Early Diagnosis

Steve Pereira

Professor of Hepatology & Gastroenterology
Institute for Liver & Digestive Health, UCL

stephen.pereira@ucl.ac.uk
@PereiraGroup
Biomarkers for early diagnosis

Overview

• Identifying symptoms earlier
• Screening high-risk groups
• Emerging diagnostics
• The practicalities
Windows of opportunity for diagnosis of pancreatic cancer

A mutation occurs

Symptoms

Diabetes?

Referral to a specialist

A visit to the family doctor

Surgery and cure

This is where we’d like to detect the disease

Secondary Screening

Education

Incurable disease
Identifying symptoms earlier

• Existing cancer referral pathways are not very effective
  ▪ ~90% do not yield a cancer diagnosis
  ▪ 1/3 cancers diagnosed through this route

• Symptoms and signs are often too late

• 50% cancers present without recognised alarm symptoms
Information Technology for GPs

- Cancer Decision support tools – risk factors + symptoms

Welcome to the QCancer®-2016 risk calculator for women: http://qcancer.org/female

Your risk of having one of the following cancers, as yet undiagnosed is:

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cancer</td>
<td></td>
<td>99.05%</td>
</tr>
<tr>
<td>Any cancer</td>
<td></td>
<td>10.95%</td>
</tr>
<tr>
<td>pancreatic</td>
<td></td>
<td>3.79%</td>
</tr>
<tr>
<td>ovarian</td>
<td></td>
<td>2.12%</td>
</tr>
<tr>
<td>other</td>
<td></td>
<td>1.67%</td>
</tr>
<tr>
<td>colorectal</td>
<td></td>
<td>1.12%</td>
</tr>
<tr>
<td>gastro-esophageal</td>
<td></td>
<td>1%</td>
</tr>
<tr>
<td>breast</td>
<td></td>
<td>0.46%</td>
</tr>
<tr>
<td>renal tract</td>
<td></td>
<td>0.27%</td>
</tr>
<tr>
<td>lung</td>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>blood</td>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td>uterine</td>
<td></td>
<td>0.099%</td>
</tr>
<tr>
<td>cervical</td>
<td></td>
<td>0.03%</td>
</tr>
</tbody>
</table>

You have a 10.95% risk of having a cancer as yet undiagnosed, and correspondingly, a 99.05% chance that you are clear.

In other words, in a crowd of 100 people with the same risk factors as you, 11 are likely to have a cancer as yet undiagnosed and 89 will not, as shown by the chart below.
• Anonymised data on > 8 million patients: 3,400 cases of PDAC (matched 6:1 with controls)
• 93% had relevant symptoms in the 2 years prior to diagnosis
• Patients attended their GP with relevant symptoms on average 3 (0-19) times
Identifying risk factors and symptoms for pancreatic cancer

• UCL Farr institute (HDR UK)
  – CPRD data from participating NHS GP surgeries (15M)
  – Data from
    • Primary care
    • Hospital Episode Statistics
    • ONS death registration data
    • Cancer registry

• QResearch (40M)

• CanTest Collaborative
Biomarkers for early diagnosis

Overview

• Identifying symptoms earlier
• **Screening high-risk groups**
• Emerging diagnostics
• The practicalities
Who should undergo surveillance?

‘High-risk’ cohorts: patients without symptoms

- **Pancreatic cancer families** *(currently CT/MR, EUS)*
  - at least two relatives with pancreatic cancer
  - associated cancer syndromes with a case of pancreatic cancer

- **Cystic tumours of the pancreas** *(currently MRI, EUS)*
  ~1-13% of the population, increased pancreatic cancer risk

- **Pancreatic cancer-associated diabetes mellitus**
354 High risk individuals for familial PDAC
EUS/MRI and/or CT annual follow-up
16 year program. Median follow-up 5.6 years.
Primary endpoint: cumulative incidence of PDAC, PANIN3, IPMN with HGD.

After initial screening:
- 7% cumulative incidence of high risk pancreatic lesions (24/354)
- 3 yr survival of HRI with PDAC > other PDAC pts (57% vs. 8.9%)
- Annual rate of malignant progression 1.6%
Identification of a Three-Biomarker Panel in Urine for Early Detection of Pancreatic Adenocarcinoma


August 2015

REG1A, TFF1 and LYVE1

Multicentre validation:
Healthy vs PDAC Stage I/II

Urine test to detect pancreatic cancer before symptoms of the killer disease show could boost survival rates to 60%, researcher predicts

- Pancreatic cancer is known as the ‘silent killer’: because survival rates are low
- The test detected the disease with 90 per cent accuracy in studies
- A clarity would mean a ‘breath of relief’ that is desperately needed

Normal  Hyperplasia  Dysplasia  Carcinoma in situ  Invasion  Metastasis

12 ± 3 years  7 ± 3 years  3 ± 1 years

‘window of opportunity’
Detection and localization of surgically resectable cancers with a multi-analyte blood test

1,005 cancer patients (93 PDAC)
- No distant metastasis (20% Stage I, 49% Stage II, 31% Stage III)
812 healthy controls

Tumor Detection
- ctDNA
- 8 Protein Markers
  - CA-125
  - CEA
  - CA19-9
  - PRL
  - HGF
  - OPN
  - MPO
  - TIMP-1
Biomarkers for early diagnosis

Overview

• Identifying symptoms earlier
• Surveillance of ‘high-risk’ groups
• Emerging diagnostics
• The practicalities
Population screening for PDAC is not feasible

- Screening for PDAC in average risk persons will fail due to low cancer prevalence
- Use of an “almost perfect test” with a 99% sensitivity and a 99% specificity for PDAC

Incidence of PDAC >50 yrs:
37/100 000 [SEER, 2018]

99% sensitivity
36 positives

99% specificity
1000 false positive
99,000 negative

Hart & Chari *Clin Gastro Hep* 2018 Sep 27.
New biomarker trials to detect upper gastrointestinal cancers earlier

17 Aug 2017

UCLH Cancer Collaborative has launched two new biomarker trials with the aim of developing simple and affordable tests that can detect upper gastrointestinal cancers earlier to improve survival.

The trials are for cancer of the pancreas – a large gland behind the stomach and next to the small intestine, and cancer of the oesophagus – the tube that connects the throat to the stomach.
Recruitment Process

- Patients with history of familial pancreatic cancer.
- Patients with vague abdominal symptoms
- Patients with cystic tumours in surveillance.

Screening

Recruitment in outpatient clinics (Gastro, HPB, MDC clinics)
Recruitment in endoscopy (in-patients).

Informed consent

Sample/data collection

Q-cancer questionnaire
Urine samples
Blood samples

Sample processing

Sample storage (-80 °C)
Accelerating diagnosis of pancreatic cancer: a 360° approach

IMPROVING BIOMARKERS FOR DIAGNOSIS

GP TOOLS TO IDENTIFY PEOPLE AT RISK

BARRIERS AND ECONOMICS FOR ADOPTION

REAL-TIME TESTING IN PEOPLE BEFORE DIAGNOSIS
NCRI Screening, Prevention & Early Diagnosis (SPED) Workshop

Call for proposal ideas for studies in Screening, Prevention or Early Diagnosis

Current National Pancreatic Cancer Clinical Research SPED Studies Portolio: stephen.pereira@ucl.ac.uk (deadline 14 Oct 2019)

• **EUROPAC**: The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer
• **ADEPTS**: Accelerated Diagnosis of neuroEndocrine and Pancreatic TumourS
• **UroPanc**: Urinary bioamarker panel for early detection of Pancreatic cancer
• **UK-EDI**: UK Early Detection Initiative for Pancreatic Cancer

Please note the deadline for the submission of proposals is **Monday 14th October at 5pm.**
To develop a test that will select a sub-population of new-onset diabetes individuals (which contains those with pancreatic cancer)
Accelarating diagnosis of pancreatic cancer

A Biomarker test panel added to ‘standard’ diagnostic pathway – for validation against CT result
B Validated biomarker test incorporated into ‘new’ diagnostic pathway
Accelerating early diagnosis research

2020 -

• Big data on risk factors and symptoms - decision support tools
• PCUK Early Diagnosis Research Alliance
• National sample collection
  - early stage pancreatic cancers
  - non-specific but concerning symptoms
  - familial PDAC, cystic tumours, T2DM, PSC
• Looking for new centres!

Blood, urine
Lab NIH SOPs