Intraductal papillary mucinous tumors (IPMN)

Pascal HAMMEL, MD, PhD

Services de Gastroentérologie-Pancréatologie & Oncology
DHU Unity, Université Paris VII-Denis Diderot
Hôpital Beaujon, AP-HP
92110 Clichy, France
Disclosures

No
Despite several hundred of original papers published concerning natural history and management of IPMN, several unanswered issues

> 1600 papers since 1993 (Pubmed)
These patients and cysts are often asymptomatic and frequently referred to as “incidentalomas” or “VOMIT” (Victims Of Medical Imaging Technology).
Pancreatic Cysts: More Answers, More Questions

« These patients and cysts are often asymptomatic and frequently referred to as “incidentalomas” or “VOMIT” (Victims Of Medical Imaging Technology). Simplistically, these cysts fall into two broad categories: (a) those with no malignant potential (pseudocysts and serous cystadenomas) and (b) those that are pre-cancerous or cancerous (mucinous cystic neoplasms [MCN] and intraductal papillary mucinous neoplasms [IPMN]) »

Wagh M, Am J Gastroenterol 2014(Editorial)
Major questions today

1- Risk factors
2- Optimal rythm of survey of benign forms
3- Imaging technics for survey
4- Natural history of IMPN with worrisome features
5- Surgery : limited resections ?
6- Postoperative survey ?
7- IMPN in high risk patients ?
1- Risk factors for IPMN

- Tobacco, alcohol: no
- Diet, BMI, fatty pancreas: unknown
- Ethnic origin: unknown
- Common risk factors with PDAC?
  - Yes for some but not for all

Table 3. Risk factors for IPMN on univariate and multivariate analyses

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>odds ratio (95% CI);</td>
<td>odds ratio (95% CI);</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td>PDAC 1st degree family history</td>
<td>3.5 (1.41–8.67);</td>
<td>2.94 (1.17–7.39);</td>
</tr>
<tr>
<td></td>
<td>0.007</td>
<td>0.022</td>
</tr>
<tr>
<td>History of chronic pancreatitis</td>
<td>12.0 (1.56–92.2);</td>
<td>10.1 (1.30–78.32);</td>
</tr>
<tr>
<td></td>
<td>0.017</td>
<td>0.027</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>1.92 (1.17–3.14);</td>
<td>1.79 (1.08–2.98);</td>
</tr>
<tr>
<td></td>
<td>0.010</td>
<td>0.025</td>
</tr>
<tr>
<td>Insulin use</td>
<td>4.75 (1.62–13.96);</td>
<td>6.03 (1.74–20.84);</td>
</tr>
<tr>
<td></td>
<td>0.005</td>
<td>0.019</td>
</tr>
</tbody>
</table>

CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm.

Capurso Am J Gastroenterol 2013
GNAS (G-protein α-subunit): activating mutation in McCune-Albright syndrome and 30%-70% of incipient IPMN, but not in PanIN or PDAC without IPMN

Polyostotic fibrous dysplasia, puberta precox and café-au-lait spots in a 62-year old man with IPMN

CT scan of IPMN

Intestinal phenotype
(IHC : MUC1 and MUC2 +ve and MUC5A -ve).

IMPN Intestinal phenotype
Colloid invasive pT3N0M0

Génotyping codon 201 of GNAS using allelic discrimination

Activating heterozygous mutation of GNAS at codon 201(R201H)

Gaujoux S & Cros J, in preparation
2- Optimal rhythm of survey

5-years risk of invasive carcinoma

MPD: 50%

BD: 3-18%

Khannoussi, Pancreatology, 2012
Lévy P, CGH;2006
Tanno S, Gut.2008
Tanno S, Pancreas.2010
Sawai Y, Endoscopy.2010
Maguchi H, Pancreas.2011
2- Optimal rythm of survey

– Should it be individualized?

– If yes, on which criteria?
  • Size
  • Number of cysts
  • Related symptoms
  • Age
  • Duration of follow-up
Consensus, Fukuoka 2012

Are any of the following high-risk stigmata of malignancy present?
- obstructive jaundice in a patient with cystic lesion of the head of the pancreas,
- enhancing solid component within cyst,
- main pancreatic duct ≥10 mm in size

Yes → Consider surgery, if clinically appropriate

No → Are any of the following worrisome features present?

- **Clinical:** Pancreatitis
  - Imaging: i) cyst ≥3 cm, ii) thickened/enhancing cyst walls, iii) main duct size 5-9 mm, iv) non-enhancing mural nodule
  - iv) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy.

If yes, perform endoscopic ultrasound

No → What is the size of largest cyst?

Inconclusive → What is the size of largest cyst?

<1 cm → CT/MRI in 2-3 years

1-2 cm → CT/MRI yearly x 2 years, then lengthen interval if no change

2-3 cm → EUS in 3-6 months, then lengthen interval alternating MRI with EUS as appropriate. Consider surgery in young, fit patients with need for prolonged surveillance

>3 cm → Close surveillance alternating MRI with EUS every 3-6 months. Strongly consider surgery in young, fit patients

Tanaka Pancreatology 2012
Are any of the following high-risk stigmata of malignancy present?

1. Obstructive jaundice in a patient with cystic lesion of the head of the pancreas.
2. Enhancing solid component within cyst.

Yes:

Consistently surve if clinical appropriate

Yes:

Consider surgery in young, fit patients with need for prolonged surveillance.
Consensus, Fukuoka 2012

Are any of the following high-risk stigmata of malignancy present?

i) obstructive jaundice in a patient with cystic lesion of the head of the pancreas, ii) enhancing solid component within cyst, iii) main pancreatic duct ≥10 mm in size

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Clinical: Pancreatitis

Imaging: i) cyst ≥3 cm, ii) thickened/enhancing cyst walls, iii) main duct size 5-9 mm, iv) non-enhancing mural nodule, iv) abrupt change in caliber of pancreatic duct with distal pancreatic atrophy.

Yes

Surgical resection (whenever possible)
**Consensus, Fukuoka 2012**

**Are any of the following high-risk stigmata of malignancy present?**
- obstructive jaundice in a patient with cystic lesion of the head of the pancreas
- enhancing solid component within cyst
- main pancreatic duct \(>10\) mm in size

**Are any of the following worrisome features present?**

**Clinical:** Pancreatitis

**Imaging:**
- cyst \(>3\) cm
- thickened/enhancing cyst walls
- main duct size 5-9 mm
- non-enhancing mural nodule
- abrupt change in caliber of pancreatic duct with distal pancreatic atrophy

< 2 cm

\[0\] \[1\] \[2\] \[3\] \[4\]

\[\text{CT} \enspace \text{MRI} \enspace \text{EUS}\]

**No**
Consensus, Fukuoka 2012

Are any of the following high-risk stigmata of malignancy present?
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< 2 cm

2-3 cm

CT  MRI  EUS
Consensus, Fukuoka 2012

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- cyst >3 cm
- thickened/enhancing cyst walls
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- abrupt change in caliber of pancreatic duct with distal pancreatic atrophy.

Take into consideration:
Age of patient, localization of IPMN, radiation with repeated CT
2- Optimal rythm of survey: yes, but...

- Safety and cost-effectiveness not proven

- Knowledge far from that of colic polyps or HCC

- Balance between:
  - *Longer intervals*
    - ↑ risk of missing cancer
  - *Shorter intervals*
    - ↓ compliance, ↑ morbidity (EUS +/- FNA, CT scan)
2- Optimal rhythm of survey: yes, but...

- Duration of follow-up: what happens beyond 5 years?
2- Duration of surveillance

• Is very long follow-up required?
  
  53 patients with BD-IPMN and survey > 5 y
  - Stable: 72%
  - Increase in size of cysts (without nodule): 15%
  - Appearance of mural nodule: 9%
  - Advanced PDAC in 2 patients, both after 84 months of F/U

BD: branch duct  PC: pancreatic cancer

Khanoussi, Pancreatology 2012
2- Duration of surveillance

• Is very long follow-up follow up required?

  53 patients with BD-IPMN and survey > 5 y
  – Stable: 72%
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  – Advanced PDAC in 2 patients, both after 84 months of F/U

Risk of malignant course persists after 5 years F/U including invasive carcinomas

Imaging survey required beyond this delay in patients who still remain operable

BD: branch duct  PC: pancreatic cancer

Khanoussi, Pancreatology 2012
## 3- Imaging technics for survey

<table>
<thead>
<tr>
<th>Exam</th>
<th>Advantage</th>
<th>Limit</th>
</tr>
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<tbody>
<tr>
<td>CT-scan</td>
<td>parenchyma</td>
<td>irradiation</td>
</tr>
<tr>
<td>MRI</td>
<td>ductal system</td>
<td>availability</td>
</tr>
<tr>
<td>PET 18FDG</td>
<td>malignant component</td>
<td>low sensitivity</td>
</tr>
<tr>
<td>EUS +/- FNA</td>
<td>the best but …</td>
<td>invasive (general anesthesia, FNA)</td>
</tr>
</tbody>
</table>
3- Imaging technics for surveillance

• Cost-effective?

• How many CT-scan, MRI and EUS to save one life?
  – The comparative cost and effectiveness of various approaches for screening and surveillance of individuals needs further evaluation
Follow-up of patients *without* worrisome features (no nodules, thick wall, cyst > 3 cm) is safe:

- 92% patients followed: no need of surgery at 4 years\(^1\)

- No morphological change in 73% of cases at 3 years\(^2\)

1: Maguchi Pancreas 2011  2: Rautou CGH 2008
4- Natural history of IMPN with « worrisome » features?

- Definition: IMPN with nodules, thick wall and/or BD > 3 cm

- Most studies that have established the value of worriesomes are surgical ones
4- Natural history of IMPN with « worrisome » features ?
4- Natural history of IMPN with « worrisome » features?

Nodule with high grade dysplasia

Mucus
4- Natural history of IMPN with « worrisome » features ?

- Natural history not known as most patients have been operated on!

→ Need of studies including patients unfit for (or who refuse) surgery and pooled data
Whipple procedure or left pancreatectomy

- Many non-invasive IPMN are over-treated

- Mortality (1-3 %) and morbidity (pancreatic insufficiency, diabetes)
5- Surgery: parenchyma-sparing resections?

- Limited pancreatectomy or enucleation?
  - Feasibility rate: 89%
  - Postoperative mortality: 1.3%
  - Overall morbidity: 61%
  - Median F/U of 50 months, endocrine/exocrine functions preserved in 92%
  - Low rate of recurrence

6- Postoperative surveillance

• In the literature, benign and malignant IPMN often mixed!

• Only two studies focusing on benign IPMN
6- Postoperative surveillance

- 186 patients operated for benign IPMN
- Median follow up: 46 months
- Recurrence in 40 patients (21%)
  - 31 new cysts
  - 6 re-resection for IPMN
  - 3 PDAC
- Margin dysplasia associated with a 3-fold increased recurrence risk
- No relationship between dysplasia grade and development of PDAC
6- Postoperative surveillance

Overall Population  
\[ n = 125 \]

Group 1  
No residual lesion after surgery  
\[ n = 83 \]

Recurrence  
\[ n = 3 \]  
All recurrences were invasive

Group 2  
Deliberately not resected lesions  
\[ n = 42 \]

Median follow-up: 4 yrs

Indication of total pancreatectomy  
\[ n = 5 \]  
No invasive lesion

Malignant lesion  
\[ n = 0 \]

No new benign lesion  
\[ n = 35 \]

Roux, DDW 2013
6- Postoperative surveillance

Overall Population
n = 125

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No residual lesion after surgery
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Deliberately not resected lesions
n = 42

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Recurrence
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All recurrences were invasive

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n = 5
No invasive lesion

Malignant lesion
n = 0

No new benign lesion
n = 35

Low risk (5% ?) and no predictive factor of recurrence

Roux, DDW 2013
6- Postoperative surveillance

- Known IPMN in the remaining pancreas follow as non-resected IPMNs

- No residual lesions and negative margin follow at 2 and 5 years?

Not evidence-based
6- Postoperative surveillance

- “Distinct” PC development at distance of BD-IPMN : IPMN = marker of risk!

- 0.7-0.9% yearly risk of cancer development
- CT or MRI at 6-month intervals: is it really feasible (compliance…)?
6- Postoperative surveillance

• Low- or moderate-grade dysplasia on resection margin:
  No evidence to modify the frequency and type of surveillance

  History/physical examination and MRI surveillance suggested twice a year

• Not evidence-based!
7- Patients at high risk (genetic) of PDAC

• Pathologically confirmed PanIN-3 lesions in pancreas of high-risk patients who had resections of IPMNs <1 cm

• High-grade dysplasia and main pancreatic duct involvement at resection of BD-IPMNs < 3 cm

• However, insufficient evidence to lower the threshold criteria for surgery in these patients with lesions identified by screening
7- Patients at high risk (genetic) of PDAC

• What happens after surgery depending on pathology?
  → We don’t know!

• Follow-up imaging recommended < 6 months after surgery if any PanIN-3 in the resected pancreas without PDAC

Canto (International Cancer of the Pancreas Screening Consortium summit) Gut 2013
Management of IMPN?

Risk of malignant transformation (prophylactic)

Cancer (if curative intent)

Symptoms

Favour surgery
Patients with IPMN have other risk than PC....

**FIGURE 1.** Cumulative incidences of nonpancreatic cancer–specific and pancreatic cancer–specific mortality in patients with high/moderate (A) and low/no (B) comorbidity.

Kawakubo, Pancreas 2013
Management of IMPN?

- **Cancer (if curative intent)**
  - Symptoms
  - Risk of malignant transformation (prophylactic)
  - Favour surgery

- **Digestive morbidity (functional)**
  - Diabetes, hypoglycemia*
  - Operative mortality
  - Life-expectancy
  - Favour abstention/observation

*When total pancreatectomy
Conclusions

• IMPN : lesion with malignant potential and marker of risk of pancreatic cancer

• Surveillance or surgical decision depend on characteristics of IPMN and… patients

• Modalities of imaging : need further assessment

• Surgery : always evaluate risk/benefit ratio
Thank you for your attention