PANCREATIC CANCERS

Kenneth Alonso, MD, FACP

Pancreatic cysts

- Often incidental findings
- Result from anomalous development of ducts
- 77% of patients with Von Lindau-Hippel disease
- 10% of patients with polycystic disease
- BUT, 5-10% of pancreatic cysts are neoplastic

Serous cystadenoma

- Predominant pancreatic cyst
- 90% women
- mean age at presentation of 70 years
- Not connected to pancreatic ductal system
- Predominantly in the tail of the pancreas
- Gross pathology:
- Encapsulated
- Central scar and calcification
- Histopathology:
- Glycogen rich cuboidal cells line cyst
- Surgical resection curative

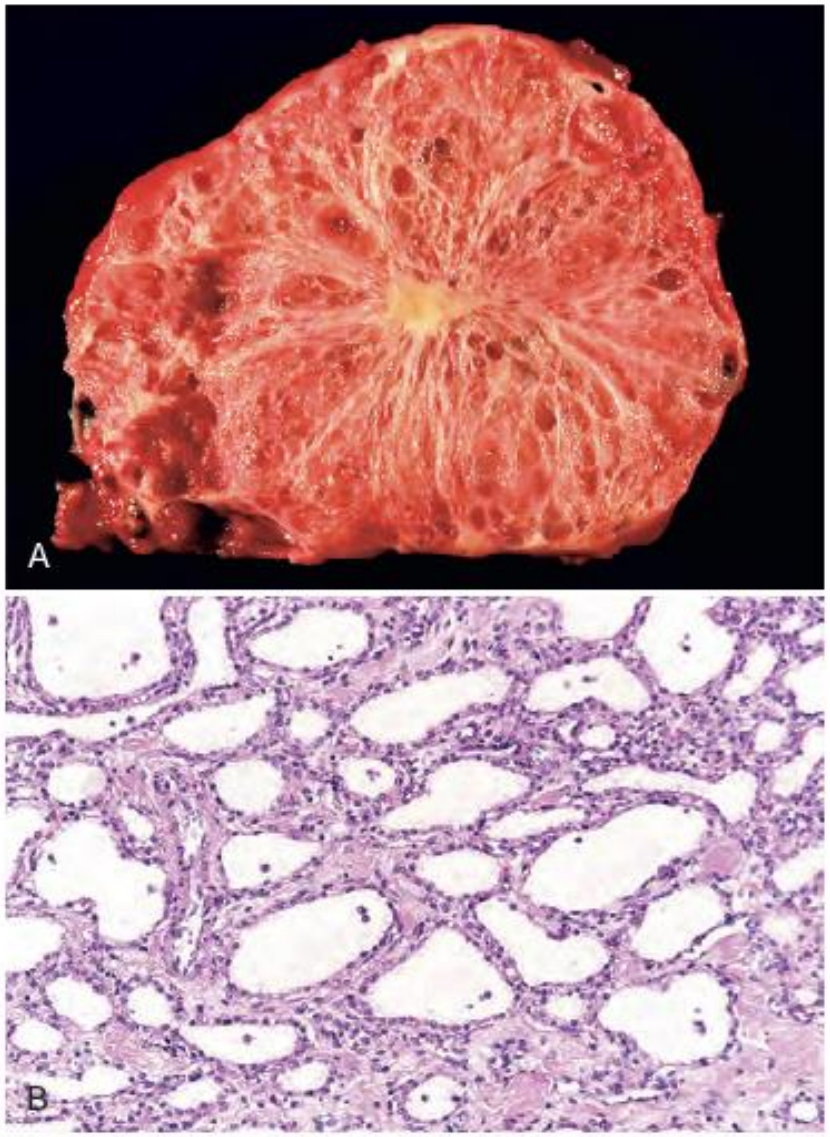


Figure 19-8 Serous cystic neoplasm (serous cystadenoma). **A,** Cross-section through a serous cystic neoplasm. Only a thin rim of normal pancreatic parenchyma remains. The cysts are relatively small and contain clear, straw-colored fluid. **B,** The cysts are lined by cuboidal epithelium without atypia.

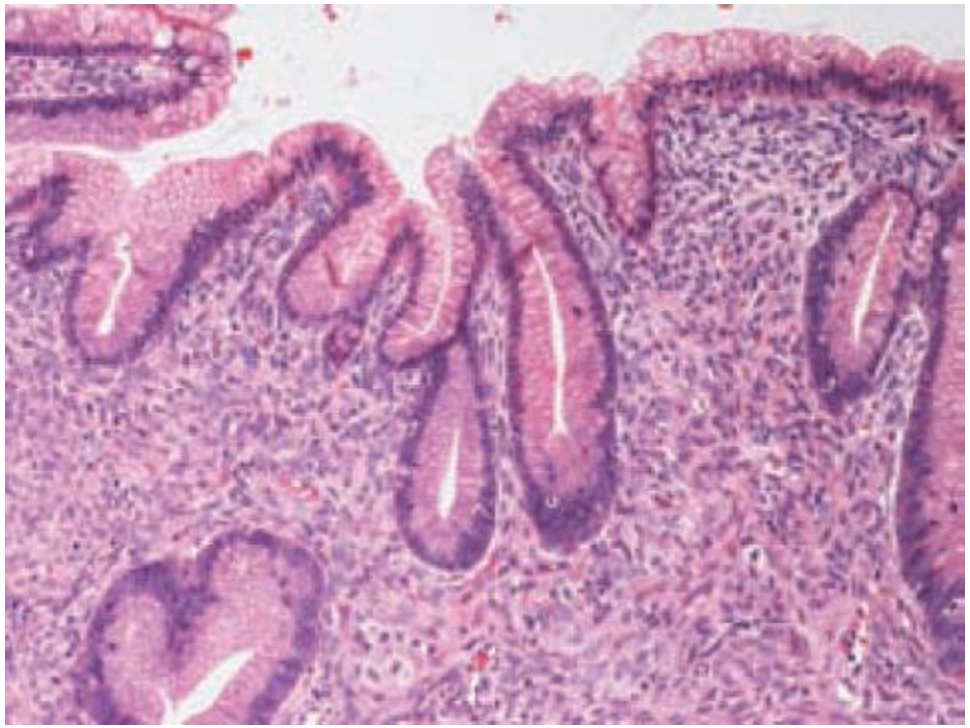
Mucinous cystic neoplasm

- 95% women
- Mean age of presentation 45 years old
- Not connected to pancreatic ductal system
- Predominantly in body and tail
- KRAS, TP53, RNF43 mutations
- Gross pathology:
- Encapsulated
- Calcification rare

Mucinous cystic neoplasm

- Histopathology:
- Lined by mucin producing columnar cells in an ovarian type stroma
- Stain for estrogen, progesterone, HCG
- High levels of CEA in cyst
- Do not recur after resection
- One-third of resected specimens contain invasive adenocarcinoma

Mucinous cystic neoplasm



There is an inner epithelial layer and an outer densely cellular “ovarian-like” stromal layer .The mucin-producing epithelium exhibits a spectrum of differentiation, ranging from histologically benign appearing columnar epithelium to severely atypical epithelium.

https://basicmedicalkey.com/mucinous-cystic-neoplasms-2/#Sec4 Accessed 01/20/2020

Solid pseudo-papillary neoplasm

- 90% women
- Mean age at presentation 30 years
- Gross pathology:
- Not encapsulated
- No calcification
- Connected to pancreatic ductal system
- Found in the head of pancreas
- β-catenin /APC pathway altered
- Locally aggressive
- Resection curative

Pancreatic ductal adenocarcinoma

- Four subtypes
- Stable
- 20%
- ≤ 50 structural variation events
- Widespread aneuploidy

Pancreatic ductal adenocarcinoma

- Locally rearranged
- 30%
- Focal event on one or two chromosomes
- Two subtypes
- Focal regions of gain/amplification
- ERBB2, MET, FGFR1, CDK6, PIK3R3 and PIK3CA
- Complex genomic rearrangements
- Broken-fusion-bridge
- Chromothripsis
- TP53 mutations common

Pancreatic ductal adenocarcinoma

- Scattered
- 36%
- Non-random chromosomal damage and <200 structural variation events
- Unstable
- 14%
- >200 structural variation events
- 50% have BRCA or PALB mutations

Intraductal papillary mucinous neoplasms

- Main duct lesion presents as acute pancreatitis
- 2/3 occur in head of pancreas
- 70% in women
- 65-70 years of age
- Diffuse or segmental enlargement of pancreatic duct noted on imaging studies
- 70% of lesions arising in main duct are malignant (intestinal, pancreatobiliary, oncocytic types)
- Neoplasms may be multifocal

Intraductal papillary mucinous neoplasms

- A branch duct lesion is asymptomatic
- Identified incidentally on CT
- Multilocular, grape-like appearance
- Mixed main duct and branch lesions (multifocal) behave as main duct lesions
- Neoplasms may be multifocal

Intraductal papillary mucinous neoplasm

- Gross pathology:
- Not encapsulated
- Histopathology:
- Lack ovarian-type stroma
- High levels of CEA and amylase in cyst
- Gastric, intestinal, pancreatobiliary types
- GNAS, KRAS, TP53, SMAD4, RNF43 mutations
- 30% recur after resection

Intraductal papillary mucinous neoplasm

- Gastric type
- Most common type
- Usually found in uncinate process.
- Arise in a branched duct
- Papillae lined by epithelial cells resembling gastric foveolar cells
- Pyloric gland-like structures found at base of papillae.
- 30% malignant

Intraductal papillary mucinous neoplasm

- MUC5 and MUC6 consistently expressed.
- Invasive pattern is that of a tubular carcinoma.
- Prognosis comparable to that of intestinal type.
- CDKN2a gene hypermethylation correlates with clinical stage

Intraductal papillary mucinous neoplasm

- Intestinal type
- Arise in a main duct
- Show a villous growth
- Expresses MUC2, MUC5, but not MUC1
- Invasive pattern is that of a colloid carcinoma

Intraductal papillary mucinous neoplasm

- Pancreatobiliary type shows arborizing papillae.
- Arise in main duct
- Only expresses MUC1 and MUC5.
- 70% malignant
- Invasive pattern is that of a tubular carcinoma
- Poorer prognosis than intestinal type.
- Pancreatobiliary duct tumors <2cm in size may be followed rather than resected initially

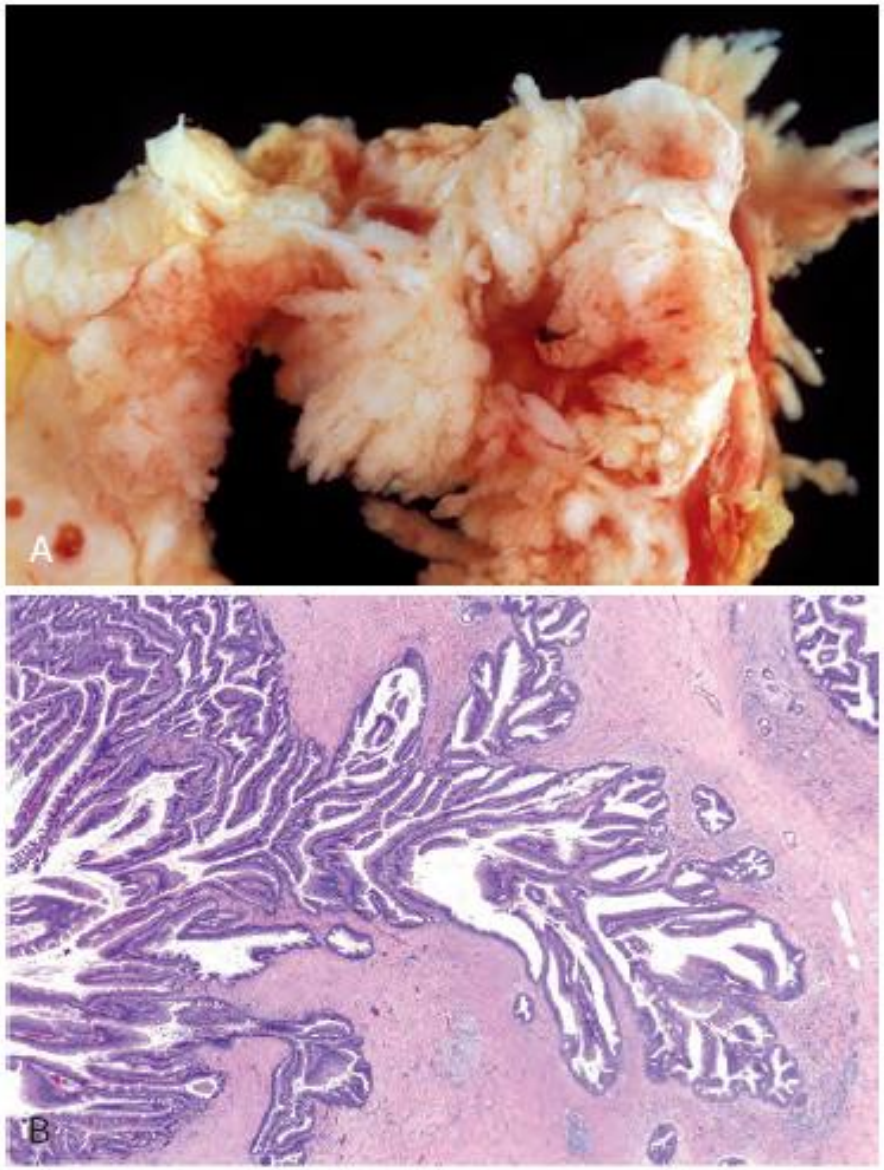
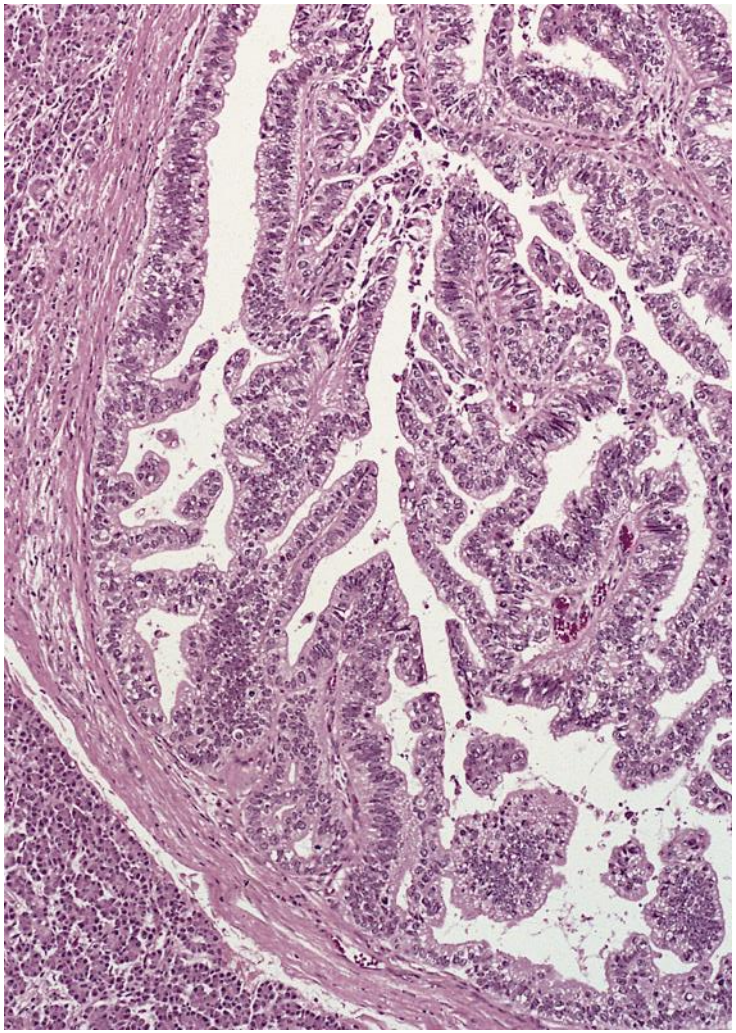


Figure 19-10 Intraductal papillary mucinous neoplasm. **A,** Cross-section through the head of the pancreas showing a prominent papillary neoplasm distending the main pancreatic duct. **B,** The neoplasm involves the main pancreatic duct *(left)* and extends down into the smaller ducts and ductules *(right)*.

Intraductal papillary tumor



Cross section through the main pancreatic duct which is filled with epithelial papillary proliferations.

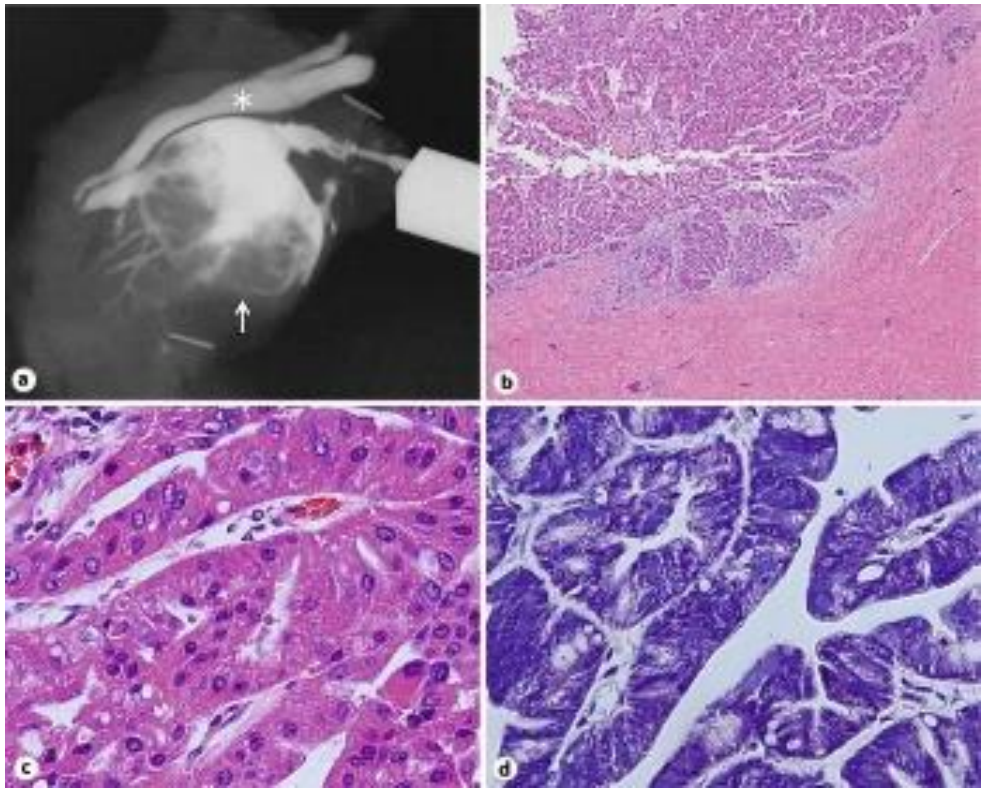
Fig. 4-33

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Intraductal oncocytic papillary neoplasm

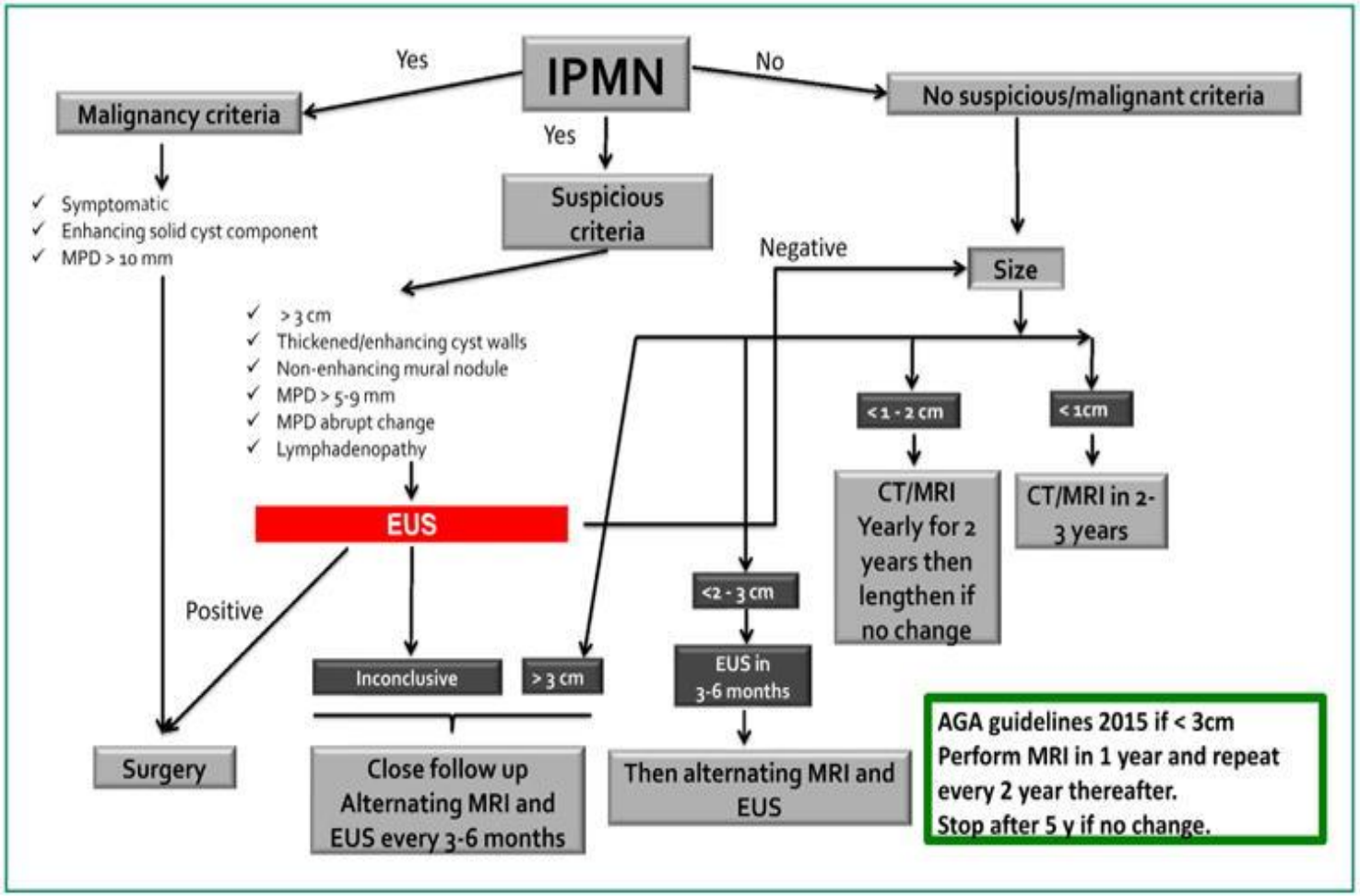
- Oncocytic type often forms large nodules in the main pancreatic duct.
- Arise in main duct
- Mean age 62 years
- Histology:
- Mucin filled cysts with nodular papillary projections
- Complex papillae with oncocytic lining
- Main cyst contains goblet cells.
- MUC1, MUC2, and MUC5AC expressed focally but inconsistently
- No KRAS mutation

IOPN



There is a localized cystic dilatation of the main pancreatic duct with luminal filling defects (arrow). The common bile duct is observed above the cystic lesion (asterisk). **b** A papillary mural nodule is recognized in the cyst with minimally invasive growth (HE stain, ×40). **c** The tumor cells have an abundant cytoplasm with eosinophilic granules. Nuclei are oval with increased chromatin and a large nucleolus by high-power magnification (HE stain, ×400). **d** PTAH stain demonstrates dense blue cytoplasmic granularity (×200).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398090/figure/F4/
Accessed 01/20/2020



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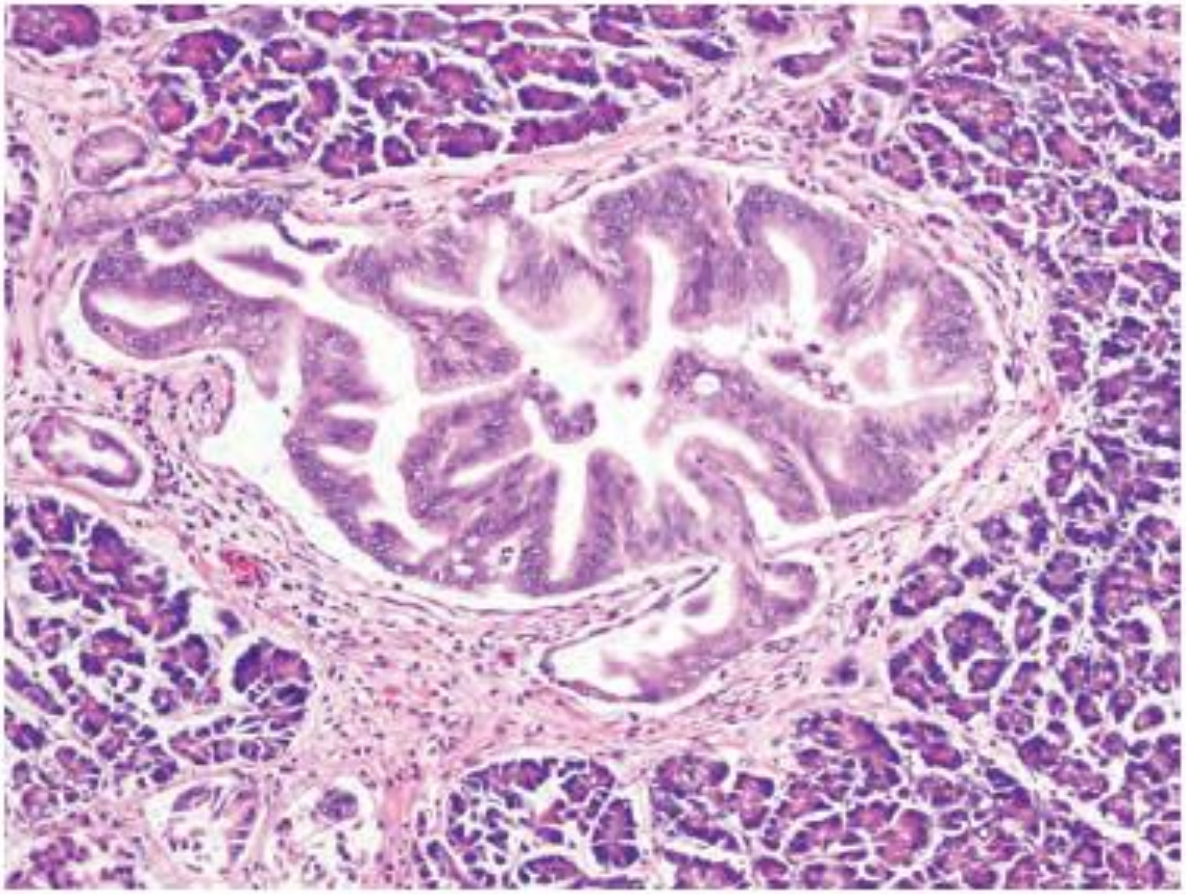
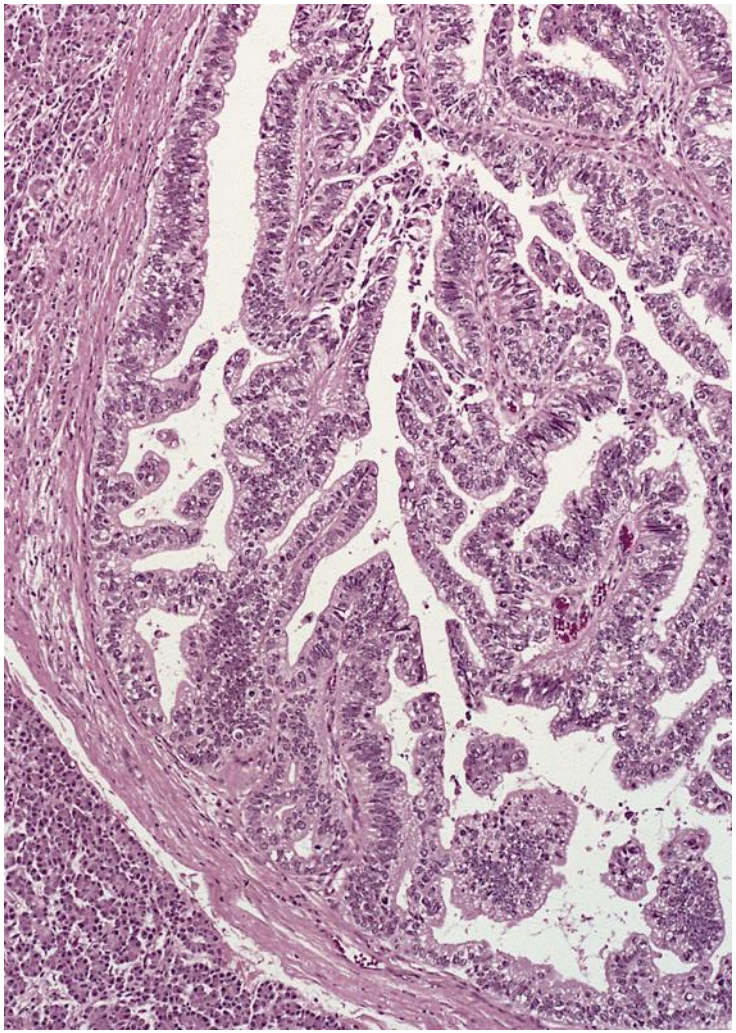


Figure 19-11 Pancreatic intraepithelial neoplasia grade 3 (PanIN-3) involving a small pancreatic duct.

Intraductal papillary tumor



Cross section through the main pancreatic duct which is filled with epithelial papillary proliferations.

Fig. 4-33

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Pancreatic carcinoma

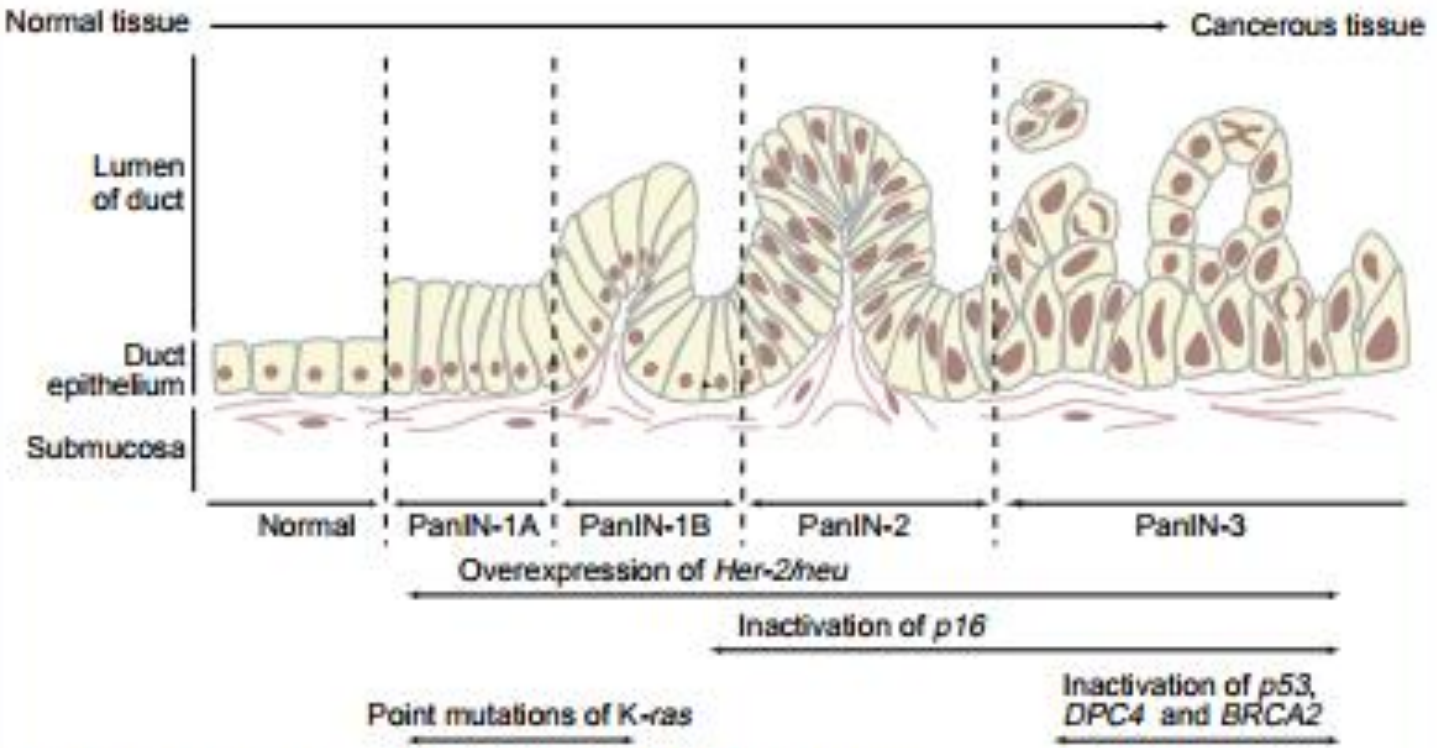
- Arise in Ductular epithelium
- 80% K-ras activated
- 95% p16 deactivated (CDKN2A).
- Mutation generally occurs in individuals from melanoma-prone families.
- 55% inactivated SMAD4 (18q21.2).
- Affects signal transduction from TGF-β family of cell surface receptors.
- A late occurrence is inactivation of p53.
- 75% of tumors

Pancreatic carcinoma

- BRCA2 mutation is a late occurrence and found in 10% of pancreatic cancers from Ashkenazi.
- Accumulation of multiple mutations more important than temporal sequence

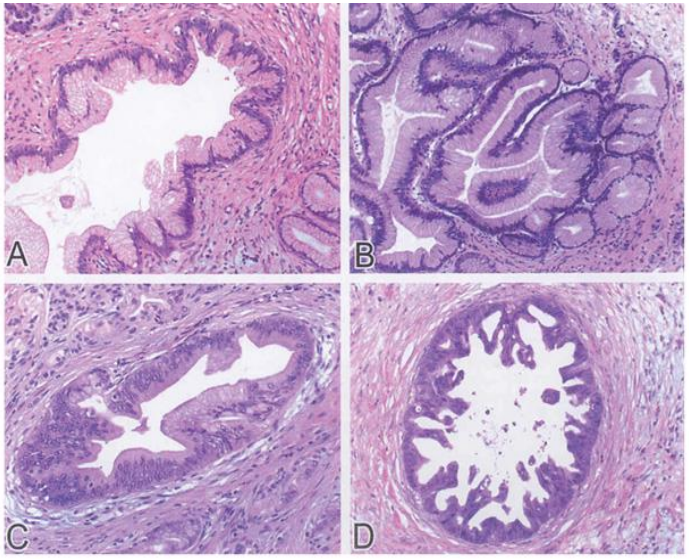
Pancreatic carcinoma

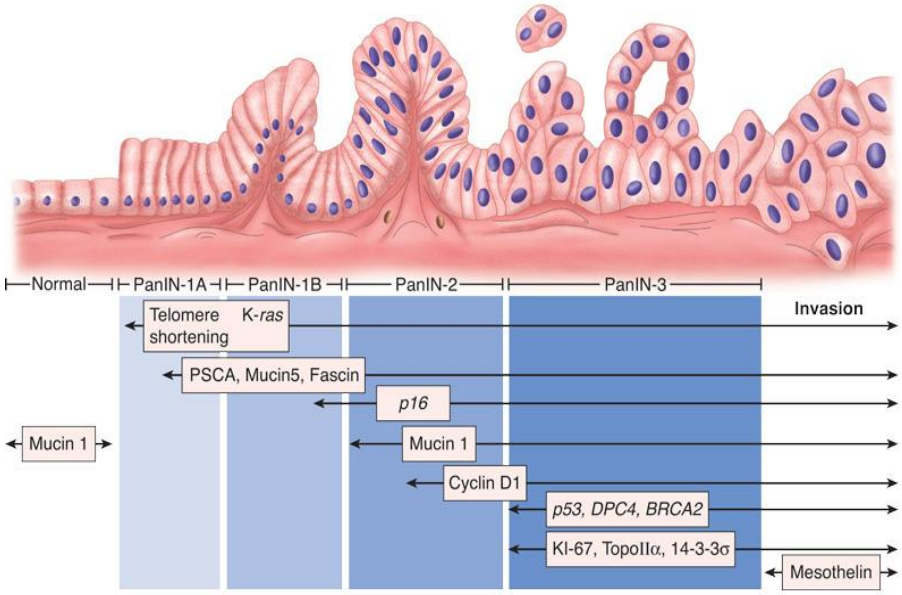
- 40%–80% have activating mutations in GNAS
- More than 50% have inactivation of RNF43 (an antagonist of WNT signaling).
- The pancreatic adenocarcinoma genome is also characterized by diverse, large-scale chromosomal changes with frequent amplifications, deletions and rearrangements.
- Accumulation of multiple mutations more important than temporal sequence



The genetic progression of pancreatic carcinoma

Oncogenesis





(From Hruban RH, Takaori K, Klimstra DS, et al: An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 28:977, 2004.)

Fig. 33-67 Accessed 02/01/2010

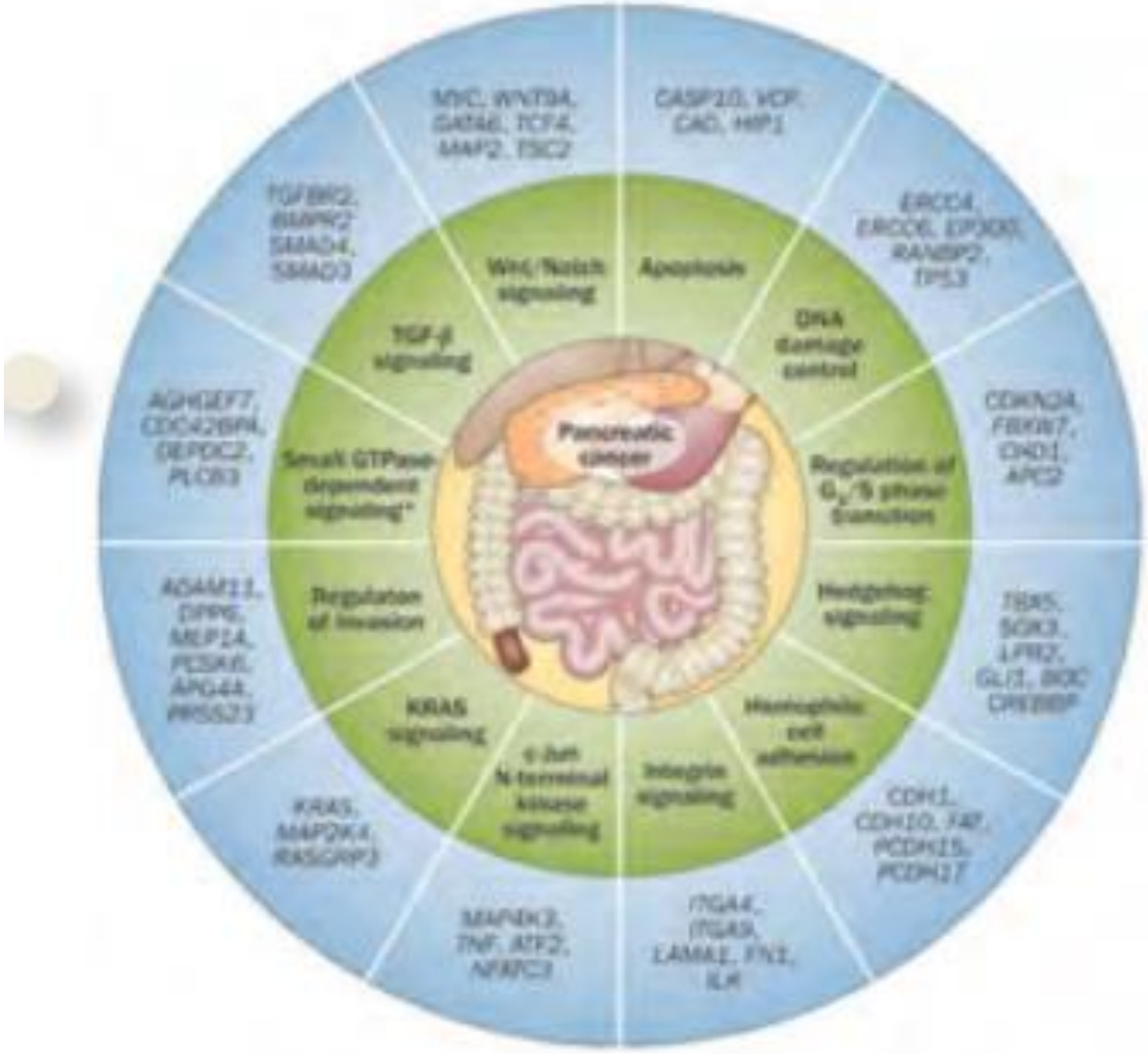

Pancreatic cancer
Wnt/Notch signaling
Apoptosis
DNA damage control
Regulation of G1/S phase transition
Hedgehog signaling
Homophilic cell adhesion
Integrin signaling
c-Jun N-terminal kinase signaling
KRAS signaling
Regulation of invasion
Smad4 GTPase-dependent signaling*
TGF-β signaling
MYC, WNT5A, GATA6, TCF4, MAP2, TSC2
CASP10, VCP, CAD, HIP1
ERCC4, ERCC6, EP300, RANBP2, TP53
CDKN2A, FBXW7, CHD1, APC2
TBX5, SOX3, LFR2, GLI3, BOC CREBBP
CDH1, CDH10, FAT, PCDH15, PCDH17
ITGA4, ITGA9, LAMA1, FN1, ILK
MAPKK3, TNF, ATF2, NFATC3
KRAS, MAP2K4, RASGRP3
ADAM12, DPP6, MEP1A, PCSK6, APG4A, PRSS23
AGHGEF7, CDC42BPA, DEPDC2, PLCB3
TGFBR2, BMPR2, SMAD4, SMAD3

Table 19-3 Somatic Molecular Alterations in Invasive Pancreatic Adenocarcinoma

Gene	Chromosomal Region	Percentage of Carcinoma with Genetic Alteration	Gene Function
Oncogenes			
KRAS	12p	90	Growth factor signal transducer
AKT2	19q	10-20	Growth factor signal transducer
MYB	6q	10	Transcription factor
NCOA3/AIB1	20q	10	Chromatin regulator
MAP2K4/MKK4	17p	5	Growth factor signal transducer
Tumor Suppressor and DNA Repair Genes			
p16/CDKN2A	9p	95	Negative cell-cycle regulator
TP53	17p	50-70	Response to DNA damage
SMAD4	18q	55	TGFβ pathway
GATA-6	18q	10	Transcription factor
RB	13q	5	Negative cell-cycle regulator
STK11	19p	5	Regulation of cellular metabolism
ATM	11q	5	DNA damage response
ARID1A	1p	4	Chromatin regulator
TGFBR1	9q	2	TGFβ pathway
TGFBR2	3p	2	TGFβ pathway

Pancreatic carcinoma

- Tobacco use and chronic pancreatitis predispose
- More frequent in Blacks.
- 60-80 years of age
- 60%, head; 15%, body; 5%, tail
- 5%, squamous carcinoma
- Often grow along nerves and invade retroperitoneum
- Very elevated CA 19-9 specific for pancreatic carcinoma.
- 10% have migratory thrombophlebitis
- Most common metastasis to pancreas is from renal cancer

Table 19-4 Inherited Predisposition to Pancreatic Cancer

Disorder	Gene	Increased Risk of Pancreatic Cancer (Fold)	Risk of Pancreatic Cancer by Age 70 (%)
Peutz-Jeghers syndrome	*STK11*	130	30-60
Hereditary pancreatitis	*PRSS1, SPINK1*	50-80	25-40
Familial atypical multiple-mole melanoma syndrome	*CDKN2A*	20-35	10-17
Strong family history (3 or more relatives with pancreatic cancer)	Unknown	14-32	8-16
Hereditary breast and ovarian cancer	Multiple, including *BRCA1, BRCA2, PALP2, BRCA2*	4-10	5
Hereditary non-polyposis colorectal cancer (HNPCC)	Multiple, including *MLH1, MSH2* (2p21)	8-10	4

Histopathology

- Hard, stellate, gray-white, poorly defined masses
- The vast majority are ductal adenocarcinomas that recapitulate to some degree normal ductal epithelium by forming glands and secreting mucin.
- Less differentiated tumors have abortive tubular structures and cell clusters
- Two features are characteristic of pancreatic cancer:
- Highly invasive
- Elicits an intense host reaction in the form of dense fibrosis (“desmoplastic response”)
- Perineural invasion is common

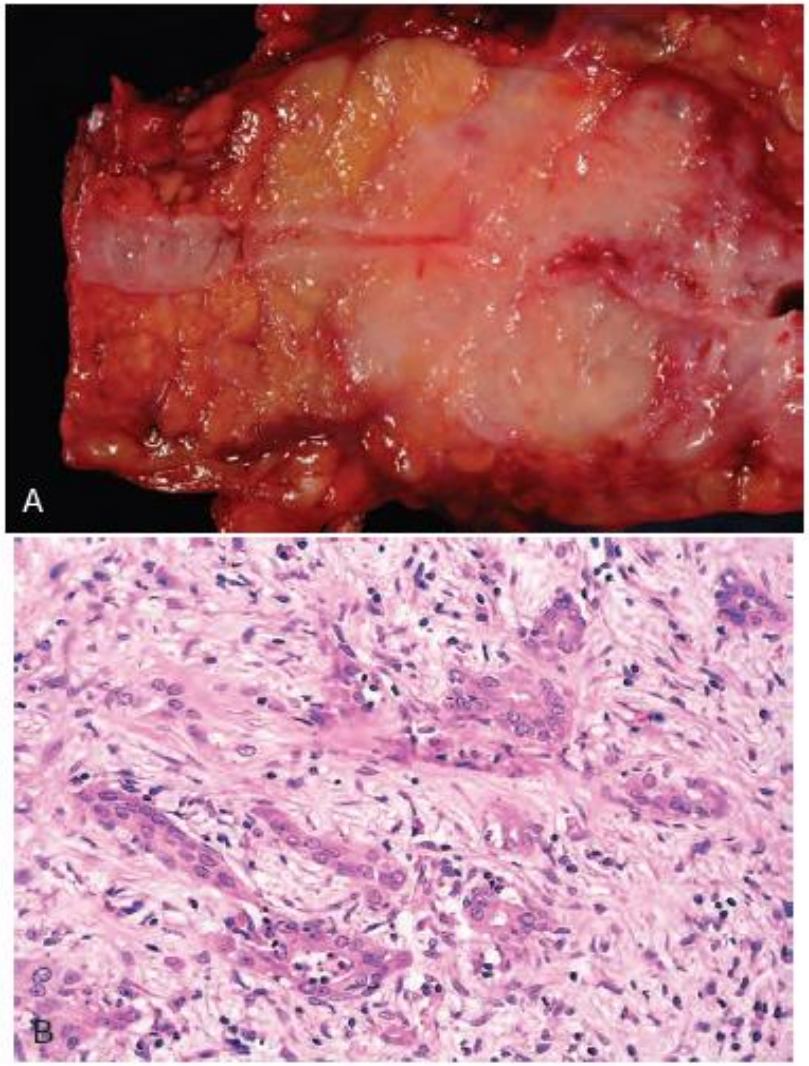
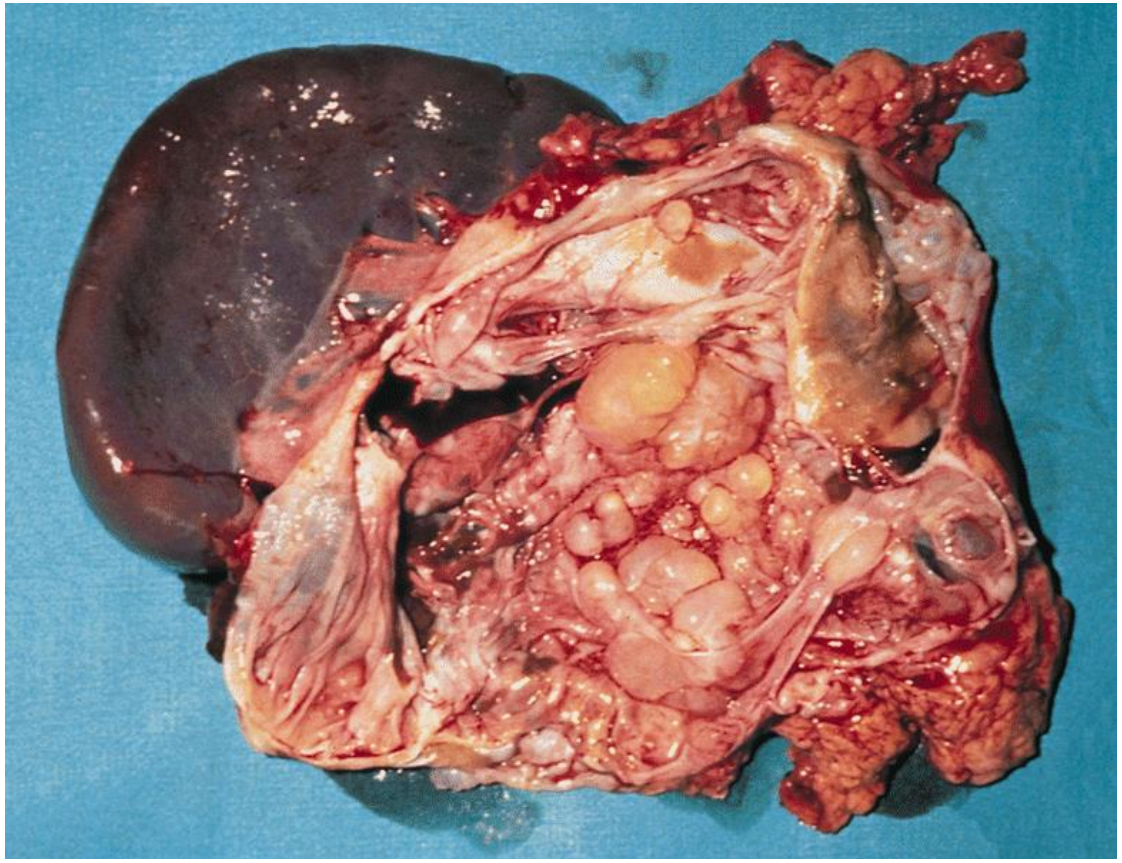


Figure 19-13 Carcinoma of the pancreas. **A,** A cross-section through the tail of the pancreas showing normal pancreatic parenchyma and a normal pancreatic duct *(left)*, an ill-defined mass in the pancreatic substance *(center)* with narrowing of the pancreatic duct, and dilatation of the pancreatic duct upstream *(right)* from the mass. **B,** Poorly formed glands are present in densely fibrotic stroma within the pancreatic substance; some inflammatory cells are also present.

Mucinous cyst adenocardinoma

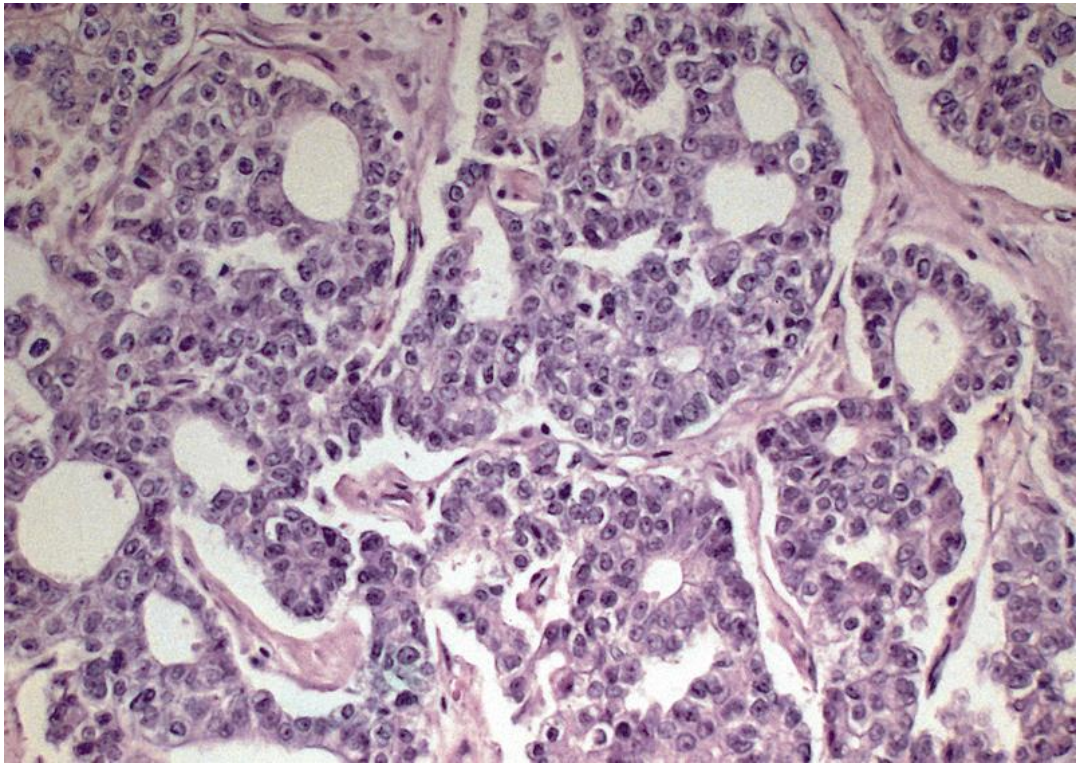


Tumor from the tail of the pancreas with adjacent spleen. The cut surface shows conspicuous, irregular, solid protuberances projecting into cystic cavities.

Fig. 4-14

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Acinar cell carcinoma

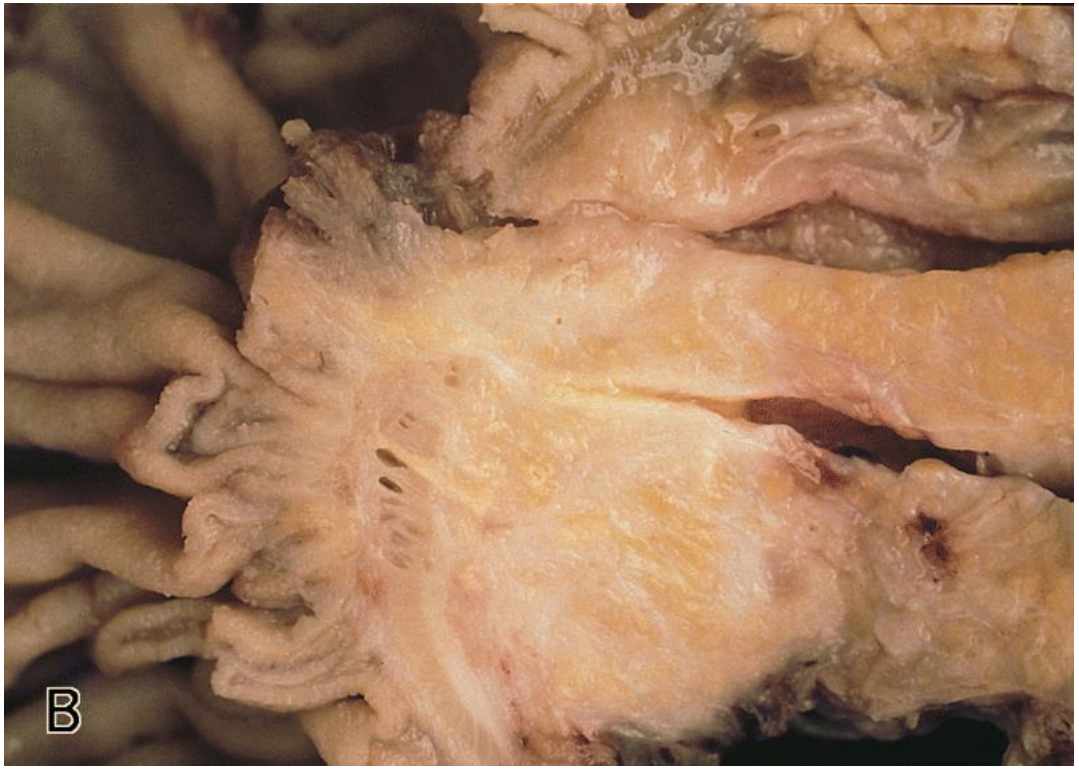


This tumor shows a pure acinar pattern, reminiscent of normal pancreatic acinar tissue.

Fig. 4-94B

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Ductal adeoncarcinoma

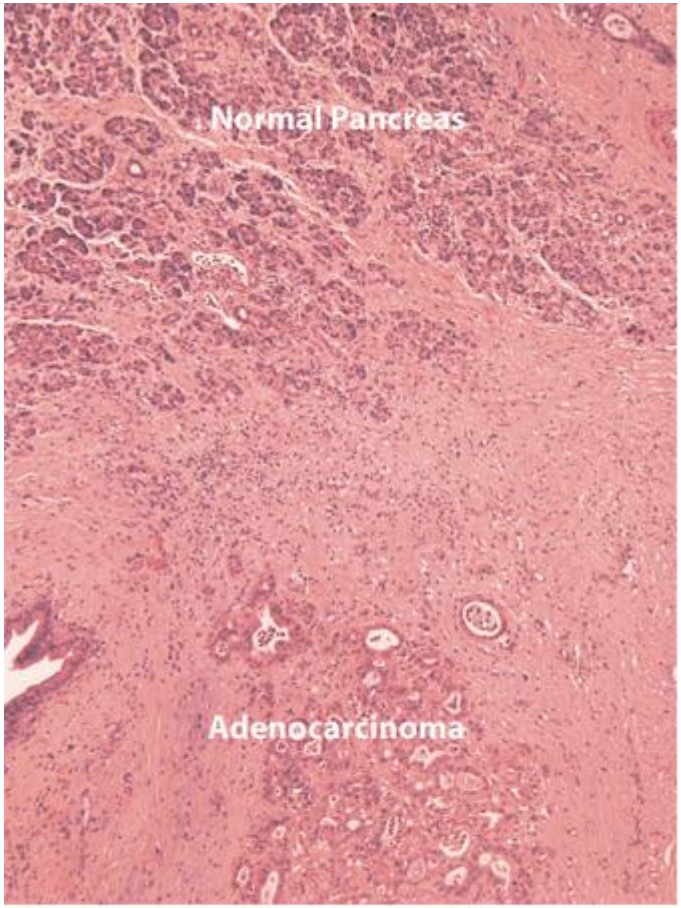


Whipple resection specimen showing a ductal adenocarcinoma with invasion of the ampulla and the duodenal wall, obstructing the common bile duct as well as the pancreatic duct. Note the ill-defined tumor demarcation.

Fig. 4-43B

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

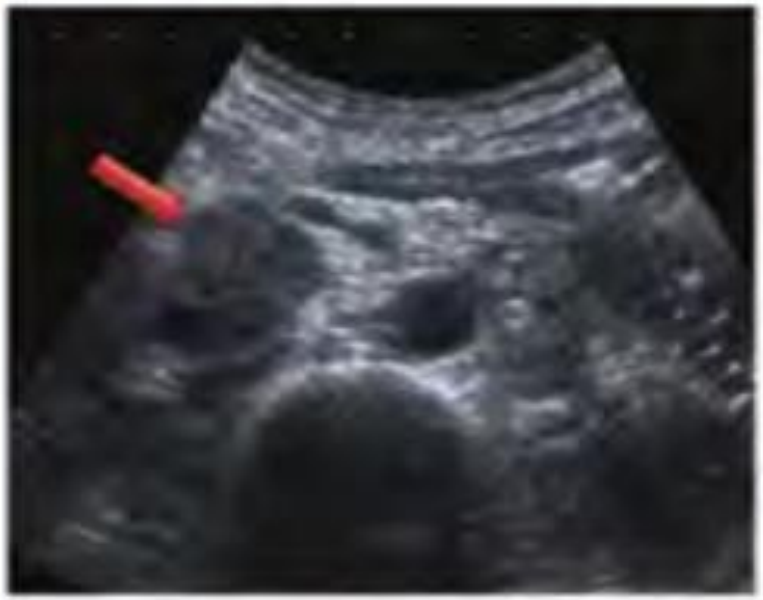
Ductular pancreatic adenocarcinoma



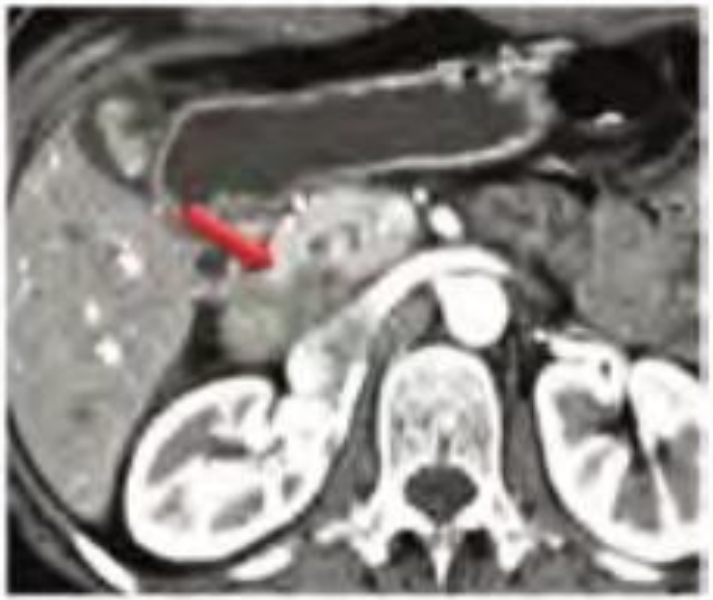
Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrograph of ductal adenocarcinoma of the pancreas with well-preserved islet cells and pancreatic architecture above and infiltrating tumor with poorly formed glandular structures below.

Fig. 15-1 Accessed 04/10/10



Hypoechoic mass, deforming gland contour with common bile duct (CBD) and dilatation



Hypoattenuation solid mass due to desmoplastic fibrotic component

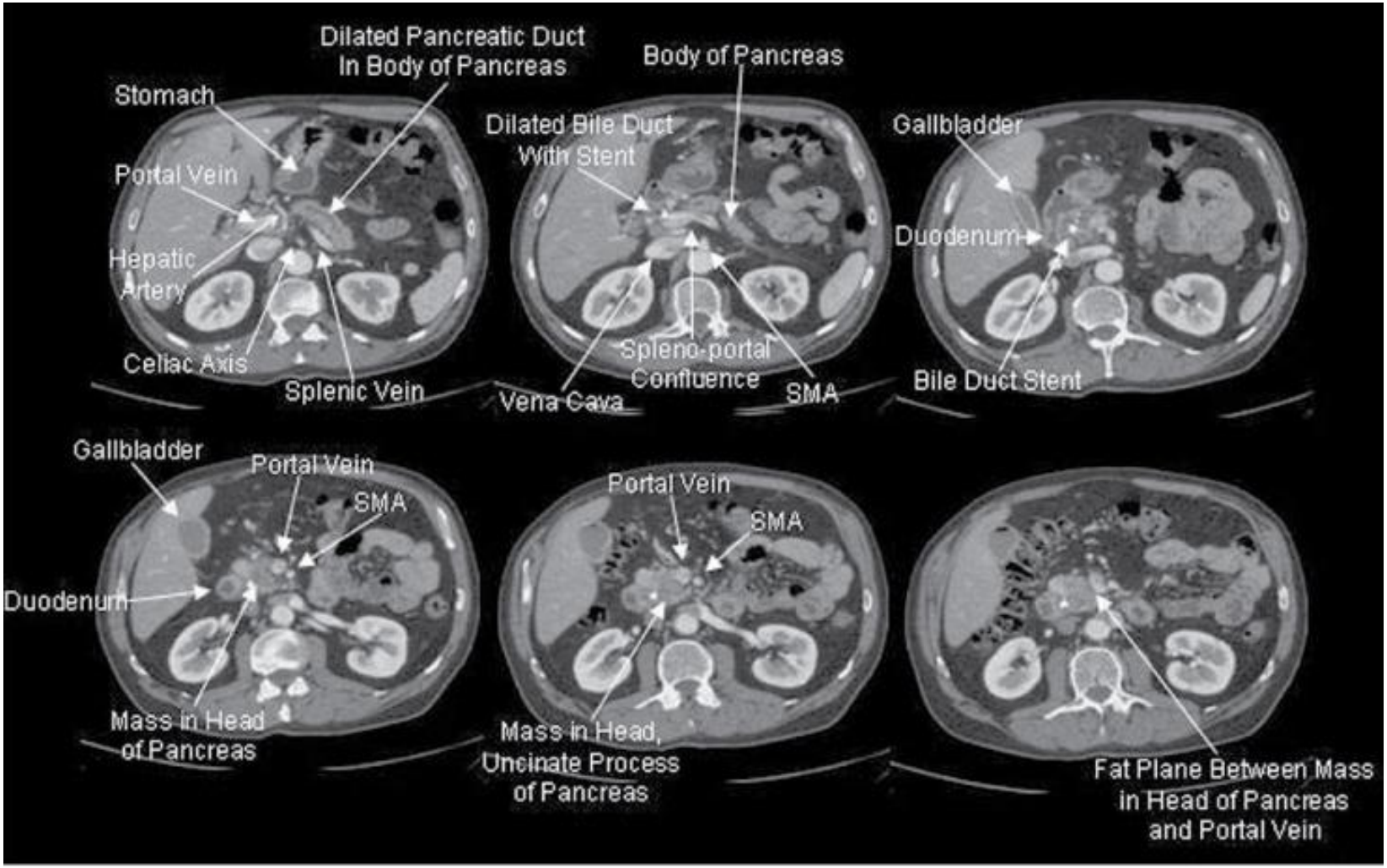
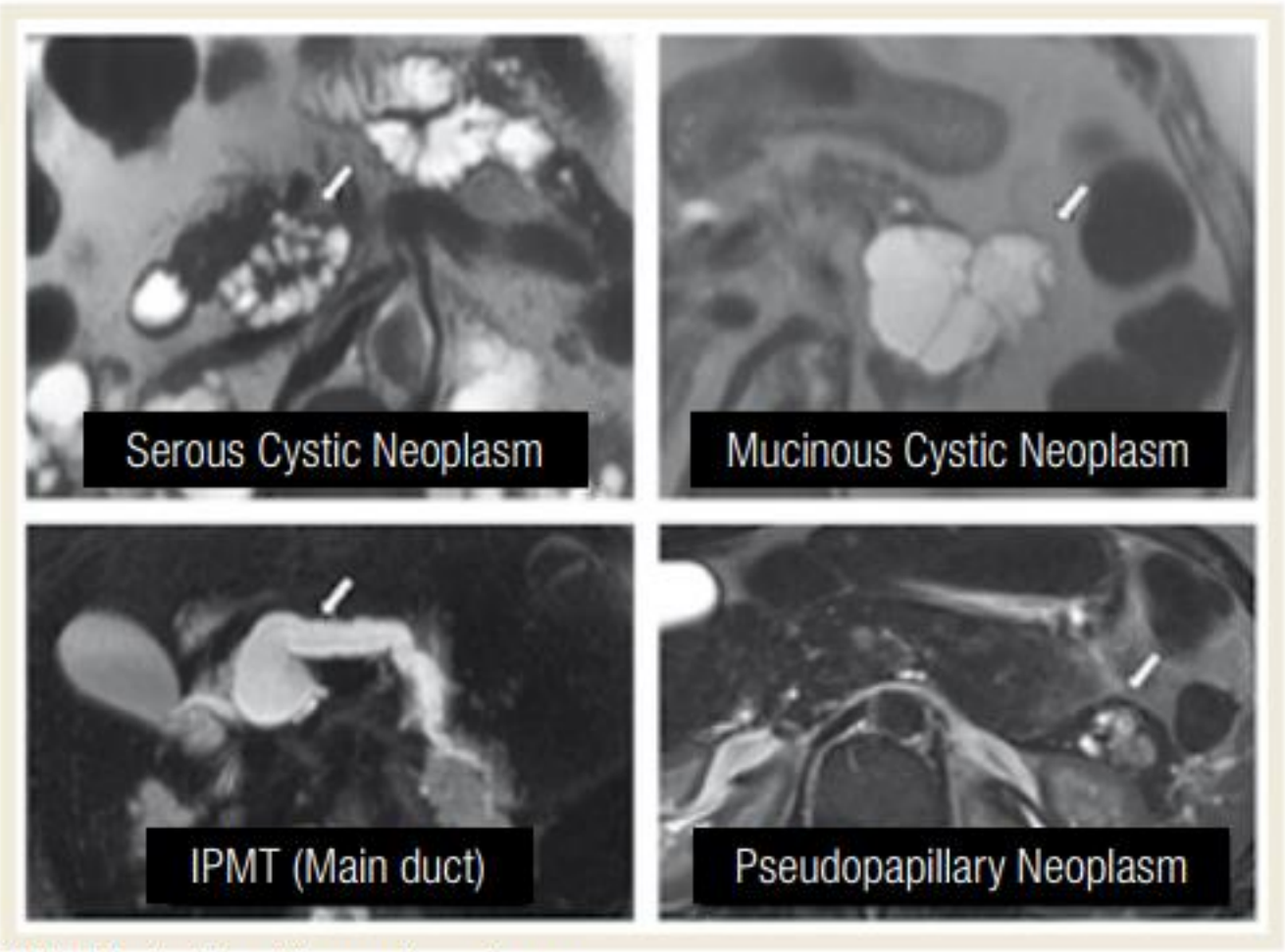


Fig. 33-68 Accessed 02/01/2010



IPMT, Intraductal papillary mucinous tumour.

Pancreatic carcinoma

- Dual contrast, helical CT (3D reconstruction).
- Arterial phase
- Permits assessment of tumor position to the celiac plexus and superior mesenteric artery (SMA).
- Venous phase
- Permits determination of the spatial relation of the tumor to the portal and splenic vein
- Permits identification of suspicious lymph nodes and distant metastases.

Pancreatic carcinoma

- 67% sensitive for lesions <1.5cm
- Nearly 100% sensitive for tumors >1.5cm.
- 95% positive predictive value in defining resectability if major vessel tumor encasement is present.
- Fine needle aspiration for diagnosing tumor with minimal risk.
- CA19-9 is not generally useful for diagnosis

Pancreatic carcinoma

- MRI represents the imaging modality of choice in the characterization of cystic pancreatic neoplasms.
- MRI and Magnetic resonance cholangiopancreatography (MRCP) are the most sensitive means for diagnosis of ductal adenocarcinoma
- Endoscopic ultrasound is comparable.
- Tumor and nodal staging.
- Detection of portal vein invasion.
- Evaluate periampullary lesions.

Pancreatic carcinoma

- Dual contrast helical CT or MRI with cholangiopancreatography (MRCP) is recommended to check for “high-risk stigmata”:
- Enhanced solid component and main pancreatic duct [MPD] >10 mm
- for “worrisome features”
- Cyst >3 cm, thickened enhanced walls, non-enhanced mural nodules
- MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy
- Lymphadenopathy

Anatomic relationships

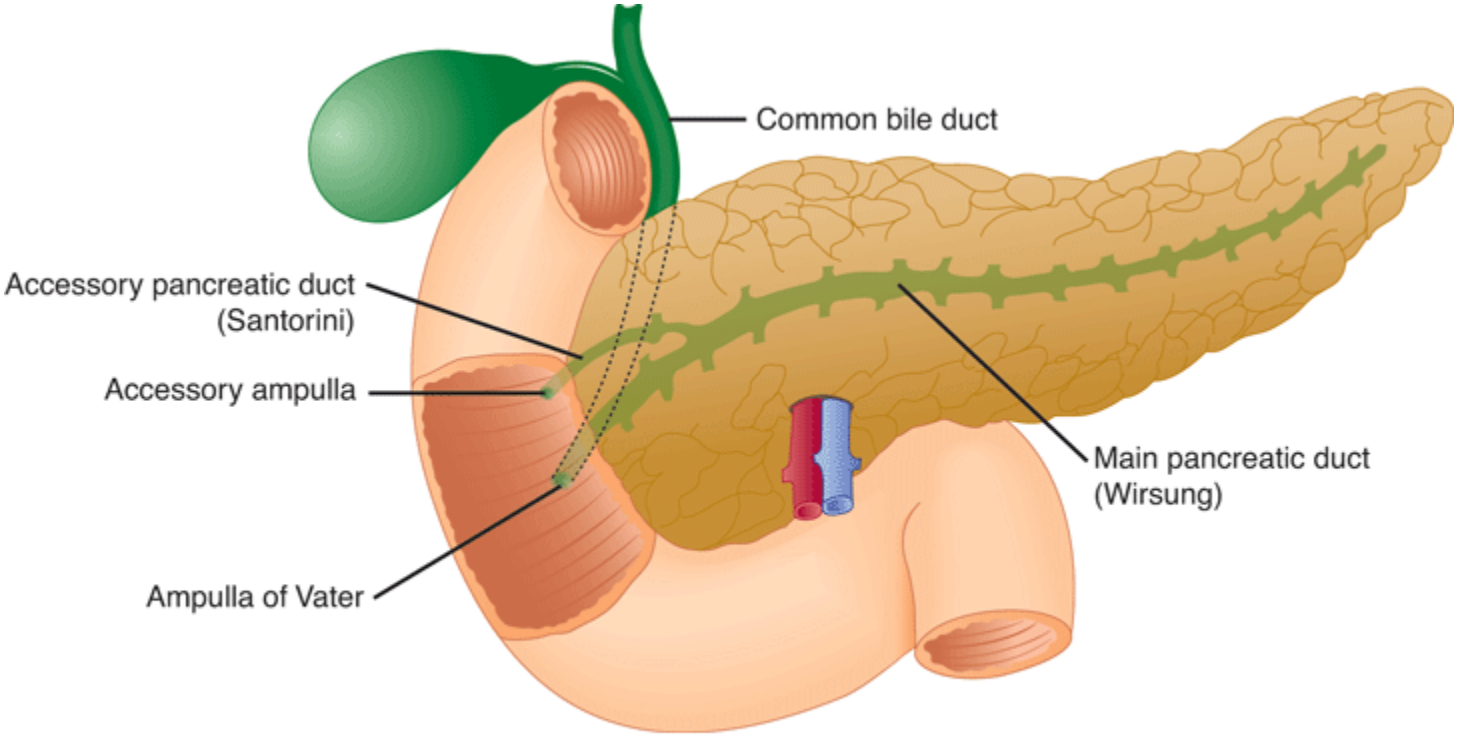
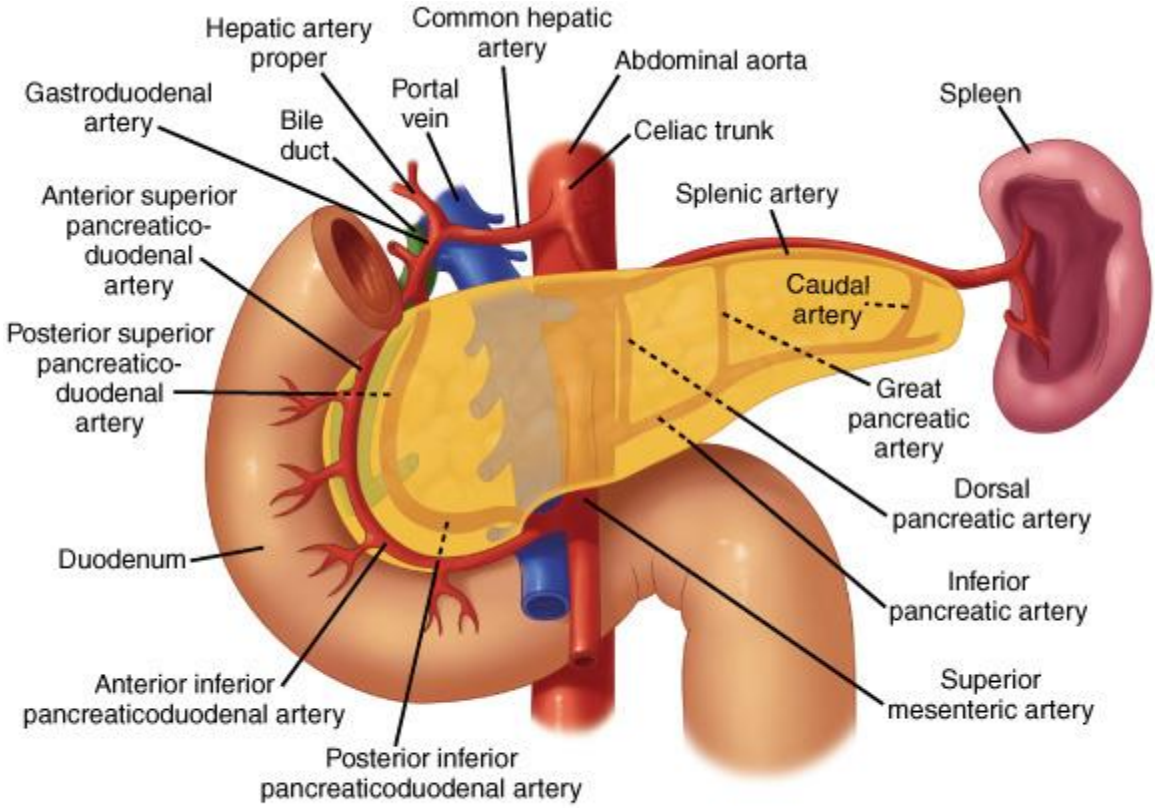


Fig. 15-1 Accessed 02/01/2010

Arterial supply to pancreas



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Fig. 33-4 Accessed 02/01/2010

Pancreatic carcinoma

- Fewer than 10% have resectable disease at diagnosis.
- If infiltration of the SMA >180°, is unresectable
- Confined to pancreas without encasement of celiac plexus or SMA and with patent portal vein.
- Borderline lesions abut but are not encased nor involve the short segment of the celiac artery.
- Reconstruction possible if hepatic artery involved but celiac artery is free of tumor.
- 70% will have local-regional recurrence following complete resection.
- If metastases, no resection is suggested

Unresectable

Distant metastases

Arterial encasement
(celiac trunk, superior mesenteric artery, or hepatic artery)

Arterial involvement
(celiac trunk, superior mesenteric artery, or hepatic artery)

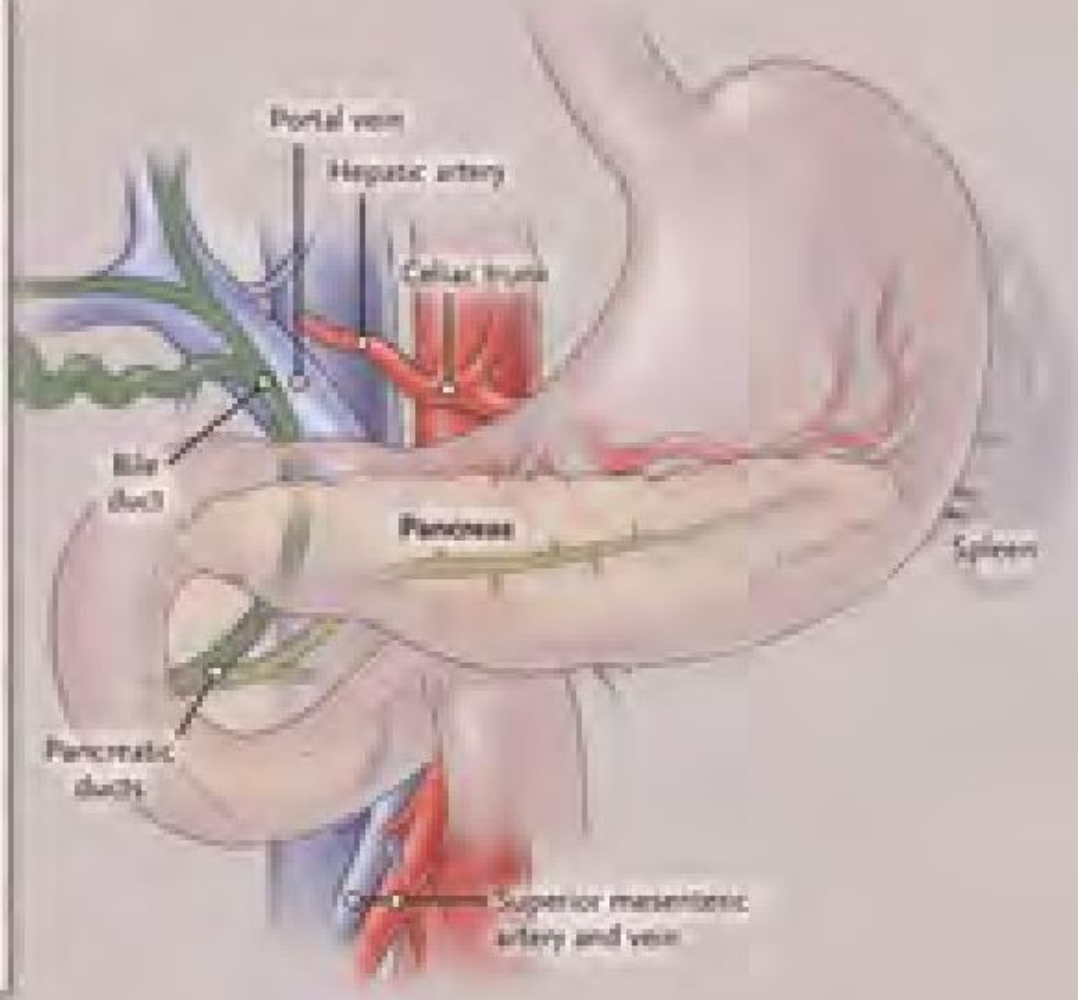
Venous encasement
(portal or superior mesenteric vein)

Venous involvement
(portal or superior mesenteric vein)

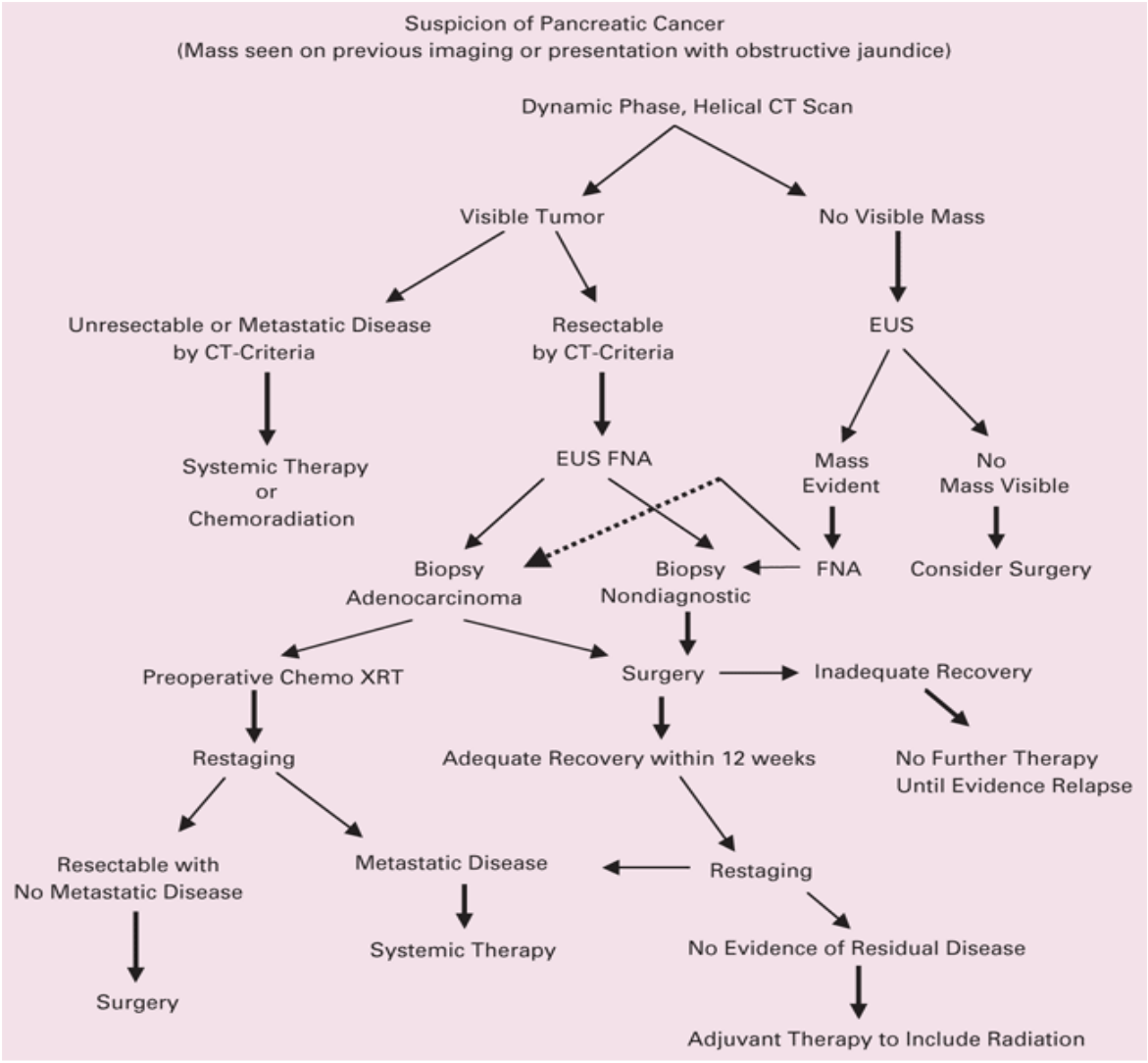
Attached to other organs

No arterial or venous involvement

Resectable



Strategy



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 15-4 Accessed 04.10/10

Treatment strategy

- Surgery is the only curative option
- Goal is tumor free margin (R0).
- For tumors in the pancreatic head, duodenopancreatectomy with or without pylorus sparing (Whipple procedure) is used.
- For tumors in the pancreatic body, duodenopancreatectomy or subtotal left pancreatic resection is performed
- For tumors in the pancreatic tail, a left sided pancreatic resection is performed

Pancreatic carcinoma

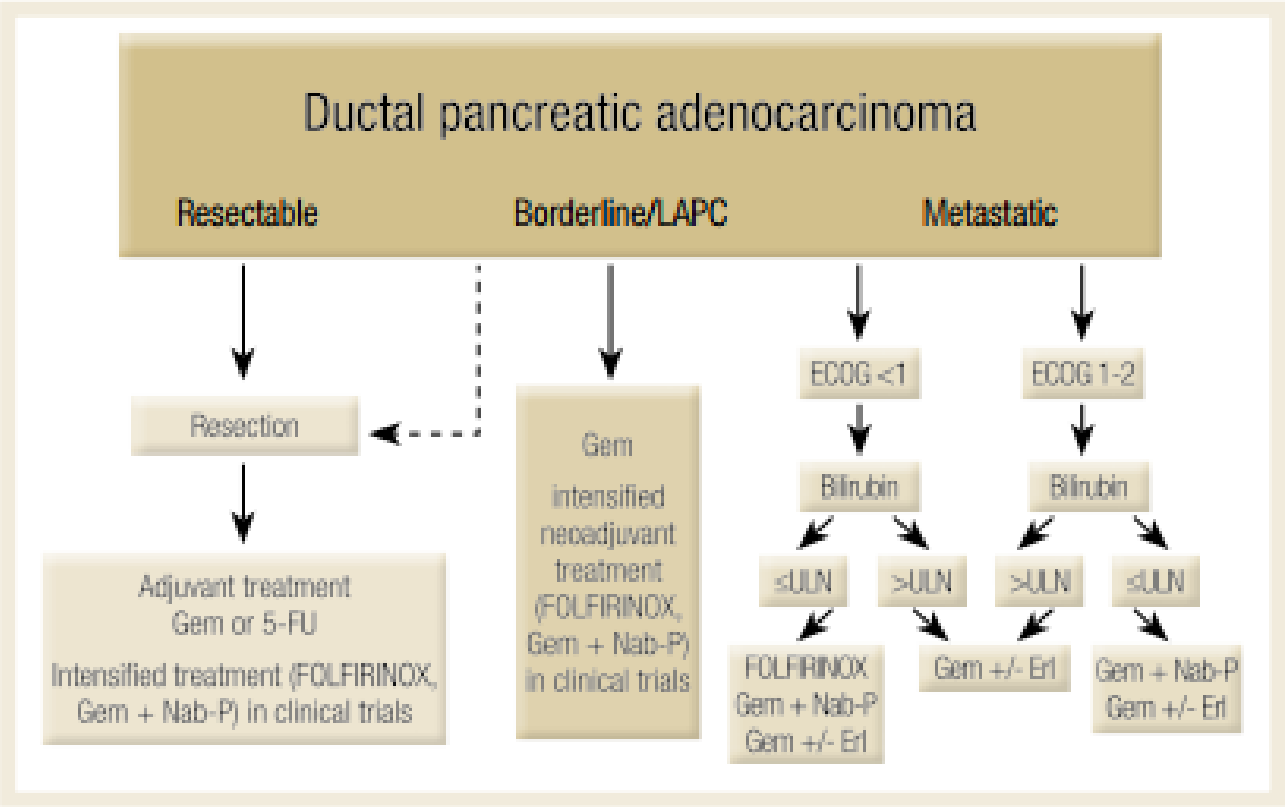
- 5 year survival following pylorus sparing Whipple procedure and chemoradiation is 17.5%.
- Locally advanced disease, 5 year survival is 6.0%; metastatic disease, 1.2%.
- Metastatic disease is treated with:
- FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, oxaliplatin)
- 30% respond (median survival, 11 months)
- However, is more toxic than gemcitabine regimens

Pancreatic carcinoma

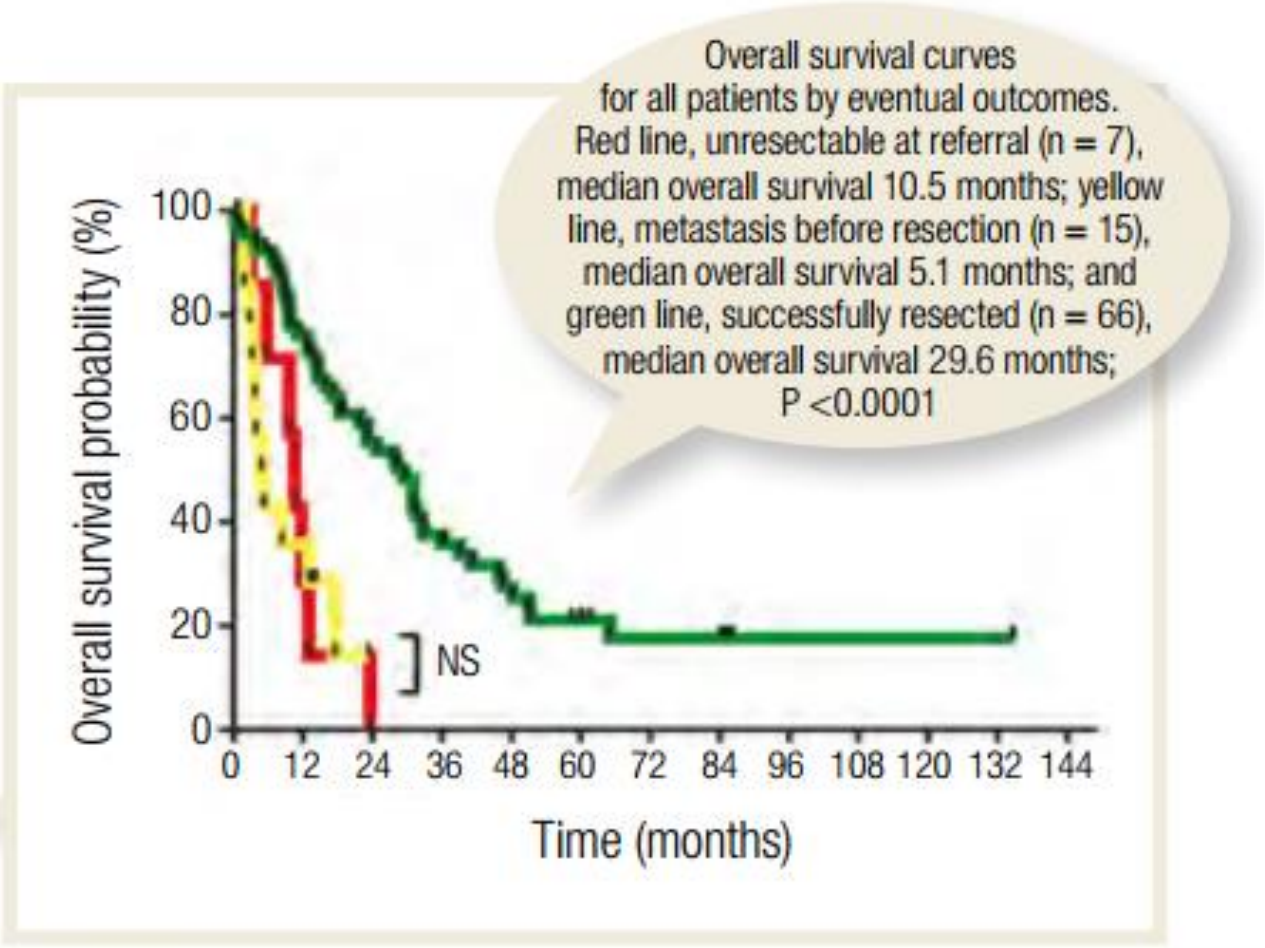
- Gemcitabine with N-albumin-bound paclitaxel (Nab-paclitaxel)
- Tolerated by those >65 years of age and Karnofsky index of 70-80
- Gemcitabine with cisplatin for those with known BRCA1/2 or PALB2 mutations.
- Gemcitabine, capecitabine, or infusion 5FU for palliation (20% respond; median survival, 6 months).

Pancreatic carcinoma

- If erlotinib, a TKI, is added to gemcitabine, only effective if patient develops typical rash associated with TKI use
- Stereotactic radiotherapy may control pain in many patients
- May have to block celiac plexus for pain control.
- Metal stent placement via endoscopy to relieve jaundice.



ECOG, Eastern Cooperative Oncology Group; Erl, erlotinib; FOLFIRINOX, 5-FU, leucovorin, irinotecan and oxaliplatin; 5-FU, fluorouracil; GEM, gemcitabine; LAPC, locally advanced pancreatic cancer; Nab-P, nab-paclitaxel; ULN, upper limit of normal.



NS, Not significant.

Pancreatoblastoma

- Mean presentation is age 5
- APC gene mutated
- AFP elevated
- Histology
- Multiple lines of differentiation and the presence of squamous nests
- Associated with Beckwith-Wiedemann syndrome
- Associated with familial adenomatous polyposis

Endocrine tumors

- Resemble giant islets.
- Regular cords of monotonous cells oriented to vasculature.
- May not be encapsulated.
- β-cell tumors most common (insulinoma).
- Blood glucose <50 mg/dL, precipitated by fasting or exercise
- Presents with confusion (neuroglycopenia).
- Amyloid deposition common in β-cell tumors.

Endocrine tumors

- Gastrinomas may arise in duodenum, pancreas, or peripancreatic tissues.
- Over half are locally invasive.
- Give rise to extreme gastric acid hypersecretion.
- 25% associated with MEN-1, are multiple.

Endocrine tumors

- Two-thirds of gastrinomas are found in the Zollinger-Ellison triangle bounded by the confluence of the cystic and common bile ducts and the second and third portions of the duodenum.
- Generally have metastasized at presentation.
- resectable if metastases in duodenum and liver; not if in lung or other organ.
- Follow with yearly gastrin levels if completely resected.
- Carcinomas rare and diagnosed only if metastasize.

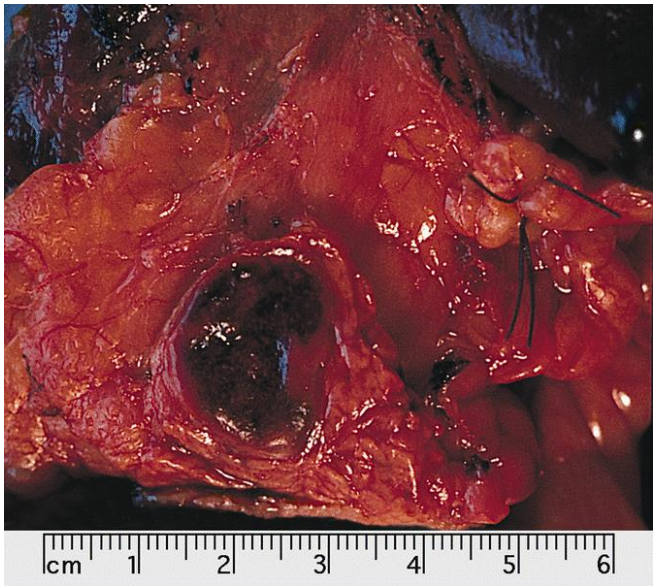
Endocrine tumors

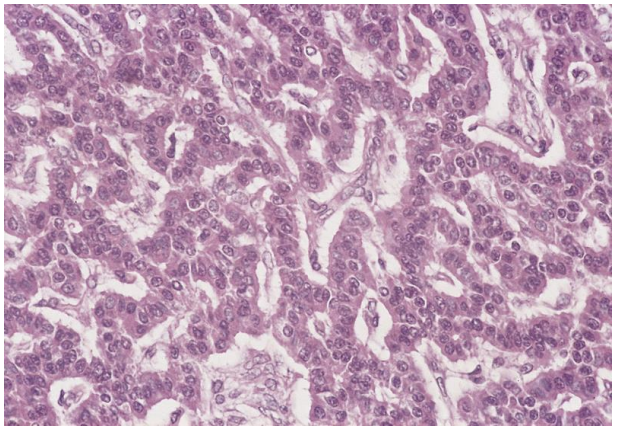
- α-cell tumors (glucagonoma) present with mild diabetes mellitus, anemia, and necrolytic migratory erythema (rash).
- Occur most frequently in perimenopausal or post-menopausal women.
- δ-tumors (somatostatinoma) are associated with diabetes mellitus, steatorrhea, hypochlorhydria, and cholelithiasis.

Endocrine tumors

- VIPoma may be invasive.
- Presents with severe watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome).
- May be associated with neural crest tumors.
- Evorlimus (mTOR inhibitor), sunitinib (tyrosine kinase inhibitor) may be effective.

Endocrine tumor



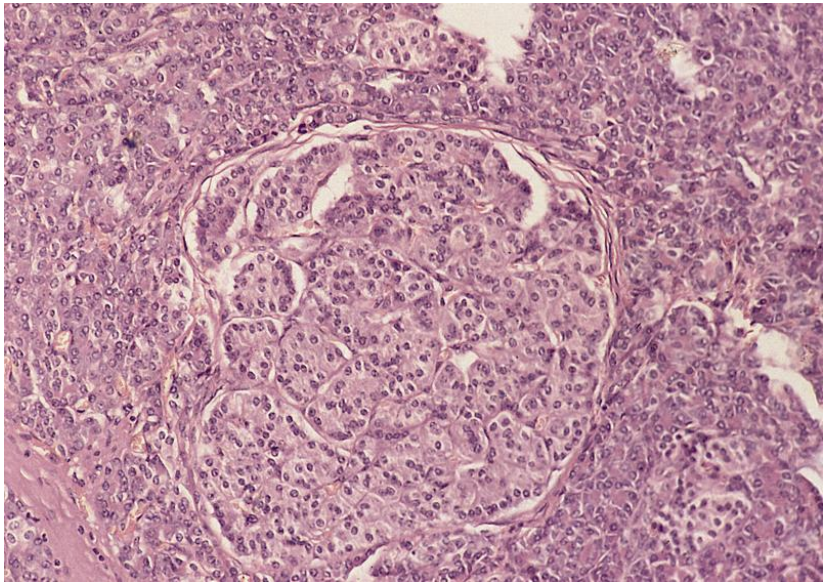


Small (2 cm in diameter) intrapancreatic tumor with expansile margins showing a relatively homogeneous, deep red, hemorrhagic appearance. (Top) Gyriform festoons separated by highly vascular stroma in a clinically nonfunctioning adenoma which was immunohistochemically glucagon- positive. (Bottom)

Figs. 5-3 and 5-8

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Islet cell adenoma



Well-demarcated, partly encapsulated growth of uniform cells forming regular microlobules. Compare with islet in the lower right corner.

Fig. 5-14

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Cancer syndromes

- Hereditary nonpolyposis colorectal cancer (Lynch II)
- Hereditary breast and ovarian cancer
- Familial atypical multiple mole melanoma syndrome
- Peutz-Jeghers syndrome
- Hereditary Pancreatitis