Intraductal papillary mucinous tumors (IPMN)

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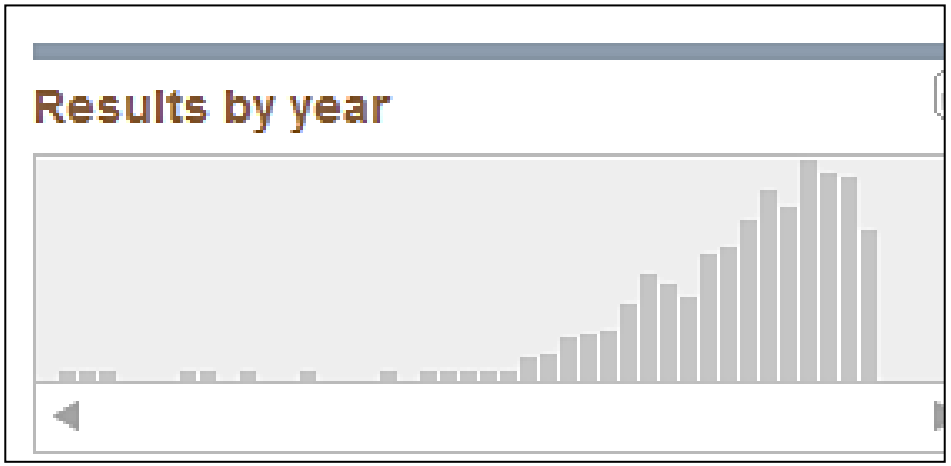
Disclosures

No

- Despite several hundred of original papers published concerning natural history and management of IPMN, several unanswered issues

> 1600 papers since 1993 (Pubmed)



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*).

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

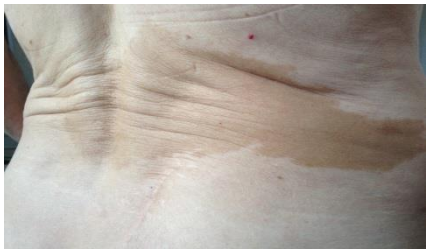
Table 3. Risk factors for IPMN on univariate and multivariate analyses

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

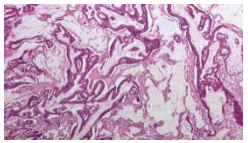
CI, confidence interval; IPMN, intraductal papillary mucinous neoplasm.

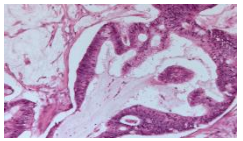
Capurso Am J Gastroenterol 2013

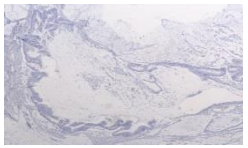
GNAS (G-protein α-subunit): activating mutation in McCune-Albright syndrome and 30%-70% of incipient IPMN, but not in PanIN or PDAC without IPMN

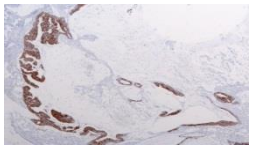


Polyostotic fibrous dysplasia, puberta precox and café-au-lait spots in a 62-year old man with IPMN



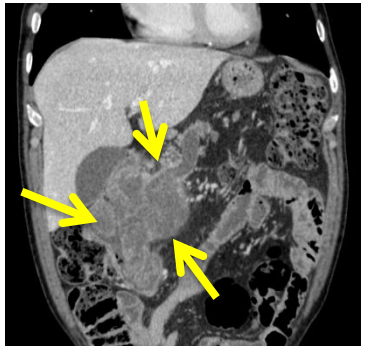






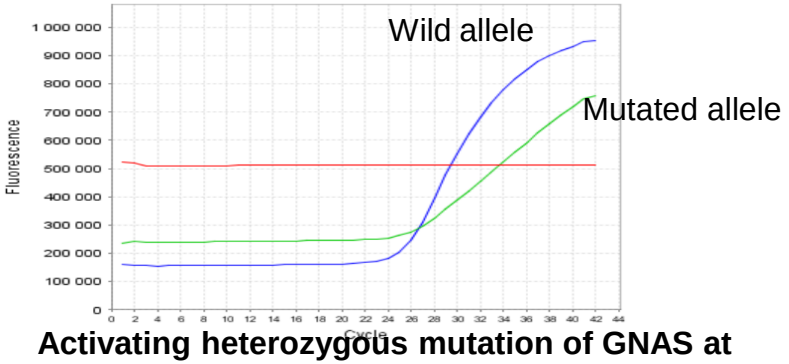
Ac anti-MUC1 Ac anti-MUC2

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



CT scan of IPMN

Génotyping codon 201 of *GNAS* using allelic discrimination



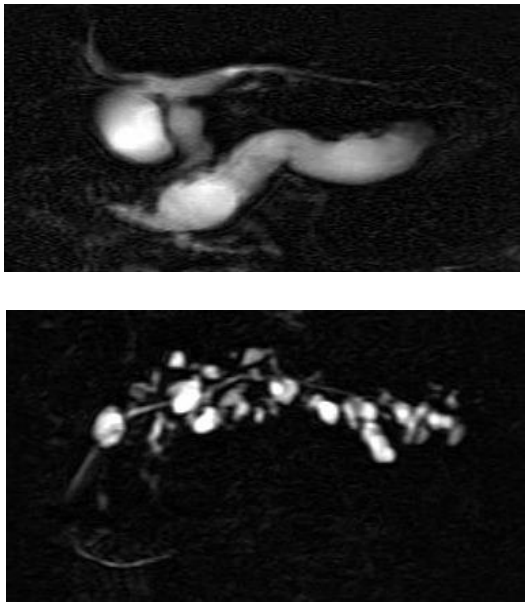
Activating heterozygous mutation of GNAS at codon 201(R201H)

IMPN Intestinal phenotype
Colloid invasive pT3N0M0

Gaujoux S & Cros J, in preparation
Matthaei H, Am J Surg Pathol 2014

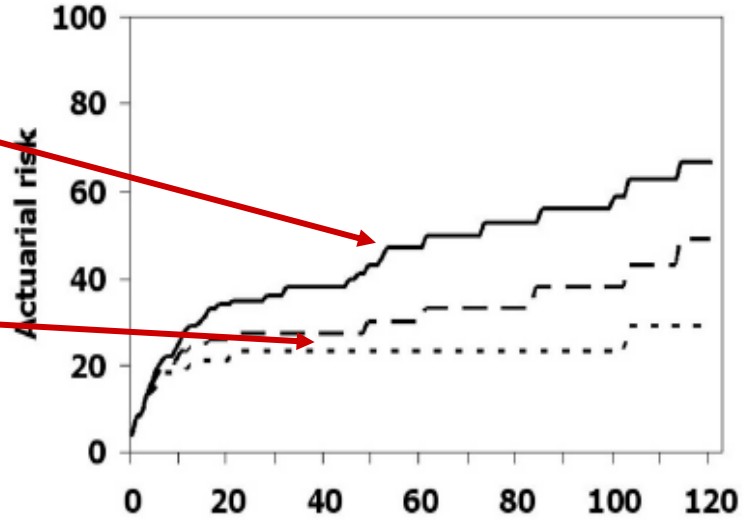
2- Optimal rythm of survey

5-years risk of invasive carcinoma



MPD: 50%

BD: 3-18%



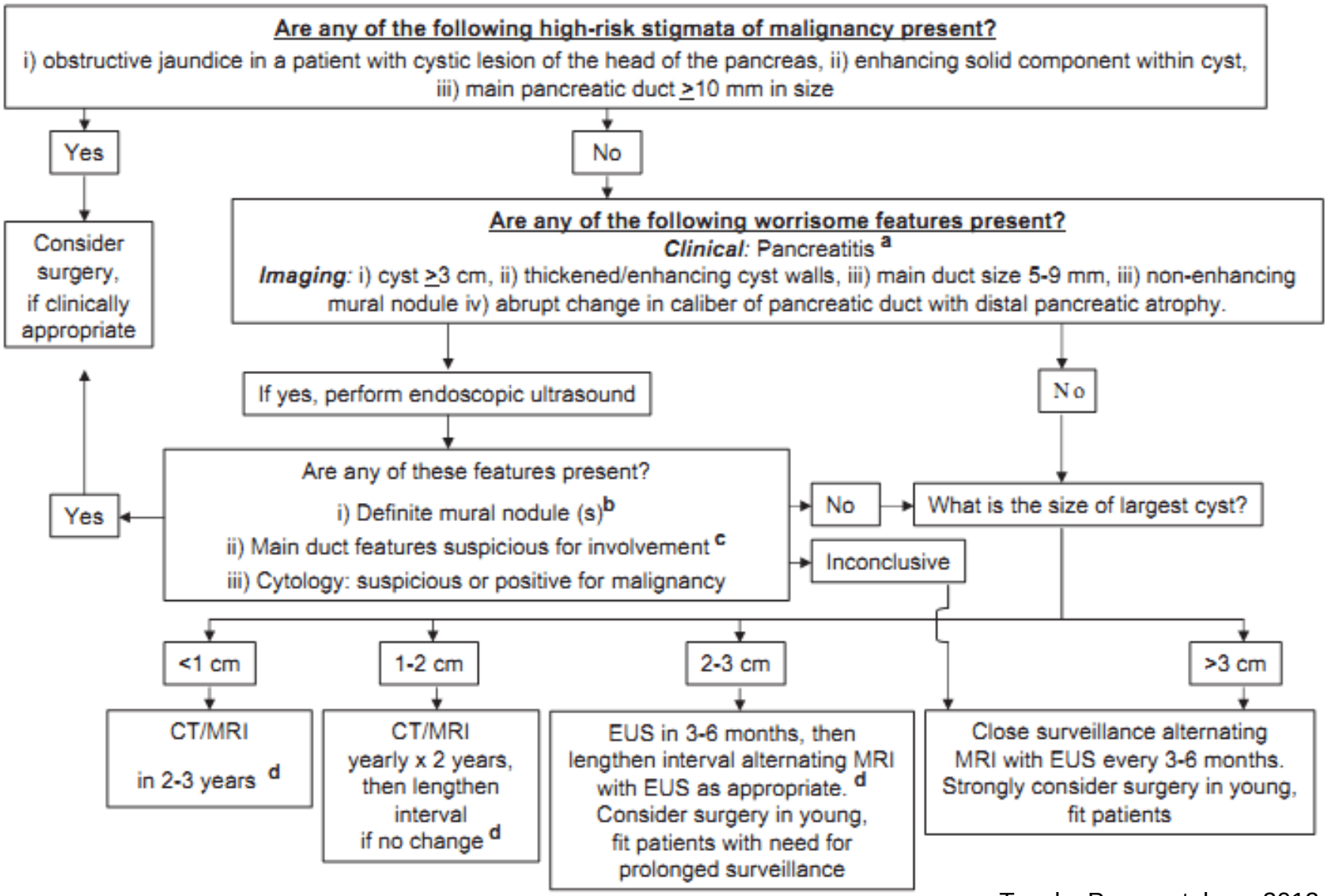
Khannoussi , Pancreatology, 2012
Lévy P, CGH;2006
Tanno S, Gut.2008
Tanno S, Pancreas.2010
Sawai Y, Endoscopy.2010
Maguchi H, Pancreas.2011

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



Tanaka Pancreatology 2012

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

Are any of the following worrisome features present?

Clinical: Pancreatitis [a]

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

Yes

Surgical resection (whenever possible)

Consensus, Fukuoka 2012

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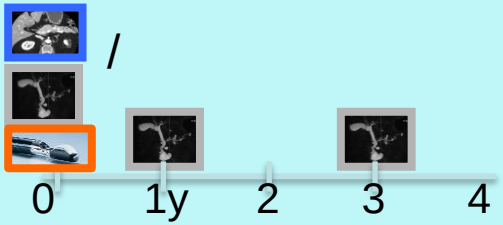
No

< 2 cm



CT MRI EUS

Consensus, Fukuoka 2012

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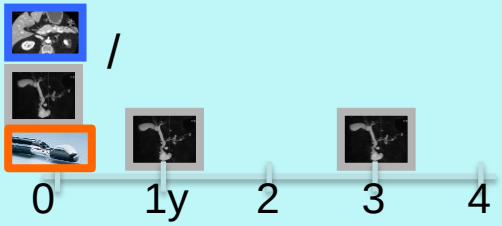
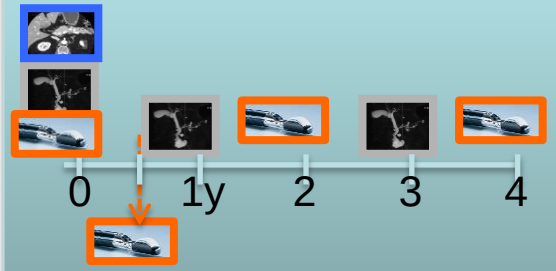


2-3 cm



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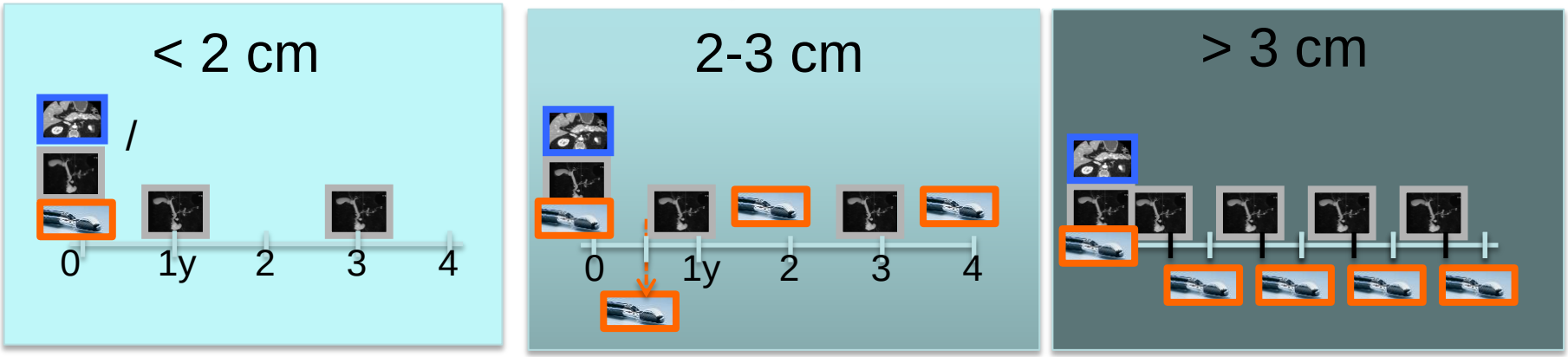
No



Take into consideration :

Age of patient, localization of IPMN, radiation with repeated CT

CT MRI EUS

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*

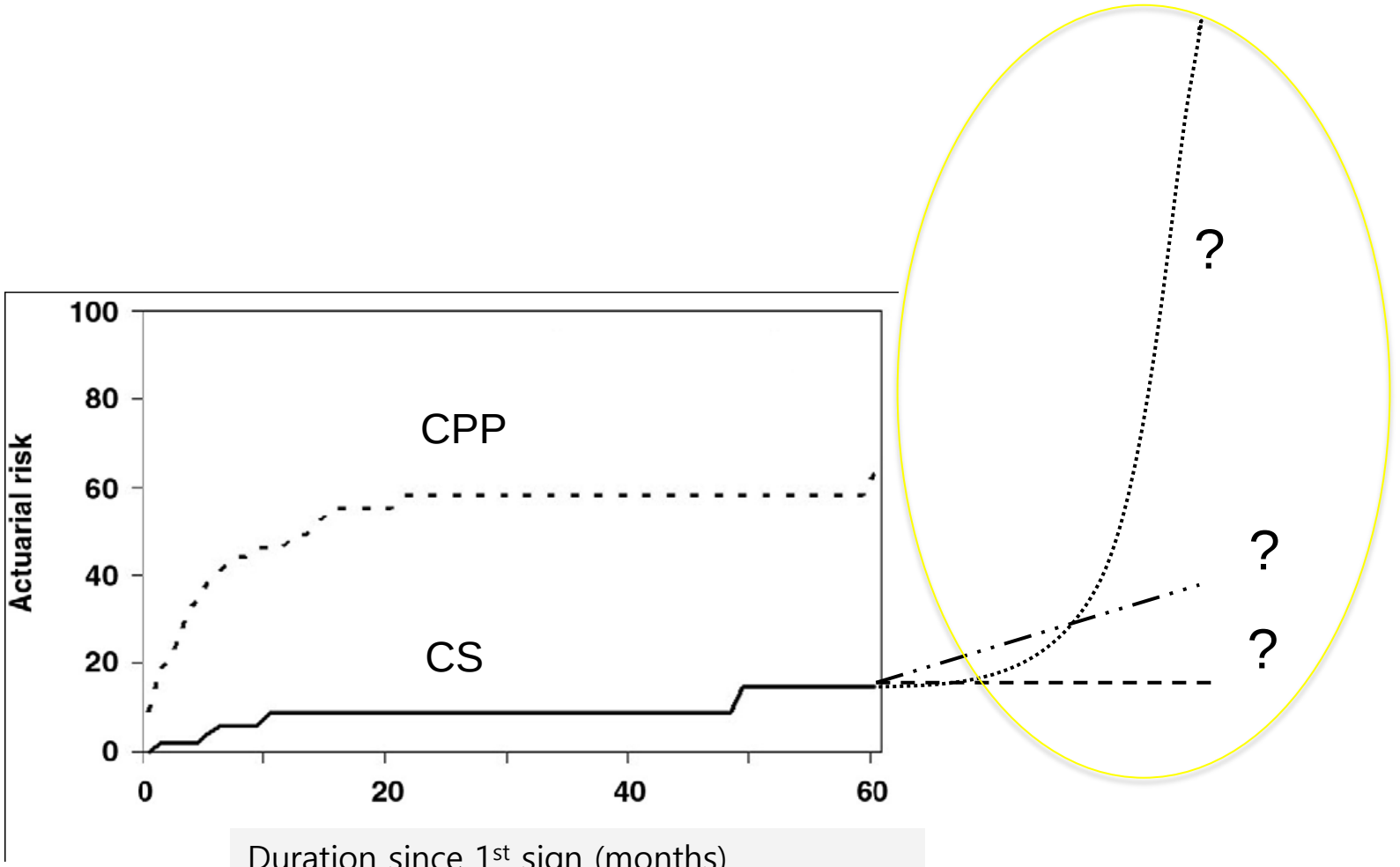
    ⇧ risk of missing cancer

  - *Shorter intervals*

    ⇩ compliance, ⇧ morbidity (EUS +/- FNA, CT scan)

2- Optimal rythm 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

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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

Exam	Advantage	Limit
CT-scan	parenchyma	irradiation
MRI	ductal system	availability
PET 18FDG	malignant component	low sensitivity
EUS +/- FNA	the best but …	invasive (general anesthesia, FNA)

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

Shin, Canto, Gastroenterol Clin North Am 2012

3- Imaging technics for surveillance

- 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]

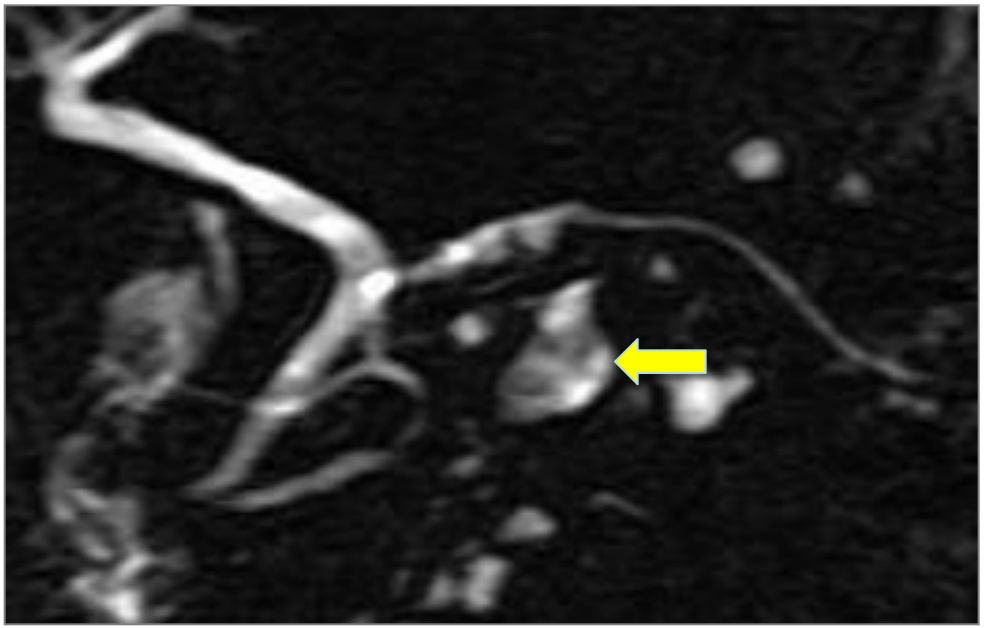
1: Maguchi Pancreas 2011 2: Rautou CGH 2008

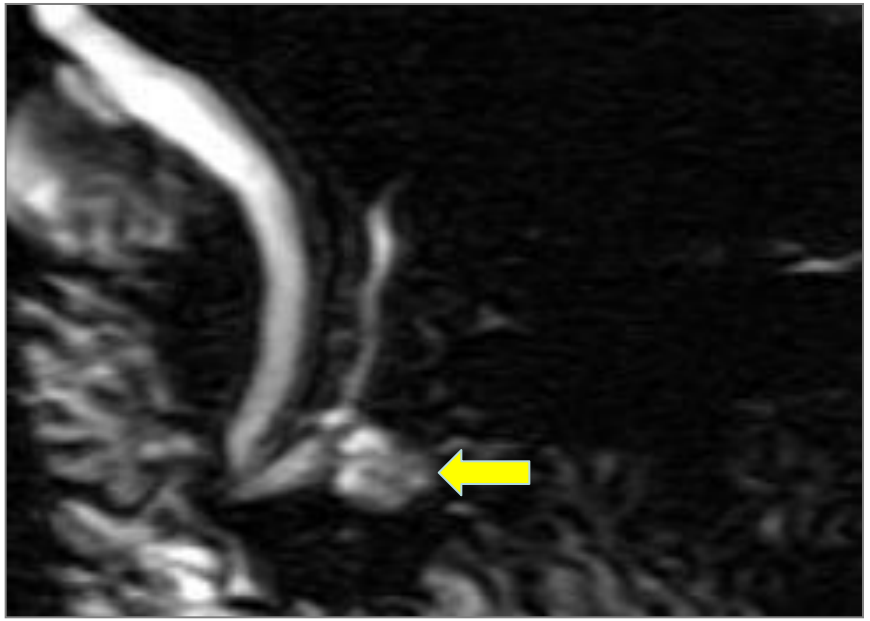
4- Natural history of IMPN with « worrisome » features ?

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

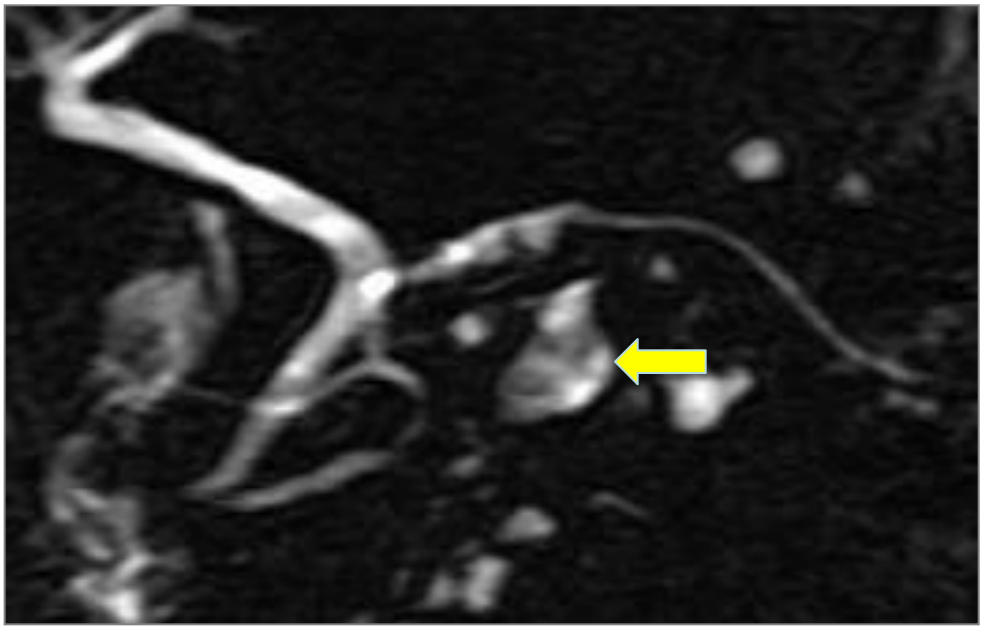
- Most studies that have established the value of worrisomes are surgical ones

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

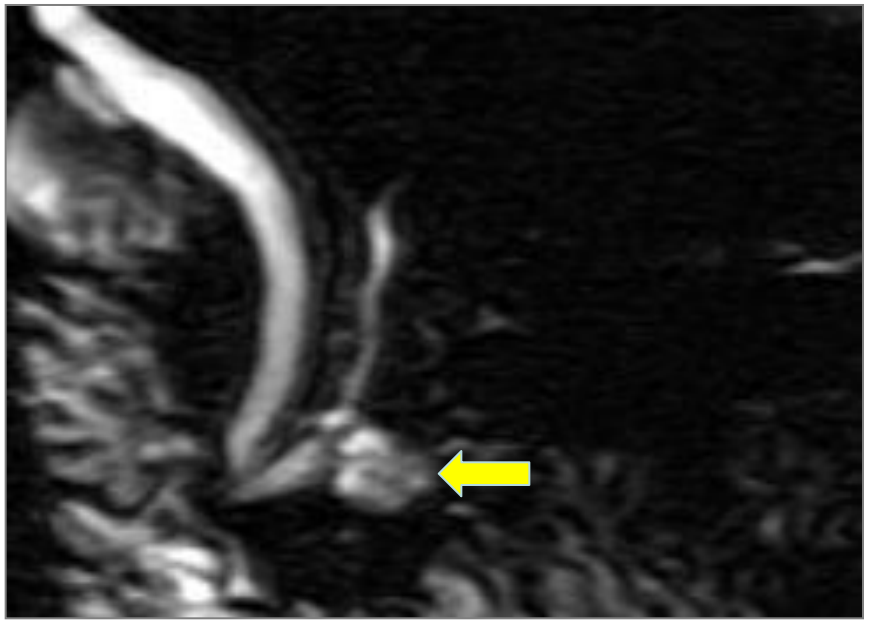




4- Natural history of IMPN with « worrisome » features ?



Nodule with high grade dysplasia



Mucus

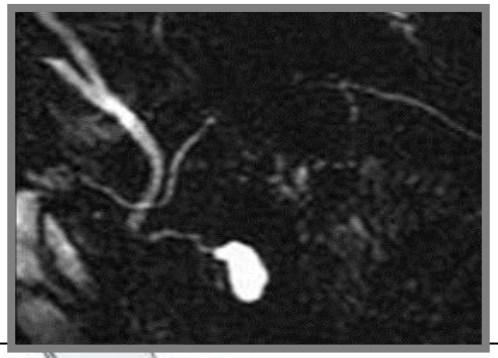
4- Natural history of IMPN with « worrisome » features ?

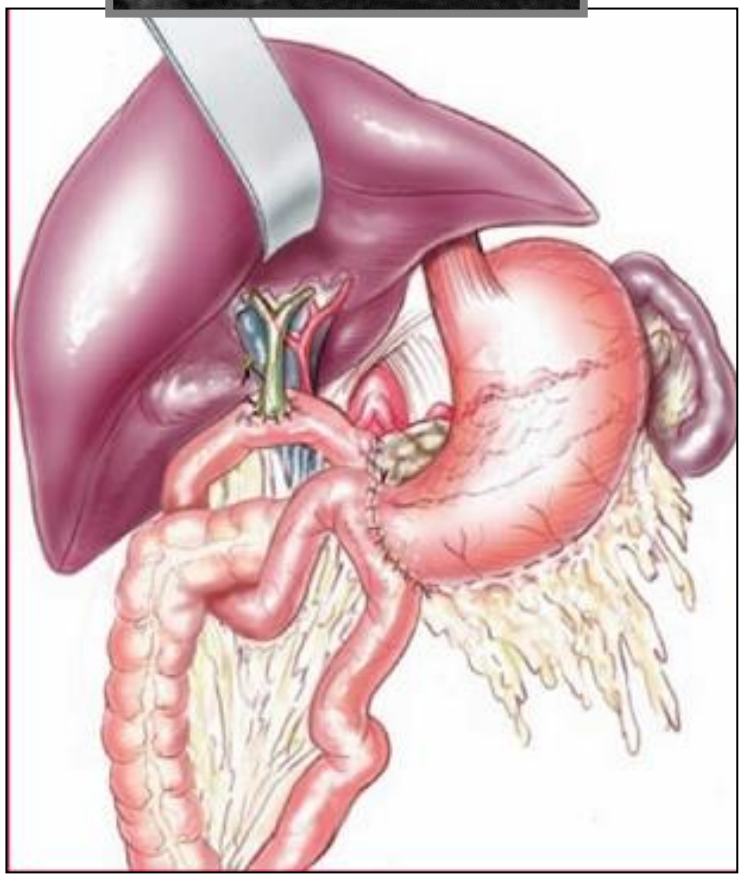
- Natural history not known as most patients have been operated on !

➡ Need of studies including patients unfit for (or who refuse) surgery and pooled data

5- Surgery : parenchyma-sparing resections?

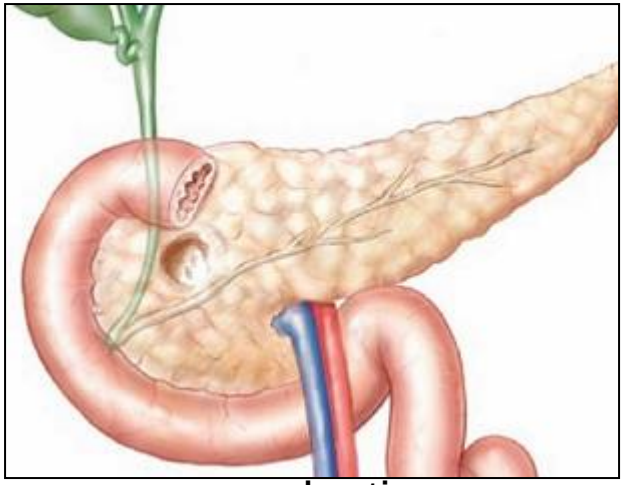
- Whipple procedure or left pancreatectomy
  - Many non-invasive IPMN are over-treated
  - Mortality (1-3 %) and morbidity (pancreatic insufficiency, diabetes)



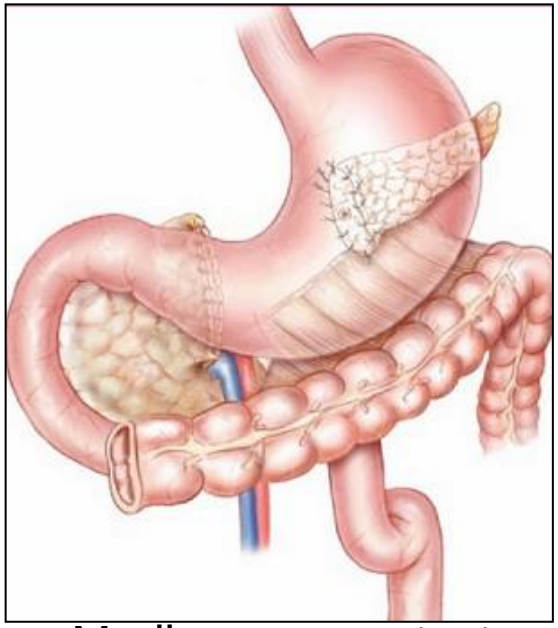


5- Surgery : parenchyma-sparing resections?

- 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



enucleation



Median pancreatectomy

Sauvanet A, Ann Surg 2014

6- Postoperative surveillance

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

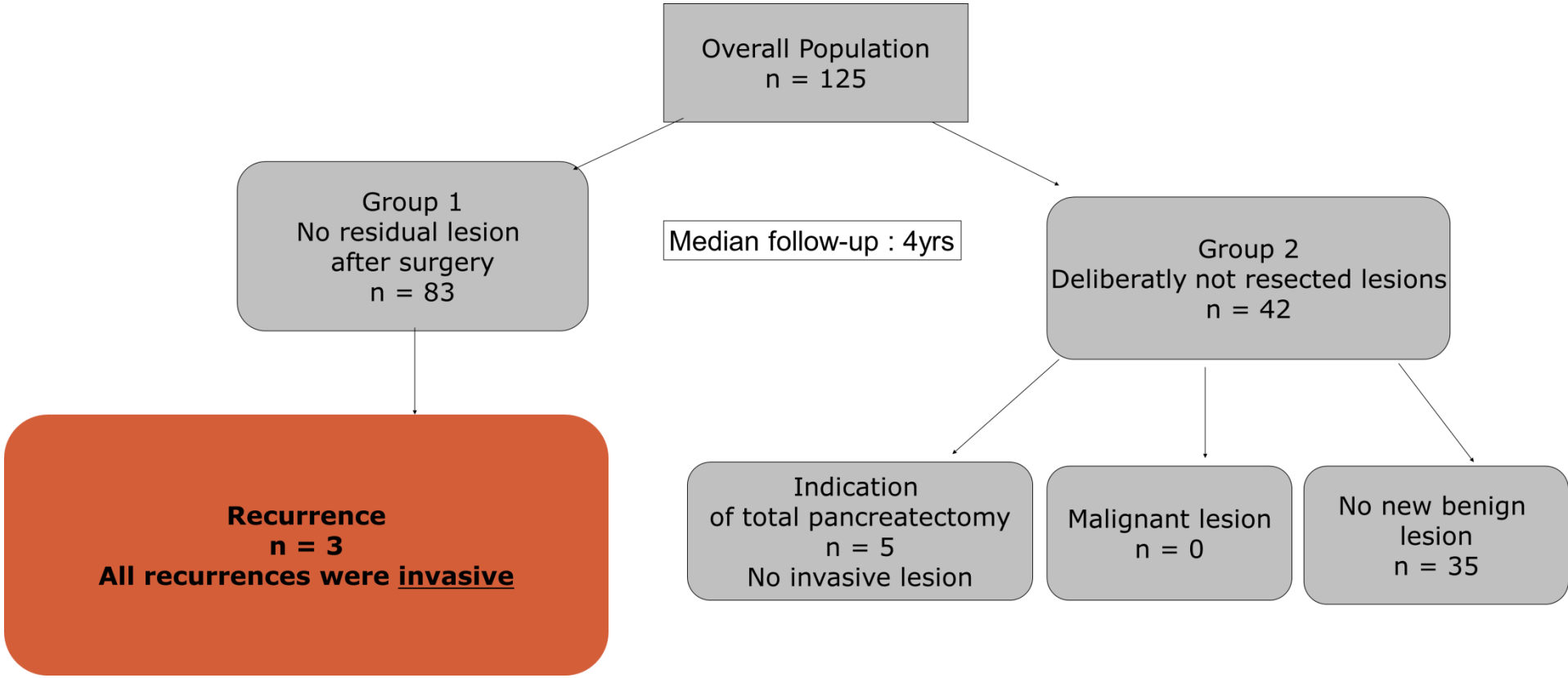
- Only two studies focusing on benign IPMN

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

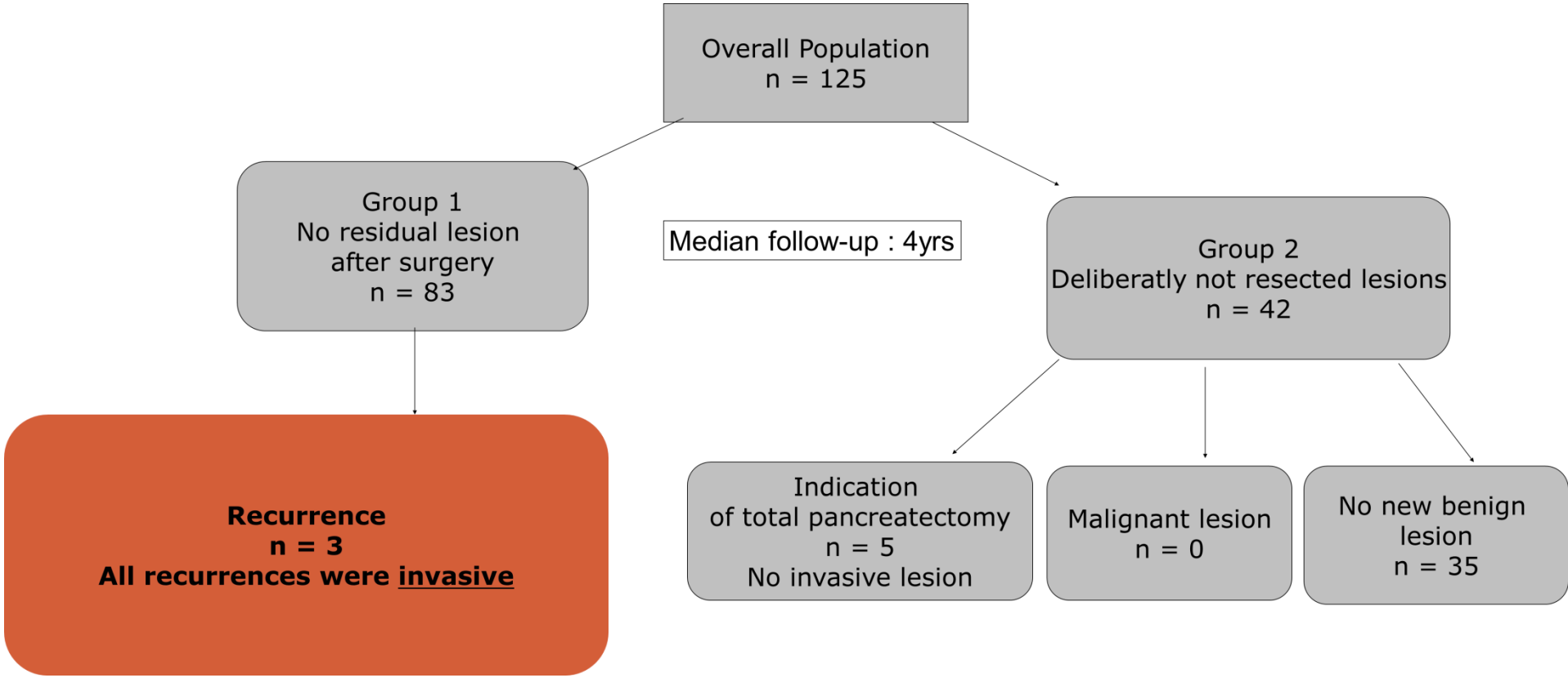
Frankel HPB 2013

6- Postoperative surveillance



Roux, DDW 2013

6- Postoperative surveillance



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

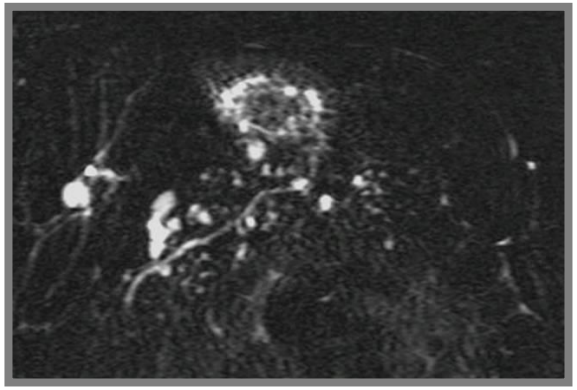
- No residual lesions and negative margin

  ➡ follow at 2 and 5 years ?

Not evidence-based

Tanaka Pancreatology 2012

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 !

Tanaka Pancreatology 2012

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

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

7- Patients at high risk (genetic) of PDAC

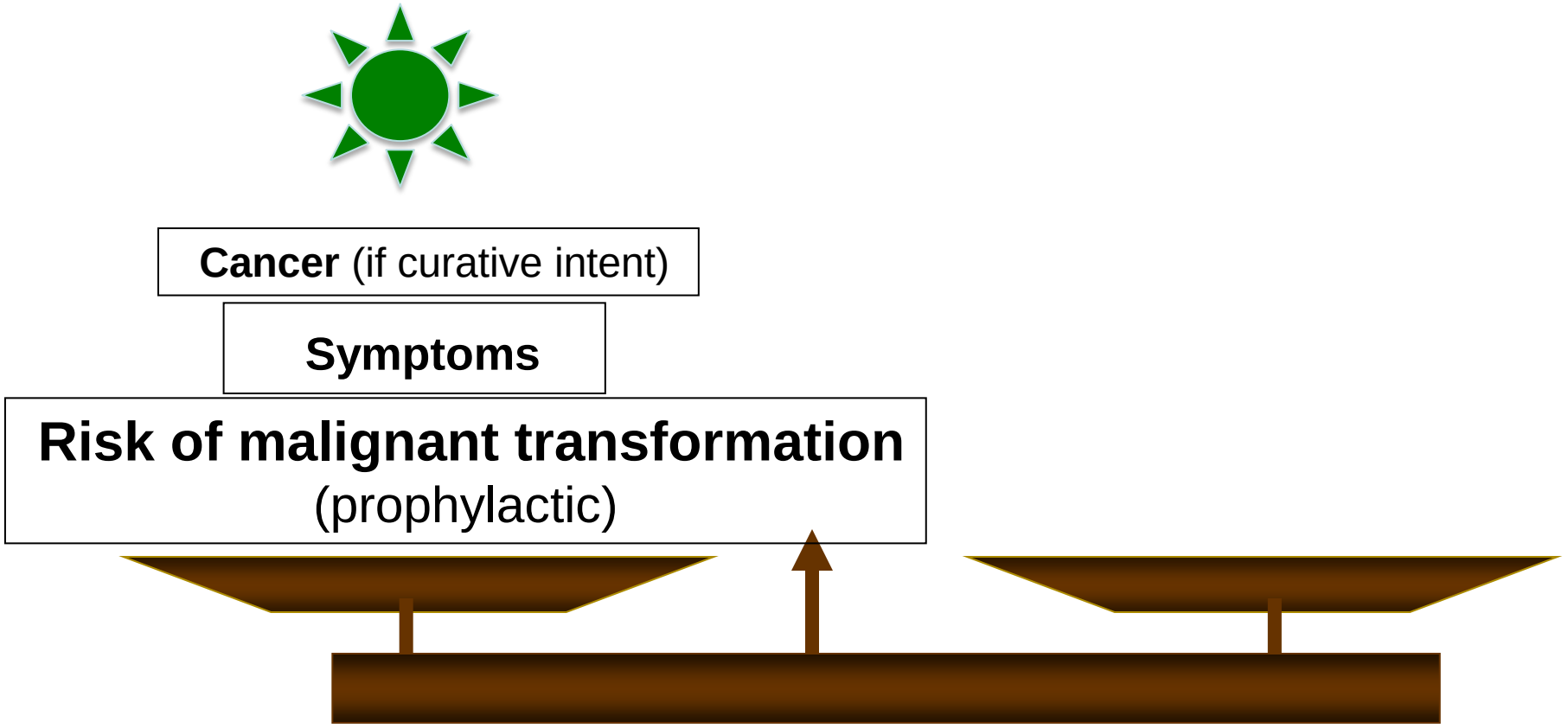
- What happens after surgery depending on pathology ?

  ➡ 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?



Favour surgery

Patients with IPMN have other risk than PC….

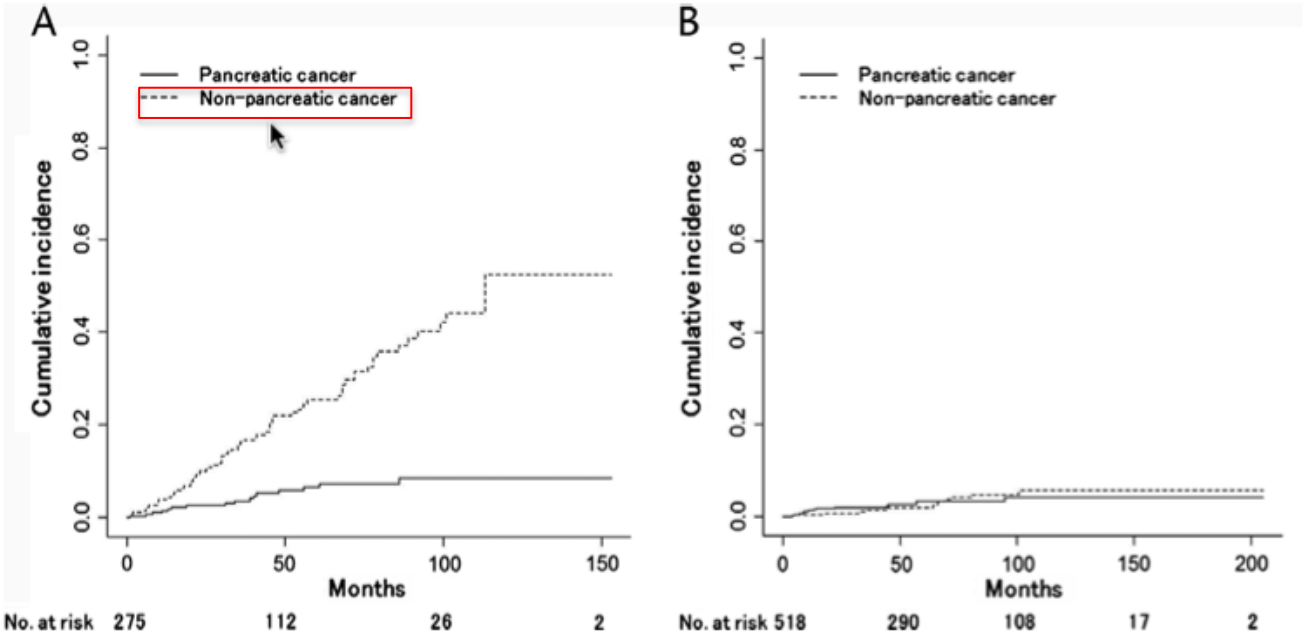
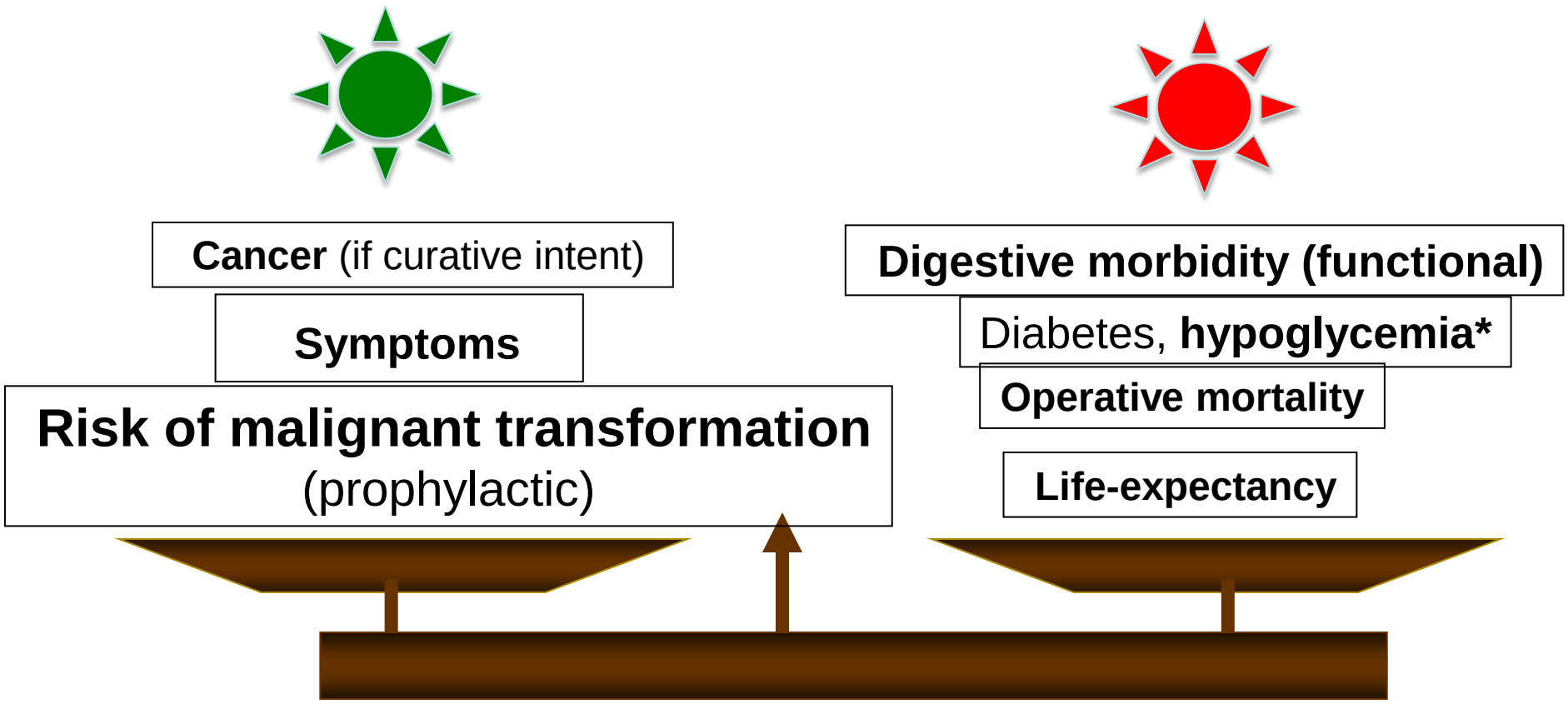


FIGURE 1. Cumulative incidences of nonpancreatic cancer–specific and pancreatic cancer–specific mortality in patients with high/moderate (A) and low/no (B) comorbidity.

Kawakubo, Pancreas 2013

Management of IMPN?



Favour surgery

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