Pancreatic Neoplasms: What Can We Do?

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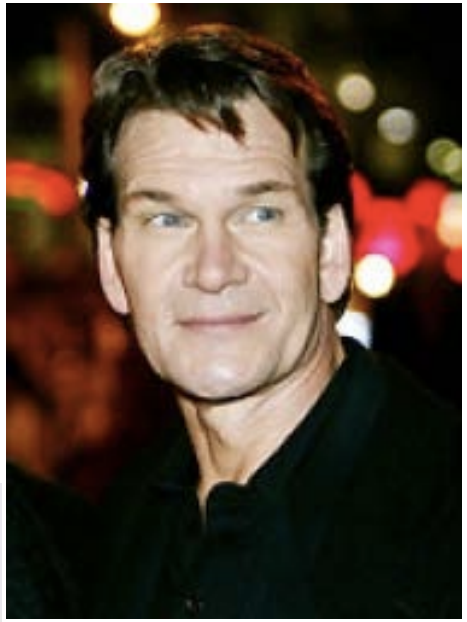
Pancreatic Neoplasms

- Ductal adenocarcinoma (85%)
- Neuroendocrine
- Cystic neoplasms



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Pancreatic Neoplasms

- Ductal adenocarcinoma (85%)
- Neuroendocrine (6%) ----→
- Cystic neoplasms

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Objectives

- Review epidemiologic facts
- How we can identify high-risk individuals
- Early detection tools
- Multi-disciplinary treatment approach

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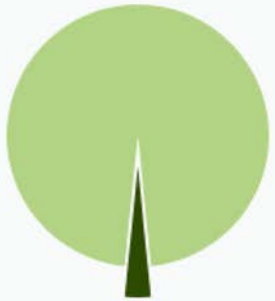
How Common is Pancreatic Cancer?

How Common Is This Cancer?

Compared to other cancers, pancreatic cancer is relatively rare.

	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	Prostate Cancer	164,690	29,430
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	Bladder Cancer	81,190	17,240
7.	Non-Hodgkin Lymphoma	74,680	19,910
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370
	-	-	-
11.	**Pancreatic Cancer**	**55,440**	**44,330**

Pancreatic cancer represents 3.2% of all new cancer cases in the U.S.



3rd most common cause of death

In 2018, it is estimated that there will be 55,440 new cases of pancreatic cancer and an estimated 44,330 people will die of this disease.

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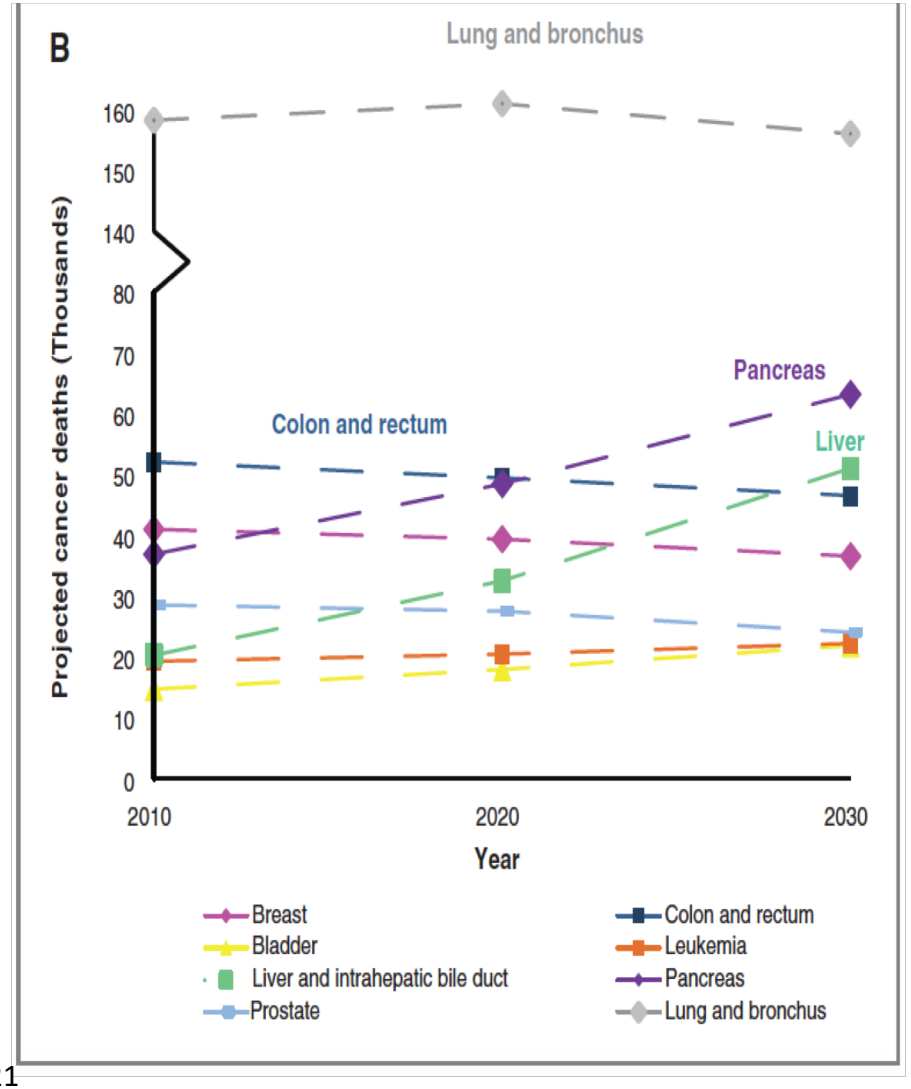
How Common is Pancreatic Cancer?

2nd leading cause of cancer deaths by 2030



~ 60,000 deaths

Lola Rahib et al. *Cancer Res* 2014;74:2913-2921

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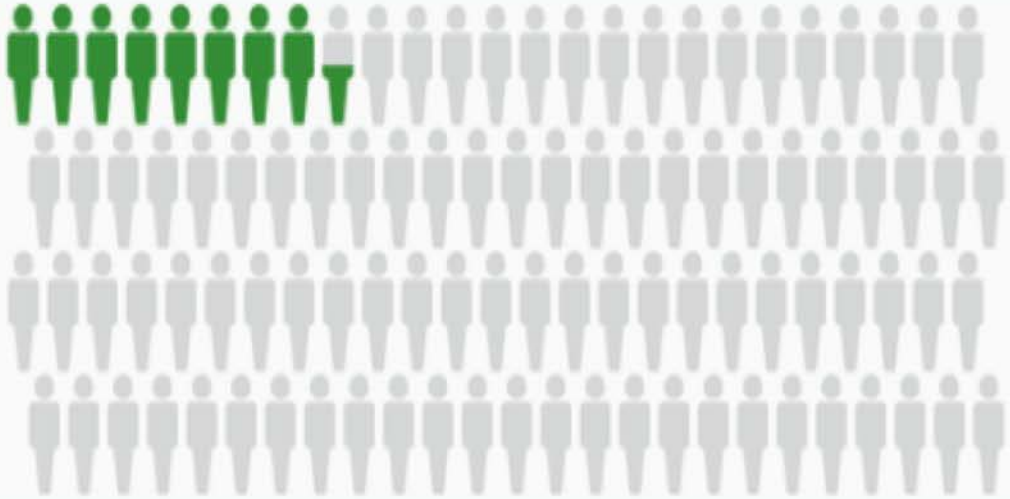
How Many People Survive 5 Years Or More after Being Diagnosed with Pancreatic Cancer?

Relative survival statistics compare the survival of patients diagnosed with cancer with the survival of people in the general population who are the same age, race, and sex and who have not been diagnosed with cancer. Because survival statistics are based on large groups of people, they cannot be used to predict exactly what will happen to an individual patient. No two patients are entirely alike, and treatment and responses to treatment can vary greatly.



Percent Surviving 5 Years

8.5%

Based on data from SEER 18 2008-2014. Gray figures represent those who have died from pancreatic cancer. Green figures represent those who have survived 5 years or more.

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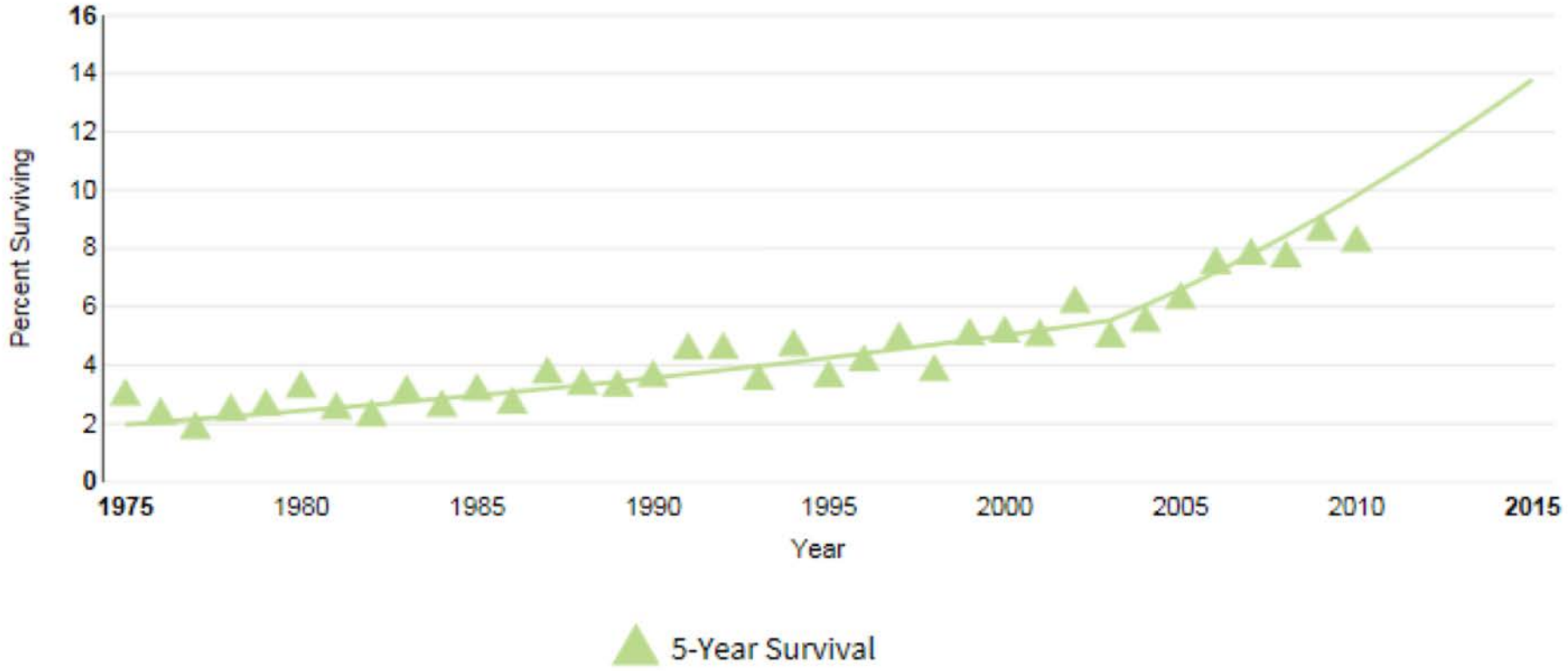
How Many Survive Pancreatic Cancer?

Any improvement?



SEER 9 5-Year Relative Survival Percent from 1975-2010, All Races, Both Sexes.
Modeled trend lines were calculated from the underlying rates using the Joinpoint Survival Model Software.

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Pancreatic Carcinoma

- Pancreatic ductal adenocarcinoma is one of the leading causes of cancer-related mortality.
- 5 year survival for patients with PC is 8.5%

- Almost always detected in advanced stage

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Pancreatic Carcinoma

What can we do?

- Prevention
  - Identify high-risk individuals
    - Screen
    - Surveillance
- Early Detection
- Expedite Treatment

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FACT

The lifetime risk of developing PC in the general population is estimated to be 1.6%.

Screening not recommended for general population

FACT

High-Risk:

Patients having a >5% lifetime risk or 5x RR of developing PC.

Screening recommended for high-risk population

Canto MI, Hruban RH, Fishman EK, et al., Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals. *Gastroenterology* 2012

Who Gets Pancreatic Cancer?

Risk Factors

Minor

- Age:
  - >55
- Gender:
  - M>>F
- Race:
  - African Americans
- Cigarette smoking
- Obesity
- Diabetes

Major

- Chronic pancreatitis
- Pancreatic cystic lesions
- Family history of PC
- Genetic Syndromes:
  - BRCA - 2
  - Familial Melanoma
  - PRSS – 1
  - Peutz – Jeghers
  - HNPCC

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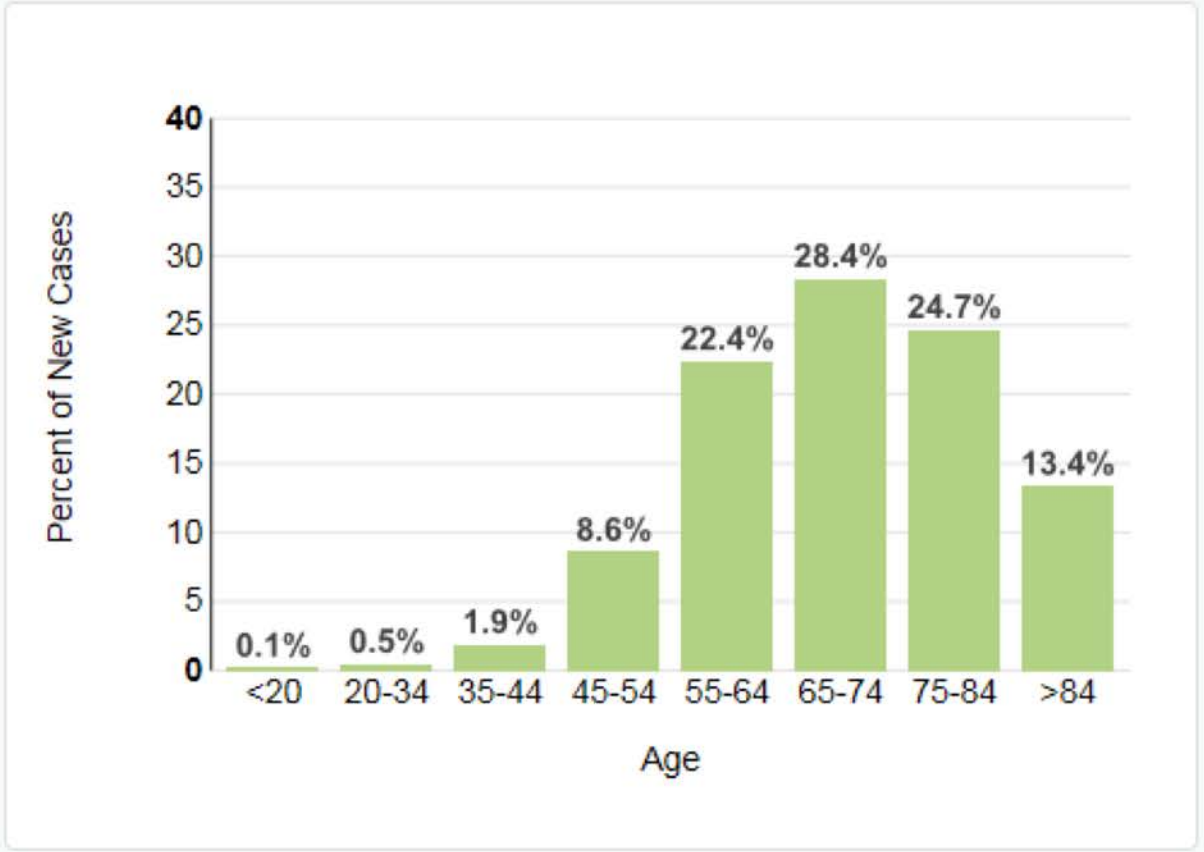
Age Distribution in PC

Percent of New Cases by Age Group: Pancreatic Cancer



Pancreatic cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis
70

SEER 18 2011-2015, All Races, Both Sexes

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Pancreatic Cancer Risk Factors

Smoking

- Meta-analysis of 82 studies 2008: RR 1.7 in current and 1.2 in former smokers.

- Cigarette smoking increases the risk of pancreas cancer : 75% compared to non smokers.

- Effect of smoking persists 10 years after cessation

Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 2008; **393**: 535-545 [PMID: 18193270 DOI: 10.1007/s00423-007-0266-2]

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Pancreatic Cancer Risk Factors

Obesity

- RR 2.08 with BMI >30 vs <25
- Burden study in UK: 12.8% of PC in men and 11.5% of PC in women
- Recent meta-analysis confirmed that both general obesity and abdominal obesity increases the risk of PC.

- Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348:1625–1638.
- Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011;105 Suppl 2:S77–S81.

Pancreatic Cancer Risk Factors

Diabetes Mellitus

- Both type 1 and 2 doubles the risk of PC
- US National Cancer Institute study: 1.8 fold increased risk particularly in Hispanic and Asian compared to White and Blacks.
- Oral antidiabetic agents and insulin associated with reduced risk of PC

Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015;44:186–198.
Batabyal P, Vander Hoorn S, Christophi C, Nikfarjam M. Association of diabetes mellitus and pancreatic adenocarcinoma: a meta-analysis of 88 studies. Ann Surg Oncol. 2014;21:2453–2462.
Li D, Tang H, Hassan MM, Holly EA, Bracci PM, Silverman DT. Diabetes and risk of pancreatic cancer: a pooled analysis of three large case-control studies. Cancer Causes Control. 2011;22:189–197
Bosetti C, Rosato V, Li D, Silverman D, Petersen GM, Bracci PM, Neale RE, Muscat J, Anderson K, Gallinger S, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. Ann Oncol. 2014;25:2065–2072.

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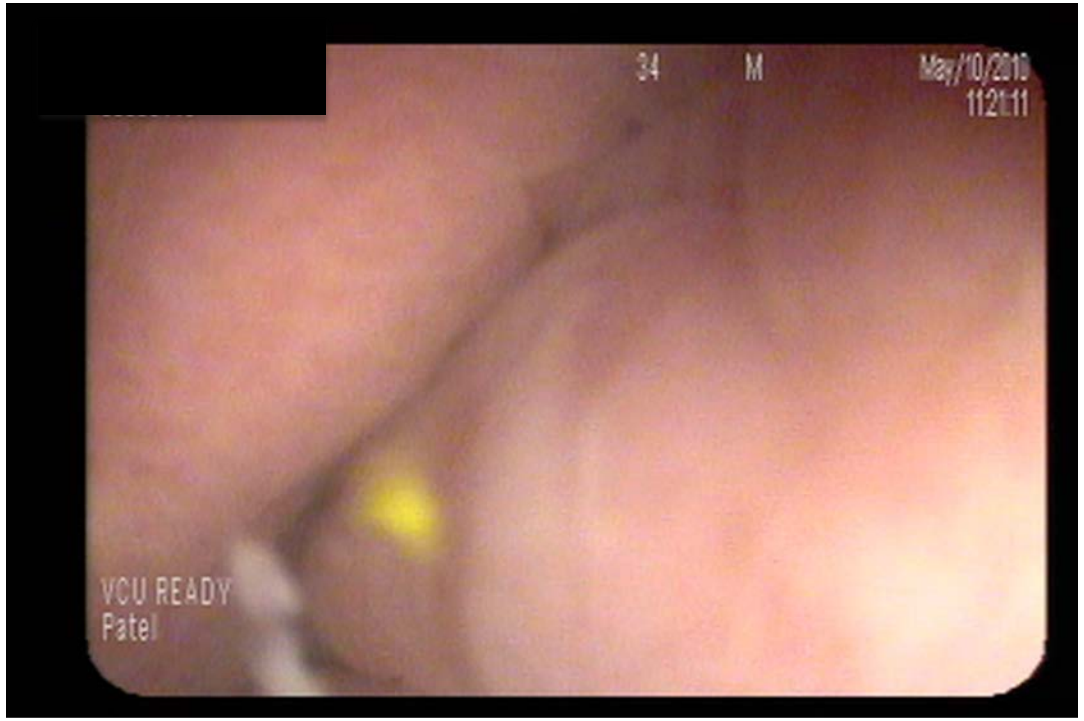
Pancreatic Cancer Risk Factors

Chronic pancreatitis



Endoscopic Ultrasound

Parenchymal

hyperechoic foci
hyperechoic strands
hypoechoic lobules
cysts
Califications
Iregular size

Ductal

Dilatation
dilated SB
irregular MD
hyperechoic margins
stones

Catalano et al. *Gastrointest Endosc.* 2009 Jun;69(7):1251-61

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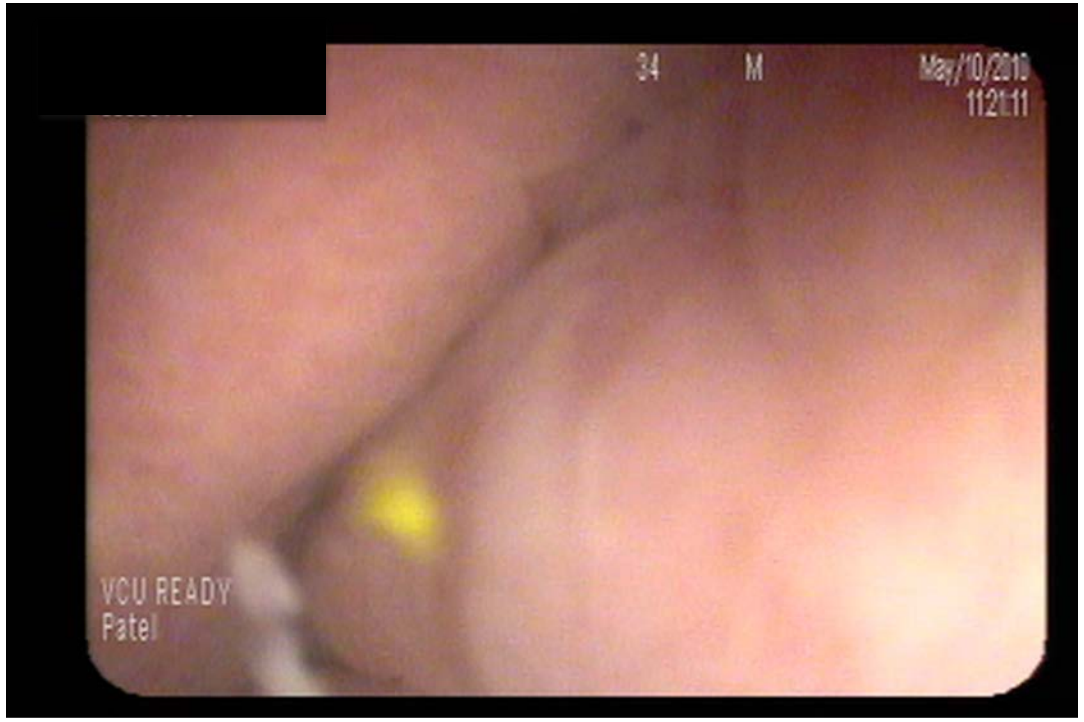
Pancreatic Cancer Risk Factors

Chronic pancreatitis



Endoscopic Ultrasound

RR: 2.7-5.1%

Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol.

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Pancreatic Cancer Risk Factors

Familial and Genetic

- Sporadic PC (85-90%)
- Genetic cause or runs in the families (10-15%)
  - Familial pancreatic cancer (FPC)
    - Pair of affected first-degree relatives (parent-child or sibling)
      - Individuals with 2 FDR: 6.4-fold risk (ie 8-12% life time risk of PC)
      - Individuals with 3 FDR: 32-fold risks (ie 40% life time risk of PC)

Pancreatic Cancer Risk Factors

Familial and Genetic

- Sporadic PC (85-90%)
- Genetic cause or runs in the families (10-15%)
  - Genetic predisposition associated with PC:

BRCA - 2
Familial Melanoma
PRSS – 1
Peutz – Jeghers
HNPCC

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Pancreatic Cancer Risk Factors

Genetic

TABLE 1. Risk stratification for pancreatic cancer per genetic mutation

Gene(s)	Common name	Risk of pancreatic cancer
STK11/LKB1[35]	Peutz-Jeghers syndrome	RR = 132 (95% CI, 44-261)
PRSS1[36]	Hereditary pancreatitis	SIR = 53 (95% CI, 23-105)
CDKN2A[37-39]	n/a	RR = 13-39
MLH1, MSH2, MSH6[17,40]	Lynch syndrome*	RR = 9-11
TP53[41]	Li-Fraumeni syndrome	RR = 7.3 (95% CI, 2-19)
CFTR[42,43]	Cystic fibrosis, hereditary pancreatitis	RR = 5.3 (95% CI, 2.4-10.1)
APC[44]	Familial adenomatous polyposis	RR = 4.46 (95% CI, 1.2-11.4)
BRCA2[45]	n/a	RR = 3-9
ATM[46]	Ataxia-telangiectasia	RR = 3.92 (95% CI, 0.44-14.2)
BRCA1[47]	n/a	RR = 2.26 (95% CI, 1.26-4.06)
Familial pancreatic cancer in 1 or 2 first-degree relatives[48,49]	n/a	RR = 4-7

RR, Relative risk; *CI*, confidence interval; *SIR*, standardized incidence ratio; *n/a*, not applicable.
*Also known as hereditary nonpolyposis colorectal cancer.

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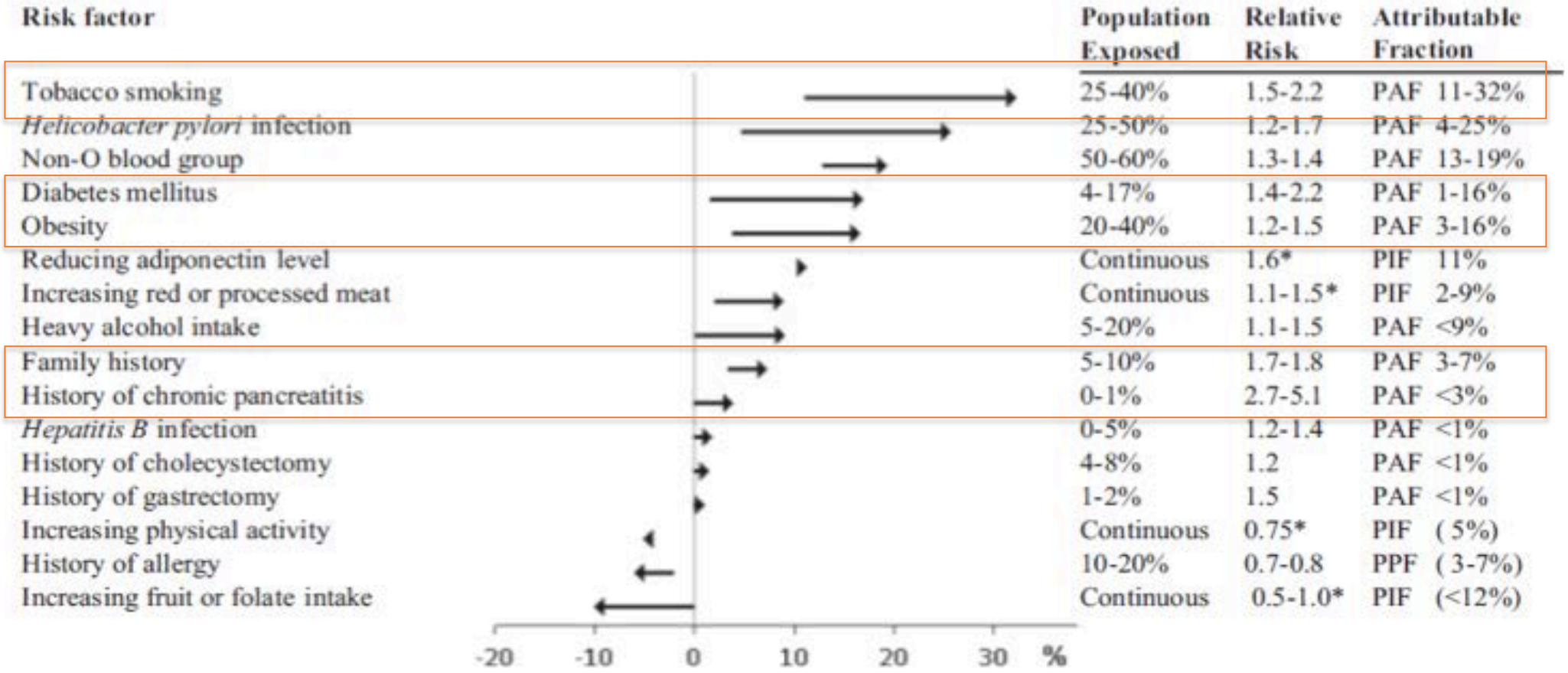
Pancreatic Cancer Risk Factors

Overview



Risk factor	Population Exposed	Relative Risk	Attributable Fraction
Tobacco smoking	25-40%	1.5-2.2	PAF 11-32%
Helicobacter pylori infection	25-50%	1.2-1.7	PAF 4-25%
Non-O blood group	50-60%	1.3-1.4	PAF 13-19%
Diabetes mellitus	4-17%	1.4-2.2	PAF 1-16%
Obesity	20-40%	1.2-1.5	PAF 3-16%
Reducing adiponectin level	Continuous	1.6*	PIF 11%
Increasing red or processed meat	Continuous	1.1-1.5*	PIF 2-9%
Heavy alcohol intake	5-20%	1.1-1.5	PAF <9%
Family history	5-10%	1.7-1.8	PAF 3-7%
History of chronic pancreatitis	0-1%	2.7-5.1	PAF <3%
Hepatitis B infection	0-5%	1.2-1.4	PAF <1%
History of cholecystectomy	4-8%	1.2	PAF <1%
History of gastrectomy	1-2%	1.5	PAF <1%
Increasing physical activity	Continuous	0.75*	PIF (5%)
History of allergy	10-20%	0.7-0.8	PPF (3-7%)
Increasing fruit or folate intake	Continuous	0.5-1.0*	PIF (<12%)

* for continuous variables the relative risk is expressed for the highest versus lowest quintile

Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol.

Pancreatic Cancer

Early Diagnosis

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Pancreatic Carcinoma

Late Symptoms

- Jaundice
- Weight loss
- Abdominal pain
- Pruritus
- Dark urine
- Acholic stools

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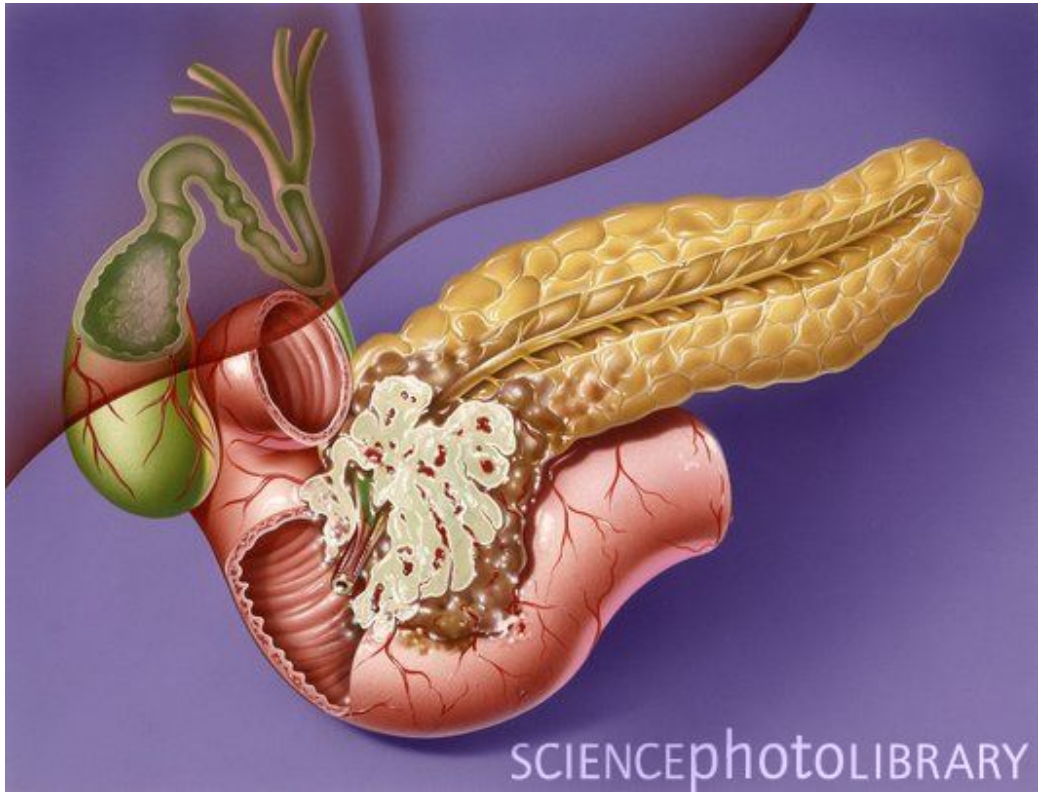
Pancreatic carcinoma

Signs

- New-onset diabetes
- Depression



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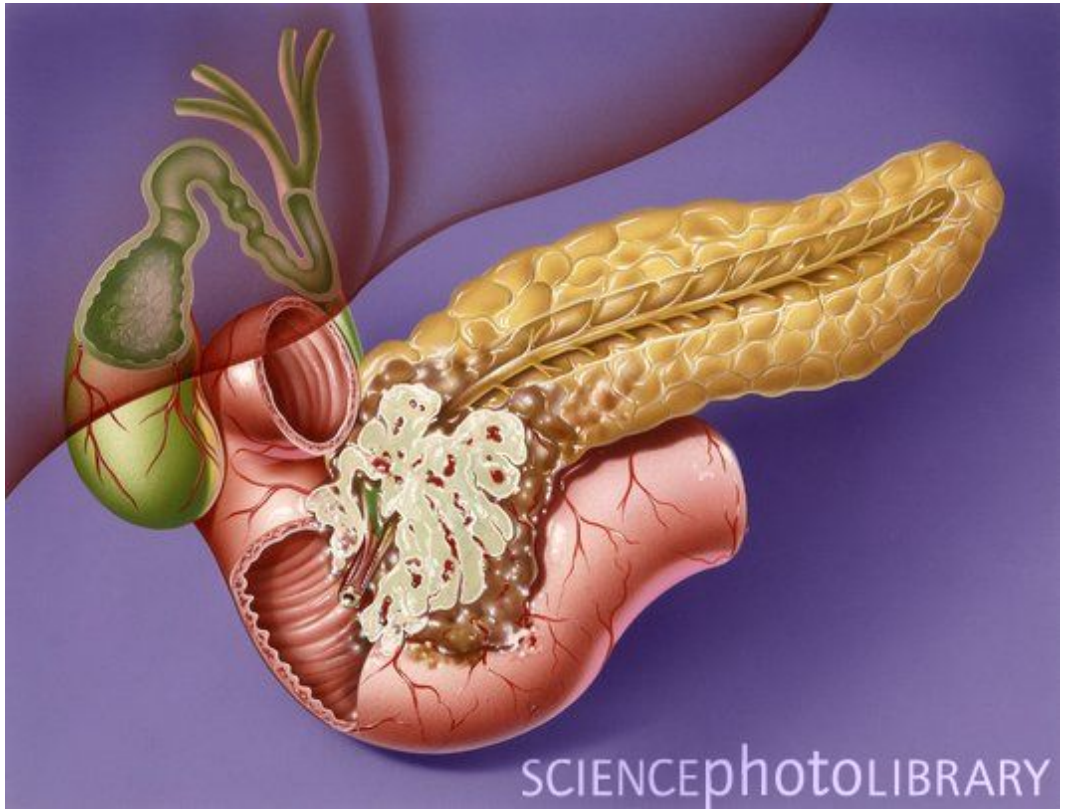
Pancreatic Carcinoma

Evaluation

- ***Blood Work***

- ***Imaging***
  - US, CT, MRI/MRCP

- ***Tissue sampling***
  - EUS/FNA
  - ERCP



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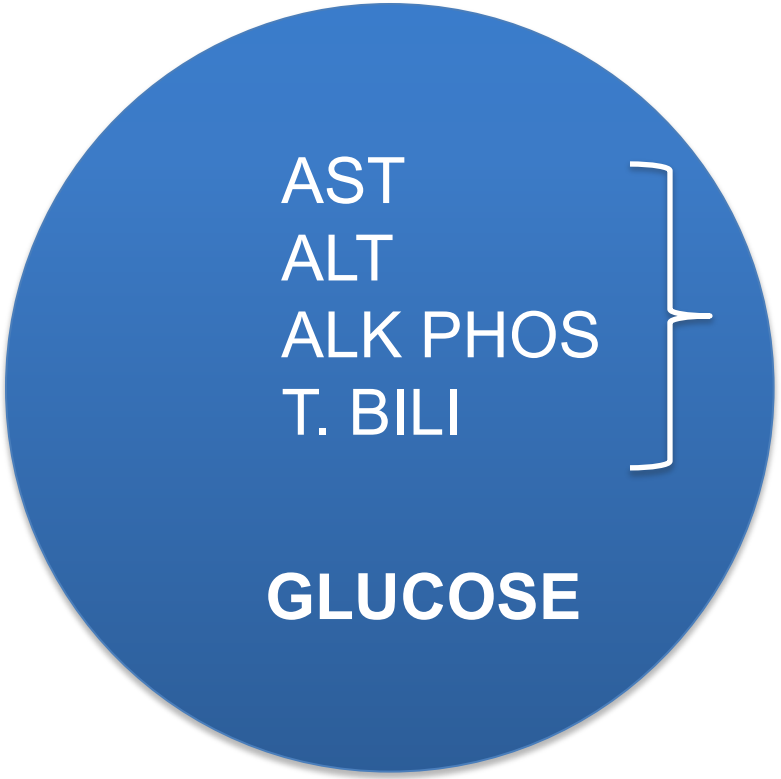
Pancreatic Carcinoma

Blood work

- Elevated Blood Chemistries:



Liver associated enzymes

CEA

CA-19-9

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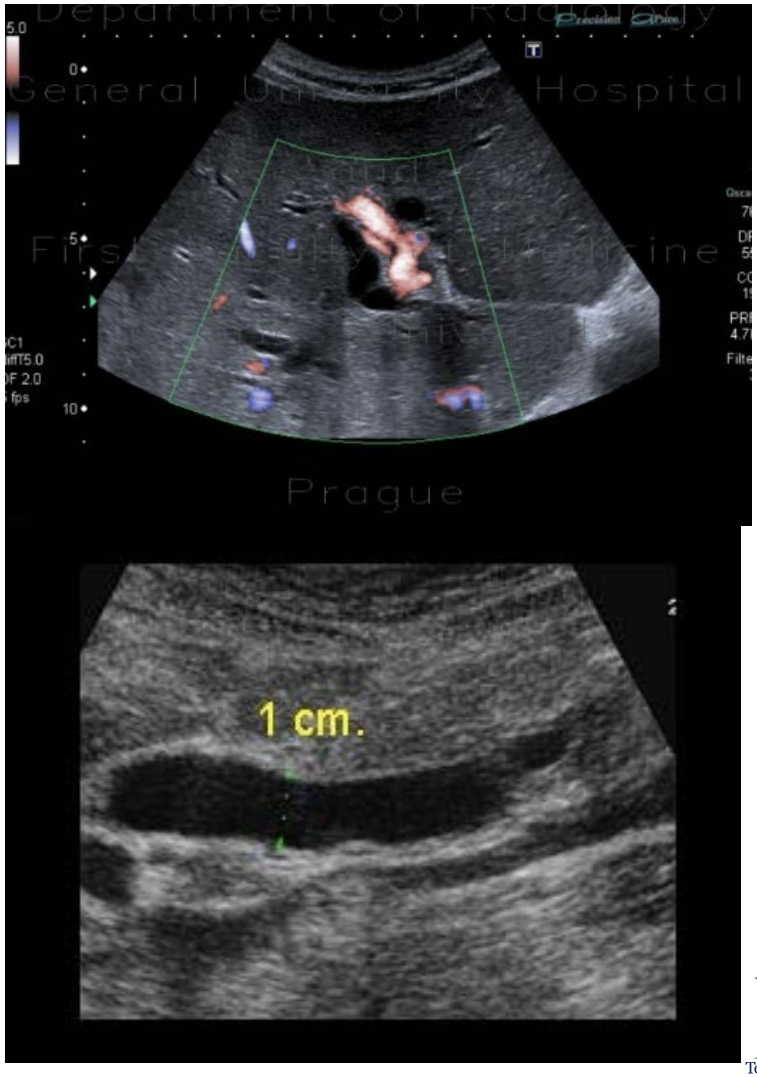
Pancreatic Carcinoma

Non-invasive imaging

- Abdominal US



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Pancreatic Carcinoma

Non-invasive imaging

<u>CT with oral and IV contrast:</u>

- Normal exam

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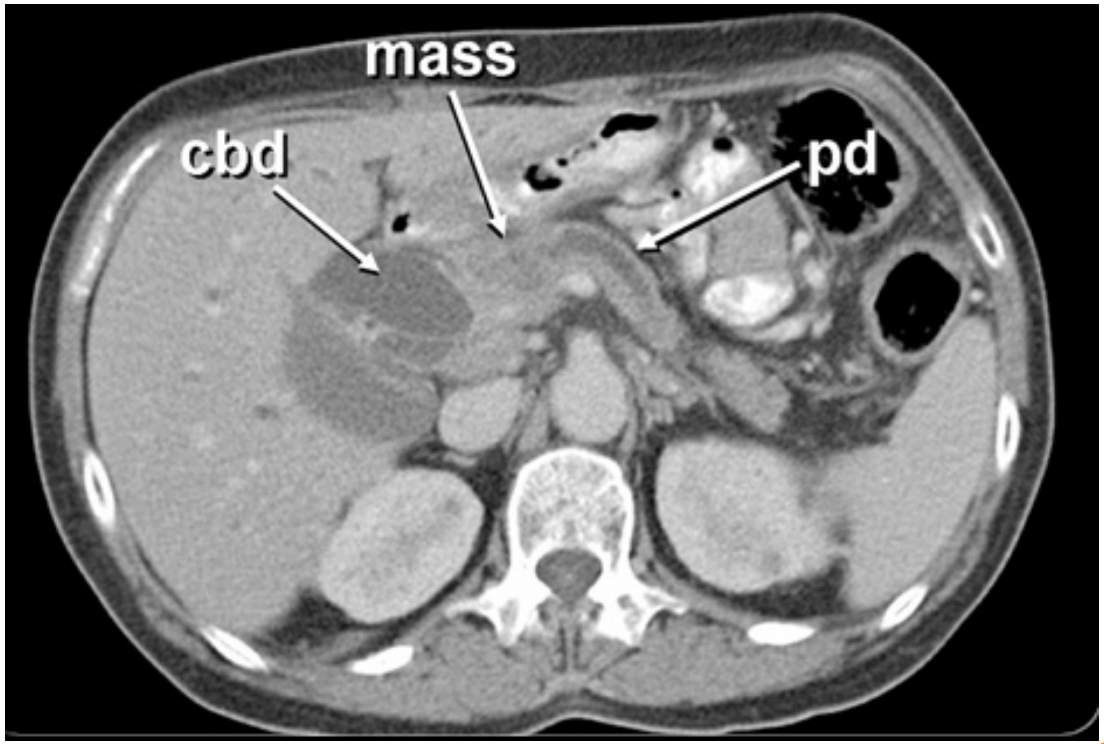
Pancreatic Carcinoma

Non-invasive imaging

- Pancreatic mass
- “double duct sign”
  - Dilated bile ducts
  - Dilated pancreatic duct

CT with oral and IV contrast:



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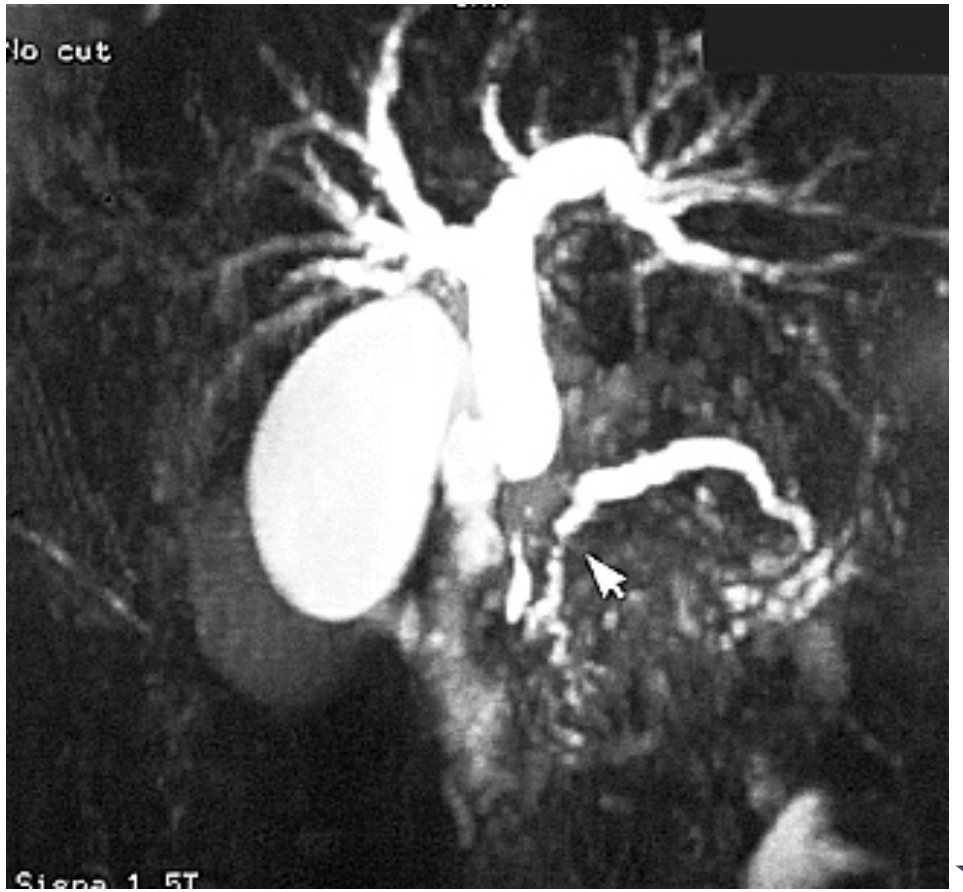
Pancreatic Carcinoma

Non-invasive imaging

MRI/MRCP:



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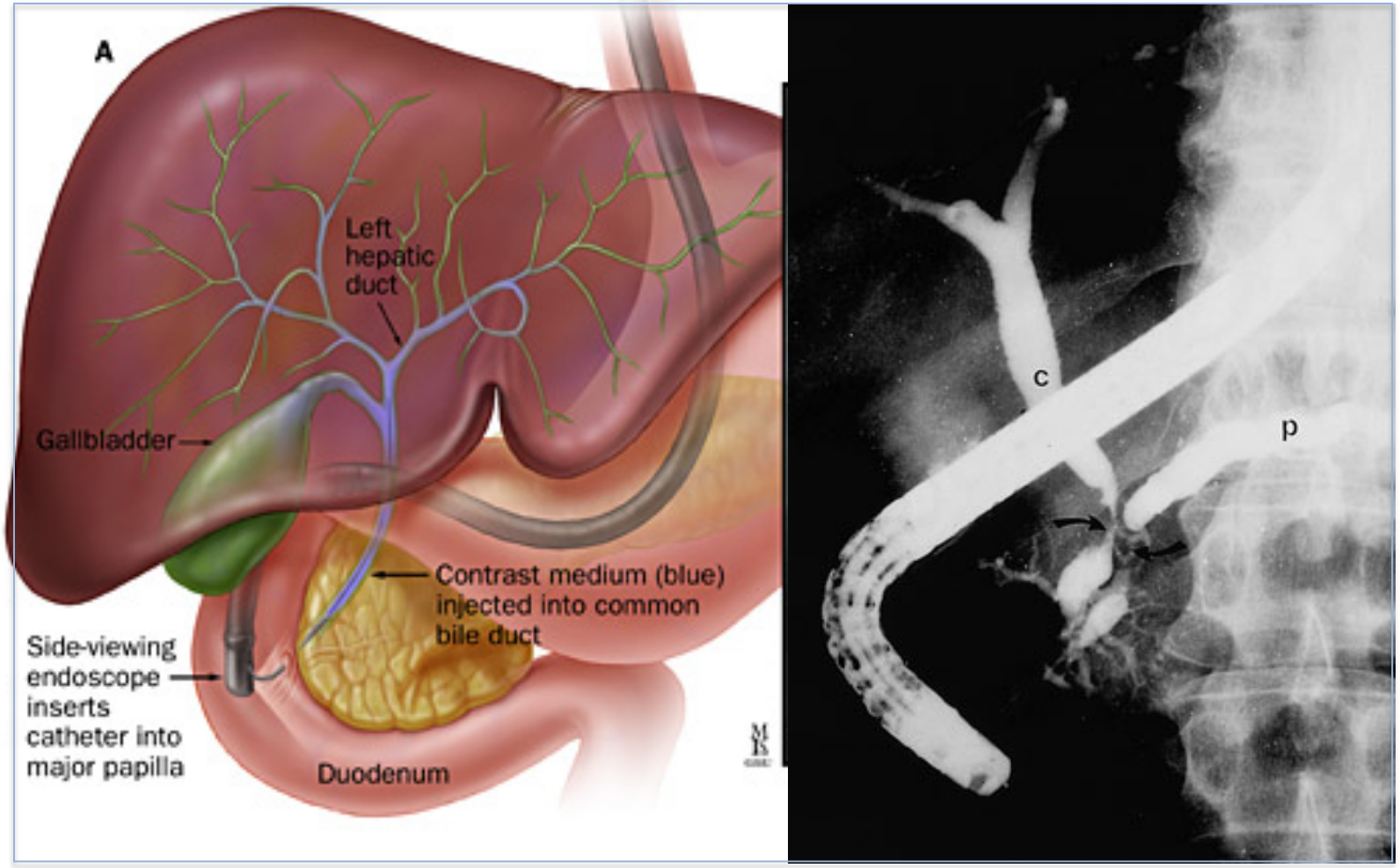
Pancreatic Carcinoma

Invasive imaging - ERCP



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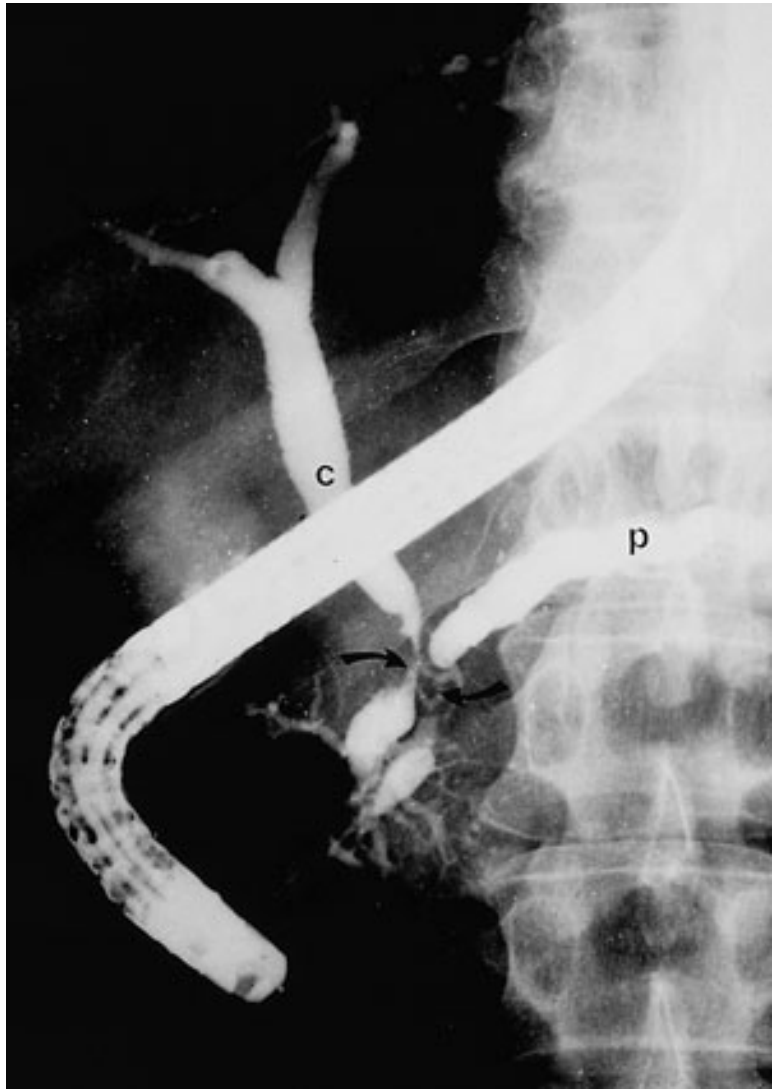
ERCP

Biliary and pancreatic strictures

Goal:

- **Sampling:**
  - **biopsy, brushing**
  - **direct bxs (Choledochoscopy)**
- Palliation of symptom
  - plastic vs metal stent



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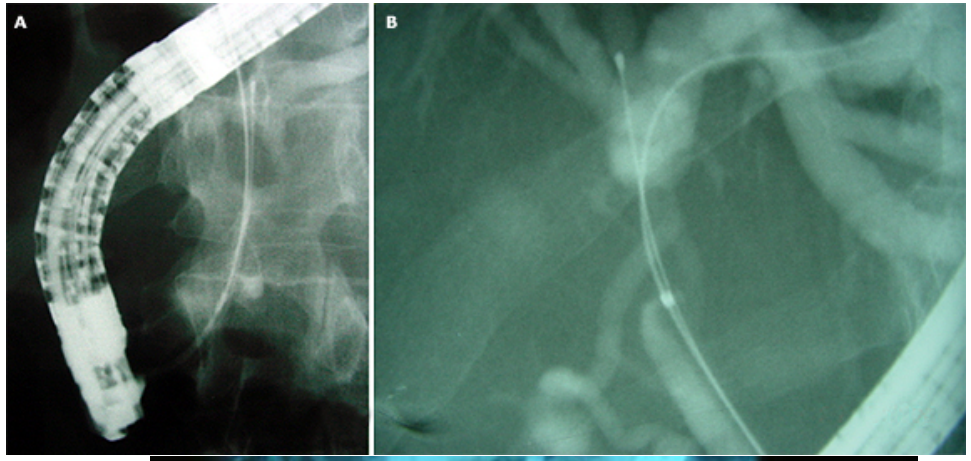
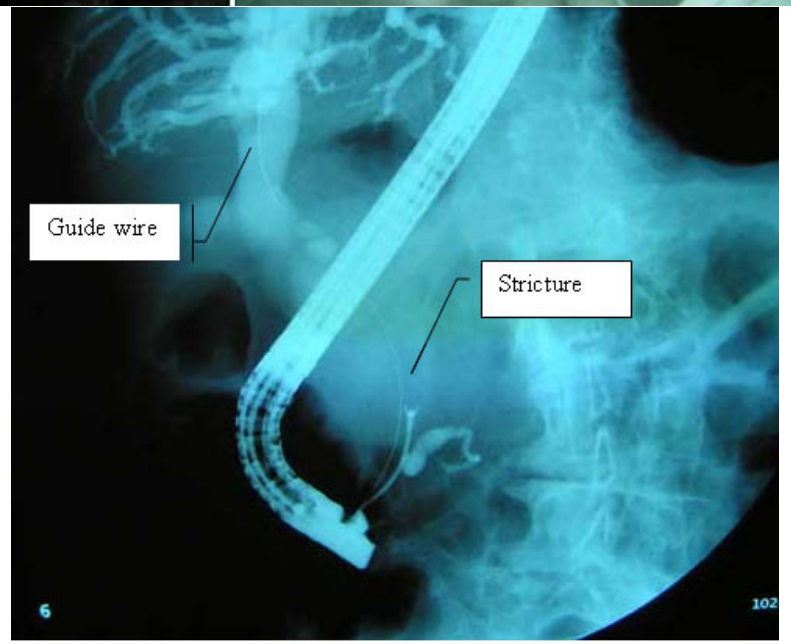
Sampling of Strictures

Yield:

- **brush** **~ 30%**
- **biopsy** **~ 30%**

35-50%





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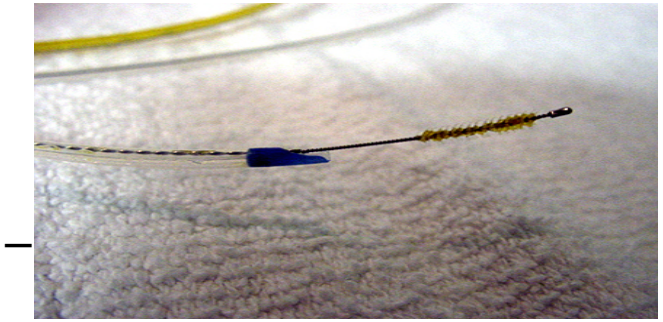

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Choledochoscopy

Directed biopsies

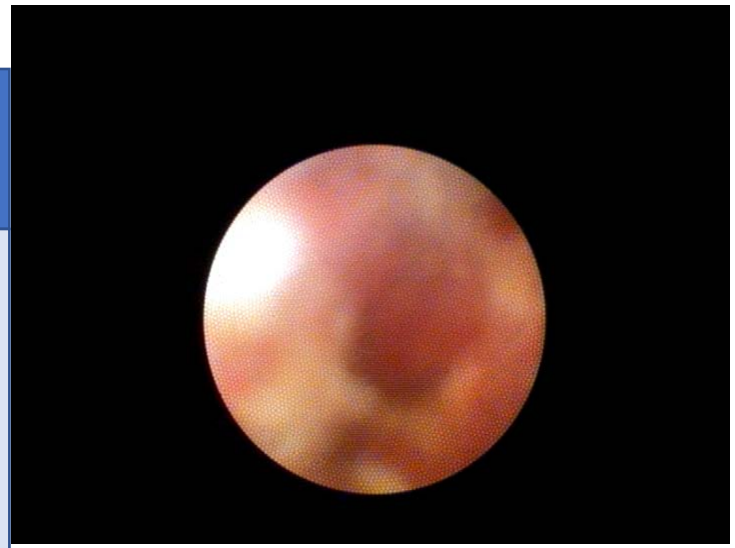
Analysis of indeterminate strictures:

intrinsic

Sensitivity	78% (21/27)
Specificity	64% (7/11)
Positive Predictive Value	95% (21/22)
Negative Predictive Value	58% (7/12)

extrinsic and intrinsic

Sensitivity	59% (23/39)
Specificity	75% (3/4)
Positive Predictive Value	100% (23/23)
Negative Predictive Value	20% (3/15)



K.F. Binmoeller et al.. Results from Biopsy of Indeterminate Biliary Strictures Does Direct Visualization Help? A Multicenter Experience

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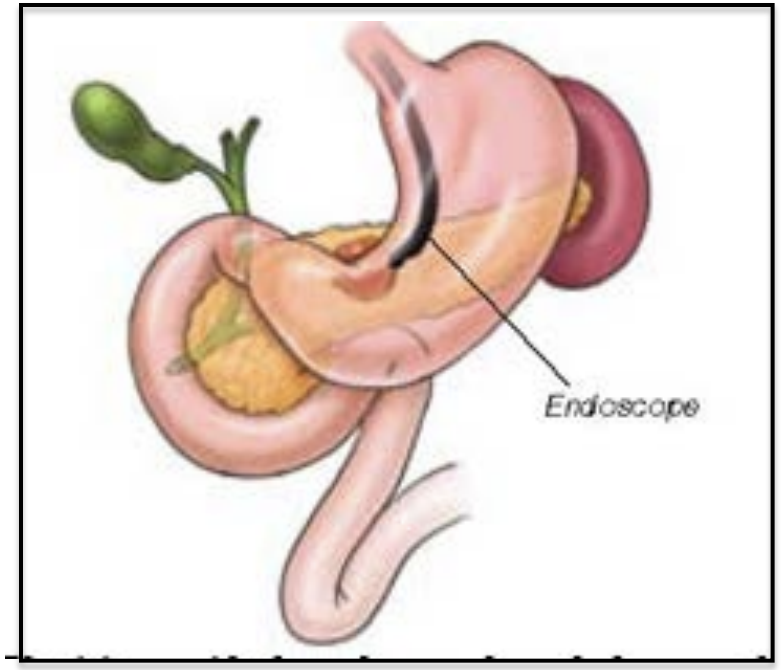
Pancreatic Carcinoma

Invasive imaging - EUS

Endoscopic **U**ltra**s**ound:



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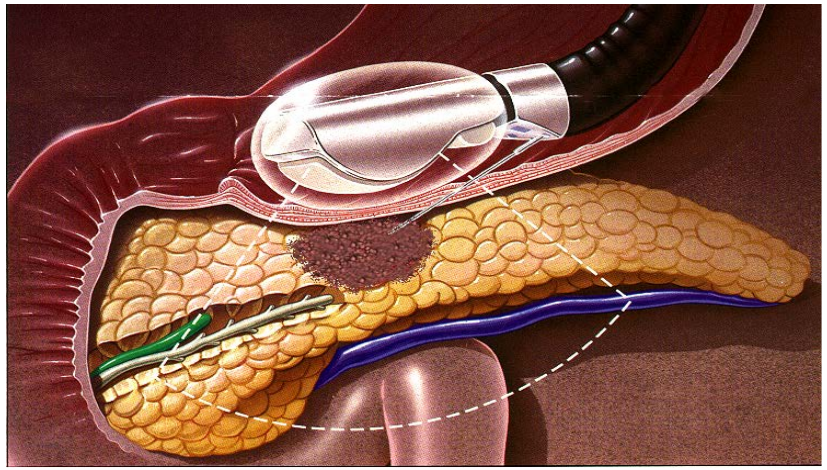
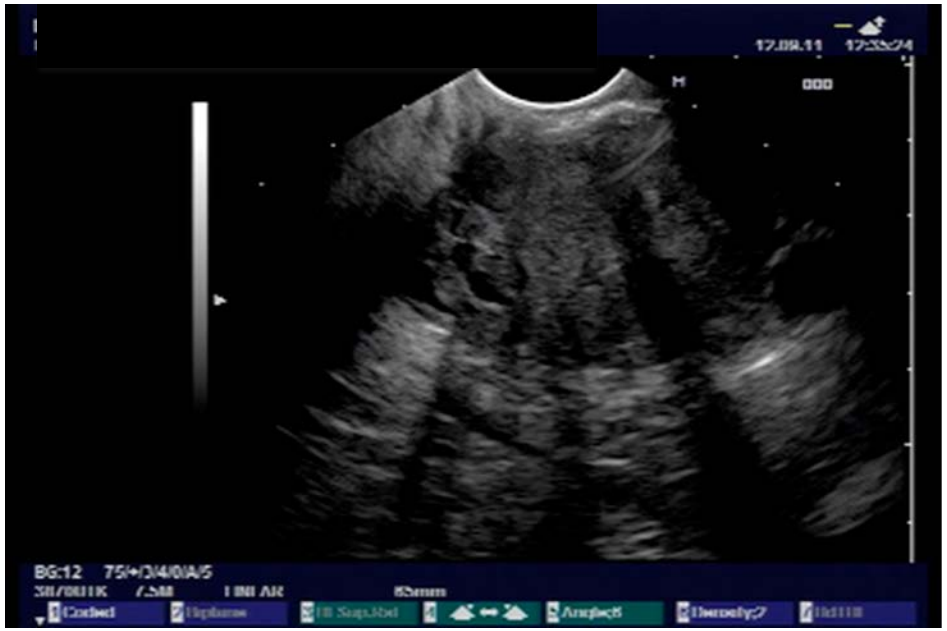
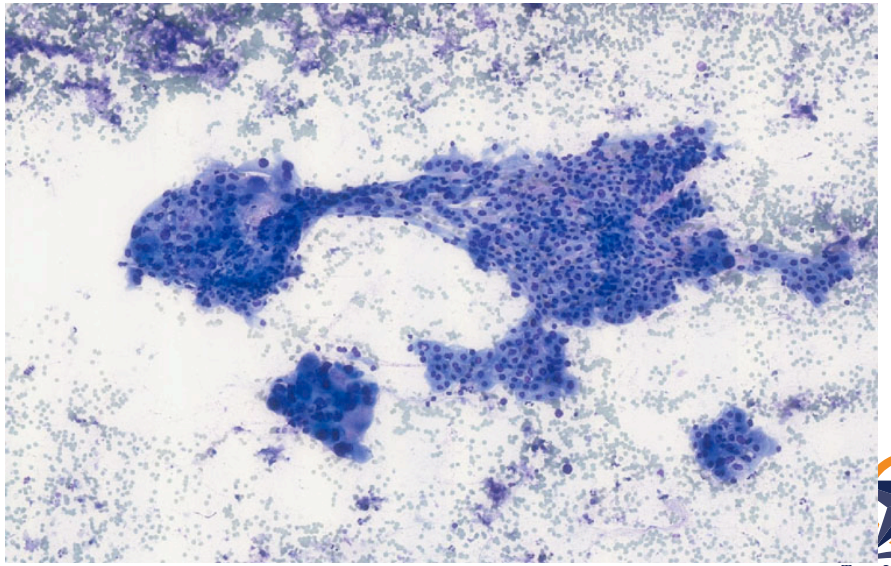
Endoscopic Ultrasound

Pancreatic cancer

Tissue acquisition: FNA







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Endoscopic Ultrasound - FNA

Sensitivity

Lesion Size (mm)	n	CT sensitivity	EUS FNA cytology correct
≤ 10	16	6%*	78%
11-20	34	38%*	81%
21-30	23	61%*	91%
>30	34	91%	95%
	107	55%*	87%

*p<.005 compared with EUS sensitivity

Patel, Catalano, Geenen et al. GIE 2005

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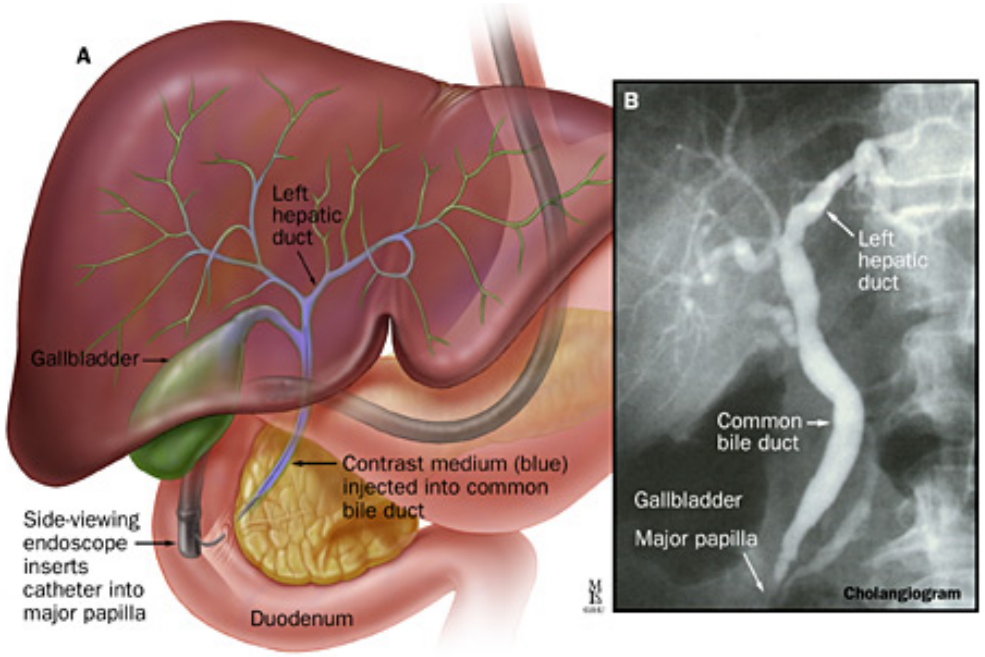
Endoscopic Retrograde CholangioPancreatography

Biliary stenting

- Safe and effective in palliating obstructive jaundice
  - CAREFUL PATIENT SELECTION
  - EMPLOY GOOD TECHNIQUE

Plastic vs Metal



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Pancreatic Carcinoma

ERCP-Palliation

- <u>GOAL</u>:

  Reestablish biliary drainage → symptom relief

- Jaundice
- Pruritus
- Abdominal pain
- Nausea/vomiting

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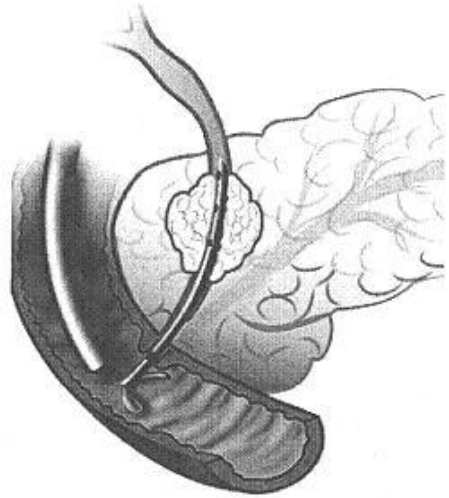
Stenting Strictures

Plastic

- Patency: 3-5 mo
- Removable
- Inexpensive



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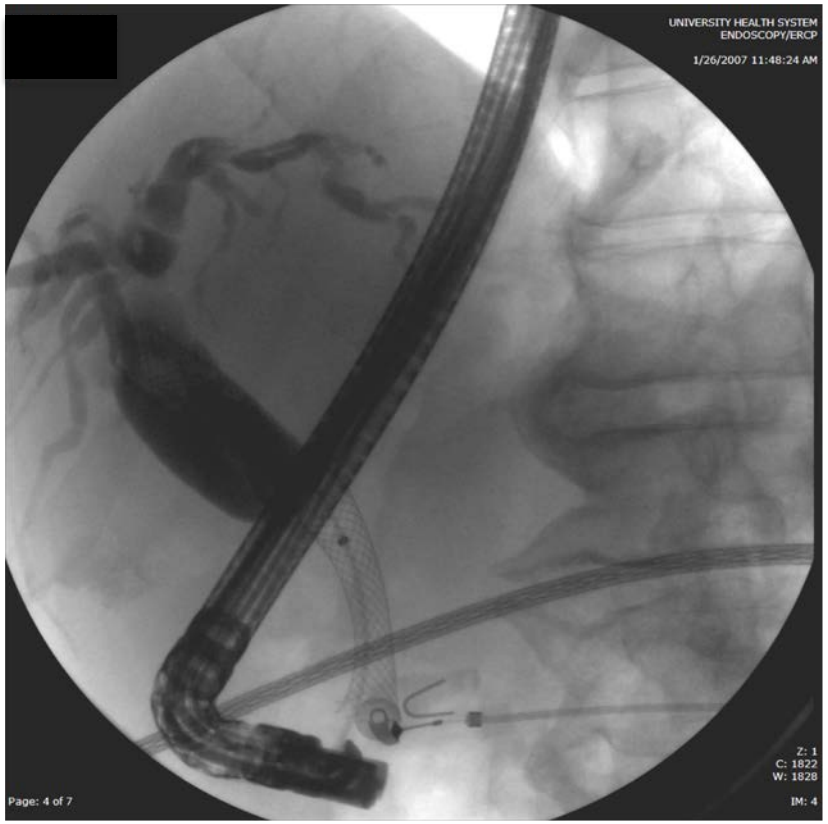
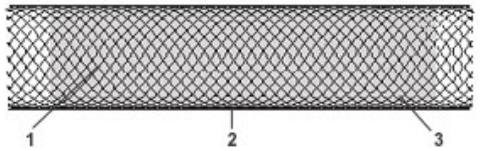
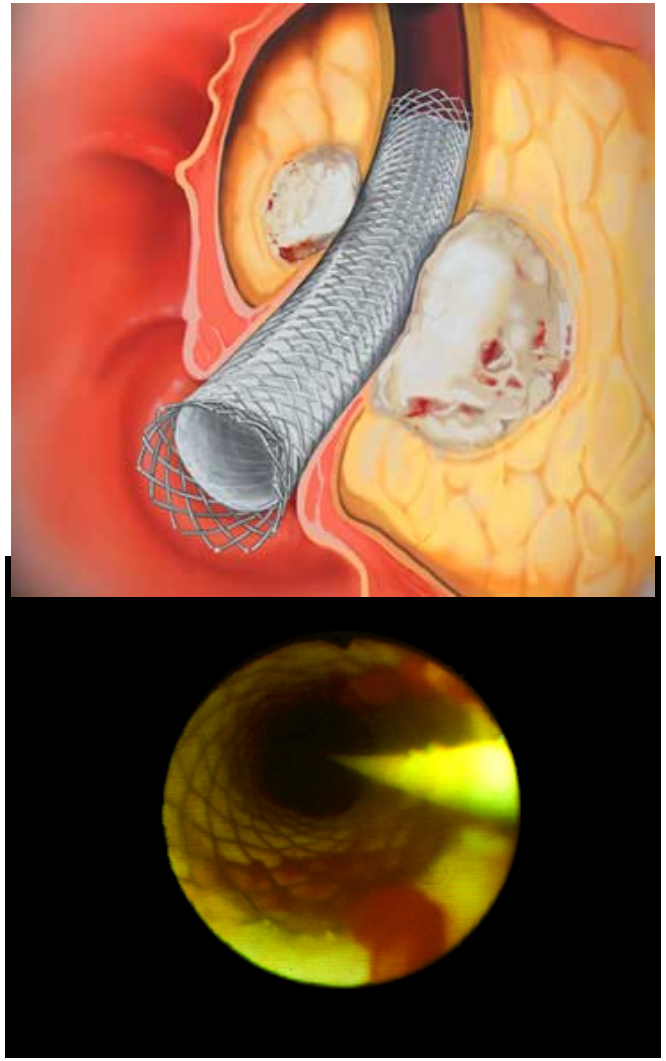
Stenting Strictures

Metal

- Patency: 9-12 mo
- Expensive +/- removable







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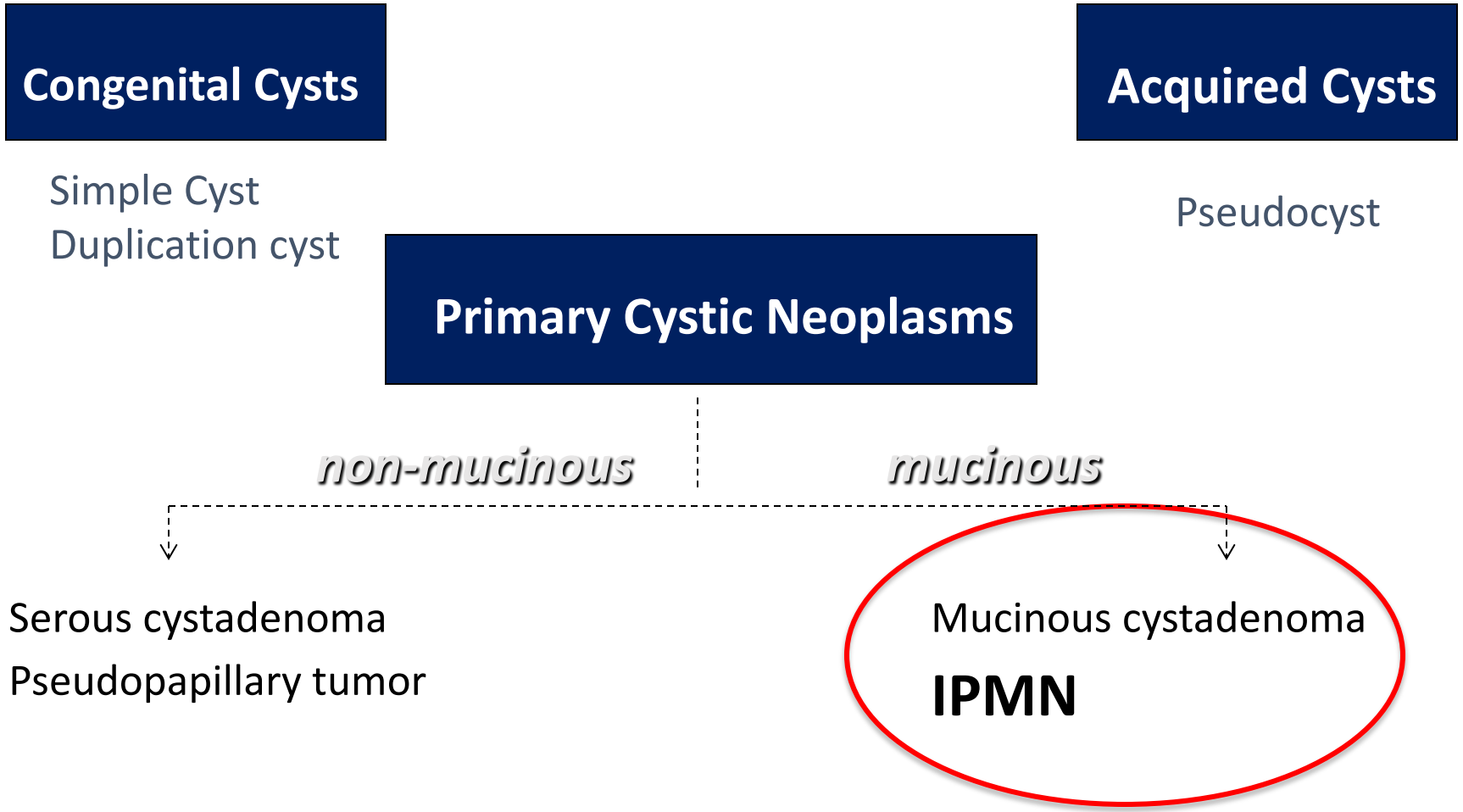
Cystic Lesions of the Pancreas



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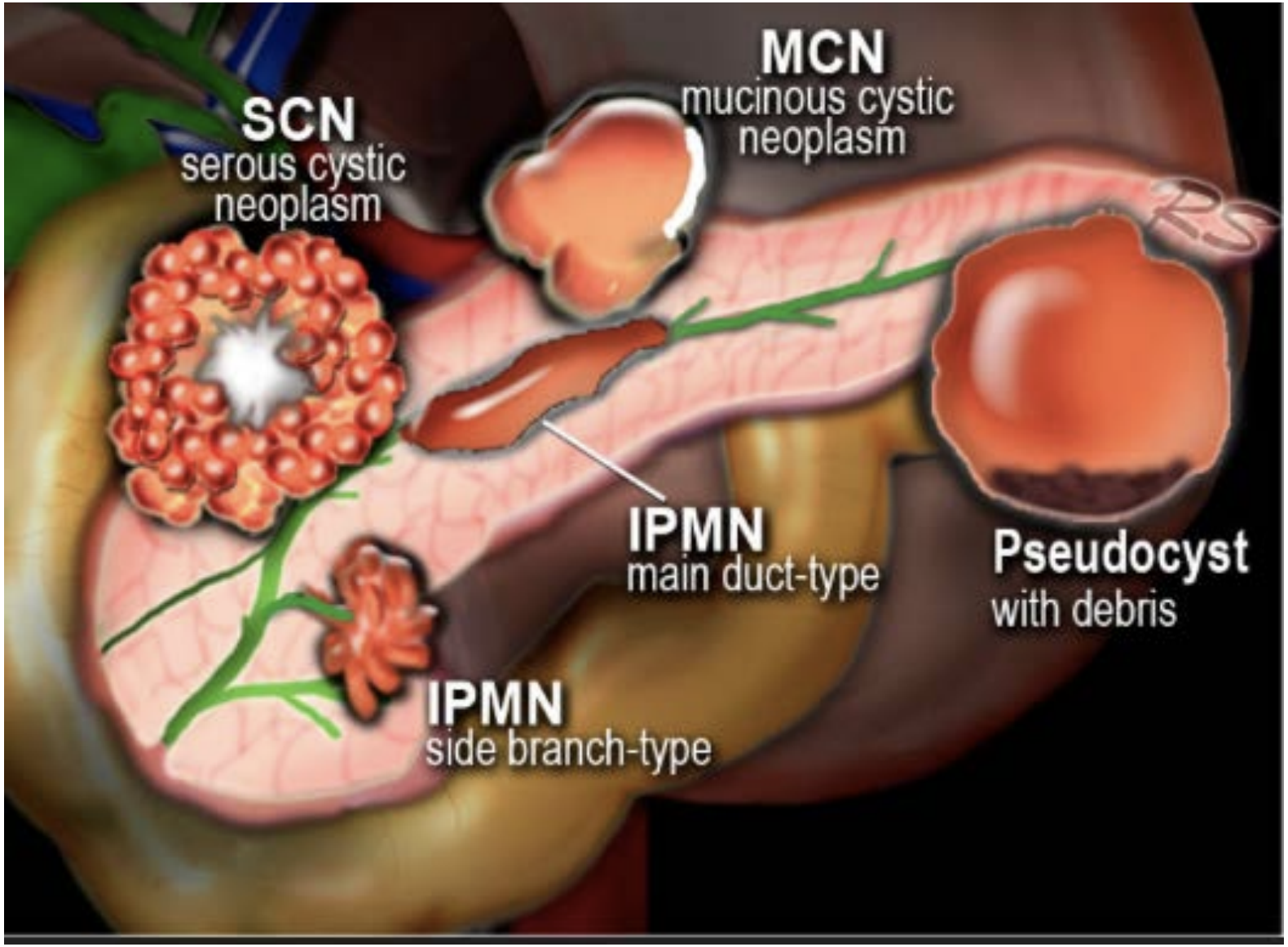
Cystic Neoplasms of the Pancreas



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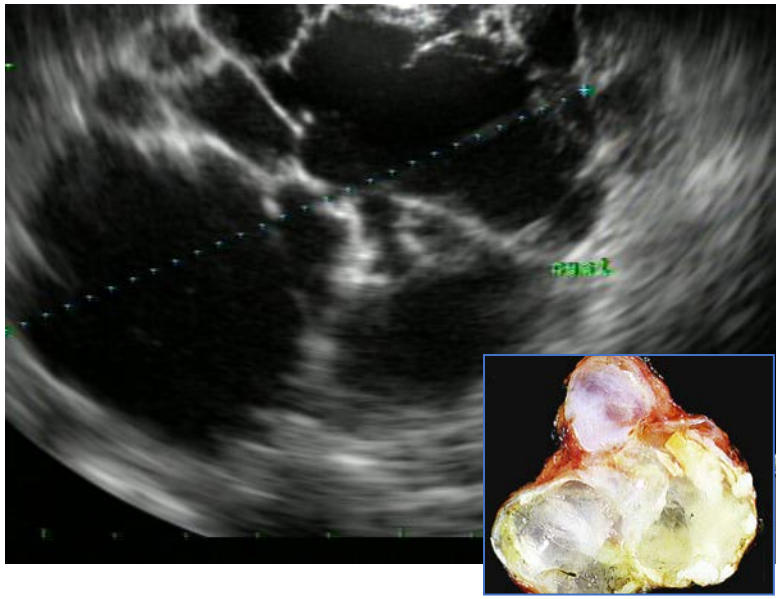
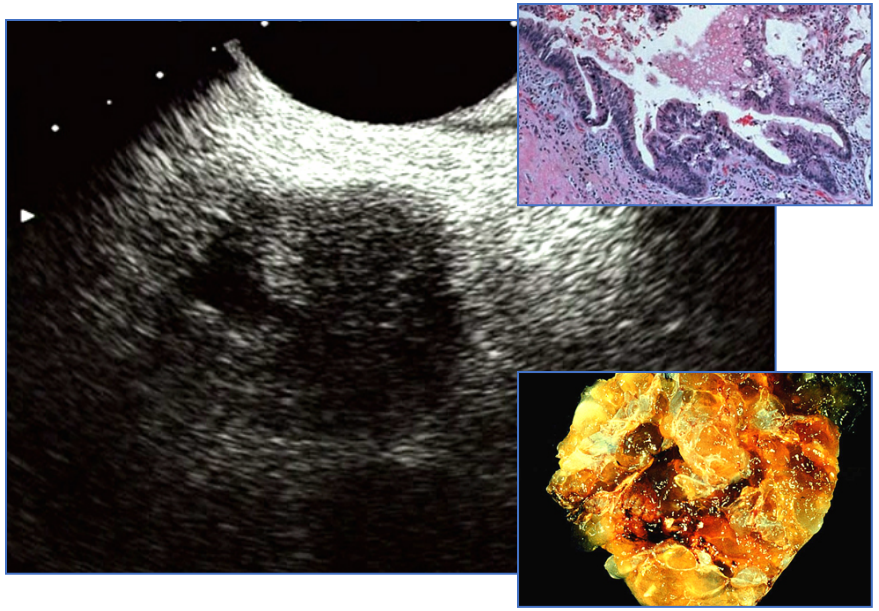
Cystic Neoplasms of the Pancreas

Mucinous cystadenoma/carcinoma





- Macrocystic lesions
- Viscous, mucoid fluid
- Fluid analysis: high CEA, low amylase, DNA analysis
- Mucin-secreting epithelial cells
- **Malignant potential**

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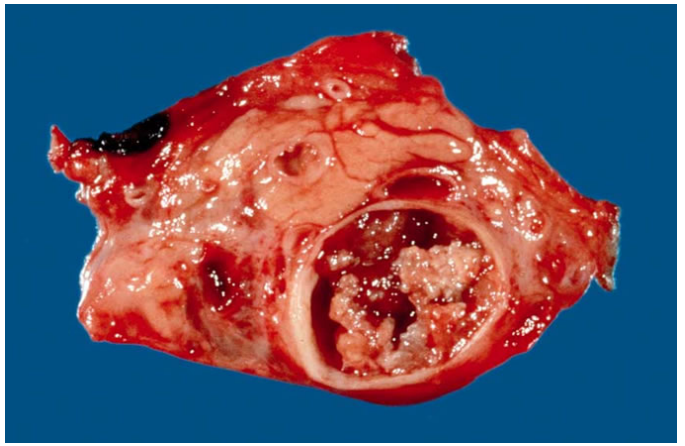
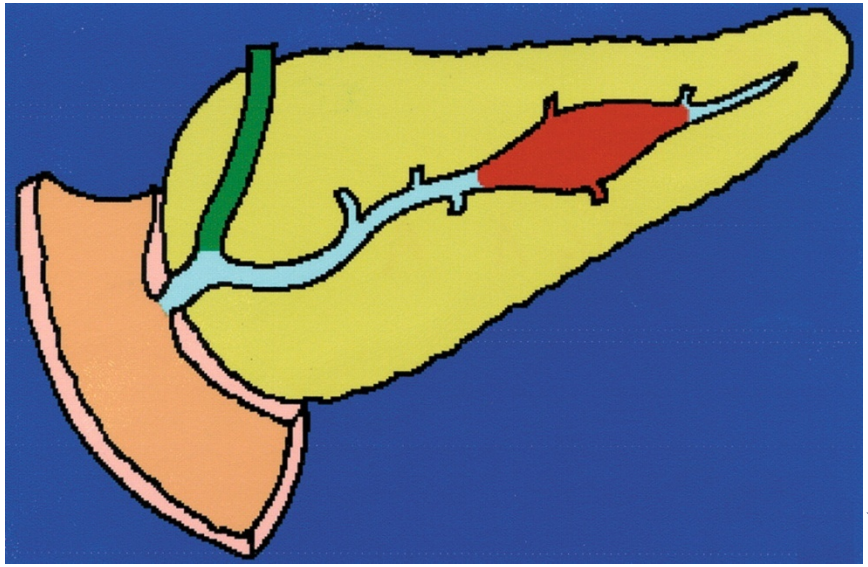
Intraductal Papillary Mucinous Neoplasm (IPMN)

- First described in 1982
- Proliferation of mucus-producing ductal epithelial cells.
- Precancerous lesion
- Rate of progression to carcinoma slow



features:

- Patulous ampullary orifice
- Dilated pancreatic duct
- Mucus secretion



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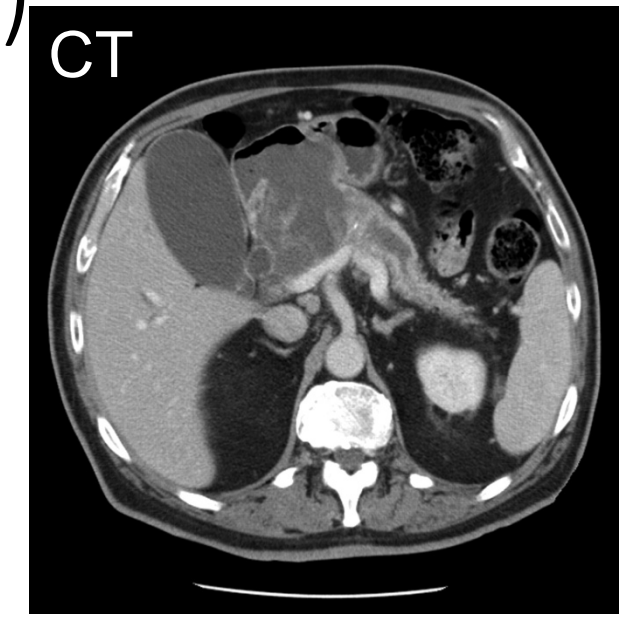
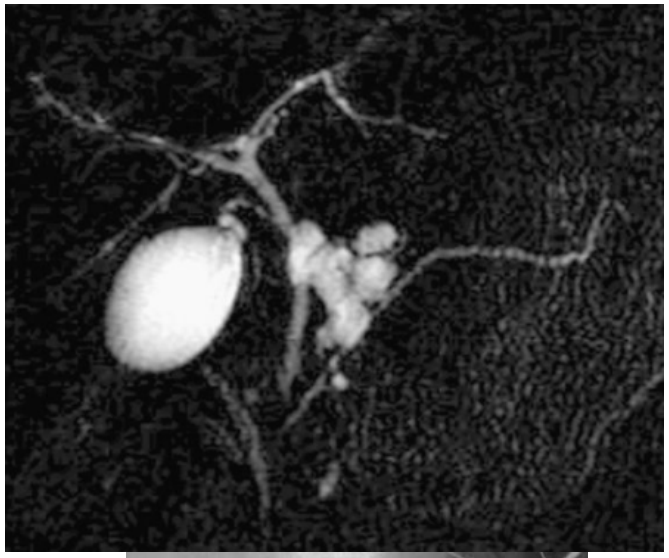
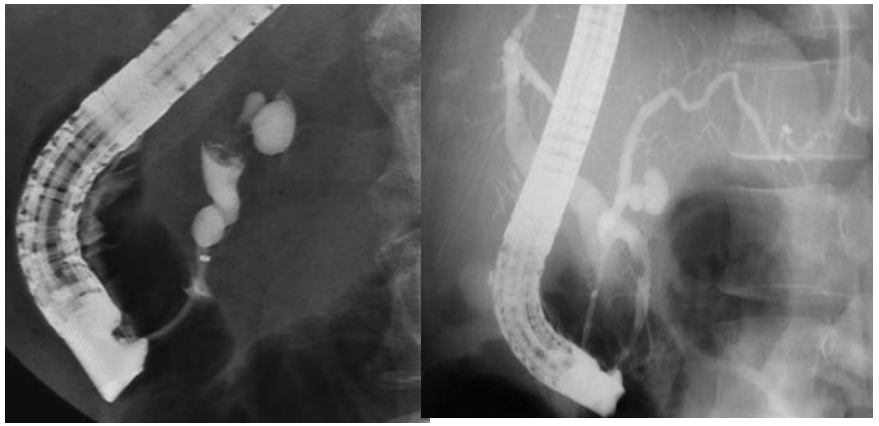
Intraductal Papillary Mucinous Neoplasm (IPMN)



MRCP



ERCP



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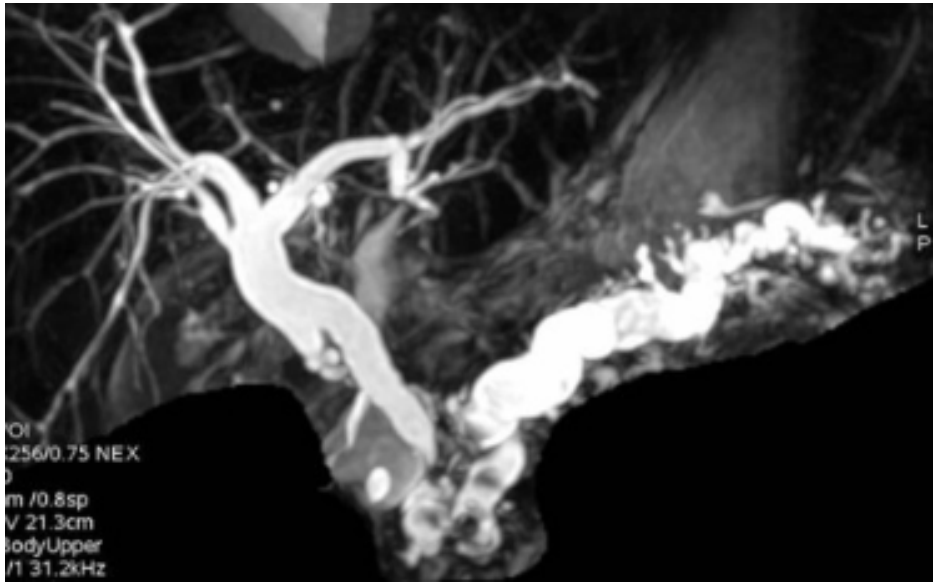
Evaluation of Intraductal Papillary Mucinous Neoplasm (IPMN)

Current limitations:

Pre-operative planning:

- Whipple
- Distal pancreatectomy
- Total pancreatectomy



What is the extent of disease ?
Is there multi-centric disease (~20%) ?

Hidetoshi et al. Cancer 107:2567

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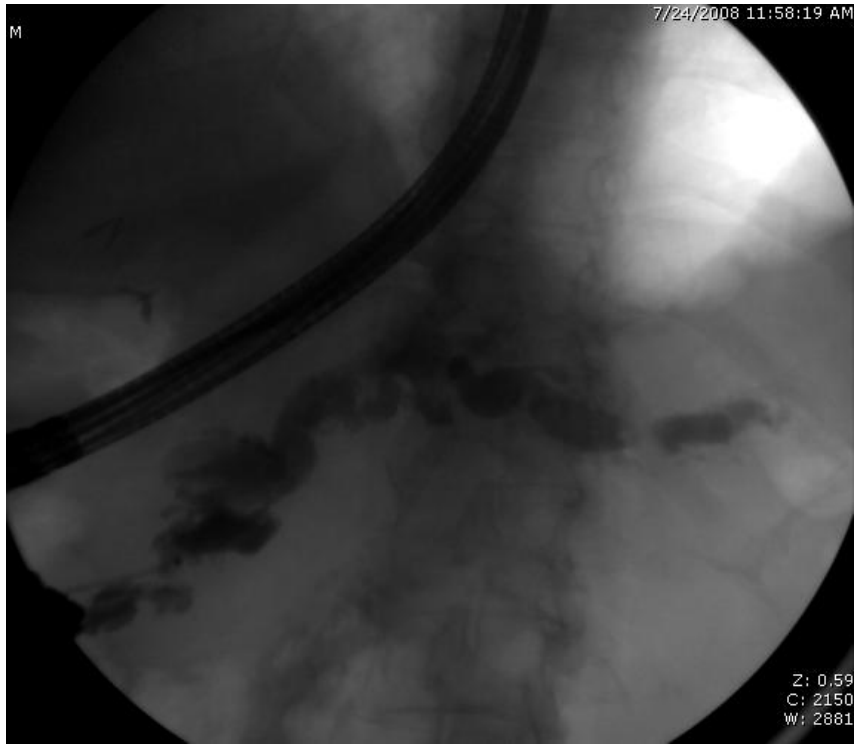
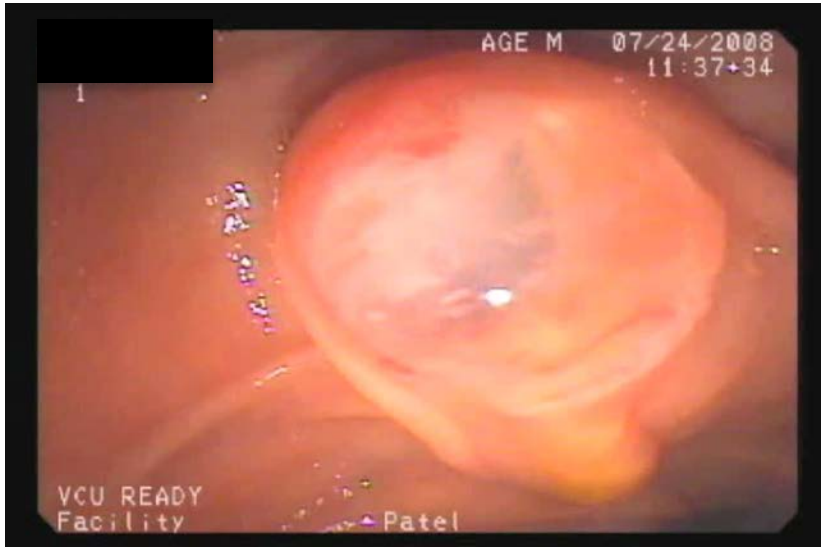
Intraductal Papillary Mucinous Neoplasm (IPMN)

Diagnosis ?





Treatment ?

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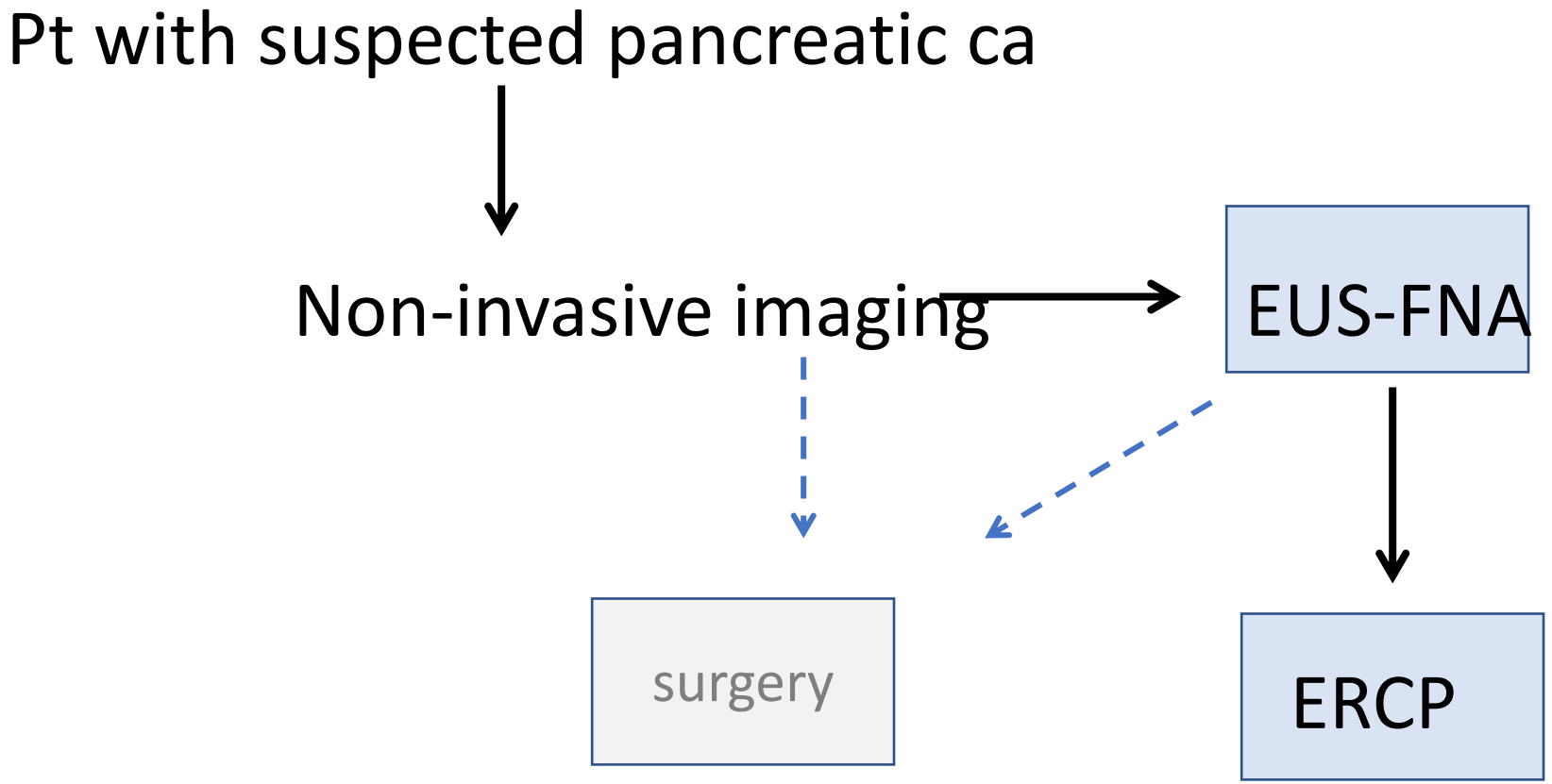
Pancreatic Carcinoma

Evaluation



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Pancreatic Carcinoma

Conclusion

- ✓ Recognize patients @ *high-risk* of developing PC.
  - Familial
  - Genetic
  - Chronic pancreatitis
  - Pancreatic cystic neoplasms
  - New-onset diabetes
  - Obesity
  - Smoking
  - Age
- ✓ Understand the modalities available for *diagnosing* pancreatic cancer:
  - EUS

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Pancreatic Carcinoma

Conclusion

- ✓ Understand the *general therapies* available:
  - Surgery for those with resectable disease
  - Neoadjuvant therapy for borderline patients
  - Endoscopic palliation