Diagnosis of PANCREATIC CANCER

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The faces of pancreatic cancer
General Facts

- 42,470 new cases in the U.S. in 2009
- 5-year survival (1999-2005) 5.7%
- 4th leading cancer killer in the U.S.
- 70-80% develop obst. jaundice; 10-20% duodenal obstruction
- Gemcitabine +/- erlotinib are only chemotherapeutic agents with proven benefits

Cooke. Surg Clinic NA 2010; Merl JOP 2010; Mortenson. AJ Surg 2005

General Facts

- Surgical results:
  - Only curative modality
  - 20% considered resectable; only 2/3 of them are truly resectable
  - 92% resected patients develop recurrence
  - Node-negative resected case has a 25% 5-year survival

Reason for poor survival

- Symptoms are minimal at early stage
- Poor awareness of warning features (MD and patient)
- Aggressive biology of pancreatic cancer
- Current modalities in pancreatic cancer detection are too insensitive

Serum markers as screening tests

<table>
<thead>
<tr>
<th>Serum marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA 19-9</td>
<td>70–90</td>
<td>90</td>
</tr>
<tr>
<td>CEA</td>
<td>16–92</td>
<td>49–93</td>
</tr>
<tr>
<td>CA 50</td>
<td>65–90</td>
<td>58–73</td>
</tr>
<tr>
<td>CA-72-4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CA-242</td>
<td>57–83</td>
<td>79–90</td>
</tr>
<tr>
<td>CA125</td>
<td>45–60</td>
<td>76–86</td>
</tr>
<tr>
<td>CA-195</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>Tissue polypeptide sp ag</td>
<td>50–98</td>
<td>22–97</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>60–99</td>
<td>60–99</td>
</tr>
<tr>
<td>Span-1</td>
<td>50–87</td>
<td>50–90</td>
</tr>
</tbody>
</table>

Pappas. Gastro Clinics 2007
High CA 19-9 is often benign

- 204 patients with high CA19-9
- 130 (63.7 per cent) had malignant conditions
- 74 (36.3 per cent) had benign conditions or no definite cause
- Levels were significantly lower in patients with benign reasons than those with malignant pathology

McLaughlin. Ir J Med Sci 1999

But CA19-9 can be very high ....

- 79 yo woman presented with cholangitis and pancreatic pseudocyst. CA19-9 was 35,500 U/mL. She was adequately treated and at two months' follow-up the CA19-9 level had returned to normal

Akdogan. Tumori. 2001
High level in benign diseases

Reports in the literature:
• 12.8% of pancreatic disease
• 38.8% of biliary tract disease
• 50% of pancreatic or biliary tract disease with obstructive jaundice
• 8.8% of pulmonary disease
• Very high level in hydronephrosis

What cells are producing CA 19-9?

Epithelial cells of the
• Pancreas
• Bile duct
• Gallbladder
• Gastrointestinal tract
• Airway
High CA 19-9: Benign conditions

- Inflammatory bowel disease
- Pancreatitis
- Cirrhosis
- Chronic hepatitis
- Cholangitis
- Bronchial cyst
- Bronchitis
- Pulmonary fibrosis
- Bronchiectasis

- Cystic fibrosis
- Endometriosis
- Benign splenic cyst
- Diabetes mellitus
- Chronic renal failure
- Thyroid disease
- Rheumatologic disease
- Hydronephrosis

Cancer with high CA 19-9

- Pancreatic
- Biliary
- Hepatocellular
- Cholangiocarcinoma
- Gastric

- Colorectal
- Ovarian
- Lung
- Breast
- Uterine

CA 19-9 is not a good screening test

- CA 19-9 is rarely elevated in health, but can occur in a variety of benign conditions
- Using CA 19-9 to screen for pancreatic cancer is rarely useful or reliable

Look for Patients at Risk

- Smoking
- Old age
- Diabetes
- Peutz-Jeghers
- Panc cyst
- Hereditary pancreatitis
- Family history
- Other cancer (BRCA, HNPCC)
- Chr pancreatitis
- IPMN
- Cystic fibrosis

Potential Warning Signs

New onset IDDM
Painless jaundice
Dull, unexplained pain
Sudden loss of appetite and weight
Recurrent pancreatitis
Unexplained delayed gastric emptying

Pancreatic lesions linked to cancer

- Chronic pancreatitis
- Cystic lesions
  - IPMN (intraductal papillary mucinous tumor)
  - Mucinous cystadenoma
  - Mucinous cystadenocarcinoma
  - Neuroendocrine tumor
- Solid lesions
  - Neuroendocrine tumor
  - Pancreatic ductal carcinoma
  - Lymphoma
  - Metastatic cancer
  - Autoimmune pancreatitis
Familial links to pancreatic cancer

**Familial pancreatic cancer (FPC):**
- ≥ 2 first-degree relatives with pancreatic ductal adenocarcinoma (in the absence of other cancers or diseases that are known to be familial)
- 1-3.5% of all ductal pancreatic cancer
- 18X (2 relatives); 57X (3 relatives)

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**IPMN**
- Fish mouth papillary orifice
- Early lesions are flat
- Profuse mucin production
- Mistaken as chronic pancreatitis
- Premalignant
- Indistinguishable from ductal pancreatic cancer

IPMN – percanerous tumor

Intraductal Papillary Mucinous N
Autoimmune pancreatitis


Autoimmune pancreatitis

Before steroid

After steroid
Lymphoplasmacytic infiltration

Familial links to pancreatic cancer

- Syndromes that shows an increased risk:
  - Familial atypical multiple mole melanoma (FAMMM) (CDKN2A)
  - Peutz-Jeghers syndrome (PJS) (36% life risk)
  - Hereditary pancreatitis (HP) (40% risk)
  - Hereditary nonpolyposis colorectal carcinoma (HNPCC) (<5% risk)
  - Familial breast and ovarian cancer (FOBC) (BRCA1, BRCA2)
  - Cystic fibrosis (CF) (CFTR)
  - Ataxia-telangiectasia (AT)
  - Familial adenomatous polyposis (FAP)
Desired characteristics of imaging tests

- Early detection
- Identify those who will need surgery
- Select out those will not benefit from surgery
- Minimal invasiveness
- Simple tissue acquisition for definitive diagnosis to guide palliation or resection
- Cost-effective
- Safe
- Local availability

Kochman. GIE 2002

Panc CA: Dysplasia to Cancer

Rosty. Hem/onc Clinics of NA. 2002
Pancreatic Intraepithelial Neoplasm

- **PanIN-1A**: Flat epithelial lesions composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin
- **PanIN-1B**: These lesions have a micropapillary, papillary or basally pseudostratified architecture
- **PanIN-2**: May be flat or papillary. They must have some nuclear abnormalities
- **PanIN-3 (CIS)**: Papillary or micropapillary lesions. True cribriforming, budding off of clusters of cells into the lumen and luminal necroses should all suggest the diagnosis of PanIN-3

Early Diagnosis of dysplasia/CA

- 7/14 FPC patients believed to have dysplasia on the basis of hx, EUS and ERCP were referred for resection
- All 7 had dysplasia in pancreatectomy specimens
- EUS findings were subtle and similar to those seen in chronic pancreatitis
- ERCP findings: ductal stricture, irregularities and small sacculations
- CT and serum markers had low sensitivity

Early Diagnosis of dysplasia/CA


Endoscopic Ultrasonography (EUS)
How good is a normal EUS?

- 80 (medium/low cancer risk) patients
  - High CA 19-9 level alone
  - Chronic abdominal pain
  - Significant weight loss without a clear etiology
  - Indeterminate CT ("enlarged head of pancreas," "heterogenous appearance," "mass cannot be excluded")

Catanzaro. Gastrointest Endosc 2003;58:836-40
Normal EUS = no pancreatic cancer

- Mean FU 23.9 months
- One with chronic pancreatitis changes subsequently found to have panc cancer
- No patient (n=58) with normal pancreas EUS developed pancreatic cancer or required pancreatic surgery during the follow-up period

Normal EUS = no pancreatic cancer

- **Conclusions**: A normal EUS of the pancreas in the setting of subtle radiologic findings, serologic abnormalities, and/or nonspecific symptoms definitively rules out pancreatic cancer
EUS is good for early detection

- EUS is the most accurate dx modality
- Both dual-phase CT and EUS had high sensitivity for pancreatic cancers >15 mm, but CT was less sensitive than EUS for cancers <15 mm (67% vs 100%)
- T and N staging by EUS has an accuracy of 85% and 70%, respectively
- EUS had sensitivity of 61% and PPV of 69% in predicting resectability vs sensitivity of 73% and PPV of 71% for MRI


EUS is good for screening & detection

EUS done on 37 FPC relatives

Multi-detector CT

- Increased speed of image acquisition
- Ability to time acquisition with vascular contrast injection
- Increased resolution
- High quality 3-D reconstruction


3D CT Rendering

David Lu. UCLA
Multi-detector CT

Vascular involvement can be readily identified

MRI & MRCP


Freeny. Gastro Clinic 1999
PET Scan for Pancreatic Cancer

Freeny. Gastro Clinics 1999

PET Scan for Pancreatic Cancer

### PET for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Total</th>
<th>Malig. (%)</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bares</td>
<td>1994</td>
<td>40</td>
<td>27 (68%)</td>
<td>92</td>
<td>85</td>
</tr>
<tr>
<td>Stollfuss</td>
<td>1995</td>
<td>73</td>
<td>43 (59%)</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Friess</td>
<td>1995</td>
<td>80</td>
<td>48 (60%)</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>Kato</td>
<td>1995</td>
<td>24</td>
<td>15 (63%)</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td>Inokuma</td>
<td>1995</td>
<td>46</td>
<td>35 (76%)</td>
<td>94</td>
<td>82</td>
</tr>
<tr>
<td>Ho</td>
<td>1996</td>
<td>14</td>
<td>8 (57%)</td>
<td>100</td>
<td>67</td>
</tr>
<tr>
<td>Zimny</td>
<td>1997</td>
<td>106</td>
<td>74 (70%)</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Imdahl</td>
<td>1998</td>
<td>48</td>
<td>27 (56%)</td>
<td>96</td>
<td>100</td>
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<tr>
<td>Clark</td>
<td>1998</td>
<td>30</td>
<td>22 (73%)</td>
<td>82</td>
<td>75</td>
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<tr>
<td>Rose</td>
<td>1998</td>
<td>65</td>
<td>52 (80%)</td>
<td>92</td>
<td>85</td>
</tr>
</tbody>
</table>

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### PET vs CT for Pancreatic cancer

#### Sensitivity Stratified by Tumor Diameter

<table>
<thead>
<tr>
<th>Tumor Diameter</th>
<th>n</th>
<th>CT</th>
<th>$^{18}$FDG-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 cm</td>
<td>14</td>
<td>18%</td>
<td>100%</td>
</tr>
<tr>
<td>2.1-4.0 cm</td>
<td>15</td>
<td>76%</td>
<td>90%</td>
</tr>
<tr>
<td>&gt;4.0 cm</td>
<td>20</td>
<td>100%</td>
<td>92%</td>
</tr>
</tbody>
</table>
### PET Scan

- Sensitivity, and even specificity, of diagnosing pancreatic cancer reported as high as 100%
- Results varied with timing of study and SUV (standardized uptake value) used as positive readings
- Not helpful in distinguishing acute pancreatitis from cancer

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### EUS vs CT for pancreatic cancer

<table>
<thead>
<tr>
<th>Series</th>
<th>Detection</th>
<th>Accuracy - resectability</th>
<th>Sens. - vas. invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EUS</td>
<td>CT</td>
<td>EUS</td>
</tr>
<tr>
<td>Legmann</td>
<td>27/27</td>
<td>25/27</td>
<td>20/22</td>
</tr>
<tr>
<td>Midwinter</td>
<td>33/34</td>
<td>26/34</td>
<td>25/30</td>
</tr>
<tr>
<td>Tierney</td>
<td>30/31</td>
<td>25/31</td>
<td>16/16</td>
</tr>
<tr>
<td>Mertz</td>
<td>29/31</td>
<td>16/31</td>
<td>16/16</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>97%</td>
<td>73%</td>
<td>91%</td>
</tr>
<tr>
<td><em>p Value</em></td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hunt. Gastro Clinic. 2002
Current status re: EUS and CT

- EUS and helical CT are complementary for staging pancreatic cancer
- EUS is a more accurate for local T staging and for predicting vascular invasion, especially in tumors <3 cm,
- Helical CT is better for the evaluation of distant metastasis and for staging larger tumors

Varadarajulu. Surg Clinic NA 2010

CT and EUS can be used together

<table>
<thead>
<tr>
<th>Criterion</th>
<th>n</th>
<th>( p^a )</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular abnormality, CT</td>
<td>16</td>
<td>&lt;0.001</td>
<td>94</td>
<td>74</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>Adenopathy &gt;1 cm, CT</td>
<td>29</td>
<td>&lt;0.001</td>
<td>76</td>
<td>74</td>
<td>69</td>
<td>80</td>
</tr>
<tr>
<td>Liver lesion, CT</td>
<td>10</td>
<td>0.06</td>
<td>70</td>
<td>60</td>
<td>18</td>
<td>94</td>
</tr>
<tr>
<td>Vascular abnormality, EUS</td>
<td>18</td>
<td>0.004</td>
<td>72</td>
<td>67</td>
<td>42</td>
<td>88</td>
</tr>
<tr>
<td>Adenopathy &gt;1 cm, EUS</td>
<td>13</td>
<td>0.03</td>
<td>69</td>
<td>64</td>
<td>30</td>
<td>90</td>
</tr>
</tbody>
</table>

\( p \) = positive predictive value, \( NP \) = negative predictive value, \( RR \) = relative risk
\( 95\% \) CI are in parentheses

Score \( \geq 2 \) are unresectable and should consider chemotherapy

Double duct sign from cancer

Reported as 95% sensitive
(Freeny. Rad Clinic NA 1989)
Used as a standard test for diagnosing pancreatic carcinoma when a CT is non-diagnostic
But ERCP is invasive, can MRCP replace ERCP?
Suspected cancer: what to do?

- Start with abdominal CT. Do not use CA19-9 or CEA
- When CT is negative, EUS is the imaging modality of choice
- Perform FNA if EUS is positive
- ERCP has a limited role in diagnosing cancer because of risks of complications
- PET scan may have a small role for early cancer, but mainly for tracking the activity of known cancer

SUMMARY

- Many new and improved diagnostic modalities are now available to detect and assess pancreatic cancer
- In spite of recent advances, the overall survival of pancreatic cancer is still among the worst of solid tumors

Rosty. Hem/onc Clinics of NA. 2002
SUMMARY

• There is the limited possibility to detect pancreatic dysplasia, thus potentially preventing cancer in the high risk populations
• Treatment options have expanded tremendously recently, along with much improved palliative modalities