Painless Jaundice

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Goals of Discussion

- Bilirubin and the diagnostic evaluation of jaundice
- Cholangiocarcinoma
- Pancreatic cancer

Bilirubin and the Diagnostic Evaluation of Jaundice

About Bilirubin

- Normal breakdown product of hemoglobin when red blood cells are broken down by the reticuloendothelial system
- Insoluble unconjugated bilirubin is transported to liver bound to albumin

About Bilirubin

- Transported across the sinusoidal membrane of the hepatocyte into the cytoplasm

- Uridine diphosphate-glucuronyl transferase conjugates the insoluble unconjugated bilirubin with glucuronic acid

About Bilirubin

- Water-soluble bilirubin monoglucuronide and bilirubin diglucuronide are created
- Conjugated bilirubin is actively secreted into the bile canaliculus

About Bilirubin

- In terminal ileum and colon, bilirubin is converted to urobilinogen
  - 10-20% of the urobilinogen is reabsorbed into the portal circulation
  - This urobilinogen is either to be re-excreted into the bile or excreted by the kidneys into the urine

About Bilirubin

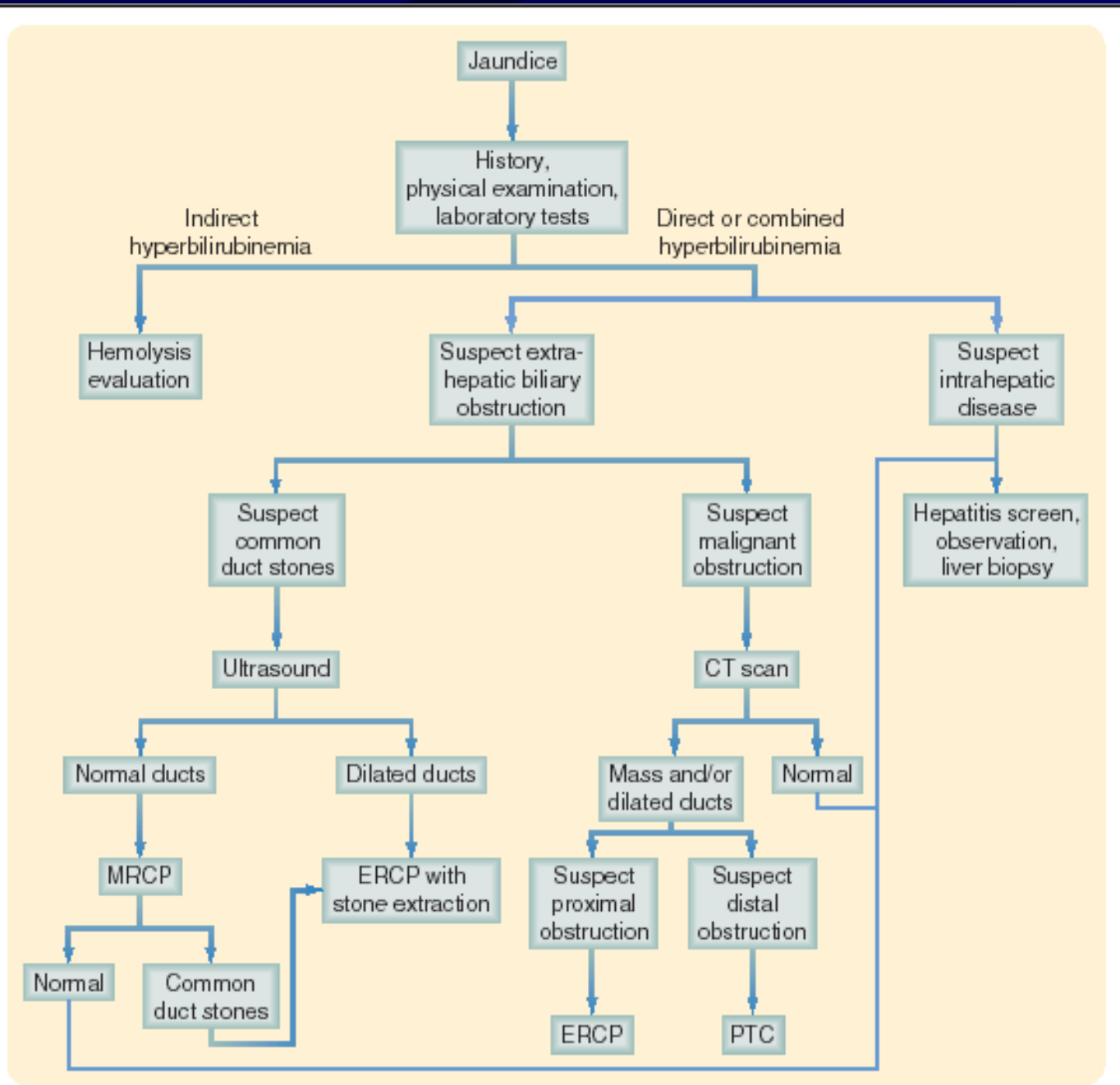
- Normal serum bilirubin = 0.5 - 1.3 mg/dL
- Jaundice: clinically apparent staining of tissues by bilirubin when levels exceed 2.0 mg/dL
- “Tea colored” urine is one of the first changes reported by patients

Evaluating Jaundice

- DDx parallels the metabolism of bilirubin
- Can be divided into two sets of disorders:
  - MEDICAL: increased production, decreased hepatocyte transport or conjugation, impaired excretion of bilirubin
  - SURGICAL: impaired delivery of bilirubin into the intestine

Differential Diagnosis of Jaundice

Abnormality in Bilirubin Metabolism	Predominant Hyperbilirubinemia	Examples
Increased production	Unconjugated	Multiple transfusions, transfusion reaction, sepsis, burns, congenital hemoglobinopathies, hemolysis
Impaired hepatocyte uptake or conjugation	Unconjugated	Gilbert's disease, Crigler-Najjar syndrome, neonatal jaundice, viral hepatitis, drug inhibition, sepsis
Impaired transport and excretion	Conjugated	Dubin-Johnson syndrome, Rotor's syndrome, cirrhosis, amyloidosis, cancer, hepatitis (viral, drug induced, or alcoholic), pregnancy
Biliary obstruction	Conjugated	Choledocholithiasis, benign stricture, periampullary cancer, cholangiocarcinoma, chronic pancreatitis, primary sclerosing cholangitis



Evaluating Jaundice

- Laboratory tests
  - Direct (conjugated) and indirect (unconjugated) bilirubin
  - Alkaline phosphatase
  - Transaminases
  - Amylase
  - CBC

Evaluating Jaundice

- Radiologic evaluation
  - confirmation of clinically suspected biliary obstruction by demonstrating intrahepatic and/or extrahepatic duct dilation
  - identification of site and cause of the obstruction
  - selection of the appropriate treatment modality for managing the jaundice

Evaluating Jaundice

- Ultrasound
  - often the initial screening test
  - extrahepatic (>10 mm) or intrahepatic (>4 mm) dilation suggests biliary obstruction
  - can identify gallstones, liver metastases, and occasionally masses of the liver and pancreas

Evaluating Jaundice

- CT Scan
  - sensitive in identifying biliary dilation
  - less sensitive than US in identifying gallstones
  - more accurate than US in identifying site and cause of extrahepatic biliary obstruction
  - Spiral CT can provide additional info regarding vascular involvement in patients with periampullary tumors

Evaluating Jaundice

- Therefore, for INITIAL radiographic evaluation:
  - if biliary obstruction from GALLSTONES is expected, use ULTRASOUND first
  - if biliary obstruction from TUMOR is expected, use CT scan first

Evaluating Jaundice

- Cholangiography
  - MR cholangiography (MRC)
    - non-invasive, provides anatomic detail regarding site of obstruction
  - Endoscopic retrograde cholangiography (ERC)
    - invasive
    - 2-5% risk of complications
    - may not be feasible in patients with altered gastroduodenal anatomy

Managing Jaundice

- Endoscopic Retrograde Cholangiography (ERC)
  - can clear retained CBD stones 85-90% of the time
  - allows for stent placement for internal decompression of biliary tract

Managing Jaundice

- Percutaneous Transhepatic Cholangiography (PTC)
  - favored in patients with more proximal bile duct obstruction involving or proximal to the hepatic duct bifurcation
  - stents can be passed across an obstructing lesion into the duodenum to permit internal drainage
  - serial dilation of stent tract permits passage of choledochoscope into biliary tree for direct visualization, biopsy, or management of obstructing lesions or stones

Cholangiocarcinoma

Cholangiocarcinoma

- Uncommon tumor
- Can be present anywhere along the intrahepatic or extrahepatic biliary tree
- Most common location: hepatic duct bifurcation (60-80% of all cases)
- Most present with painless jaundice

Cholangiocarcinoma

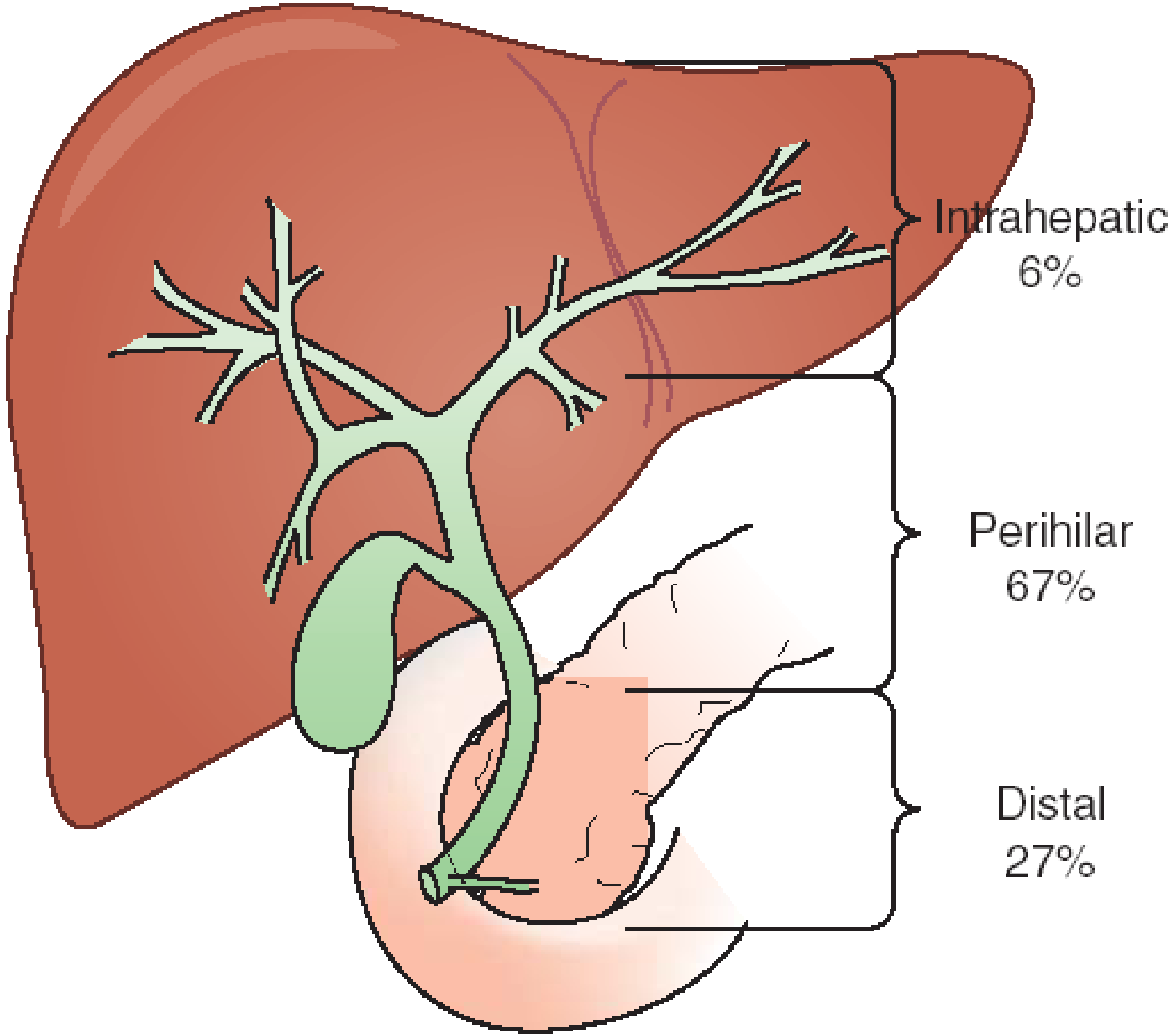
- Incidence
  - 2,500 to 3,000 new cases each year in the US
  - 1 in 100,000 people per year
  - equal frequency in men and women
  - incidence increases with age

Cholangiocarcinoma

- Risk factors ("stasis, stones, infection")
  - primary sclerosing cholangitis
    - extrahepatic, occuring in 5th decade of life
  - choledochal cysts
    - risk increases steadily with age
  - hepatolithiasis
    - 5-10% risk of cholangiocarcinoma
  - liver flukes, thorotrast, dietary nitrosamines, exposure to dioxin

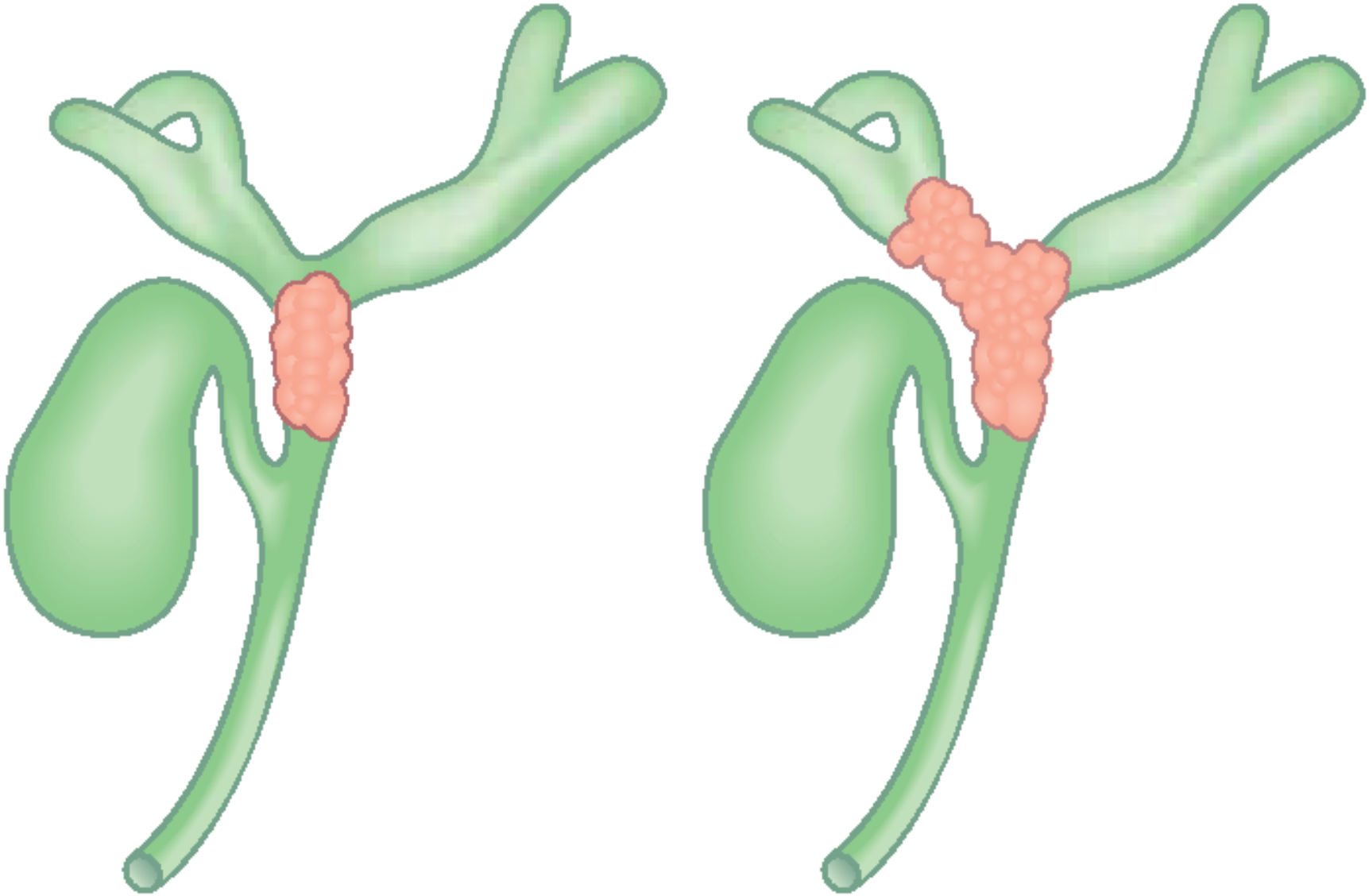
Cholangiocarcinoma

- Staging and Classification
  - intrahepatic
    - treated with hepatectomy
  - perihilar
    - treated with resection of BD w/hepatic resection
  - distal
    - treated with pancreatoduodenectomy



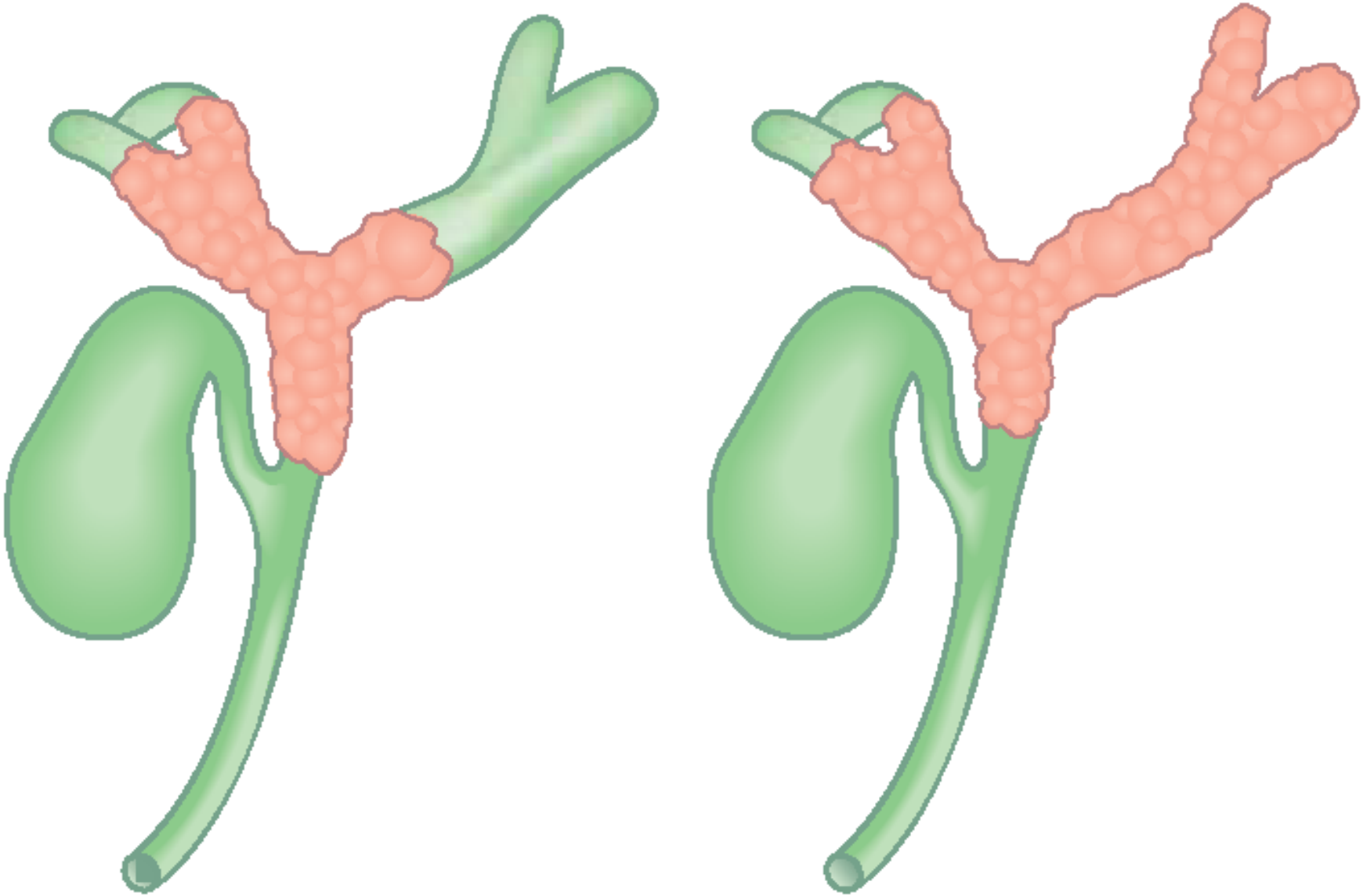
Cholangiocarcinoma

- Perihilar cholangiocarcinoma (Bismuth anatomic classification)
  - Type I tumor
    - confined to common hepatic duct
  - Type II tumor
    - involve bifurcation without involvement of secondary intrahepatic ducts



Cholangiocarcinoma

- Perihilar cholangiocarcinoma (Bismuth anatomic classification)
  - Type IIIa and IIIb tumors
    - extend to either right (IIIa) or left (IIIb) secondary intrahepatic ducts
  - Type IV tumor
    - involve the secondary hepatic ducts on both sides



Cholangiocarcinoma

TABLE 52-9 -- TNM Staging for Extrahepatic Cholangiocarcinoma

T1	Tumor confined to bile duct	
T2	Tumor invades beyond the wall of the bile duct	
T3	Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left)	
T4	Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M0	No distant metastasis	
M1	Distant metastasis	
Stage	**Stage Grouping**	
IA	T1 N0 M0	Limited to bile duct
IB	T2 N0 M0	Invade periductal tissues
IIA	T3 N0 M0	Locally advanced w/o LN metastases
IIB	T1 N1 M0	Locally advanced with regional LN metastases
	T2 N1 M0	
	T3 N1 M0	
III	T4 Any N M0	Locally advanced and unresectable
IV	Any T Any N M1	With distant metastases

Adapted from Greene F, Page D, Fleming I, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Cholangiocarcinoma

- Clinical presentation
  - Jaundice in >90% of patients with perihilar or distal tumors
  - Patients with intrahepatic cholangiocarcinoma are rarely jaundiced until late in disease
  - Pruritis, fever, mild abdominal pain, fatigue, anorexia, weight loss

Cholangiocarcinoma

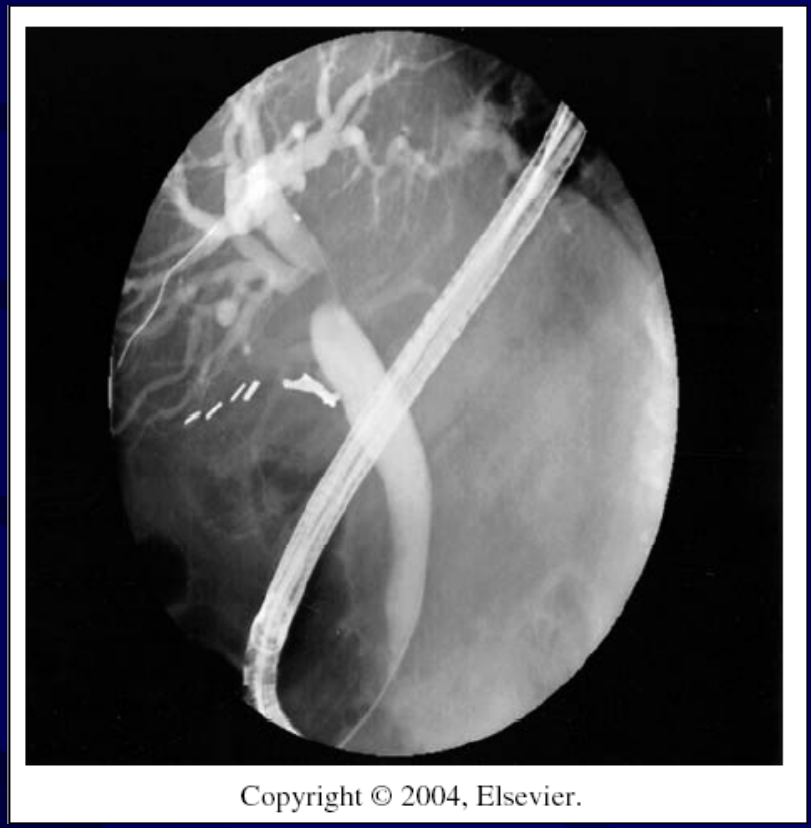
- Diagnosis
  - Total serum bilirubin >10 mg/dL
  - Elevated levels of alkaline phosphatase
  - Serum CA 19-9 may be elevated

Cholangiocarcinoma

- Diagnosis (cont'd)
  - CT for evaluation
    - intrahepatic tumors easily visualized
    - perihilar and distal tumors often difficult to identify
    - trends
      - hilar tumors: dilated intrahepatic biliary tree, normal extrahepatic biliary tree and gallbladder
      - distal tumors: dilated intrahepatic and extrahepatic biliary tree and dilated gallbladder

Cholangiocarcinoma

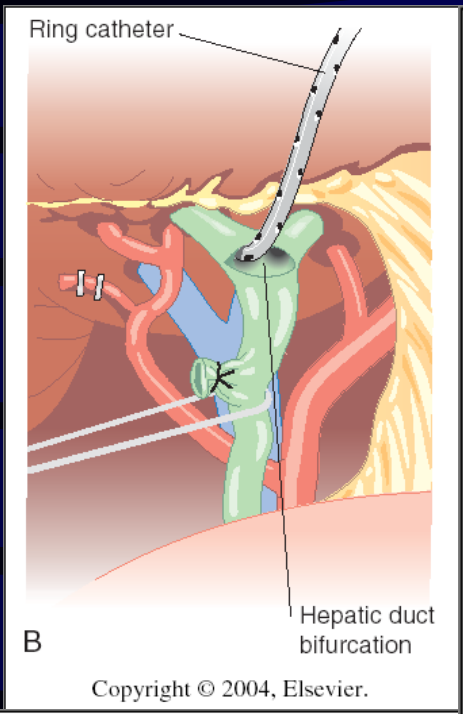
- Diagnosis (cont'd)
  - Cholangiography (ERC or PTC)
    - most proximal extent of tumor is the most important feature in determining resectability in patients with perihilar tumors
    - MRC has diagnostic accuracy comparable to ERC and PTC

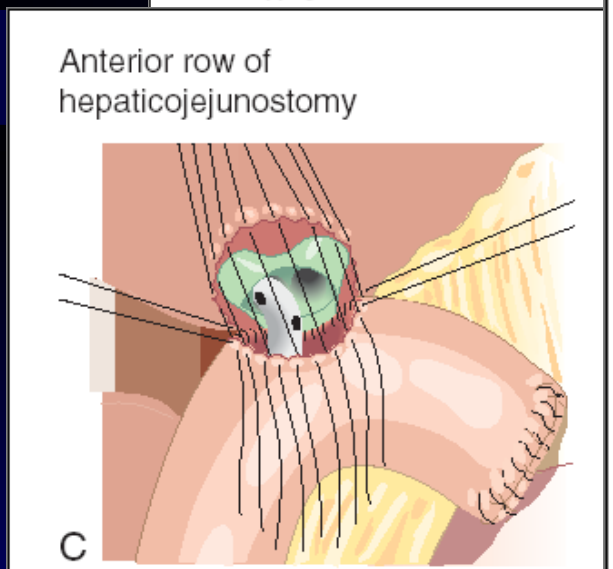


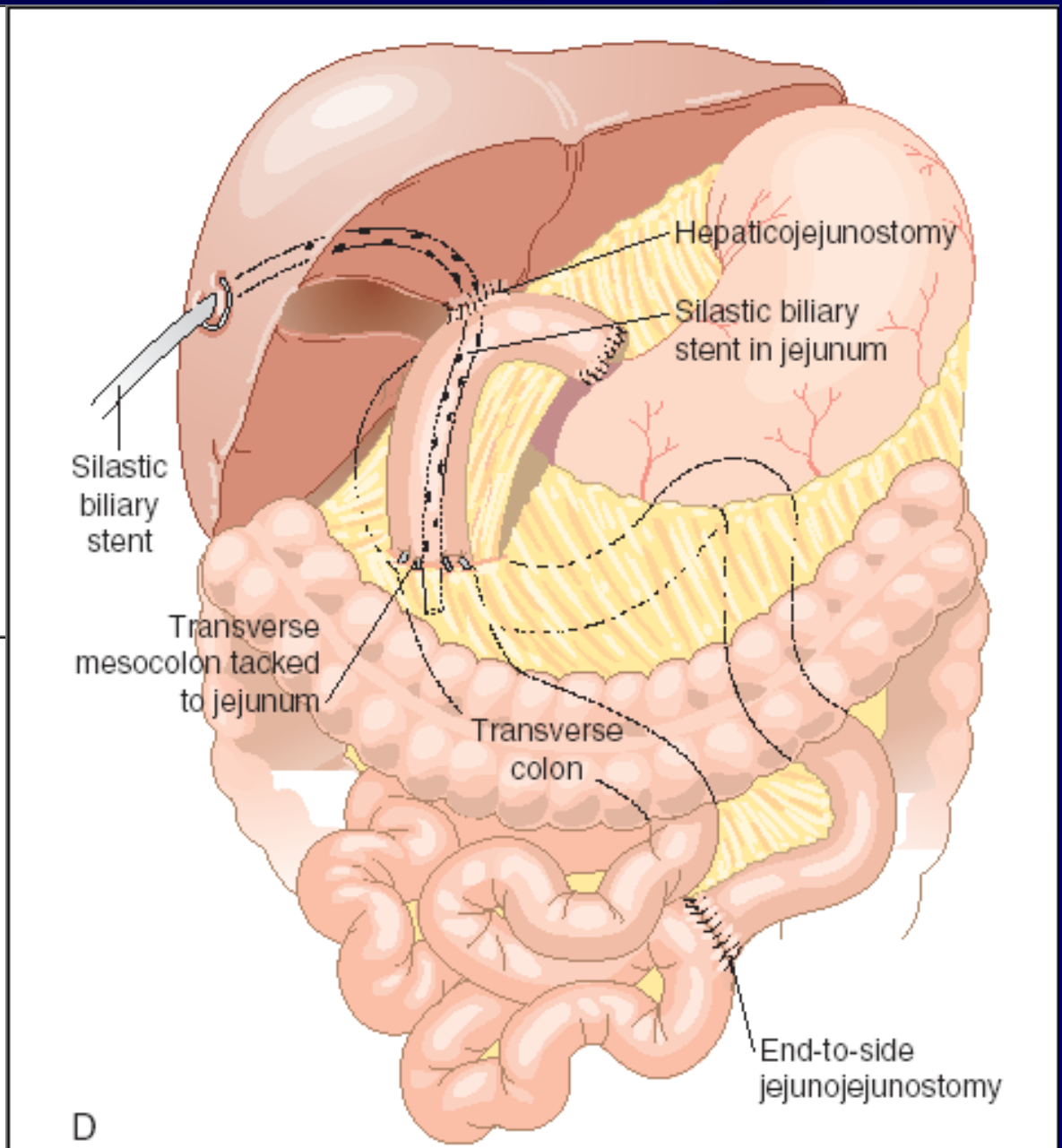
Cholangiocarcinoma

- Management
  - Curative treatment = complete resection
  - Intrahepatic tumor: partial hepatectomy
  - Perihilar tumor
    - If involving the hepatic duct bifurcation or proximal common hepatic duct (Bismuth I or II): hepaticojejunostomy
    - If involving the right or left hepatic duct (Bismuth IIIa or IIIb): right or left hepatic lobectomy

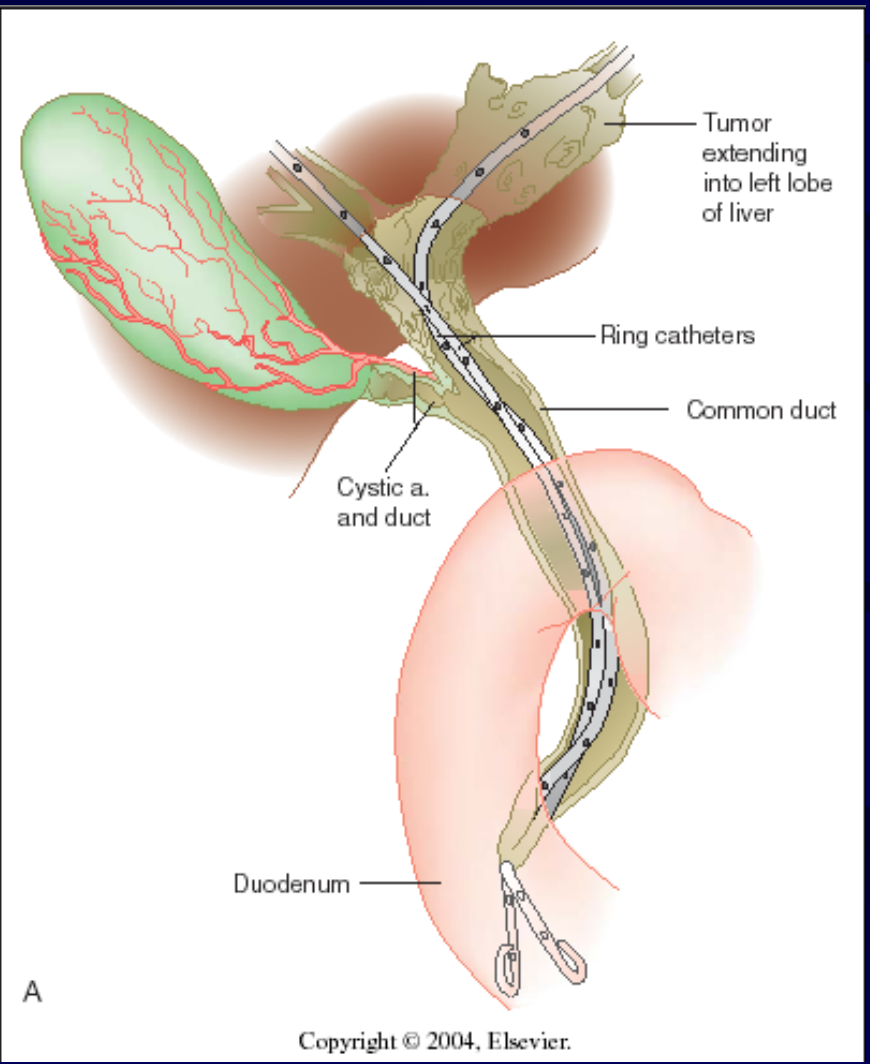
Hepaticojejunostomy at bifurcation of hepatic duct

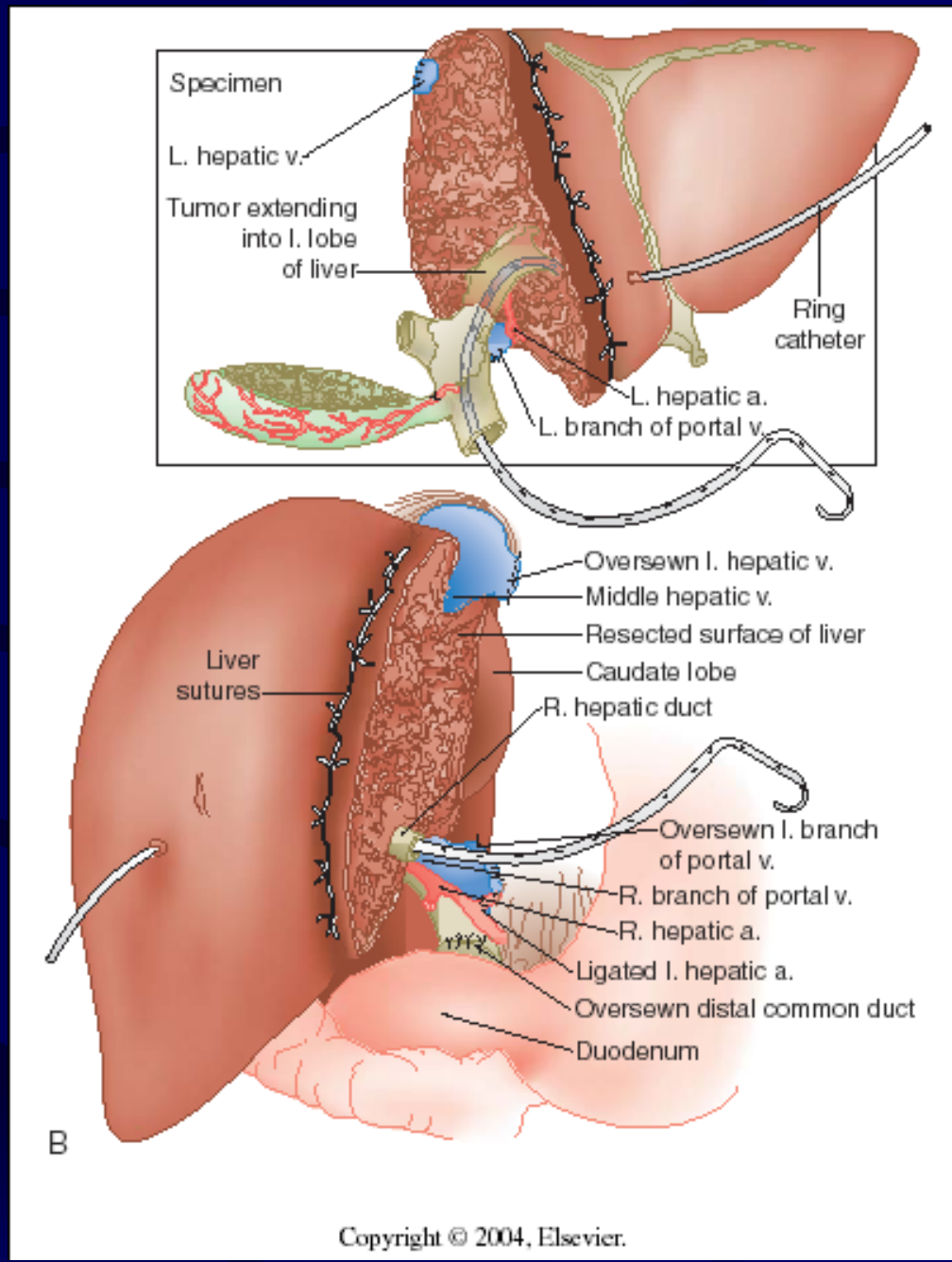


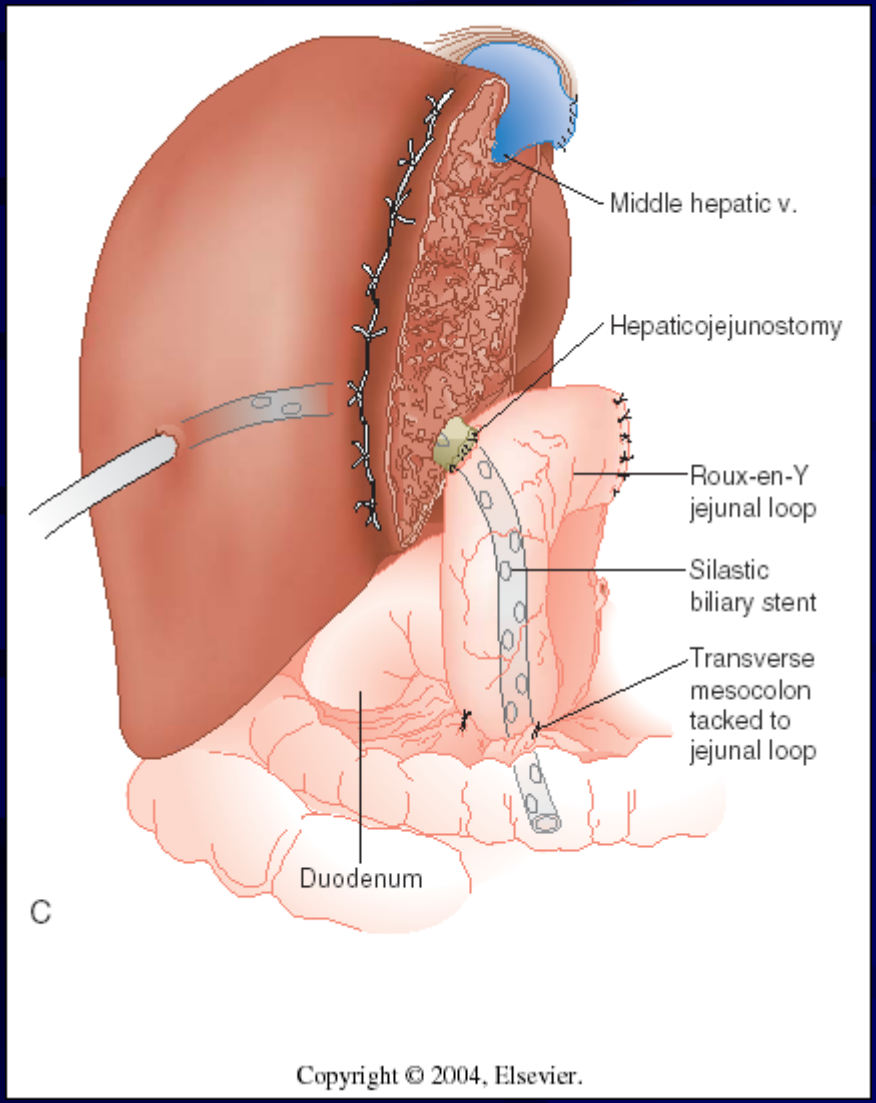




Left hepatic lobectomy for Bismuth Type IIIb perihilar cholangiocarcinoma







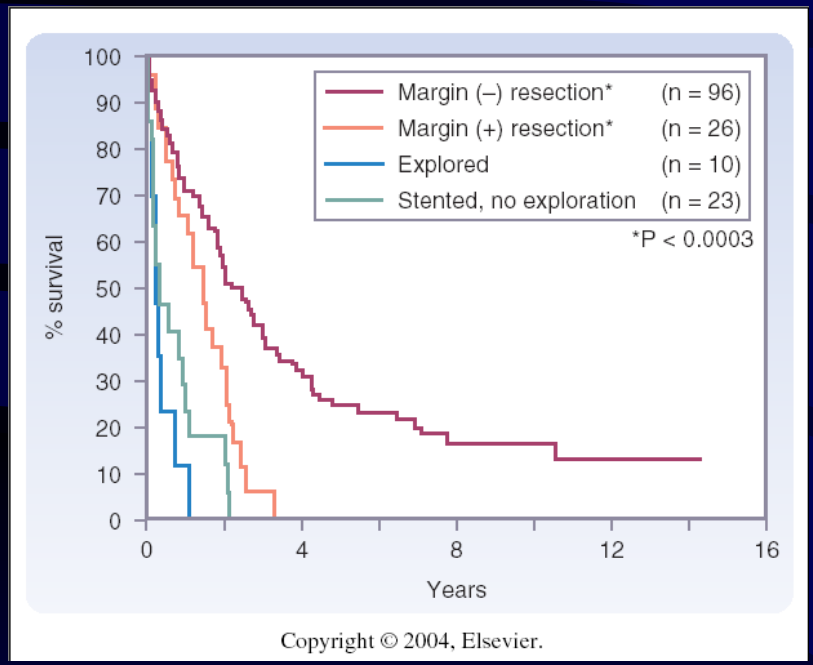
Cholangiocarcinoma

- Management (cont'd)
  - Distal tumor: pancreatoduodenectomy
  - Nonoperative palliation for unresectable tumor
    - Percutaneous biliary drainage for perihilar tumors
    - Endoscopic drainage for distal tumor

Cholangiocarcinoma

- Management (cont'd)
  - For exploratory laparatomy and unresectable tumor:
    - extensive metastatic disease: biliary stent placement + cholecystectomy
    - locally advanced, unresectable perihilar tumors: cholecystectomy, Roux-en-Y hepaticojejunostomy proximal to tumor, and gastrojejunostomy

Cholangiocarcinoma



- Chemotherapy has not been shown to improve survival in resected or unresected cholangiocarcinoma
- No prospective RCTs have been reported on the efficacy of external beam radiotherapy.

Pancreatic Cancer

Pancreatic Cancer

- Affects 25,000 to 35,000 people in the US each year
- 4th or 5th leading cause of cancer-related death in the US
- Increased frequency in men > women, blacks > whites
- 80% of cases occur between 60 - 80 years of age

Pancreatic Cancer

- Risk factors
  - Hx of hereditary or chronic pancreatitis
  - Cigarette smoking
  - Occupational exposure to carcinogens

  - NOT coffee drinking, which was once considered a risk factor

Pancreatic Cancer

- Pathology
  - ductal adenocarcinoma: 80-90% of all pancreatic neoplasms
  - 70% arise in pancreatic head of uncinate process
  - grossly, are hard, irregular, gritty masses that are poorly demarcated and yellow-gray
  - at time of Dx, usually > 3cm in diameter with distant metastasis

Pancreatic Cancer

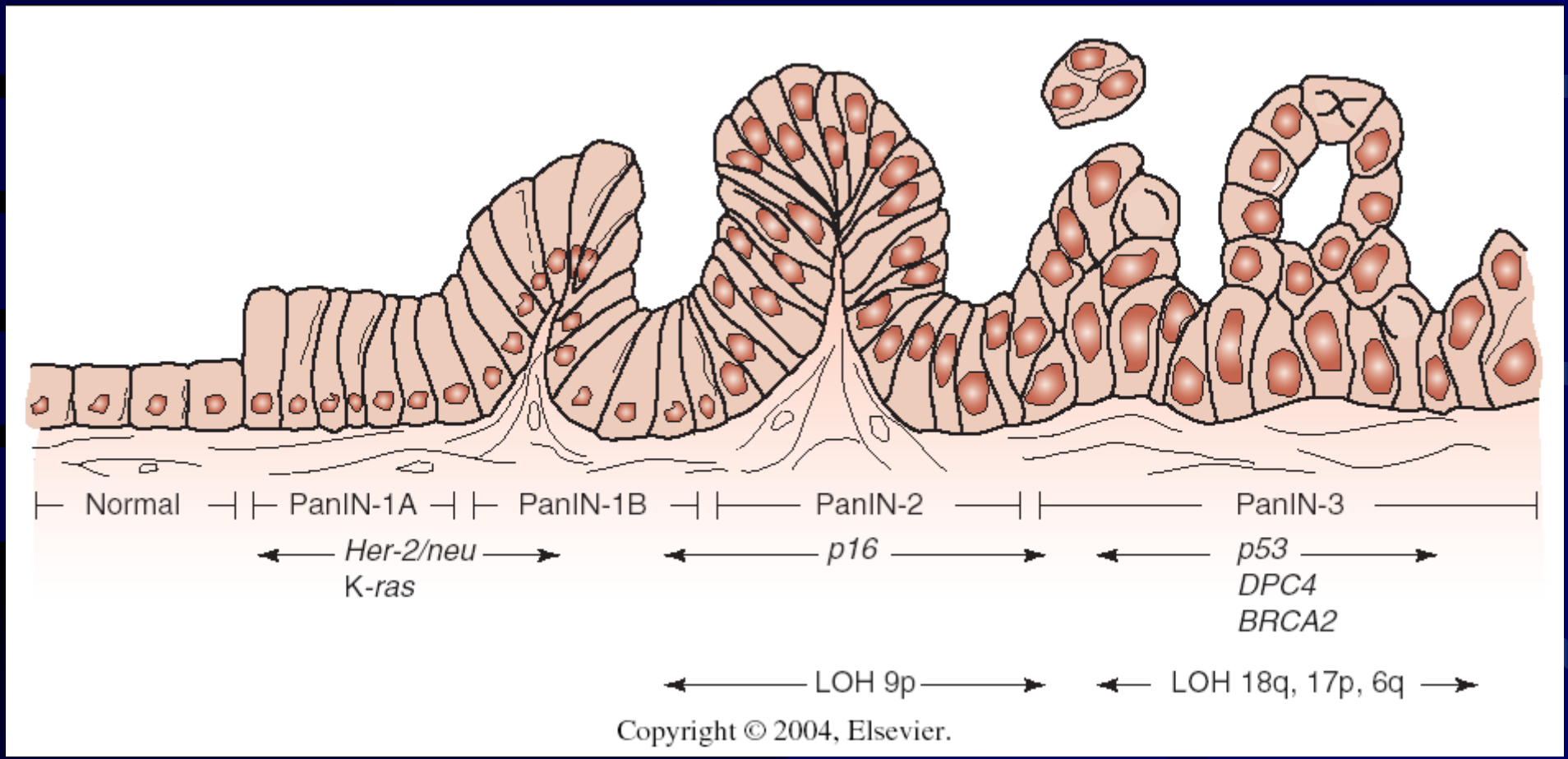
- Pathology (cont'd)
  - degree of differentiation, mitotic index, and amount of mucous vary considerably
  - halo of chronic pancreatitis frequently surrounds tumor
  - perineural growth with invasion into neighboring nervous plexuses can cause abdominal and back pain

Pancreatic Cancer

- Pathology (cont'd)
  - other types of pancreatic cancer
    - mucinous noncystic carcinoma
    - signet ring cell carcinoma
    - adenosquamous carcinoma
    - anaplastic carcinoma
    - giant cell carcinoma
    - sarcomatoid carcinoma
    - acinar cell carcinoma
    - pancreatoblastoma
    - leiomyosarcoma, liposarcoma, plasmacytoma, lymphoma

Pancreatic Cancer

- Molecular Biology - Three types of genetic abnormalities
  - Activation of growth-promoting oncogenes (e.g. K-*ras*, ~90%)
  - Mutations that result in inactivation of tumor suppressor genes (e.g. *p53*, ~75%; *p14, SMAD*)
  - Excessive expression of growth factors and their receptors (e.g. EGF, HER2, HER3, HER4)
  - THEORY: Pancreatic cancer evolves in a step-wise fashion due to accumulation of multiple gene abnormalities



Pancreatic Cancer

- Hereditary Pancreatic Cancer Syndromes
  - Pancreatic cancer incidence is increased in families with:
    - Hereditary nonpolyposis colon cancer (HNPCC)
    - Familial breast cancer (with *BRCA2* mutation)
    - Peutz-Jeghers syndrome
    - Ataxia-telangiectasia
    - Familial atypical multiple mole melanoma (FAMMM)
    - Hereditary pancreatitis

Pancreatic Cancer

- Signs and Symptoms
  - in head or uncinate process of pancreas:

Frequent

Weight loss (92%)

Pain (72%)

Jaundice (82%)

Dark urine (63%)

Light stools (62%)

Anorexia (64%)

Infrequent

Nausea (37%)

Weakness (35%)

Pruritus (24%)

Vomiting (37%)

Unexplained pancreatitis, steatorrhea, ascites

Pancreatic Cancer

- Signs and Symptoms (cont'd)
  - in neck, body, or tail of pancreas:

Frequent	*Infrequent*
Weight loss (100%)	Jaundice (7%)
Pain (97%)	Dark urine (5%)
Weakness (43%)	Light stool (6%)
Nausea (45%)	Prurities (4%)
Anorexia (33%)	
Vomiting (37%)	

Pancreatic Cancer

- Signs and Symptoms (cont'd)
  - New onset diabetes (due to factor inhibiting insulin release or inducing peripheral insulin resistance)
  - Trousseau's syndrome (unexplained migratory thrombophlebitis)
  - Courvoisier's sign: palpable gallbladder due to bile duct obstruction by tumor

Pancreatic Cancer

- Signs and Symptoms (cont'd)
  - Signs of metastatic spread
    - Sister Mary Joseph's node: subumbilical deposit
    - Blummer's shelf: pelvic peritoneal deposit
    - Virchow's node: left supraclavicular LAD
    - Malignant ascities (caused by peritoneal carcinomatosis)

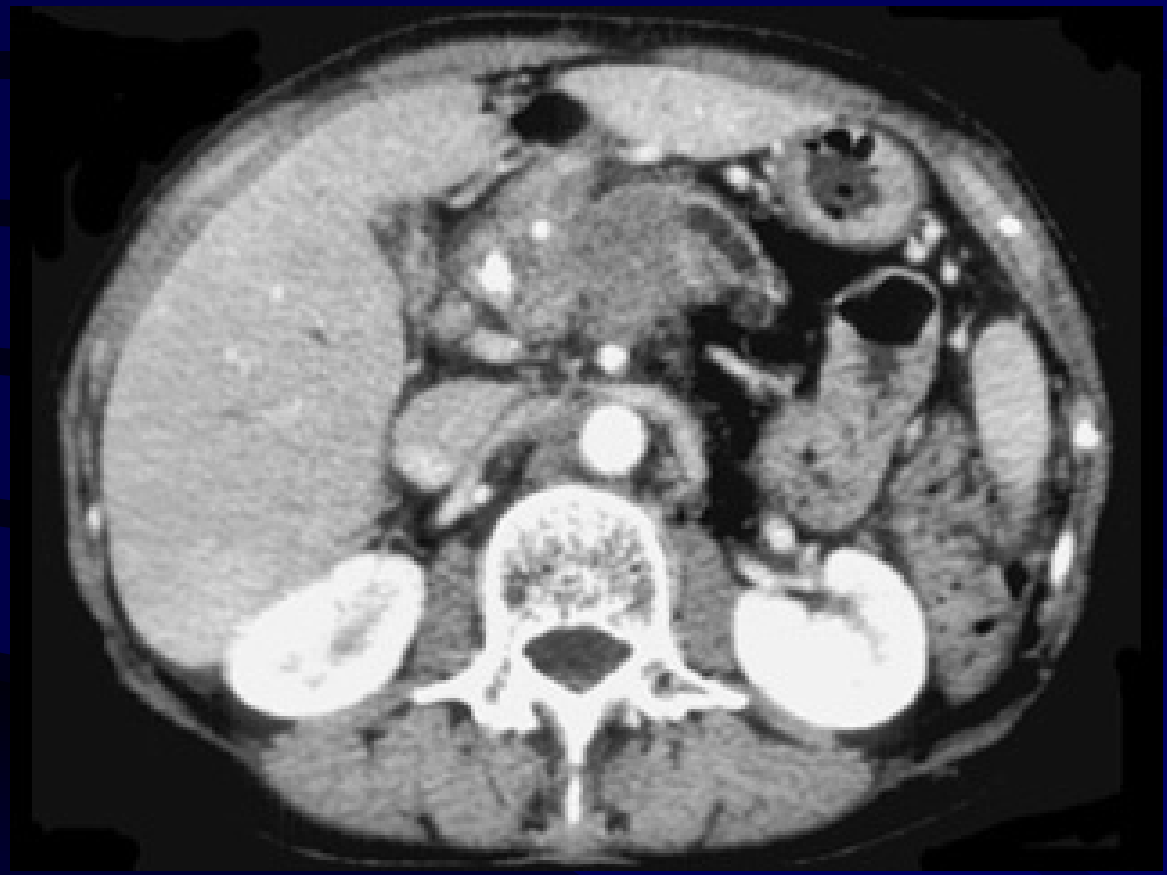
Pancreatic Cancer

- Blood tests
  - elevated bilirubin and alkaline phosphatase
  - CEA*
  - CA 19-9*
    - if > 37 U/mL, sensitivity = 86%, specificity = 87%
    - also elevated in other causes of jaundice (e.g. cholangitis)

* if extremely elevated, indicates unresectable and/or metastatic disease

Pancreatic Cancer

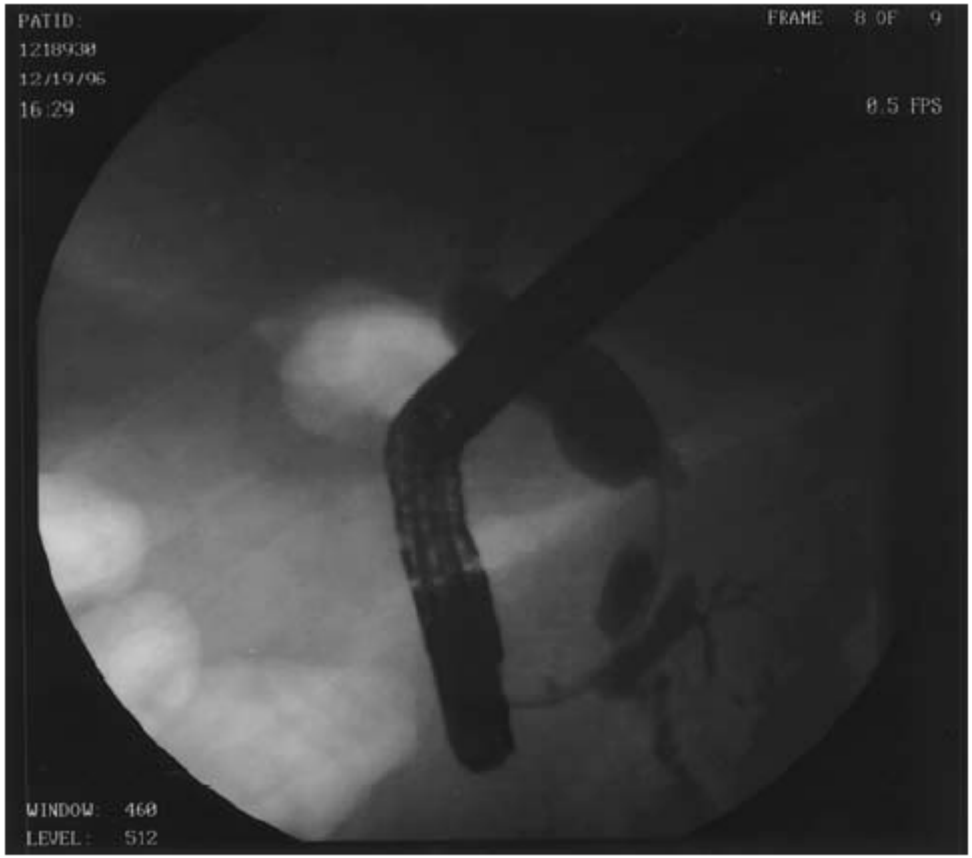
- Imaging studies
  - Ultrasound
    - can determine presence of pancreatic mass (cystic vs. solid) or stones
  - Triple phase CT of pancreas
    - IV contrast CT with images of arterial, parenchymal and venous phase of contrast perfusion of pancreas
    - tumor appears as hypodense mass with poorly demarcated edges, +/- dilated pancreatic duct
    - specificity = 95%, sensitivity > 95% for tumors > 2cm

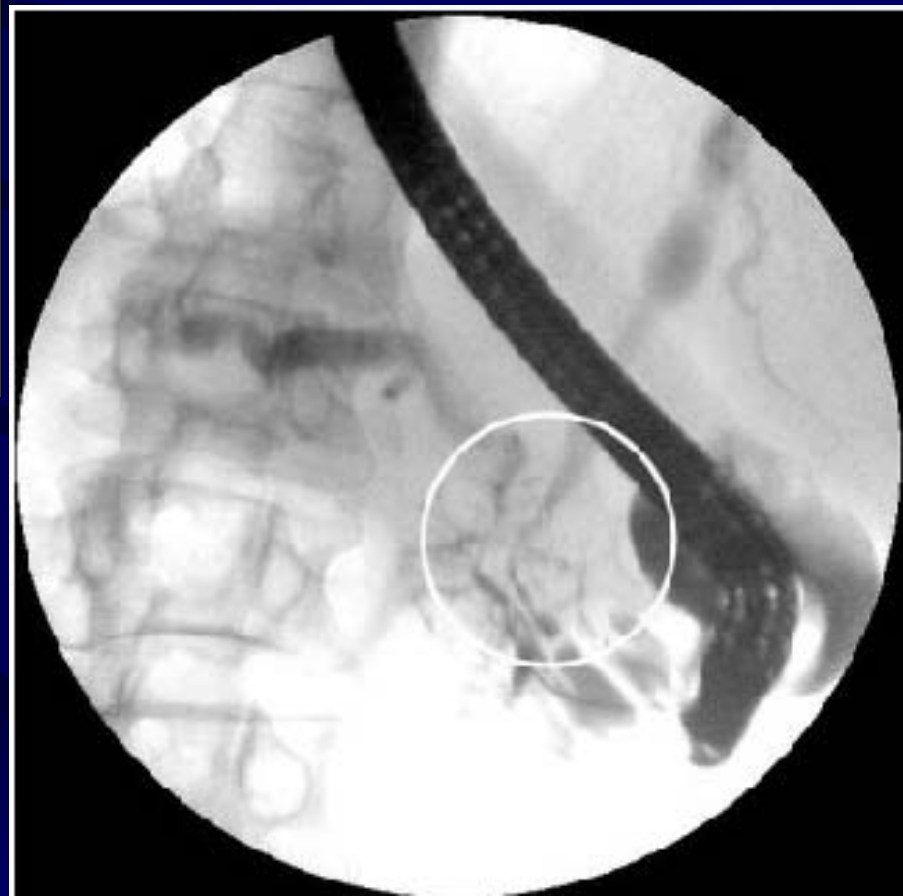


Abdominal CT demonstrating mass at head of pancreas

Pancreatic Cancer

- ERCP
  - can identify stones and lesions, define location of bile duct obstruction, identify ampullary and periampullary lesions
  - however, malignant lesions may not be excluded by ERCP, necessitating resection anyway
  - double duct sign (superimposable bile duct and pancreatic duct strictures with proximal duct dilation) is suggestive of pancreatic head cancer





Two examples of double-duct sign

Pancreatic Cancer

- Role of biopsy
  - for unresectable tumors
    - Percutaneous CT or US guided bx
    - Endoscopic transduodenal biopsy
  - for resectable tumors
    - Bx not recommended as positive result confirms need for resection, and negative result is inconclusive
    - without preop bx, 5-10% of resected lesions will be benign

Pancreatic Cancer

- Staging - TNM system
  - T1: confined to pancreas, < 2 cm diameter
  - T2: confined to pancreas, > 2 cm diameter
  - T3: extend beyond pancreas, no arterial (celiac/SMA) involvement, +/- portal/SMV involvement, potentially resectable

Pancreatic Cancer

- Staging - TNM system (cont'd)
  - T4: extend beyond pancreas, arterial involvement, not resectable
  - N1: positive regional nodes
  - M1: distant metastasis

Pancreatic Cancer

TABLE 53-3 -- American Joint Committee on Cancer: TNM System for Staging of Pancreatic Cancer

Stage	T Status	N Status	M Status
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Adapted from AJCC Cancer Staging Handbook, 6th ed. New York, Springer, 2002, pp 179–188.

Stage 1 and 2 cancers are amenable to resection.

Stage 3 and 4 cancers are considered to be unresectable.

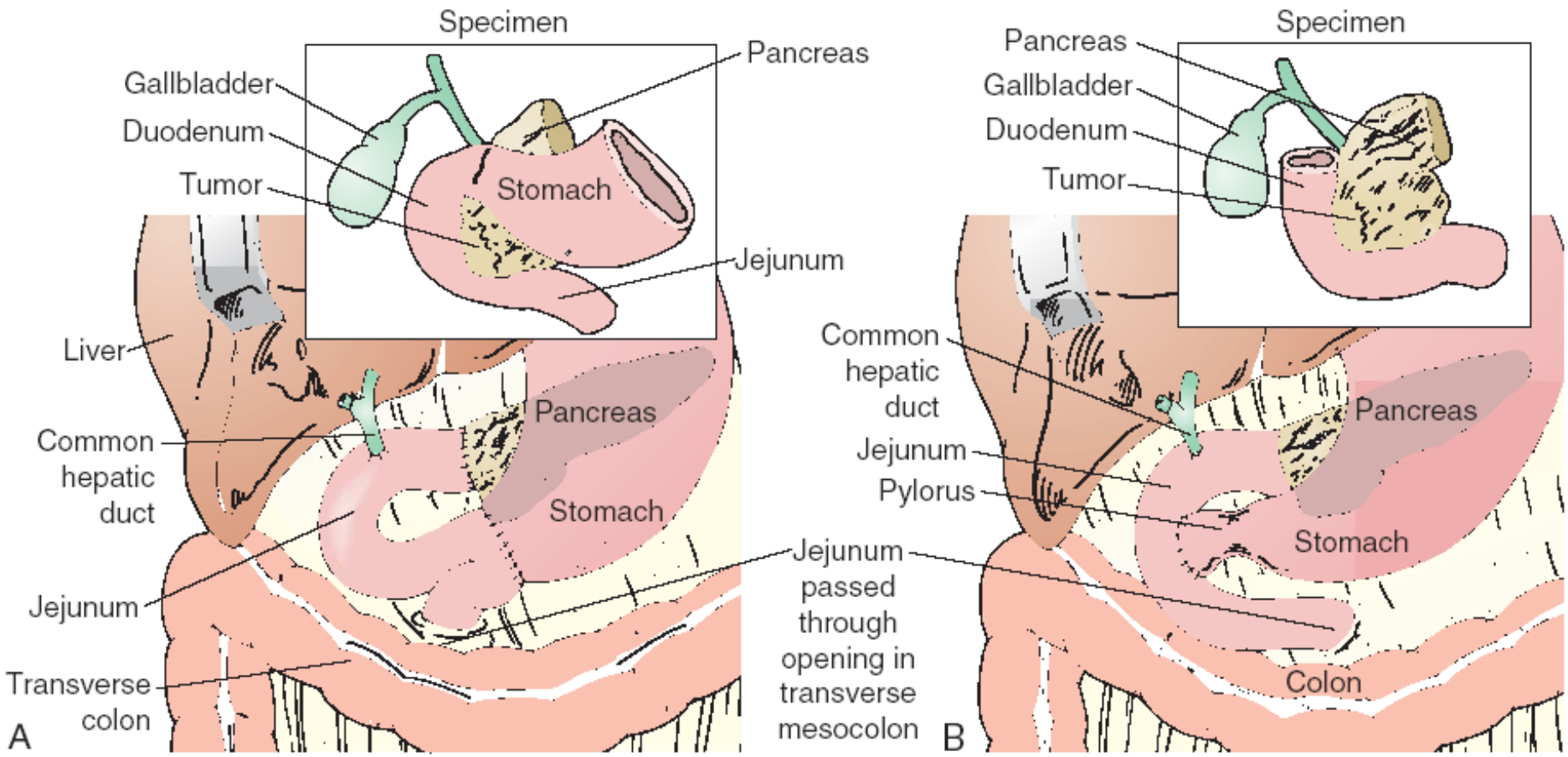
Stage 3 survival = 8-12 months. Stage 4 survival = 3-6 months.

Pancreatic Cancer

- Utility of staging laparoscopy
  - Deemed controversial for head tumors as radiographic imaging can, in most cases, delineate resectable from non-resectable cases
  - Bilioenteric/gastroenteric bypass still beneficial for patients with unappreciated vascular involvement by tumor
  - Laparoscopy may be useful for body/tail lesions, where there is little role for bypass

Pancreatic Cancer

- Resection of Head and Uncinate Process Tumors
  - tumors account for 70% of pancreatic tumors
  - resected by pancreatoduodenectomy +/- preservation of pylorus and proximal duodenum
    - also with cholecystectomy, hepaticojejunostomy, and gastrojejunostomy or duodenojejunostomy



Pancreatic Cancer

- Complications of pancreatoduodenectomy
  - mortality 2-4%
  - anastomotic leaks, intra-abdominal abscesses
  - leakage from pancreatic anastamosis (pancreatic fistula) ~ 15-20% of patients
    - incidence/duration of pancreatic fistula is not reduced by somatostatin analogues (octreotide)

Pancreatic Cancer

- Complications of pancreatoduodenectomy
  - delayed gastric emptying (15-40%)
    - questionably due to removal of cells (along with duodenum) which secrete motilin
    - erythromycin is useful in treating condition, which resolves with time
  - pancreatic malabsorption and steatorrhea due to exocrine insufficiency, or obstruction of pancreatic-jejunal anastomosis
    - Tx with exogenously administered pancreatic enzymes

Pancreatic Cancer

- Long term results of pancreatoduodenectomy for ductal CA
  - Overall 5-yr survival: 10-15%
    - Resection with negative margins: 26%
    - Resection with positive margins: 8%
  - Dependent on tumor diameter, diploid/aneuploid DNA content, and lymph node status

Pancreatic Cancer

- Resection of body and tail tumors
  - distal pancreatectomy +/- splenectomy for malignant tumors
  - 10% of such tumors are resectable
  - overall 5-yr survival: 8-14%
- Complications
  - subphrenic abscess (5-10%), pancreatic duct leak (20%)
    - if pancreatic fistula forms, amount of output (NOT time of closure) is altered by somatostatin analogues

Pancreatic Cancer

- Palliative Non-surgical Treatment
  - establishing diagnosis & relieving symptoms of jaundice, gastric outlet obstruction, and pain
    - percutaneous CT or US guided bx
    - percutaneous/endoscopic biliary decompression
    - endoscopic placement of endoluminal stents in duodenum
    - narcotic medications, percutaneous radiographically guided celiac plexus nerve block

Pancreatic Cancer

- Palliative Surgical Management
  - for pts undergoing laparotomy for dz found to be unresectable
  - biliary tract decompression: cholecystojejunostomy or choledochojejunostomy
  - gastrojejunostomy for duodenal compression (25% of patients)
  - Celiac plexus nerve block w/50% ethanol soln

Pancreatic Cancer

- A final word about chemoradiation therapy…
  - best results achieved with radiation therapy combined with either 5-fluorouracil or gemcitabine
  - Gastrointestinal Tumor Study Group (GITSG): combination of 5-fluorouracil with radiation therapy could increase the 2-yr survival rate for patients with tumor-free resection margins from 18% to 43%

The End

This presentation can be downloaded at:
www.chaitannarsule.com/surgery/