Screening in familial pancreatic cancer

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Disclosure

No conflicts related to the presentation

Otherwise: AstraZeneca, Baxalta, Celgene, Ipsen, Merck Serono, Novartis, Pfizer, Roche, Sanofi
Early (current imaging stage) detection

Curability

Molecular alterations

PanIN

IPMN

MCN

LAPC

Resectable cancer

Tumor mass

Metastatic

Symptoms

Histological lesions

Imaging detection

n cells

> 10 y (?)

5-10 y (?)

1-2 y

1 y

death

Early (current imaging stage) detection
Familial pancreatic cancer (PC)

• Genetic susceptibility in 5% of PC

• We know precancerous lesions (Pan-IN, IPMN), found in families at risk

• Early resection can cure $\geq 80\%$ of patients with malignant but non invasive IPMN

• Two forms (genetic syndrome, aggregation)

Pan-IN: pancreatic intraepithelial neoplasia
IPMN: Intraductal Papillary Mucinous Tumour
Population at risk for (familial) PC

Familial aggregation
(gene(s) ?)

Genetic syndrome

BRCA 2
Familial melanoma
(CDKN2A/p16))
Peutz-Jeghers
(STK11/LKB1)
Hereditary Pancreaticis
(PRSS1)

(Theoretical) risk of pancreatic cancer ≥ 5-10%
Screening of relatives to be envisaged

+ 1 case of Pancreatic cancer In the family
Screening of pancreatic cancer: Who?

- **Not general population** screening, as for familial colon and breast cancer

- **Selected patients**: 
  
  ≥ 3 relatives affected (1\(^{st}\), 2\(^{d}\) or 3\(^{st}\) degree)
  
  - ≥ 2 relatives affected (1\(^{st}\) degree)
  
  - BRCA1-2 or CDKN2A (p16) and a 1\(^{st}\) or 2\(^{d}\) degree relative with PC
  
  - Hereditary pancreatitis
  
  - Peutz-Jeghers syndrome

Canto M, Gut 2012 (CAPS meeting)
# Imaging techniques for screening in high risk patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantage</th>
<th>Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT scan</td>
<td>parenchyma</td>
<td>cumulative radiation</td>
</tr>
<tr>
<td>MRI</td>
<td>ductal system / diffusion</td>
<td>availability</td>
</tr>
<tr>
<td>PET 18FDG</td>
<td>malignant component</td>
<td>low sensivity for early degenerescence</td>
</tr>
<tr>
<td>EUS +/- FNA</td>
<td>high accuracy</td>
<td>invasive <em>(general anesthesia, FNA)</em></td>
</tr>
</tbody>
</table>

Khashab Pancreas 2013
High risk patients eligible for screening
Yes, but ensure:

- Willingness to follow long screening, multiple exams
- Willingness to undergo EUS with possible FNA when indicated
- Willingness to undergo surgery if abnormality on screening

Exclusion:
- Medical/surgical contraindications to undergo EUS
- Previous surgery precluding EUS (i.e., Billroth or Roux-en-Y anastomosis)
- Pregnancy
- Short life-expectancy

Klapman J & Malafa M, Cancer Control 2008
Aim of screening? What is a successful screening?

D1 Find and treat a resectable cancer is an aim

D2 PanINs: potential value to detect and treat

D3 IPMN: potential value to detect and treat

D4 PanIN-3 multifocal: success of screening

D5 Detection and treatment high grade IPMN: success

D6 Detection and treatment of cancer T1N0M0: success

D8 Detection and treatment cancer >T1N0M0 and RO: success
Result of screening in high risk patients: Literature

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Type of high risk</th>
<th>Screening modalities</th>
<th>Relevant lesions</th>
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<td>Brentall 1999</td>
<td>14</td>
<td>FPC</td>
<td>CT+MRI+EUS</td>
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Adapted from Poruk, Ann Surg 2014
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Various methods used, various rates of « abnormalities » at screening (1%-50%)
Definition of « relevant » lesion: not homogeneous


Adapted from Poruk, Ann Surg 2014
High risk patients: Result of screening in the literature

Summary of Current Screening Efforts for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Institution</th>
<th>Year</th>
<th>High-Risk Subjects Screened</th>
<th>Premalignant Lesions Identified</th>
<th>Malignant Lesions Identified</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentnall et al.</td>
<td>University of Washington, Seattle</td>
<td>1999</td>
<td>14</td>
<td>7</td>
<td>0</td>
<td>108</td>
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<tr>
<td>Canto et al.</td>
<td>Johns Hopkins University, Baltimore</td>
<td>2004</td>
<td>38</td>
<td>5</td>
<td>1</td>
<td>110</td>
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<tr>
<td>Canto et al.*</td>
<td>Johns Hopkins University, Baltimore</td>
<td>2006</td>
<td>78</td>
<td>6</td>
<td>1</td>
<td>109</td>
</tr>
<tr>
<td>Poley et al.</td>
<td>Erasmus University, Rotterdam</td>
<td>2009</td>
<td>44</td>
<td>7</td>
<td>3</td>
<td>115</td>
</tr>
<tr>
<td>Langer et al.</td>
<td>Phillips University, Marburg</td>
<td>2009</td>
<td>76</td>
<td>4</td>
<td>0</td>
<td>113</td>
</tr>
<tr>
<td>Vema et al.</td>
<td>Columbia University, New York</td>
<td>2010</td>
<td>51</td>
<td>4</td>
<td>2</td>
<td>116</td>
</tr>
<tr>
<td>Ludwig et al.</td>
<td>Memorial Sloan-Kettering, New York</td>
<td>2011</td>
<td>109</td>
<td>7</td>
<td>1</td>
<td>114</td>
</tr>
<tr>
<td>TOTALS</td>
<td></td>
<td></td>
<td>410</td>
<td>36</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* Also identified 1 IPMN out of 138 normal controls evaluated
Results of screening

- 230 high-risk patients participating in prospective cohort
- Predictable that relevant lesions arise in the coming years
  - Estimated age for cancer: 65 y
  - Median age inclusion: 52 y
  - Estimated time to develop cancer: 10-15 y
  - Over 10% risk in the cohort
- In 106 patients:
  - Development and resection of premalignant lesion: n=1
  - Progression of abnormalities: n=10
  - New lesions in screening interval: n=4

Bruno M, communication ESMO 2015
Results of screening

Retrospective assessment of systematic screening in high-risk relatives 2000-2011

3 tertiary centers
- Philipps University, Marburg, Germany
- Ramon y Cajal University Hospital, Madrid, Spanien
- Leiden University, Holland: germline mutation CDKN2A gene
• **3 European centers** (Marburg, Madrid, Leiden)

Non syndromic Familial Pancreatic Cancer (FPC) (2 cases: n=134; 3 cases: n=80)

or CDKN2A

• **Systematic screening since 2002** (Marbourg) / 2010 (Madrid)

• **Median age** : 42.8 y (27-81), **median duration of follow-up**: 2.8 y

• **EUS and MRI** (EUS/3 years only when normal MRI since 2011 in Germany)

• **Overall** : 618 MRI and 402 EUS performed
Results of screening (non syndromic FPC)

Tumour diagnosed in 3 cases / 214 = **1.4 %** of the population studied

**Pancreatic adenocarcinoma** pT3N1 (9N+/22) / 53 year-old woman
Diagnosis 26 months after MRI screening (lack of compliance)
Total pancreatectomy, metastatic course, death 38 months after surgery

Cystic lesion evolutive (7 mm then 10 mm) / 47 year-old woman
« malignant cells » on EUS fine-needle aspiration material
Left pancreatectomy + splenectomy
**Serous cystadenoma with « atypical changes » but no cancer »**

Neuroendocrine tumour grade 2, size 5 mm, tail / 48 year-old woman
Diagnosis : EUS fine-needle aspiration
Left pancreatectomy
Results of screening (non syndromic FPC)

• Cystic lesions: 112/214 patients (52%)
• Pancreatic Surgery: 13 patients
  Left pancreatectomy (n=7); Whipple (n=1); total pancreatectomy (n=5)
• Lesions at risk: 4/13 (1.9% population screened)
  - PanIN3 (n=3)
  - IPMN high grade dysplasia (n=1)
Other:
  - PanIN2 multifocal + branch duct IPMN low grade dysplasia (n=4)
  - PanIN1 (n=2)
  - Serous cystadenoma (n=3)
Results of screening: Beaujon’s experience

Population: 258 relatives at risk from 152 families

BRCA2  n=28 (11%) de 14 familles
BRCA 1 n=3 (1.2%)
FAMMM  n=1 (0.4%)
PRSS1  n=3 (1.2%)
SPINK1  n=3 (1.2%)
Lynch  n=5 (2%)

Criteria insufficient for screening
Non syndromic FPC
 Syndromic FPC
Results of screening: Beaujon’s experience

Dépistage :

95 patients screened

- n = 84 pursuit of observation
  - n = 6 operated
  - n = 1 biopsy

- n = 84 without lesions
  - n = 36 without lesions
  - n = 47 lesions identified

- n = 11 operated after screening

- n = 11 with former known lesions

Résultats
Results of screening: Beaujon’s experience

Abnormalities: n = 48 (57%)

- IPMN main pancreatic duct
- IPMN branch ducts
- Cystic lesion < 5 mm
- Lesion evokative of PanIN
- Chronic pancreatitis features
- Neuroendocrine tumour
- Serous cystadenoma
- Mass
Results of screening: Beaujon’s experience

Surgical resection

- 17 patients ➔ 18 % of patients screened
- FPC: n = 14
- Syndromic (BRCA 2): n = 3

Type of surgery:

- Left pancreatectomy: n = 11
- Whipple: n = 2
- Median pancreatectomy: n = 2
- Total pancreatectomy: n = 1
- Enucleation n = 1
Results of screening: Beaujon’s experience

<table>
<thead>
<tr>
<th>Histology</th>
<th>N patients</th>
<th>%</th>
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<tr>
<td><strong>PanIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PanIN 1</td>
<td>14</td>
<td>87</td>
</tr>
<tr>
<td>PanIN 2</td>
<td>10</td>
<td>62</td>
</tr>
<tr>
<td>PanIN 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>IPMN main pancreatic duct</strong></td>
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<td><strong>Cancer</strong></td>
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Rentability = 17%
Detection of small IPMN

Courtesy Dr L. Palazzo
Two concerns:

Diagnosis and degree of dysplasia/malignancy?

Diffuse precancerous condition in the pancreas? (Pan-IN)

43-year old woman, 2 FPC related
Screening: Cystic lesion and EUS-FNA

Pro
Simple, reproducible

Contra
Morbidity (acute pancreatitis)
Poorly informative tissue sample
Low value of cyst fluid analysis in IPMN
Cystic lesion: What resection?

Two options:

Larger pancreatectomy:
- Left
- Median

Enucleation

43-year old woman, 2 FPC related
43-year old woman, 2 FPC related

Cystic lesion: What resection?

Concerns/advantages:

Larger pancreatectomy:
- Left:
  - Fistula: 30-50%
  - Diabetes: 8%-20%
  - Death: 1%-2%
- Median:
  - Fistula: 70%
  - Diabetes: < 5%
  - Death: 1%

More informative for path

Enucleation
- Fistula: 30%-50%
- Diabetes: 0%
- Death: 1%

No parenchyma for path
Mass developed in a cyst
Small mass, likely benign. Histology?
Small mass, likely benign. Histology?
Chronic pancreatitis-like features

Pretty difficult!

1- Can be unspecific (alcohol-tobacco), 10%-30% « false positive »

2- If you propose to biopsy, how to obtain histology?
Chronic pancreatitis-like features

Hereditary pancreatitis: the most at risk for cancer, but very difficult to screen!
Detection of likely malignant mass

59-year old woman… Bilateral breast cancer and IPMN

BRCA2 mutation

Breast cancer(s)

IPMN
Detection of a mass, likely malignant.

Genetic counselling June 2010

- BRCA2 mutation
- Breast cancer
- IPMN
- Pancreatic cancer

Asymptomatic tumour at systematic screening
Mrs D... 52 y– June 2010: mutation BRCA2, sister with IPMN screening
EUS with contrast: suspicion of malignant mass
Locally advanced adenocarcinoma
Neoadjuvant FOLFIRINOX then chemoradiotherapy
January 2011: Pancreaticoduodenectomy + adjuvant gemcitabine
May 2016: still in complete remission
Limits of screening

EUS is an accurate technic

But...

- Need expertise for pancreas examination
- Knowledge of FPC literature
- Which lesions searching for? How interpret them?
- Then, what management propose?
Blood and pancreatic juice?

No valuable serum tumor marker for very early lesion

CA 19.9: Sensitivity and specificity insufficient

Other: Not (yet) robusts
Surveillance can generate anxiety

Mr D… 52 y

Serous cystadenoma
Management ?
Surveillance and anxiety

- Post-test questionnaire in 69 patients
- EUS: not perceived as more burdensome than MRI
- While 1/3 of patients worried about cancer, it was not related to surveillance
- Anxiety and depression levels comparable to general population
- Overall: perception that advantages > disadvantages
Limits and questions about pancreas screening

- Effect of systematic screening on survival: not proven
- Level of cancer risk in syndromic and non syndromic susceptibility? Low precision
- Genetic determinism in non syndromic Familial Pancreatic Cancer forms?
- Natural history of precancerous lesions in relatives at risk?
Limits and questions about pancreas screening

- Difficulties to identify Pan-IN using imaging technics
- Lesions can be multifocal
- Numerous exams in relatives screened, most often normal: availability of EUS/MRI?
- Morbidity of pancreatic surgery
- Psychological impact of screening?
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→ Need to identify serum markers, genetic/epigenetic alterations, proteomic

→ Collaborative studies in high risk patients
Thank you for attention