Pancreatic Cancer

*The Killer that must be discovered early*

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Pancreatic cancer (adenocarcinoma) is one of the most lethal cancer types. It is discovered at an advanced stage and is resistant to therapy.
Pancreatic cancer (adenocarcinoma) is one of the most lethal cancer

- 5 year survival rate after complete surgical resection – 15 to 25%.

- Development of adjuvant therapies for pancreatic CA lagged significantly behind those of other major solid organ tumours eg breast, lung, colon and prostate CA
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<td>Head of pancreas, Others</td>
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Epidemiology – Disease Pattern of Pancreatic Cancer

![Bar chart showing the global new cases of cancer by type. The chart indicates that lung cancer is the most common, followed by liver, stomach, colorectal, breast, and other cancers. The chart highlights the proportion of cancer deaths and the number of new cases globally.]
Epidemiology – Disease Pattern of Pancreatic Cancer

• Uncommon in people < 40 years old
• Median age: 70 years old
• More common in Men

• High incidence of cancer mortality:
  – 8th most common cause of cancer death in Males
  – 9th most common cause of cancer death in Females
Epidemiology – Disease Pattern of Pancreatic Cancer

- Uncommon in people < 40 years old
- Median age: 70 years old
Epidemiology – Disease Pattern of Pancreatic Cancer

• Incidence rate in men:
  – 8.5/100,000 for men in highly developed countries
  – 3.3/100,000 for less developed countries

• Incidence rate in women:
  – 5.6/100,000 for women in highly developed countries
  – 2.4/100,000 in less developed countries
Epidemiology – Disease Pattern of Pancreatic Cancer

- Incidence: 6.2 ASW per 100,000 population
- Mortality: 6.5 ASW per 100,000 population
Epidemiology – Disease Pattern of Pancreatic Cancer

- Not as common as Colorectal, Breast and lung cancers in Singapore
- But high incidence of cancer mortality
- Due to late presentation and usually aggressive disease behaviour of the cancer
• Mode of spread of pancreatic CA:
  – Blood stream – to liver, lung and bones
  – Lymphatics – to surrounding lymph nodes and remote lymph nodes eg neck LN
  – Direct invasion to surrounding structures eg vessels
  – Peritoneal lining (transcoelomic spread) – peritoneal nodules, ascites etc
Risk Factors of Pancreatic Cancer

Lifestyle & Environmental: Smoking, heavy alcohol, residential radon exposure

Race/ Ethnic factors: African-American men & women, Ashkenazi Jewish heritage

Known Inherited Genetic: Familial pancreas CA, FAMMM, Hereditary pancreatitis, BRCA2, Peutz Jegher syndrome, von Hippel Lindau, Li-Fraumeni etc

High Risk Occupation: dry cleaning, chemical plant, sawmills, uranium miners, electrical equipment manufacturing workers

Factors a/w Pancreatic CA

HIV, Hepatitis B, H Pylori infection, DM, pancreatitis, obesity

Yeo et al Cancer J 2013
Risk Factors of Pancreatic Cancer

Smoking

- Linear association of smokers with risk of developing pancreatic cancer.
- Smokers 1 to 3X increase risk
- Related to amount and duration of smoking
- Risk persists beyond cessation of smoking
Risk Factors of Pancreatic Cancer

Family History and Inherited Genetic Disorders

– 5 to 10% of all pancreatic adenocarcinomas – hereditary

– If familial PC – 1° family members – 9 X increased risk
  – If sporadic PC -- 1° family members -- 2 X increased risk

– BRCA2 mutation family members – 6 to 19% increased risk

– If familial PC – 3 or more family members affected – 57 X increased risk
# Risk Factors of Pancreatic Cancer

## Table 3. Inherited Syndromes and Susceptibility Genes Associated With Increased Risk of Pancreas Cancer

<table>
<thead>
<tr>
<th>Inherited Syndromes</th>
<th>Susceptibility Gene/Chromosomal Mutation Region</th>
<th>Increased Risk of Pancreas Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1 (7q35)</td>
<td>50- to 80-fold</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colorectal cancer</td>
<td>hMSH2, hMSH1, hPMS2, hMSH3, hPMS1, hMSH6/GTBP(2,3)</td>
<td>Undefined ↑ risk</td>
</tr>
<tr>
<td>Hereditary breast and ovarian cancer</td>
<td>BRCA2 (13q12-q13), BRCA1</td>
<td>3.5- to 10-fold</td>
</tr>
<tr>
<td>Familial atypical multiple mole</td>
<td>p16 (9p21)</td>
<td>20- to 34-fold</td>
</tr>
<tr>
<td>Melanoma syndrome (FAMMM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1 (19p13)</td>
<td>75- to 132-fold</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM (11q22-23)</td>
<td>Undefined ↑ risk</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>DP 2.5 (5q12-21)</td>
<td>Undefined ↑ risk</td>
</tr>
<tr>
<td>Familial pancreatic cancer</td>
<td>BRCA2 (4q32-34)</td>
<td>5- to 10-fold ↑ PC</td>
</tr>
<tr>
<td>Von Hippel-Lindau syndrome</td>
<td>VHL (3p25)</td>
<td>↑ Neuroendocrine tumors</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>CFTR (7q31)</td>
<td>↑ PC and GI cancers</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>p53 (17p13.1)</td>
<td>↑ PC</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>FANC or FANCG (3p22-26, 9p13, 9q22.3, 16q24.3)</td>
<td>Slight ↑ PC</td>
</tr>
<tr>
<td>ABO blood group</td>
<td>rs9543324(13q22)</td>
<td>20- to 26-fold</td>
</tr>
<tr>
<td>Undefined familial PC</td>
<td>rs401681(5p.33)</td>
<td>Undefined ↑ risk</td>
</tr>
</tbody>
</table>

↑ = increased risk of pancreas cancer.


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Yeo et al Cancer J 2013
Diabetes

- DM is both a causal risk factor for pancreatic CA and a clinical manifestation of pancreatic CA inducing alterations in islet cell function and loss of β cell mass.
- Hyperglycaemia or frank DM – 50 to 80% of patients with pancreatic CA.
- Long term DM – at least 2 to 3 X increase in incidence of pancreatic CA
- GDM – HR 7.06 (95% CI 1.69 – 29.45) compared to non-GDM cases (Israeli study 185,000 women over 14 years)
Risk Factors of Pancreatic Cancer

Pancreatitis

- 1.34% of all pancreatic CA presented with pancreatitis

- **Chronic pancreatitis** – 3% of pancreatic CA
  - Highly developed countries is excess alcohol consumption, typically more than 6 drinks per day for 20 years

- **Hereditary pancreatitis**
  - Autosomal inherited disease
    - Usually begins in childhood or early adulthood
    - Is associated with a PRSS1 (7q35) mutation.

Lowenfels et al NEJM 1993
### Risk Factors of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Normal duct</th>
<th>PanIN-1A</th>
<th>PanIN-2</th>
<th>PanIN-3</th>
<th>Adenocarcinoma</th>
</tr>
</thead>
</table>
| - Low cuboidal cells  
- Single cell layer | - Elongated cells  
- Mucin production | - Nuclear abnormalities:  
- e.g. enlargement, some loss of polarity, crowding | - Budding into lumen  
- Severe nuclear atypia  
- Mitosis, some abnormal | - Invasive growth  
- Marked stromal reaction (desmoplasia) |

#### Genetic Alterations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBB2, EGFR</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td></td>
</tr>
<tr>
<td>INK4A</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td></td>
</tr>
<tr>
<td>SMAD4/DPC4</td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td></td>
</tr>
<tr>
<td>Telomerase</td>
<td></td>
</tr>
</tbody>
</table>

### Premalignant Disease Process

- e.g. IPMN, MCN, PanIN
Risk Factors of Pancreatic Cancer

- Mucinous cystic neoplasm
  - Risk of malignancy – 25%
  - Features suggestive of malignancy:
    - Mural nodule
    - Solid component
    - Large size
    - Elevated tumour marker
Risk Factors of Pancreatic Cancer

Intraductal Papillary Mucinous Neoplasm

- Risk of malignancy: Main duct IPMN – 60%, branched-duct IPMN – 30%
- Solid component, mural nodules, size >3cm
Clinical Presentation of Pancreatic Cancer

Symptoms of Pancreatic Cancer

If you persistently experience one or more of these symptoms which are not normal for you, DO NOT IGNORE:

- Low mood or depression
- Indigestion
- Irritable Bowel Syndrome
- Fatigue
- New on associated

Common Misdiagnoses:

- Gallstones
- Gastritis
- Liver disease

Contact your doctor straight away!
Clinical Presentation of Pancreatic Cancer

Head of pancreas
Jaundice, Tea coloured Urine, pale stool, itchiness

Body and tail of pancreas
Back pain, LOW, localised left sided pain etc
Clinical Presentation of Pancreatic Cancer

- Head of pancreas/uncinate process
  - Tea coloured urine and pale stool
  - Jaundice
  - Itchiness
  - Loss of weight, loss of appetite
Clinical Presentation of Pancreatic Cancer

- Body/tail of pancreas
  - Back pain
  - LOW
• Requires **high index of suspicion**!
• Blood tests:
  – Liver function test – obstructive jaundice
  – Tumour markers (non-specific): ↑ CA 19-9, ↑ CEA etc
• Imaging studies: Ultrasound of liver, CT scan, MRI etc
• Biopsy of the tumour to confirm diagnosis
Diagnosis of Pancreatic Cancer

- Role of CA 19-9
  - Screening of >10,000 asymptomatic patients – Pancreatic CA – 0.04%
  - Screening of 4,500 symptomatic patients – 1.9%
  - False elevations are frequently observed in benign pancreatobiliary obstruction
  - Ca 19-9 – valuable in prognostication – very high value in the absence of biliary obstruction – metastatic or unresectable disease
  - Useful for long term follow up for recurrence.

Mann et al Eur J Surg Oncol 2000
Diagnosis of Pancreatic Cancer

- Imaging modalities: Ultrasound HBS
  - Dilated intrahepatic and extrahepatic bile ducts
  - Mass at head of pancreas (body and tail difficult to visualise)
  - Liver metastasis
Diagnosis of Pancreatic Cancer

- Imaging modalities: CT scan of the pancreas/liver
Diagnosis of Pancreatic Cancer

- Imaging modalities: CT scan of the pancreas/liver
Diagnosis of Pancreatic Cancer

- Imaging modalities: CT scan of the pancreas/liver
Diagnosis of Pancreatic Cancer

• Imaging modalities: CT scan of the pancreas/ liver
  – Confirm location of tumour
  – Invasion into surrounding structures
  – Invasion into vital vascular structures eg coeliac axis, SMA etc
  – Liver metastasis
  – Peritoneal metastasis
  – Lung metastasis
Diagnosis of Pancreatic Cancer

- Imaging modalities: MRI of the pancreas
  - Shows the same information as CT scan
  - But may be able to show additional characteristics if CT scan yields equivocal findings
• Biopsy of pancreatic lesion
  – The usual modalities are EUS-FNA (Endoscopic fine needle aspiration of pancreatic lesion)

• Biopsy of metastatic lesion
  – Ultrasound or CT guided percutaneous biopsy of liver lesion
  – Ultrasound aspiration of abdominal ascites for cytology
Diagnosis of Pancreatic Cancer

• Interpretation of EUS-FNA results
  – Cytology – adenocarcinoma, SPPT, NET etc
  – Biochemistry – CEA, Amylase
  – K-ras
  – Mucin
Diagnosis of Pancreatic Cancer

- Imaging modalities: PET scan
  - Shows metabolic activity of the tumour
  - Extent of tumour metastasis
Treatment of Pancreatic Cancer

- Surgically Resectable Pancreatic Cancer (Stage I or II)
- Locally advanced/ Unresectable Pancreatic Cancer (Stage III)
- Metastatic Pancreatic Cancer (Stage IV)
Treatment of Pancreatic Cancer

Figure 3. Anatomy and Surgical Resectability of Pancreatic Cancer.
Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases.
Pancreaticoduodenectomy (Whipple’s operation) for Head of pancreas tumour/ Uncinate process tumour
Treatment of Pancreatic Cancer

- Open vs Laparoscopic Whipple’s operation
Treatment of Pancreatic Cancer

• Open Whipple’s operation
Distal/ Subtotal pancreatectomy for body or tail of pancreas tumour
Treatment of Pancreatic Cancer

- Open vs Laparoscopic distal pancreatectomy operation

Keyhole removal of distal pancreas
Treatment of Pancreatic Cancer

Surgical bypass (Double or triple bypass) for unresectable head of pancreas tumour
Treatment of Pancreatic Cancer

Endoscopic metal stent placement for unresectable head of pancreas cancer
Treatment of Pancreatic Cancer

Pancreatic Cancer

Curative Rx
- Surgery
- Adjuvant chemotherapy

Palliative Rx
- Biliary stenting
- Gastric outlet stenting
- Bypass surgery
- Pain management
- Symptomatic Rx

Symptomatic Rx
### Treatment of Pancreatic Cancer

#### Table 2. Adjuvant Therapy for Pancreatic Cancer.*

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Treatment</th>
<th>Survival</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>43</td>
<td>Observation</td>
<td>10% at 2 yr</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td>20% at 2 yr</td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td>218</td>
<td>Observation</td>
<td>26% at 2 yr</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil plus radiotherapy</td>
<td>34% at 2 yr</td>
<td></td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>289</td>
<td>Observation</td>
<td>16.9 mo (median)†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoradiotherapy</td>
<td>13.9 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluorouracil</td>
<td>21.6 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoradiotherapy plus fluorouracil</td>
<td>19.9 mo</td>
<td></td>
</tr>
<tr>
<td>CONKO-01</td>
<td>368</td>
<td>Observation</td>
<td>10.4% at 5 yr</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>20.7% at 5 yr</td>
<td></td>
</tr>
<tr>
<td>ESPAC 3</td>
<td>1088</td>
<td>Fluorouracil</td>
<td>23.0 mo (median)†</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>23.6 mo</td>
<td></td>
</tr>
<tr>
<td>RTOG 9704</td>
<td>451</td>
<td>Fluorouracil plus radiotherapy</td>
<td>22% at 5 yr</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine plus radiotherapy</td>
<td>18% at 5 yr</td>
<td></td>
</tr>
<tr>
<td>JASPAC-01</td>
<td>378</td>
<td>S-1 (oral fluoropyrimidine)</td>
<td>70% at 2 yr</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gemcitabine</td>
<td>53% at 2 yr</td>
<td></td>
</tr>
</tbody>
</table>

- Role of adjuvant therapy in pancreatic cancer
- Definitive role after potentially curative surgery but role of radiotherapy is controversial
Treatment of Pancreatic Cancer

- Role of neoadjuvant therapy in pancreatic cancer
  - Very selected patients who presented with borderline resectable tumours – may be able to undergo neoadjuvant chemoradiotherapy to downstage the tumour
  - If good response, can consider resection of the tumour at later time
  - Post-chemoRT $R_0$ resection rate: 70.7% vs 59.7% ($p<0.0001$) with survival 20.5 months vs 9.5 months -- resectable

Only 15 to 20% of patients present at resectable stage.

70% of pancreatic cancer occurs at the head/uncinate process region.

Remaining 20% to 30% occurs at the body and tail.

Prognosis of tumour at the body and tail tends to be poorer as often presents with metastatic disease/advanced stage.

Prognosis

Figure 1.2: Ten year relative survival (%), adults (15-99 years), selected cancers, England and Wales: survival trends for selected cancers 1971-2007

- Testis
- Melanoma
- Hodgkin’s lymphoma
- Breast (females)
- Uterus
- Prostate
- Cervix
- Larynx (males)
- Colon
- Bladder
- All cancers
- Kidney
- Ovary
- Leukaemia
- Myeloma
- Stomach
- Oesophagus
- Brain
- Lung
- Pancreas

Period of diagnosis

(1) 1971-1991 Cohort analysis - actual survival
(2) 2007 Hybrid analysis - predicted survival
Prognosis

Pancreatic Cancer Survival Rates

% 5 Year Survival Time Periods

Note: Adjusted rates. Moffitt survival rates are higher for all stages of pancreatic cancer.
Source: Cancer Registry Data and Florida Data, Internal Analysis prepared by Corporate Business Development – Corporate Planning
## Prognosis

### Table 1. AJCC Staging for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Primary Tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ (also includes PanIN III classification)
- T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

**Regional Lymph Nodes (N)**

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

**Distant Metastasis (M)**

- M0: No distant metastasis
- M1: Distant metastasis

*From AJCC, 7th Edition.*

### Table 2. AJCC Stage, 6th Edition Correlates With Survival in Patients With Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>All Patients</th>
<th>Nonresected</th>
<th>Resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>10.0</td>
<td>6.8</td>
<td>24.1</td>
</tr>
<tr>
<td>IB</td>
<td>9.1</td>
<td>6.1</td>
<td>20.6</td>
</tr>
<tr>
<td>IIA</td>
<td>8.1</td>
<td>6.2</td>
<td>15.4</td>
</tr>
<tr>
<td>IIB</td>
<td>9.7</td>
<td>6.7</td>
<td>12.7</td>
</tr>
<tr>
<td>III</td>
<td>7.7</td>
<td>7.2</td>
<td>10.6</td>
</tr>
<tr>
<td>IV</td>
<td>2.5</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Total</td>
<td>4.4</td>
<td>3.5</td>
<td>12.6</td>
</tr>
</tbody>
</table>

*Adapted from Bilimoria et al. Cancer, 2007.*
Conclusion

• Surgery is the only treatment modality that can help achieve better long term outcome
• Only 10 to 20% of patients with pancreatic adenocarcinoma present at resectable state
• Early detection is key to better outcome
• Seek medical attention early if develops suspicious symptoms
The End

Thank You for Your Attention

Alfred_kow@nuhs.edu.sg