Current Diagnostic Tools for Pancreas Cancer

Luis F. Lara, M.D.

Objectives

- Epidemiology and risk factors
- Pre-malignant lesions
- Genetic alterations
- Diagnosis
  - Imaging
  - Tumor markers
- Early diagnosis strategy
Ductal Adenocarcinoma of the Pancreas (PanCA)

- 4th leading cause of CA death in the United States
- Males (13/100,000) > Females (10.3/100,000)
  - Lifetime risk 1.3% or 1 in 75
- African-Americans higher risk
- > 60 y/o

Factors that affect survival

- 80-90% unresectable at diagnosis
- Another 25-30% unresectable at time of surgery
- 7% limited to pancreas
  - 95% exocrine pancreas
  - 70% involve the head
- 26% LN involved, 52% metastasis
- Early lesion resection 25% to 100% 5 year survival
Risk Factors

- Smoking
- Chronic pancreatitis
- Occupational exposure
- Diet
- Obesity
- Diabetes Mellitus
- Coffee

Metabolic Syndrome?

- Smoking
  - 25% of all pancreatic CA
  - 1/2 ppd--------2.4 fold
  - 25 or more---- 3 fold
  - > 5 pack-years OR 4.2
  - Males
  - PanCA 10-20 years earlier in smokers
  - Risk levels off 10 to 15 years after quitting, but never equal to non-smokers

Rulyak, et al Gastroenterology 2003
Fuchs, et al Arch Intern Med 1996
Risk Factors

• Chronic Pancreatitis (CP)
  – 2% q 10 years
• Alcohol
  – No association with PanCA
  – Does not increase risk of PanCA in CP
• Work
  – 5 x risk in certain workers (metallurgic, combustibles)

Alguacil, Occup Environ Med 2003

Risk Factors

• DM
  – Develops in 60-80% PanCA
  – Higher incidence of PanCA diagnosis especially within 2 years of developing DM
  – “PanCA-induced” DM 2 to 3 yrs before the diagnosis of PanCA
  – 8 x increased risk of PanCA

Chari, et al Gastroenterology 2001
Everhart, et al JAMA 1995
Gapstur, et al JAMA 2000
Incidence of PanCA among new onset DM vs non-diabetics


DM and PanCA

- At new onset DM PanCA is “resectable” up to 6 months before the dx
- PanCA is associated with progressive increase in FBG 24 to 36 months prior to the diagnosis.
  - Suspect it in patients with new onset DM and a FHx of PanCA, or PanCA associated syndrome
  - No FHx of DM and > 50 years old
  - “Unstable” chronic pancreatitis

High Risk PanCA Groups

- Hereditary (Familial) PanCA
- Tropical pancreatitis
- Hereditary Pancreatitis
- Syndrome Associated PanCA
  - Familial atypical multiple mole melanoma (FAMMM)
  - Cystic Fibrosis
  - HNPCC, FAP, BRCA2
  - Peutz-Jeghers
  - Ataxia-Telangiectasia

Familial Risk

- One first degree relative x 2.3
- Two first degree relatives x 6.4
- >2 first degree relatives x 32
- Risk increases with number of affected relatives
### Hereditary PanCA

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Organs</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMMM</td>
<td>p16</td>
<td>skin</td>
<td>34x</td>
</tr>
<tr>
<td>HNPCC</td>
<td>mismatch repair gene</td>
<td>GI/GU</td>
<td>?</td>
</tr>
<tr>
<td>Breast CA</td>
<td>BRCA1</td>
<td>ovarian</td>
<td>2x</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>prostate</td>
<td>10x</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11/LKB1</td>
<td>GI</td>
<td>4x</td>
</tr>
<tr>
<td>FAP</td>
<td>APC</td>
<td>GI, liver, brain</td>
<td>5x</td>
</tr>
<tr>
<td>CF</td>
<td>CFTR</td>
<td>GI</td>
<td>32x</td>
</tr>
<tr>
<td>HP</td>
<td>PRSS1</td>
<td>GI</td>
<td>50x</td>
</tr>
<tr>
<td>Familial PanCA</td>
<td>?</td>
<td>?</td>
<td>32x</td>
</tr>
<tr>
<td>Young onset</td>
<td>numerous</td>
<td>blood</td>
<td>?</td>
</tr>
<tr>
<td>PanCA</td>
<td>FANC-C, FANC-G</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

### Precursor Lesions

- **PanIN**: Pancreatic intra-epithelial neoplasia
- **MCN**: Mucinous cystic neoplasm
- **IPMN**: Intrapapillary mucinous neoplasm
PanIN

- Microscopic lesions in the ducts
- Are present in PanCA
- Progression from early (PanIN1) to advanced (PanIN3) and PanCA well documented


Precursor Lesions

Wilentz, et al Cancer Res 1999
IPMN

- Thick mucus producing pre-malignant and malignant lesions
  - Main pancreas duct
  - Side branches
  - Both
- Usually affect the gland in different places
- Progression to malignancy about 30% at 7 years

Courtesy J. Sreenarasimhaiah, M.D.
MCN

- Mostly in women
- Body and tail of the pancreas
- Usually a solitary lesion
- Rarely PanCA if < 5 cm
- Probably more “benign” than PanIN

Courtesy J. Sreenarasimhaiah, M.D.
**Precursor Lesions**

- They are the potential “polyps” in PanCA
- Could be our best window of opportunity to prevent PanCA

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**Genetic Alterations in PanCA**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Role</th>
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<tbody>
<tr>
<td>K-ras</td>
<td>&gt;90%</td>
<td>oncogene</td>
</tr>
<tr>
<td>p16/CDKN2A</td>
<td>&gt;95%</td>
<td>tumor suppressor (TS)</td>
</tr>
<tr>
<td>p53</td>
<td>50-75%</td>
<td>TS</td>
</tr>
<tr>
<td>DPC4</td>
<td>55%</td>
<td>TS</td>
</tr>
<tr>
<td>19q/AKT2</td>
<td>10-20%</td>
<td>amplicon</td>
</tr>
<tr>
<td>6q/MYB</td>
<td>10%</td>
<td>amplicon</td>
</tr>
<tr>
<td>20q/AIB1</td>
<td>10%</td>
<td>amplicon</td>
</tr>
<tr>
<td>BRCA2</td>
<td>10%</td>
<td>TS</td>
</tr>
<tr>
<td>LKB1/STK11</td>
<td>4%</td>
<td>TS</td>
</tr>
<tr>
<td>MKK4</td>
<td>4%</td>
<td>TS</td>
</tr>
<tr>
<td>TGF-β</td>
<td>&lt;5%</td>
<td>TS</td>
</tr>
<tr>
<td>RB1</td>
<td>&lt;5%</td>
<td>TS</td>
</tr>
</tbody>
</table>

The Genomic Instability

- DNA instability with rearrangements occur at different times of tumor progression.
- Actually, clonal populations evolve from the primary tumor over a period of time.
- Thus the primary tumor may take 11.6 yrs to evolve, 6.8 years for clones to evolve, and then 2 years to death.
Proteomics

- Protein and genome
  - Study of proteins
    - Molecules made of amino acids by information from genes
    - Have many functions
- Proteins are highly variable
- Compliments genomics

Mesothelin

- Present on mesothelial cells
- Pleura, peritoneum, pericardium
- Over-expressed in ovarian, lung and pancreas malignancy

Soluble member(s) of the mesothelin/megakaryocyte potentiating factor family are detectable in sera from patients with ovarian carcinoma

Scholler, et al Proc Natl Acad Sci 1999
• Developed a dipstick test (antibody) to detect mesothelin in urine or blood
• > 90% accuracy when used on patients (and mice) with known pancreas cancer

Mesothelin/MPF
• May help diagnose mesothelial cancers
• Could be targets for treatment
• 151 patients
• 15 healthy controls
• 52 benign disease
• 33 benign pancreas disease (CP, acute pan)
• 42 pancreas cancer
• 9 biliary cancer

Mesothelin/MPF

<table>
<thead>
<tr>
<th></th>
<th>Number (female)</th>
<th>Age</th>
<th>Mesothelin nmol/L</th>
<th>MPF ng/mL</th>
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</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>15 (11)</td>
<td>31</td>
<td>0.58</td>
<td>8.33</td>
</tr>
<tr>
<td>Benign disease</td>
<td>52 (27)</td>
<td>47</td>
<td>0.71</td>
<td>9.39</td>
</tr>
<tr>
<td>Benign pancreas ds</td>
<td>33 (13)</td>
<td>59</td>
<td>0.69</td>
<td>7.52</td>
</tr>
<tr>
<td>Pancreas CA</td>
<td>42 (21)</td>
<td>67</td>
<td>0.71</td>
<td>7.93</td>
</tr>
<tr>
<td>Biliary CA</td>
<td>9 (6)</td>
<td>64</td>
<td>0.66</td>
<td>8.94</td>
</tr>
</tbody>
</table>

Imaging

- Transcutaneous Ultrasound (US)
- Computed Axial Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Endoscopic Ultrasound (EUS)
- Endoscopic Retrograde Cholangio-pancreatography (ERCP)
Transcutaneous Ultrasound

- Widely available and usually the first imaging tool
- Dependent on the operator and the patient’s body habitus
- Poor imaging due to overlying gas
- Contrast enhanced US
  - Possibly helpful for staging and vessel involvement


CT Scan

- Widely available and very effective tool to diagnose PanCA and to evaluate extent of disease, and to r/o other diagnosis
- Multidetector CT (MDCT) can acquire images at 0.5mm intervals at 64, 128 and now 256 slices in shorter acquisition times
- Images are put together (reformatted) and allow imaging in the axial and sagittal planes, including 3-D projections

CT Scan

• CT technique:
• Double or triple-phase CT scan
  – Power contrast injection
• No contrast
• Arterial phase
• Pancreas phase (40 seconds after contrast)
• Portal vein phase (65 sec after contrast)


CT Scan

• PanCA appears as a hypoattenuating lesion (does not take up contrast)
• Sometimes it’s isoattenuating (same as the rest of the pancreas)
• Other changes to look for:
  – Change in the outline or contour of the pancreas
  – Dilatation of pancreas duct and of bile duct
  – Distant disease

CT Scan

- Can determine the disease with a sensitivity of 90% (those that have the disease)
- Can assess resectability with a specificity (those that can be resected) of 50 to 100%
- Have a positive predictive value of 95% (correctly diagnoses those with the disease)
- CT angiography has a negative predictive value of 96% (patients correctly diagnosed as not having tumor involvement)

CT

• Pros
  – Widely available
  – Can evaluate distant disease
  – Can determine unresectability reasonably well
  – Select patients for surgery

• Cons
  – Limited by type of CT scan that is available and what protocol is followed (“pancreas protocol”)
  – Ability to detect tumors is limited when < 1.5 cm, and not very good at determining lymph node involvement
MRI

- Helpful when patients have renal failure or an allergy to iodinated contrast
- Better soft tissue contrast with gadolinium
- Lesions appear hypodense (take up less contrast than normal tissue)
- May identify smaller tumors compared to CT scan
- Greater ability to evaluate the bile ducts and the pancreas duct


MRCP

- MR cholangio-pancreatography
- An excellent tool to evaluate the bile duct
  - stone disease
- Limited ability to establish a diagnosis for biliary stricture
- Enhanced MRCP with pancreas stimulation may also help evaluate the pancreas duct.
MRI

• Pros
  – Can evaluate distant disease
  – Possibly better to evaluate cysts
  – Possibly better at finding small lesions

• Cons
  – More expensive than CT
  – Less spatial resolution compared to MDCT
  – Sensitivity (ability to find disease) is 84 to 94% vs 91 to 100% for MDCT

PET

- Identifies disease where the tracer FDG (18-fluorodeoxyglucose) is taken up by the active tumor cells
- Useful for identifying metastasis
EUS

- Unique ability to place the probe next to the pancreas and adjacent structures
  - Obtain tissue or aspirate
  - Decreased risk of “seeding”
- Much more sensitive when compared to CT scan:
  - 86 to 100% EUS vs 60-70% CT for tumor
  - 80% EUS vs 50% CT for nodal and adjacent blood vessel involvement
  - CT is superior to EUS for metastatic disease
  - Decreased risk of malignant “seeding”

Buxbaum, et al JOP 2010

EUS-Tissue is the Issue!

- Absence of tissue leads to misdiagnosis
- Avoid surgery in non-PanCA
- Limitations
  - Paucity of tissue
  - Cytologist dependent
- CEA, cyst fluid analysis dor DNA mutations, K-ras, microRNA expression, proteomics
EUS

- **Pros**
  - Ability to sample tissue
  - Establish diagnosis---small tumors and r/o PanCA
  - Establish lymph node involvement
  - Stage the disease---and avoid surgery (50%)

- **Cons**
  - Not widely available
  - Operator dependent
  - FNA issues

Courtesy J. Sreenarasimhaiah, M.D.
### Tumor Markers

<table>
<thead>
<tr>
<th>%</th>
<th>PaCA</th>
<th>CP</th>
<th>NonPanCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA19-9</td>
<td>&gt;85</td>
<td>20</td>
<td>20-70</td>
</tr>
<tr>
<td>CEA</td>
<td>45</td>
<td>10</td>
<td>10-50</td>
</tr>
<tr>
<td>CARS</td>
<td>45</td>
<td>20</td>
<td>10-50</td>
</tr>
<tr>
<td>CA 50</td>
<td>80</td>
<td>15</td>
<td>20-50</td>
</tr>
<tr>
<td>DuPan 2</td>
<td>75</td>
<td>10</td>
<td>10-80</td>
</tr>
<tr>
<td>Span 1</td>
<td>80</td>
<td>15</td>
<td>20-60</td>
</tr>
</tbody>
</table>

Brentnall, et al, in De Vita Principles and Practice of Oncology 1993

### CA19-9 elevation in PanCA

<table>
<thead>
<tr>
<th>PPV</th>
<th>w/o</th>
<th>&gt;37 U/ml</th>
<th>&gt;100 U/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>62%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>CT</td>
<td>71%</td>
<td>89%</td>
<td>100%</td>
</tr>
<tr>
<td>ERCP</td>
<td>62%</td>
<td>80%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Sensitivity/specificity 80-90%
65% of resectable PanCA have CA19-9 elevation

70,940 screened pts
1,063 (1.5%) had CA 19-9 >37 U/mL
4 PanCA (0.4%)
2/4 resectable

“The early PanCA diagnosis problem”

• The performance of diagnostic tests are established in the presence and absence of disease

• The ability of these tests to diagnose “resectable” PanCA or the disease in a pre-malignant state is unknown

Surveillance strategies

• EUROPAC
• Johns Hopkins
• Patients > 40 (50) years old
• Two first degree relatives with PanCA or >3 relatives with PanCA
• Genetic predisposition (BRCA2, p16) if a relative has PanCA
• Syndromes associated with PanCA

http://www.fiv.ac.uk/www/surgery/europac.html
Surgical Justification

- Intervention in patients with a genetic CA predisposition is organ removal
- Pancreas abnormalities, such as Pan-IN lesions may precede the clinical diagnosis
- BUT....
- Not everybody develops PanCA
- Significant complications from interventions

Schwarz Ann Surg Oncol 2006

Screening for early pancreatic neoplasia

- 78 patients; 6 PJS
- Annual EUS/CT scan
- 8/78 have developed pancreas neoplasia within one year of surveillance
  - 6 IPMN, 1 PanIN-3, 1 CA in situ
  - 2 lesions missed by CT

MRI Surveillance in *p16-Leiden* Mutation

- Familial atypical multiple mole melanoma syndrome
- Germline mutation in *CDKN2A* gene (*p16*)
- *p16-Leiden* have a 15 to 20% risk of PanCA by age 75
- MRI/MRCP every year in 67 patients.
- PanCA diagnosed in 7

Vasen, et al Gastroenterology 2011

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MRI Surveillance in *p16-Leiden* Mutation

- 4/7 smoked
- 4 tumors in the tail, one in the body and 2 in the head.
- 3/7 found during the first MRI/MRCP
- 5/7 had surgery
- 3/5 had a R0 resection
- 2/3 alive to study end

Vasen, et al Gastroenterology 2011
• If you don’t expect to conquer you have already lost

Simon Bolivar
La Victoria de Junín, Jose Joaquin de Olmedo

PanCA Surveillance Protocol

High Risk Patients
- Pancreas islet transplant
- Resection
- Total Pancreatectomy

Positive
- Cytology
- Biopsy
- PJ aspirate

Tissue bank
Tissue
abnormal

Genetic markers
- K-ras
- Telomerase

CA 19-9/CEA yearly
- GTT yearly
- EUS yearly
- CT/MRCP yearly
- Monitor weight q 6 months
Conclusion

- Identify high risk behavior and change it
- DM usually not related to pancreas cancer
  - Not ready to screen new onset DM for this disease
- CT/MRI and EUS compliment each other
- There are precursor lesions (cysts)
- Identify high risk patients and determine if they qualify for surveillance
- Combination of clinical suspicion, lab abnormalities, imaging and gene/protein tests-within reasonable costs