CHRONIC HEPATIC INJURY

Kenneth Alonso, MD, FACP

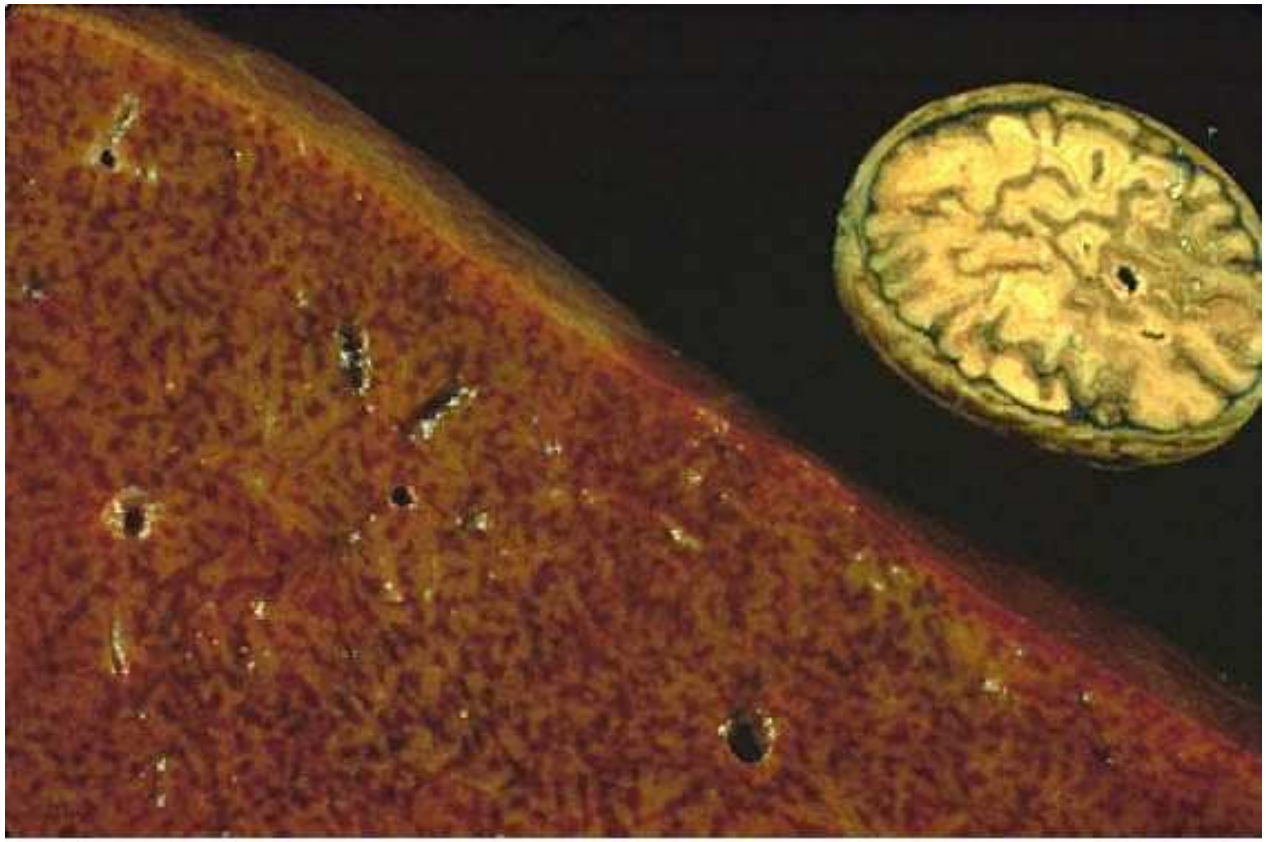
Liver size

- Half of all palpable livers are not enlarged.
- No evidence that a substantial proportion of persons with chronic cirrhosis have small livers.
- Unequivocal reduction in size is noted in fulminant hepatic failure, however.
- Percuss in the mid-clavicular line to measure the vertical height of the liver.
- The liver measures 8-11 cm in men 5-6 feet (1.5-1.8m) tall; 6-8 cm in women of similar heights.

Spleen size

- Percuss for the spleen in the right lateral decubitus position.
- If dullness is present >8cm above costal margin, the spleen is probably enlarged (positive likelihood ratio, LR+, 3.6; LR- 0.4).
- If the spleen is palpated when the patient is supine, it is probably enlarged (LR+, 8.2; LR-, 0.4).
- If percussion is negative, there is no need to palpate for the spleen.
- Radiographic examination is used to determine spleen size.

Congestion



Exaggeration of the functional hepatic lobules in chronic passive congestion of the liver (nutmeg liver). A nutmeg is at the upper right. This may lead to cirrhosis if chronic.

(Courtesy of L Friedman.) Fig. Ch 16
Accessed 04/02/2010

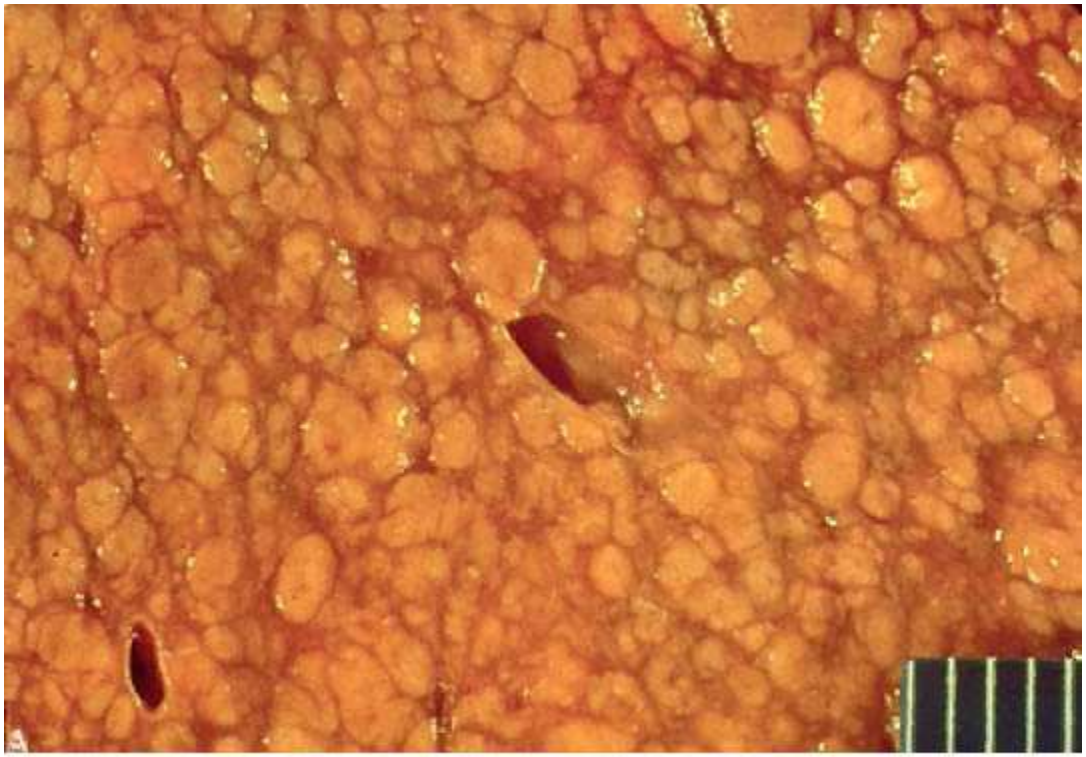
Frequency of cirrhosis

- In those cultures where alcohol is consumed, alcoholic liver disease accounts for 60-70% of cases
- Viral hepatitis, 10%
- Biliary disease accounts for 5-10% of cases.
- Primary hemochromatosis accounts for 5% of cases.
- Wilson's Disease and α_1-antitrypsin deficiency occur rarely.
- Schistosomiasis in endemic areas and Budd-Chiari syndrome (hepatic vein thrombosis) are other possible causes.
- Cirrhosis is not seen with HAV.

Patterns of cirrhosis

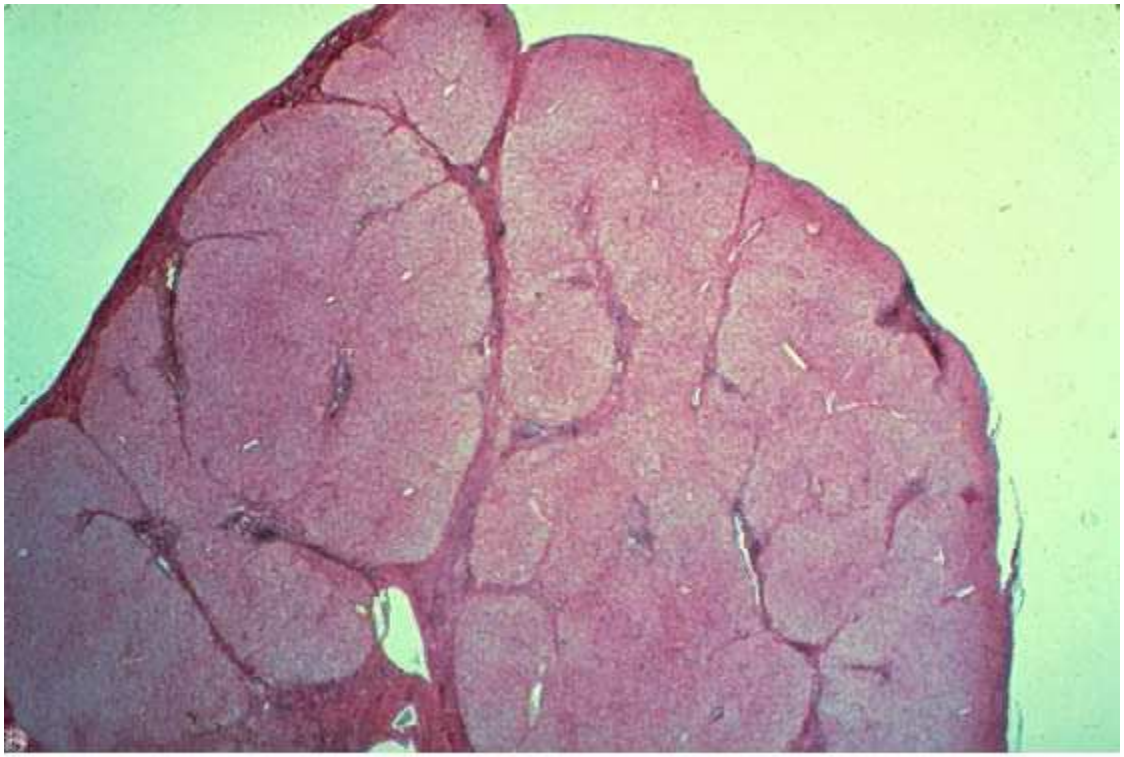
- A micro-nodular pattern is noted when regenerated hepatic lobules are roughly the same size (continuous injury)
- Alcoholic liver disease
- A macro-nodular pattern is noted when regenerated hepatic lobules differ markedly in size (temporal separation of insult)
- Hepatitis
- Abstaining alcoholic
- With massive hepatic destruction, regenerated hepatic lobules are often much increased in size.

Macro-nodular cirrhosis



(Courtesy of L Friedman.) Fig. Ch. 16 Accessed 04/02/2010

Post-necrotic macronodular cirrhosis



Portal areas show extensive fibrosis. Fibrosis extends from portal area to portal area. Hepatic areas are nodular and vary in size.
H&E 2x

(Courtesy of L Friedman.) Fig. Ch 16 Accessed 04/02/2010

Hemochromatosis

- Hemochromatosis reflects life-long iron accumulation.
- Symptoms usually appear after the liver has accumulated 20 gm storage iron.
- Normally, the liver stores 0.5gm Iron.
- Principally noted in northern Europeans (1 in 8 is a carrier).
- Presents around age 40
- Males predominate (5-7:1).
- When diagnosed in women, it is generally 10-20 years after menopause. (Menses cause loss of iron).

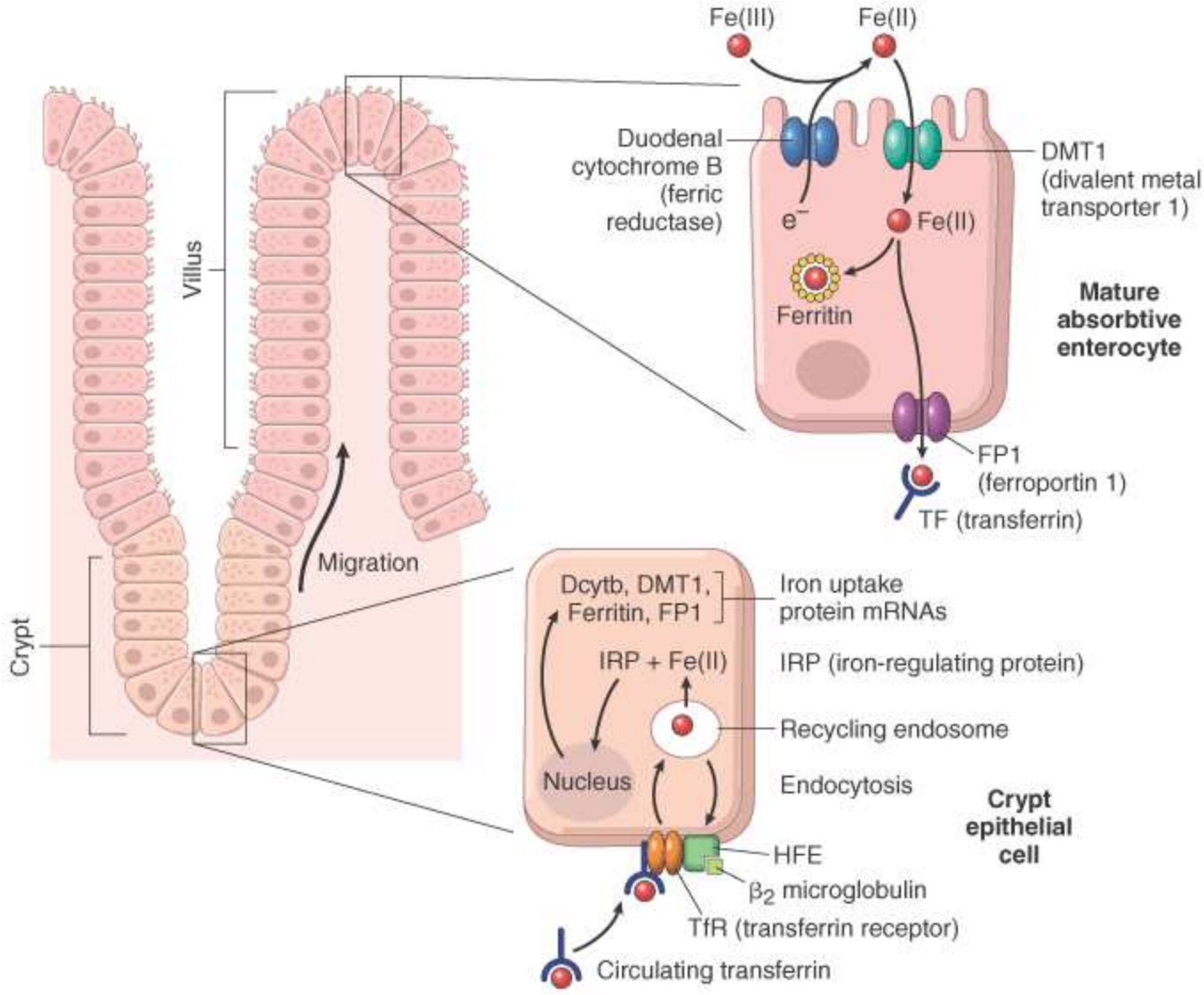
Hemochromatosis

- Cirrhosis develops in 60% of patients
- Degenerative joint disease (chondrocalcinosis) in 40%
- Acute synovitis
- Hypogonadism in 25-50% (deranged hypothalamic pituitary axis)
- Restrictive cardiomyopathy (interstitial fibrosis)
- Hemosiderin as ferritin is deposited principally in hepatocytes, but also in
- Islet cells of the pancreas, producing type 1 diabetes mellitus, and in
- Skin, increasing melanin production.
- This complex is called “bronze diabetes” (75-80%)

Hemochromatosis

- Total body content of iron is tightly regulated by intestinal absorption.
- Excessive iron is toxic as iron catalyzes lipid peroxidation.
- The free radicals produced also react with iron.
- Stimulates fibrosis.

Iron absorption and transport



Hemochromatosis

- HFE and TfR2 gene mutations cause the classic form of hemochromatosis.
- Transferring receptor 2 is highly expressed in hepatocytes; mediates the uptake of transferrin bound iron.
- H63D (Histidine to aspartate at postion 63 is a second common mutation and is noted world-wide.)
- Decrease hepcidin synthesis.

Hemochromatosis

- The HFE gene produces an HLA class I-like molecule that regulates intestinal absorption of iron by enabling the binding of iron to transferrin at the transferrin receptor.
- The gene is found at 6p21.3, close to HLA-A3 locus.
- Mutation permits net transfer at maximum, resulting in iron overload. Net iron accumulation of 0.5-1.0 gm/yr.
- The C28Y mutation of HFE gene (affects β-2 microglobulin domain) is of limited penetrance.
- Heterozygous frequency 11%
- Found in >70% of cases of hereditary hemochromatosis

Hemochromatosis

- Lack of hepcidin expression causes hemochromatosis.
- Hepcidin is a liver expressed antimicrobial peptide, encoded by the HAMP gene
- Binds to the cellular iron efflux channel ferroportin, causing internalization and proteolysis of the channel, preventing the release of Fe^{2+} from intestinal cells and macrophages.
- A serine protease (TMPRSS6) acts as an iron sensor and suppresses HAMP expression.
- Hepcidin lowers plasma iron levels.

Hemochromatosis

- Juvenile hemochromatosis
- More severe form than is adult hemochromatosis.
- HAMP and HJV mutations
- Hemojuvelin (HJV) regulates iron uptake as well. Expressed in liver, heart, and skeletal muscle.
- Decreases hepcidin synthesis.

- Neonatal hemochromatosis develops in utero and is not a hereditary condition.
- Unknown origin.
- Buccal biopsy to confirm extrahepatic Iron deposition.

Hemochromatosis

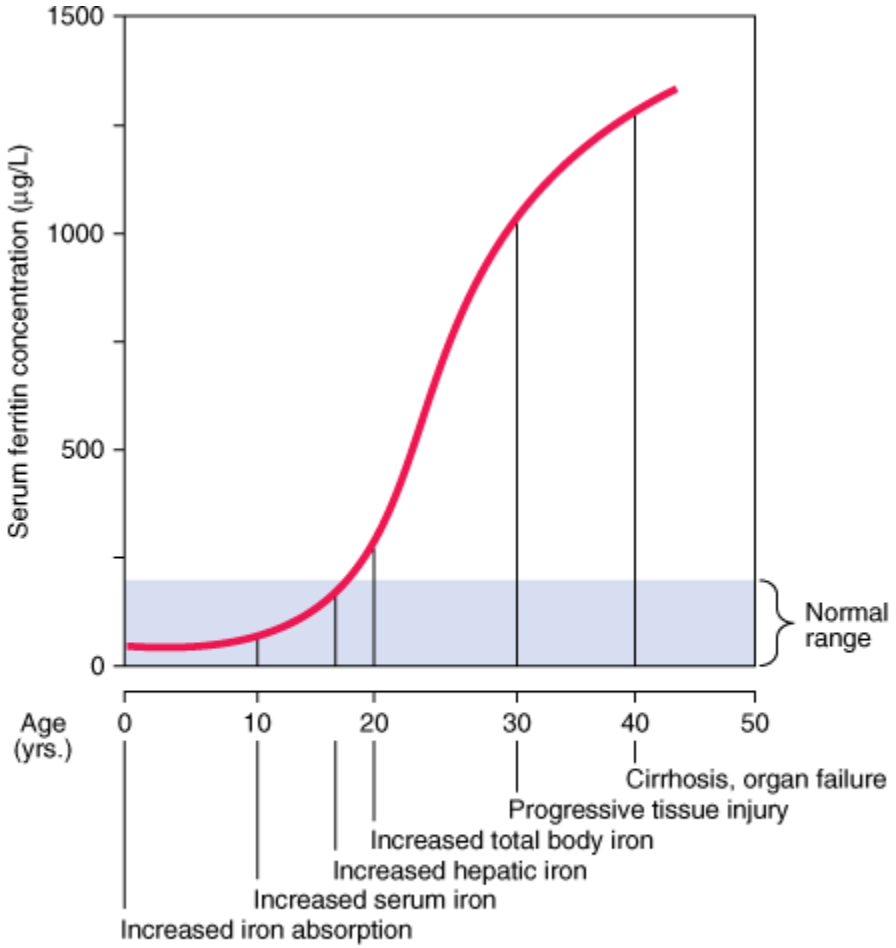


Fig. 351-2
Accessed 03/01/2010

Hemochromatosis

- Liver biopsy to confirm diagnosis
- Iron is present as golden granules in periportal hepatocytes
- Stain blue with Prussian blue.
- Progression and fibrosis develop slowly.
- Pancreas highly pigmented, with diffuse sclerosis
- Cardiac myopathy
- Synovitis
- May precipitate pseudo-gout.

Hemochromatosis

- Lower levels of stored iron
- Frequent therapeutic phlebotomy or
- Desoxiferramine (iron chelator)
- Ferritin levels to follow therapy

Secondary hemochromatosis

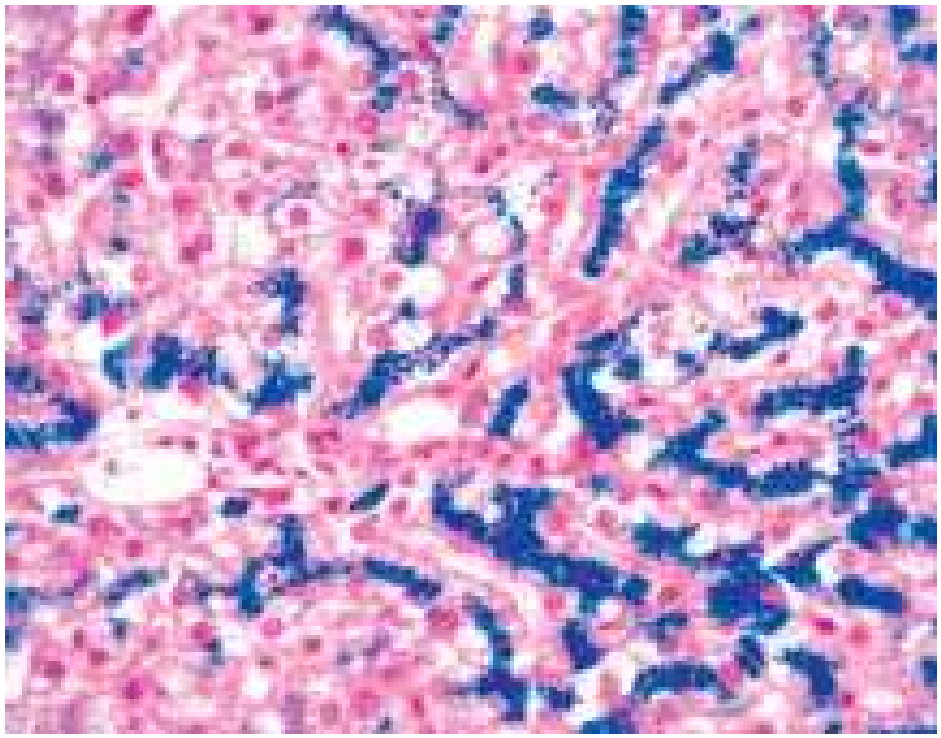
- Parenteral iron overload
- Excessive transfusion
- Long term hemodialysis
- Sickle cell disease
- Myelodysplastic syndromes);
- Ineffective erythropoiesis
- β-thalassemia
- Pyruvate kinase deficiency);
- Increased iron intake.
- Macrophages, not hepatocytes, involved.

Table 18-7 Classification of Iron Overload

I. Hereditary hemochromatosis
Mutations of genes encoding HFE, transferrin receptor 2 (TfR2), or hepcidin Mutations of genes encoding HJV (hemojuvelin: juvenile hemochromatosis) (Neonatal hemochromatosis)*
II. Hemosiderosis (secondary hemochromatosis)
A. Parenteral iron overload Transfusions Long-term hemodialysis Aplastic anemia Sickle cell disease Myelodysplastic syndromes Leukemias Iron-dextran injections
B. Ineffective erythropoiesis with increased erythroid activity β-Thalassemia Sideroblastic anemia Pyruvate kinase deficiency
C. Increased oral intake of iron African iron overload (Bantu siderosis)
D. Congenital atransferrinemia
E. Chronic liver disease Alcoholic liver disease Porphyria cutanea tarda
F. Neonatal hemochromatosis

*Neonatal hemochromatosis develops in utero and does not appear to be a hereditary condition.

Hemochromatosis



Prussian blue stain demonstrating iron deposition in Kupffer cells.

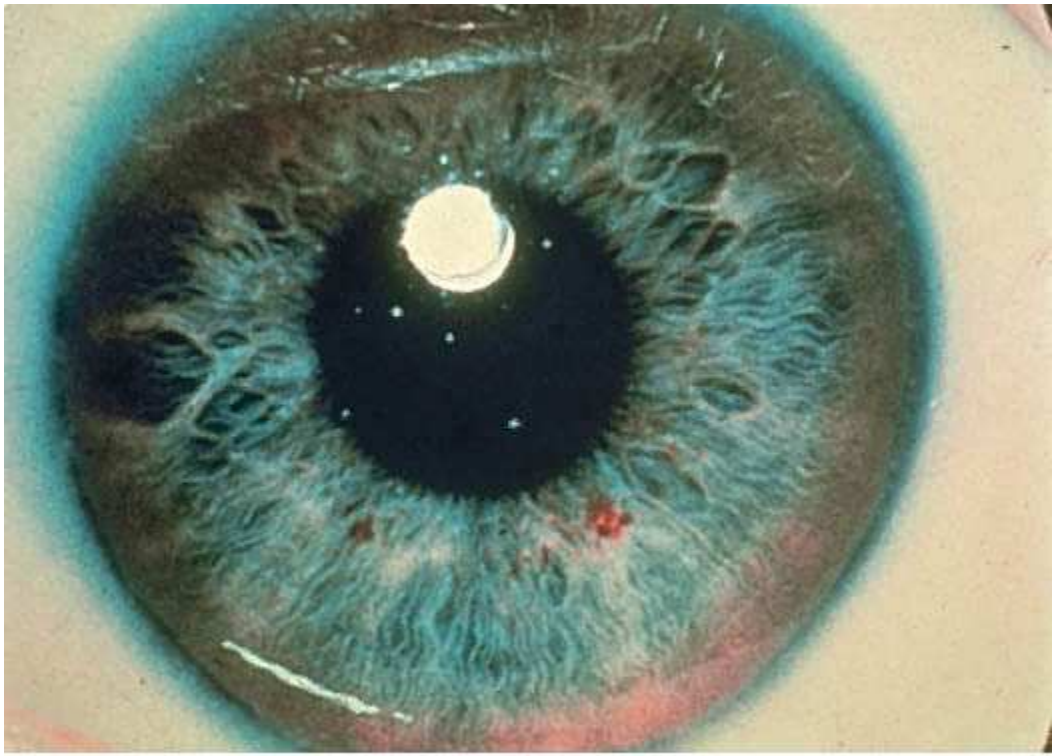
Wilson's disease

- Mild behavioral changes
- Parkinson-like syndrome or
- Psychosis
- May see atrophy and cavitation of the putamen.
- May lead to acute liver failure
- Green-brown deposits of Copper in Descemet's membrane in the limbus of the Cornea is diagnostic (Kayser-Fleischer ring).
- May be absent in 50% of patients

Wilson's disease

- Autosomal recessive.
- ATP7B gene at 13q14.3 (ATPase 2 Copper transporting enzyme)
- 40% of cases in Northern Europeans have same mis-sense mutation.
- Microscopically mimics hepatitis.
- Ratio of alkaline phosphatase to total bilirubin <4.0 with AST/ALT > 2.2 is diagnostic (in liver failure)

Kayser-Fleischer ring



(Reproduced, with permission, from Yarze JC, Martin P, Munoz SJ, Friedman LS: Wilson's disease: Current status. Am J Med 1992;92:643.)

Fig. Ch. 16
Accessed 03/01/2010

Wilson's disease

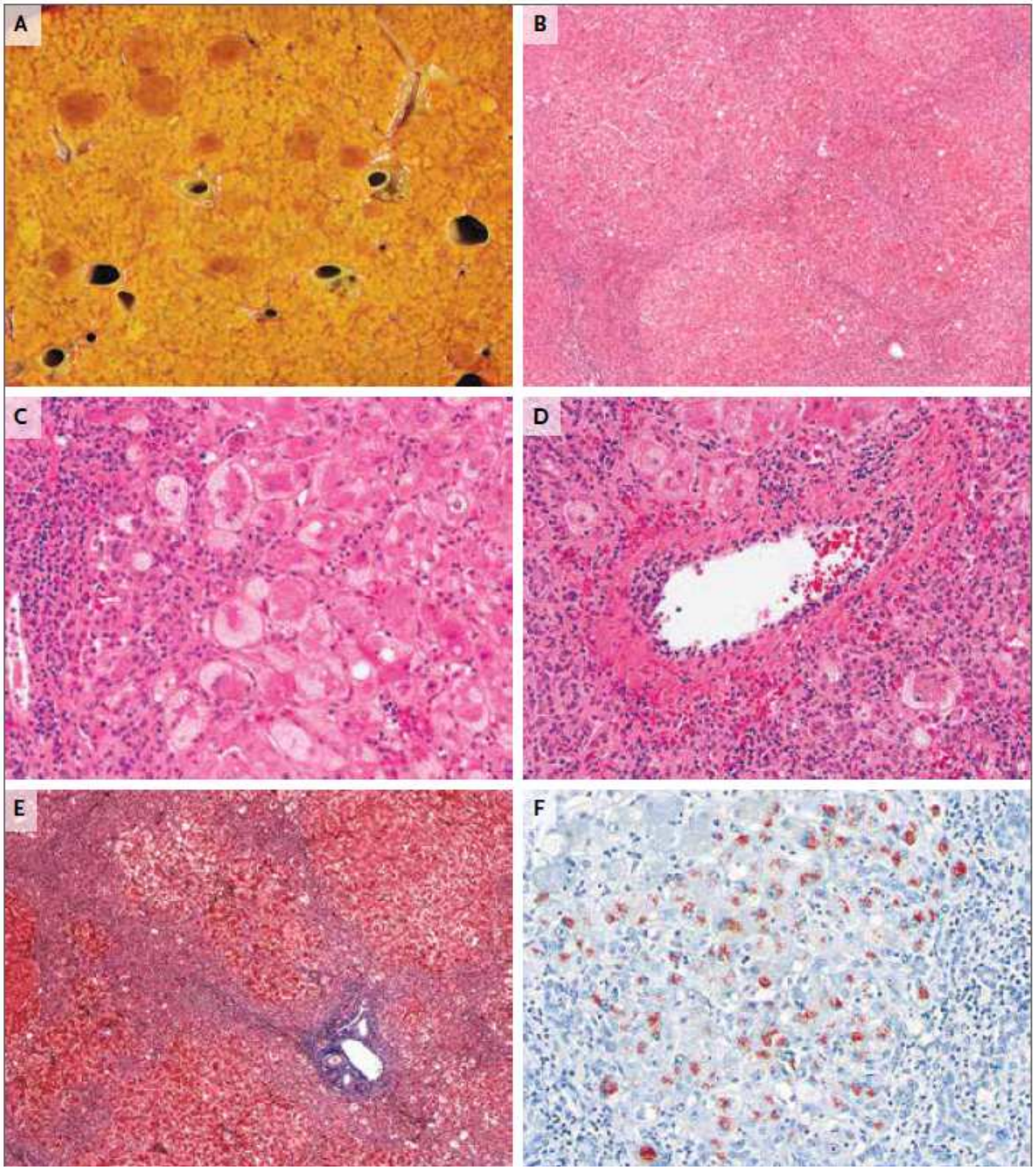
- Majority of patients are compound heterozygotes containing different mutations of the disease gene (ATP7B) on each allele at13q14.3.
- ATP7B codes for a transmembrane Cu^{2+} transporting ATPase located on the hepatocyte canalicular membrane.
- Permits binding to ceruloplasmin.

Wilson's disease

- Copper is absorbed in the stomach and duodenum (2-5 mg/d)
- Complexed with albumin
- Transferred to liver
- In the liver Cu^{2+} is bound with an α-2 globulin to form ceruloplasmin.
- This protein circulates.
- 5% bound to albumin
- Copper is excreted in the bile.

Wilson's disease

- The hepatic capacity for incorporating Cu^{2+} is reached by 5 years of age.
- Non-ceruloplasmin bound circulating Cu^{2+} leads to:
- Hemolysis
- Deposition of Cu^{2+} in basement membranes
- In the absence of a Kayser-Fleischer ring, must demonstrate hepatic Cu^{2+} content >.250 ug/ g dry weight liver to confirm the diagnosis.
- Ceruloplasmin levels will be low.
- Urinary excretion of Cu^{2+} following penicillamine challenge will be elevated.



NEJM.org Cases in Primary Care (2017) Accessed 12/10/2019

Treatment of Wilson's disease

- Penicillamine now made synthetically (trientine)
- Resembles cysteine
- Chelator
- May be used in pregnancy.
- Unlikely to worsen neurological symptoms
- Non-synthetic form induces lupus-like reaction in 20%
- Non-synthetic form may precipitate myasthenia gravis and/or Lambert-Eaton syndrome
- Inhibits vitamin B_6 function

Treatment of Wilson's disease

- Zinc (Zn^{2+}) administered as well to block intestinal absorption of Cu^{2+}.
- Foods high in Copper are avoided: shellfish, liver, nuts, chocolate, mushrooms.
- Adequate renal function is necessary for drug therapy.
- Transplantation is curative.

Manganese related cirrhosis

- Manganese shares absorption and excretion paths with iron.
- Excess manganese in diet as well as disruption of excretion pathways may lead to tissue accumulation.
- Manganese containing enzymes:
- Superoxide dismutase
- Mitochondrion
- Arginase
- Required for urea cycle in liver.

Manganese related cirrhosis

- Manganese activated enzymes:
- Pyruvate carboxylase and phosphophenylpyruvate carboxykinase are critical for gluconeogenesis in the liver.
- Glutamine synthetase
- Excess Mn^{2+} release in liver disease contributory to hepatic encephalopathy.
- Mn^{2+} deposited in caudate and globus pallidus.
- Best detected with MRI.
- Serum levels not correlated with extent of deposition.

α_1-antitrypsin deficiency

- 10-20% of affected newborns present with neonatal hepatitis with cholestatic jaundice
- The disease may remain silent until cirrhosis appears later in life.
- PAS positive, diastase resistant acidophilic bodies are seen in hepatocyte cytoplasm.
- Liver transplant in severe disease

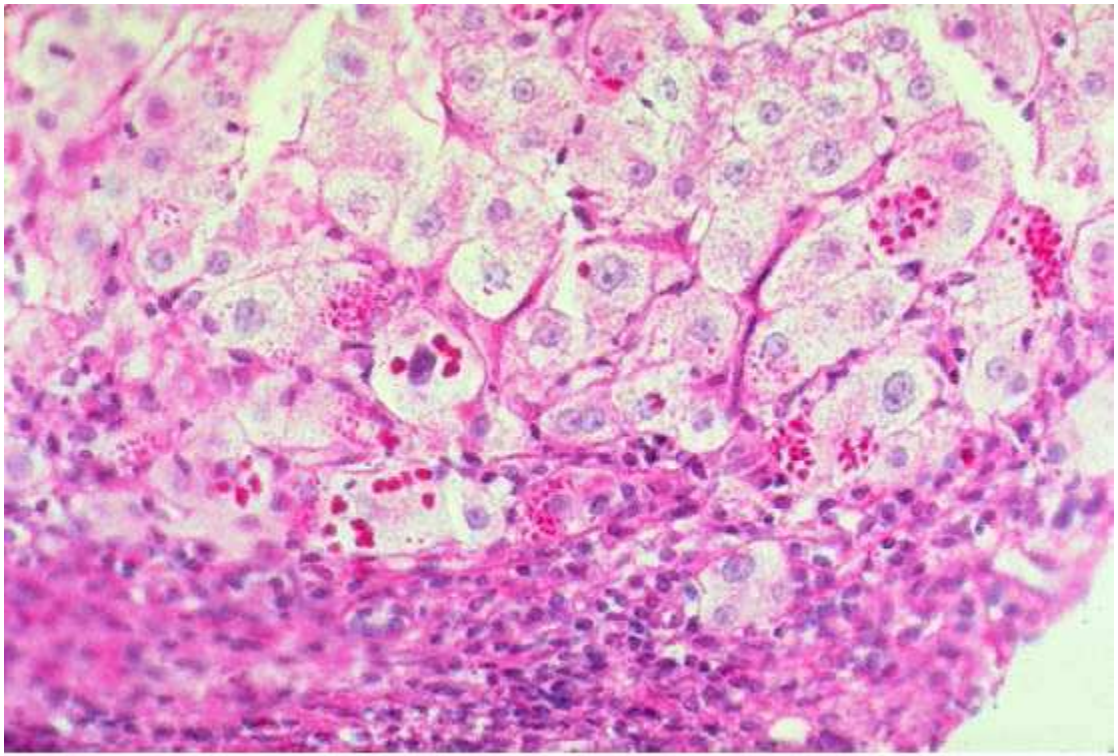
α_1-antitrypsin deficiency

- Autosomal recessive.
- α_1-AT gene is on chromosome 14. Polymorphic.
- Expression of alleles, however, is autosomal codominant
- Rare to have disease in heterozygotes.
- PiZ is most common clinically significant mutation.
- Loss of inhibition of elastase
- Loss of inhibition of cathepsin G
- Loss of inhibition of proteinase 3
- <u>Leads to development of pulmonary emphysema</u>
- Smoking aggravates.

α_1-antitrypsin deficiency

- Glutamate to lysine at position 342 leads to abnormally folded protein that polymerizes.
- Homozygotes have only 10% of normal α_1-AT levels.
- α_1-AT protein is abnormally folded and retained in the endoplasmic reticulum of hepatocytes. (PAS-positive globular bodies)
- Autophagocytic response is chief cause of liver injury
- Perhaps by autophagocytising mitochondria.
- Liver does not suffer from a lack of protease activity.

α_1-antitrypsin deficiency



PAS positive, diastase resistant acidophilic bodies are seen in hepatocyte cytoplasm.

(Courtesy of L Friedman.) Fig. Ch. 16
Accessed 04/02/2010

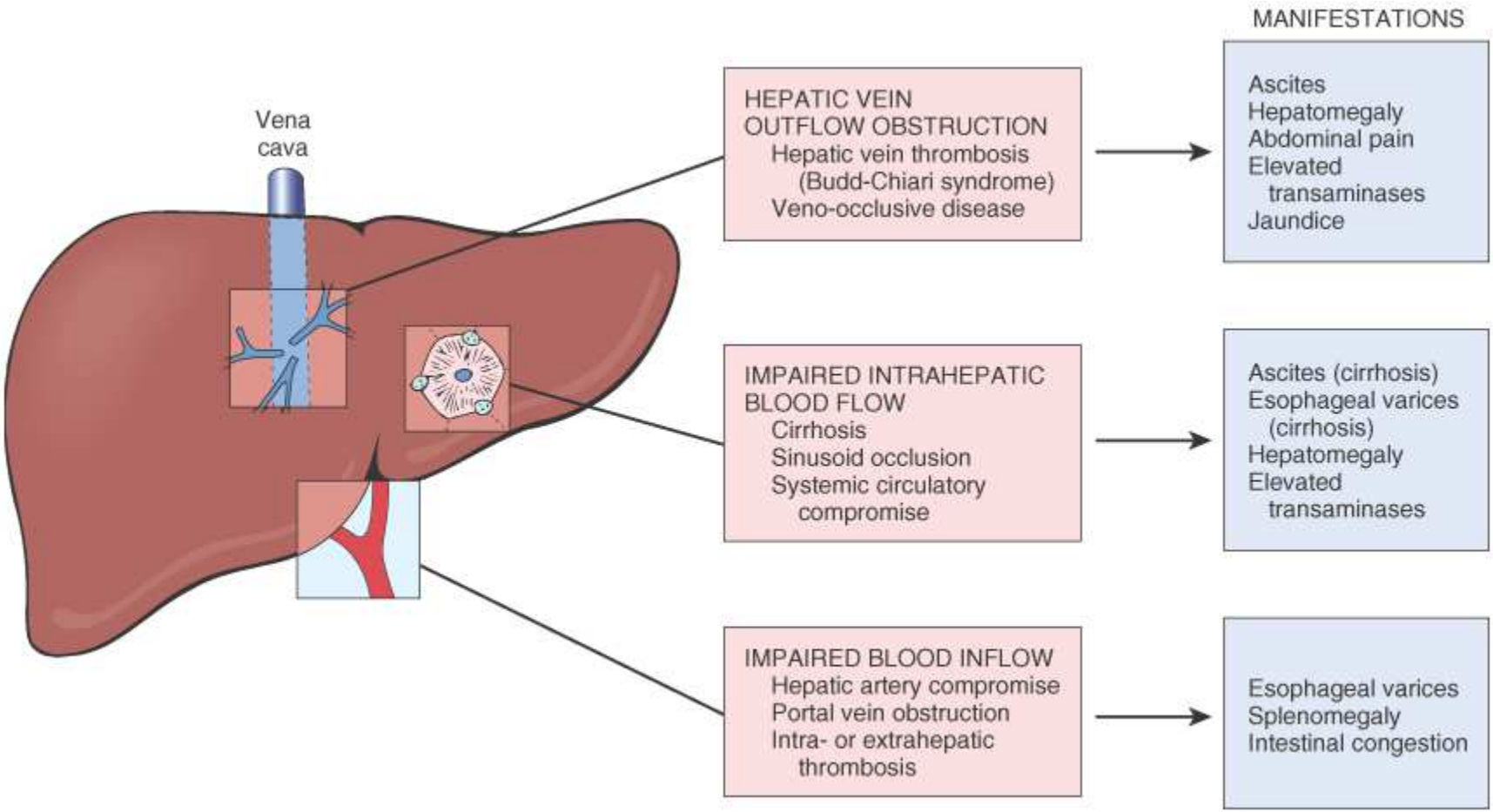
Complications of liver disease

- Jaundice.
- Hypoalbuminemia may lead to peripheral edema.
- Vitamin K dependent procoagulant synthesis is impaired.
- A prolonged prothrombin time is a poor prognostic factor (INR is a ratio)
- Impaired estrogen metabolism
- Breast enlargement (men); amenorrhea (women)
- Spider angiomata of the skin and palmar erythema are the local vasodilatory effects of impaired estrogen metabolism.
- Dupuytren's contracture

Table 18-2 Location and Causes of Portal Hypertension

Prehepatic causes
Obstructive thrombosis of portal vein
Structural abnormalities such as narrowing of the portal vein before it ramifies in the liver
Intrahepatic causes
Cirrhosis from any cause
Nodular regenerative hyperplasia
Primary biliary cirrhosis (even in the absence of cirrhosis)
Schistosomiasis
Massive fatty change
Diffuse, fibrosing granulomatous disease (e.g., sarcoid)
Infiltrative malignancy, primary or metastatic
Focal malignancy with invasion into portal vein (particularly hepatocellular carcinoma)
Amyloidosis
Posthepatic causes
Severe right-sided heart failure
Constrictive pericarditis
Hepatic vein outflow obstruction

Blood flow abnormalities



Impaired blood flow through the liver

- Peliosis hepatis
- Sinusoidal dilation with impeded blood flow through liver
- Etiology unknown although seen with sex hormone administration
- Asymptomatic
- May lead to potentially fatal intra-abdominal hemorrhage.

Sinusoidal obstruction syndrome

- Veno-occlusive disease
- Damaged endothelium sloughs and obstructs sinusoidal blood flow
- Follows high dose chemotherapy
- Histopathology:
- Centrilobular necrosis
- Hepatocellular necrosis
- Fibrous obliteration of venules.
- CT diagnosis
- Mortality 30%

Budd-Chiari syndrome

- Two or more major hepatic veins obstructed (or thrombosed)
- Single hepatic vein obstruction is clinically silent.
- Hepatic damage as a consequence of intrahepatic blood pressure
- Centrilobular congestion and necrosis

Budd-Chiari syndrome

- Abdominal pain with hepatomegaly
- 7% of pregnant patients including puerperium.
- 5% may develop hepatic failure
- Associated with
- Myeloproliferative disorders
- Proteins C or S deficiency
- Factor V Leiden
- Antiphospholipid syndrome
- Paroxysmal nocturnal hemoglobinuria (30%)
- Polycythemia vera

Portal hypertension

- Intrahepatic causes include:
- Resistance to intrahepatic blood flow due to intrasinusoidal hypertension from compression by regenerative nodule
- Hyperdynamic circulation as there is vasodilatation of splanchnic circulation with increased venous flow into portal vein

Congestive splenomegaly with hypersplenism

- The degree of splenic enlargement does not necessarily correlate with other features of portal hypertension.
- Increased destruction of red cells

Ascites

- Sinusoidal hypertension drives fluid into space of Disse where it is removed by hepatic lymphatics.
- There is Increased hepatic lymphatic flow exceeding capacity of thoracic duct to recirculate lymph (>1L/day) which leads to percolation into the peritoneal cavity
- Increased capillary perfusion pressure due to vasodilatation and Na^+ and water retention increases perfusion pressure of interstitial capillaries, leading to extrusion into peritoneal cavity.
- Low protein serous fluid clinically detectable when 500ml accumulate in peritoneal cavity

Ascites

- Clinically detectable when >500ml collected in abdomen.
- Prevalence of ascites 1% in general medical population.
- Develops over 5 years in 30% of patients with compensated cirrhosis.
- Absence of ankle swelling or increase in abdominal girth with excludes diagnosis of ascites (negative likelihood ratio, LR-, of 0.1).
- Serum albumin – ascites albumin gradient >1.1 mg/dL has an LR+ of 4.6 and an LR- of 0.06 for ascites.

Ascites

- Secondary hyperaldosteronism may contribute as well.
- Spironolactone is the diuretic of choice.
- Loop diuretic may be added.
- Weight loss should not exceed 0.5 kg/d in the absence of peripheral edema or 1 kg/d if peripheral edema present.
- NSAIDs and aspirin blunt the natriuretic effect of diuretics and should be avoided.

Spontaneous bacterial peritonitis

- Usually caused by Enterobacteriacie or Streptococcus pneumoniae.
- Patients have fever, pain, and generalized abdominal tenderness.
- Ascitic fluid contains large number of neutrophils.
- May precipitate hepato-renal syndrome.
- 10% prevalence in cirrhotic patients.
- 70% recur; mortality rate of 20%.
- Intravenous cefotaxime.

Therapy

- Spontaneous bacterial peritonitis is treated with 3rd generation cephalosporin.
- Quinolones may also be used.
- Prophylaxis may be required following an episode of spontaneous bacterial peritonitis.
- Nonselective beta-blockers in dosages sufficient to reduce the resting heart rate by 25% have been shown to be effective in primary prophylaxis for first-time variceal bleeding and for preventing recurrent variceal bleeding.
- The addition of a long-acting nitrate has been shown to improve portal hemodynamics.

Portal vein – systemic venous shunts

- Blood flow is reversed from portal to systemic circulation.
- May see:
- Esophageal varices (seen in 40%)
- Hemorrhoids
- Prominent periumbilical venous collaterals via falciform ligament (umbilical vein remnant) (caput medusae)

Portal vein – systemic venous shunts

- Congestive splenomegaly with hypersplenism
- The degree of splenic enlargement does not necessarily correlate with other features of portal hypertension.
- Esophageal varices
- Portal pressures exceed 12 mmHg.
- Left gastric vein empties into portal system; engorgement leads to esophageal venous enlargement
- 33% die at time of first bleed; 70% recurrent bleeding in first year.

Therapy

- Stop the hepatotoxin exposure.
- Dietary sodium restriction in combination with diuretics furosemide and spironolactone.
- The use of a transjugular intrahepatic portosystemic shunt (TIPS) is superior to paracentesis in the reduction of refractory ascites.
- However, TIPS is associated with significantly greater development of hepatic encephalopathy and does not improve overall survival rate compared with serial paracentesis.
- There is a risk for recurrent portal hypertension due to stent thrombosis or fibrosis.

Esophageal varices

- 40% of individuals with advanced cirrhosis of the liver
- Cause massive hematemesis and death in about 50%
- Each episode of bleeding is associated with a 30% mortality.
- Abdominal wall collaterals appear as dilated subcutaneous veins extending from the umbilicus toward the rib margins (caput medusae)

Esophageal varices

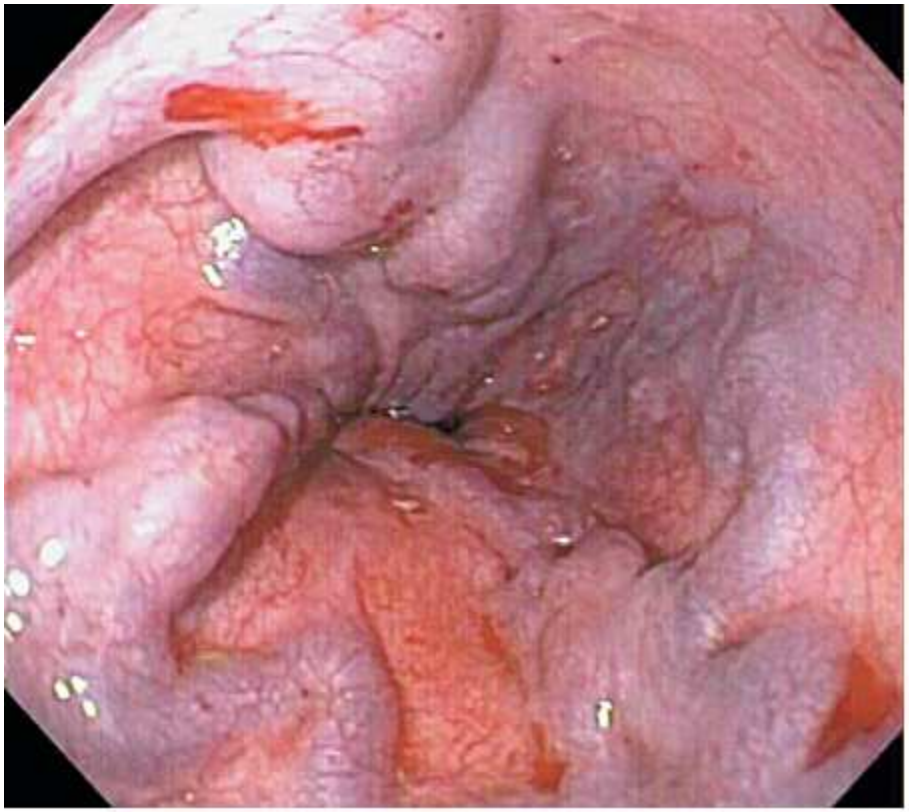


Fig. e25-16
Accessed 03/01/2010

Therapy

- Endoscopic sclerotherapy and/or ligation is generally the preferred method of treating an acute variceal bleed.
- β-blockers can be used to lower blood pressure to limit active variceal bleeding.
- Octreotide or vasopressin/nitroglycerin has also been employed to control acute variceal bleeding.
- Endoscopic therapy with pharmacotherapy has been the most successful approach.
- Balloon tamponade is considered only in refractory cases.
- Porto-systemic shunting reduces the incidence of rebleeding. Hepatic metabolic function may worsen.

Encephalopathy

- Some urea can be excreted into the intestine.
- Bacteria in the intestine metabolize urea to ammonia.
- Ammonia absorbed through the intestine goes into the portal circulation.
- Ammonia is generally converted to urea by the liver.
- However, as protein synthesis is diminished, little urea is produced.
- Excess accumulation of ammonia results.
- The kidneys excrete ammonia directly into the urine.
- There is no return of Nitrogen to the liver.

Encephalopathy

- Diversion of splanchnic blood flow places a metabolic load on the liver which aggravates hepatic function.
- Muscle protein breakdown is sent to the liver as alanine.
- Most tissues sequester ammonia by synthesizing glutamine (glutamate synthase removes ammonia) and sending it primarily to the liver to be converted into urea.

Encephalopathy

- Excess production of glutamine in the brain may impair neurotransmission:
  - depletes TCA cycle intermediates.
  - reduces NADH, and, later, ATP production.
  - GABA production diminishes.
- Excess glutamine also increases mitochondrial permeability. Brain edema may be seen.
- Clinical manifestations:
- Disturbances in consciousness
- Rigidity and hyper-reflexia
- Asterixis (wrist flap) is characteristic

Encephalopathy

- Converting glutamate to glutamine in the brain depletes TCA cycle intermediates.
- This reduces NADH, and, subsequently, ATP production.
- Further, GABA production diminishes.
- This may impair neurotransmission
- Excess glutamine also increases mitochondrial permeability.
- Brain edema may be seen.
- In severe liver disease, asterexis (wrist-flap) is commonly found.

Encephalopathy

- Elevated ammonia levels correlate with encephalopathy.
- Treatment includes sterilization of the gut.

Acute hepatic failure

- Acute liver failure is defined as an acute liver illness associated with encephalopathy and coagulopathy that occurs within 26 weeks of the initial liver injury in the absence of pre-existing liver disease.
- 80-90% of hepatic function has been lost.
- Rapidly fatal without liver transplant.

Acute hepatic failure

- Massive hepatic necrosis characteristic of acetaminophen toxicity (47% of all cases in adults).
- Other drugs and toxins account for 14%
- Azithromycin, particularly in women
- Hepatitis A, 4%. Hepatitis B, 8%.
- In Asia, Hepatitis B and E are usual causes
- In children, major cause are acetaminophen (29%), autoimmune disease (10%), and metabolic disease (9%)
- Encephalopathy is absent in up to 50% of young.

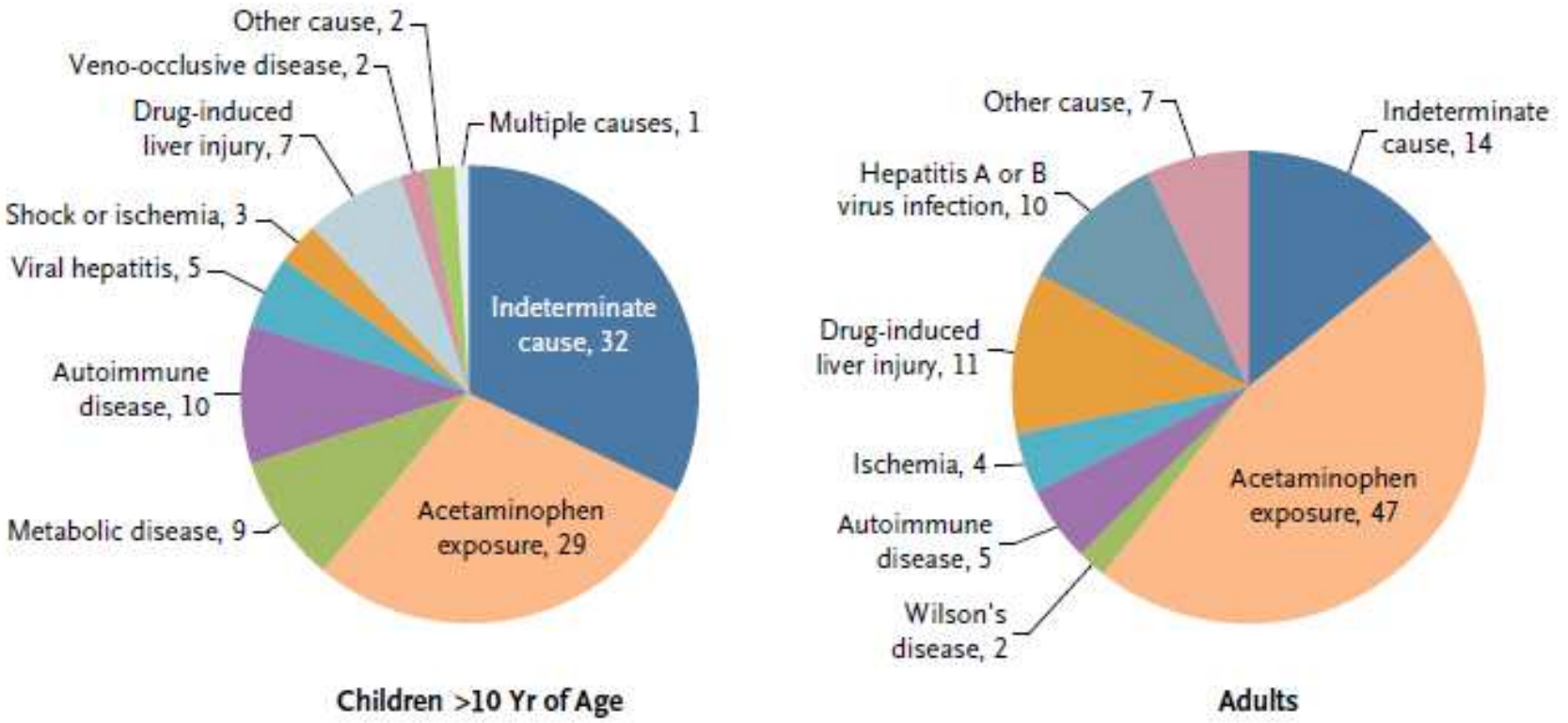


Figure 2. Causes of Acute Liver Failure in Children and Adults.

Data are adapted from Lee et al.[1] and Squires and Alonso.[3] The numbers shown are percentages. Among children older than 10 years of age, Wilson's disease accounted for 90% of metabolic disease.

NEJM.org Cases in Primary Care (2017)
Accessed 12/10/2019

Acute hepatic failure

- Acute liver failure usually displays massive hepatic necrosis, with broad regions of parenchymal loss surrounding islands of regenerating hepatocytes.
- The livers are small and shrunken.
- The prominence of scar and of ductular reactions in depends upon the duration of the insult.
- Toxic injury takes place within hours or days while viral injury may take weeks or months.

Acute hepatic failure

- Hepatic dysfunction without necrosis is seen in:
- Reye's syndrome
- Interferes with carnitine metabolism
- Acute fatty liver of pregnancy
- Mitochondrial dysfunction
- Tetracycline and valproate toxicity
- Mitochondrial dysfunction

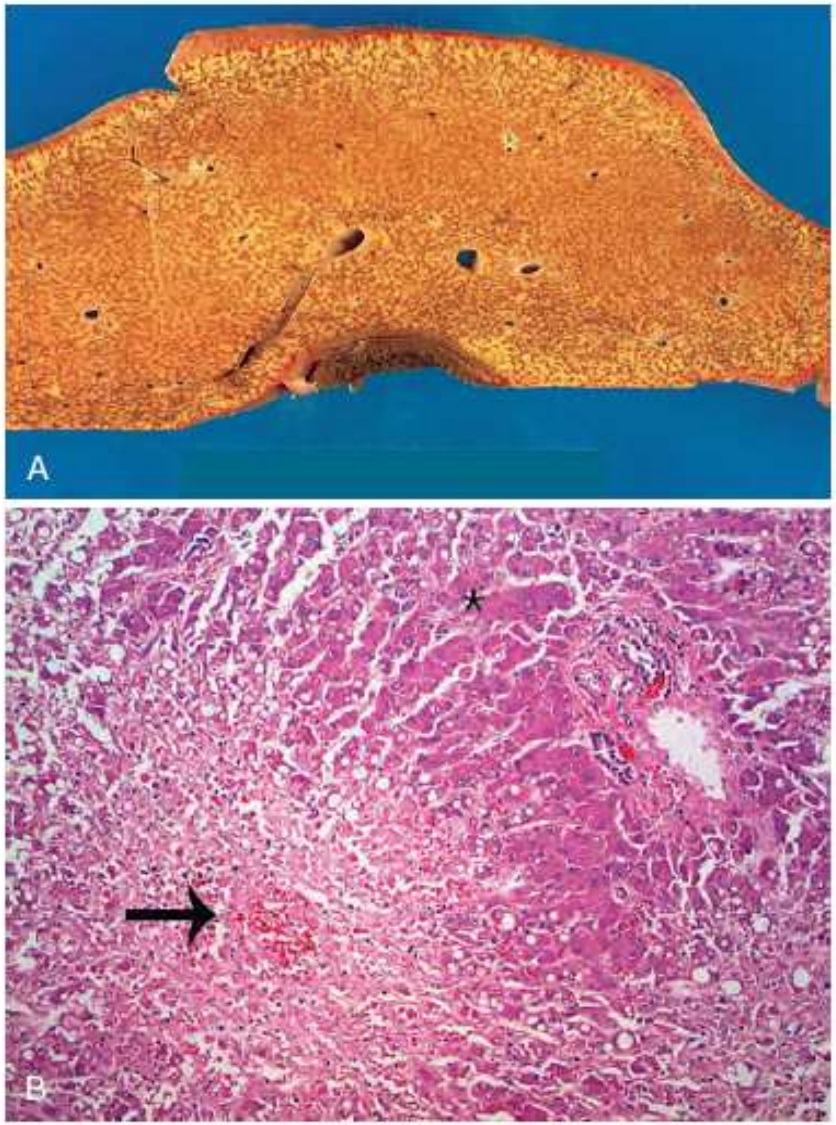


Figure 18-6 **A,** Massive necrosis, cut section of liver. The liver is small (700 g), bile-stained, soft, and congested. **B,** Hepatocellular necrosis caused by acetaminophen overdose. Confluent necrosis is seen in the perivenular region (zone 3) *(large arrow)*. Residual normal tissue is indicated by the asterisk. (Courtesy Dr. Matthew Yeh, University of Washington, Seattle, Wash.)

Chronic hepatic failure

- The leading causes of chronic liver failure worldwide include chronic hepatitis B, chronic hepatitis C, nonalcoholic fatty liver disease, and alcoholic liver disease
- Cirrhosis occurs diffusely throughout the liver
- Comprised of regenerating parenchymal nodules surrounded by dense bands of scar and variable degrees of vascular shunting

Chronic hepatic failure

- Biopsy specimens demonstrating narrow, densely compacted fibrous septa separated by large islands of intact hepatic parenchyma are likely to have less portal hypertension.
- Ductular reactions increase with advancing disease
- Those with broad bands of dense scar, often with dilated lymphatic spaces, with less intervening parenchyma, are likely to be progressing toward portal hypertension and, therefore, to end-stage disease.

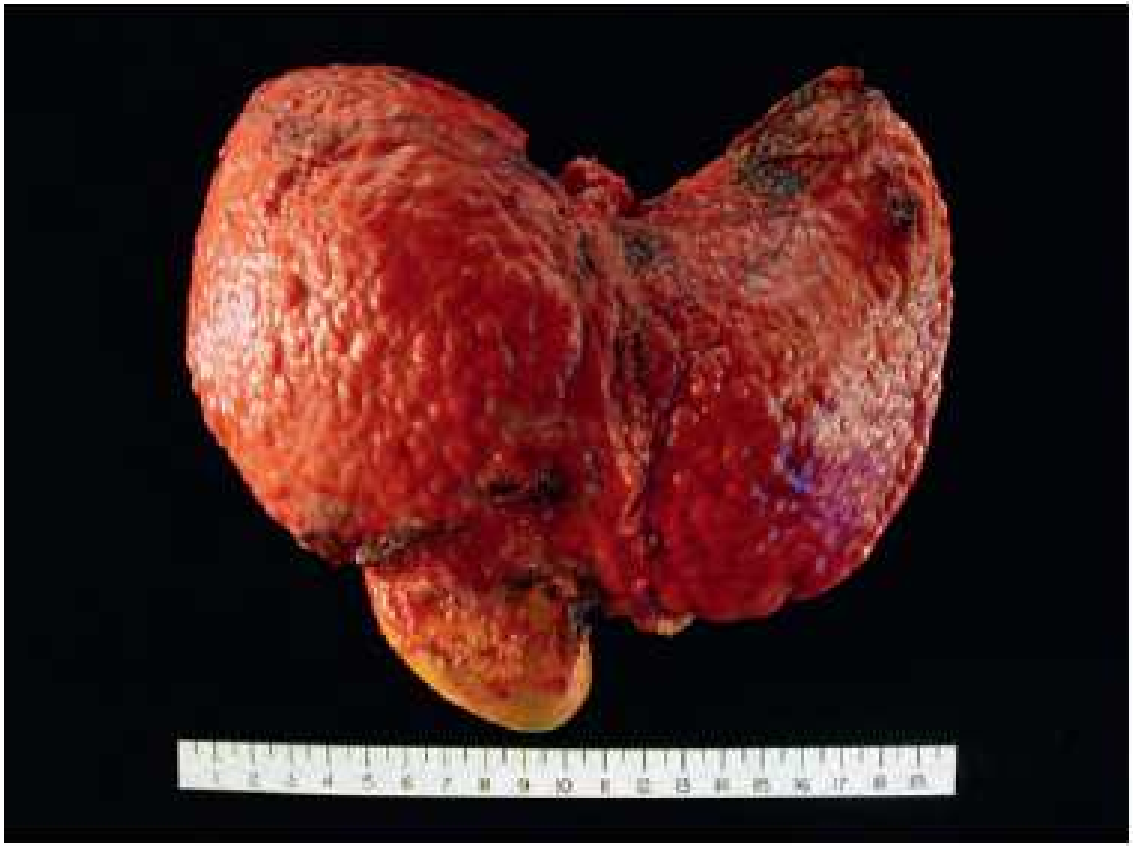


Figure 18-7 Cirrhosis resulting from chronic viral hepatitis. Note the depressed areas of dense scar separating bulging regenerative nodules over the liver surface.

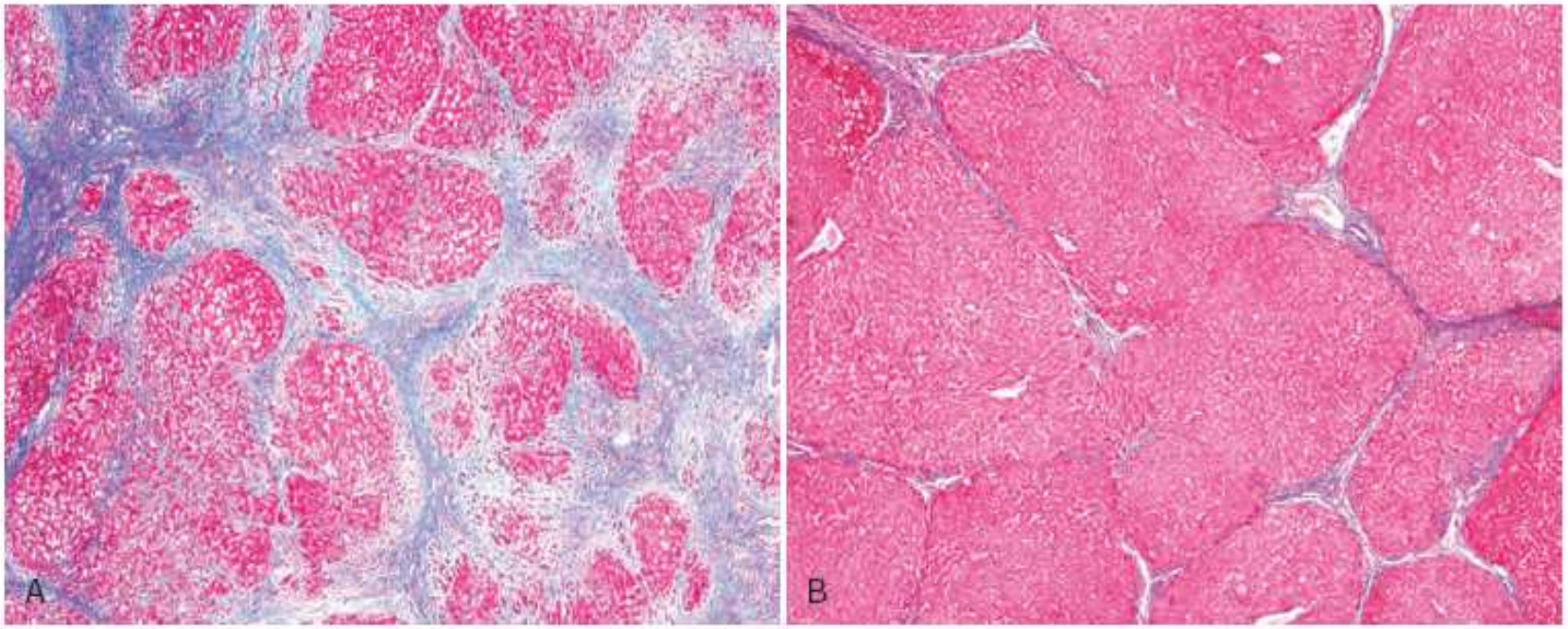


Figure 18-8 Alcoholic cirrhosis in an active drinker (A) and following long-term abstinence (B). **A,** Thick bands of collagen separate rounded cirrhotic nodules. **B,** After a year of abstinence, most scars are gone. (Masson trichrome stain) (Courtesy Drs. Hongfa Zhu and Isabel Fiel, Mount Sinai School of Medicine, New York.)

Hepatic failure

- Fetor hepaticus
- A musty body odor appreciated when splanchnic blood is shunted from the portal to the systemic circulation.
- Mercaptans formed by intestinal bacteria acting on ingested sulfur-containing amino acids.
- Impaired estrogen metabolism may lead to hyperestrinism:
- Palmar erythema, and spider angiomata of the skin are local vasodilatory changes
- Gynecomastia, hypogonadism, female hair pattern (men)
- Endometrial hyperplasia (women).

Hepatorenal syndrome

- 20% of patients with hepatic failure die of this syndrome
- Mortality rate is over 80%
- This syndrome occurs in the absence of:
- Urinary tract obstruction
- Volume depletion,
- Hypotension
- Renal disease.

Hepatorenal syndrome

- Decreased renal perfusion secondary to:
- Systemic vasodilatation and renal afferent arteriole vasoconstriction
- Activation of the renal sympathetic nervous system as well as production of vasoactive mediators.
- Decreased GFR (creatinine clearance below 40ml/min).
- The ability to concentrate urine is retained.
- There is neither proteinuria nor hematuria.
- Urine Sodium levels are low (<20mEq/L)
- Serum creatinine >1.5gm/dL in absence of diuretics (and following a trial of volume expansion).

Hepato-renal syndrome

- Type I presents with doubling of serum creatinine (or increase to >2.5 mg/dL) in two weeks. Acute renal failure.
- Type 2 presents with slowly progressive rise of serum creatinine. Refractory ascites.
- Incidence in cirrhosis and ascites of 18% at 1 year; 39% at 5 years.
- May treat with hemodialysis (equivalent to a creatinine clearance of 10ml/min),
- Vasopressin analogues
- Liver transplantation definitive therapy.

Hepatopulmonary syndrome

- 30% of patients with cirrhosis and portal hypertension.
- Develop intrapulmonary vascular dilatation.
- Blood transit time too rapid to permit adequate oxygenation. Ventilation-perfusion mismatch.
- Hypoxia and dyspnea worse when upright as gravity exacerbates mismatch.
- May be due to hepatic production of vasodilators such as NO.
- May see cutaneous spider nevi.
- Mortality rate higher in those patients with this syndrome than those without it.

Portopulmonary hypertension

- Pulmonary artery hypertension in a setting of portal hypertension.
- Hyperdynamic.
- May result from endothelin-1 vasoconstrictors from liver.
- May represent impairment of prostaglandin E.
- Clubbing and dyspnea on exertion may be only presentation.

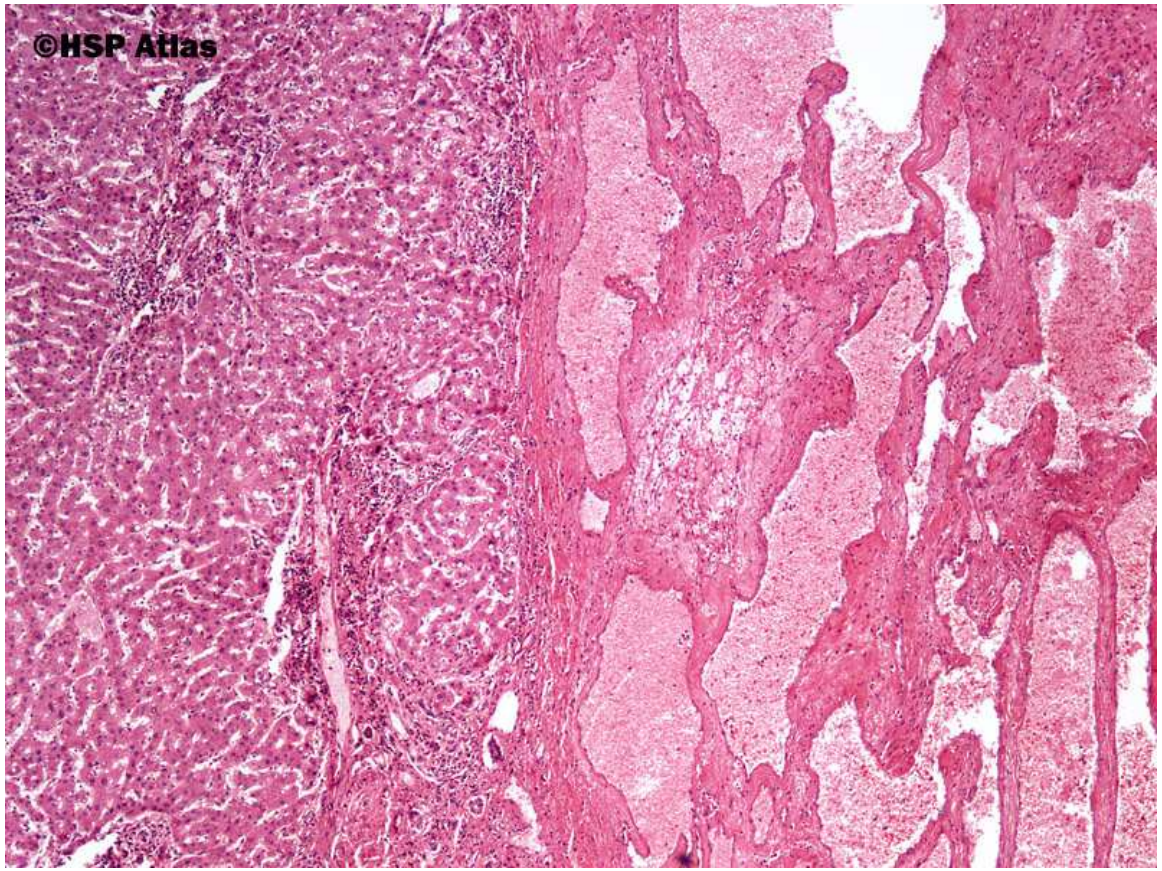
Therapy

- Vasopressin analogs may improve renal perfusion by reversing splanchnic vasodilation in hepato-renal syndrome.
- Somatostatin analogs
- α-adrenergic agonists
- Mortality rates >80%.
- Liver transplantation is only effective therapy.
- Criteria for liver transplantation are a rising bilirubin, a rising AST, and an abnormal prothrombin time (or rising INR).

Benign hepatic masses

- Cavernous hemangioma
- Most commonly occurring benign hepatic mass.
- Rarely ruptures.
- Identify on CT.
- Do not biopsy.

Cavernous hemangiona



http://www.patologia.cm.umk.pl/atlas/gastrointestinal/liver/hemangioma/#&gid=1&pid=4
Accessed 12/10/2019

Liver compressed by subcapsular lesion of vascular channels lined by flattened endothelial cells.

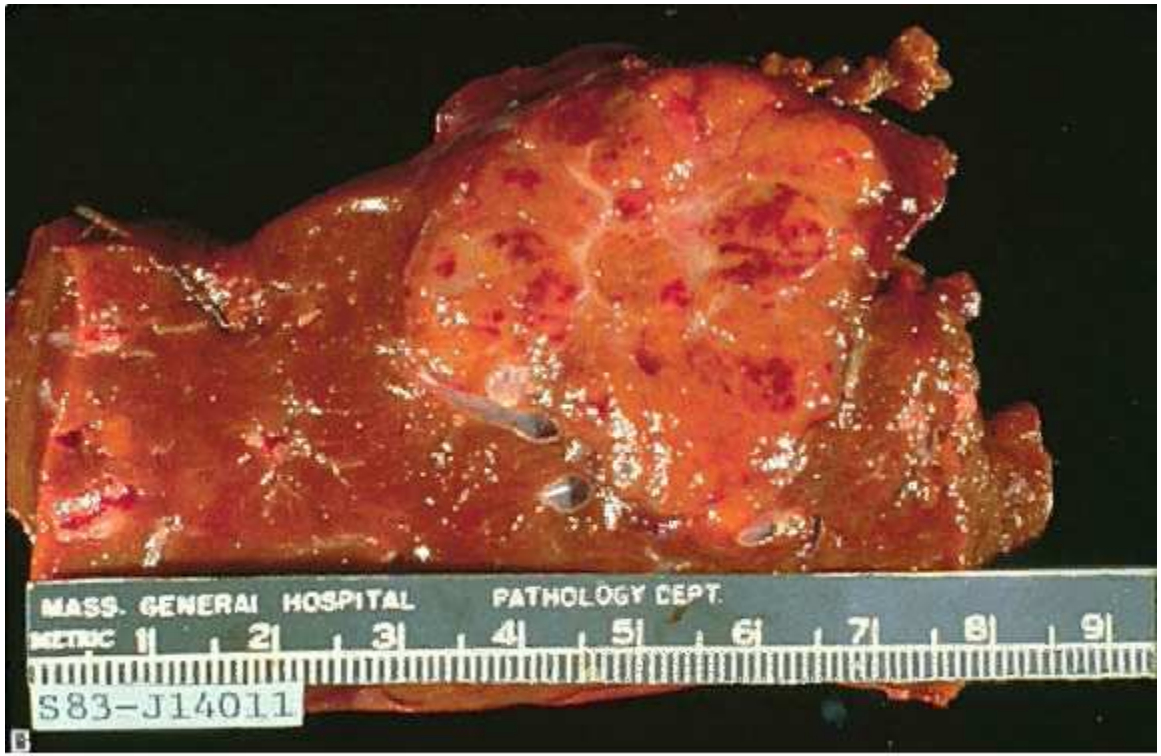
The vascular channels are separated by fibrous stroma.

Organizing thrombi are frequently present and as they undergo sclerosis, the entire lesion may be replaced by a fibrous nodule.

Benign hepatic masses

- Focal nodular hyperplasia
- Often an incidental finding.
- Preserves normal liver structure.
- Often a central vascular core with stellate fibrous septae radiating to the periphery.
- Fibromuscular hyperplasia of arteries in central core
- Thought to initiate hypoxic injury in liver
- More common in women.
- Not treated unless painful.

Focal nodular hyperplasia



(Courtesy of L Friedman.) Fig. Ch. 16

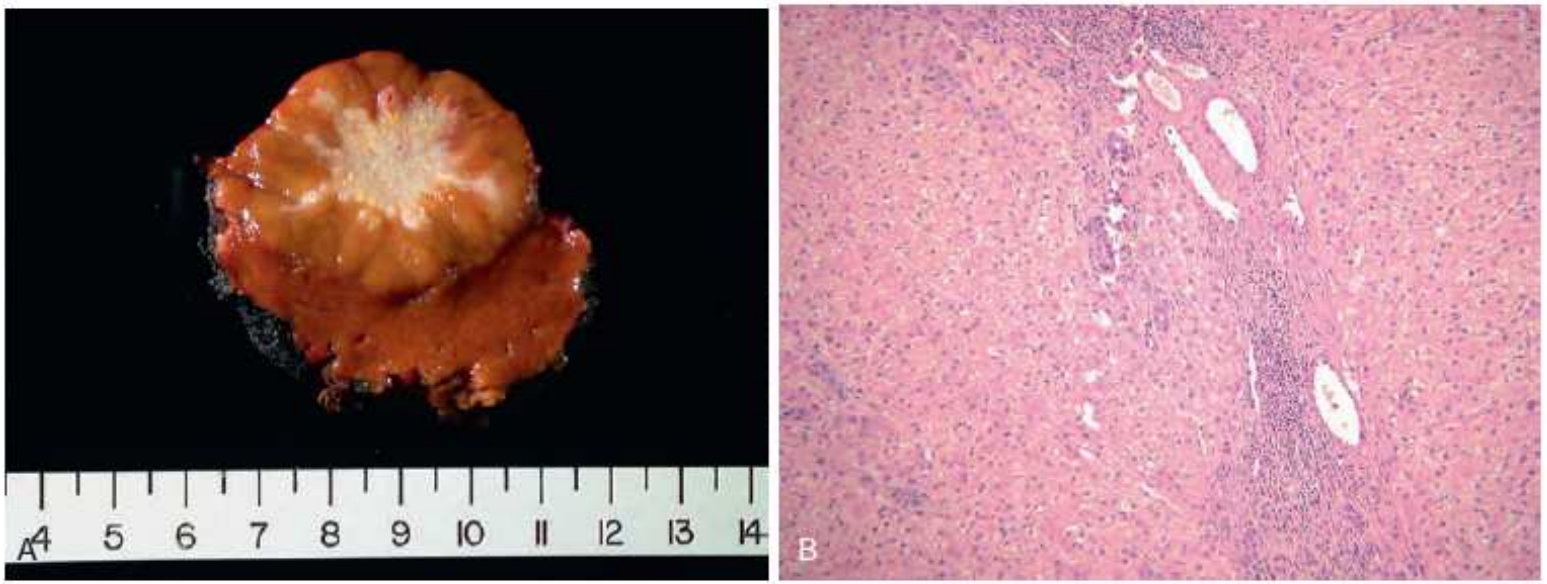
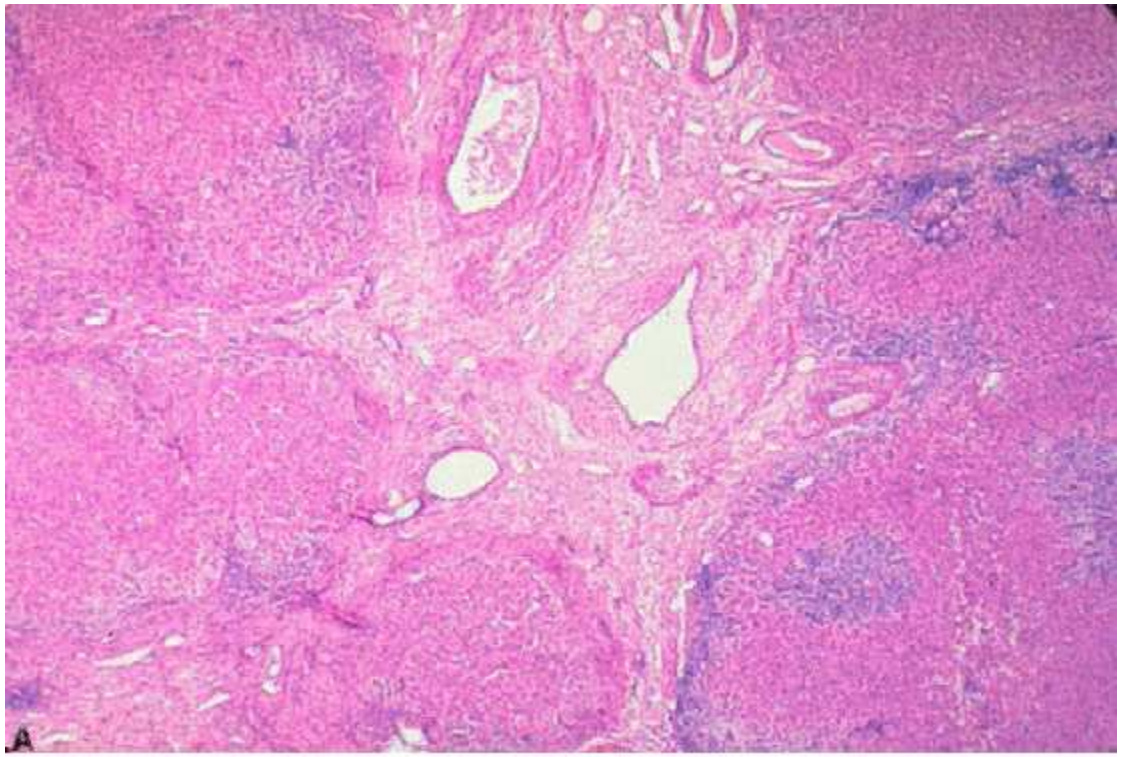


Figure 18-51 Focal nodular hyperplasia. **A,** Resected specimen showing lobulated contours and a central stellate scar. **B,** Low-power micrograph showing a broad fibrous scar with hepatic arterial and bile duct elements and chronic inflammation present within parenchyma that lacks normal architecture due to hepatocyte regeneration.

Focal nodular hyperplasia



(Courtesy of L Friedman.) Fig. Ch. 16

Nodular regenerative hyperplasia

- Liver transformed into nodules
- Similar to micronodular cirrhosis, but without fibrosis.
- Plump hepatocytes are surrounded by rims of atrophic hepatocytes.
- Nodular regenerative hyperplasia can lead to the development of portal hypertension
- Occurs in association with conditions affecting intrahepatic blood flow, including solid-organ (particularly renal) transplantation, hematopoetic stem cell transplantation, and vasculitis.
- It also occurs in HIV disease as well as SLE
- Incidental finding

Hepatocellular adenoma

- Women, principally
- 20-40 years of age.
- Oral contraceptives are thought to be an etiologic factor as well as are anabolic steroids.
- Regress when hormones withdrawn.
- May rupture during pregnancy
- It is also seen in those with glycogen storage disease Ia and with Fanconi anemia.
- Generally solitary and in the right lobe
- Often large when identified.
- Cold (no uptake) on Technetium-albumin scan (lack Kupffer cells).

Hepatocellular adenoma

- Five subtypes:
- (1) Inactivating mutations of HNF1-α (HA-H, 35%)
- 90% are somatic mutations of TCF1 (HNF1A) gene
- < 5% heterozygous germline mutations of CYP1B1 gene
- Resultant increase in lipogenesis by promotion of fatty acid synthesis and by downregulation of liver type fatty acid binding protein (LFABP)

Hepatocellular adenoma

- Germline mutation responsible as well for Maturity onset diabetes of youth type 3 (MODY-3).
- Somatic mutation necessary as well in MODY-3 if hepatocellular adenoma to develop.
- Microscopic examination:
- Steatosis.
- Some areas show. prominent pericellular staining or almost complete circling of small groups of hepatocytes by reticulin fibers

Hepatocellular adenoma

- (2) Inflammatory (HA-I, 35%)
- Associated with Non-alcoholic fatty liver disease
- Activating mutation of IL6ST gene producing gp130 (IL-6 co-receptor); leads to constitutive JAK-STAT signaling
- Microscopic examination:
- Irregular, poorly circumscribed borders; inflammatory infiltrates and sinusoidal dilatation; may have "pseudoportal tracts," which are islands of thick walled arteries with no definite bile ducts but associated ductular reaction .
- Express C-reactive protein and serum amyloid A

Hepatocellular adenoma

- (3) β-catenin activation (HA-B, 10%)
- Mutations in exon 7 - 8 and exon 3 result in stabilization of β-catenin protein and increased or non-transient activation of WNT/β-catenin signaling pathway
- Glutamine synthetase (target for β-catenin) diffusely elevated
- Very high risk for malignant transformation

Hepatocellular adenoma

- Microscopic examination:
- Pseudoacinar arrangement
- Cytologic abnormalities including nuclear pleomorphism and atypia, multinucleation, prominent nucleoli
- Steatosis is rare
- No significant inflammation

Hepatocellular adenoma

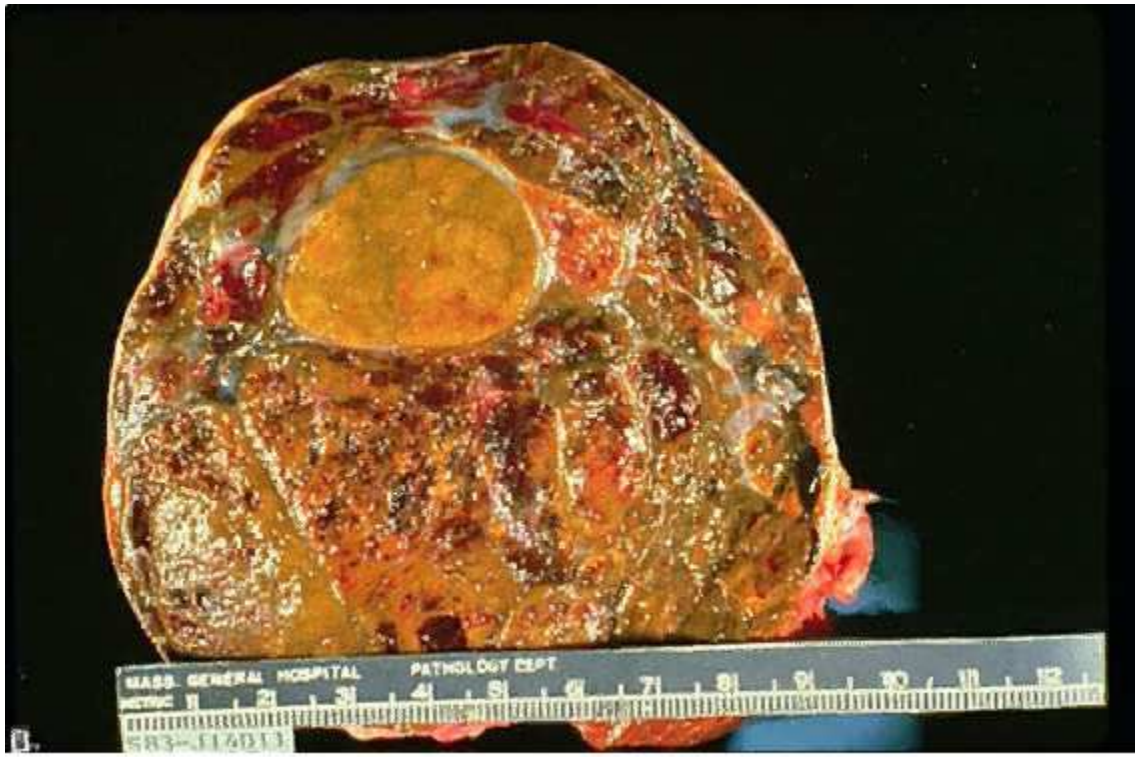
- (4) Sonic hedgehog (SHH) mutated (HA-sh, 5%)
- Activation of sonic hedgehog pathway via fusion of promoter of INHBE with GLI1
- Also upregulation of argininosuccinate synthase 1, which may indicate increased risk of hemorrhage
- (5) Unspecified (HA-U, 7%)
- Morphology characteristic of adenoma but no specific characteristics of the individual subtypes
- Lesions with extensive hemorrhage and necrosis are currently grouped into this subtype

Hepatocellular adenoma

- Risk of malignant transformation:
- Male sex
- β-catenin mutation
- Large tumors

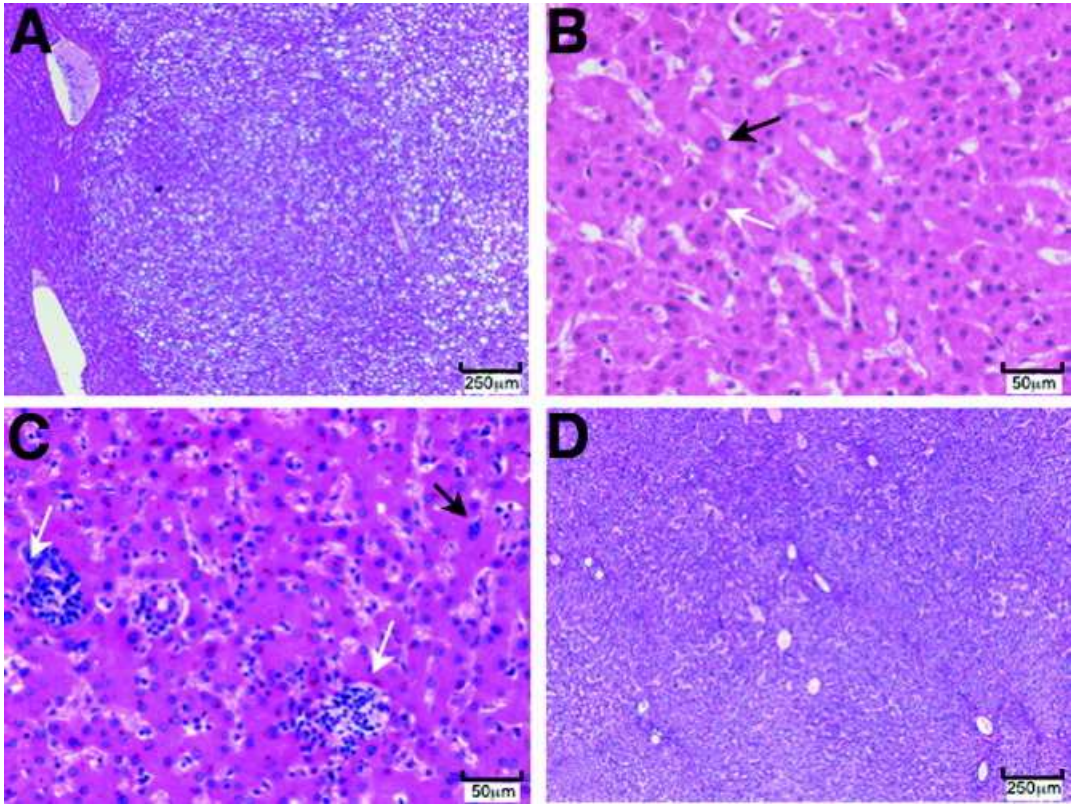
- Treatment:
- Surgical excision if tumor in man, irrespective of size
- Surgical excision in women if tumor >5cm and there are β-catenin mutations
- Else, withdraw oral contraceptives and follow

Hepatocellular adenoma



(Courtesy of L Friedman.) Fig. Ch. 16

Zucman-Rossi, J, Jannot, E, Tran Van Nhieu, J, et al, “Genotype–phenotype correlation in hepatocellular adenoma: New classification and relationship with HCC”, **Hepatology, Volume: 43, Issue: 3, Pages: 515-524, First published: 22 February 2006, DOI: (10.1002/hep.21068)**



Main characteristic morphological features in adenomas. (A) Typical aspect of a HNF1α–mutated adenoma with marked steatosis, no cytological abnormalities, and no inflammatory infiltrate. (B) A β-catenin–activated adenoma presenting pseudo-glandular formation (white arrow) and some cytological abnormalities with hyperchromatic nuclei (black arrow) (C) Adenoma with neither HNF1α nor β-catenin mutations presenting focal inflammatory infiltrate (white arrow) and some cytological abnormalities with hyperchromatic nuclei (black arrow) (D) Adenoma with neither HNF1α nor β-catenin mutations and without any morphological particularities: no steatosis, no cytological abnormalities, and no inflammatory infiltrate

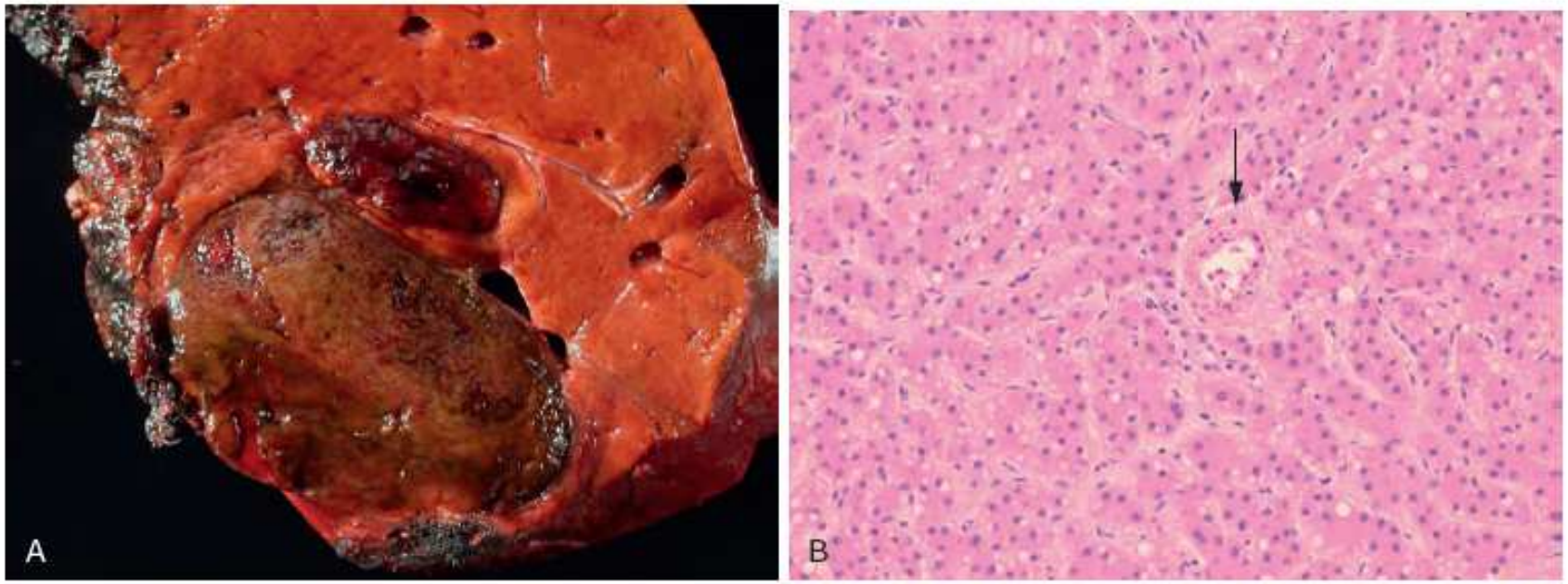
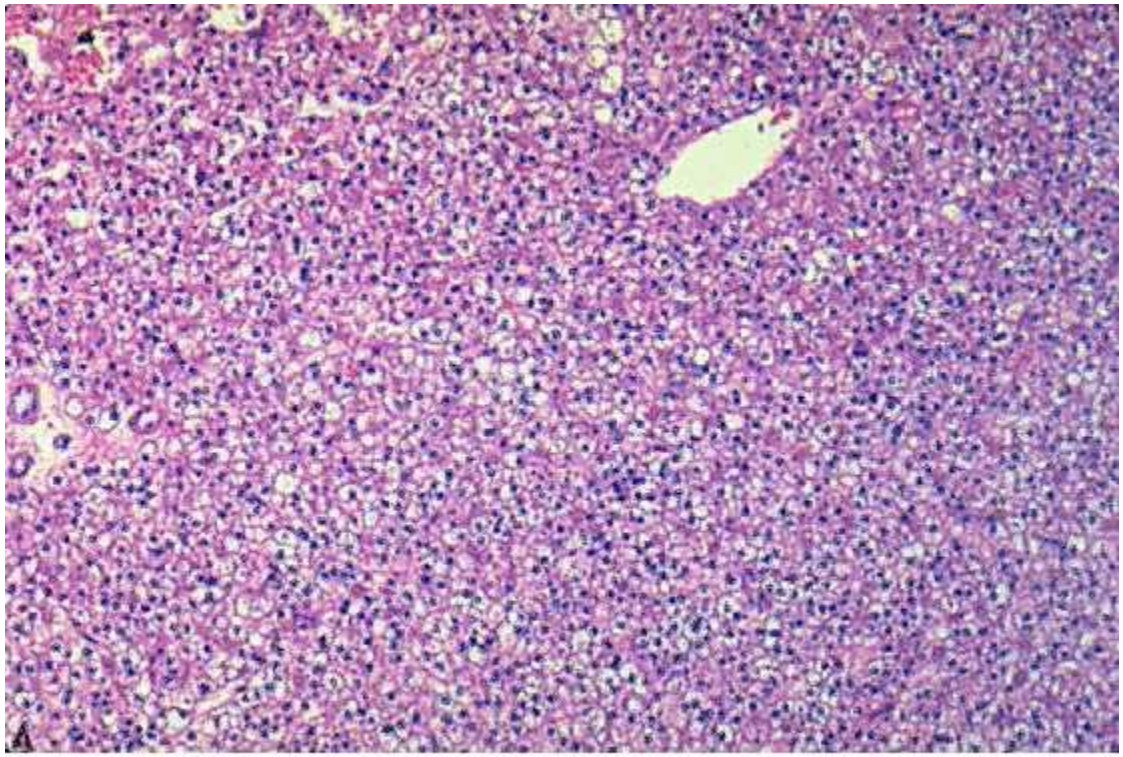


Figure 18-53 Liver cell adenoma. **A,** Resected specimen presenting as a pendulous mass arising from the liver. **B,** Microscopic view showing cords of hepatocytes, with an arterial vascular supply *(arrow)* and no portal tracts.

Hepatocelluar adenoma



Courtesy of (L Friedman.) Fig. Ch. 16

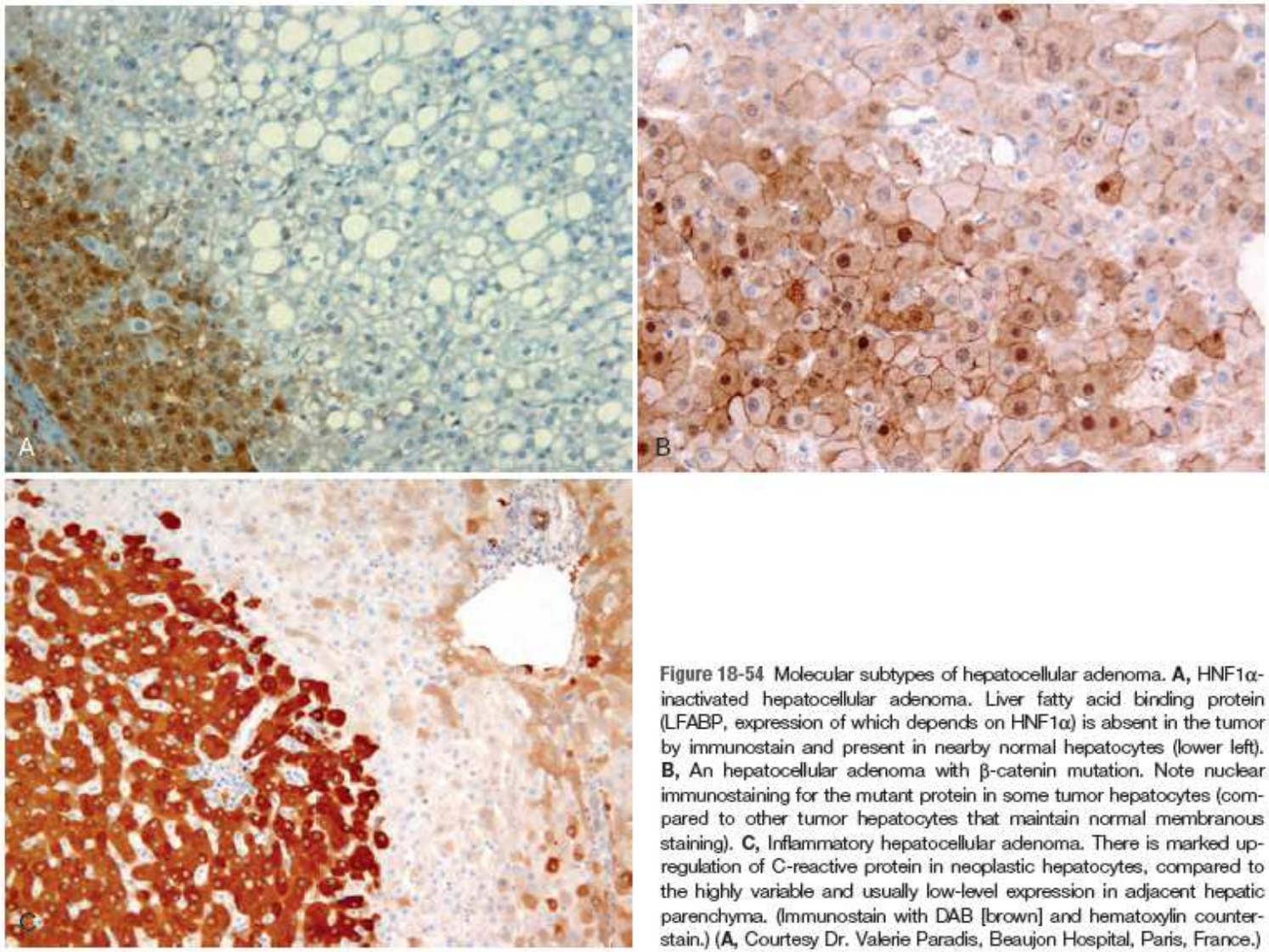


Figure 18-54 Molecular subtypes of hepatocellular adenoma. **A,** HNF1α-inactivated hepatocellular adenoma. Liver fatty acid binding protein (LFABP, expression of which depends on HNF1α) is absent in the tumor by immunostain and present in nearby normal hepatocytes (lower left). **B,** An hepatocellular adenoma with β-catenin mutation. Note nuclear immunostaining for the mutant protein in some tumor hepatocytes (compared to other tumor hepatocytes that maintain normal membranous staining). **C,** Inflammatory hepatocellular adenoma. There is marked up-regulation of C-reactive protein in neoplastic hepatocytes, compared to the highly variable and usually low-level expression in adjacent hepatic parenchyma. (Immunostain with DAB [brown] and hematoxylin counterstain.) (**A,** Courtesy Dr. Valerie Paradis, Beaujon Hospital, Paris, France.)

Hepatocellular carcinoma

- Most common liver cancer
- High incidence in Asia secondary to HBV as well as aflatoxin use
- Incidence in US related to HCV
- 50-60 years of age
- Men (3-8:1)
- Over one-third are asymptomatic
- Abdominal pain
- Fever (due to liver cell necrosis)
- Rapid liver enlargement in a cirrhotic patient
- May be focal, multifocal, or diffusely infiltrating
- Commonly invade portal and hepatic veins

Hepatocellular carcinoma

- Intrahepatic metastases
- Become more likely once tumors reach 3 cm in size.
- Metastases are usually small, satellite tumor nodules around the larger, primary mass.
- The vascular route is also the most likely route for extrahepatic metastasis, especially by the hepatic venous system.
- Hematogenous metastases, especially to the lung, tend to occur late in the disease.
- Occasionally invade the portal vein (causing portal hypertension) or inferior vena cava. The latter can even extend into the right side of the heart.
- Lymph node metastases are less common

Hepatocellular carcinoma

- Causes include:
- Post-necrotic cirrhosis due to chronic HBV or HCV infection
- Alcoholic cirrhosis
- Non-alcoholic fatty liver disease
- Non-alcoholic steatohepatitis
- Aspergillus aflatoxin (peanuts, mold)
- Hereditary hemochromatosis
- Wilson's disease
- α_1-antitrypsin deficiency
- Primary biliary cirrhosis

Etiology of HCC at the Molecular Level

	EGFr	RAF	Telomerase	DNA methylation	p53
HBV			●		
HCV	●	●			
EtOH				●	
Obesity	●				●

Thorgeirsson, S; et al. Nature Genetics, 31: 2002

Hepatocellular carcinoma

- AFP elevated (the cancer assay is not the same one utilized in obstetric cases to evaluate fetal state)
- May produce:
- Erythropoietin
- Insulin-like factor
- Parathormone related protein
- Fibrolamellar variant (5%) occurs in those 20-40 years of age without underlying liver disease.

Hepatocellular carcinoma

- Hepatocellular carcinoma associated with HBV.
- HBV X-protein, a transcriptional activator, main promoter of cellular transformation. PKC and NF-κB stimulated.
- Hepatocellular carcinoma caused by HCV is not common in HBV prevalent populations.

Hepatocellular carcinoma

- Hepatocellular carcinoma associated with HCV.
- (Core protein localizes in outer mitochondrial membrane and endoplasmic reticulum, promoting oxidative stress. The non-structural proteins NS3 and NS5A also promote oxidative stress.)
- HCV induces TNF-α related insulin resistance.
- Alcohol potentiates oxidative stress; it also leads to changes in the hyper-variable region of the HCV genome and is associated with resistance to interferon-α.

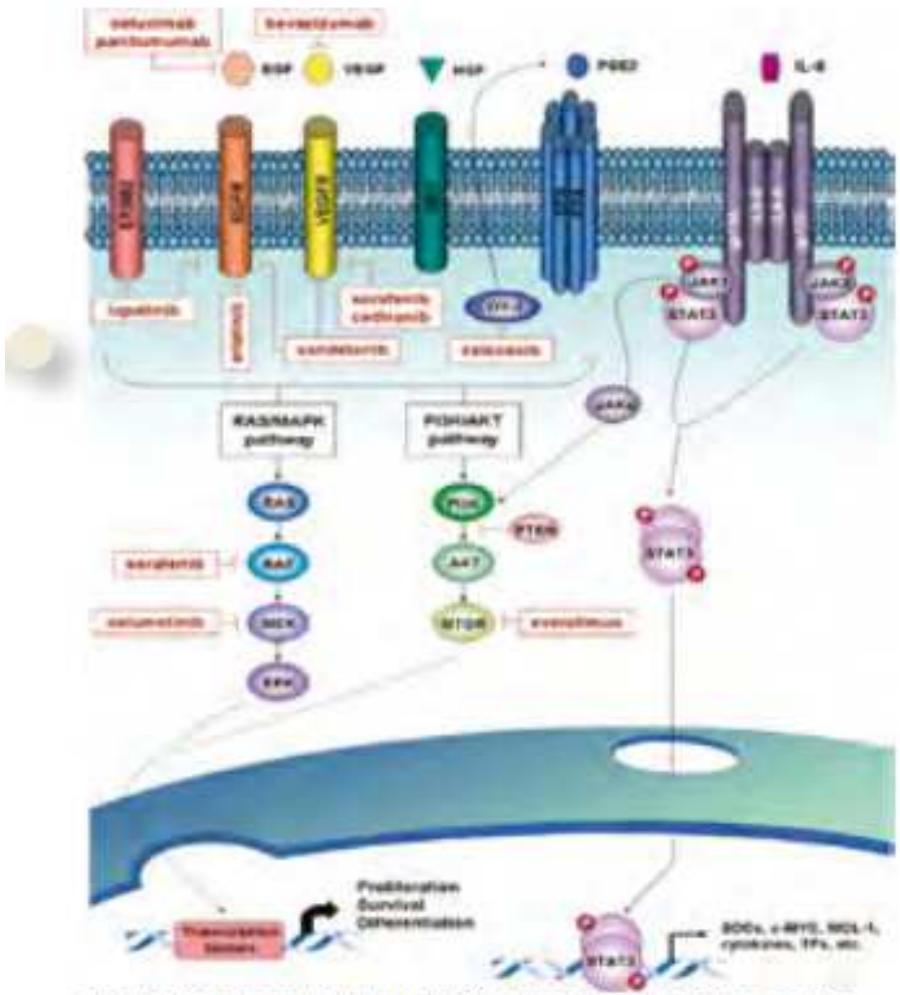
Hepatocellular carcinoma

- Alcohol inhibits the expression of BCL-2 in hepatocytes.
- Aflatoxin leads to p53 loss
- TGF-β induced apoptosis depressed.
- May arise from liver stem or fetal cells
- Thought to promote tumor formation in the cirrhotic liver.
- MYC , C-MET, and HH abnormalities also noted.
- p53, p27, p16 functions lost in cirrhosis as well.

Hepatocellular carcinoma

- Wnt/β-catenin and PI3K/Akt pathways activated in 50% of hepatocellular cancers.
- Early mutational event
- Loss of p53 is an early event as well
- Small cell change is thought to be directly premalignant.
- Large cell change is at least a marker of increased risk of cancer in the liver as a whole, but in hepatitis B they may also be directly premalignant.
- Dysplastic nodules are found in cirrhosis.

The main mutations in hepatocarcinogenesis include the tumor suppressor gene TP53 and the beta-catenin gene. Molecular profiling of HCC has shown alteration of many signaling cascades: epidermal growth factor receptor (EGFR) and RAS signaling, mTOR, insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF) and C-MET pathways.



EGF, Epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IL-6, interleukin-6; IL-6-R, interleukin-6 receptor; PGE2, prostaglandin 2; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 18-12 Precursor Lesions of Hepatocellular Carcinoma and Cholangiocarcinoma

	Hepatocellular Carcinoma					Cholangiocarcinoma		
	Hepatocellular Adenoma	Small Cell Change	Large Cell Change	Low Grade Dysplastic Nodule	High Grade Dysplastic Nodule	BilIN-3	Mucinous Cystic Neoplasm	Intraductal Papillary Biliary Neoplasia
Focality in liver	Single or multiple (adenomatosis)	Diffuse	Diffuse	Single or multiple	Single or multiple	Diffuse or multifocal	Single	Focal or diffuse
Premalignant	Yes	Yes	In some HBV*	Uncertain*	Yes	Yes	Yes	Yes
Association with cirrhosis	Rare	Common	Common	Usual	Usual	Sometimes	No	No
Commonly associated diseases	NAFLD, Sex hormone exposures Glycogen storage diseases	HBV, HCV, Alcohol, NAFLD, A1AT, HH, PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	HBV, HCV, Alcohol, NAFLD, A1AT, HH PBC	PSC, Hepatolithiasis, Liver flukes	None	None
Occurrence without identified predisposing condition	Occasional	No	No	No	No	Yes	Yes	Yes
Need for surveillance cancer screening	± depending on presence of predisposing condition	Yes	Yes	Yes	Yes	Yes	No	Yes

*While these are not certain to be directly premalignant, they are always at least an indication of increased risk for malignancy in the liver as a whole.
BilIN-3, Biliary intraepithelial neoplasia, high grade; NAFLD, nonalcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; A1AT, α_1-antitrypsin deficiency; HH, hereditary hemochromatosis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

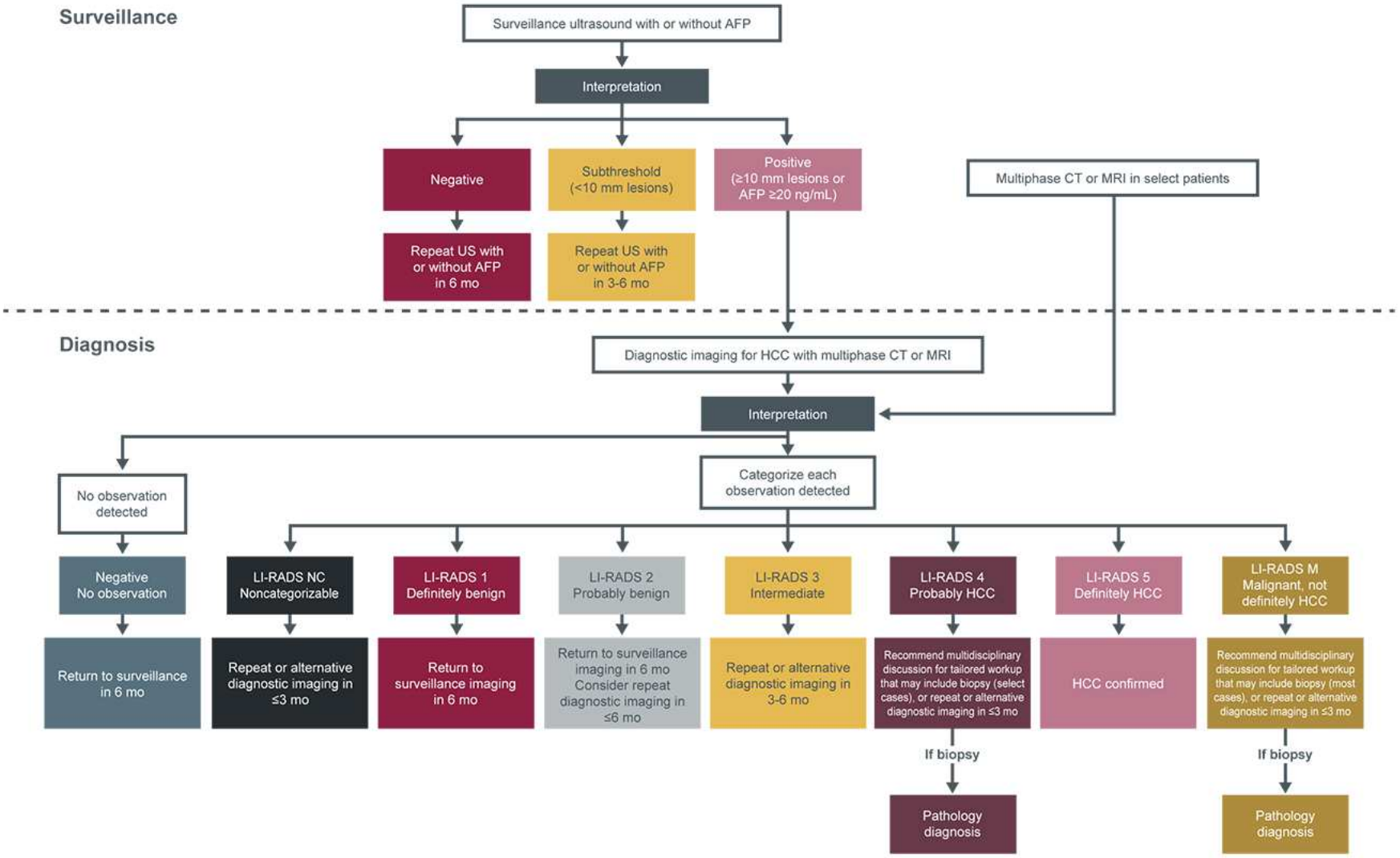
Screening criteria

- Screen all who have a history of Hepatitis C
- Screen all Asian men over 40 years old who have a history of Hepatitis B; Asian women, over 50 years old
- Screen HBV carriers and those with HBV and HIV
- Screen all with cirrhosis
- AFP and Ultrasound are used together
- AFP >100, likely malignancy
- Ultrasound mass >10mm size, likely malignant
- Active viral infection reduces image quality
- If lesion >10mm or AFP>20, screen with dynamic enhanced contrast MRI or CT

Liver imaging reporting

- LR-1 angioma, focal fibrosis, scar, cyst likely
- LR-2 also, cirrhotic nodule
- LR-3 with or without arterial phase enhancement
- Approximately one third are malignant (biopsy)
- LR-M, target lesion not characteristic of hepatocellular carcinoma
- Approximately one third are malignant (biopsy)
- LR-4 no arterial phase or no rim arterial phase enhancement
- Approximately 80% of masses are malignant
- LR-5 enhancing capsule
- Approximately 97% of masses are malignant

Figure 5: AASLD Algorithm for HCC Surveillance and Diagnosis



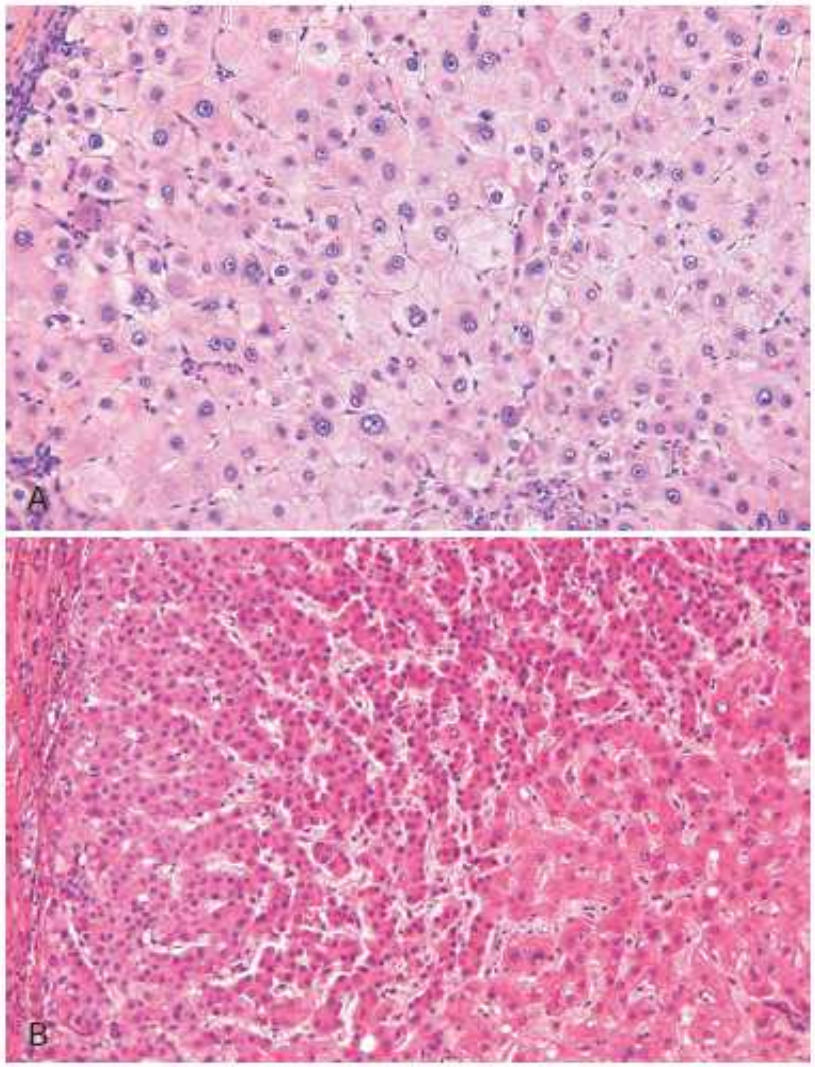


Figure 18-57 **A,** Large cell change. Large hepatocytes with large, often atypical nuclei are scattered among normal-size hepatocytes with round, typical nuclei. **B,** Small cell change. The abnormal cells have a high nuclear-to-cytoplasmic ratio and are separated by thickened plates. Normal-appearing hepatocytes are in the lower right corner. (Courtesy Dr. Young Nyun Park, Yonsei Medical College, Seoul, South Korea.)

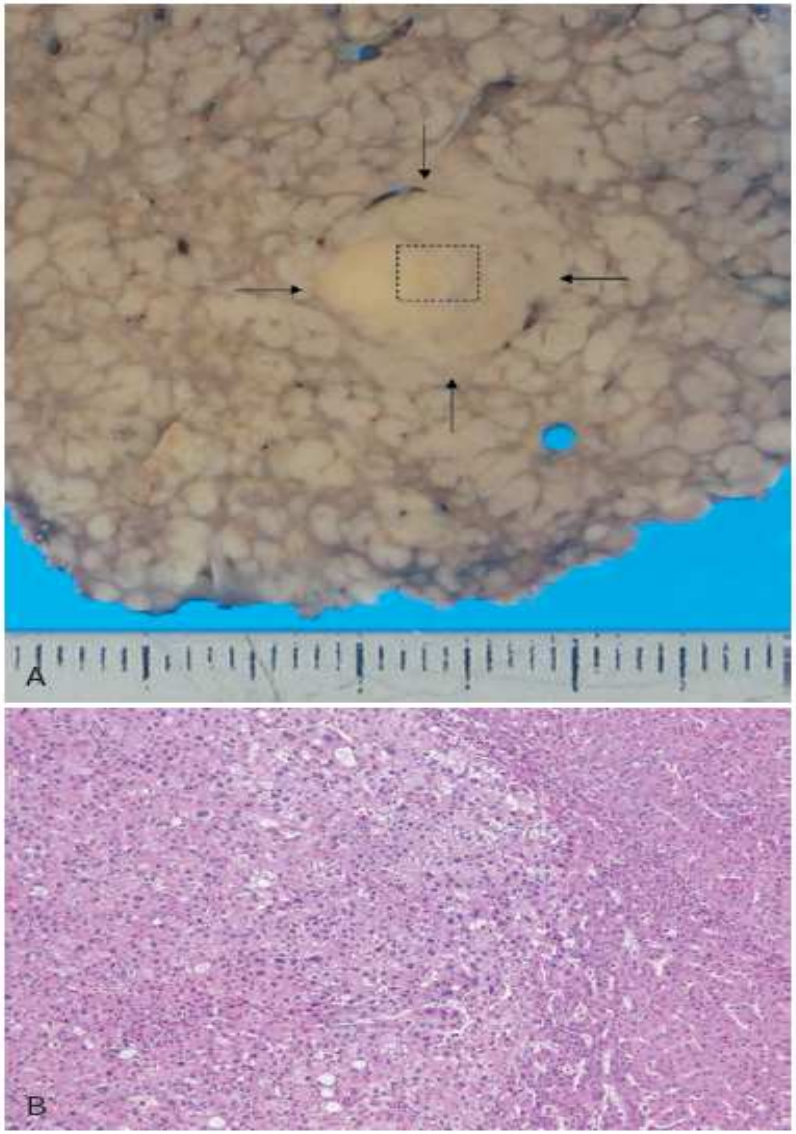
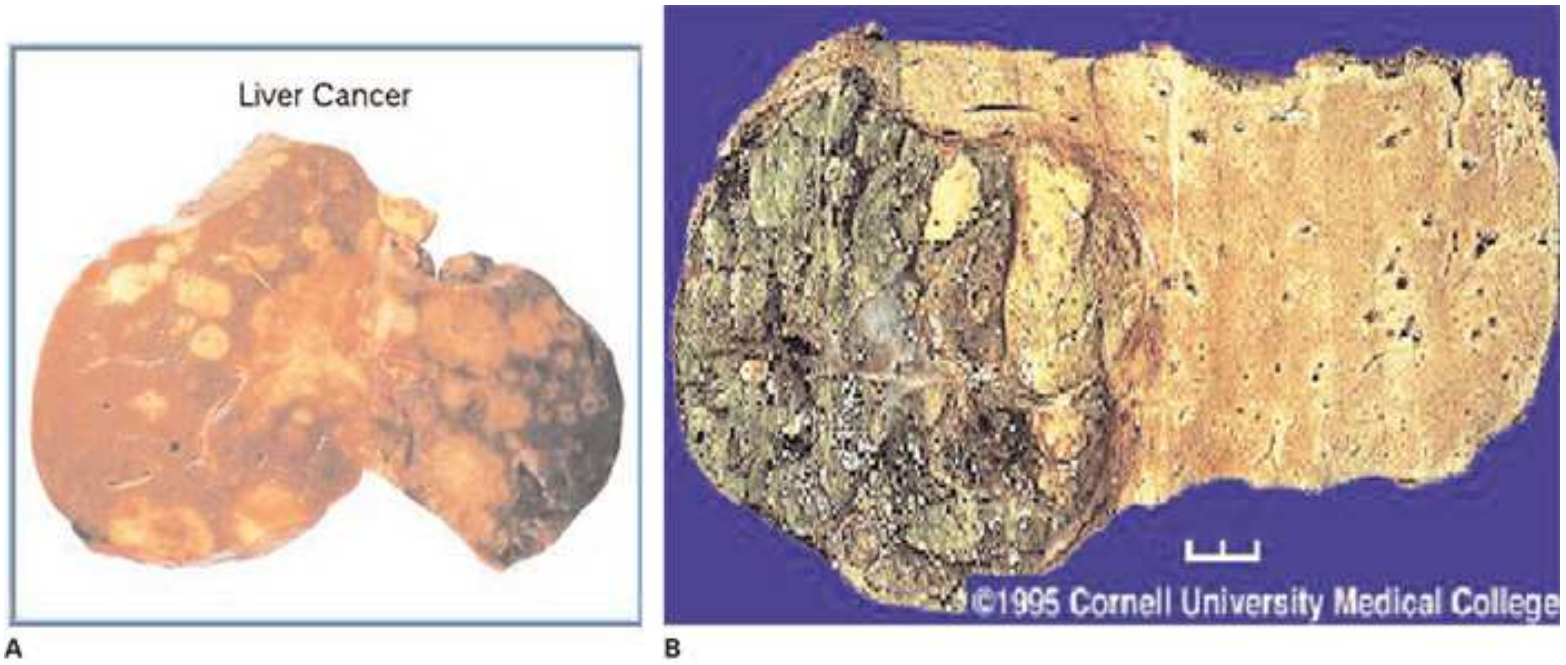


Figure 18-58 **A,** Hepatitis C–related cirrhosis with a distinctively large nodule *(arrows)*. Nodule-in-nodule growth suggests an evolving cancer. **B,** Histologically the region with in the box in **A** shows a well-differentiated hepatocellular carcinoma (HCC) (right side) and a subnodule of moderately differentiated HCC within it (center, left). (Courtesy Dr. Masamichi Kojiro, Kurume University, Kurume, Japan.)

Hepatocellular cancer



A B

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

Fig. 15-9 Accessed 04/10/2010

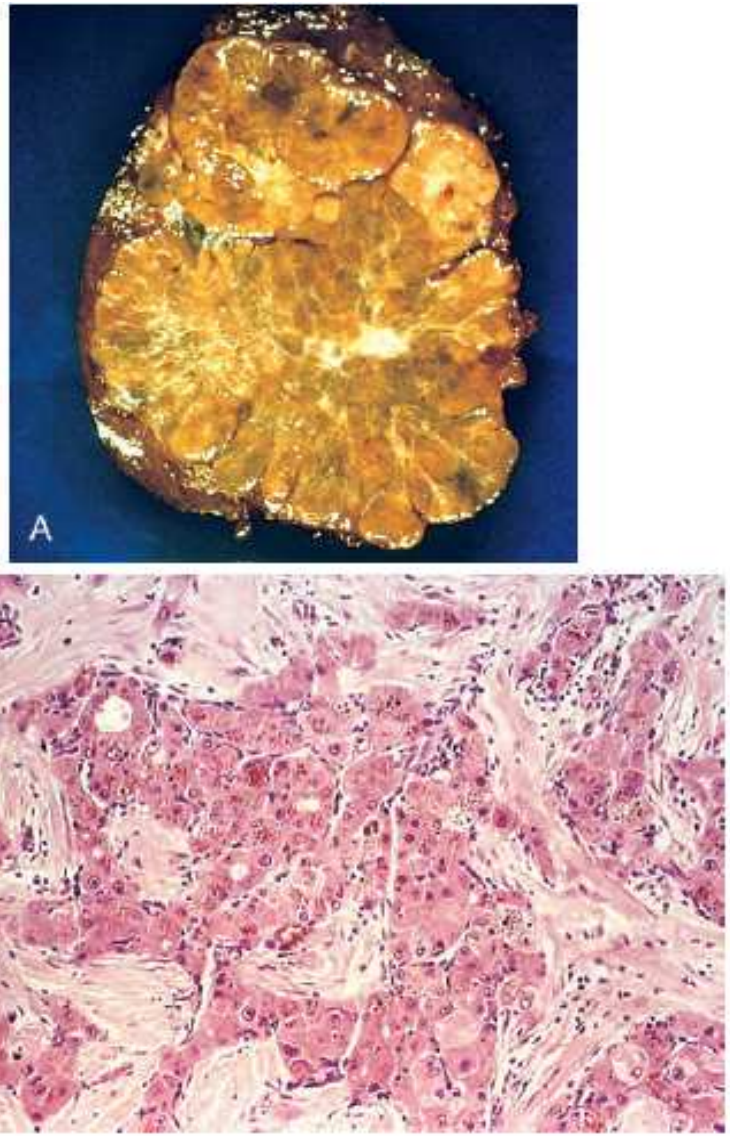


Figure 18-59 Fibrolamellar carcinoma. **A,** Resected specimen showing a well demarcated nodule. **B,** Microscopic view showing nests and cords of malignant-appearing, oncocytic hepatocytes separated by dense bundles of collagen.

Hepatocellular cancer

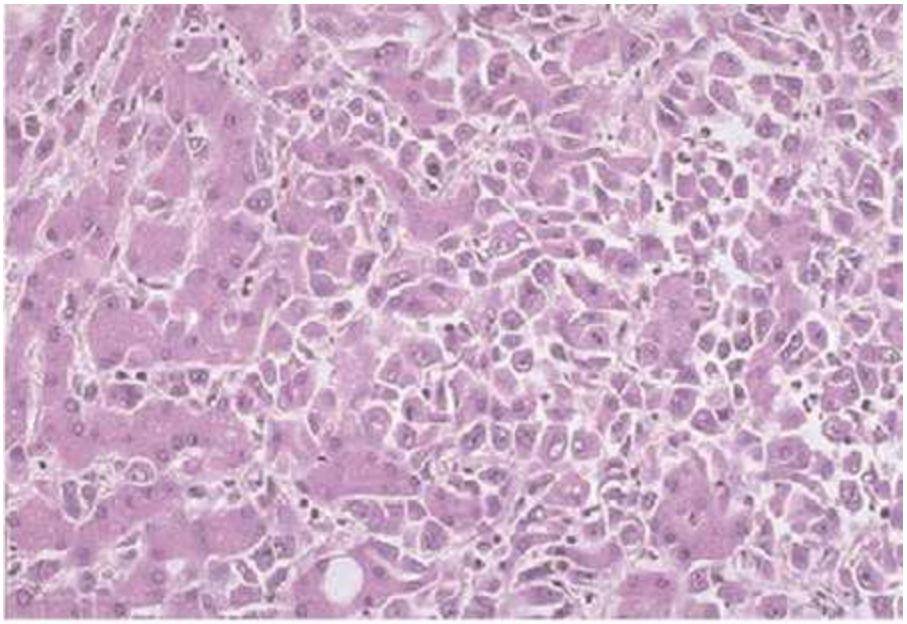


Fig. 15-10 Accessed 04/10/2010

Shown here is a moderately well differentiated neoplasm of polygonal cells in a trabecular patern. Rare nests and acini are identified.

Hepatocellular cancers may be univocal, multifocal, or diffuse.

There is a propensity to invade vascular structures.

The fibrolamellar variant is associated with marked fibrosis.

Prognosis and staging

- The Barcelona (BCLC) staging classification is the only classification that provides treatment recommendations for each of the assigned stages (early, intermediate, advanced, end-stage) based on best treatment options currently available.
- It has been validated in Europe, Asia, and the US.
- The BCLC is based on tumor size, number of tumor nodules, the presence of portal vein thrombosis, liver function (Child-Pugh score, portal hypertension, bilirubin level), performance status, and systemic symptoms.

Therapeutic approach

- Fewer than 20% are surgical candidates
- If detected at very early stage (single nodule <3cm) or early stage (single nodule <5cm or three nodules each <3cm), resection or ablation or liver transplant may be curative (>70% 5-year survival).
- No bilirubin abnormality
- Minimal portal hypertension
- 50-80% treated lesions recur; 15-20%, post-transplant
- Fever >38.6°C, microvascular invasion, hilar nodes are poor prognostic factors.
- Portal vein invasion excludes liver transplant

Therapeutic approach

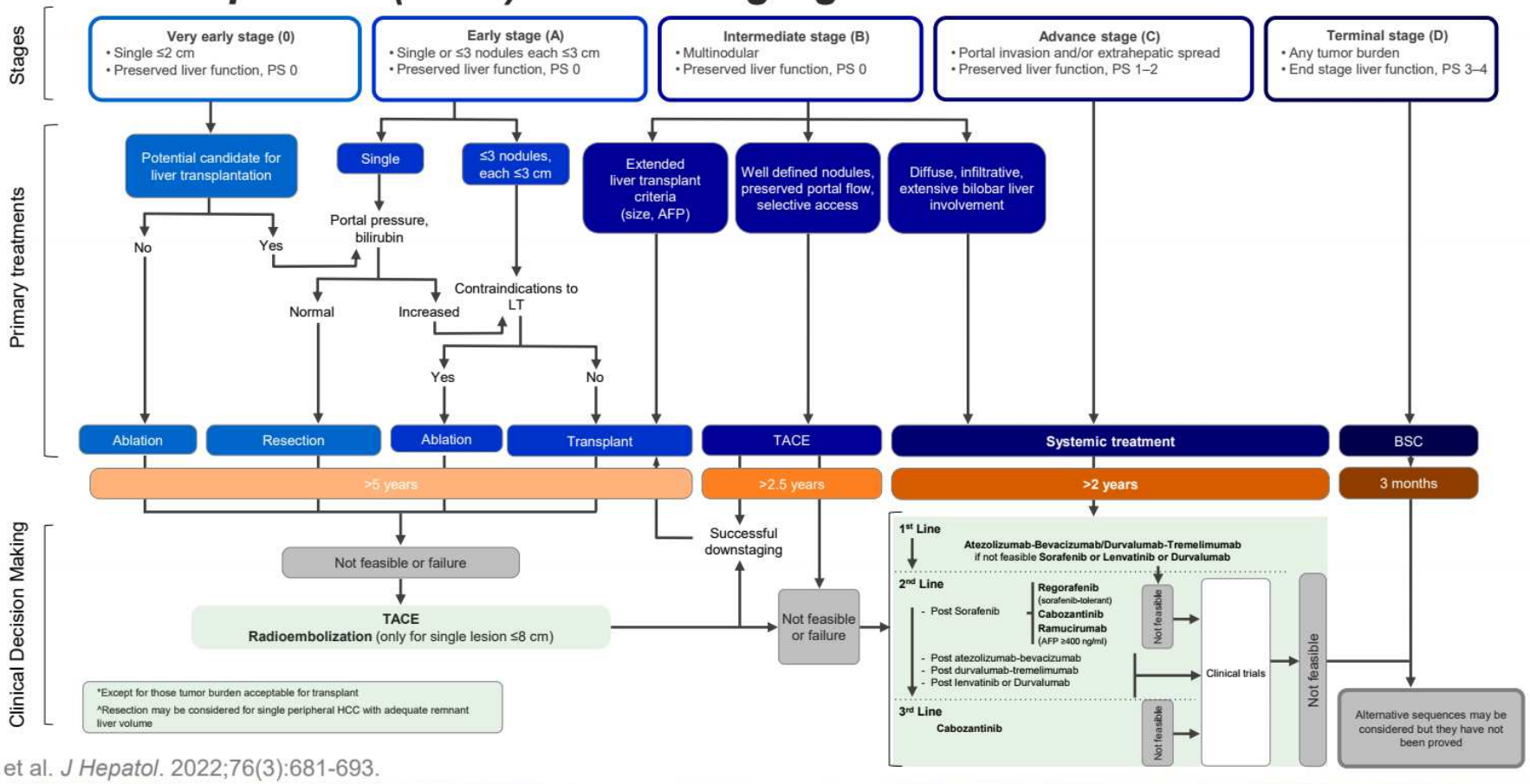
- Tumor is supplied by hepatic artery; liver, by portal vein.
- Multinodular lesions best treated with trans arterial chemoembolization
- 20 month median survival
- Hepatic arterial infusion chemotherapy with 5FU, doxorubicin, and mitomycin-C following gallbladder removal may lead to response in unresectable cases.
- ^{90}Yt also employed as alternative agent for hepatic arterial therapy.

Therapeutic approach

- If portal invasion, metastases, or nodal involvement, atezolizumab with bevacizumab is superior to single agent sorafenib or levantinib (tyrosine kinase inhibitors) as is durvalumab with tremelimumab
- Post-sorafenib, regorafenib, cabozantinib, or ramucirumab as second line therapy
- Must have failed sorafenib
- Ramucirumab effective if AFP>400 ng/ml
- Ipilimumab with pembromizulab as second line therapy
- Lung is most common site of metastasis

Potential Treatment Strategy

The Updated (2022) BCLC Staging and Treatment Guidance



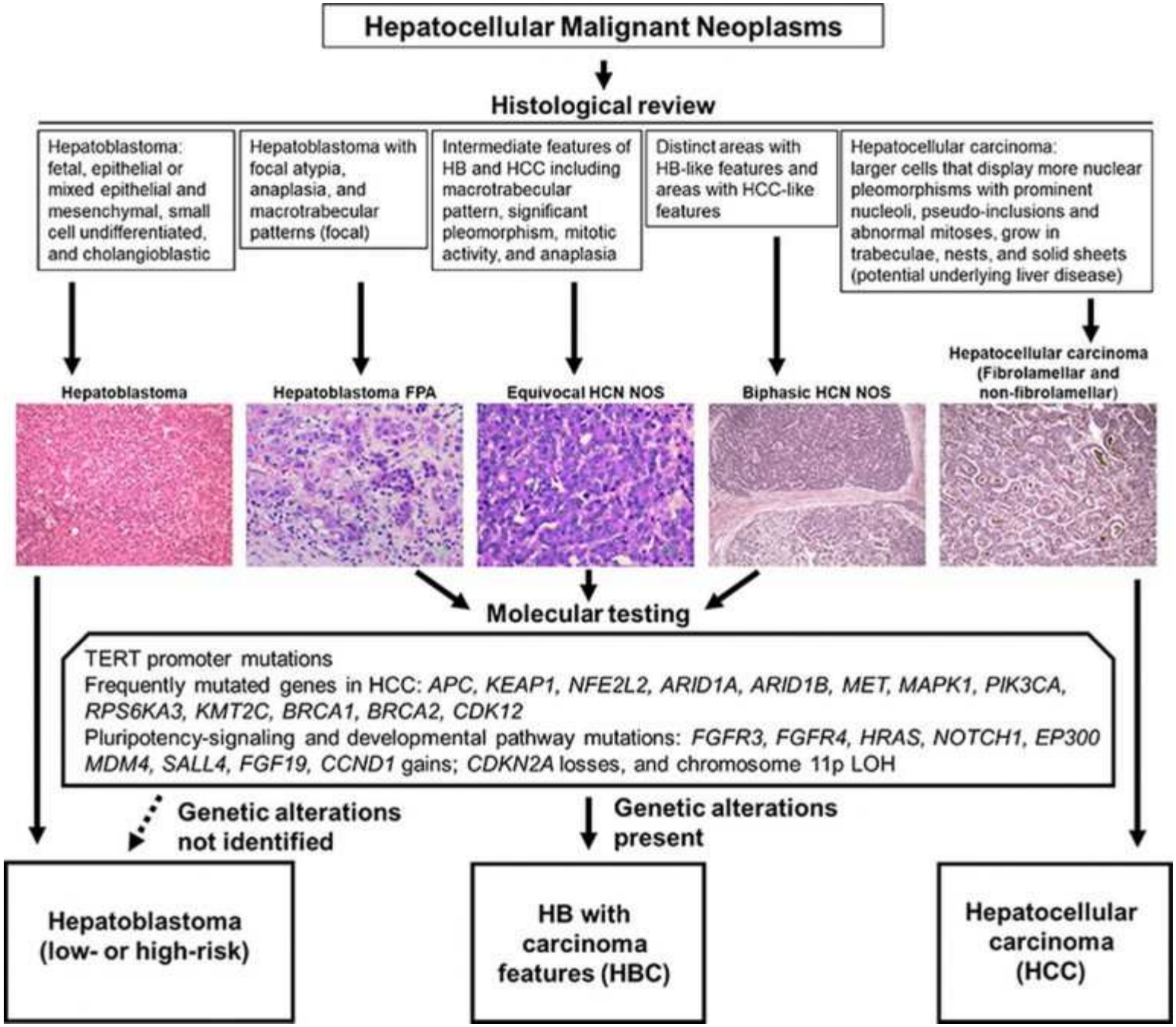
Reig M, et al. *J Hepatol*. 2022;76(3):681-693.

Hepatoblastoma

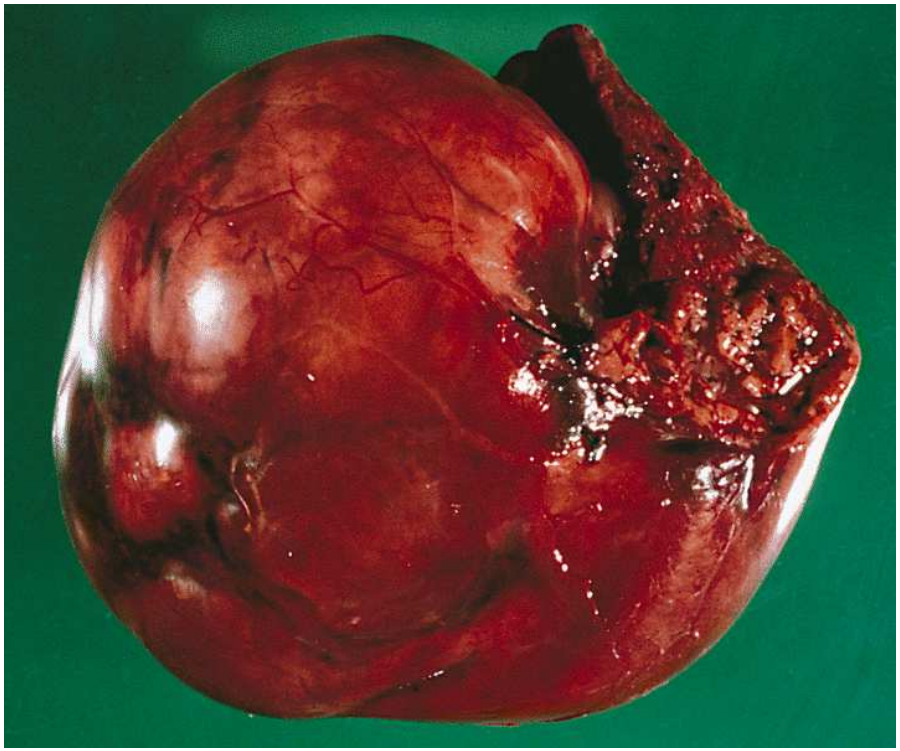
- Most common liver tumor in children.
- Peak age, 3 years.
- Hepatocellular cancer incidence varies little with age from birth to 19 years of age
- Single mass. 60-65% involve right lobe.
- No evidence of cirrhosis.
- Survival rate 70% after resection (25% if hepatocellular cancer).
- Elevated AFP.
- 11p15.5 allele loss (as in Beckwith-Wiedemann syndrome).
- 2% of hepatoblastoma patients have hemi-hypertrophy.

Hepatoblastoma

- Associated with familial adenomatous polyposis as the tumor has mutations in the Wnt/β-catenin gene.
- FOXG1, a regulator of TGF-β pathway, highly expressed in hepatoblastoma.
- Epithelial type composed of fetal or embryonal cells forming acini, tubules, or papillary structures recapitulating liver development.
- Foci of mesenchymal differentiation seen in mixed type.
- Advanced stage disease treated with cisplatin, vincristine, 5FU or cisplatin, doxorubicin chemotherapy followed by resection if possible.
- Resection associated with survival.


Hepatocellular Malignant Neoplasms
Histological review
Hepatoblastoma: fetal, epithelial or mixed epithelial and mesenchymal, small cell undifferentiated, and cholangioblastic
Hepatoblastoma with focal atypia, anaplasia, and macrotrabecular patterns (focal)
Intermediate features of HB and HCC including macrotrabecular pattern, significant pleomorphism, mitotic activity, and anaplasia
Distinct areas with HB-like features and areas with HCC-like features
Hepatocellular carcinoma: larger cells that display more nuclear pleomorphisms with prominent nucleoli, pseudo-inclusions and abnormal mitoses, grow in trabeculae, nests, and solid sheets (potential underlying liver disease)
Hepatoblastoma
Hepatoblastoma FPA
Equivocal HCN NOS
Biphasic HCN NOS
Hepatocellular carcinoma (Fibrolamellar and non-fibrolamellar)
Molecular testing
TERT promoter mutations
Frequently mutated genes in HCC: APC, KEAP1, NFE2L2, ARID1A, ARID1B, MET, MAPK1, PIK3CA, RPS6KA3, KMT2C, BRCA1, BRCA2, CDK12
Pluripotency-signaling and developmental pathway mutations: FGFR3, FGFR4, HRAS, NOTCH1, EP300 MDM4, SALL4, FGF19, CCND1 gains; CDKN2A losses, and chromosome 11p LOH
Genetic alterations not identified
Genetic alterations present
Hepatoblastoma (low- or high-risk)
HB with carcinoma features (HBC)
Hepatocellular carcinoma (HCC)

Hepatoblastoma

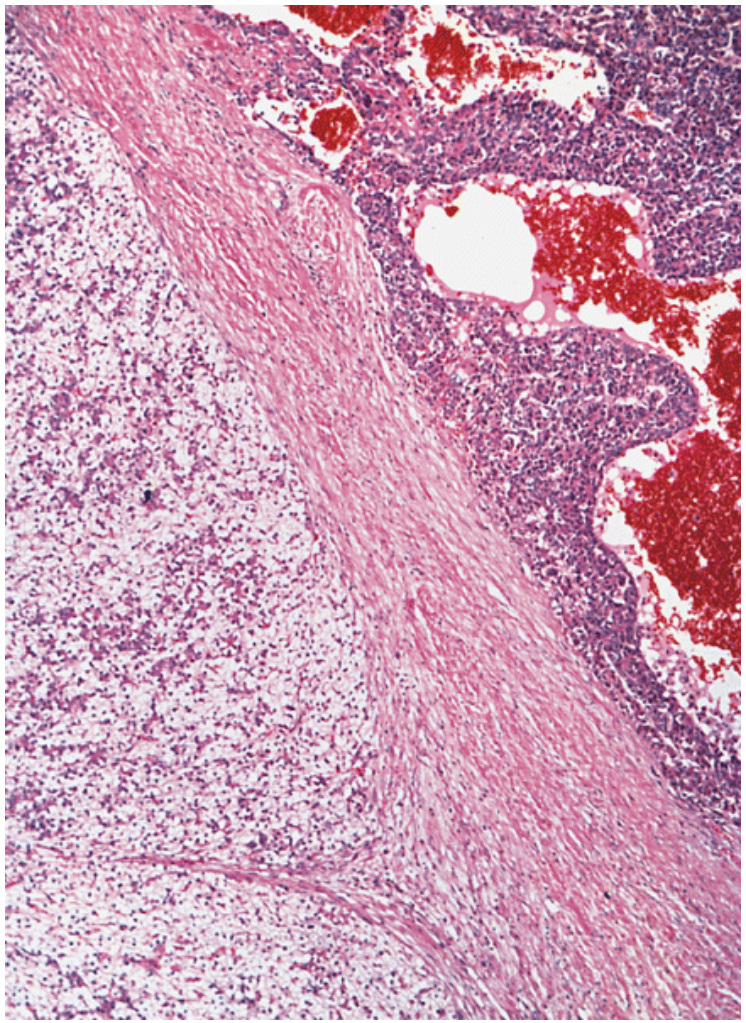


The external surface shows a bulging, red-tan mass resected from the right lobe, which displays an intact smooth capsule traversed by many blood vessels.

Fig. 6-1

Ishak, KG, Goodman, ZD, Stocker, JT. “Tumors of the liver and intrahepatic bile ducts.” Atlas of Tumor Pathology, Third Series, Fascicle 31. Armed Forces Institute of Pathology, Washington, D.C. 2001.

Hepatoblastoma



Fetal epithelial cells with a high cytoplasmic lipid concentration (bottom left) are separated by a band of fibrous connective tissue from a vascular mass of more "immature" appearing embryonal cells (top right).

Fig. 6-14

Ishak, KG, Goodman, ZD, Stocker, JT. “Tumors of the liver and intrahepatic bile ducts.” Atlas of Tumor Pathology, Third Series, Fascicle 31. Armed Forces Institute of Pathology, Washington, D.C. 2001.

Angiosarcoma

- Associated with 25 - 42% associated with exposure to androgen steroids, arsenic, Thorotrast, vinyl chloride.
- Patients with exposure to Thorotrast or vinyl chloride may have synchronous cholangiocarcinoma or hepatocellular carcinoma
- Cases with above known causes usually have latent period of 20 - 35 years, are accompanied by fibrosis or cirrhosis, have precursor conditions of hypertrophy and atypia of hepatocytes and sinusoidal lining cells but are histologically similar to idiopathic cases

Angiosarcoma

- 75% men, usually age 50+ years; rare in children
- Nonoperative biopsy may cause severe bleeding and death
- Most patients die within 6 months from hepatic failure or intra-abdominal bleeding
- Metastasizes widely, often to lung (vinyl chloride cases usually don't have distant metastases)

Angiosarcoma

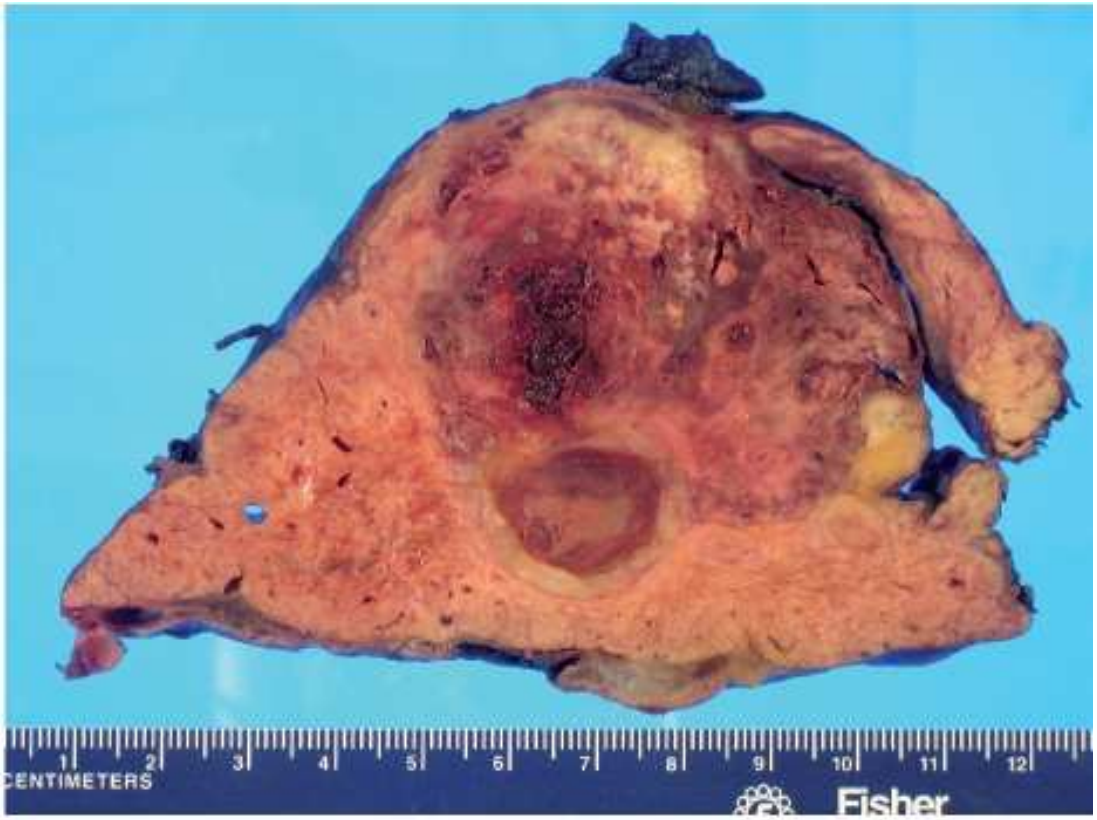
- Multicentric, involves right and left lobes
- Diffusely infiltrative, hemorrhagic and gray white solid nodules with blood filled cavities
- Thorotrast associated tumors have subcapsular hepatic and splenic deposits of yellow chalky material

Angiosarcoma

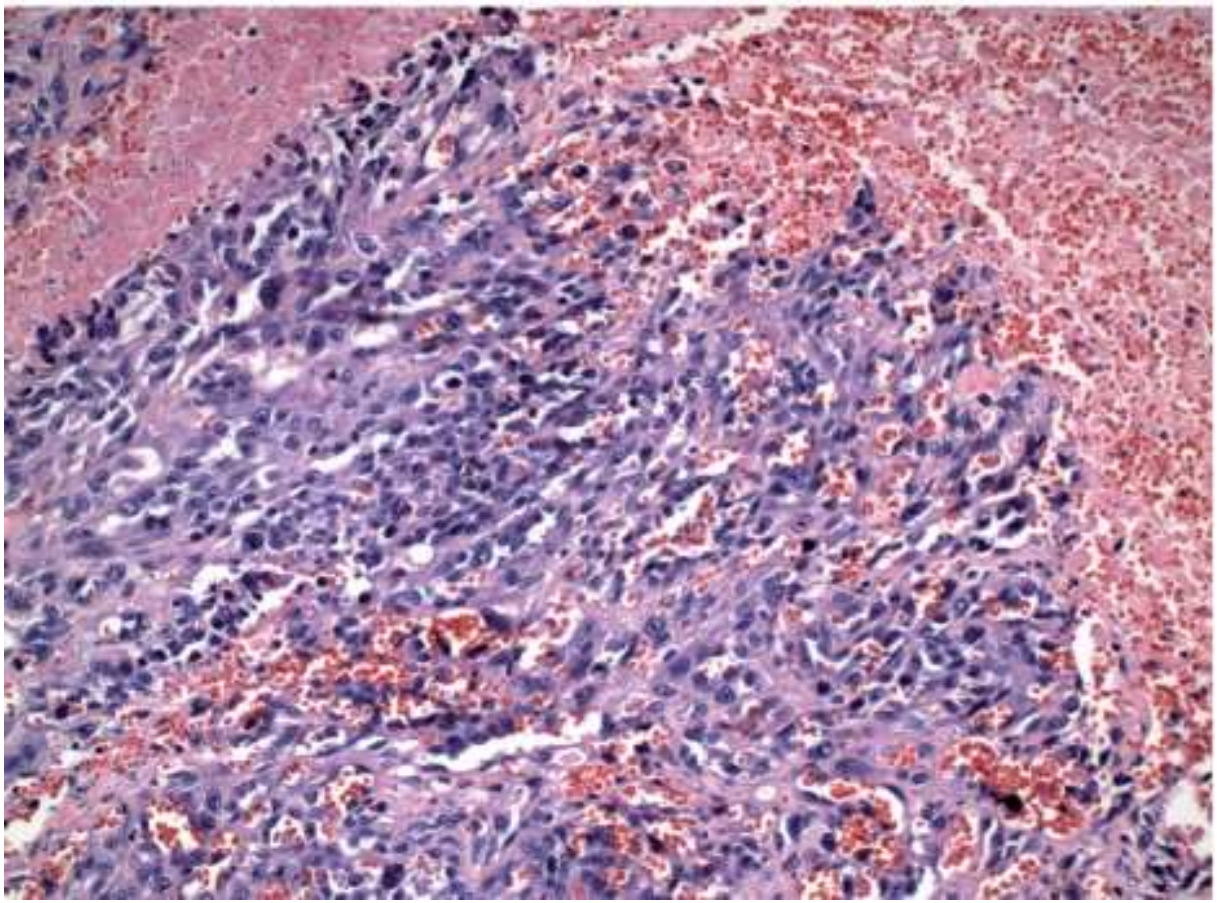
- Tumor composed of infiltrative, freely anastomosing vascular channels
- Tumor cells grow along sinusoids adjacent to hepatic cords
- Tumor cells have abundant, pale eosinophilic cytoplasm, poorly defined cell borders, are usually pleomorphic with hyperchromatic nuclei but may be only mildly atypical

Angiosarcoma

- Also variably prominent nucleoli, blood filled cavities present are lined by tumor cells that may be papillary
- 75% have vascular invasion of portal or hepatic vein branches; frequent mitotic activity



Cioffi-Pretti, JL, et al.,
Rare Tumors. 2009 Dec 28; 1(2): e33. doi: 10.4081/rt.2009.e33
Accessed 04/20/2021



Cioffi-Pretti, JL, et al.,
Rare Tumors. 2009 Dec 28; 1(2): e33. doi:
10.4081/rt.2009.e33
Accessed 04/20/2021

Cholangiocarcinoma

- Associated with:
- Fluke infection (Asia)
- Primary sclerosing cholangitis
- HCV infection
- Caroli's disease (congenital fibropolycystic disease of the biliary system).
- Up to 60% of cholangiocarcinoma is perihilar (Klatskin tumor) while 10% are intrahepatic.

Cholangiocarcinoma

- 10% of all hepatic cancers
- 50-70 years of age
- Associated with liver fluke infection in Southeast Asia
- IL-6 overexpression and AKT activation
- IL-6 drives JAK/STAT signaling
- Cholangiocarcinomas do not make bile, but the cells do make mucin.
- The majority occur at the hilum (bifurcation of right and left ducts).

Cholangiocarcinoma

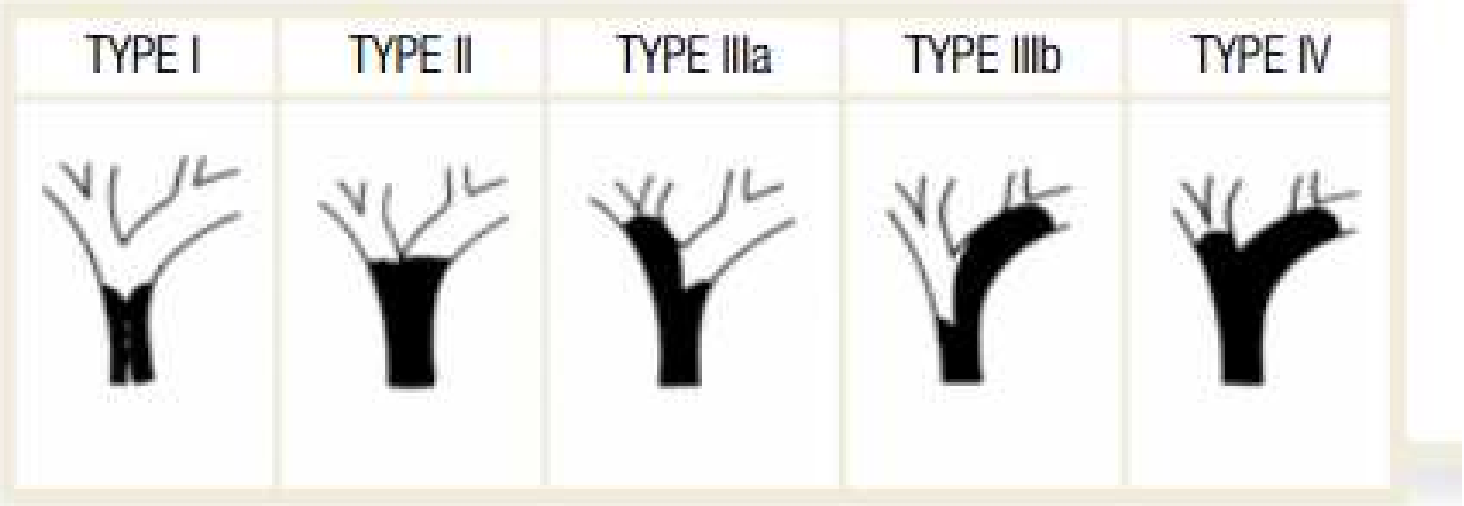
- The anti-apoptotic protein MCL-1 is increased.
- KRAS and TP53 mutations are common
- COX2, ERBB2, C-MET expression increased.
- Amplification of EFGR and diminished function of p16/ink4A have also been noted.
- FGFR2 mutation at 10q26.13 gives rise to a gene fusion product
- Targeted by futibatinimib
- KMT2C mutation at 7q36.1 common in Asians

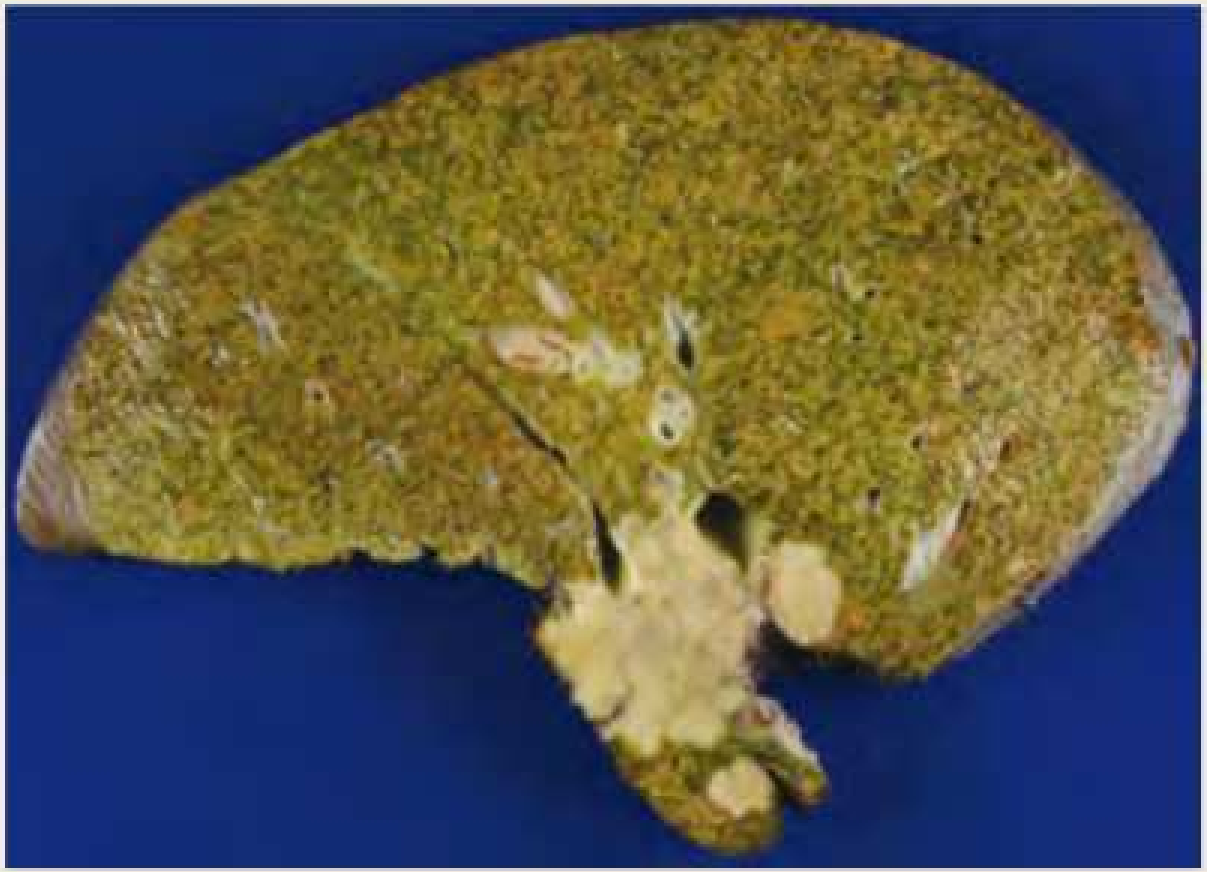
Cholangiocarcinoma

- Extrahepatic origin
- Tumors appear as firm, gray nodules within the bile duct wall; some may be diffusely infiltrative lesions; others are papillary, polypoid lesions.
- Intrahepatic origin
- Occur in the non-cirrhotic liver and may track along the intrahepatic portal tract system creating a branching tumor within a portion of the liver
- 10% exclusively intrahepatic

Cholangiocarcinoma: classification

Bismuth–Corlette classification





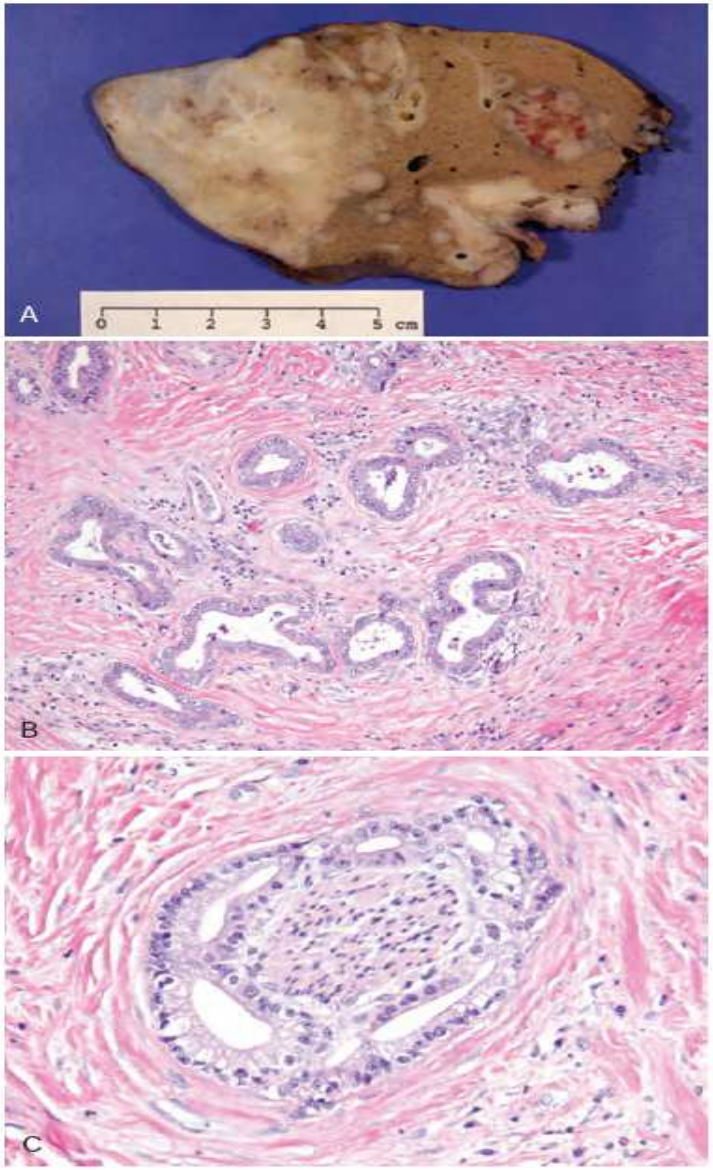
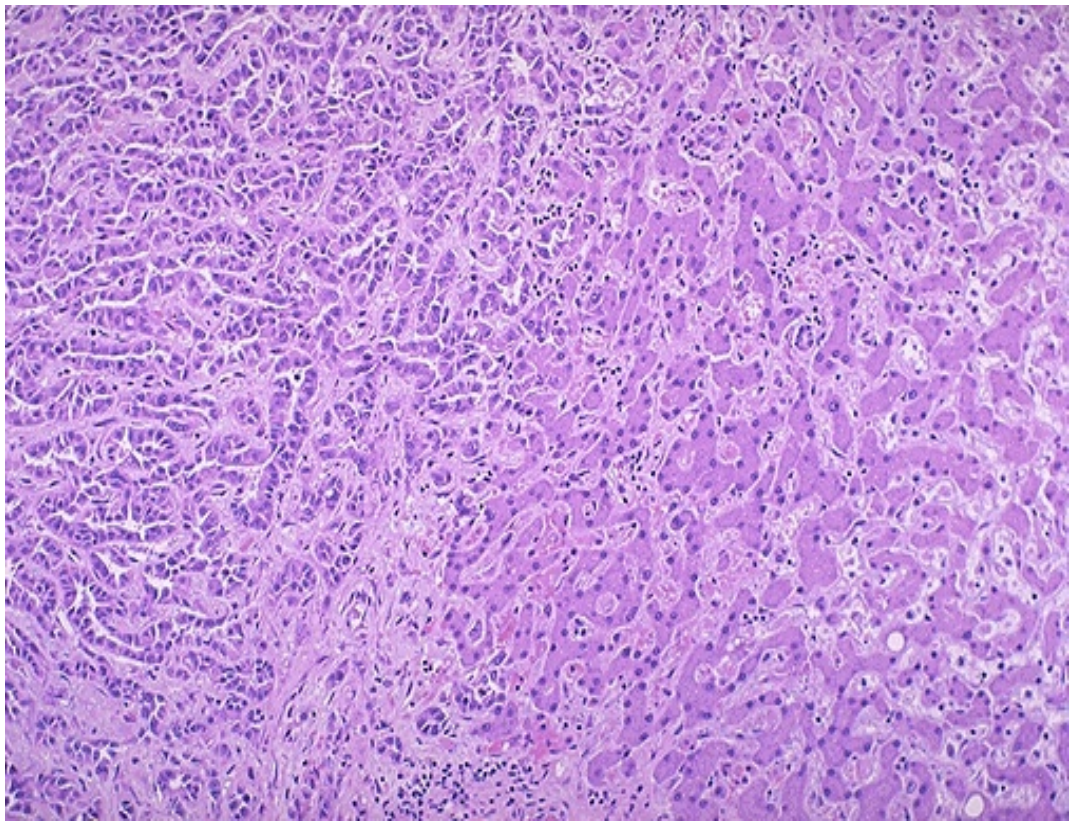


Figure 18-60 Cholangiocarcinoma. **A,** Multifocal cholangiocarcinoma in a liver from a patient with infestation by the liver fluke *Clonorchis sinensis*. **B,** Invasive malignant glands in a reactive, sclerotic stroma. **C,** Perineural invasion by malignant glands, forming a wreathlike pattern around the central, trapped nerve. (**A,** Courtesy Dr. Wilson M.S. Tsui, Caritas Medical Centre, Hong Kong.)

Cholangiocarcinoma



The carcinoma at the left has a glandular appearance that is most consistent with a cholangiocarcinoma.

A liver cancer may have both hepatocellular as well as cholangiolar differentiation.

https://webpath.med.utah.edu/LIVEHTML/LIVER032.html
Accessed 12/10/2019

Arterial supply to pancreas

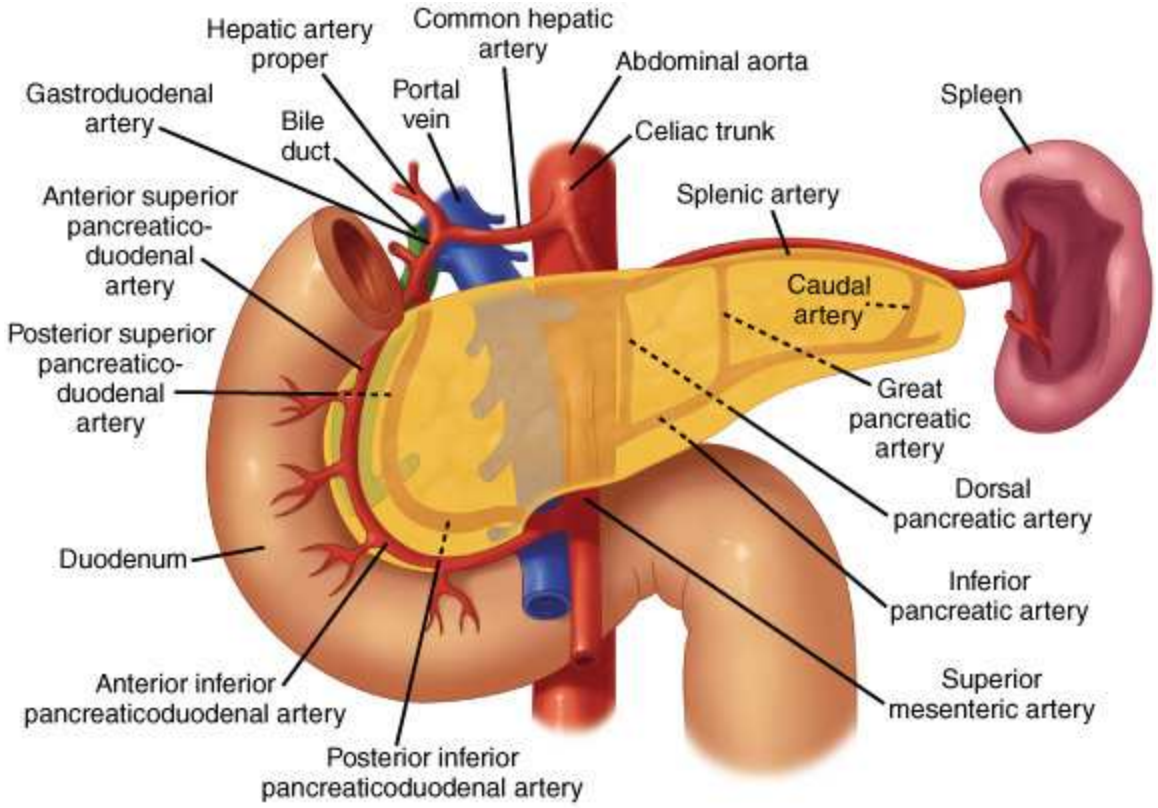
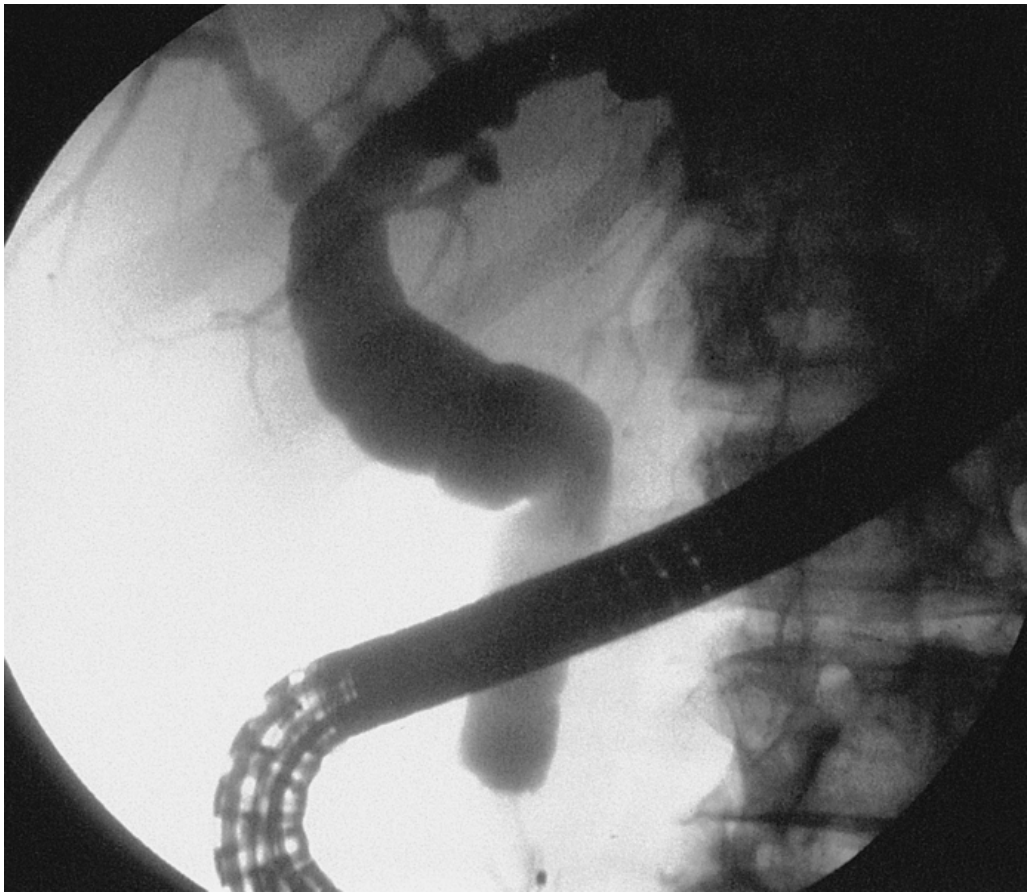


Fig. 33-4 Accessed 02/01/2010

Biliary tract cancer

- Bile duct lesions generally present with obstruction
- Polyps >1cm diameter have the greatest malignant potential.
- MRI-cholangiopancreatography is the optimal imaging procedure to outline local anatomy.
- Porcelain gallbladder can be associated with cancer in 20% of patients.

Bile duct obstruction

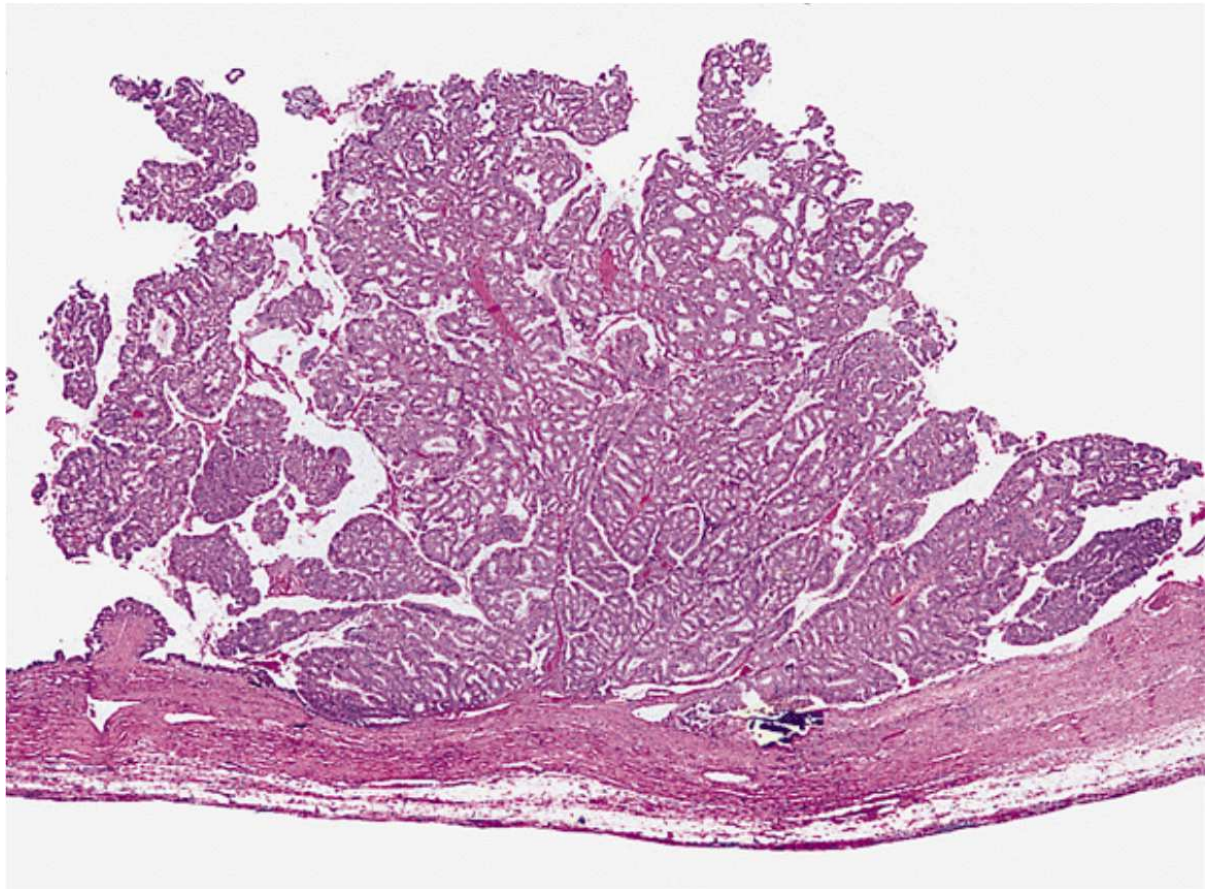


The ERCP reveals a tight, irregular, distal common bile duct stricture caused by a well-differentiated adenocarcinoma.

Fig. 12-4

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Pyloric gland adenoma

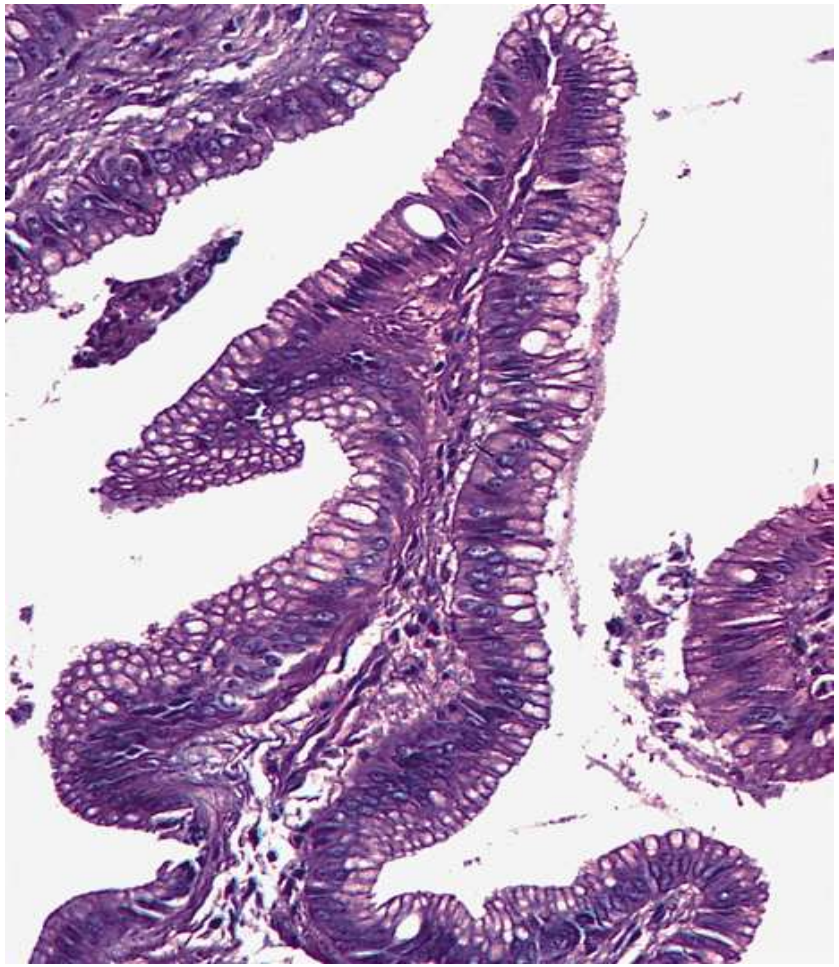


Low- power view of a sessile pyloric gland adenoma containing some dilated glands.

Fig. 3-5L

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Biliary adenoma



A papillary adenoma is composed of fibrovascular stalks that extend outward into the lumen of the gallbladder. They are lined by tall, columnar, mucus- secreting cells.

Fig. 3-19

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Gallbladder adenocarcinoma

- Generally present with pain and right upper quadrant mass.
- 3:1 women
- 50-60 years of age
- Primarily affects the fundus (60%), body (30%) or neck (10%) of gallbladder
- Aggressive cancer, with an overall 5 year survival rate of < 10%
- Cholelithiasis, Salmonella, E. Coli, and H. pylori infections predispose.

Gallbladder adenocarcinoma

- Up to 50% are detected incidentally in routine cholecystectomy specimens due to absence of gross abnormalities
- Peritoneal seeding is uncommon.
- Noninvasive papillary carcinomas, regardless of size and differentiation, do not metastasize
- Invasive papillary carcinomas have the most favorable prognosis

Gallbladder adenocarcinoma

Histologic types:

Biliary type adenocarcinoma

75% of cases:

Intestinal type adenocarcinoma:

Mucinous carcinoma:

Comprised of > 50% extracellular mucin

Clear cell carcinoma:

Sheets of clear cells in an alveolar arrangement separated by blood vessels

Gallbladder adenocarcinoma

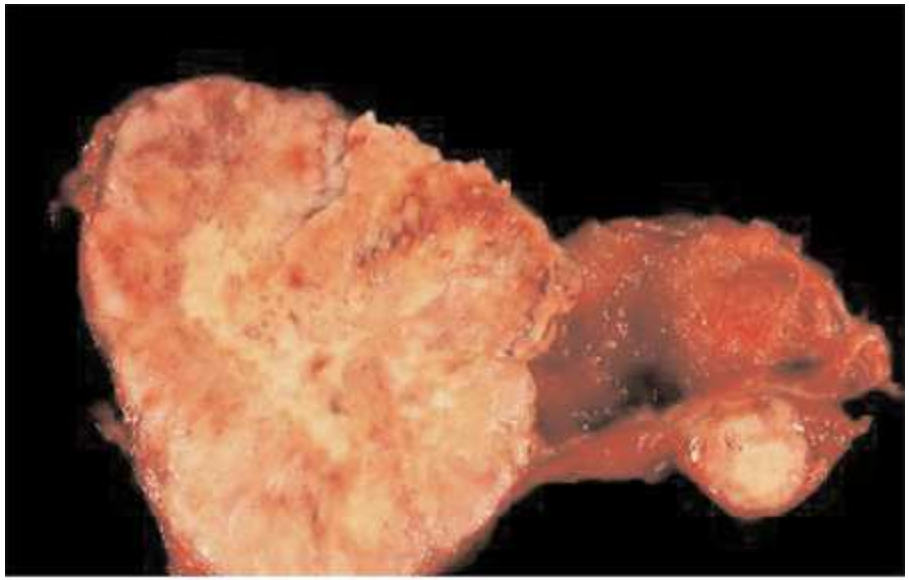
Signet ring cell carcinoma:

Signet ring cells are the predominant or exclusive component

Hepatoid carcinoma:

Sarcomatoid carcinoma (carcinosarcoma)

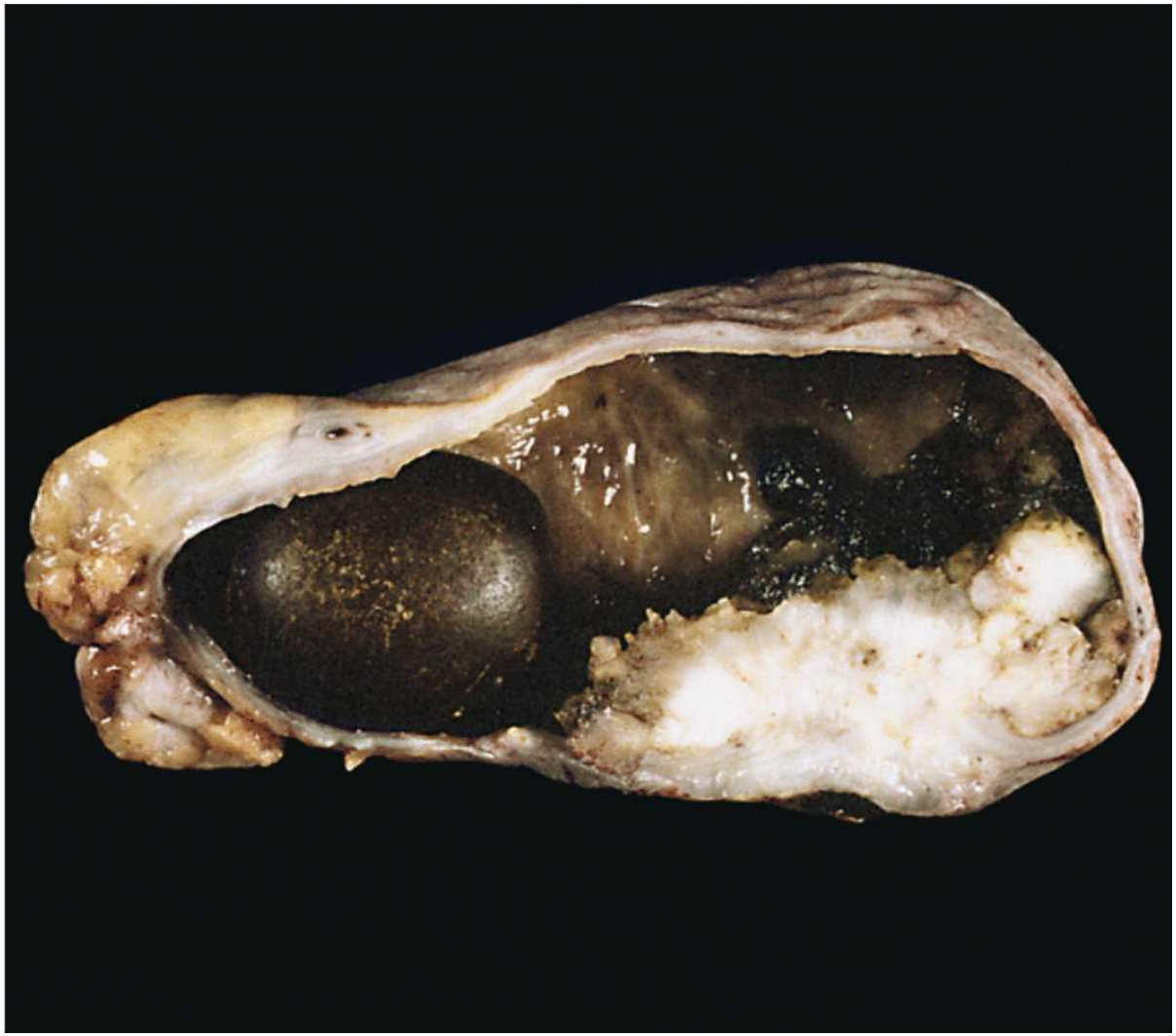
Gallbladder carcinoma



Gallbladder lumen is filled with tumor.

Fig.15-12 Accessed 04/10/2010

Adenocarcinoma



Gallbladder excised for cholelithiasis. A small infiltrating carcinoma was found in a thickened area of the fundus. Early changes may be mistaken for cholecystitis.

Fig. 6-3

Albores-Saavedra, J, Henson DE, Klimstra ,DS, “Tumors of the extrahepatic bile ducts, and ampulla of Vater.” Atlas of Tumor Pathology, Third Series, Fascicle 27. Armed Forces Institute of Pathology, Washington, D.C. 2000.

Treatment of gallbladder adenocarcinoma

- Hilar / portal lymphadenectomy, plus resection of hepatic bed and the common bile duct to achieve negative margins, is necessary for tumors that extend into a muscle or beyond (pT1b - pT3)
- Recurrence common
- High histologic grade (poor differentiation) and vascular invasion have adverse outcomes
- Rokitansky-Aschoff sinus involvement by carcinoma and cystic duct margin status are suspected predictors of progression

Treatment of gallbladder adenocarcinoma

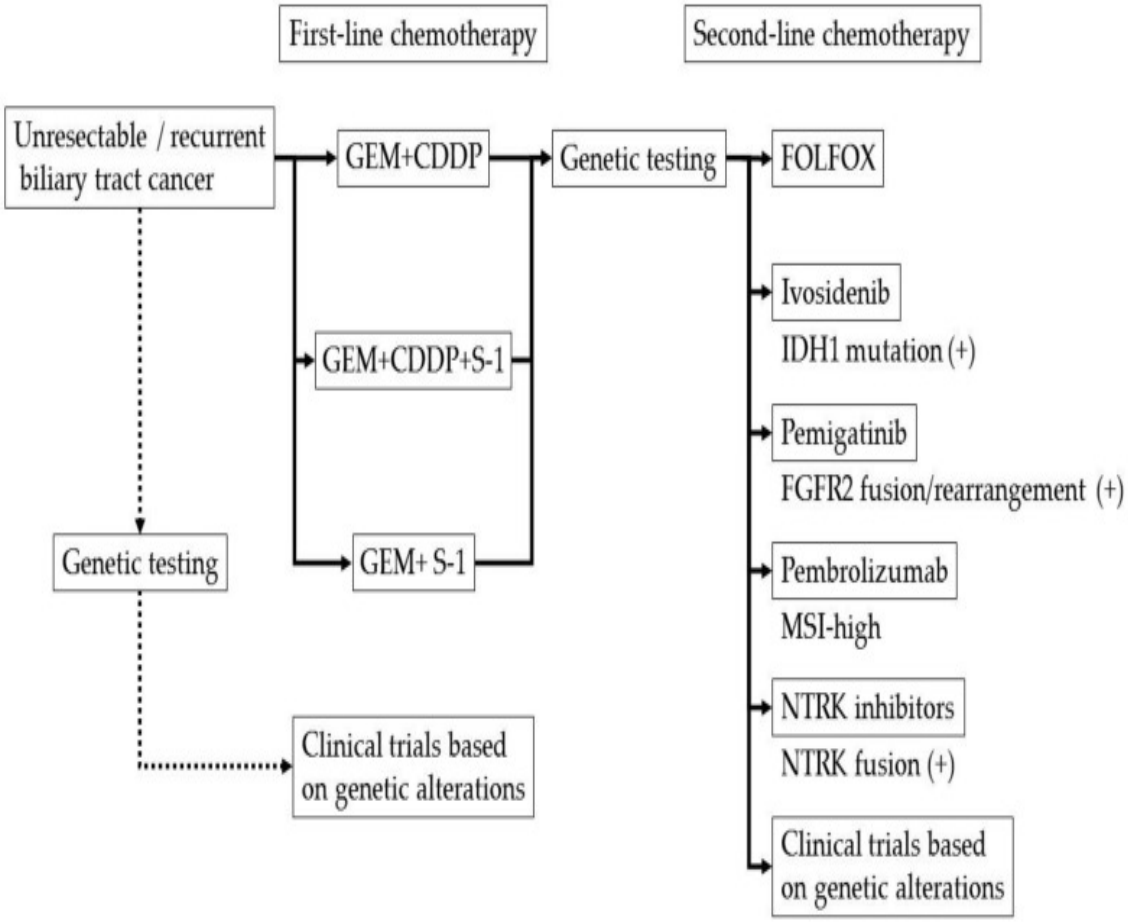
- Chemotherapy or radiation for metastatic tumors
- 20% above bifurcation; else, evenly divided between hepatic and common bile duct.

Treatment approach for biliary tract cancer

- Peritoneal seeding is uncommon
- <30% considered for curative resection
- Intrahepatic disease is treated with resection of involved liver.
- Hilar disease below or reaching the confluence of right and left hepatic ducts is treated with en bloc resection of extrahepatic bile ducts, gallbladder, regional lymph nodes, and a Roux-en-Y hepaticojejunostomy, as well as resection of segments V and IVB of the liver is performed.

Treatment approach for biliary tract cancer

- Tumors occluding the common duct may be stented.
- Else, extended right and left hepatectomy is added to the resection.
- Distal disease is treated with pancreaticoduodenectomy
- Improved results with cisplatin and gemcitabine chemotherapy.


First-line chemotherapy
Second-line chemotherapy
Unresectable / recurrent biliary tract cancer
GEM+CDDP
GEM+CDDP+S-1
GEM+ S-1
Genetic testing
Genetic testing
FOLFOX
Ivosidenib
IDH1 mutation (+)
Pemigatinib
FGFR2 fusion/rearrangement (+)
Pembrolizumab
MSI-high
NTRK inhibitors
NTRK fusion (+)
Clinical trials based on genetic alterations
Clinical trials based on genetic alterations

TRANSPLANT CRITERIA

Transplantation

- Patients with cirrhosis should be referred for transplantation when they develop evidence of hepatic dysfunction (Child-Turcotte-Pugh score ≥7 and MELD score ≥10)
- OR
- When they experience their first major complication (ascites, variceal bleeding, or hepatic encephalopathy).
- Patients with cirrhosis and severe hepatopulmonary syndrome have an extremely poor prognosis and require expedited evaluation.
- Survival without transplant is <2 years.

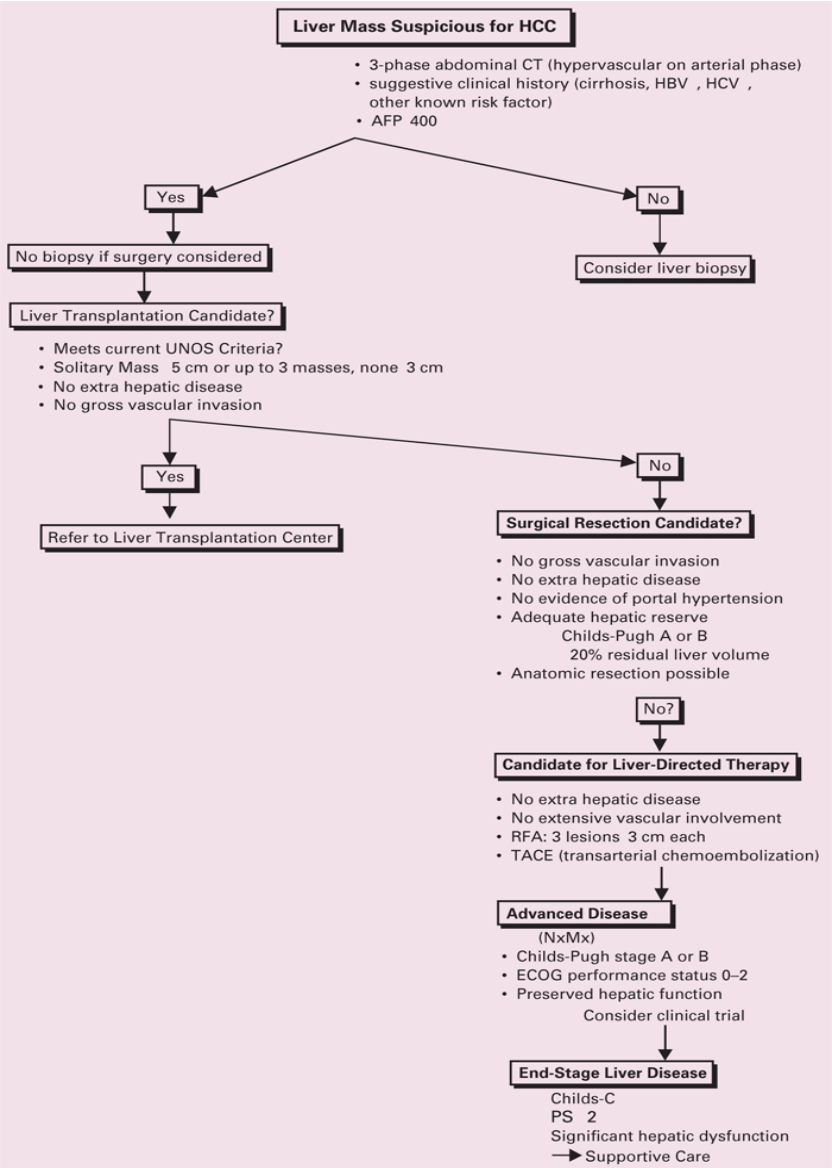
Prognosis and staging

- The Barcelona (BCLC) staging classification is the only classification that provides treatment recommendations for each of the assigned stages (early, intermediate, advanced, end-stage) based on best treatment options currently available.
- It has been validated in Europe, Asia, and the US.

Prognosis and staging

- The BCLC is based on:
- Tumor size
- Number of tumor nodules
- The presence of portal vein thrombosis
- Liver function
- Child-Pugh score
- Portal hypertension
- Bilirubin level
- Performance status
- Systemic symptoms.

Strategy



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

Fig. 15-13 Accessed 04/10/2010

Child-Turcotte-Pugh score

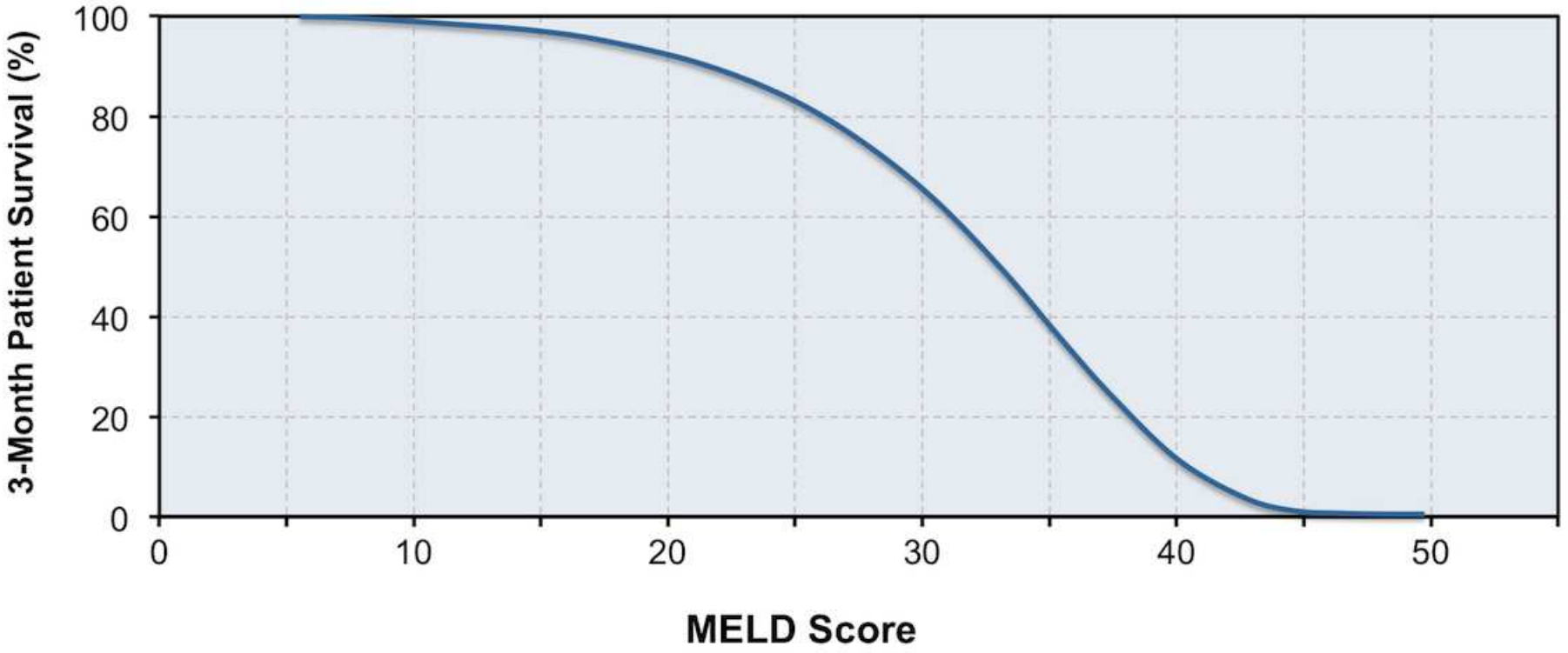
Measure	1 point	2 points	3 points
Total bilirubin, (mg/dL)	(<2)	(2–3)	(>3)
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (seconds) OR	<4.0	4.0–6.0	> 6.0
INR	<1.7	1.7–2.3	> 2.3
Ascites	None	Mild (or diuretic responsive)	Moderate to severe (or refractory)
Hepatic encephalopathy	None	Grade I–II	Grade III–IV

CTP score is obtained by adding the score for each parameter
CTP class: A = 5-6 points B = 7-9 points C = 10-15 points

CPT Class and survival

Points	Class	Three month mortality	One-year survival	Two-year survival
5–6	A	4%	84%	78%
7–9	B	11%	89%	81%
10–15	C	40%	45%	35%

Estimated 3-Month Survival Based on MELD Score



https://www.hepatitisc.uw.edu/go/management-cirrhosis-related-complications/liver-transplantation-referral/core-concept/all#timing-cirrhosis-related-liver-transplantation-use-prognostic-scoring-systems

Accessed 12/30/2019

MELD score and survival

MELD Score	Mortality
≤9	1.9%
10–19	6.0%
20–29	19.6%
30–39	52.6%
≥40	71.3%

- The survival rate at 3 years is 78 percent
- The survival rate at 3 years is 72 percent at 5 years
- The survival rate at 20 years is about 53 percent.

MELD score

- Candidates who are at least 12 years old receive an initial MELD(i) score equal to:
- $MELD(i) = 0.957 \times \ln(Cr) + 0.378 \times \ln(bilirubin) + 1.120 \times \ln(INR) + 0.643$
- Then, round to the tenth decimal place and multiply by 10.
- If MELD(i) > 11, perform additional MELD calculation as follows:
- $MELD = MELD(i) + 1.32 \times (137 - Na) - [\, 0.033 \times MELD(i) \times (137 - Na)\,]$

MELD score

- Additional rules:
- All values in US units (Cr and bilirubin in mg/dL, Na in mEq/L, and INR unitless).
- If bilirubin, Cr, or INR is <1.0, use 1.0.
- If any of the following is true, use Cr 4.0:

  Cr >4.0.

  ≥2 dialysis treatments within the prior 7 days.

  24 hours of continuous veno-venous hemodialysis (CVVHD) within the prior 7 days.
- If Na <125 mmol/L, use 125. If Na >137 mmol/L, use 137.
- Maximum MELD = 40.

Caveats

- The following conditions are automatically assigned a MELD Score of 22, with a 10% increase in score every 3 months from diagnosis.
- Hepatocellular carcinoma (HCC) with one lesion between 2 - 5 cm or two to three lesions <3 cm (Milan criteria), provided no vascular invasion or extrahepatic disease.
- Hilar cholangiocarcinoma

Caveats

- Hepato-pulmonary syndrome with PaO_2 <60 mmHg on room air.
- Porto-pulmonary hypertension, with mean pulmonary artery pressure (mPAP) >25 mmHg at rest but maintained <35 mmHg with treatment.
- Hepatic artery thrombosis 7–14 days post-liver transplantation.
- Cystic fibrosis with FEV1 (forced expiratory volume in 1 second) <40%.

Caveats

- Familial amyloid polyneuropathy, as diagnosed by identification of the transthyretin (TTR) gene mutation by DNA analysis or mass spectrometry in a biopsy sample and confirmation of amyloid deposition in an involved organ.
- Primary hyper-oxaluria with evidence of alanine glyoxylate aminotransferase deficiency
- Initial score of 28 with a 10% increase in score every 3 months from diagnosis.
- These patients require combined liver-kidney transplantation

PELD score

- PELD Score = 0.480 x Ln bilirubin + 1.857 x Ln (INR) -0.687 x Ln albumin + 0.436 if the patient is less than 1 year old
- If the patient is 1-2 years-old, and has >2sd evidence of growth failure, add 0.667 to the score.
- Multiply the score by 10 and round to the nearest whole number.
- Laboratory values less than 1.0 are set to 1.0 for the purposes of the PELD score calculation