Early diagnosis of Pancreatic cancer

Understanding Pancreatic Cancer: from diagnosis to treatment
George Eliot Hospital NHS Trust
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Consultant HPB Surgeon
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Objectives

• Early diagnosis.. Why?
• Pancreas anatomy
• Epidemiology
• Risk factors
• Screening
• Presentation
• Investigations
• Future trends
Why early diagnosis?

![Graph showing survival rates by stage.](image)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A</td>
<td>681</td>
<td>492</td>
<td>314</td>
<td>210</td>
<td>135</td>
<td>61</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>1548</td>
<td>1044</td>
<td>588</td>
<td>358</td>
<td>227</td>
<td>99</td>
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<tr>
<td>Stage 2A</td>
<td>581</td>
<td>350</td>
<td>179</td>
<td>105</td>
<td>75</td>
<td>36</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>3591</td>
<td>2110</td>
<td>992</td>
<td>518</td>
<td>300</td>
<td>135</td>
</tr>
<tr>
<td>Stage 3</td>
<td>2068</td>
<td>1049</td>
<td>421</td>
<td>196</td>
<td>87</td>
<td>40</td>
</tr>
</tbody>
</table>
# STAGING (TNM)

## TABLE 1: TNM staging of pancreatic tumors

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of a primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ*</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to the pancreas, ≤ 2 cm in diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to the pancreas, &gt; 2 cm in diameter</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node(s) metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node(s) metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis (no pathologic M0; use clinical M to complete stage group)</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis</td>
<td>NO</td>
<td>M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1</td>
<td>NO</td>
<td>M0</td>
</tr>
<tr>
<td>IB</td>
<td>T2</td>
<td>NO</td>
<td>M0</td>
</tr>
<tr>
<td>II A</td>
<td>T3</td>
<td>NO</td>
<td>M0</td>
</tr>
<tr>
<td>II B</td>
<td>T1–3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>T4</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

* This also includes the “PanINIII” classification

Anatomy
Pancreatic (solid) tumours

Pathology

Ductal adenocarcinoma accounts for about 85% of all neoplasms. And more than 95% of all pancreatic cancers arise from the exocrine (digestive enzymes) elements.

Cancers that arise from the endocrine cells (neuroendocrine, islet cells) account for 5% or less.
Pancreatic (cystic) tumours
Epidemiology (1)

- In the UK approximately 10000 patients are diagnosed with pancreatic carcinoma every year and almost all will die of the disease (<5% survival)

- It is a disease of Western/industrialised countries – 4th leading cause of cancer-related deaths in US although only 10th commonest

Change in pancreatic cancer incidence rates since the early 1990s, UK
Epidemiology (2)

Trends in Incidence and Survival

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New Cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number per 100,000 Persons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-Year Relative Survival

- 1975: 3.0%
- 1980: 3.3%
- 1985: 3.2%
- 1990: 3.7%
- 1994: 4.7%
- 1998: 3.8%
- 2002: 6.2%
- 2006: 7.3%
Risk factors (1)

- 10 -15% of PC attributable to genetic causes
- 5 -10% of patients with PC have a family history of PC

Hereditary risk factors – High risk individuals

1. Genetic predisposition syndromes associated with PC

2. Familial pancreatic cancer (FPC)

“Family with a pair of affected first-degree relatives (parent-child or sibling pair) who do not meet criteria for a known PC-associated genetic predisposition syndrome”
### Inherited cancer syndromes associated with increased risk of pancreatic cancer

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s)</th>
<th>Lifetime risk of pancreatic cancer, percent</th>
<th>Locus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast/ovarian cancer</td>
<td>BRCA2, BRCA1</td>
<td>3 to 5</td>
<td>13q</td>
</tr>
<tr>
<td></td>
<td>PALB2</td>
<td>Unknown</td>
<td>16p</td>
</tr>
<tr>
<td>Familial atypical multiple mole melanoma syndrome</td>
<td>CDKN2A</td>
<td>10 to 19</td>
<td>9p</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK 11</td>
<td>11 to 36</td>
<td>19p</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>Unknown</td>
<td>5q</td>
</tr>
<tr>
<td>Hereditary nonpolyposis colon cancer (Lynch II)</td>
<td>DNA mismatch repair genes</td>
<td>4</td>
<td>2p, 3p, 7p</td>
</tr>
<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1, SPINK1</td>
<td>25 to 40</td>
<td>7q, 5q</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>Unknown</td>
<td>11q</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome</td>
<td>P53</td>
<td>Unknown</td>
<td>17p</td>
</tr>
</tbody>
</table>

FPC

• Susceptibility gene that is carried by approximately 7 in every 1000 individuals

• The risk of PC for a member of a FPC family is 9 times higher than for the sporadic pancreatic cancer

• Referral for genetic evaluation

• Screening (optimal strategy unclear – EUS/MRCP; no survival improvement demonstrated yet)
**Risk factors (2)**

**Non-familial risk factors**

- Non-hereditary chronic pancreatitis (cumulative risk 4% at 20 years)

- **New onset diabetes mellitus** and insulin resistance (RR 2)

- (ABO – increased susceptibility for non-O groups)
Risk factors (3)

- Pre-malignant cystic lesions (IPMNs – MCNs)
- Cigarette smoking (RR 2.5)
- Obesity and physical inactivity (BMI>30 RR 1.8)
- (Diet – coffee consumption – NSAIDs)
There is no available screening for pancreatic cancer in people who are at average risk!

Challenges to early detection of PC
1. Occurs in small % of population
2. Traditional imaging not an effective tool
3. No validated biomarkers
Pancreatic cancer (C25): 2012-2013
Percentage of Cases by Route to Diagnosis, Adults Aged 15-99, England

Source: cruk.org/cancerstats
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Cancer Research UK, full URL of the page, Accessed [month] [year].
Pancreatic Cancer (C25): 2014
Proportion of Cases Diagnosed at Each Stage, All Ages

Source: cruk.org/cancerstats

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Cancer Research UK, full URL of the page, Accessed [month] [year].
Presentation - symptoms

Most common symptoms: pain, jaundice and weight loss

- Asthenia – 86 percent
- Weight loss – 85 percent
- Anorexia – 83 percent
- Abdominal pain – 79 percent
- Epigastric pain – 71 percent
- Dark urine – 59 percent
- Jaundice – 56 percent
- Nausea – 51 percent
- Back pain – 49 percent
- Diarrhoea – 44 percent
- Vomiting – 33 percent
- Steatorrhea – 25 percent
- Thrombophlebitis (Trousseau’s syndrome – 3 percent)
Presentation - signs

- Jaundice – 55 percent
- Hepatomegaly – 39 percent
- Right upper quadrant mass – 15 percent
- Cachexia – 13 percent
- Courvoisier's sign (non-tender but palpable distended gallbladder at the right costal margin) – 13 percent
- Epigastric mass – 9 percent
- Ascites – 5 percent
Tumors in the head of the pancreas are more likely to have jaundice

PPV of jaundice in over 60s is 22%
Tumors in the **body or tail** are more likely to present with pain or weight loss.
Diagnostic tests

- Blood tests – LFTs
- CA 19.9
- USS
- CT abdomen and pelvis “pancreatic protocol”
- +/- EUS + FNA
- +/- Liver MRI (liver mets)
- +/- PET-CT (selectively used at present)
- Chest CT (staging)
- Laparoscopy +/- biopsy (staging)
CA 19.9

- Guidelines recommend **against** the use of CA 19-9 as a screening test for pancreatic cancer

- Limited sensitivity for small cancers and poor PPV even in symptomatic patients

- CA 19.9 requires the presence of Lewis blood group antigen (absent in up to 10% of population)

- Raised in benign diseases and jaundiced patients
Conditions associated with increased serum levels of the tumor marker CA 19-9

<table>
<thead>
<tr>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic exocrine and neuroendocrine cancers</td>
</tr>
<tr>
<td>Biliary cancer (gallbladder, cholangiocarcinoma, ampullary cancers)</td>
</tr>
<tr>
<td>Hepatocellular cancer</td>
</tr>
<tr>
<td>Gastric, ovarian, colorectal cancer (less often)</td>
</tr>
<tr>
<td>Lung, breast, uterine cancer (rare)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cholangitis</td>
</tr>
<tr>
<td>Cirrhosis and other cholestatic diseases (including gallstones)</td>
</tr>
</tbody>
</table>

USS

- High sensitivity for bile duct dilatation
- Level of obstruction

- Pancreatic tumours > 3 cm: 95% sensitivity
- Operator-dependent
CT (1)

- Triple phase helical multidetector row
- 100% sensitivity for tumours > 2 cm
- Ill-defined hypoattenuating mass
- Smaller lesions can be iso-attenuating
- Pancreatic duct cut-off
CT (2)

“Double duct sign”
CT for staging

- No distant metastases
- No arterial or venous involvement
- Attachment to other organs (e.g., spleen)
- Venous involvement (SMV or portal) less than 180 degrees, as long as there is suitable vessel proximal and distal to the areas of involvement for reconstruction
- Gastroduodenal artery encasement up to the common hepatic artery with other short segment encasement or abutment of the hepatic artery, but without extension to celiac trunk
- Tumor abutment of the SMA less than one-half the circumference of the vessel wall.
- Greater than 180 degree encasement or occlusion/thrombus of SMA, unreconstructable SMV or SMV-portal vein confluence occlusion
- Direct involvement of the inferior vena cava, aorta, celiac trunk or hepatic artery, as defined by absence of a fat plane between low density tumor and these structures on CT or EUS.
- Metastases to lymph nodes beyond the peripancreatic tissues
- Distant metastases
• Once pancreatic ca is suspected the next step is staging, not bx
• Fit patient with resectable disease do not require bx
• However, if in doubt: EUS + FNA (dd: chronic pancreatitis, autoimmune pancreatitis

• Unlikely to cause intraperitoneal spread
• Sensitivity: 90% - Specificity: 96%
PET-CT

- Relies upon functional activity to differentiate between malignant and benign processes.
- Utility in diagnosis and staging is controversial.
- Possible benefit is detection of small volume metastases.
- False negatives in hyperglycaemic patients – false positives in pancreatitis/local inflammation caused by stenting.

- PET-PANC – UK multicenter prospective randomised trial might point towards incorporation of PET in staging of pancreatic cancer.
**ERCP**

- **NOT TO BE USED AS DIAGNOSTIC MODALITY**
- Used for decompression of biliary system (+ brushings)
- Sensitivity of brushings for detection of cancer is 50% (in comparison EUS + FNA is 92%)
- Has a mortality of 0.2-0.3% with risks of bowel perforation (0.5%), bleeding (2%), pancreatitis (3%)
- Decompression is not always necessary before surgery
Early detection of PC – future trends

- 5-years survival rate for stage 0 is 85% (JPCR)
- TS1a as “early pancreatic cancer” (up to 10 mm PC)

Genetic progression model (Hruban et al.)

- Normal epithelium
- Carcinoma in situ
- Invasive carcinoma
- Metastasis

11.7 y \(\rightarrow\) 6.8 y \(\rightarrow\) 2.7 y

Stage O (PCIS) \(\rightarrow\) Stage I or II \(\rightarrow\) Stage III or IV

(2-3 y)

Chance to diagnose at early stage
Early detection of PC – future trends

DEF Screening Model for Sporadic Pancreatic Cancer

General Population

First Sieve

DEFINE: at risk population

Second Sieve

ENRICH: at risk cohort

FIND: “early” lesion

Localyze “Early” Lesion

High Risk Group

Phenotype, Serologic Biomarker, Non-Invasive Imaging
Summary of image and pathological findings of PCIS.

MPD, main pancreatic duct; PanIN, pancreatic intraductal neoplasm; PCIS, pancreatic cancer in situ
Conclusions

- Awareness on pancreatic cancer
- Look out for red flag symptoms and risk factors
- Low threshold for CT scan
- In doubt refer/ask advice to tertiary pancreatic center