

# Neoplasms of the Exocrine Pancreas

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With some past papers included

# Epidemiology and Risk Factors

- 265,000 people annually
- 74% of patients die within the first year after diagnosis
- The worst prognosis of all malignancies with a 5-year survival rate of only 6%

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Seigel R, Naishadham D, Jemal A. Cancer statistics 2012. CA: A Cancer Journal for Clinicians. 2012; 62:10–29.

# Epidemiology and Risk Factors

- Complex interaction of genetic and environmental factors
- Most patients >60 years old
- Slightly more common in men than women
- **Risk factors**
  - **Smoking twofold<sub>1</sub>**
  - **Diets high in fat and low in fiber**
  - **Diabetes<sub>2</sub>**
  - **Chronic pancreatitis, especially familial pancreatitis<sub>3</sub>**



## Past Paper:

Q. Risk factor for pancreatic cancer?

Q. Most risk factor implicated in pancreatic cancer?

Answer: Smoking

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1. Gold EB, Goldin SB: Epidemiology of and risk factors for pancreatic cancer. Surg Oncol Clin N Am. 1998;7:67

2. Jean M, Lowy A, Chiao P et al.: The Molecular Biology of Pancreatic Cancer. New York: Springer-Verlag; 2002

3. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am. 2000;84:565–575.

# Genetics of Pancreatic Cancer

- 10% has inherited genetic predisposition.
- Family history of pancreatic cancer in a first-degree relative has twofold increased risk
- The K-ras oncogene 90%<sup>1</sup>
- The HER-2/neu oncogene<sup>2</sup>
- Multiple tumor-suppressor genes are deleted and/or mutated in pancreatic cancer
  - p53
  - p16
  - DPC4 (Smad 4)
  - BRCA2<sup>1</sup>
- Most pancreatic cancers have three or more of the above mutations

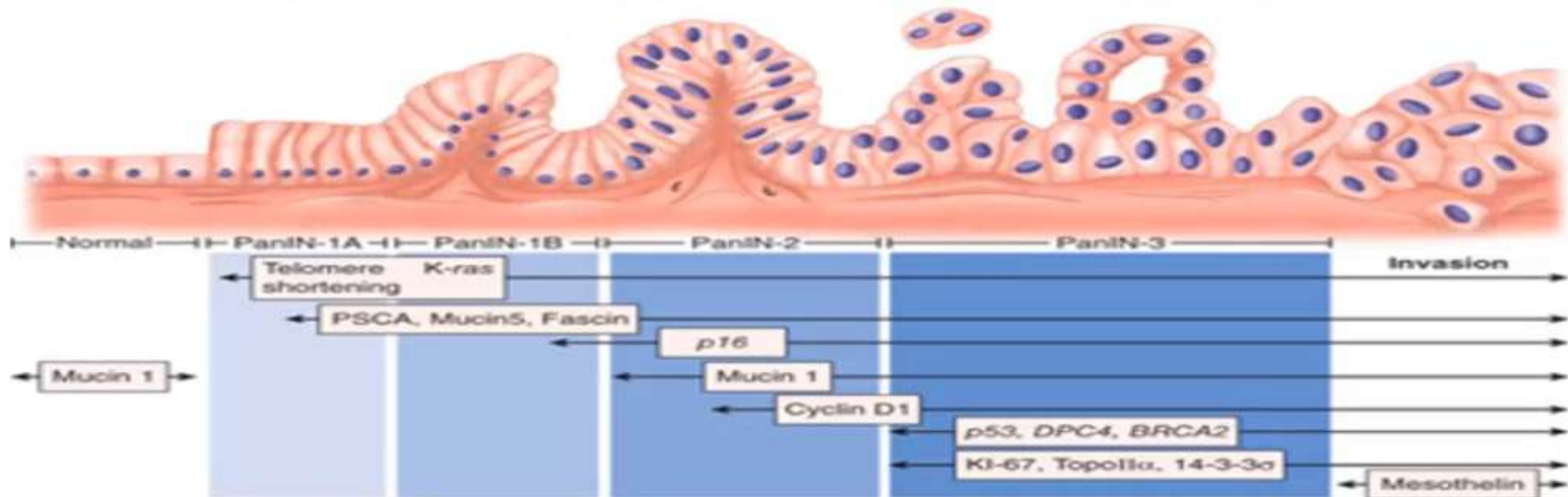
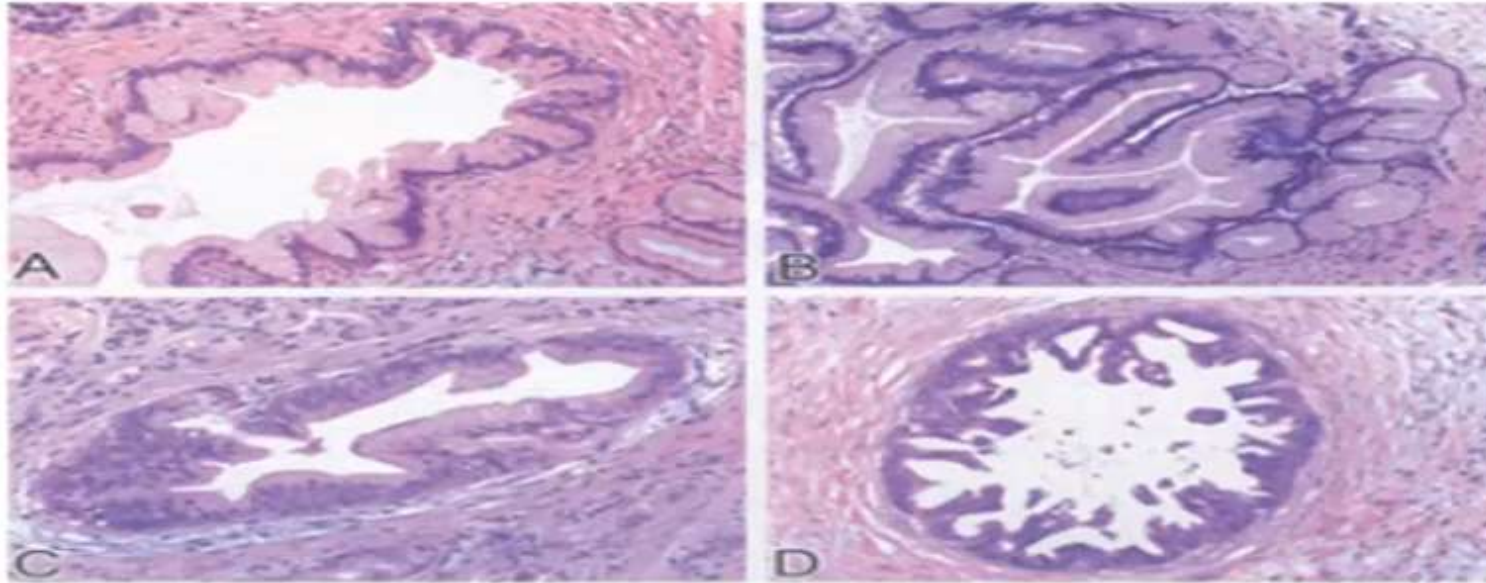
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1. Berger D, Fischer W. Inherited Pancreatic Cancer Syndromes. New York: Springer-Verlag; 2002

2. Jean M, Lowy A, Chiao P et al.: The Molecular Biology of Pancreatic Cancer. New York: Springer-Verlag; 2002

- ★ Mutations in K-ras → PSCA/Mucin5 → turns it into pancreatic intraepithelial neoplasia (This is like carcinoma-in-situ, which is not invasive tumor)
- ★ There's 3 stages of intraepithelial neoplasia with more mutations happening in genes at the cellular level, till it turns into an invasive tumor when the cell invades the lamina propria
- ★ What causes these mutations? Some genetic predisposition (inherited or environmental factors)

# Pathology





# Pathology

## • Location

- 65% Head or uncinate process
- 15% The body
- 10% The tail
- Diffuse involvement of the gland



### Past Paper:

Q. Chronic pancreatitis, all true, except:

- A) Abscess
- B) Pseudocyst:
- C) dilated ducts
- D) DM
- E) Constipation

Answer: E

\*This question isn't related to this lecture

# Pathology

- **Histologic Types**

- Ductal adenocarcinoma 75%
- Adenosquamous carcinoma
- Acinar cell carcinoma

# Diagnosis and Staging

★ Not like other GIT tumors, because the pancreatic tumor doesn't have a wall and a lumen. We depend on the size of the tumor

- **Tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor we mean that we have a tumor that has distant metastases, but we're unable to know where the primary tumor is
- Tis: Carcinoma in situ
- T1: Tumor is limited to the pancreas and is  $\leq 2$  cm in greatest dimension
- T2: Tumor is limited to the pancreas and is  $> 2$  cm in greatest dimension
- T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)



# Diagnosis and Staging

- **Regional lymph nodes (N)**
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis
- **Distant metastasis (M)**
  - MX: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

# Diagnosis and Staging

Stage	T	N	M	Description
IA	1	0	0	Limited to pancreas $\leq 2$ cm
IB	2	0	0	Limited to pancreas $> 2$ cm
IIA	3	0	0	Extends beyond pancreas but does not involve arteries
IIB	1-3	1	0	Any tumor without artery involvement with lymph node involvement
III	4	Any	0	Tumor involves arteries (unresectable)
IV	Any	Any	1	Any tumor with distant metastases

# Diagnosis and Staging

- **8%** localized stage
- **27%** spread to regional lymph nodes or directly beyond the primary site
- **53%** metastasized (distant stage)
- **The corresponding 5-year relative survival rates**
  - **23.3%** for localized
  - **8.9%** for regional
  - **1.8%** for distant
- The overall 5-year relative survival rate **5.8%**<sup>1</sup>

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Howlader N, Noone AM, Krapcho M et al. SEER Cancer statistics review 1975-2009 (Vintage 2009 populations) National Cancer Institute, Bethesda. Available at: [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/).

# Diagnosis

- Lack of tools for early diagnosis small tumors in the pancreas won't have any symptoms (early stages are usually asymptomatic)
- The majority of patients present with pain and jaundice
- **On physical examination** (Late stages usually)
  - Weight loss
  - Skin is icteric
  - Palpable distended gallbladder 25% of patients
- More fortunate patients have tumors situated such that biliary obstruction and jaundice occurs early and prompts diagnostic tests

# Diagnosis

- A low threshold for ordering a CT scan with “pancreatic protocol” elderly patients with unexplained, persistent, although vague, abdominal pain.
- New-onset diabetes in an elderly patient, especially if combined with vague abdominal pain
- CA19-9 are elevated in about 75% of patients with pancreatic cancer. However, CA19-9 is also elevated in about 10% of patients with benign diseases of the pancreas, liver, and bile ducts. it's neither sensitive nor specific for diagnosis pancreatic cancer  
it's used if it's elevated with a patient that has pancreatic mass (so it makes it more likely that this pancreatic mass is malignant)  
so, the combination of both (elevation of tumor marker CA19-9 & evidence of pancreatic mass) is enough to say that the patient is most likely having a pancreatic cancer.  
But, CA19-9 alone ISN'T DIAGNOSTIC!

- ★ The most common cause of obstructive jaundice is common bile duct stones, but with pancreatic cancer, the gallbladder has no stones.
- ★ Pancreatic cancer jaundice is painless (Courvoisier sign: palpable, non-tender gallbladder) , in contrast to patients with obstructive jaundice due to gallbladder stones that causes common bile duct stone, who present with painful jaundice

# Diagnosis

- In patients presenting with jaundice
- **Abdominal ultrasound**
  - bile duct dilation with absence of stones
- **CT scan**
  - Detect the tumor
  - Assess resectability how much the tumor is invading major vessels, because pancreas is located in a very critical area (surrounded by very critical tissues like aorta, IVC, SMA, Celiac trunk)
  - Liver metastasis



# CT scan

- **CT findings that indicate a tumor is unresectable**

in 80% of cases, CT scan findings continues to be resectable in operation room.  
In 20% of cases, CT scan says it's resectable, but it's found to be the opposite in operation room.

- Involvement of  $\geq 180$  degrees of the celiac axis, hepatic or superior mesenteric artery
- Enlarged lymph nodes outside the boundaries of resection example: lymph nodes located at the celiac trunk or para-aortic vessels away from the tumor
- Ascites means there's transcoelomic spread (peritoneal metastasis)
- Distant metastases (e.g., liver).



## Past Paper:

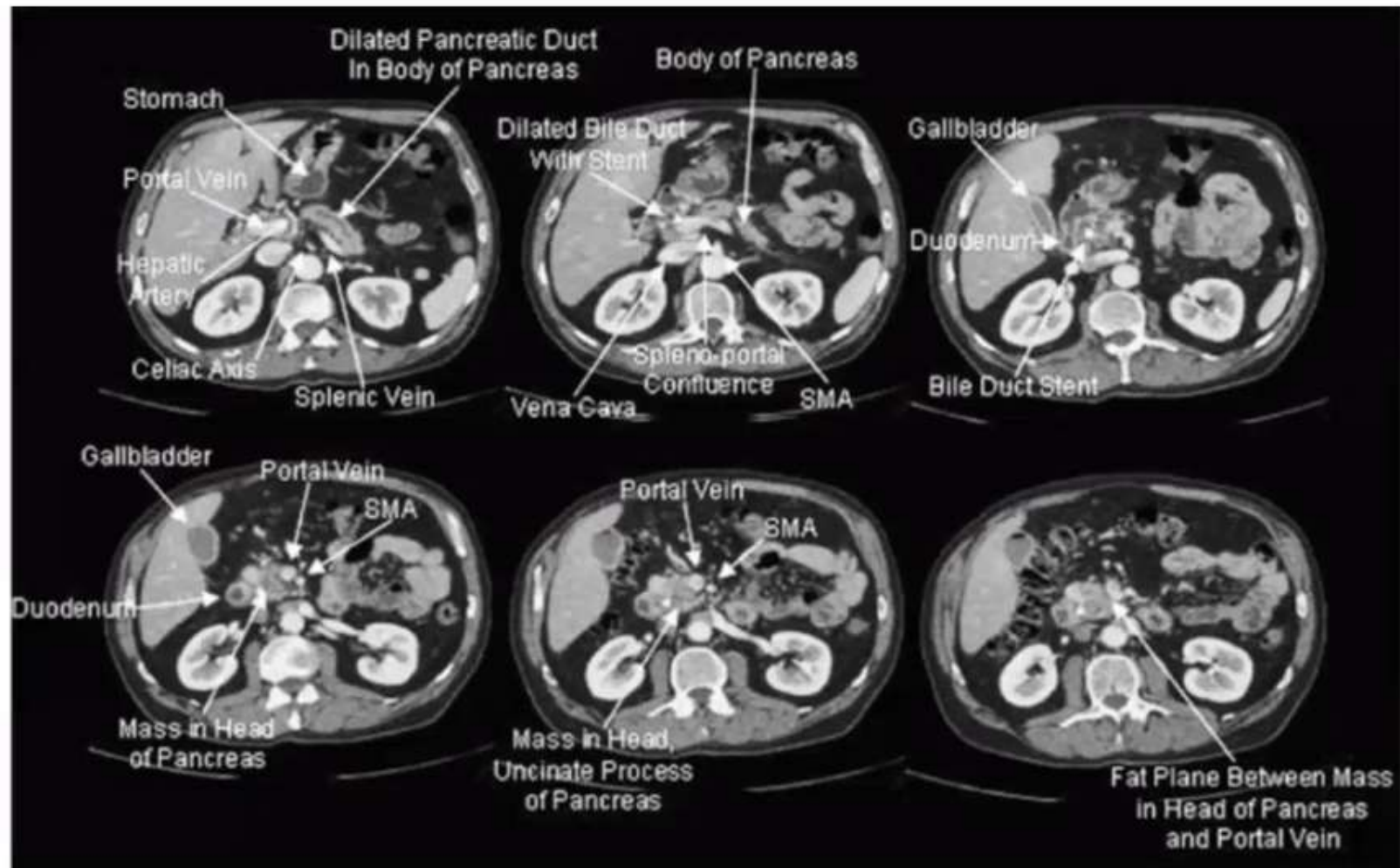
Q. Least common presenting symptom in the carcinoma of the head of pancreas:

- A) Jaundice
- B) Hemobilia
- C) Back pain

Answer: B

\*Hemobilia: bleeding into biliary tract

Tumor of the pancreas will be seen as hypodense mass (because it doesn't take the IV contrast)



★ To avoid the mistakes in CT scan, we do the diagnostic laborascopy

# Diagnosis

Before doing diagnostic labaroscropy, when we see a CT scan finding that indicates a mass in the head of pancreas, an adjunct investigations for CT have to be made to confirm the presence of the mass, also to confirm the tissue biopsy and we can do it by endoscopic ultrasound

- **EUS** Endoscopic ultrasound (Better than CT in detecting small masses)
  - Detect small pancreatic masses that could be missed by CT scanning. & when taking biopsies from small masses
  - Advantage for transluminal biopsy of pancreatic masses, although a tissue diagnosis before pancreaticoduodenectomy is not required. However, in specific patients a histologic diagnosis may be necessary such as for those in a neoadjuvant clinical trial or before chemotherapy in advanced tumors.
  - EUS is a sensitive test for portal/superior mesenteric vein invasion, although it is somewhat less effective at detecting superior mesenteric artery invasion.
- When all of the current staging modalities are used, their accuracy in predicting resectability is reported to be about **80%**
- **20% laparatomy with no need**

3 Indications for biopsy of pancreatic mass:

1. when the diagnosis is suspicious (not being a malignant mass)
2. when we want to give a neoadjuvant treatment to decrease the size of the tumor (to convert it to resectable tumor)
3. when the tumor has known to be unresectable and has distal metastases or the patient can't go for surgery, so we take a biopsy to give chemotherapy as a primary treatment

# Diagnosis

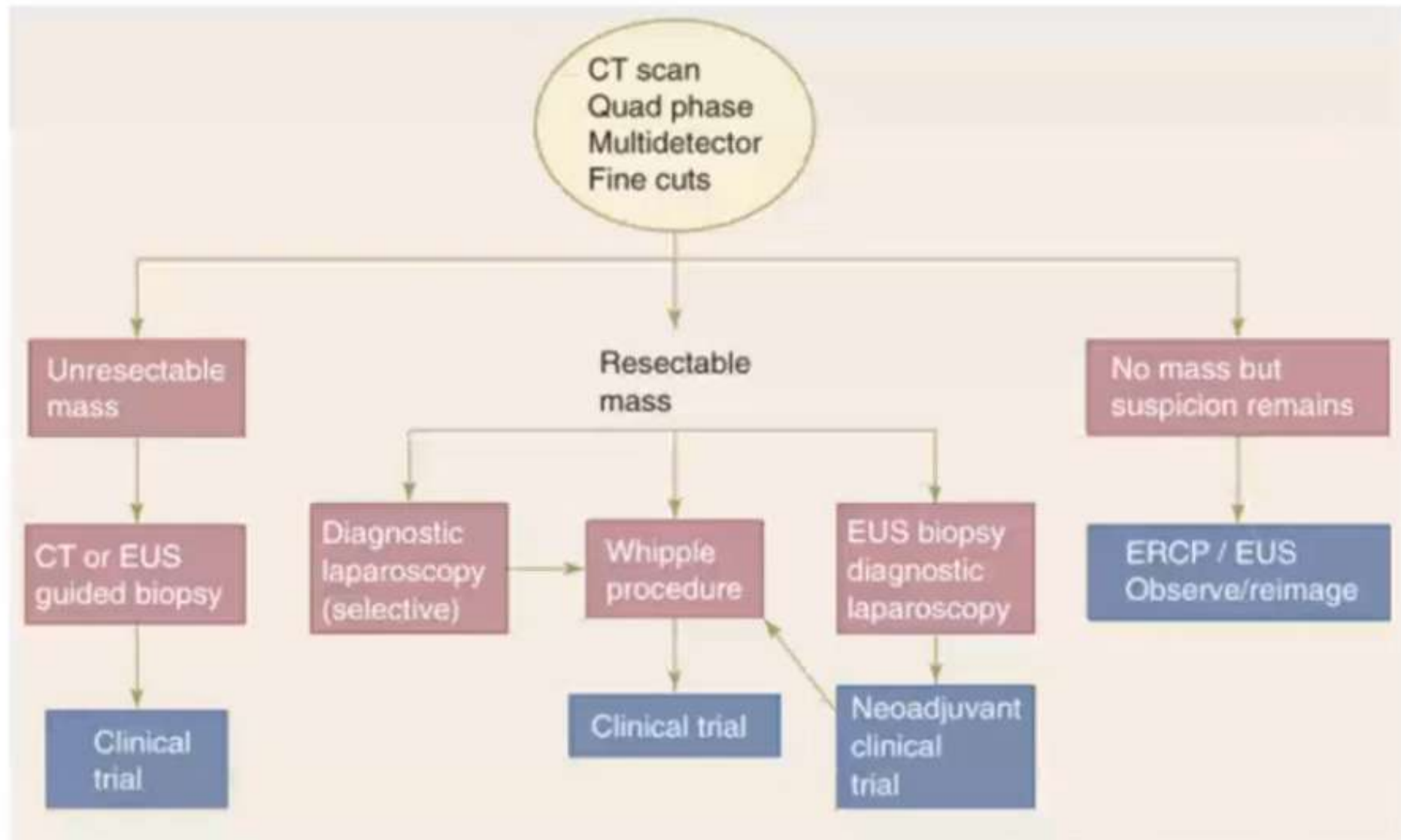
- **Preliminary laparoscopy** has been advocated for patients with disease felt to be resectable by CT imaging
- Diagnostic laparoscopy with the use of US is reported to improve the accuracy of predicting resectability to about 98%



Usually, the scenario is like this:

Patient presents with painless jaundice. Ultrasound has shown that there's no gallbladder stones or common bile duct stones.

Next step: Always do CT scan with IV contrast with pancreatic protocol (we call it Quadruple phase)



# Palliative Surgery and Endoscopy

- **Pain**

- Oral narcotics: Sustained-release preparations of morphine sulfate
- Celiac plexus nerve block

- **Jaundice**

- Bile duct stent
- Operative bypass: choledochojejunostomy

- **Duodenal obstruction**

- 20% of patients
- Prophylactic?



Past Paper:

Q. Pancreatic cancer tumor marker:

- A) CA19-9
- B) HCG
- C) CA 15-3
- D) Alpha-FP

Answer: A

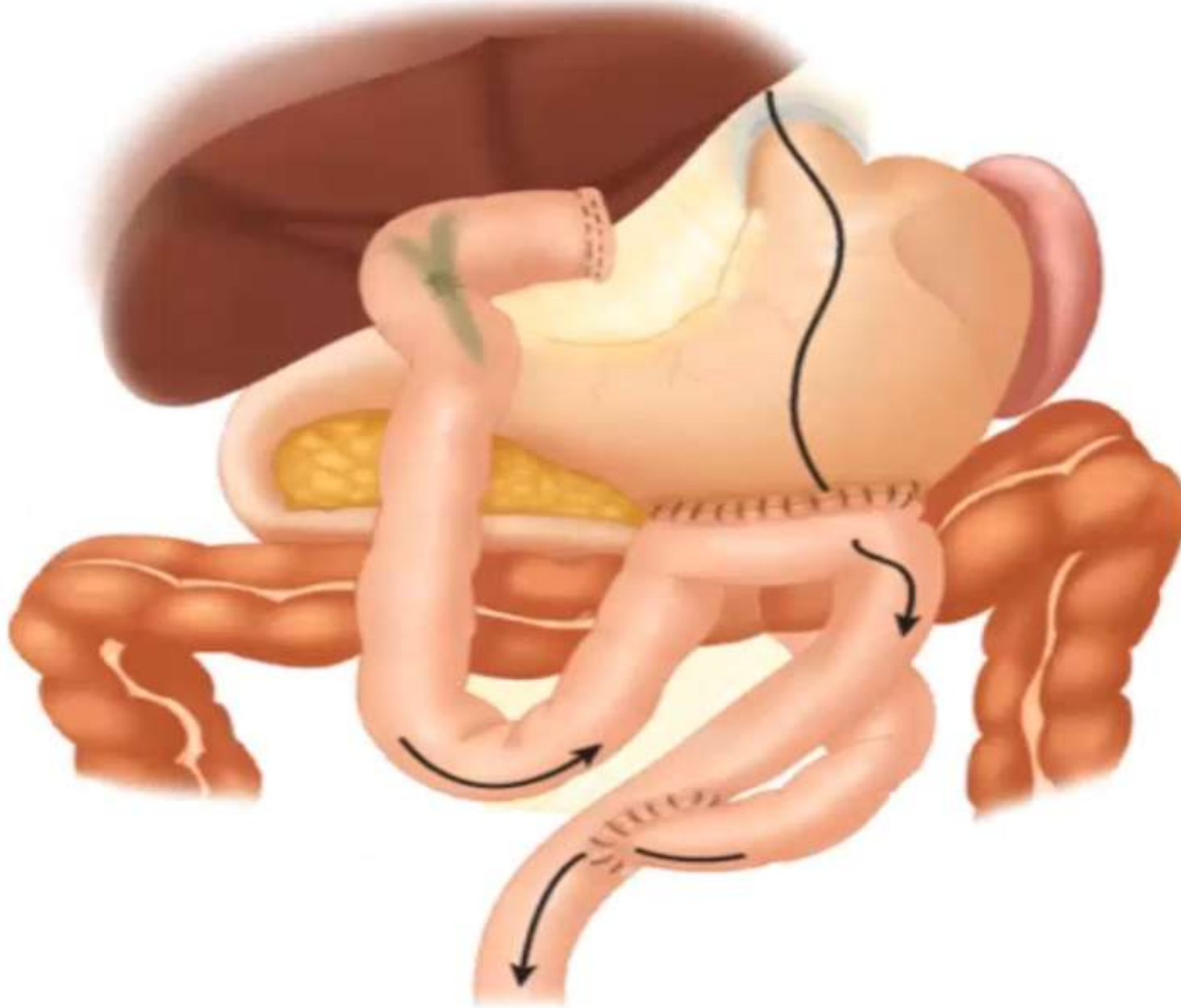


★ The usual scenario for palliative surgery with pancreatic cancer:

A CT scan that has shown a pancreatic tumor that's unresectable. So, how are we going to bypass the obstructive jaundice?

We ask the gastroenterologist to do a metallic stent (stenting for common bile duct). If not possible, then we go with choledochojejunostomy

When there's duodenal obstruction, we go with gastrojejunostomy,  
when there's no duodenal obstruction, we don't do prophylactic gastrojejunostomy

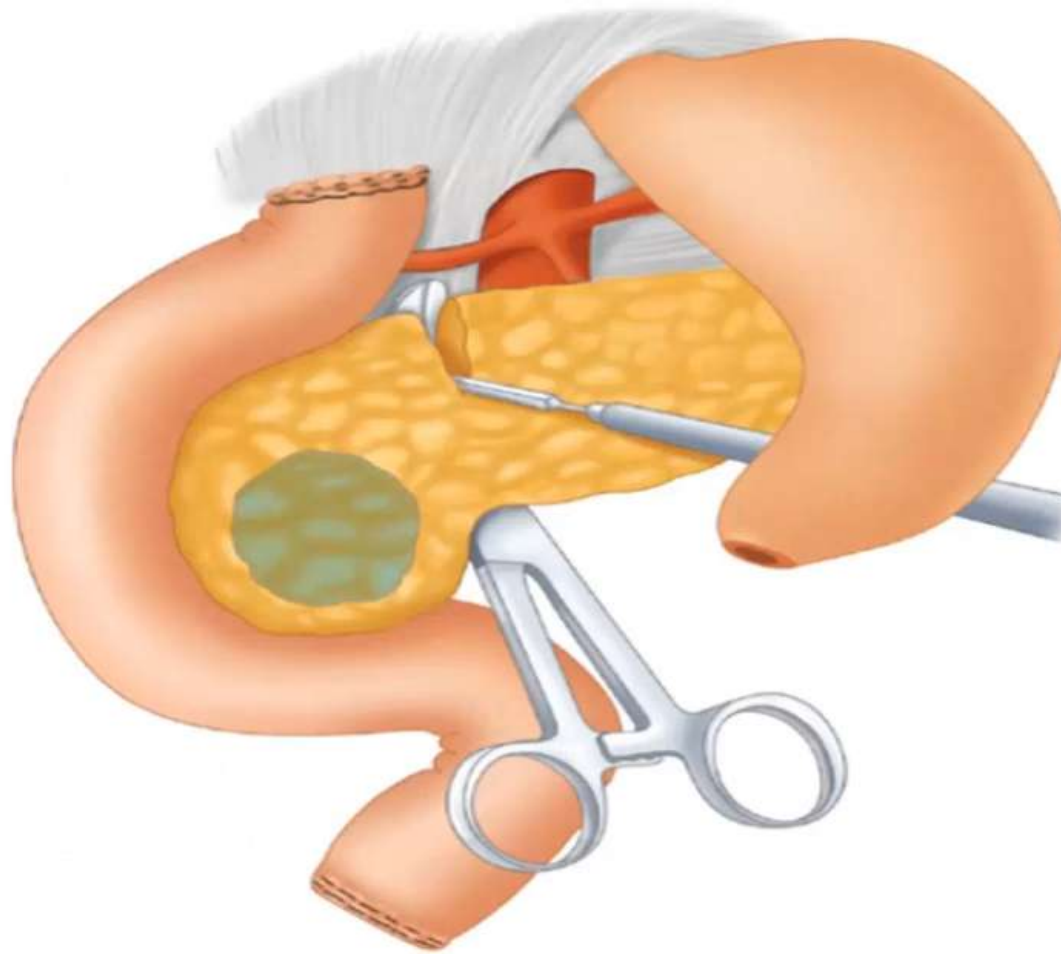


# **Palliative Chemotherapy and Radiation**

- **Gemcitabine**
  - Symptomatic improvement, improved pain control and performance status, and weight gain
  - survival is improved by only 1 to 2 months
- **Erlotinib**
  - very minimal improvement in overall survival in combination with gemcitabine.
- **5-fluorouracil (5-FU) and capecitabine**
  - radiosensitizer in patients receiving radiation therapy

# Pancreaticoduodenectomy

- **Findings contraindicating resection**
  - Liver metastases (any size)
  - Celiac lymph node involvement
  - Peritoneal implants
  - Hepatic hilar lymph node involvement
- **Findings not contraindicating resection**
  - Invasion at duodenum or distal stomach
  - Involved peripancreatic lymph nodes
  - Involved lymph nodes along the porta hepatis that can be swept down with the specimen

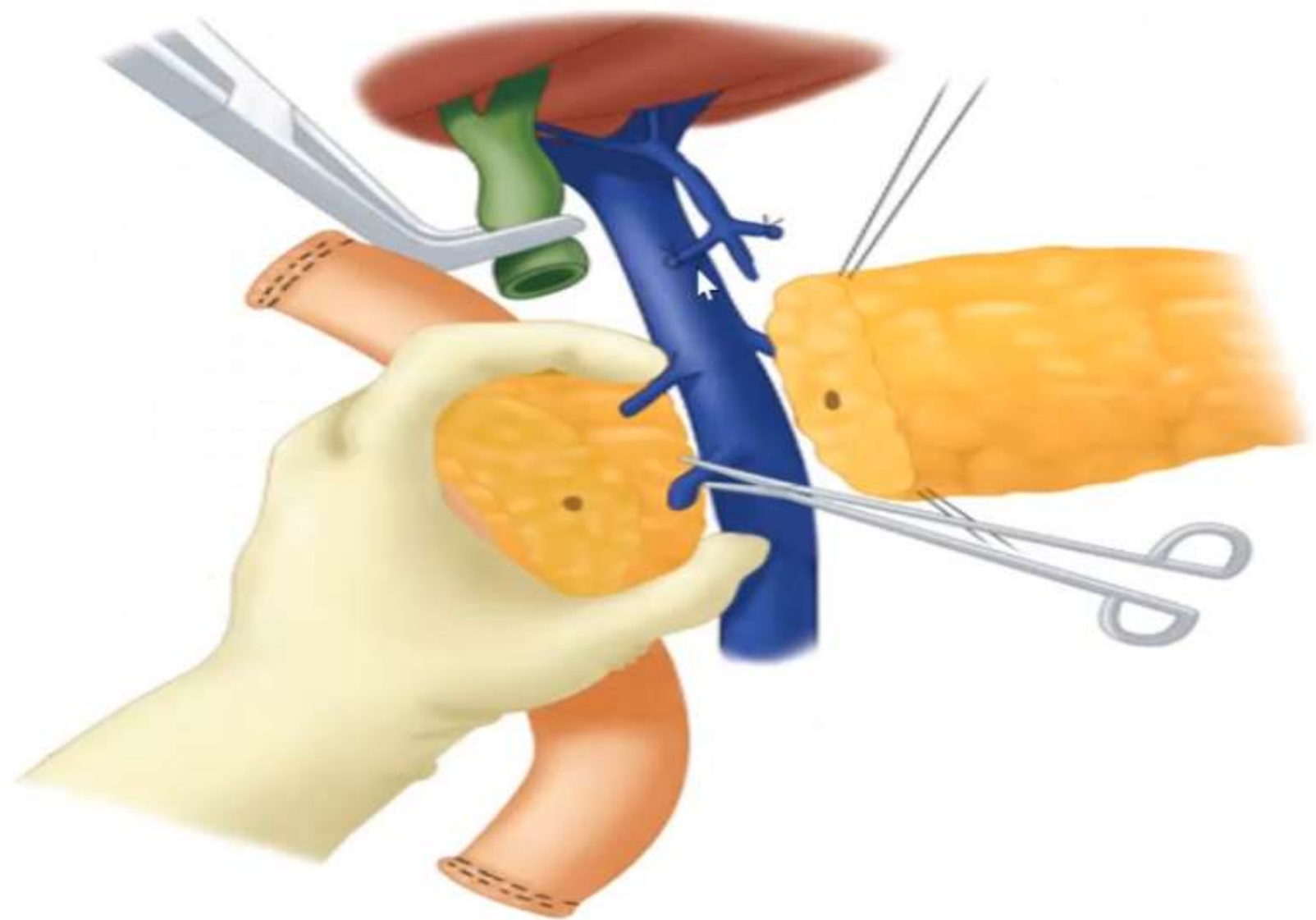


### Past Paper:

Q. Pancreatic adenocarcinoma, false:

- A) 70% in the head
- B) 90% ductal
- C) in resectable , 20% 5-yr survival
- D) p16 mutation is found in more than 90% (this is true)
- E) papillary and mucinous cystadenocarcinoma are worse prognosis

Answer: E







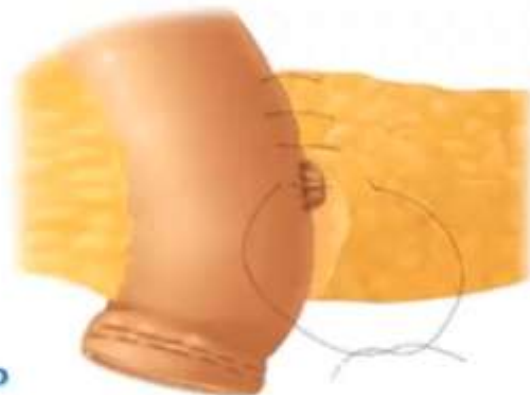
A



B



C



D



E



# Complications of Pancreaticoduodenectomy

- The operative mortality rate for pancreaticoduodenectomy <5%
- The most common causes of death are sepsis, hemorrhage, and cardiovascular events
- Postoperative complications are unfortunately still very common, and include delayed gastric emptying, pancreatic fistula, and hemorrhage.