Pancreatic cancer

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Objectives

At the completion of this talk the attendees will:

1. Be able to describe the presenting symptoms of pancreatic cancer
2. Have an understanding of the steps involved in diagnosis
3. Appreciate the challenges in managing pancreatic cancer
Pancreatic Anatomy

- The pancreas is a soft, elongated, flattened organ
- 12 - 20 cm in length
- Weighs 70 - 110 g in adults
- The pancreas lies posterior the stomach
Pancreatic anatomy
Pancreatic function

- **Exocrine function:** Production and secretion of digestive enzymes and bicarbonate
- **Endocrine function:** Regulation of blood glucose
The acinus
Pancreatic Enzymes

- Lipase - Fat digestion
- Amylase - Enzyme which digests starch and glycogen.
- Proteases - Protein digestion

* When measuring ‘injury’ to the pancreas, we typically measure blood levels of lipase and amylase, but not proteases.
A case: Arnold Colhurst

- A.C. is a pleasant 64 year old Civil Engineer, planning to retire in 6 months
- One morning his wife commented that he “looked a little yellow”
- Upon looking at himself closely in the mirror, he indeed did note yellowing of the sclera (whites of the eyes).
- He recalled his mother having jaundice when he was a child, but it resolved and she lived to age of 84, dying from complications of a broken hip
- A.C. booked an appointment with his Family Physician two days later
Family Doctor visit

- **History**
  - He has had no pain. His stools are pale, and urine is dark (looks like Coca cola). He has lost perhaps 5 – 7 lbs over the last month, and attributed to eating healthier

- **Past Medical History**
  - Borderline diabetic, Hypertension

- **Medications**
  - Hydrochlorothiazide, Baby aspirin

- **Social history**
  - Ex smoker, having quit a decade ago. Drinks Bottle of red wine on weekends

- **Family history**
  - Mom with jaundice, cause unknown, but likely due to viral hepatitis
On examination

- Vital signs normal
- Scleral icterus
- No Virchow’s nodes
- Liver palpable in the mid clavicular line, 4 cm below costal margin (not tender)
- No abdominal ascites
- Otherwise normal
Lab tests arranged

- **Liver Enzymes**
  - ALT 462 (n < 50)
  - AST 368 (n < 50)
  - ALP 720 (n < 90)
  - GGT 480 (n < 50)
  - Lipase 60 (n < 90)

- **Liver function tests**
  - INR 1.8 (n < 1.2)
  - Albumin 28 (n : 35 – 42)
  - Total bilirubin 124 (n < 22)
  - Direct bilirubin 68 (n < 5)
  - Indirect bilirubin 56 ( n < 17)
The physiology of bile

1. Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.

2. Reabsorbed bile salts are recycled by enterohepatic circulation.

3. 5% of bile salts are lost in feces.

4. 95% of bile salts are reabsorbed by the small intestine.
Differentiating the cause of jaundice

Elevated total bilirubin

- Pre hepatic
  (Indirect >> direct)
- Hepatic
  (Direct > indirect)
- Post hepatic
  (Direct >> indirect)
Approach to elevated indirect bilirubin

**Elevated indirect bilirubin**

- **Increased bilirubin production**
  - Hemolysis
  - Impaired RBC synthesis

- **Impaired hepatic uptake**
  - CHF
  - Portosystemic shunts
  - Drugs (e.g. Rifampin)

- **Impaired bilirubin conjugation**
  - Gilberts’s syndrome
  - Neonates
  - Hyper thyroidism
  - Chronic liver disease
Approach to elevated direct bilirubin

1. Ultrasound/CT
2. No obstruction
   - Hepatocellular (ALT/AST >> ALP/GGT)
3. Obstruction
   - Cholestatic (ALP/GGT >> ALT/AST)
   - Benign vs malignant causes
Where to go from here with Arnold?

- Do an ultrasound?
- Do a CT?
- Do an MRI?
- Do an ERCP?
Abdominal ultrasound
MRI
Approaches to tissue acquisition

- ERCP
- Percutaneous biopsy
- EUS
- Open surgical
What is ERCP?

- ERCP is an acronym which stands for Endoscopic Retrograde Cholangio-Pancreatography
- It is a method for accessing the common bile duct and pancreatic ducts
The patient is sedated. A endoscope with a side-viewing camera is advanced through the mouth, down to the second part of the duodenum where the ampulla is identified. The ampulla is entered with a catheter and dye is injected and viewed with fluoroscopy (xray technology). To access the bile duct, the ampulla is cut open (sphincterotomy).
A: Normal ampulla  
B: A sphincterotomy has been performed to access the CBD.  
C: The ampulla is dilated with a balloon  
D: A stone is extracted with a basket.
Brush cytology

- Small brush used to obtain cells from a tumour invading the bile duct
- Yields a diagnosis 50 – 60 % of the time when cancer is present
Complications of ERCP

- Pancreatitis (5 – 10%)
- Bleeding (1%)
- Perforation (0.5 – 1%)
- Cholangitis (<1%)
- Issues relating to sedation
Radial echoendoscope
Linear echoendoscope
Technique

- Air is the enemy in EUS
- Balloon on tip (water filled) is used to create an echo window
- Fluid can be instilled into lumen as well and air removed
EUS

Diagram of the five-layer echo pattern of the normal gastrointestinal wall

MUCOSA (superficial & muscularis mucosa)

SUBMUCOSA

MUSCULARIS PROPRIA

ADVENTITIA (SEROSA)

Courtesy of Mary Lee Kohnsky, DO and Kenneth Birnmoeller, MD.
FNA for solid tumors

- Usually 3 - 5 passes made with needle
- Sample smeared on a slide
- Cytotechnologist evaluates on site
- Diagnostic yield is > 90% when cancer is present
Cytology
Complications of EUS +/- FNA

- **EUS alone**
  - Higher rates of sedation, longer procedures than standard endoscopy
  - Perforation (0.001%)
  - Bleeding (0.001)
  - Infection (1/ million)

- **With FNA**
  - Perforation (0.1%)
  - Bleeding (0.5%)
  - Pancreatitis (0.6 – 2%)
  - Infection (low except if cystic lesion)
Percutaneous biopsy
Would you choose surgery?

“...and this is Ralph, your anesthesiologist.”
Back to our patient.....

- Underwent ERCP with brush cytology and a plastic stent was placed in the bile duct to treat the jaundice.
- Cytology results: “Atypical, not diagnostic”
- Referred for an EUS: Biopsy confirms adenocarcinoma of pancreas
Pancreatic Cancer

- Most pancreatic cancers are adenocarcinomas (85%), arising from the ductal epithelium (exocrine pancreas)
- Third most common GI cancer (behind colon and rectal cancers)
- Most patients > 45 y/o
- Poor prognosis:
  - 20% 5-year survival if surgically resectable
  - <10% 5-year survival if lymph nodes involved or other metastasis
Epidemiology of Pancreatic Cancer in Canada (2016 Estimates)

Annual pancreatic cancer diagnosed
5,200

2,600 men

2,600 women

Cases of Pancreatic Cancer in Nova Scotia
150

70 men

80 women

Pancreatic Cancer is the 10th most common cancer in men and 9th in women in Canada.
## Distribution of New Cancer Cases

<table>
<thead>
<tr>
<th></th>
<th>Males 102,900 New cases</th>
<th>Females 99,500 New cases</th>
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</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>21.0%</td>
<td>25.8%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>14.1%</td>
<td>14.1%</td>
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<tr>
<td>Lung and bronchus</td>
<td>14.0%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Bladder</td>
<td>6.4%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4.3%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Kidney and renal pelvis</td>
<td>4.0%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.6%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.4%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Oral</td>
<td>3.1%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>2.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1.7%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Liver</td>
<td>1.7%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>1.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Testis</td>
<td>1.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Larynx</td>
<td>0.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Breast</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td><strong>All other cancers</strong></td>
<td><strong>10.7%</strong></td>
<td><strong>8.9%</strong></td>
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Canadian Cancer Statistics 2016
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<td>11.6%</td>
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<td>5.8%</td>
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Risk factors

Non-modifiable risk factors:
- Peutz Jeghers syndrome
- Familial pancreatitis
- Increases with age
- Men > women
- African American > white
- BRCA 2 positivity

Modifiable risk factors:
- Chronic pancreatitis 15 X
- Cigarette smoking 2 – 3 X
- Obesity 2 X
- Type 2 Diabetes 2 X
- Alcohol >30 g per day 1.2 X
- ?Occupational exposure
Symptoms

- Symptoms depend on where in the pancreas the cancer develops
- Pancreatic body or tail:
  - Weight loss
  - Abdominal pain
- Head of pancreas
  - Jaundice with dark urine and pale stools
Other symptoms that can occur

- Pain in the upper abdomen that radiates to the back which is new, significant and persistent that is relieved by leaning forward
- Back pain
- Diabetes which is new-onset and not associated with weight gain
- Vague indigestion (dyspepsia) or abdominal discomfort (not responding to prescribed medication)
- Loss of appetite
- Nausea and vomiting
- Pain when eating
- Steatorrhea (fatty stools that are often pale and smell foul)
Physical Exam

- Patient may be jaundiced with scleral icterus (yellow sclera)
- Epigastric mass
- Palpable liver (if mets to liver)
- Left supraclavicular lymph nodes (Virchow’s nodes)
- Signs of weight loss
Tumour markers (CA 19-9)

- Carbohydrate Antigen 19 – 9 (CA 19-9)
  - Sensitivity 79 – 81%
  - Specificity 82 – 90%
- CA 19-9 < 100 implies resectability
- CA 19-9 > 100 implies metastatic or locally invasive disease
- Important limitations:
  - Lack of Lewis blood group antigen in 5 – 10%
  - False positives in obstructive jaundice (10 – 60%)
How do we treat pancreatic cancer?
## Staging

<table>
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<tr>
<th>stage</th>
<th>TNM classification</th>
<th>clinical classification (in terms of treatment)</th>
<th>median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>resectable</td>
<td>24.1</td>
</tr>
<tr>
<td>IA</td>
<td>T1, N0, M0</td>
<td>resectable</td>
<td>20.6</td>
</tr>
<tr>
<td>IB</td>
<td>T2, N0, M0</td>
<td>resectable</td>
<td>15.4</td>
</tr>
<tr>
<td>IIA</td>
<td>T3, N0, M0</td>
<td>resectable</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>T1/2/3, N1, M0</td>
<td>locally advanced potentially resectable</td>
<td>12.7</td>
</tr>
<tr>
<td>III</td>
<td>T4, N0/1, M0</td>
<td>locally advanced unresectable</td>
<td>10.6</td>
</tr>
<tr>
<td>IV</td>
<td>T1/2/3/4, N0/1, M1</td>
<td>metastatic</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Surgery best option for cure

< 20% are considered curative by surgery

< 20% 5 year survival with surgery
Chemotherapy if non-resectable

In 2010: A substantial treatment advance
The PRODIGE 4 - ACCORD 11 trial

FOLFIRINOX
Primary endpoint: OS

Gemcitabine

342 patients

No prior chemo
PS 0-1
< 76 yrs
Measurable metastatic disease
T. bilir < 1.5 x ULN

Stratification:
• Center
• PS: 0 vs. 1
• 10 tumor location: head vs. other

Conroy, ASCO 2010, NEJM 2011
Overall survival

FOLFIROX: 11.1 mo
Gemcitabine: 6.8 mo

HR=0.57 : 95%CI [0.45-0.73]

Stratified Log-rank test, p<0.0001

Number at risk
Gemcitabine  171 134 89 48 28 14 7 6 3 2 2 2
Folfrinox  171 146 116 81 62 34 20 13 9 5 3 2 2

Probability

Months

Dalhousie University
FACULTY OF
MEDICINE
Should I screen her for pancreatic cancer?

- No screening protocol has ever been shown to prevent or alter natural history of pancreatic cancer.
- **EXPERT opinion:**
  - Hereditary chronic pancreatitis
  - Peutz-Jeghers syndrome
  - Family history of pancreatic cancer in three relatives, at least one of which is first degree relative.
  - Known BRCA2 positive patient.
Back to Arnold

- Arnold had tumour in his liver and therefore was not a surgical ‘candidate’
- He underwent Folfirinox chemotherapy and in follow up 14 months later he was doing well with no evidence of progression on CT
Thank you!