic Cancer?

- Earlier Detection and Diagnosis

- Who is at high risk for pancreatic cancer?
Pancreatic Cancer

Risk Factors

Age, gender, race
Smoking
Family history
Body mass index
Pancreatitis
Diabetes
Pancreatic Cancer: Risks Factors

- **Cigarette Smoking:**
  Smokers have a 2- to 3-fold increase in PC.
  Smoking may be implicated in as many as 30% of PC's.

- **Diabetes:**
  Long-standing history increases risk.
  Relative risk 1.5-2.0
  Newly-diagnosed diabetes might be a sign of PC.

- **Family History:**
  Relative risk about 1.5-2.
  Strongly increased risk in families with multiple individuals w/PC.

- **Pancreatitis:**
  A strong but uncommon risk factor.
  Risk may be increased 15-fold.
Diabetes Mellitus

- 45-65% prevalence of DM in PC
- 5.2-13.6% prevalence of PC in new onset diabetics (<3 years) with cancer-related symptoms
- 8x higher risk of PC within 3 years of diagnosis of DM (or 1% of those >50)

Question:

Can the onset of diabetes mellitus be used to identify earlier and curable pancreatic cancer?
Familial Pancreatic Cancer

A family history of pancreatic cancer is found in about 10% of pts diagnosed with pancreatic cancer.

Pancreatic Cancer

**FPC Syndromes**

Hereditary Breast - Ovary Cancer (BRCA2)*
Hereditary Pancreatitis (PRSS1)
HNPCC/Lynch II (hMSH2 and hMLH1)
Peutz-Jeghers Syndrome (STK11/LKB1)
(FAMMM) Familial Atypical Multiple Mole Melanoma Syndrome: p16 (CDKNA2)
Cystic Fibrosis

*The most common associated genetic abnormality found in families with two or more affected relatives.*
## Estimated Risk for PC

<table>
<thead>
<tr>
<th>Individual</th>
<th>Risk</th>
<th>Age 50 years (%)</th>
<th>Age 70 years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No History</td>
<td>1</td>
<td>.05</td>
<td>0.5</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3.5-10x</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>FAMMM</td>
<td>20-34x</td>
<td>1.6</td>
<td>16</td>
</tr>
<tr>
<td>p16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>50-80x</td>
<td>2.5-4</td>
<td>24-40</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>72x</td>
<td>6.6</td>
<td>36</td>
</tr>
</tbody>
</table>
Can those at increased risk, be “monitored or screened” to increase earlier detection?

• Most early detection is incidental
  – Malignant cystic lesions
  – IPMN
Screening for Pancreatic Neoplasia in High Risk Individuals: The Challenges

- Screening for pancreatic neoplasia has not gained wide acceptance
- The best way to screen individuals at higher than average risk has not been established
- Screening is not covered by Medicare or private insurance payers
Protein categories identified in pancreatic cancer

Chen R et al. Mol Cell Proteomics 2005;4:523-533
### Core Signaling Pathways in Human Pancreatic Cancers Revealed by Global Genomic Analyses

**Table 2. Core signaling pathways and processes genetically altered in most pancreatic cancers**

<table>
<thead>
<tr>
<th>Regulatory Process or Pathway*</th>
<th>Number of genetically altered genes detected</th>
<th>Fraction of tumors with genetic alteration of at least one of the genes</th>
<th>Representative altered genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apoptosis</td>
<td>9</td>
<td>100%</td>
<td>CASP10, VCP, CAD, HIP1</td>
</tr>
<tr>
<td>DNA damage control</td>
<td>9</td>
<td>83%</td>
<td>ERCC4, ERCC6, EP300, RANBP2, TP53</td>
</tr>
<tr>
<td>Regulation of G1/S phase transition</td>
<td>19</td>
<td>100%</td>
<td>CDKN2A, FBXW7, CHD1, APC2</td>
</tr>
<tr>
<td>Hedgehog signaling</td>
<td>19</td>
<td>100%</td>
<td>TBX5, SOX3, LRP2, GLI1, GLI3, BOC, BMPR2, CREBBP</td>
</tr>
<tr>
<td>Homophilic cell adhesion</td>
<td>30</td>
<td>79%</td>
<td>CDH1, CDH10, CDH2, CDH7, FAT, PCDH15, PCDH17, PCDH18, PCDH9, PCDHB16, PCDHB2, PCDHGA1, PCDHGA11, PCDHGC4</td>
</tr>
<tr>
<td>Integrin signaling</td>
<td>24</td>
<td>67%</td>
<td>ITGA4, ITGA9, ITGA11, LAMA1, LAMA4, LAMA5, FN1, ILK</td>
</tr>
<tr>
<td>JNK signaling</td>
<td>9</td>
<td>96%</td>
<td>MAP4K3, TNF, ATF2, NFATC3</td>
</tr>
<tr>
<td>KRAS signaling</td>
<td>5</td>
<td>100%</td>
<td>KRAS, MAP2K4, RASGRP3</td>
</tr>
<tr>
<td>Regulation of invasion</td>
<td>46</td>
<td>92%</td>
<td>ADAM11, ADAM12, ADAM19, ADAM5220, ADAMTS15, DPP6, MEP1A, PCSK6, APG4A, PRSS23</td>
</tr>
<tr>
<td>Small GTPase-dependent signaling (other than KRAS)</td>
<td>33</td>
<td>79%</td>
<td>AGHGEF7, ARHGEF9, CDC42BPA, DEPDC2, PLCB3, PLCB4, RP1, PLXNB1, PRKCG</td>
</tr>
<tr>
<td>TGF-β signaling</td>
<td>37</td>
<td>100%</td>
<td>TGFBR2, BMPR2, SMAD4, SMAD3</td>
</tr>
<tr>
<td>Wnt/Notch signaling</td>
<td>29</td>
<td>100%</td>
<td>MYC, PPP2R3A, WNT9A, MAP2, TSC2, GATA6, TCF4</td>
</tr>
</tbody>
</table>

* A complete listing of the gene sets defining these signaling pathways and processes and the statistical significance of each gene set are provided in table S8.
Flow chart for biomarker discovery and development using proteomic profiling

Chen R et al. Mol Cell Proteomics 2005;4:523-533
Earlier Detection and Screening for Pancreatic Cancer

Molecular Markers

- Telomerase activity
- mRNA for hTERT
- Mutated K-ras
- Cathepsin E
- Detection of DNA promoter hypermethylation
- Proteomics
A New Susceptibility Locus for Autosomal Dominant Pancreatic Cancer Maps to Chromosome 4q32-34

Michael A. Eberle,¹,* Roland Pfützer,⁵,*,+ Kay L. Pogue-Geile,⁵ Mary P. Bronner,⁴ David Crispin,³ Michael B. Kimmey,³ Richard H. Duerr,⁵ Leonid Kruglyak,¹,²,⁺ David C. Whitcomb,⁵,⁶,+ and Teresa A. Brentnall³,+
Identification of the *PALLID* Gene
A new approach to identify a cancer gene in 4q32:
Check expression of all genes in normal and abnormal tissue

Detecting Pancreatic Cancer at an Early Stage

Precursor Lesions

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

- Epithelial proliferation in the small pancreatic ducts
- Three grades based on degree of atypia
- Believed to be involved in the genetic progression model for pancreatic cancer

Pancreatic Cancer

Progression Model

Normal Duct Histology

- PanIN-1
  - IPMN mild dysplasia
- PanIN-2
  - IPMN mod dysplasia
- PanIN-3/PanCa
  - IPMN severe dysplasia

Genetic Progression

Screening Window?

[Diagram showing progression model with stages from normal duct histology to invasive pancreatic cancer and genetic progression markers.]
The challenge for earlier detection

Pancreatic Intraepithelial Neoplasia (PanIN)

<table>
<thead>
<tr>
<th></th>
<th>PanIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually clinically detected</td>
<td>No</td>
</tr>
<tr>
<td>Usually grossly visible</td>
<td>No</td>
</tr>
<tr>
<td>Usually grossly visible mucin</td>
<td>No</td>
</tr>
<tr>
<td>Well-formed papillae</td>
<td>No</td>
</tr>
<tr>
<td>Muc2 expression</td>
<td>No</td>
</tr>
<tr>
<td>Abrogation of DPC4/MADH4</td>
<td>30% in PanIN-3</td>
</tr>
<tr>
<td>Associated with invasive colloid carcinoma</td>
<td>No</td>
</tr>
</tbody>
</table>
Pancreatic Cancer

PanIN Progression Model

Oncogene

\( K-ras \)

Tumor Suppressor Genes

\( p16, p53, \quad BRCA2, \quad DPC/SMAD4 \)

Telomerase

Flat duct lesion
PanIn-1A

Papillary duct lesion
PanIn-1B

Papillary duct lesion + atypia
PanIn-2

Ca in situ
PanIn-3

From Hruban et al *Ann Onc*, 1999
Adenoma-Dysplasia Sequence

- **Microscopic**
  - PanIN 1-3
  - ? Molecular Markers

- **Macroscopic**
  - IPMN
    - Adenoma-malignancy
  - Endoscopic imaging
    - Papilla-Nodules-Masses
  - Loss of Heterozygosity (LOH)
Imaging Modalities

Is earlier detection possible with current imaging modalities?
Earlier Detection and Screening for Pancreatic Cancer

Contrast CT
MRI and MRCP
PET
ERCP
EUS

Imaging
Endoscopy
<table>
<thead>
<tr>
<th>Modality</th>
<th>Issues</th>
</tr>
</thead>
</table>
| Multidetector CT | • Suboptimal for early pancreatic neoplasia  
                  • Concern for repeat radiation exposure |
| MRI/MRCP       | • Little published data on accuracy or yield  
                  • High Cost                                   |
| ERCP           | • Invasive – Risk of pancreatitis               |
| EUS            | • Improved accuracy  
                  • Highly operator dependent  
                  • Interobserver variability                  |

EUS versus Multidetector CT

Prospective study of 120 pts with known PC

- EUS was more sensitive for detecting a pancreatic mass (98% vs 86% for CT)
- EUS was more accurate for tumor staging (67% vs 41% for CT)
- EUS was equivalent for nodal staging (44% vs 47% for CT) and predicting resectability (68% vs 64% for CT)

PET

- PET has been studied in the evaluation of pancreatic cancer.

- PET has a high sensitivity (~ 90 percent) for detecting pancreatic cancer, but only moderate specificity (~ 70 percent) since benign inflammatory lesions can mimic cancer.

- A pitfall of PET is that it provides limited anatomic information - which can be overcome by combining it with CT.

Fine Needle Aspiration
FNA of Pancreatic Cancer
EUS Guided FNA for Diagnosing Pancreatic Tumors

- Sensitivity = 90%
- Specificity = 100%
- Accuracy = 94%
- Good for lesions as small as sub-cm
- Can Sample the Primary, LNs, & liver lesions
- Yield is enhanced with on-site cytopathologist
- May require up to 3-5 passes

EUS for Detecting and Staging Pancreatic Cancer

Advantages

• Diagnostic imaging and fine needle aspiration biopsy of suspicious lesions during a single procedure

• Accurate staging and determination of resectability

• Best modality for small lesions
Early Diagnosis and Treatment of Pancreatic Dysplasia in Patients with a Family History of Pancreatic Cancer

- **Objective:** Develop a surveillance program that can identify and treat patients who have precancerous conditions of the pancreas and/or a family history of pancreatic cancer.
- **Design:** Prospective cohort study.
- **Patients:** 14 patients from three kindreds with a history of pancreatic cancer were enrolled.
- **Interventions:** EUS, ERCP, spiral CT, and serum CEA and CA19-9 analysis were performed in all patients. Four affected patients were tested for the K- *ras* mutation.
- **Main Outcome Measurement:** Pancreatic dysplasia was determined by histologic evaluation.

ERCP in High Risk Kindreds

- All patients who have undergone pancreatic resection for dysplasia had abnormal ERCP’s
  - Dilated main pancreatic duct
  - Saccular side branches
  - Focal strictures
  - Main duct and side branch irregularity
  - Terminal ectasia of side branches
ERCP in Familiar Pancreatic Cancer: Ectatic Side Branches and Main Duct Irregularity
EUS Detects Abnormalities in Familial Pancreatic Cancer

- EUS findings of chronic pancreatitis are present in ~60% of high risk individuals:
  - Hypoechoic lobules; echogenic strands/foci, duct walls; dilated/ectatic ducts; cysts

- Abnormal EUS imaging predicts abnormal pancreatography (ERP)
  - Normal EUS \rightarrow normal ERCP

Screening High Risk Families: CAPS2

- A prospective controlled study of screening EUS and CT followed by ERCP in 78 at-risk relatives and 149 control subjects
- High prevalence of CP-like changes:
  - 72% by EUS
  - 68% by ERCP
- 10% treated by subtotal pancreatectomy
  - IPMNs
  - carcinoma-in-situ (1 pt)

Surveillance and Natural History of High Risk Patients Who Inherit Pancreatic Cancer

Screening/surveillance protocol as an empiric approach for patients at increased risk for PC

Surveillance Program

- Surveillance started at age 40 or 10 years prior to the earliest age of PC in the family
- **Endoscopic studies:**
  - EUS: Radial scanning at 5MHz
  - ERCP if EUS findings abnormal
- **Laboratory studies:**
  - CEA, CA19-9 and random blood glucose were obtained on most patients
  - If possible, a 2 hour glucose tolerance test and/or HgbA1c was measured
100 Familial PC Patients in Surveillance (1996-2007)

• **73 different families**
  – mean age at entry into surveillance = 54 years
  – mean age of earliest onset of PC = 53 years
  – mean number of affected family members with PC= 2.4

• Heterogeneous group of kindreds with different genetic causes:
  – Known genetic mutations in 18 patients

• **Mean years of surveillance = 5**
Did Surveillance Detect Advanced Pancreatic Neoplasia in a High Risk Cohort?

- 2 patients (2%) developed cancer

- 20 patients (20%) developed advanced pancreatic neoplasia
  - 12 HGD (Panin3)
  - 8 LGD (Panin2)

- All had abnormal EUS, ERCP
- CT, CA 19-9, CEA were not able to predict abnormalities in high risk patients
## Surrogate Markers of Progression

<table>
<thead>
<tr>
<th></th>
<th>Normal EUS Cohort</th>
<th>Abnormal EUS Cohort</th>
<th>Cohort with PanIN or Cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal glucose</td>
<td>3/16 (19%)</td>
<td>15/29 (50%)</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>(GTT, HgA1C, Hx DM)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p=0.02*
Study’s Conclusions:

- Pancreatic cancer is diagnosable at the pre-invasive stage
- Early detection can cure impending pancreatic cancer
- Glucose abnormalities may help detect patients at risk of progression
# Yield of Screening in High Risk Individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Modality</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saunders et al</td>
<td>100</td>
<td>EUS</td>
<td>22%</td>
</tr>
<tr>
<td>Canto et al</td>
<td>78</td>
<td>EUS</td>
<td>10%</td>
</tr>
<tr>
<td>Canto et al</td>
<td>36</td>
<td>EUS</td>
<td>5.3%</td>
</tr>
<tr>
<td>Poley et al</td>
<td>17</td>
<td>EUS</td>
<td>18%</td>
</tr>
</tbody>
</table>

Feasibility and Yield of Screening in Relatives From Familial Pancreatic Cancer Families

Emmy Ludwig, MD, Sara H. Olson, PhD, Sharon Bayuga, MPH, Jennifer Simon, MA, Mark A. Schattner, MD, Hans Gerdes, MD, Peter J. Allen, MD, William R. Jamagin, MD and Robert C. Kurtz, MD

OBJECTIVES: Pancreatic adenocarcinoma is a lethal disease. Over 80% of patients are found to have metastatic disease at the time of diagnosis. Strategies to improve disease-specific outcome include identification and early detection of precursor lesions or early cancers in high-risk groups. In this study, we investigate whether screening at-risk relatives of familial pancreatic cancer (FPC) patients is safe and has significant yield.

METHODS: We enrolled 309 asymptomatic at-risk relatives into our Familial Pancreatic Tumor Registry (FPTR) and offered them screening with magnetic resonance cholangiopancreatographic (MRCP) followed by endoscopic ultrasound (EUS) with fine needle aspiration if indicated. Relatives with findings were referred for surgical evaluation.

RESULTS: As of 1 August 2009, 109 relatives had completed at least one cycle of screening. Abnormal radiographic findings were present on initial screening in 18/109 patients (16.5%), 15 of whom underwent EUS. A significant abnormality was confirmed in 9 of 15 patients, 6 of whom ultimately had surgery for an overall diagnostic yield of 8.3% (9/109). Yield was greatest in relatives >65 years old (35%, 6/17) when compared with relatives 55–65 years (3%, 1/31) and relatives <55 years (3%, 2/61).

CONCLUSIONS: Screening at-risk relatives from FPC families has a significant diagnostic yield, particularly in relatives >65 years of age, confirming prior studies. MRCP as initial screening modality is safe and effective.
Screening for Pancreatic Cancer

- The USPSTF found *no evidence* that screening for pancreatic cancer is effective in reducing mortality.
- **Recommends against routine screening for pancreatic cancer in asymptomatic adults** using abdominal palpation, ultrasonography, or serologic markers.
- There is a potential for significant harm due to the very low prevalence of pancreatic cancer, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment.
- As a result, the USPSTF concluded that the harms of screening for pancreatic cancer exceed any potential benefits.
Cystic Lesions of the Pancreas

1. Simple cysts
2. Pseudocysts
3. Cystic neoplasms
   • Mucinous cystadenoma/adenocarcinoma
   • Serous cystadenoma
   • Intraductal papillary mucinous neoplasm (IPMN)
   • Papillary cystic neoplasm
4. Neuroendocrine and ductal adenocarcinoma with cystic degeneration
Cystic Neoplasms are surprisingly common

– In the past... it was thought that
  • Pancreatic cystic lesions were rare
  • Pancreatic cysts are all benign and congenital diseases
  • Pancreatic cystic lesions spontaneously resolve
# Cystic Lesions of the Pancreas

<table>
<thead>
<tr>
<th>Type</th>
<th>Malignant potential</th>
<th>Communication with duct</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple (retention) cyst</td>
<td>None</td>
<td>Sometimes</td>
<td>Developmental</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>None</td>
<td>Frequent</td>
<td>Post-inflammatory</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
<td>Very Low</td>
<td>Rarely</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
<td>High</td>
<td>Occasionally</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>IPMN</td>
<td>High</td>
<td>Yes</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Solid pseudopapillary neoplasm</td>
<td>Moderate</td>
<td>Occasionally</td>
<td>Neoplastic</td>
</tr>
</tbody>
</table>

IPMN = Intraductal papillary mucinous neoplasm
Malignancy Arising from Cysts

• 197 pts with pancreatic cystic lesions enrolled
• 80 IPMN and 117 with non-IPMN cysts were followed for 4 yrs with imaging and blood tests twice a year
• PC developed in 7 pts during the observation period (0.95% per year), infiltrating ductal carcinoma in 5 and IPMN in 2.
• Observed incidence of malignancy was 22.5 times higher than expected mortality from this cancer among general population.

Accurate Diagnostic Information is CRUCIAL!

High risk factors supersede in management

- Cyst size greater 3 cm go for resections (International/ASGE guidelines)
- Other high risk factors
  - Mural nodules
  - Septations
  - Duct dilation
  - Cyst wall thickening
Defining the Problem

- Without any risk factors what is the true nature of the cyst and its potential risk of progression to malignancy?
Useful Diagnostic Tests

- EUS FNA can be used to perform cyst aspiration
- Cyst fluid can be analyzed for:
  - CEA
  - Amylase
  - Cytology
  - Molecular diagnostics
Challenges in Diagnosis

• Pooled data from 12 studies and 450 pts was reviewed.
• Cysts with an amylase concentration <250 U/L were SCA, MCA, or MCAC (sensitivity 44%, specificity 98%).
• CEA <5 ng/mL suggested a SCA or PC (sensitivity 50%, specificity 95%).
• CEA >800 ng/mL strongly suggested mucinous cystic lesion (sensitivity 48%, specificity 98%).
• Cytologic examination revealed malignant cells in 48% of MCAC (n = 111).

Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis.
CEA can identify mucinous cysts…

… but not malignancy

Comparison of CEA performance

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugge (2004)</td>
<td>112</td>
<td>79</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Nagula (2010)</td>
<td>97</td>
<td>70</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>Morris-Stiff (2010)</td>
<td>47</td>
<td></td>
<td>93</td>
<td>43</td>
</tr>
<tr>
<td>Park (2010)</td>
<td>124</td>
<td>72</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>PANDA (2009) &gt;143 ng/mL</td>
<td>76</td>
<td>74</td>
<td>64</td>
<td>83</td>
</tr>
</tbody>
</table>
Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: A report of the PANDA study

**TABLE 2. Analysis comparing nonmucinous and mucinous pancreatic cysts**

<table>
<thead>
<tr>
<th></th>
<th>Nonmucinous/benign (25)</th>
<th>Mucinous (88)</th>
<th>Statistical significance</th>
<th>Performance characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of mutations</td>
<td>0.8</td>
<td>1.7</td>
<td><em>P &lt; .001</em></td>
<td>Mutation-1, sensitivity and specificity 62%, AUC 0.67</td>
</tr>
<tr>
<td>k-ras mutation</td>
<td>1/25</td>
<td>40/88</td>
<td><em>P &lt; .0001</em> (.0003)</td>
<td>Sensitivity 45%, specificity 96%</td>
</tr>
<tr>
<td>k-ras followed by allelic loss</td>
<td>0/25</td>
<td>17/88</td>
<td><em>P = .017</em> (.038)</td>
<td>Sensitivity 19%, specificity 100%</td>
</tr>
<tr>
<td>MALA</td>
<td>58.8%</td>
<td>78.3%</td>
<td><em>P &lt; .0001</em></td>
<td>MALA 65%, sensitivity and specificity 66%, AUC 0.79</td>
</tr>
<tr>
<td>DNA amount (OD)</td>
<td>8/25</td>
<td>40/88</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean CEA (log transformation to correct for extreme values)</td>
<td>39.6</td>
<td>454.8</td>
<td><em>P &lt; .001</em></td>
<td>CEA 148 mg/mL, sensitivity and specificity 68%, AUC 0.74</td>
</tr>
</tbody>
</table>

*NS, Not significant; OD is a measure of DNA amount at 260/280 wavelength; cycle threshold value on quantitative PCR is a measure of DNA quality/amplifiability. *P < .05* is considered significant (Yates’ correction for continuity given in parenthesis).
Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: A report of the PANDA study

TABLE 3. Analysis comparing premalignant with malignant pancreatic cysts

<table>
<thead>
<tr>
<th></th>
<th>Premalignant (48)</th>
<th>Malignant (40)</th>
<th>Statistical significance</th>
<th>Performance characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean no. of mutations</td>
<td>1.49</td>
<td>2.1</td>
<td><em>P = .04</em></td>
<td></td>
</tr>
<tr>
<td>k-ras mutation</td>
<td>20/48</td>
<td>21/40</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>k-ras followed by allelic loss</td>
<td>2/48</td>
<td>15/40</td>
<td><em>P &lt; .0001 (0.0002)</em></td>
<td>Sensitivity 37%, specificity 96%</td>
</tr>
<tr>
<td>MALA</td>
<td>67.3%</td>
<td>91.7%</td>
<td><em>P &lt; .0001</em></td>
<td>MALA 82%, sensitivity and specificity 82%, AUC 0.90</td>
</tr>
<tr>
<td>DNA amount (OD)</td>
<td>10/48</td>
<td>30/40</td>
<td><em>P &lt; .0001 (0.0001)</em></td>
<td>OD 10, sensitivity and specificity 77%, AUC 0.79</td>
</tr>
</tbody>
</table>

*OD is a measure of DNA amount at 260/280 wavelength; cycle threshold value on quantitative PCR is a measure of DNA quality/amplifiability. *P < .05 considered significant (Yates' correction for continuity given in parenthesis).*

“Elevated amounts of pancreatic cyst fluid DNA, high-amplitude mutations and specific mutation acquisition sequences are indicators of malignancy.”

Diagnostic Algorithm Based on Cyst Fluid Analysis

EUS

Single cyst

Viscous
CEA>200

MCN
IPMN

Low Viscosity
CEA<200

Serous
Pseudocyst

Multiple cysts – IPMN

• Side branch
• Main duct

• Consider Molecular Analysis of cyst fluid to gauge risk level of cyst
• Consider Surgery based on EUS findings and cytology
## Decision making in pancreatic cystic disease

<table>
<thead>
<tr>
<th>Cross sectional imaging and endoscopic ultrasound</th>
<th>Cyst size, solid component, connection to/dilation of the duct system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyst fluid chemistry - CEA, amylase, other markers</td>
<td>Mucinous cyst formation, pseudocyst</td>
</tr>
<tr>
<td>Cyst fluid cytology</td>
<td>Presence of mucinous and dysplastic/malignant cells</td>
</tr>
<tr>
<td>Molecular analysis testing: DNA quantity &amp; quality</td>
<td>Mucinous cyst formation, actively proliferating lining</td>
</tr>
<tr>
<td>KRAS oncogene point mutation</td>
<td>Mucinous cyst formation, actively proliferating lining</td>
</tr>
<tr>
<td>Loss of heterozygosity (LOH)</td>
<td>Mucinous cyst formation, actively proliferating lining</td>
</tr>
</tbody>
</table>
Pancreatic Cysts

WHO SHOULD GET RESECTED?
Surgical outcomes of cysts

- 83% are benign
- High morbidity and hospital volume-dependent mortality
- **Inadequate diagnostic information** - cyst size, symptoms, high risk features still results in high percentage of benign disease

<table>
<thead>
<tr>
<th>TABLE II. Final Pathology From Resected Specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant (n = 65, 83%)</td>
</tr>
<tr>
<td>Mucinous cystadenoma</td>
</tr>
<tr>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>IPMN without invasion</td>
</tr>
<tr>
<td>Pseudocyst</td>
</tr>
<tr>
<td>Other benign</td>
</tr>
<tr>
<td>Malignant (n = 13, 17%)</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>Mucinous cystadenocarcinoma</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
</tr>
<tr>
<td>Solid pseudopapillary</td>
</tr>
<tr>
<td>GIST</td>
</tr>
<tr>
<td>Spindle cell neoplasm</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
</tr>
</tbody>
</table>

IPMN

- Initially identified in 1982
- 0.5 % to 10% of all exocrine tumors
- 25% of all cystic tumors
- Peak incidence 6th – 7th decade of life
- Male predominance
- Mostly in the head of the pancreas
- Multifocality is common
Types of IPMN

Main Duct

Side branch

International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas

Masao Tanaka\textsuperscript{a}  Suresh Chari\textsuperscript{b}  Volkan Adsay\textsuperscript{c}  Carlos Fernandez-del Castillo\textsuperscript{d}  Massimo Falconi\textsuperscript{e}  Michio Shimizu\textsuperscript{f}  Koji Yamaguchi\textsuperscript{a}  Kenji Yamao\textsuperscript{g}  Seiki Matsuno\textsuperscript{h}

Size $<1$ cm
\hspace{1cm} \rightarrow MR or thin slice CT in 1 year
\hspace{1cm} \rightarrow Size $<1$ cm
\hspace{1cm} \rightarrow Size 1–2 cm

Size 1–3 cm
\hspace{1cm} \rightarrow EUS and MRCP or ERCP
\hspace{1cm} \rightarrow High-risk stigmata:
\hspace{2cm} Mural nodules
\hspace{2cm} Dilated main duct
\hspace{2cm} Positive cytology
\hspace{1cm} \rightarrow No
\hspace{1cm} \rightarrow MR or CT
\hspace{2cm} 1–2 cm every 6–12 mo$^*$
\hspace{2cm} 2–3 cm every 3–6 mo
\hspace{1cm} \rightarrow No
\hspace{1cm} \rightarrow Symptomatic, size $>3$ cm or positive high-risk stigmata
\hspace{1cm} \rightarrow Yes
\hspace{1cm} \rightarrow Resection

Size $>3$ cm
\hspace{1cm} \rightarrow See Clinical Question 3b
\hspace{1cm} \rightarrow Yes
MAIN-DUCT & MIXED-TYPE IPMN SHOULD ALL BE RESECTED IN GOOD SURGICAL CANDIDATES WITH GOOD LIFE EXPECTANCY IN TERTIARY CENTERS
"BRANCH-DUCT IPMN WITH SYMPTOMS, >3CM, MURAL NODULES, INTERVAL CHANGE IN MRCP SHOULD BE RESECTED IN GOOD OPERATIVE CANDIDATES AT TERTIARY CENTERS"
ASYMPTOMATIC AND <3CM BRANCH-DUCT IPMN WITHOUT RISK FACTORS CAN BE SAFELY OBSERVED “
Thank You!
Case Presentation

• 69 year-old male accountant with HTN, AODM, and a strong family history of pancreatic cancer including:
  1. Sister diagnosed at age 73
  2. Paternal aunt diagnosed in her 70s
  3. Paternal uncle diagnosed in his 60s
  4. First cousin diagnosed in his 50s
• Non-smoker
• Asymptomatic, no jaundice, no wt loss
Case Presentation

- Major ampulla w/gaping orifice
- Dilated PD in HOP (6 mm)
- Tail of the Pancreas w/dilated PD
Case Presentation
Case Presentation

- Doing well post-op
- Diabetes under good control
- Diarrhea controlled with pancreatic enzymes
- Weight Stable
- Sister just diagnosed with gynecologic malignancy