Pancreatic Cancer

Opportunities in prevention, early detection and treatment

Megan Morsi, MS, PA-C

Disclosures

Megan Morsi, MS, PA-C

No financial relationships to disclose

Objectives

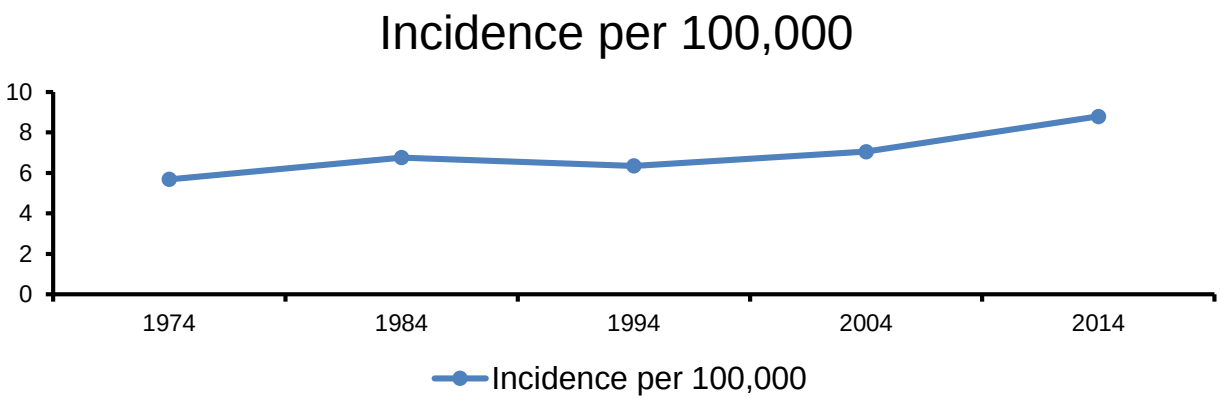
- Understand the epidemiology of pancreatic ductal adenocarcinoma
- Identify the challenges to diagnosis and treatment
- Discuss opportunities to improve early detection and treatment

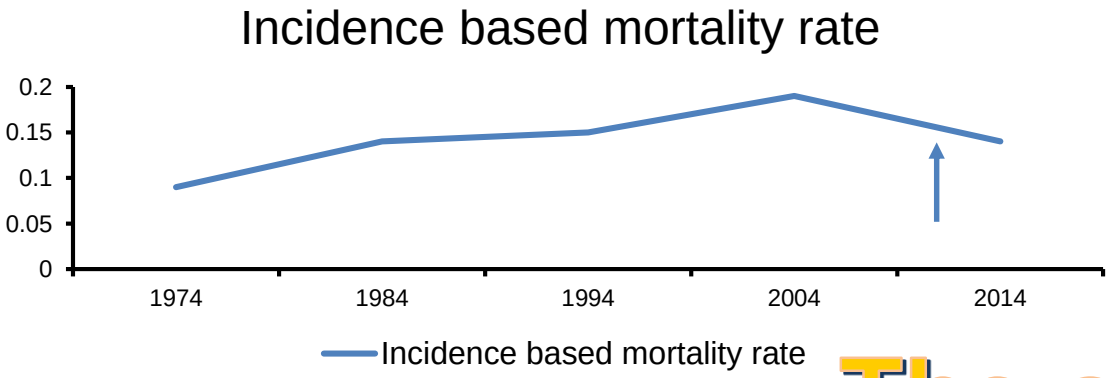
Epidemiology

The challenge:

- Pancreatic cancer (PC) is the fourth leading cause of cancer death in the US
- Pancreatic cancer accounts for 3% of all cancers
  - 7% of all cancer related deaths
- About 57,600 patients diagnosed in the US per year
- Lifetime risk of developing pancreatic cancer for an average risk individual is 1/64 (1.56%)

Epidemiology

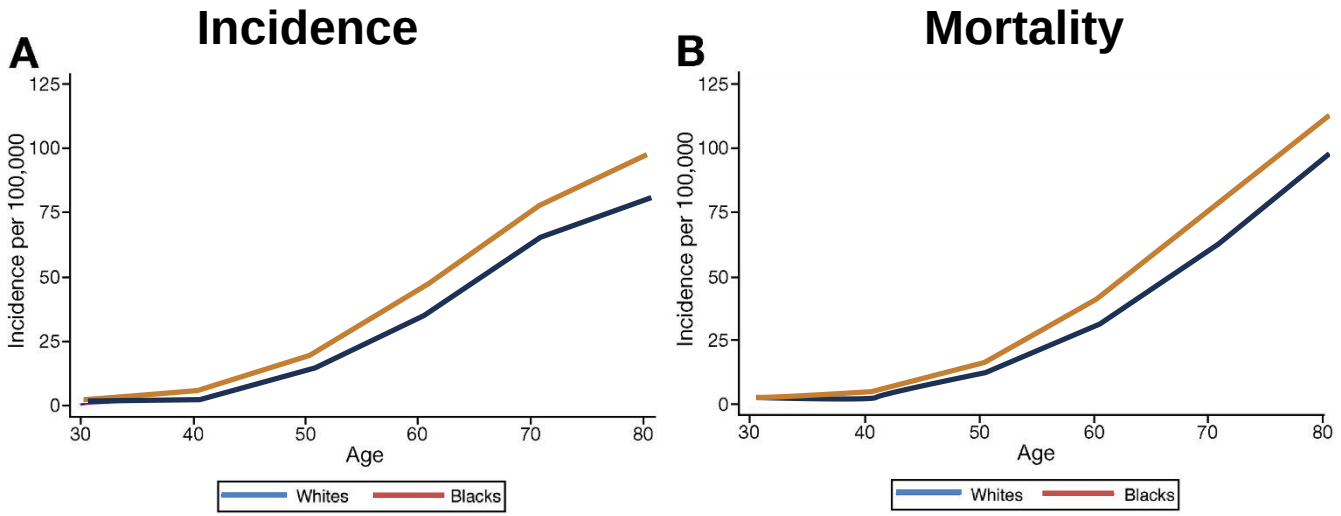




The opportunity

Epidemiology

- Racial disparities in Black and White patients exist in the US and vary based on age, geography and stage



Age-specific incidence (*A*) and mortality (*B*) rates of pancreatic cancer by 10-year age group and race, National Program of Cancer Registries. (*A*) Incidence and (*B*) mortality by race from 2001 to 2015.

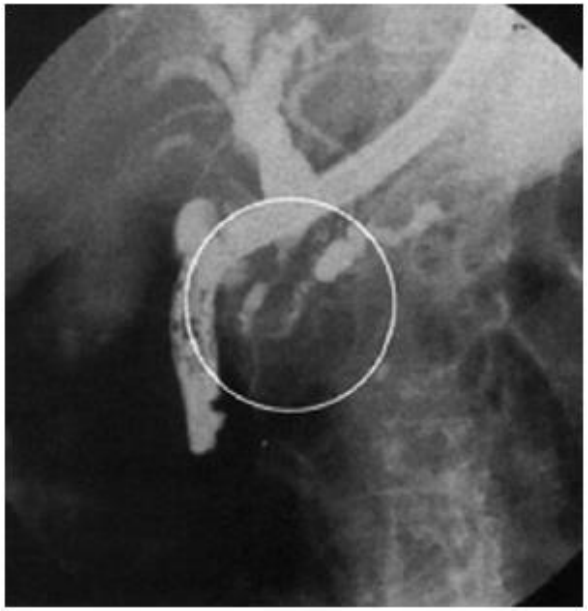
Clinical Presentation

- Painless jaundice
- Weight loss
- Anorexia
- Epigastric pain with or without radiation to the back

Physical Exam

- Palpable abdominal mass
- Supraclavicular nodes
- Peritoneal nodules (Sister Mary Joseph node)

ERCP with double duct sign



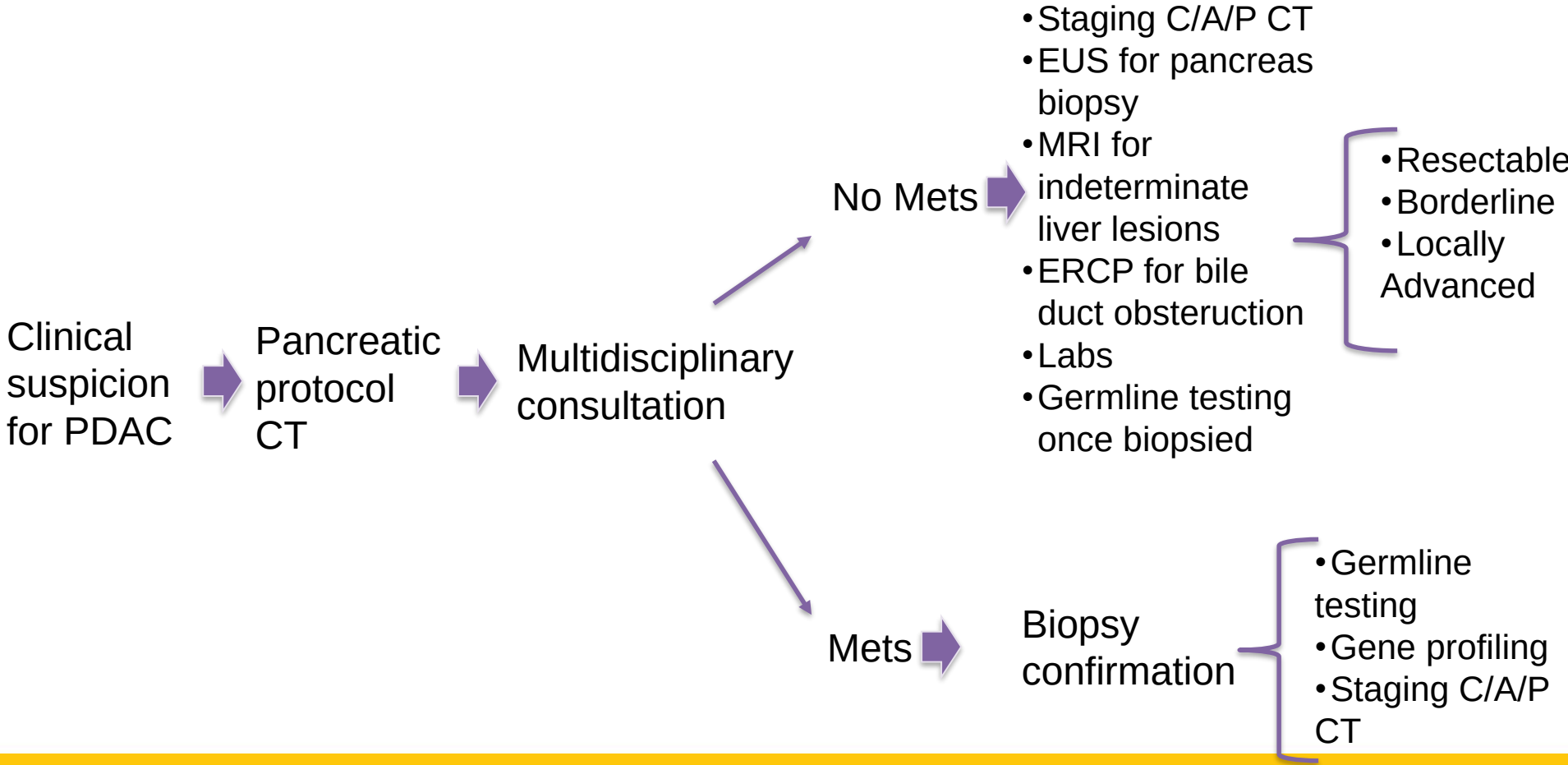
Work-Up

- EUS/FNA
  - +/- ERCP for biliary decompression
- CA 19-9, hepatic function panel
- CT chest/abdomen/pelvis
  - +/- MR
  - +/- PET

Differential Diagnoses

- Benign
  - Chronic pancreatitis
  - Autoimmune pancreatitis
  - Choledocholithiasis
- Malignant
  - Cholangiocarcinoma
  - Duodenal adenocarcinoma
  - Metastatic from breast, melanoma or renal cell
  - Pancreatic neuroendocrine tumors

Treatment – systemic therapy



Staging

Table 2. American Joint Committee on Cancer (AJCC) eighth edition staging system for pancreatic cancer			
Primary tumor (T)	**Regional lymph nodes (N)**		**Distant metastases (M)**
T1 Maximum tumor diameter ≤2 cm	N0 No regional lymph node metastasis		M0 No distant metastasis
T1 Maximum tumor diameter >2 cm but ≤4 cm	N1 Metastasis to 1-3 regional lymph nodes		M1 Distant metastasis
T3 Maximum tumor diameter >4 cm	N2 Metastasis to ≥4 regional lymph nodes		
T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)			
Stage			
Stage IA **Resectable**	T1	N0	M0
Stage IB **Borderline Resectable**	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB **Locally Advanced**	T1-T3	N1	M0
Stage III	Any T T4	N2 Any N	M0 M0
Stage IV **Metastatic**	Any T	Any N	M1

Staging

Resectable

- No arterial involvement
- <180 degrees contact with SMV and portal vein

Borderline Resectable

- <180 degree abutment of the superior mesenteric artery (SMA)
- Abutment to encasement of the hepatic artery
- Severe superior mesenteric vein (SMV) or portal vein infringement
- Short segment SMV occlusion

Locally Advanced

- >180 degree abutment of the SMA
- SMV or portal vein obliteration
- Involvement of the celiac axis
- Long segment SMV occlusion

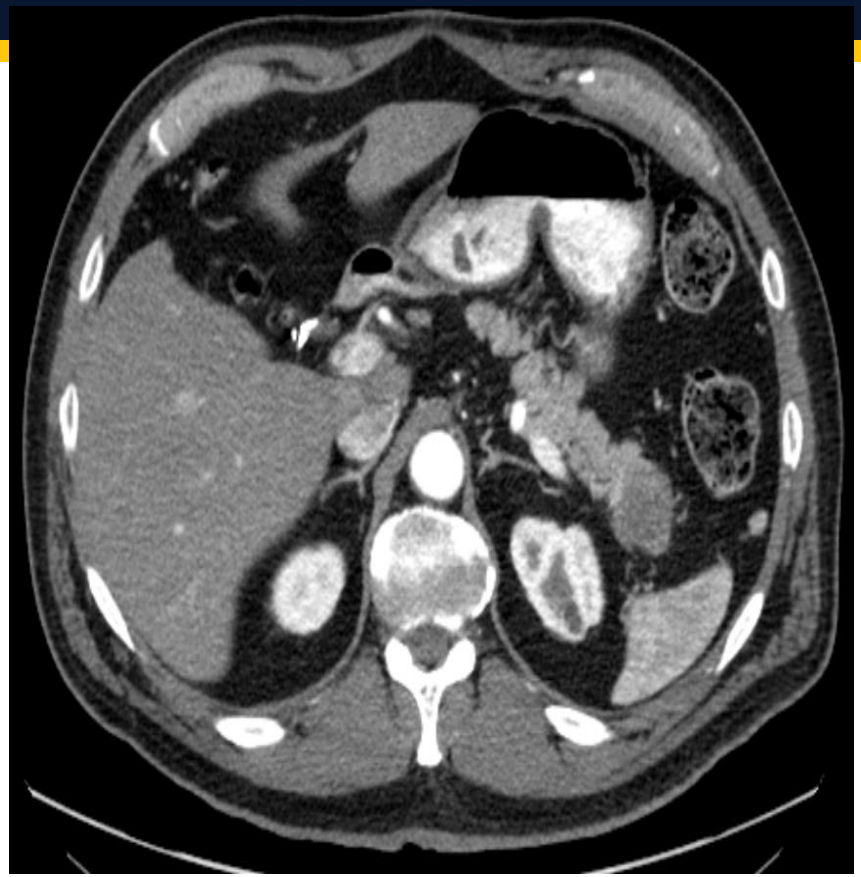
Treatment

2.2021 NCCN Guidelines

Potentially Resectable

- Separate from all vessels
- Low CA 19-9

- 2 Treatment options
  - Surgery upfront
    - Diagnostic Lap first
  - Neoadjuvant therapy



Allen PJ. JAMA 45(3):234 2010

Borderline Resectable Tumors

- Overall goal: to get to surgery with R0 resection
- Chemotherapy first
  - Gemcitabine vs. 5-FU based regimen
  - Treatment for 2-4 months
- Goal of chemo:
  - Stable disease
  - Decreasing CA 19-9 or CEA
  - No metastatic disease

Borderline Resectable Tumors

- Radiation
  - Short course
  - Long course
- What chemo with radiation?
  - Gemcitabine
  - Capecitabine
- Goal of radiation:
  - Improve chances of R0 resection
  - Decrease viability of cancer cells within the tumor

Radiation

- Toxicities
  - Dependent on field
  - Common issues
- Recovery
  - 4-6 weeks rest prior to surgery
  - High protein intake and activity level
- Very important to see surgeon prior to starting radiation!

Pancreaticoduodenectomy

- Experience matte
- Mortality <5%
- Morbidity 30-60%
- 6-10 hour surgery
- Consider j-tube placement

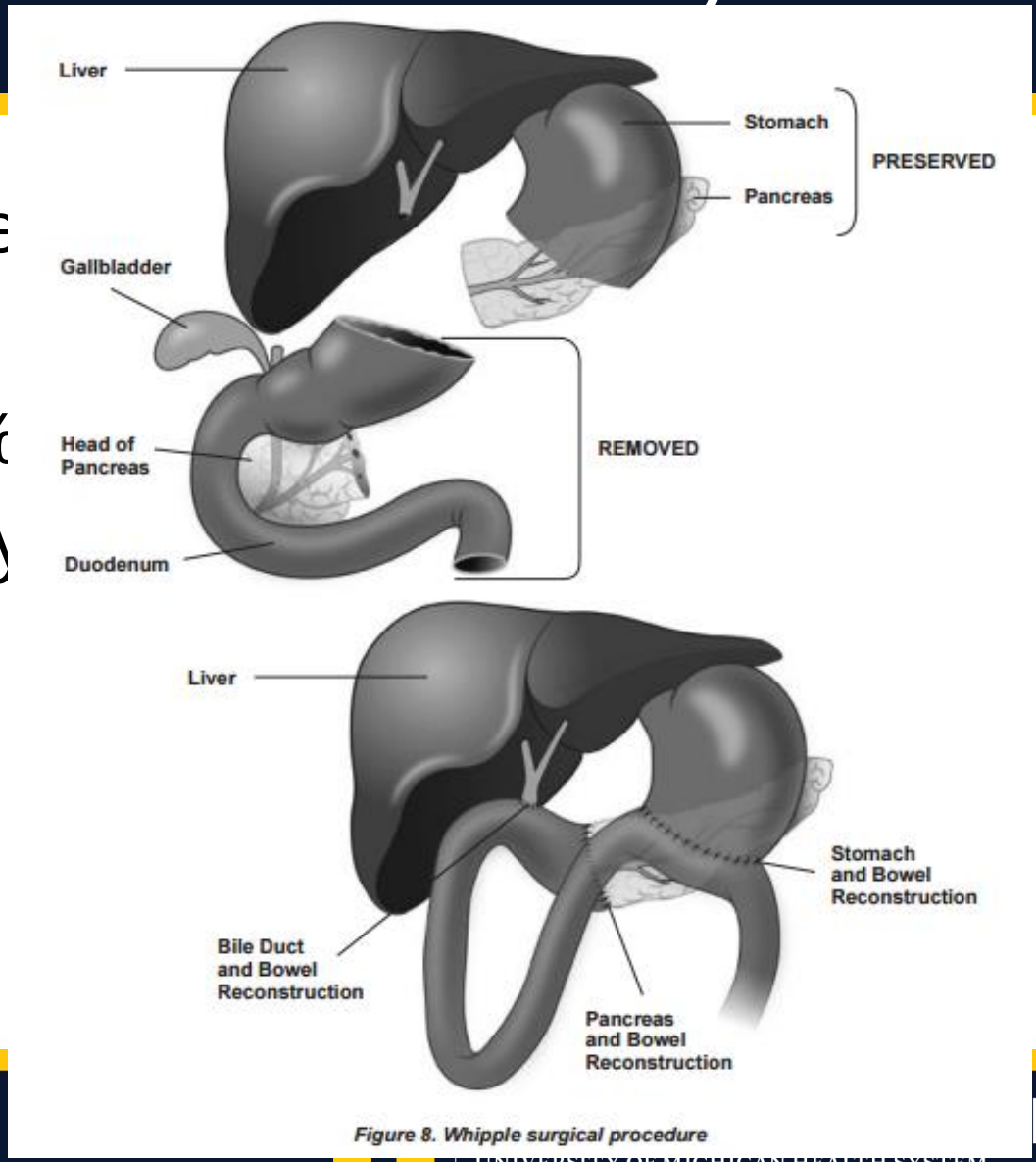


Figure 8. Whipple surgical procedure

Distal Pancreatectomy

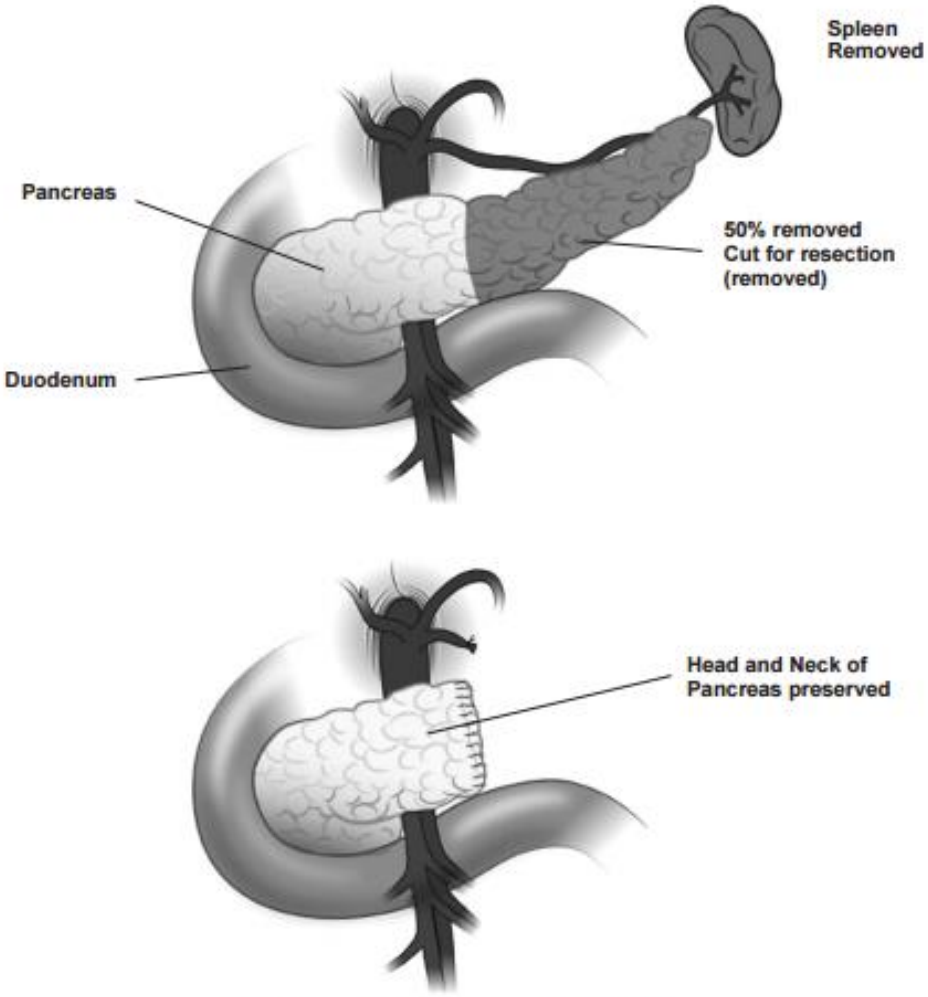


Figure 9. Distal pancreatectomy surgical procedure

- Less complications then Whipple
- Easier recovery
- 4-5 hour surgery
- Morbidity 20-30%

Complications

Pancreaticoduodonectomy (Whipple Procedure)

- Pancreatic leak
- Abscess
- Hemorrhage
- Delayed gastric emptying

Distal Pancreatectomy

- Pancreatic leak

Post Surgery

- 2 important factors:
  - Patient recovery
  - Pathology report
- Standard of care: Gemcitabine for 6 months
  - Delays disease recurrence
- Role of radiation?

Long Term Surgery Sequelae

- Diabetes
- Pancreatic Insufficiency
- Malnutrition

First Line Chemotherapy

- Three FDA approved choices
  - Gemcitabine +/- erlotinib
  - Gemcitabine + nab-paclitaxel
  - 5-Fluorouricil, oxaliplatin, irinotecan (FOLFIRINOX)

- Clinical Trials

Second Line Chemotherapy

- Consider first line response/progression
- Option of gemcitabine + _____
  - Cisplatin
  - Oxaliplatin
  - Capecitabine
  - Taxotere + Capecitabine
- FOLFOX

Treatment

The opportunity

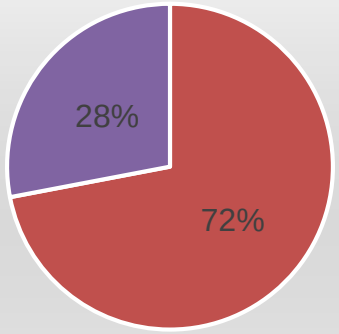
TRENDS IN PANCREATIC CANCER CLINICAL TRIALS

Treatment

The opportunity

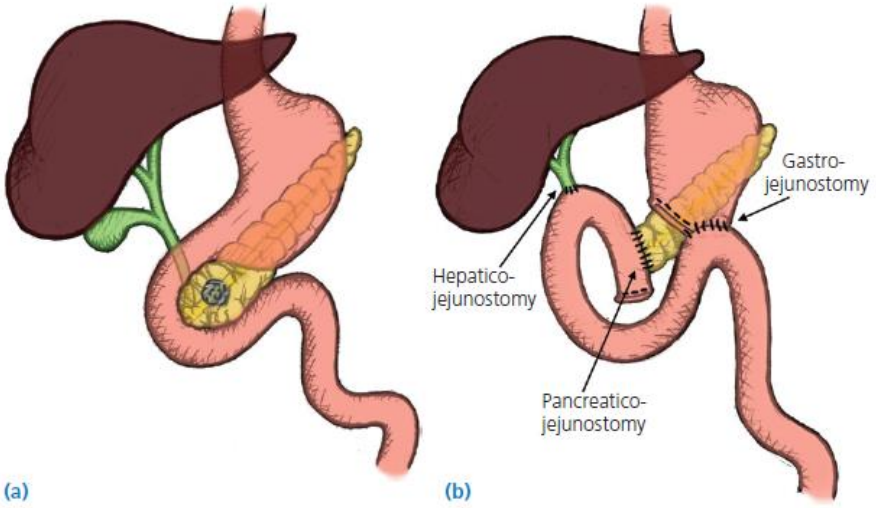
Median Overall Survival (years)

Patients with actionable mutations



Prognosis

- Resectable
  - Median survival 20 – 24 months
  - 5 year survival 15 – 20%
- Locally Advanced
  - Medial survival 8 – 14 months



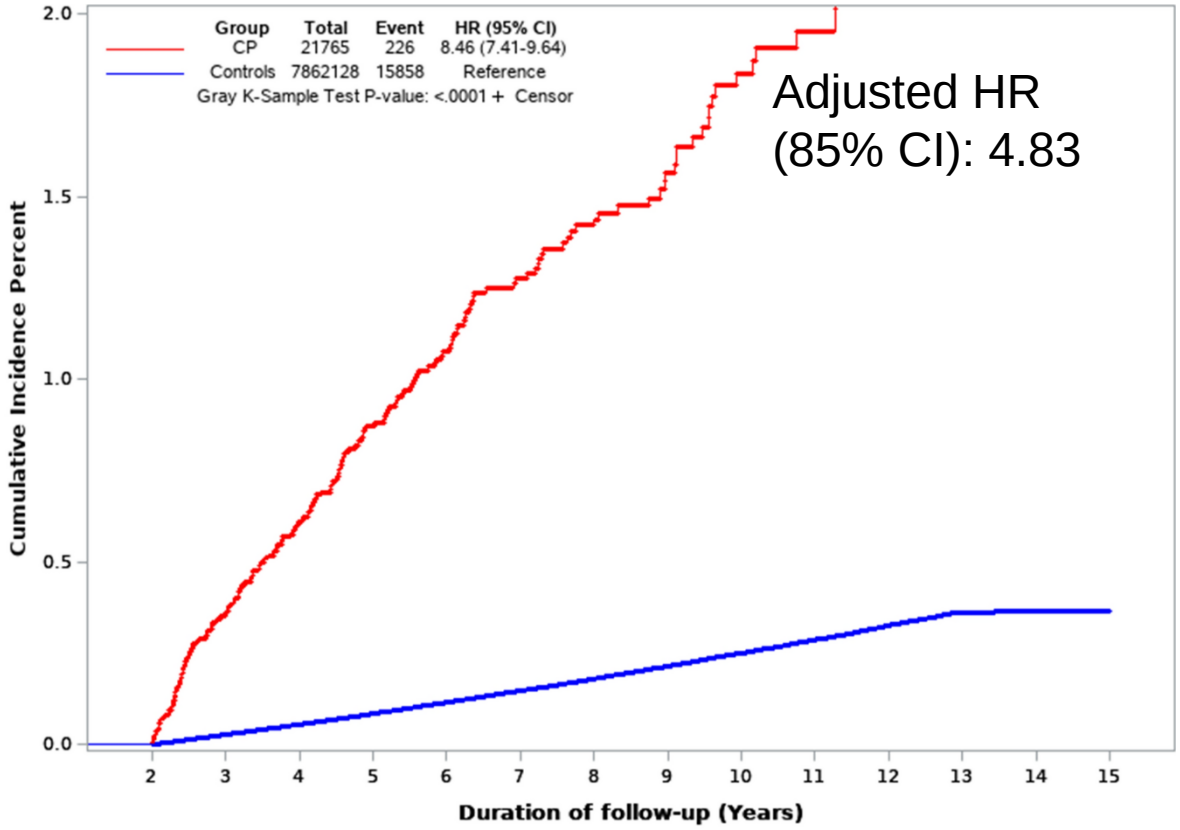
Complications

- Pain
- Biliary Obstruction: 65-75% of patients
- Duodenal obstruction (Gastric outlet obstruction) 10-25% of patients
- Anxiety/Depression
- Cachexia
- Exocrine pancreatic insufficiency
- Thromboembolic disease
- GI bleeding: rare

Who Is at Risk

- Modifiable
  - Chronic pancreatitis*
  - Smoking
  - New diabetes*
  - Obesity
  - Workplace exposures such as dry cleaning chemicals and metal working
- Non-modifiable
  - Age
  - Gender (M>F)
  - Race
  - Family History
  - Genetic syndromes

Who is at risk: Chronic Pancreatitis



Patients-at-Risk

CP	21765	18032	14901	12074	9601	7498	5716	4233	2949	1872	966	192	29	2
Controls	7862128	7190590	6552063	5982767	5433868	4882473	4346159	3788551	3192892	2561311	1919579	1076403	90099	14193

Who's at Risk: Chronic Pancreatitis

2020 International Consensus Guidelines

1. Survey patients with PRSS1 mutations

2. Do NOT survey patients with SPINK1 p. N34S mutation

3. Surveillance should be undertaken in pancreatic specialty centers

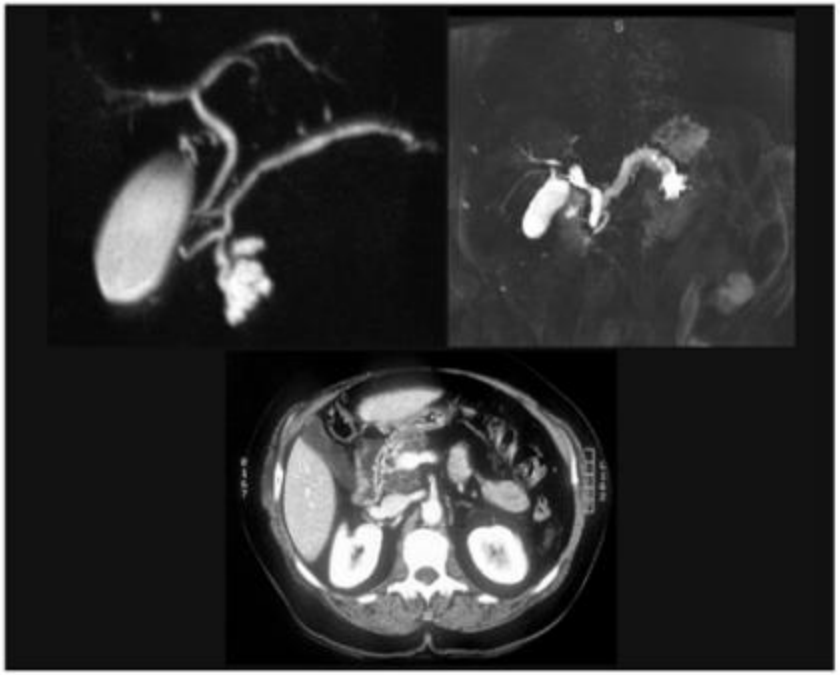
4. Surveillance should only be introduced after the age of 40 years and stopped when the patient would no longer be suitable for surgical intervention

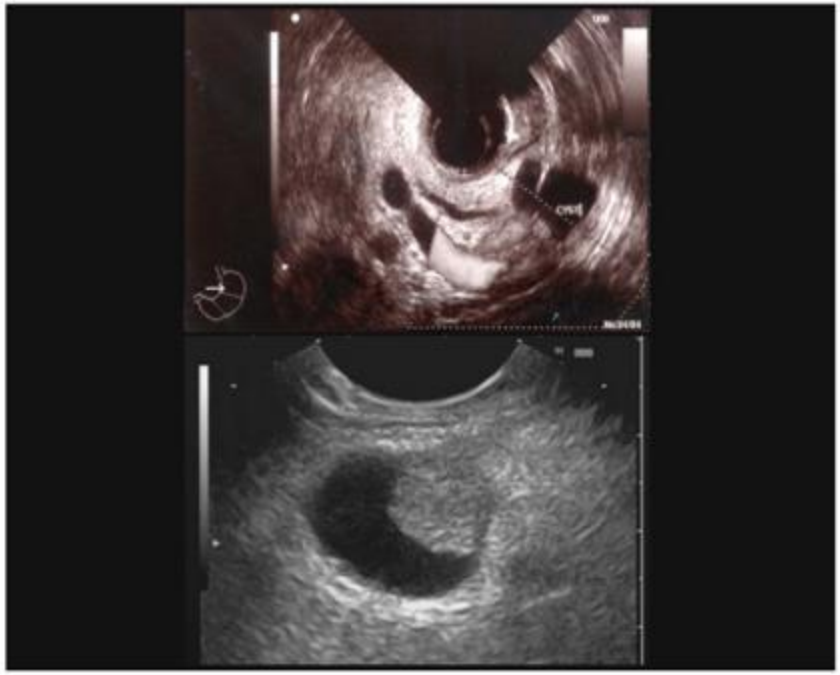
Who is at risk: Pancreatic cysts

AGA Guidelines (2015)

- Cyst < 3 cm without a solid component or a dilated duct undergo MRI for surveillance in 1 year then every 2 for a total of 5 years if no change
- Cyst with at least 2 high risk features: size > 3, main duct dilation, solid component should be examined with EUS-FNA
- Patients with a solid component and a dilated pancreatic duct and/or concerning features should undergo surgery
- MRI every 2 years following surgical resection if HGD or invasive cancer is identified

Who is at risk: Pancreatic cysts



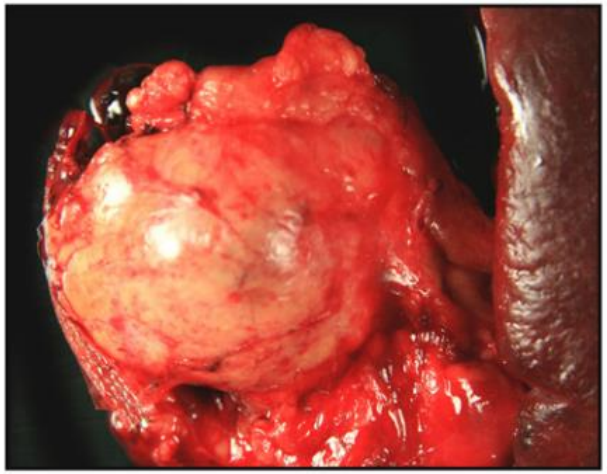


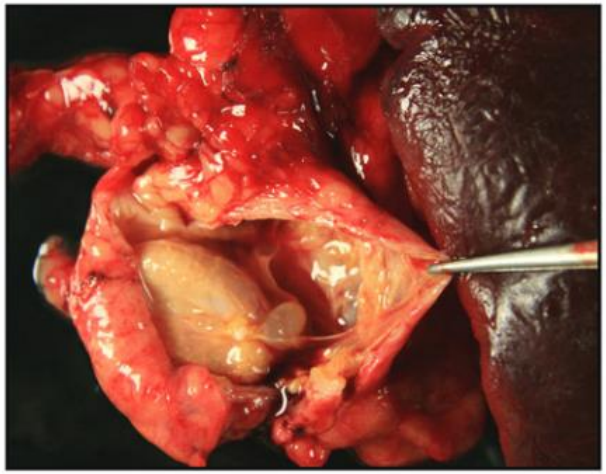
Cross sectional imaging Endoscopic Ultrasound

Gastroenterology 2013 1441303-1315DOI: (10.1053/j.gastro.2013.01.073)

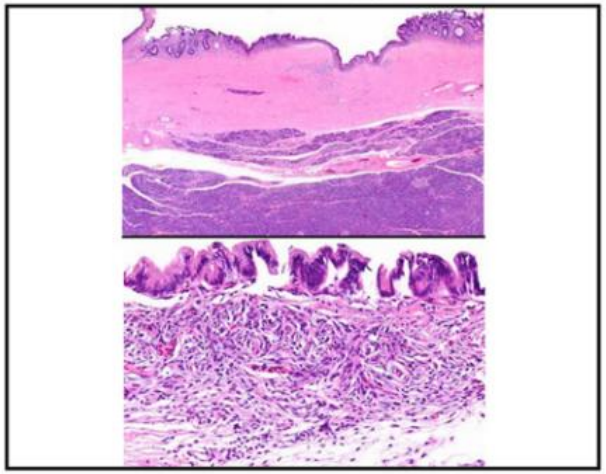
Who is at risk: Pancreatic Cysts

Surgical Resection

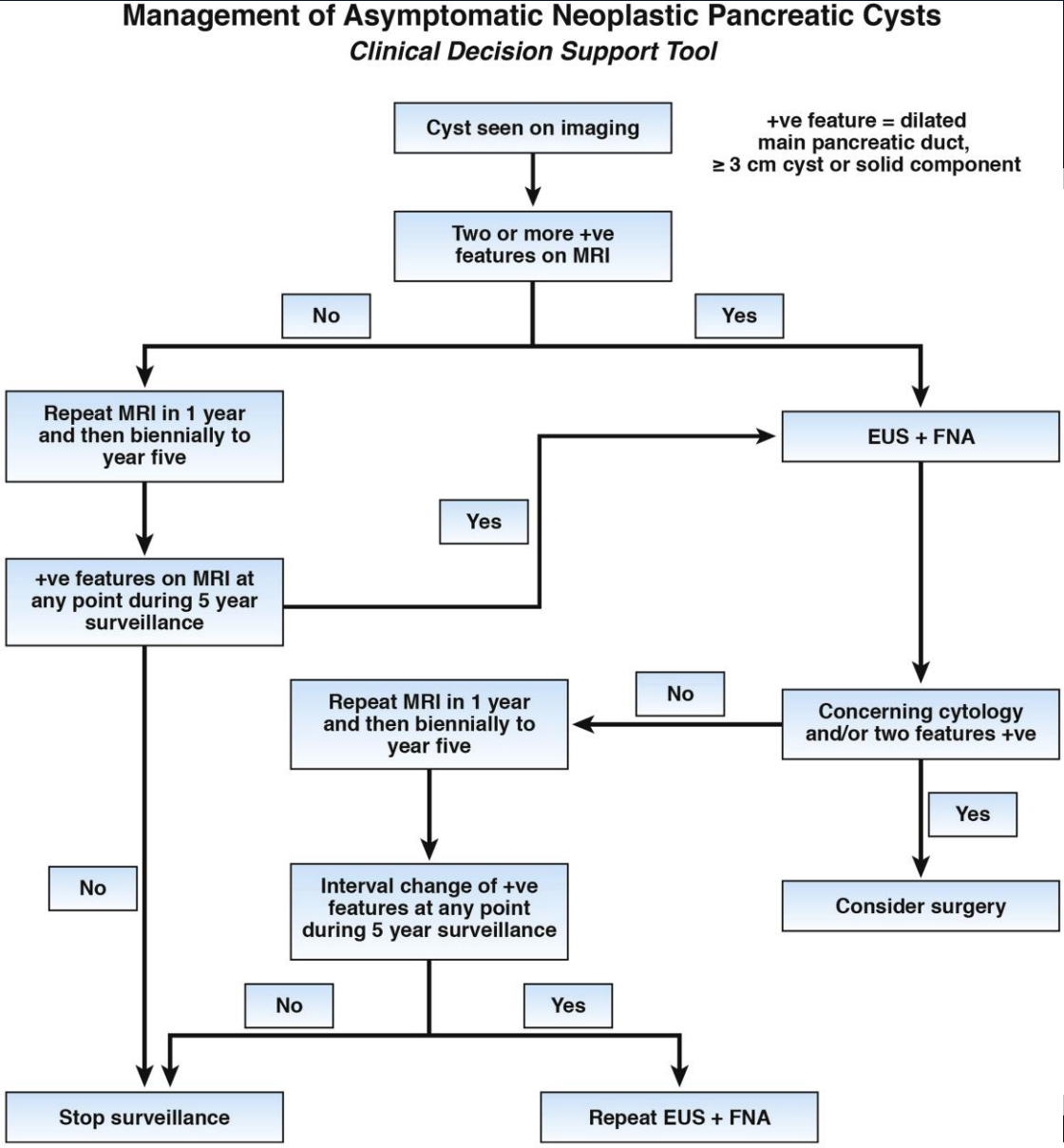




Histology



Gastroenterology 2013 1441303-1315DOI: (10.1053/j.gastro.2013.01.073)



Gastroenterology 2015 148DOI: (10.1053/j.gastro.2015.02.048)

Who Is at Risk: Genetic syndromes

Genetic Syndromes

- **Peutz-Jeghers syndrome**, caused by defects in the *STK11* gene. This syndrome is also linked with polyps in the digestive tract and several other cancers.
- **Hereditary breast and ovarian cancer syndrome**, caused by mutations in the *BRCA1* or *BRCA2* genes
- **Hereditary breast cancer**, caused by mutations in the *PALB2* gene
- **Familial atypical multiple mole melanoma (FAMMM) syndrome**, caused by mutations in the *p16/CDKN2A* gene and associated with skin and eye melanomas
- **Familial pancreatitis**, usually caused by mutations in the *PRSS1* gene
- **Lynch syndrome**, also known as hereditary non-polyposis colorectal cancer (HNPCC), most often caused by a defect in the *MLH1* or *MSH2* genes

International Cancer of Pancreas Surveillance Consortium (CAPS) Guidelines

Who?

- All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation)
- All carriers of a germline *CDKN2A* mutation
- Carriers of a germline *BRCA2, BRCA1, PALB2, ATM, MLH1, MSH2,* or MSH6 gene mutation with **at least one affected first-degree blood relative**
- Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

International Cancer of Pancreas Surveillance Consortium (CAPS) Guidelines

When?

Mutation carriers: For CDKN2A, Peutz-Jegher syndrome	Start at age 40
BRCA2,ATM, PALB2 BRCA1, MLH1/MSH2	Start at age 45 or 50 or 10 years younger than youngest affected blood relative
Familial pancreatic cancer kindred (without a known germline mutation)	Start at age 50 or 55 or 10 years younger than the youngest affected blood relative

There is no consensus on the age to end surveillance

International Cancer of Pancreas Surveillance Consortium (CAPS) Guidelines

How?

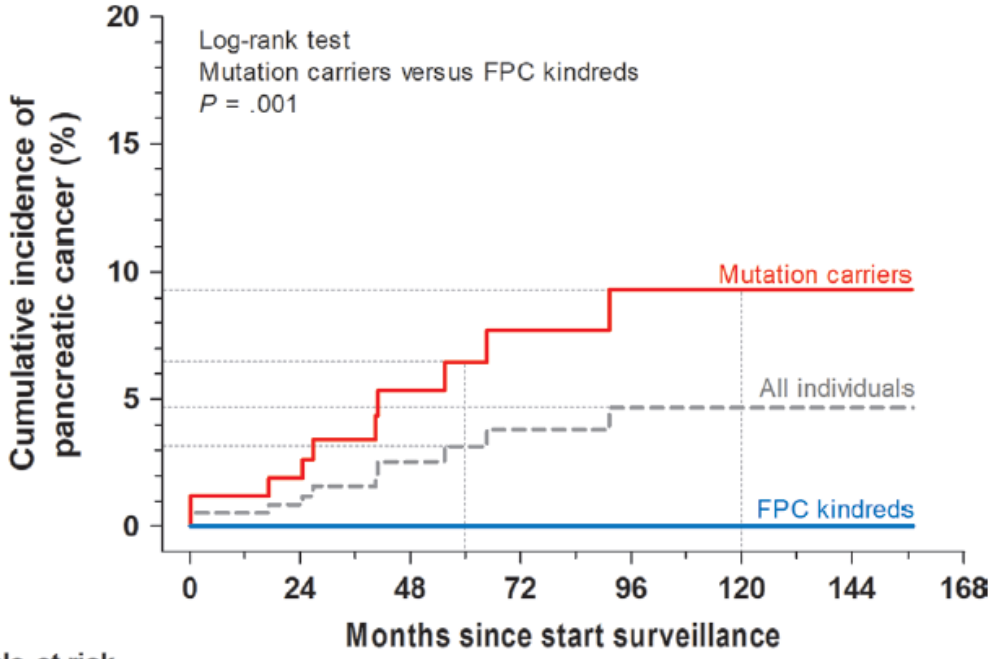
At Baseline	MRCP/MRI OR EUS* Fasting glucose or HbA1C
During Follow-up	Alternate MRI/MRCP and EUS (no consensus if and how to alternate) Fasting glucose or HbA1C
On indication	Serum CA 19-9 → concerning features by imaging EUS with FNA → cystic lesions with worrisome features, solid lesions >5 mm, and asymptomatic MPD stricture CT → asymptomatic PD stricture of unknown etiology

International Cancer of Pancreas Surveillance Consortium (CAPS) Guidelines

Interval?

12 months	If imaging is normal
3 or 6 months	If concerning abnormalities for which surgery is not immediately indicated
Surgery	If imaging is highly suspicious for malignancy or (+) FNA on EUS

Is this effective?



Individuals at risk								
All individuals	366	289	183	124	106	61	12	0
Mutation carriers	165	131	91	64	54	31	7	0
FPC kindreds	201	158	92	60	52	30	5	0

Overbeek KA, et al. Gut 2021;0:1–9. doi:10.1136/gutjnl-2020-323611 3

Advances in Early Detection

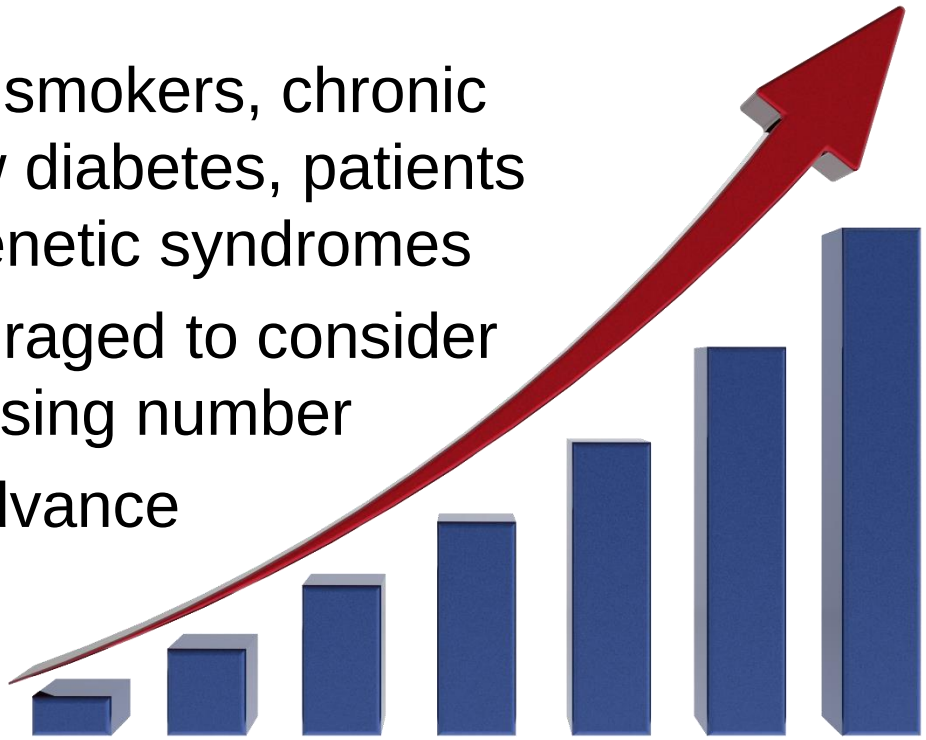
Biomarkers: a biological “marker” measured in bodily fluid used to understand the biology or physiology of a patient

Risk Biomarker: a serological test to assess one’s risk

Detection biomarkers: a serological marker of a tumor ie: CA 19-9

Take Home Points

1. The incidence of pancreatic cancer is increasing
2. High risk groups include: smokers, chronic pancreatitis patients, new diabetes, patients with a family history or genetic syndromes
3. Patients should be encouraged to consider participation in our increasing number of clinical trials to help advance this disease



More information…

[CancerSEEK]

immunovia

[Immunovia]

Galleri™

[Galleri]

PANCREATIC CANCER ACTION NETWORK

[PANCAN]

Citations

Fanta P, Lowy A. Adenocarcinoma of pancreas. In: Podolsky DK et al., eds. Yamada's Textbook of Gastroenterology, Sixth ed. John Wiley & Sons, Ltd. 2016.

Farrell JJ, Fernández-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology. 2013 Jun;144(6):1303-15.

Goggins M, Overbeek KA, Brand R, et al. International Cancer of the Pancreas Screening (CAPS) consortium. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut*. 2020 Jan;69(1):7-17.

Greenhalf W, Lévy P, Gress T, Rebours V, Brand RE, Pandol S, Chari S, Jørgensen MT, Mayerle J, Lerch MM, Hegyi P, Kleeff J, Castillo CF, Isaji S, Shimosegawa T, Sheel A, Halloran CM, Garg P, Takaori K, Besselink MG, Forsmark CE, Wilcox CM, Maisonneuve P, Yadav D, Whitcomb D, Neoptolemos J; Working group for the International (IAP – APA – JPS – EPC) Consensus Guidelines for Chronic Pancreatitis. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology. 2020 Jul;20(5):910-918.

Munigala, S., Subramaniam, D.S., Subramaniam, D.P. *et al.* Incidence and Risk of Pancreatic Cancer in Patients with a New Diagnosis of Chronic Pancreatitis. *Dig Dis Sci* (2021).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. *Pancreatic Adenocarcinoma Version 1*. 2020. 2020 Jan 1;National Comprehensive Cancer Network

Overbeek KA, et al. Long Term Yeild of Pancreatic Cancer Surveillance in High Risk Individuals. Gut 2021.

Pishvaian MJ, Blais EM, Brody JR et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. Lancet Oncol. 2020 Apr;21(4):508-518.

Saad AM, Turk T, Al-Husseini M.J. et al. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. *BMC Cancer*. 2018;18, 688.

Tavakolli et al. Racial disparities and trends in pancreatic cancer incidence and mortality in the United States. *Clin Gastroenterol Hepatol.* 2020;18:171–178

Vege SS, Ziring B, Jain R, Moayyedi P; Clinical Guidelines Committee; American Gastroenterology Association. American gastroenterological association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015 Apr;148(4):819-22;