RISK OF PROGRESSION AMONG LOW RISK IPMNS IN A LARGE MULTICENTER SURVEILLANCE COHORT STUDY

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Significance

- The highest incidence of pancreatic cancer has been in North America and Europe, and is expected to be over 50,000 new cases annually in each

- IPMNs are common incidental findings that carry a risk of malignant transformation:
  - MD-IPMN: up to 70%\(^1\)
  - All BD-IPMN: 6-51%\(^1\)
  - Low risk BD-IPMN (<3 cm, no nodules, asymptomatic): 0-10%\(^2\)

- Conflicting evidence regarding the optimal surveillance of low risk IPMN
  - Some studies demonstrated the safety of a non-operative approach
  - Other studies found high rates of malignancy in patients who underwent resection for “low risk” IPMN, either malignant transformation or distinct PDAC

\(^1\)Tanaka et al. 2012. Pancreatology
\(^2\)Crippa et al. 2016. Digestive and Liver Disease
Side branch IPMN: MRCP Image
Main duct IPMN

Combined main duct and side branch
Combined side branch/main duct

High grade dysplasia
IPMN and other Pancreatic Cysts are Very Common

- Percentage of all (non-pancreatic) MRI with pancreatic cystic lesion
- Mayo Clinic 2005-15
- Increasing prevalence correlated with improved MRI hardware and software

Morris, M, Wallace MB, CGH 2016;14:585
Aims

We aimed to study the natural history of low risk IPMN cysts under surveillance to identify:

■ The incidence of malignant transformation
■ Baseline characteristics predictive of:
  - Progression to malignancy
  - The development of high risk or worrisome features
  - Significant cyst growth
Study design

- Retrospective review of endoscopic and radiologic databases between 2003-2013 to include the following patients:
  - Cyst < 3 cm in largest diameter
  - Main duct ≤ 5 mm in diameter
  - No high risk or worrisome features
  - No suspicion of malignancy on EUS-FNA
  - Surveillance ≥ 12 months

- We evaluated for the following outcomes:
  - Progression by size only (≥ 2 mm or >20% growth over surveillance)
  - Development of worrisome or high risk features
  - Development of high grade dysplasia or malignancy
Our cohort

Adults with pancreatic cysts
2584

Patients with at least 2 imaging studies
1329

Adequate surveillance
784

Patients with IPMN
540

Patients with low risk IPMN
479

Only 1 imaging study
1255

Surveillance less than 12 months
545

Cysts that did not meet IPMN criteria
244

High risk or worrisome features present
61
Our cohort: baseline characteristics

- Total: 479 patients with IPMN diagnosed between 1998-2013
- Male: 40%
- Age, mean: 66 years
- Race: 86% white
- Diabetes: 24%
- Cancer, any other than PDAC: 36%
- Smokers (ever): 45%
- Family history of PDAC: 9.4%
- Length of surveillance: Average: 48 months  Range: 12-157 months
Average cyst growth in progressors stratified by initial cyst size

<table>
<thead>
<tr>
<th>Initial cyst size</th>
<th>Progressors, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 2.9 cm</td>
<td>36 (57%)</td>
</tr>
<tr>
<td>1 - 1.9 cm</td>
<td>102 (47%)</td>
</tr>
<tr>
<td>0 - .9 cm</td>
<td>98 (50%)</td>
</tr>
</tbody>
</table>

* Significant difference
Type of progression stratified by cyst size

- **Indication for Resection, %**
  - 0 - 9 mm: 1.0
  - 10 - 19 mm: 10.6
  - 20 - 29 mm: 31.7

- **Mass or mural nodule, %**
  - 0 - 9 mm: 0.5
  - 10 - 19 mm: 3.7
  - 20 - 29 mm: 1.6

- **Main duct involvement, %**
  - 0 - 9 mm: 0.0
  - 10 - 19 mm: 2.8
  - 20 - 29 mm: 7.9

- **Final size > 3 cm, %**
  - 0 - 9 mm: 0.5
  - 10 - 19 mm: 5.0
  - 20 - 29 mm: 25.4

* p<.05
### Development of new worrisome features or high risk stigmata during surveillance (n=47)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients: Number, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk stigmata</strong></td>
<td></td>
</tr>
<tr>
<td>Suspicious or malignant cytology</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Mass or mural nodule</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Main duct involvement</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>0</td>
</tr>
<tr>
<td><strong>Worrisome features</strong></td>
<td></td>
</tr>
<tr>
<td>Size &gt; 3 cm</td>
<td>23 (49%)</td>
</tr>
<tr>
<td>Abrupt change in duct with distal atrophy</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Thickened cyst walls/septations</td>
<td>14 (30%)</td>
</tr>
<tr>
<td>Recurrent pancreatitis</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>
Baseline characteristics predictive of development of worrisome or high risk features

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Progressors by feature (N=47)</th>
<th>Non-progressors (N=243)</th>
<th>p</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>68 (12)</td>
<td>66 (11)</td>
<td>.107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, ever</td>
<td>25 (57%)</td>
<td>99 (43%)</td>
<td>.102</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes*</td>
<td>17 (36%)</td>
<td>54 (23%)</td>
<td>.049</td>
<td>1.9 (1.3-3.8)</td>
<td>4.4 (1.4-14.3)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>3 (6.4%)</td>
<td>3 (1%)</td>
<td>.057</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer*</td>
<td>7 (37%)</td>
<td>6 (7%)</td>
<td>.001</td>
<td>10.9 (3.3-36)</td>
<td>12.3 (3.1-48.8)</td>
</tr>
<tr>
<td>Family history of PDAC</td>
<td>2 (6%)</td>
<td>21 (9%)</td>
<td>.749</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of chronic pancreatitis</td>
<td>2 (6%)</td>
<td>9 (4%)</td>
<td>.617</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of acute pancreatitis</td>
<td>2 (6%)</td>
<td>18 (8%)</td>
<td>.657</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial cyst size &gt; 2 cm*</td>
<td>19 (40%)</td>
<td>27 (11%)</td>
<td>&lt;.001</td>
<td>5.4 (2.7-11)</td>
<td>3.1 (0.9-11.0)</td>
</tr>
<tr>
<td>Cyst fluid CEA, ng/mL*</td>
<td>1237 (13, 4674)</td>
<td>24 (3.7, 97)</td>
<td>.035</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifocality</td>
<td>19 (51%)</td>
<td>93 (38%)</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Baseline characteristics predictive of cyst growth

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Progressors by size only (N=189)</th>
<th>Non-progressors (N=243)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>67 (11)</td>
<td>66 (11)</td>
<td>.282</td>
</tr>
<tr>
<td>Smoker, ever</td>
<td>80 (44%)</td>
<td>99 (43%)</td>
<td>.875</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41 (22%)</td>
<td>54 (23%)</td>
<td>.916</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>4 (2%)</td>
<td>3 (1%)</td>
<td>.704</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>10 (13%)</td>
<td>6 (7%)</td>
<td>.139</td>
</tr>
<tr>
<td>Family history of PDAC</td>
<td>18 (10%)</td>
<td>21 (9%)</td>
<td>.771</td>
</tr>
<tr>
<td>History of chronic pancreatitis</td>
<td>5 (3%)</td>
<td>9 (4%)</td>
<td>.540</td>
</tr>
<tr>
<td>History of acute pancreatitis</td>
<td>9 (5%)</td>
<td>18 (8%)</td>
<td>.263</td>
</tr>
<tr>
<td>Initial cyst size &gt;2 cm</td>
<td>17 (9%)</td>
<td>27 (11%)</td>
<td>.471</td>
</tr>
<tr>
<td>Cyst fluid CEA, ng/mL</td>
<td>101 (15, 357)</td>
<td>24 (3.7, 97)</td>
<td>.147</td>
</tr>
<tr>
<td>Multifocality</td>
<td>66 (35%)</td>
<td>93 (38%)</td>
<td>.474</td>
</tr>
</tbody>
</table>
Results: Patients meeting resection criteria

- In patients who had an indication for resection (n=45), the majority did not get surgery.

- Those who had surgery were younger at diagnosis (mean 62 vs. 70 years) and had higher cyst fluid CEA (median 4404 vs. 51 ng/mL).

- In patients who did not have surgery, 50% had size > 3 cm as the only indication, compared to 25% of patients who had surgery.
Indications of resection by histological outcome

<table>
<thead>
<tr>
<th>Surgical pathology</th>
<th>n</th>
<th>Mean age, years</th>
<th>Diabetes (%)</th>
<th>Mean surveillance, months</th>
<th>Indications for resection:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Positive cytology</td>
</tr>
<tr>
<td>IPMN Invasive Cancer</td>
<td>1</td>
<td>77</td>
<td>0%</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>IPMN HGD/CIS</td>
<td>3</td>
<td>63</td>
<td>100%</td>
<td>46</td>
<td>1</td>
</tr>
<tr>
<td>IPMN LGD/MCN</td>
<td>8</td>
<td>62</td>
<td>25%</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>1</td>
<td>48</td>
<td>0%</td>
<td>29</td>
<td>1</td>
</tr>
</tbody>
</table>

HGD/CIS, high grade dysplasia/ carcinoma-in-situ; LGD, low grade dysplasia; MCN: mucinous cystic neoplasm
Discussion

- This is the largest retrospective cohort for surveillance of low risk IPMNs
- 236/479 people had progression: 20% developed worrisome or high risk features and 80% only had size increase
- There was a small rate of proven malignant transformation (1.9%) and development of HGD (0.6%) in our surveillance cohort
- In univariate analysis, history of prostate cancer, diabetes, higher cyst fluid CEA and initial cyst size >2 cm were predictors of development of worrisome or high risk features
  - The strongest predictors in multivariate analysis were prostate cancer and diabetes
Limitations

- Retrospective study
- No consensus on the definition of “progression” or “low risk”
- No interval data between initial and final study
- Patients who had surgery before 12 months of surveillance, potentially falsely lowering our rate of malignant transformation in low risk lesions
- Lesions >3 cm who are otherwise “low risk” (some are under surveillance)
- Small sample size of resections / malignancy
Future plans

■ Expanded data set with >800 patients from 3 institutions

■ PACYFIC study – PAncreatic CYst Follow up, an International Collaboration
PACYFIC study
Pancreatic Cyst Follow-up, an International Collaboration

Visit our website to join the study:
www.pacyfic.net
So far: 44 participating centers

**The Netherlands**
- AMC Amsterdam
- UMC Groningen
- UMC Maastricht
- UMC Leiden
- UMC Utrecht
- UMC Radboud, Nijmegen
- OLVG/Lucas Andreas, Amsterdam
- Maasstadziekenhuis, Rotterdam
- Antonius ziekenhuis Nieuwegein
- Martini ziekenhuis, Groningen
- Albert Schweitzer ziekenhuis, Dordrecht
- Catharina ziekenhuis, Eindhoven
- Isala klinieken, Zwolle
- Medisch Spectrum Twente
- Meander Medisch Centrum, Amersfoort
- Gele ziekenhuizen, Apeldoorn
- Haga ziekenhuis, den Haag
- Spaarne Gasthuis, Haarlem
- Rijnstate ziekenhuis, Arnhem
- Canisius-Wilhelmina Ziekenhuis
- Ziekenhuis Amstelland, Amstelveen

**Europe**
- Greifswald University Hospital, Germany
- Heidelberg University hospital, Heidelberg, Germany
- Tampere University Hospital, Finland
- Karolinska University Hospital, Sweden
- Shalgrenska University Hospital, Gotenburg, Sweden
- University Hospital Linkoping, Linkoping, Sweden
- Royal Free Hospital, London, United Kingdom
- Hospital Beaujon, Clichy, France
- Università Cattolica del Sacro Cuore, Rome, Italy
- Ospedale San Raffaele, Milano, Italy
- Ospedale Sant'Andrea, Rome, Italy
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- Università di Bologna, Policlinico S. Orsola-Malpighi, Italy
- U.O. Gastroenterologia AUSL di Imola, Italy
- University Hospital of Santiago de Compostella, Spain
- Hospital Universitario Sanchinarro, Madrid, Spain
- Hospital Universitario de la Princesa, Madrid, Spain
- Araba University Hospital, Vitoria-Gasteiz, Spain
- Pauls Stradins Clinical University Hospital, Riga
- Clinical Center of Serbia, Belgrade, Serbia
- University of Szeged, Szeged, Hungary
Online, interactive data collection

Add Cyst - enter cyst morphology at time of diagnosis

Click on pancreas and slide to select cyst location or select from list

- **Location**: Head
- **Year of diagnosis**: 2016
- **Month**: 1
- **Size**: 25 mm
- **Pattern**: Multilocular

**Multilocular pattern**

- Microcystic
- Macrocystic
- Not possible to determine

- **Cyst wall > 2mm**: No
- **Solid components**: No
- **Calcifications**: No
- **PD Communication**: No

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