

Screening in familial pancreatic cancer

Pascal Hammel, MD, PhD

Digestive Oncology Unit & Genetic counselling
Hôpital Beaujon, Clichy (AP-HP)
University Paris VII, Denis Diderot

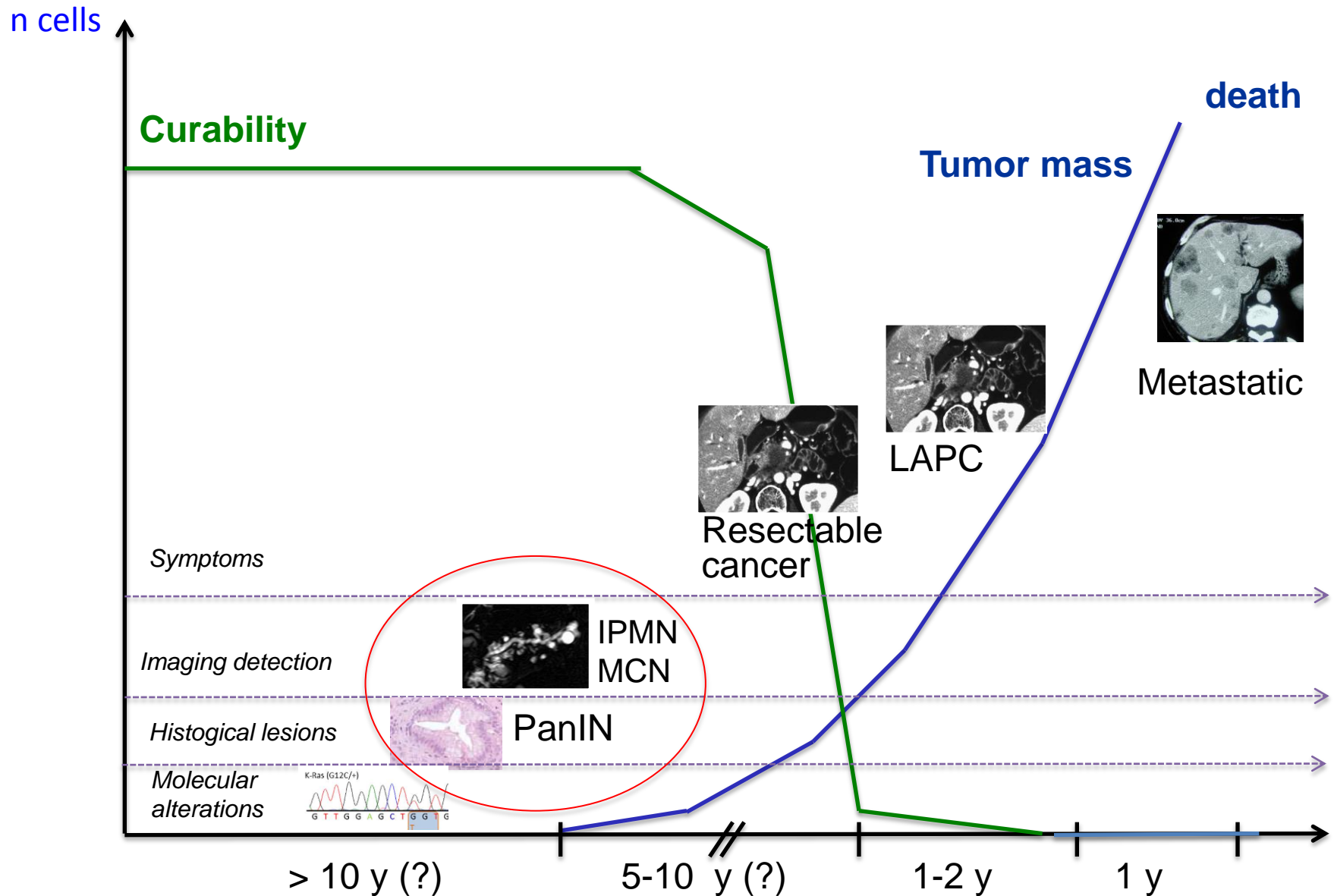


Disclosure

**No conflicts related to the
presentation**

Otherwise : AstraZeneca, Baxalta, Celgene, Ipsen, Merck
Serono, Novartis, Pfizer, Roche, Sanofi

Early (current imaging stage) detection



Familial pancreatic cancer (PC)

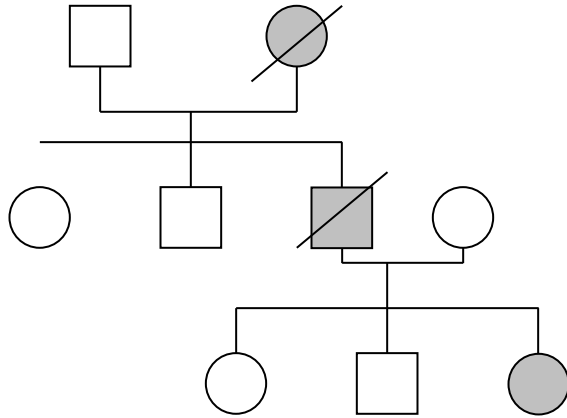
- Genetic susceptibility in **5% of PC**
- We know **precancerous lesions** (Pan-IN, IPMN), found in families at risk
- Early resection can cure \geq **80% of patients with malignant but non invasive IPMN**
- **Two forms** (genetic syndrome, aggregation)

Pan-IN : *pancreatic intraepithelial neoplasia*

IPMN : Intraductal Papillary Mucinous Tumour

Population at risk for (familial) PC

Familial aggregation (gene(s) ?)



Genetic syndrome



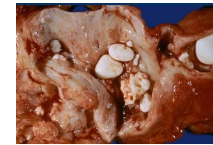
BRCA 2



Peutz-Jeghers
(STK11/LKB1)



Familial melanoma
(CDKN2A/p16)



Hereditary Pancreaticis
(PRSS1)

+ 1 case of
Pancreatic cancer
In the family

(Theoretical) risk of pancreatic cancer $\geq 5-10\%$

Screening of relatives to be envisaged

Screening of pancreatic cancer: Who?

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

. **Selected patients :**

≥ 3 relatives affected (1st, 2^d or 3st degree)

- ≥ 2 relatives affected (1st degree)

- BRCA1-2 or CDKN2A (p16) and a 1st or 2^d degree relative with PC

- Hereditary pancreatitis

- Peutz-Jeghers syndrome

Imaging techniques for screening in high risk patients

Procedure	Advantage	Limit
CT scan	parenchyma	cumulative radiation
MRI	ductal system / diffusion	availability
PET 18FDG	malignant component	low sensitivity for early degeneration
EUS +/- FNA	high accuracy	invasive (general anesthesia, FNA)

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

International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

Marcia Irene Canto,¹ Femme Harinck,² Ralph H Hruban,³ George Johan Offerhaus,⁴ Jan-Werner Poley,² Ihab Kamel,⁵ Yung Nio,⁶ Richard S Schulick,⁷ Claudio Bassi,⁸ Irma Kluijdt,⁹ Michael J Levy,¹⁰ Amitabh Chak,¹¹ Paul Fockens,¹² Michael Goggins,¹ Marco Bruno,² on behalf of the International Cancer of the Pancreas Screening (CAPS) Consortium

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

Author	n	Type of high risk	Screening modalities	Relevant lesions
Brentall 1999	14	FPC	CT+MRI+EUS	50%
Kimmey 2002	46	FPC	EUS+ERCP	26%
Canto 2004	38	FPC, PJ	CT+MRI+EUS	5.3%
Canto 2006	78	FPC, PJ	CT+MRI+EUS	1.3%
Poley 2009	44	FPC, PJ, BRCA, p16, p53, HP	CT+MRI+EUS	23%
Langer 2009	76	FPC, BRCA	EUS+ERCP	1.3%
Verna 2010	51	FPC, p16, BRCA	EUS+ERCP	12%
Ludwig 2011	109	FPC, BRCA	EUS+ERCP	8.3%
Vasen 2011	79	p16	MRI,ERCP	18%
Al Sukhni 2011	262	FPC, PJ, BRCA, p16, HP	CT+MRI+EUS+ERCP	7.3%
Schneider 2011	72	FPC, BRCA, PALB2	EUS+ERCP	15%
Canto 2012	216	FPC, PJ, BRCA	CT+MRI+EUS	43%/2.3%
Bartsch 2016	253	FPC (non CDKN2A)	MRI+EUS	8.3%/17.6%
Beaujon 2016	93	FPC, PJ, BRCA, HP	CT+MRI+EUS	15%

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Various methods used, various rates of « abnormalities » at screening (1%-50%)
 Definition of « relevant » lesion : not homogeneous

High risk patients: Result of screening in the literature

Summary of Current Screening Efforts for Pancreatic Cancer

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

* 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

Results of screening

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ORIGINAL REPORT

Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers

Hans Vasen, Isaura Ibrahim, Carmen Guillen Ponce, Emily P. Slater, Elvira Matthäi, Alfredo Carrato, Julie Earl, Kristin Robbers, Anneke M. van Mil, Thomas Potjer, Bert A. Bonsing, Wouter H. de Vos tot Nederveen Cappel, Wilma Bergman, Martin Wasser, Hans Morreau, Günter Klöppel, Christoph Schicker, Martin Steinkamp, Jens Figiel, Irene Esposito, Evelina Mocci, Enrique Vazquez-Sequeiros, Alfonso Sanjuanbenito, Maria Muñoz-Beltran, José Montans, Peter Langer, Volker Fendrich, and Detlef K. Bartsch

See accompanying editorial doi:10.1200/JCO.2016.66.5265

Retrospective assessement 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
- } Non syndromic familial pancreatic cancer

Benefit of Surveillance for Pancreatic Cancer in High-Risk
Individuals: Outcome of Long-Term Prospective Follow-Up
Studies From Three European Expert Centers

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- 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)

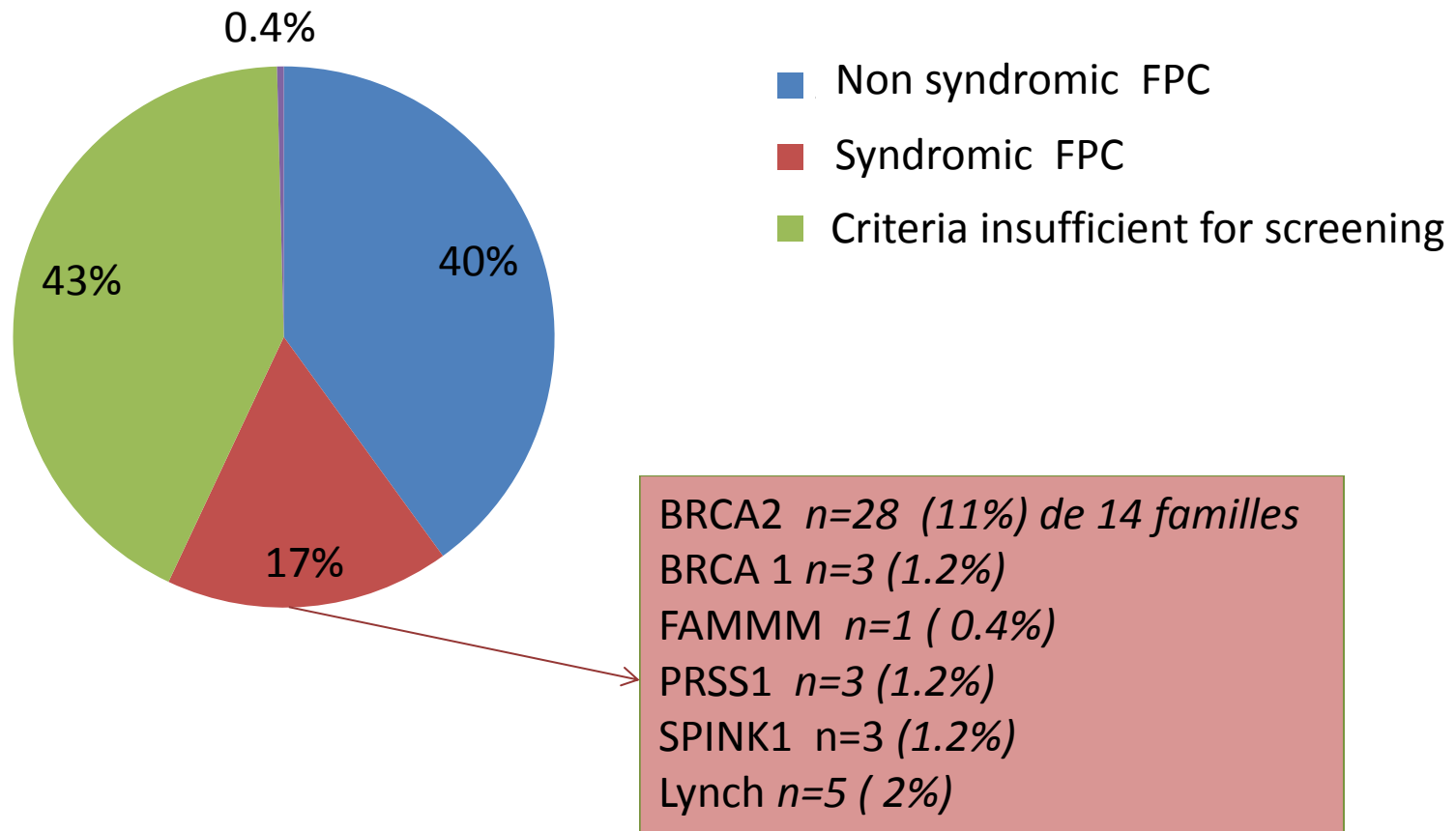
- **Lesions at risk : 4/13** (1.9% population screened)
 - PanIN3 (n=3)
 - IPMN high grade dysplasia (n=1)

Other :

- PanIN2 multifocal + branch duct IPMN low grade dysplasia (n=4)
- PanIN1 (n=2)
- Serous cystadenoma(n=3)

Results of screening: Beaujon's experience

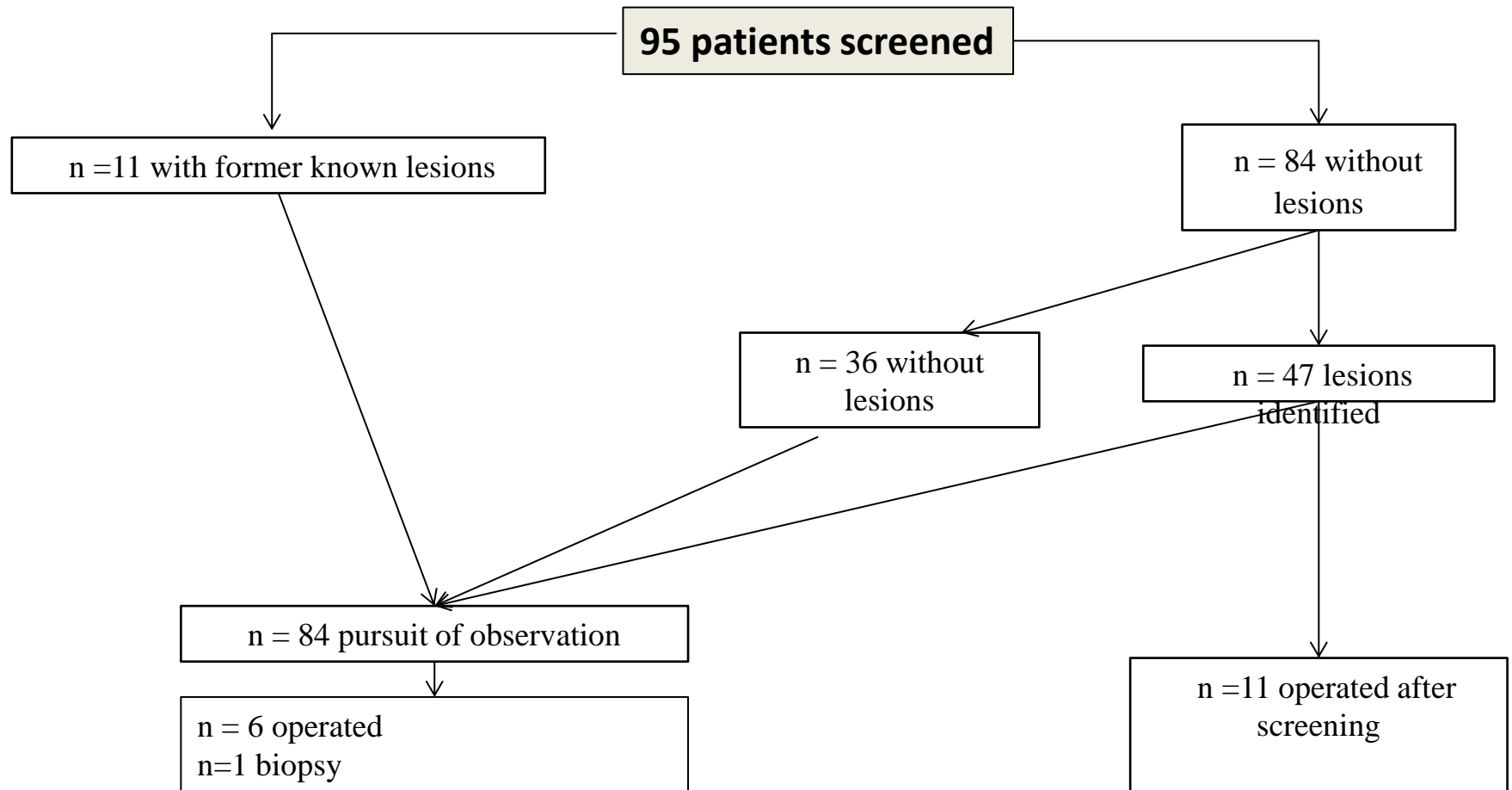
Population : 258 relatives at risk from 152 families



Results of screening: Beaujon's experience

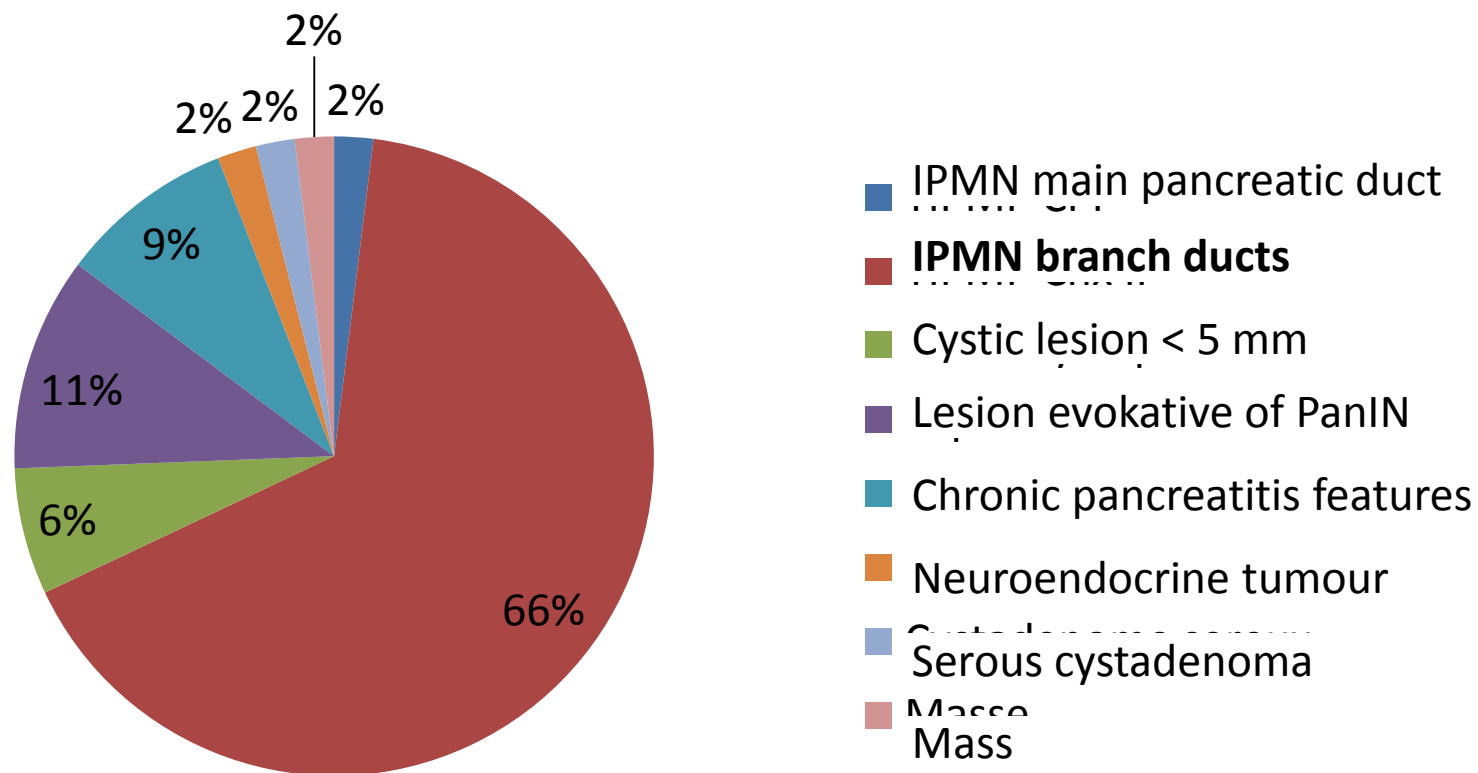
Résultats

Dépistage :



Results of screening: Beaujon's experience

Abnormalities : n= 48 (57%)



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 :

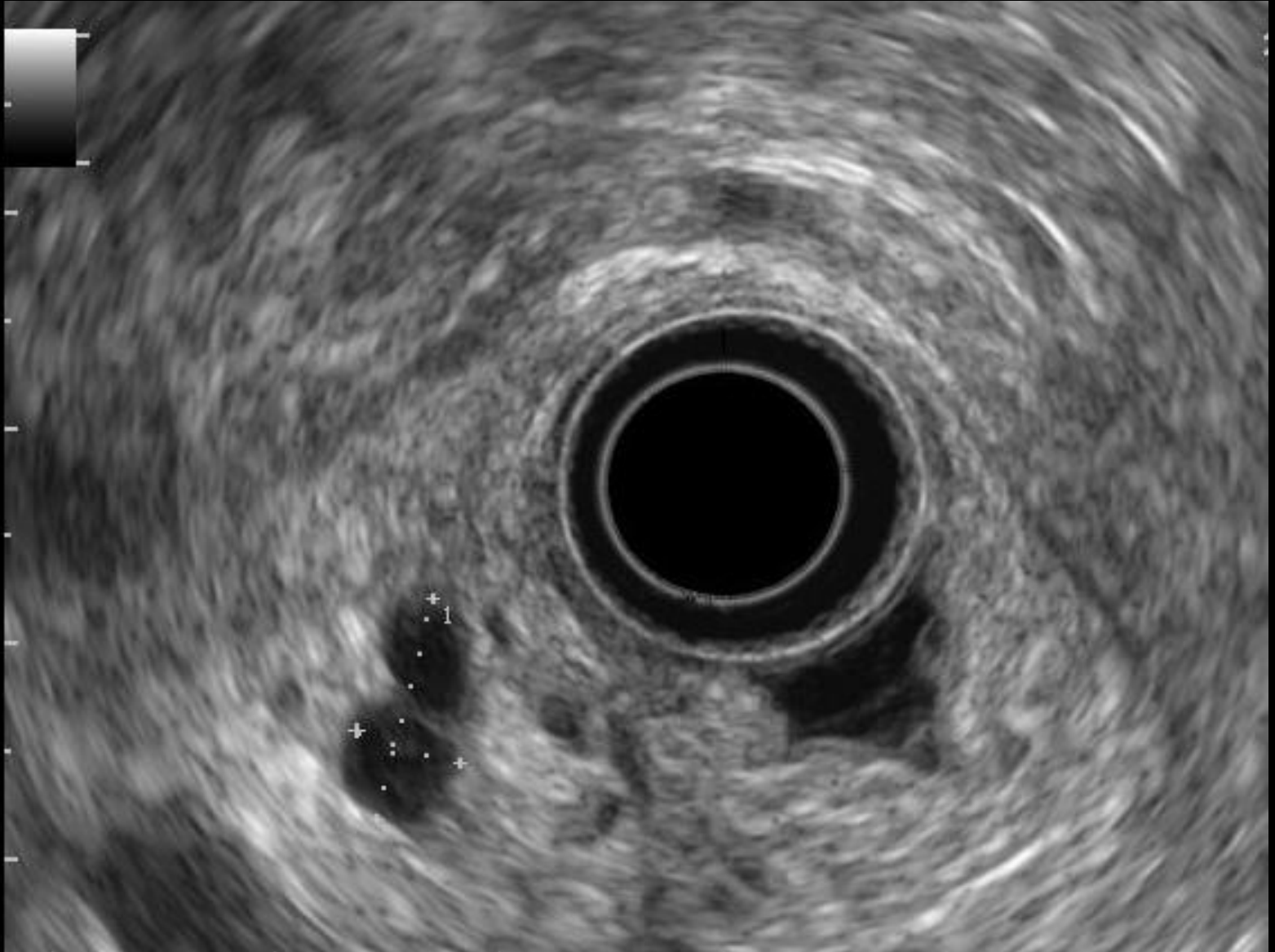
- Left pancreatectomy: n = 11
- Whipple: n = 2
- Median pancreatectomy : n = 2
- Total pancreatectomy : n = 1
- Enucleation n = 1

Results of screening: Beaujon's experience

Histology	N patients	%
PanIN		
PanIN 1	14	87
PanIN 2	10	62
PanIN 3	0	0
IPMN main pancreatic duct		
Low grade dysplasia	1	6
Moderate dysplasia	2	11
Severe dysplasia	1	6
IPMN branch ducts		
Low grade dysplasia	9	56
Moderate dysplasia	7	43
Severe dysplasia	2	12
Cancer	2	12

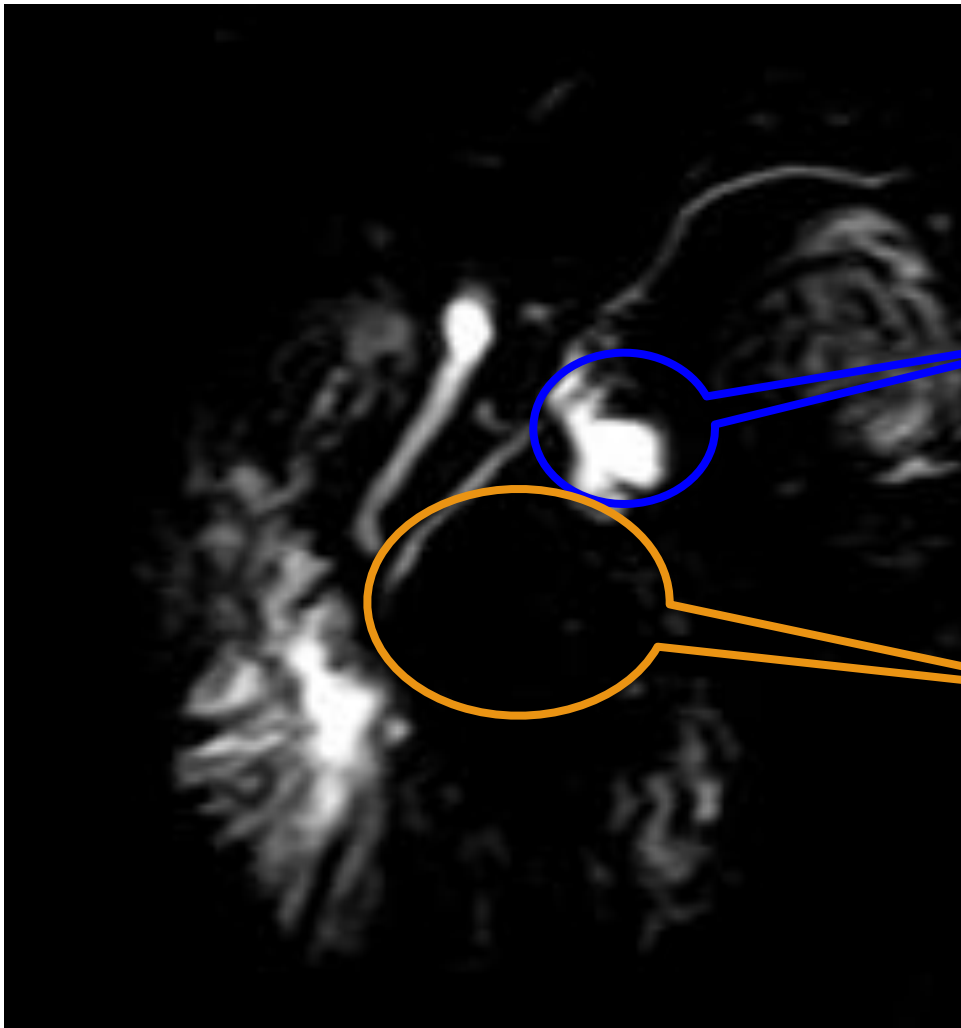
Rentability = 17%

Detection of small IPMN



Courtesy Dr L. Palazzo

FPC and screening: Enlarged duct



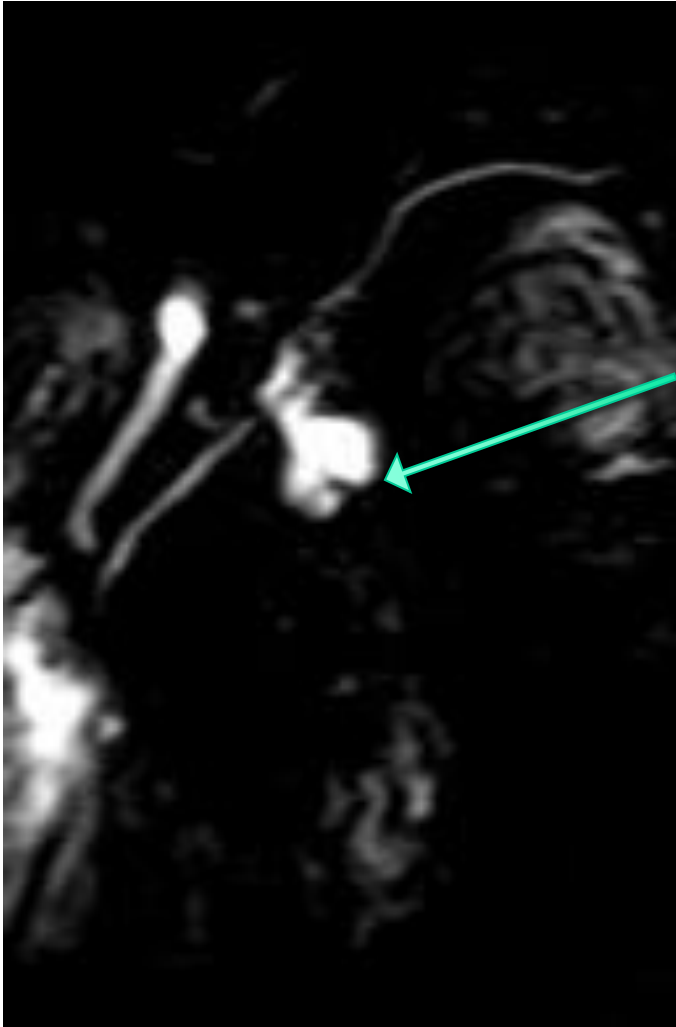
Two concerns :

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

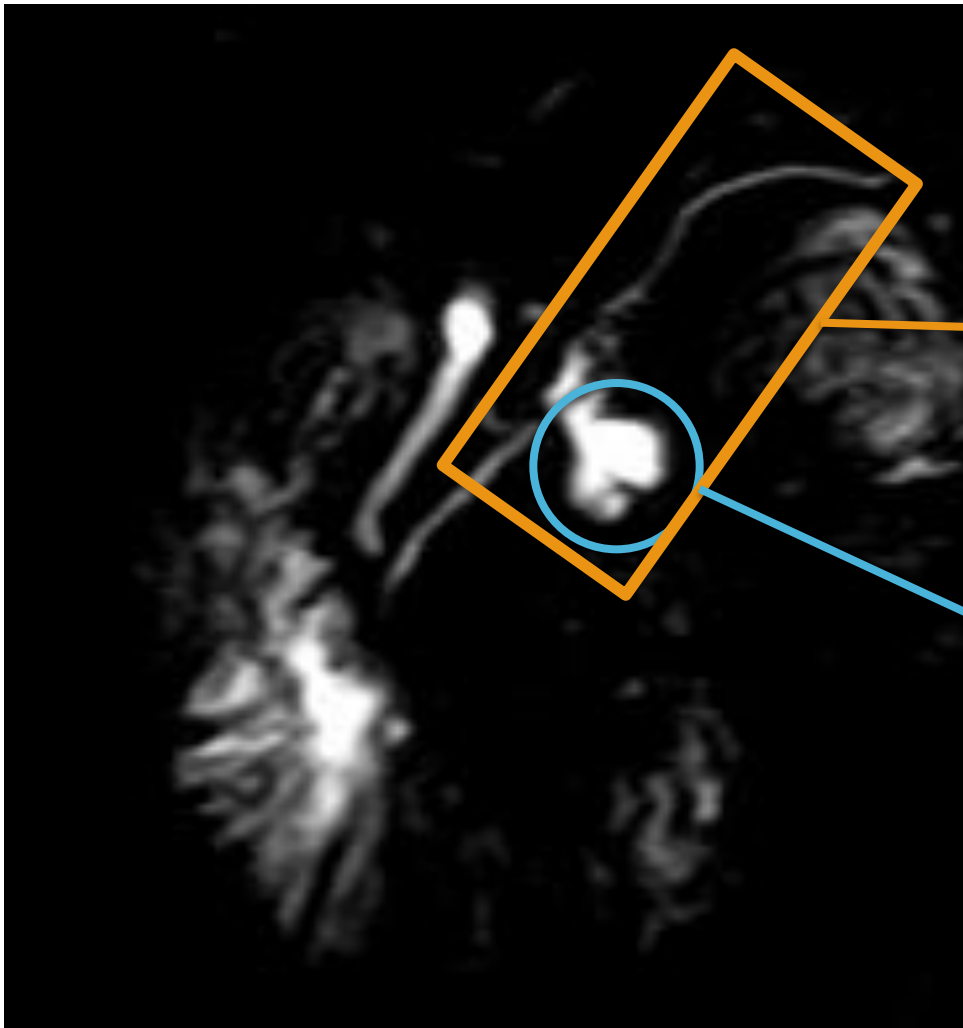


Pro
Simple, reproducible

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

Cystic lesion: What resection ?

Concerns/advantages :

Larger pancreatectomy:

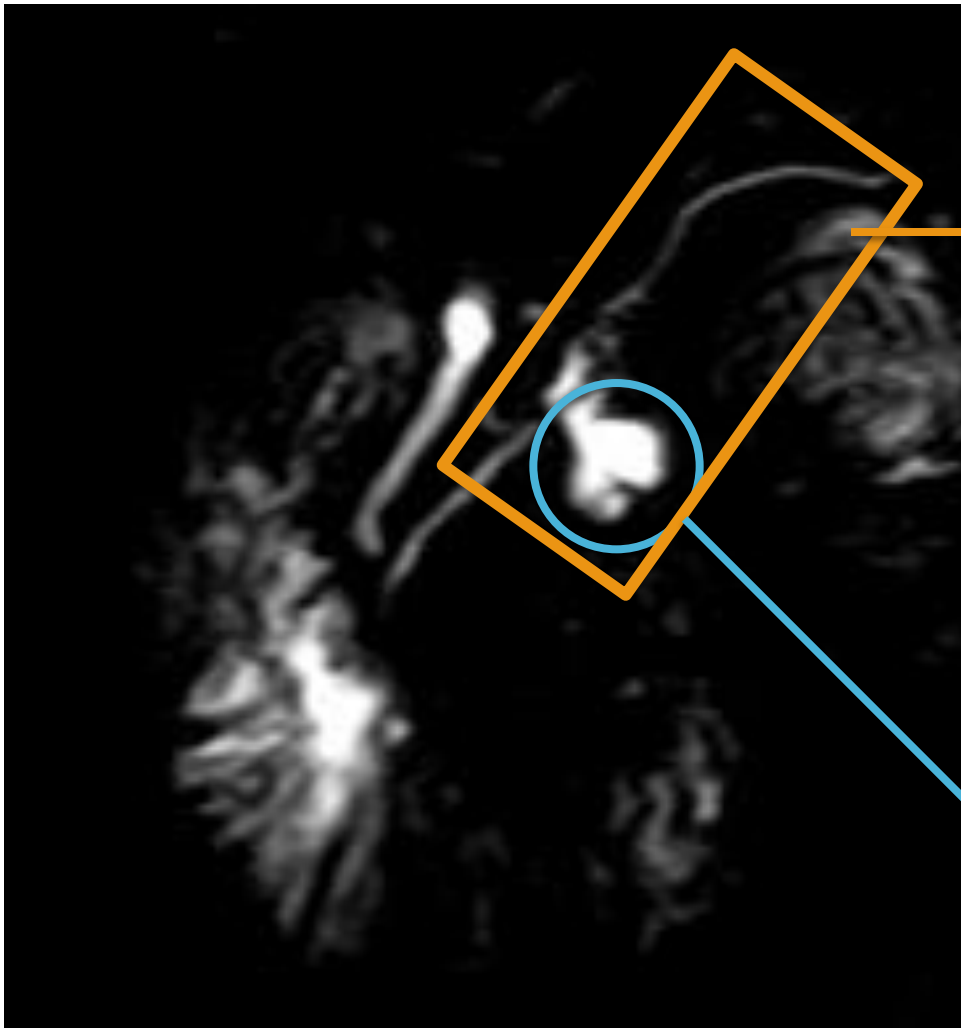
- Left:
 - . Fistula: 30-50%
 - . Diabetes: 8%-20%
 - . Death: 1%-2%
- Median:
 - . Fistula: 70%
 - . Diabetes: < 5%
 - . Death: 1%

More informative for path

Enucleation

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

No parenchyma for path



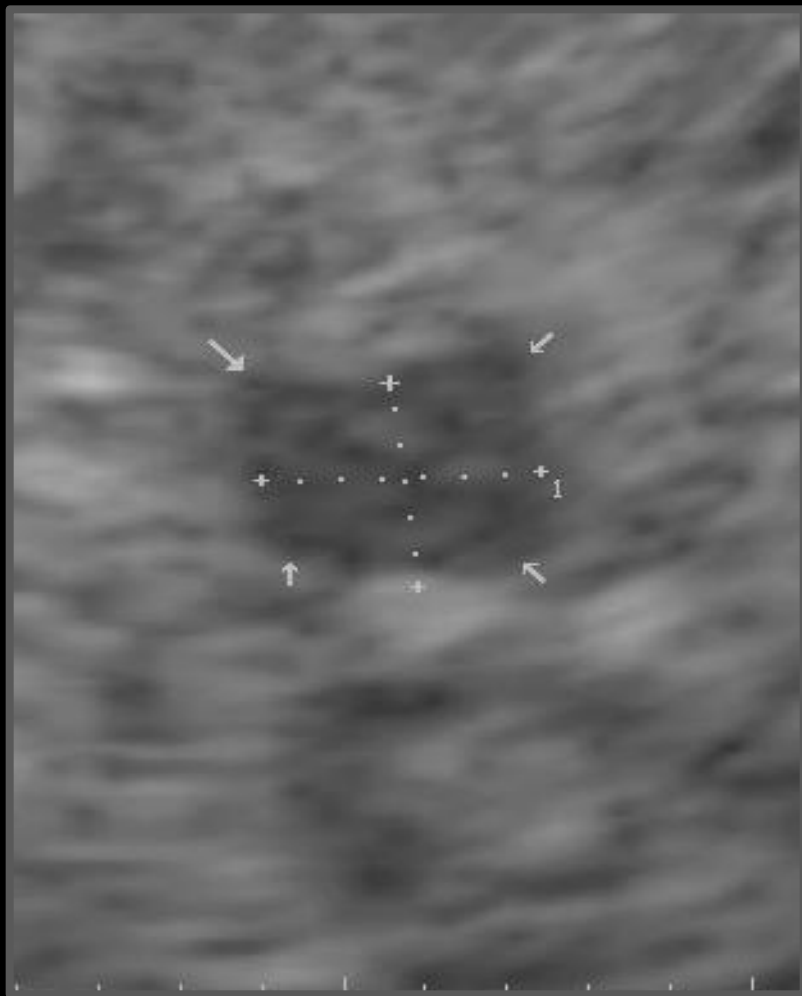
43-year old woman, 2 FPC related

Mass developed in a cyst

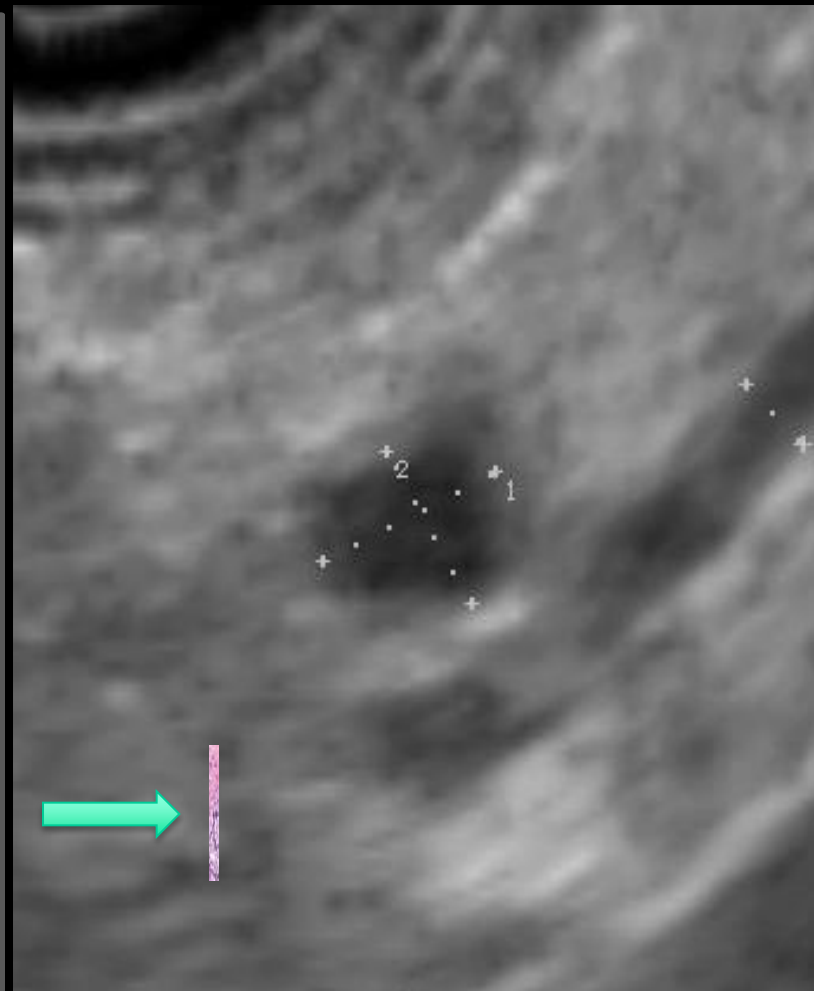
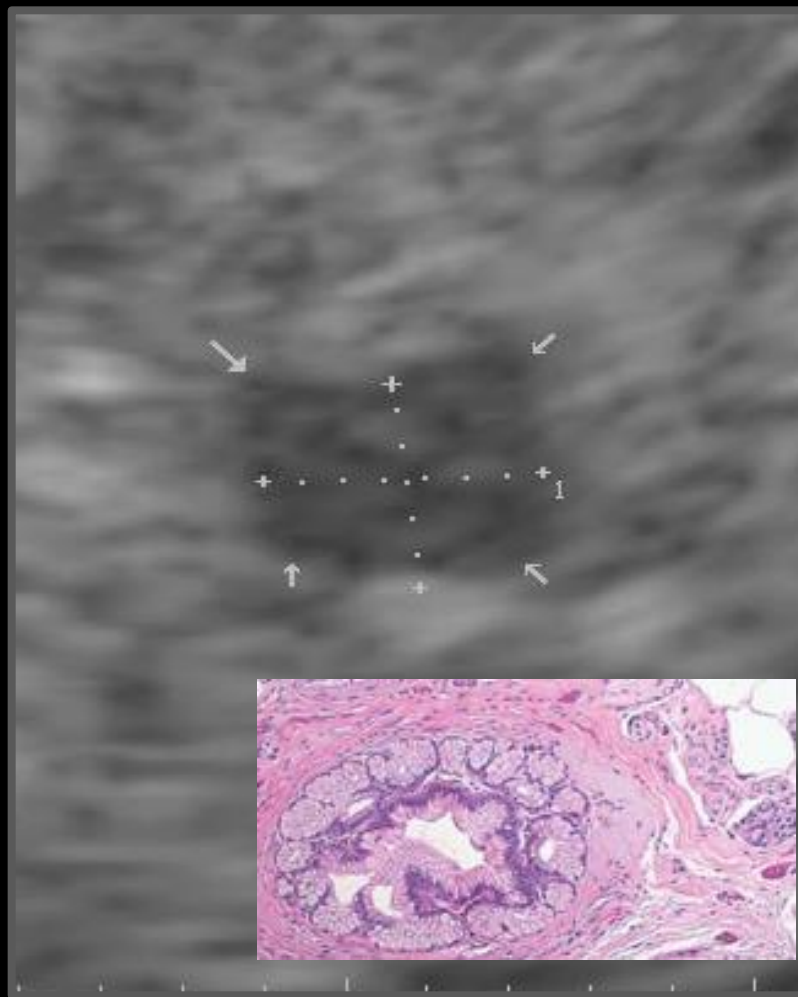


Courtesy Dr L. Palazzo

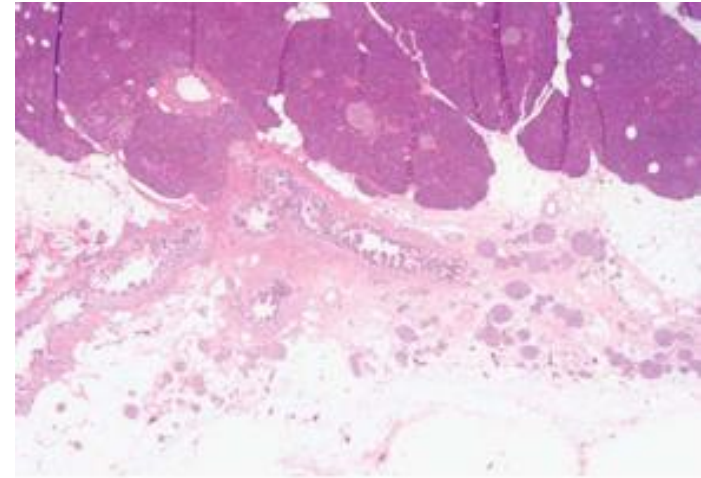
Small mass, likely benign. Histology?



Small mass, likely benign. Histology?



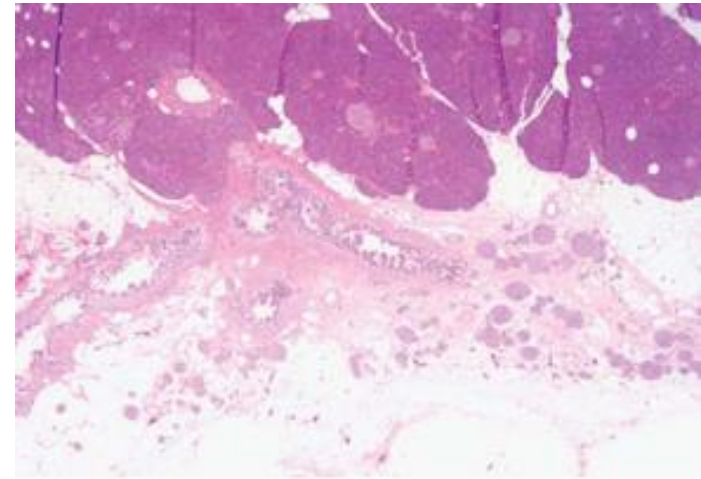
Chronic pancreatitis-like features



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

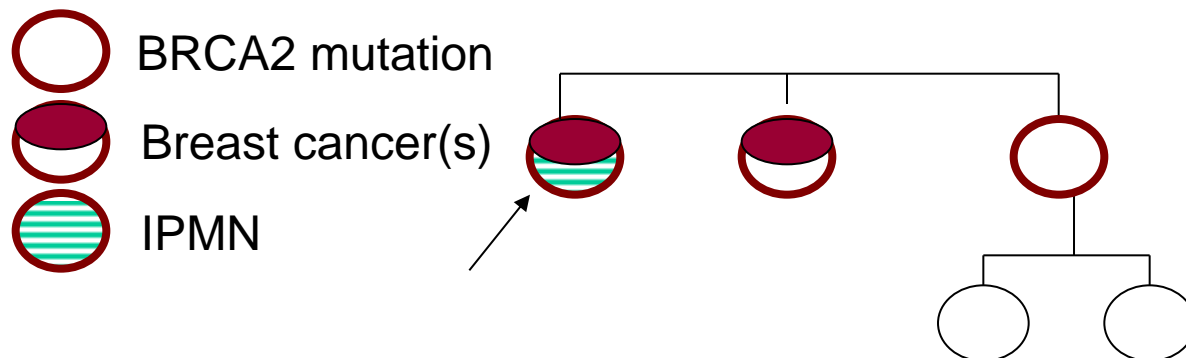
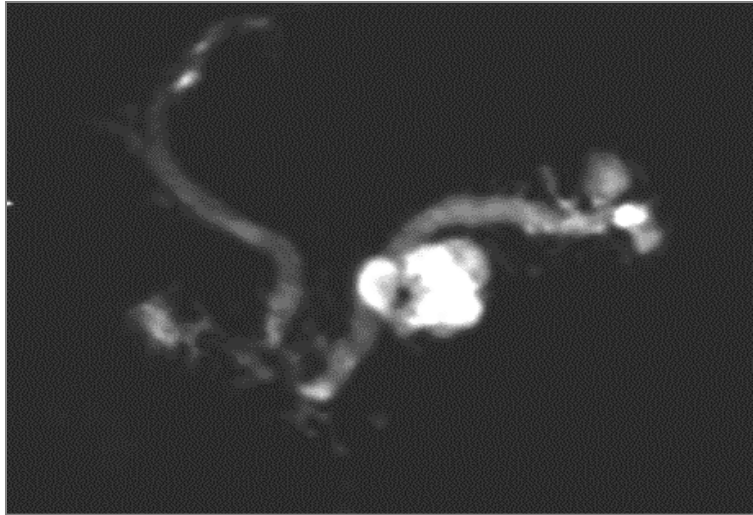


Hereditary pancreatitis: the most at risk for cancer, but very difficult to screen!



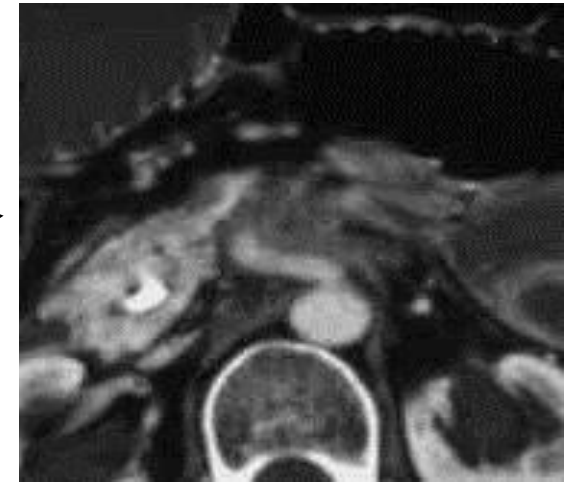
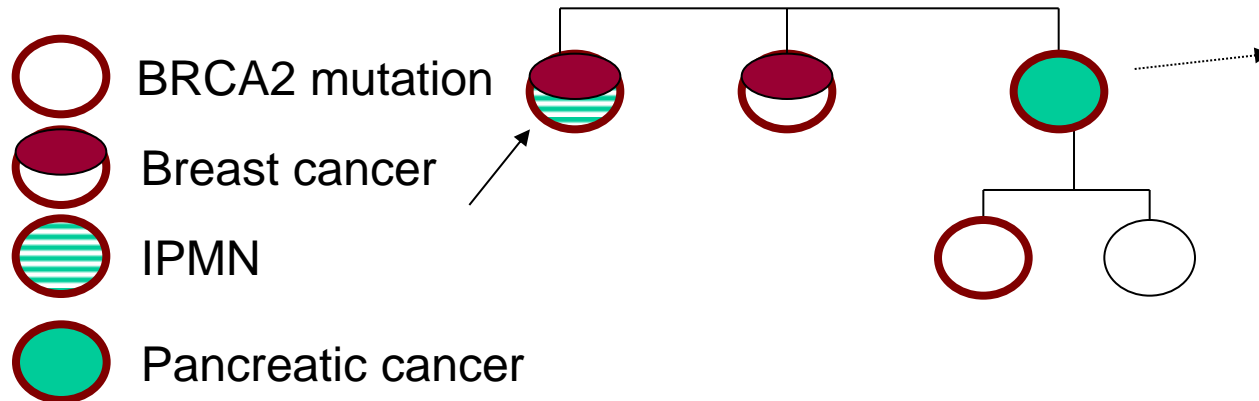
Detection of likely malignant mass

59-year old woman.... Bilateral breast cancer and IPMN



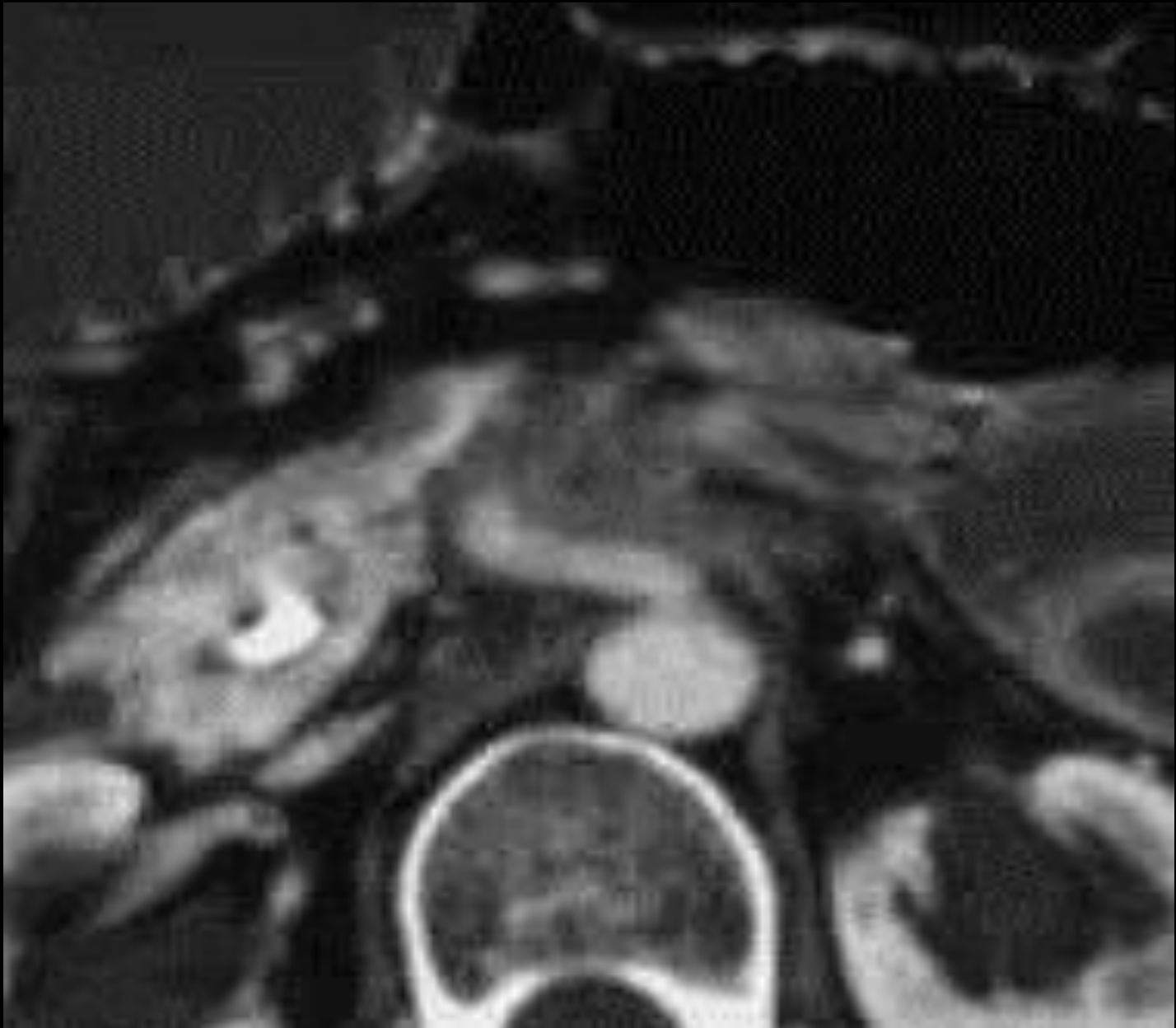
Detection a of mass, likely malignant

Genetic counselling June 2010

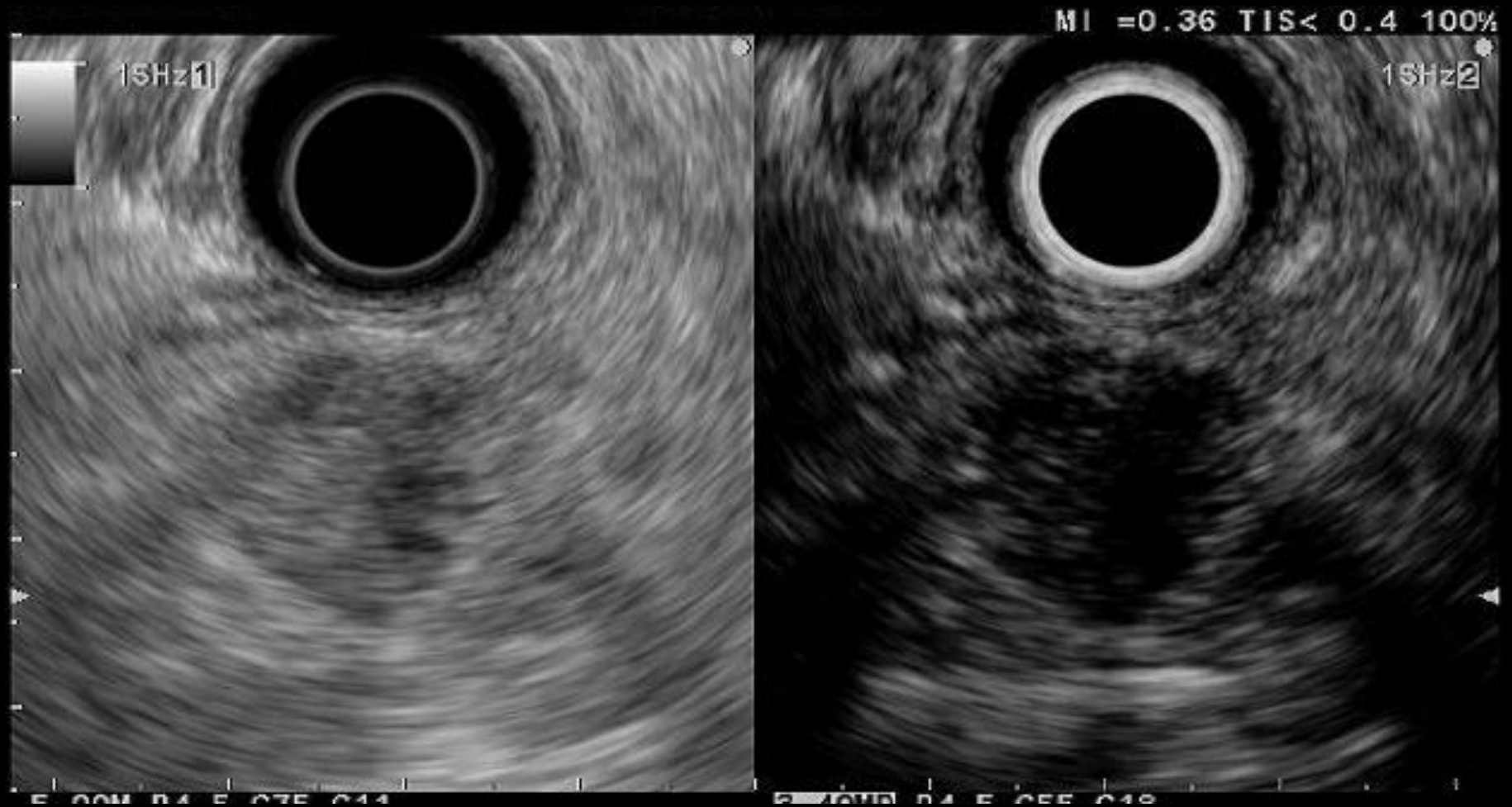


Asymptomatic tumour
at systematic screening

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?

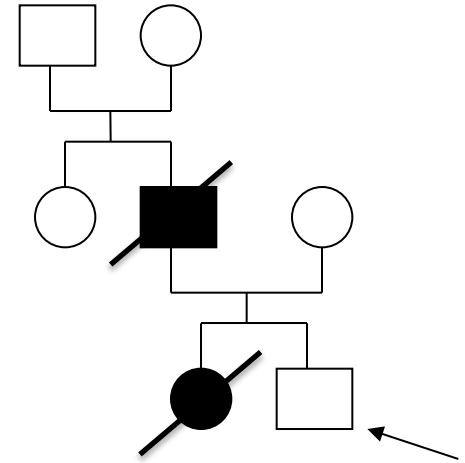
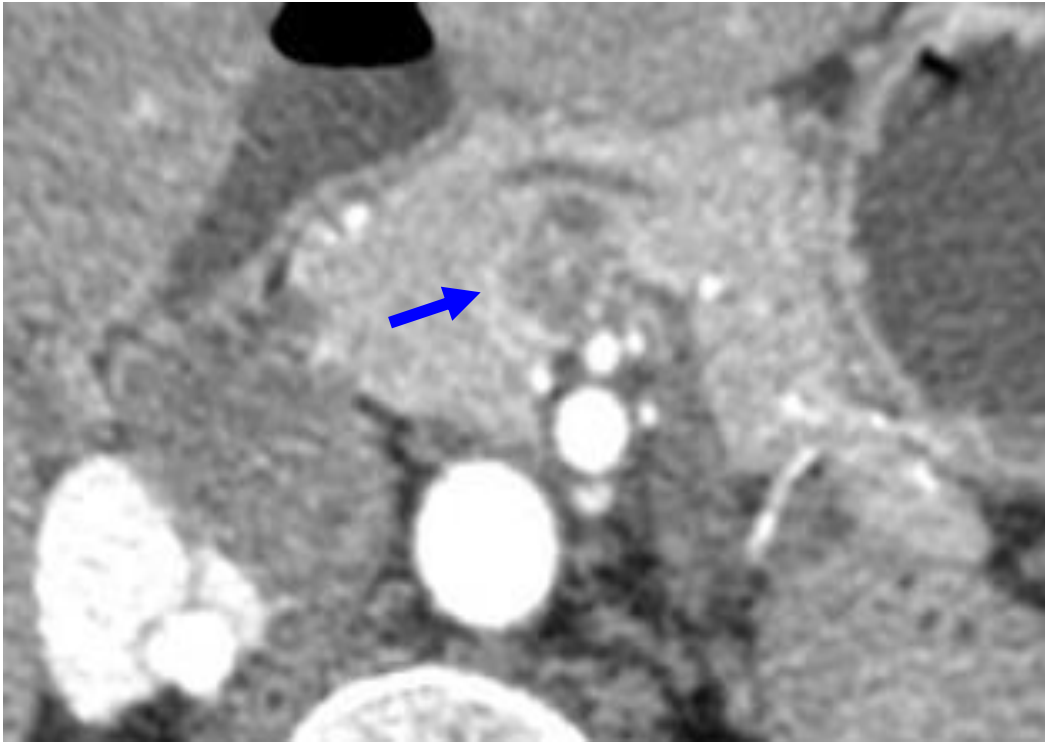
No valuable serum tumor marker for very early lesion

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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 - Morbidity of pancreatic surgery
 - Psychological impact of screening?
- Need to identify serum markers, genetic/epigenetic alterations, proteomic
- Collaborative studies in high risk patients

Thank you for attention