Fundamental Liver Pathology

Part 2

APPROVED

Diana Cardona, MD

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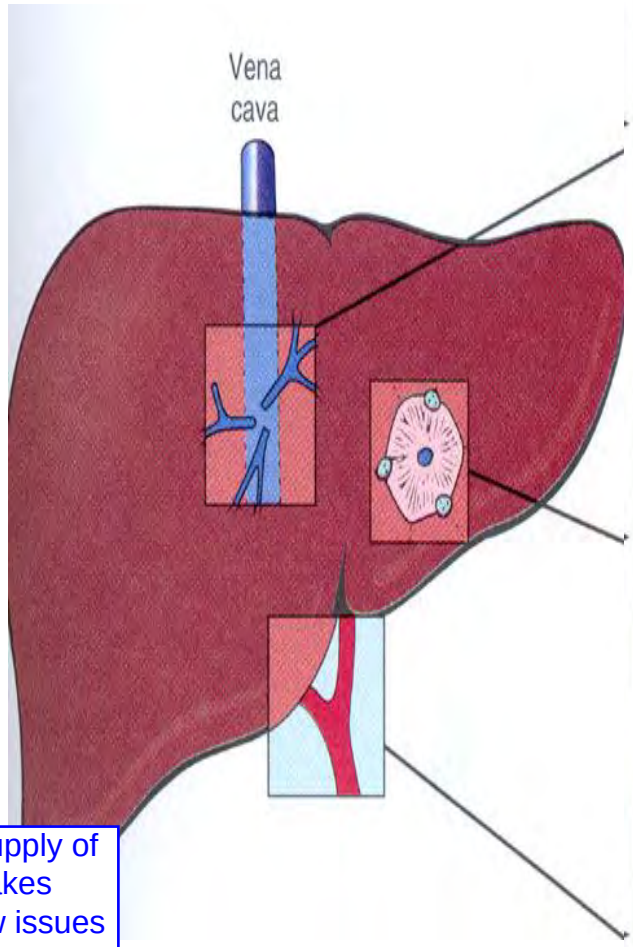
I've also included some notes from First Aid 2010 on the slides. They'll be in these red boxes :)

Vascular Injury

Could involve venous problems with hepatic vein outflow or even with CHF causing backup into the liver

- Hepatic Venous Outflow Compromise
  - Budd-Chiari
  - Veno-Occlussive Disease
- Impaired Blood Flow Through the Liver
  - Passive Congestion
  - Cirrhosis
- Impaired Blood Flow Into the Liver
  - Hepatic Artery or Portal Vein compromise
  - Thrombosis

The dual supply of the liver makes blood inflow issues to the liver relatively uncommon



The more downstream the obstruction is, the more severe the injury is

Budd-Chiari

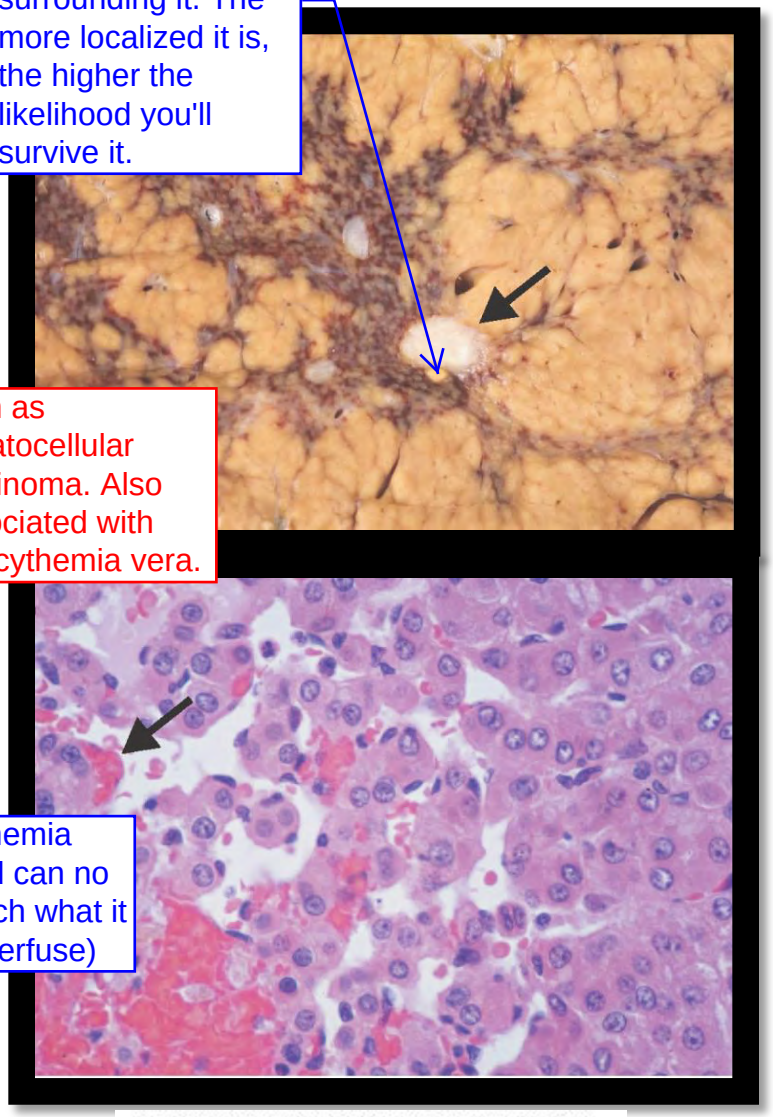
- Hepatic vein thrombosis syndrome
  - Associated with conditions of increased thrombotic tendency (pregnancy, intra-abdominal cancer)
  - 30% of cases are idiopathic
  - High mortality rate
- Morphology:
  - Centrilobular congestion and sinusoidal dilatation
  - Centrilobular necrosis

This is a thrombus that is more localized. It has a lot of necrosis surrounding it. The more localized it is, the higher the likelihood you'll survive it.

such as hepatocellular carcinoma. Also associated with polycythemia vera.

because blood can no longer exit liver

due to ischemia (new blood can no longer reach what it needs to perfuse)



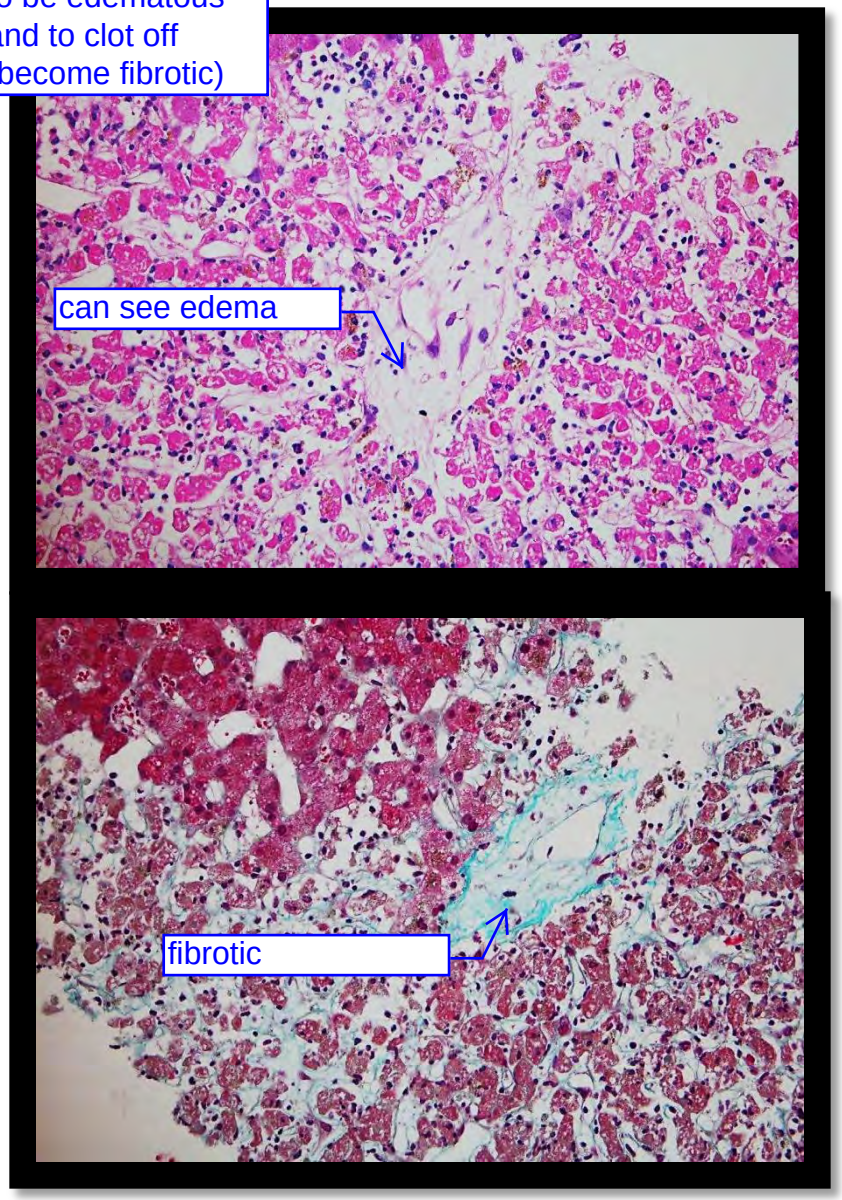
From First Aid 2010: Budd-Chiari: Occlusion of IVC or hepatic veins -->congestive liver disease (hepatomegaly, ascites, abdominal pain, and eventual liver failure). May develop varices and have visible abdominal and back veins. Absence of JVD.

Veno-Occlussive Disease

also problems with blood exiting the liver

- AKA- Sinusoidal Obstruction Syndrome
  - Originally associated with Jamaican bush-tea
  - Now associated with BM transplant and chemo/radiation
  - Mortality rate is up to 30%
- Morphology:
  - Central venous areas have swollen endothelium and collagen deposition
  - Eventual venous obliteration and associated hepatocellular ishemia

cause central vein to be edematous and to clot off (become fibrotic)



Passive Congestion

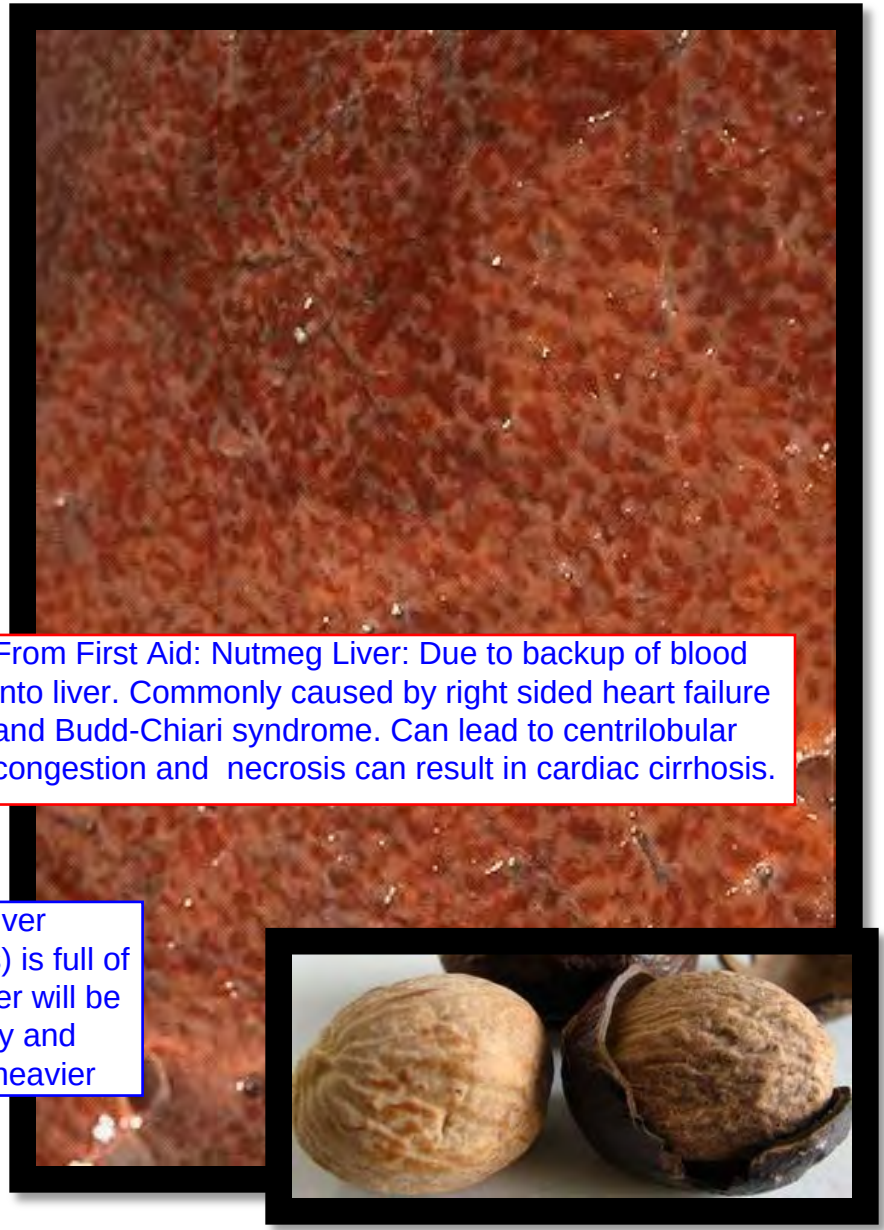
problems with blood flow in the liver and exiting the liver

- Chronic right sided heart failure leads to chronic passive congestion
  - Morphology:
    - Centrilobular sinusoidal congestion
    - Liver plate atrophy

- If left sided heart failure also occurs:

when heart failure worsens

  - Gross:
    - "Nutmeg liver"
  - Morphology:
    - Centrilobular hemorrhagic necrosis



From First Aid: Nutmeg Liver: Due to backup of blood into liver. Commonly caused by right sided heart failure and Budd-Chiari syndrome. Can lead to centrilobular congestion and necrosis can result in cardiac cirrhosis.

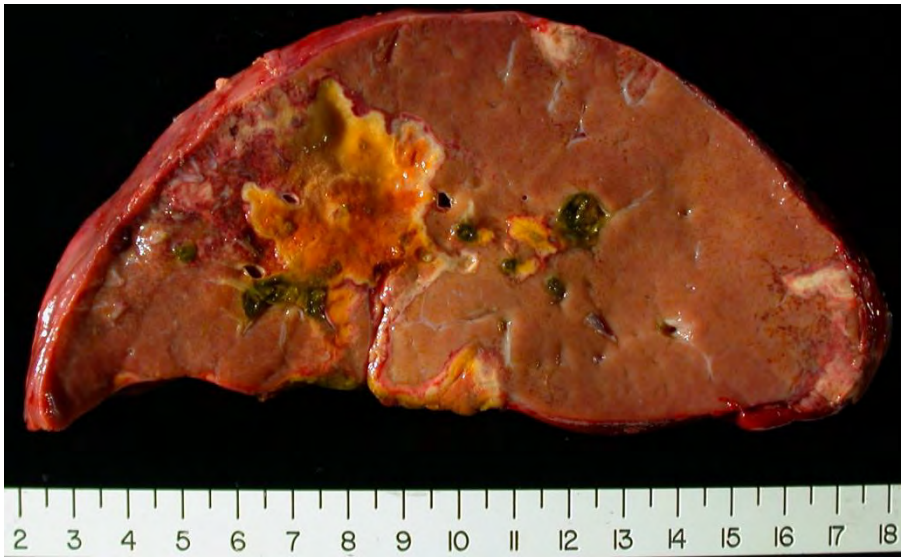
because liver (sinusoids) is full of blood - liver will be very boggy and enlarged/heavier

Impaired Inflow of Blood

very rare

- Hepatic artery obstruction
  - Infarcts to liver are rare because of dual blood supply
    - i.e. following liver transplant hepatic artery thrombosis may cause infarction and loss of organ

      can result in fulminant hepatic necrosis and failure and require another transplant
- Portal vein obstruction
  - Manifests as symptoms of portal hypertension: esophageal varices, splenomegaly
    - i.e. metastatic tumor causing hilar lymph node enlargement and compression of the portal vein



Regeneration and Fibrosis

- Following injury, the liver has the ability to regenerate back to its normal state.
- However, with repeated injury, inflammation and/or toxic insult fibrous tissue is formed.
  - Initially, fibrosis may form in the portal tracts, central veins, and/or within the sinusoids.
  - With time, fibrous strands can link regions of the liver (portal-portal, portal-central), this is called **bridging fibrosis**
  - With continued liver injury, the liver becomes subdivided into nodules of regenerative hepatocytes surrounded by the fibrous tissue-- c**irrhosis**.
- Grossly, cirrhosis can be described as micronodular (nodules <3 mm in size) or macronodular.

which can become nodules of fibrosis

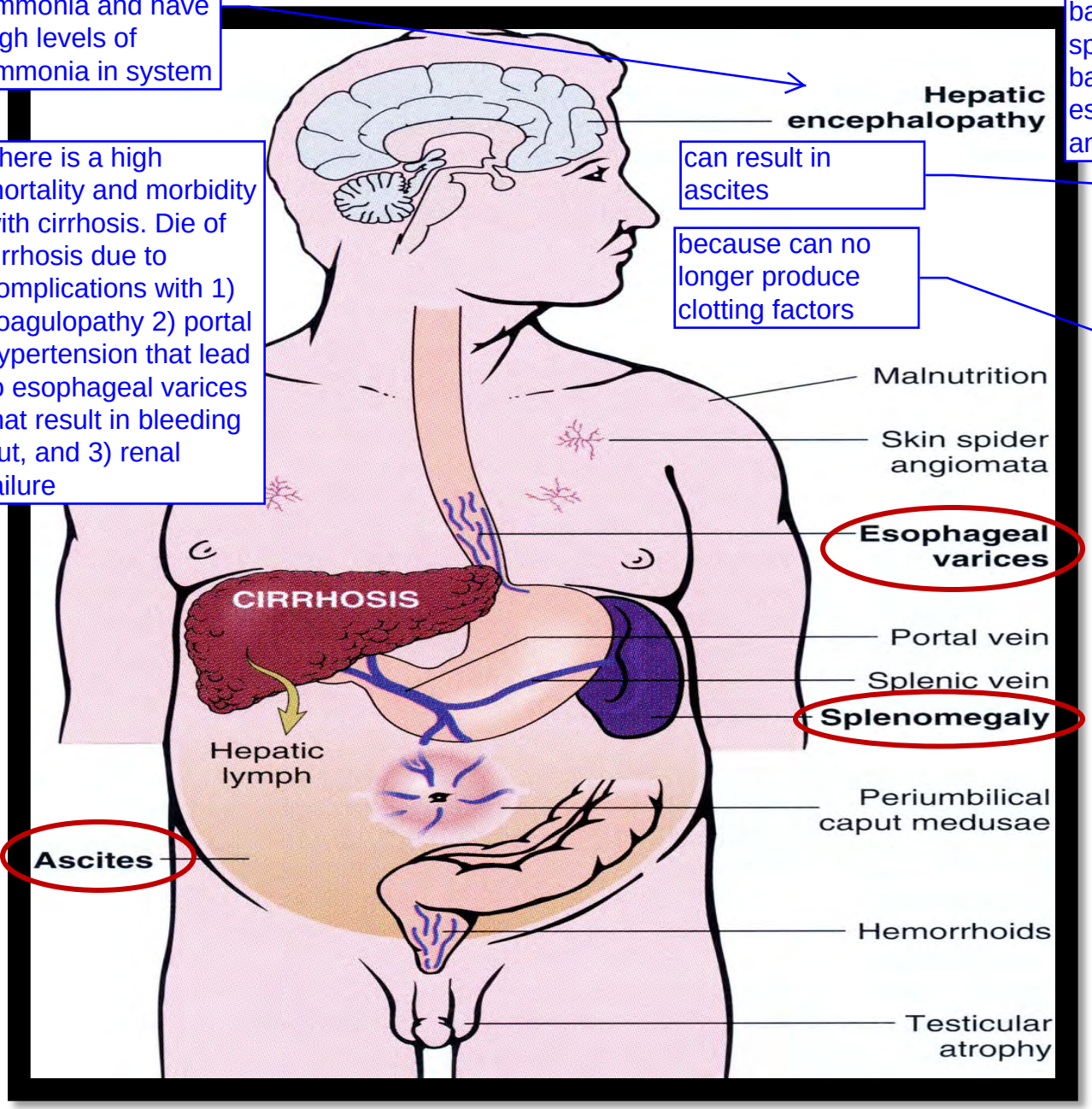
macronodular is more common

Clinical Consequences

because cannot metabolize ammonia and have high levels of ammonia in system

With cirrhosis, blood flow can't go into liver normally because everything is fibrotic -->backup into portal vein --> backup into splenic vein -->backup into spleen --> backup into GI tract --> backup into esophagus (can develop esophageal varices and hemorrhoids in an attempt to get blood back to heart.)

There is a high mortality and morbidity with cirrhosis. Die of cirrhosis due to complications with 1) coagulopathy 2) portal hypertension that lead to esophageal varices that result in bleeding out, and 3) renal failure



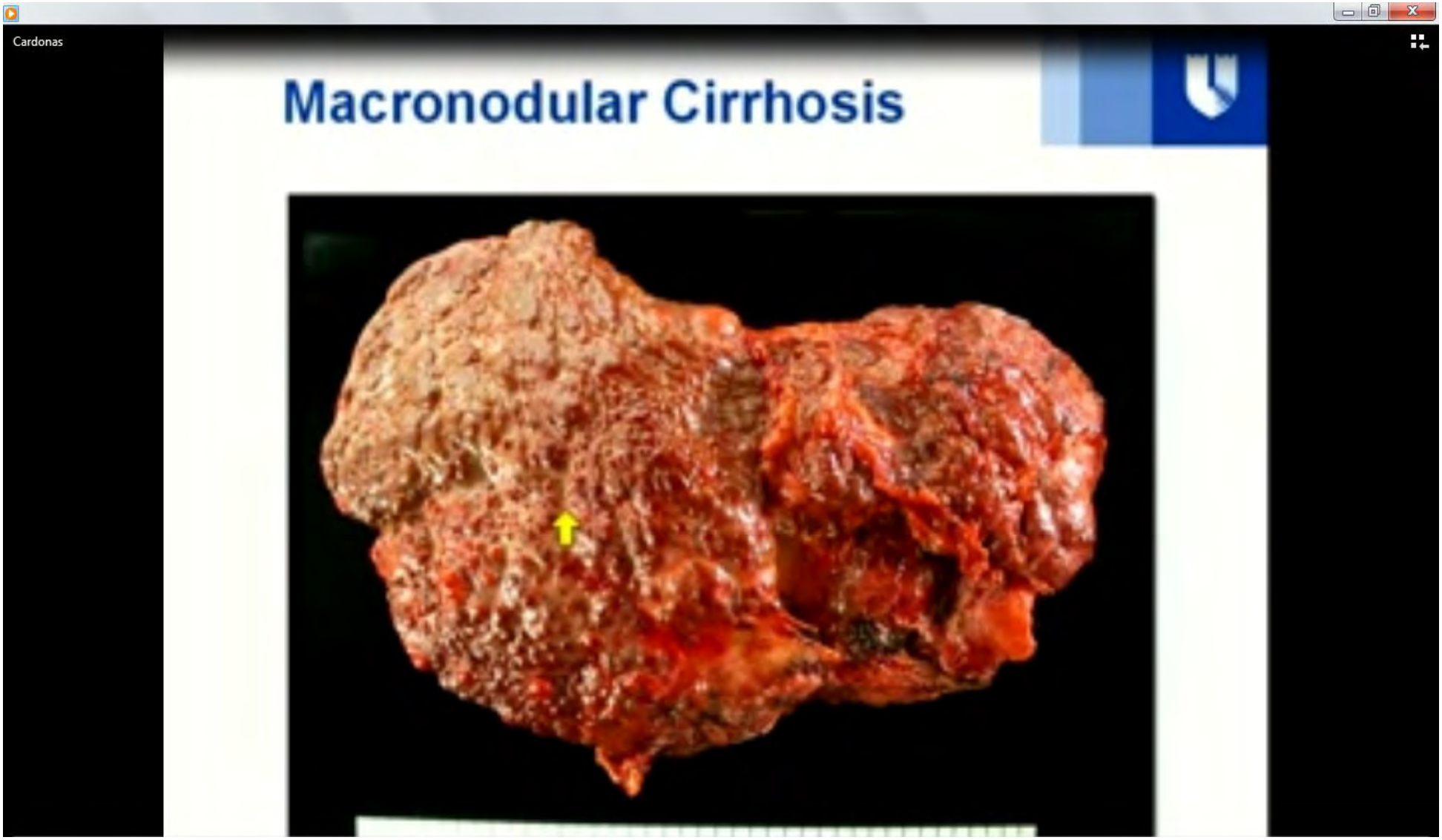
can result in ascites

because can no longer produce clotting factors

- Portal HTN
  - Shunts
- Coagulopathy
- Hepatorenal syndrome
- Hepatopulomary syndrome
- Marked risk of **hepatocellular carcinoma**

#1 risk of hepatocellular carcinoma is cirrhosis

With cirrhosis, you also reduce albumin production

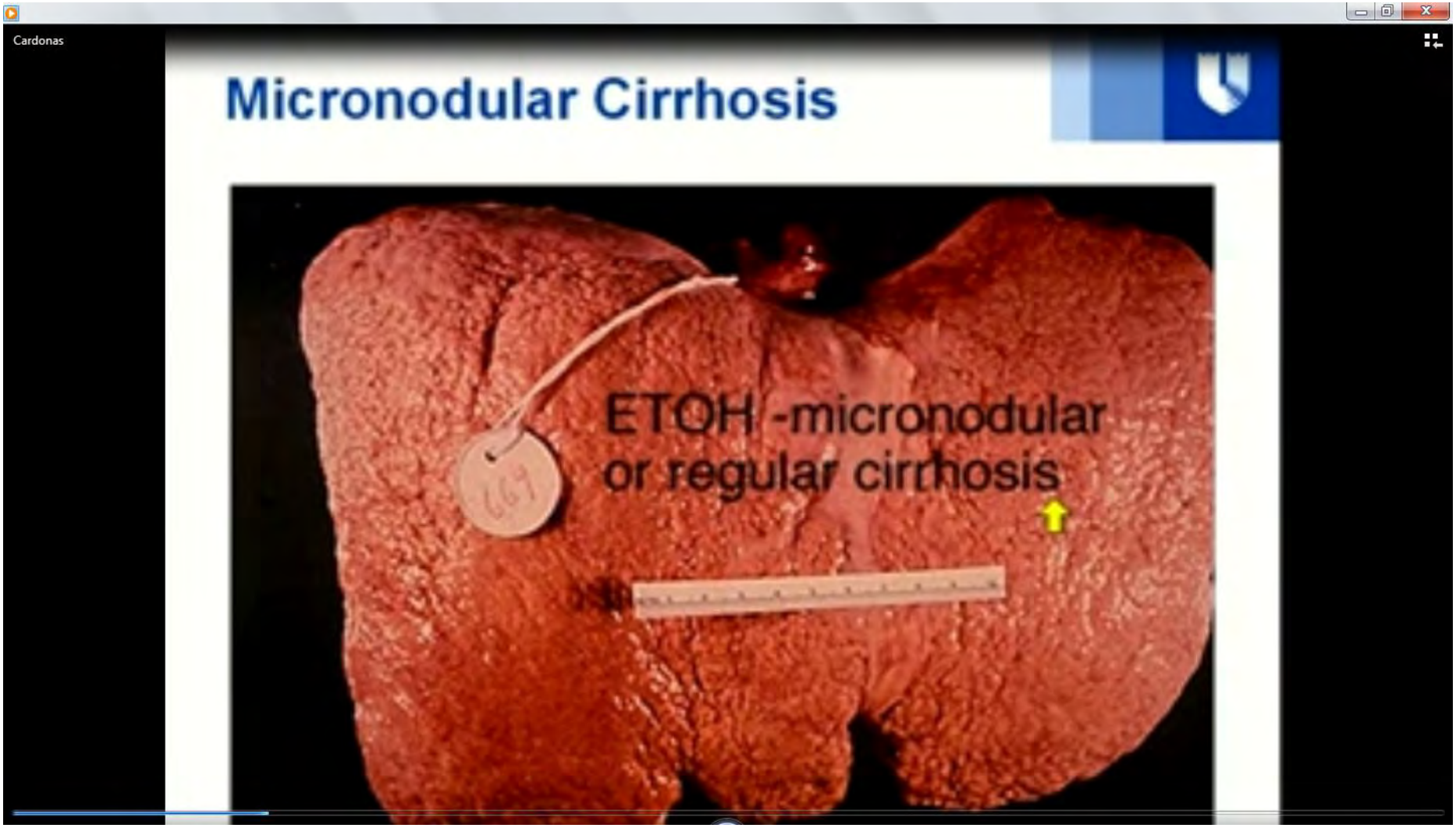


the liver is lumpy bumpy

Macronodular Cirrhosis

can see the variability of nodular size, large nodules

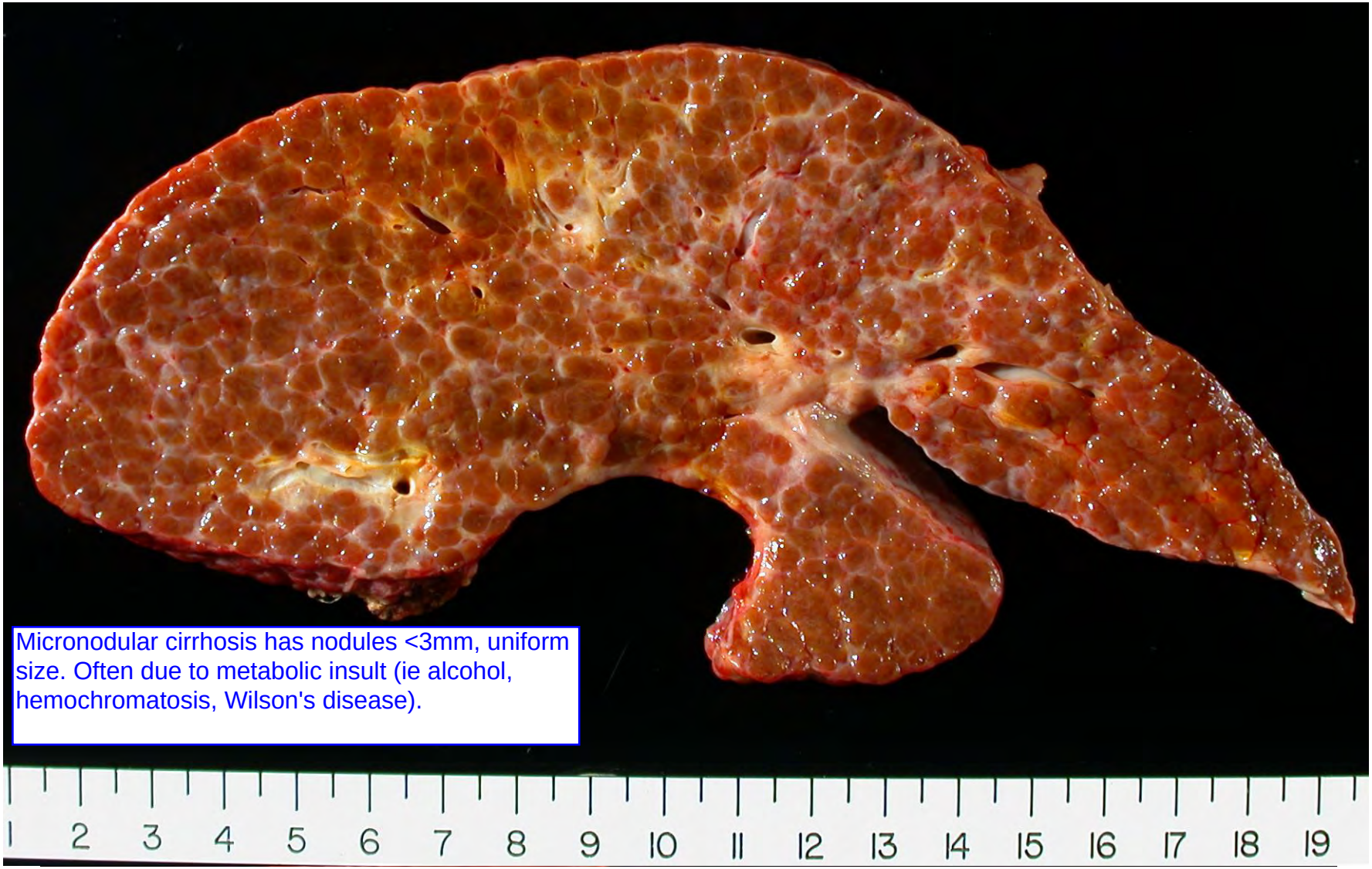
Macronodular cirrhosis usually has nodules >3mm, varied size. Usually due to significant liver injury leading to hepatic necrosis (ie postinfectious or drug-induced hepatitis). Carries increased risk of hepatocellular carcinoma



finely nodular throughout the capsule, looks irregular

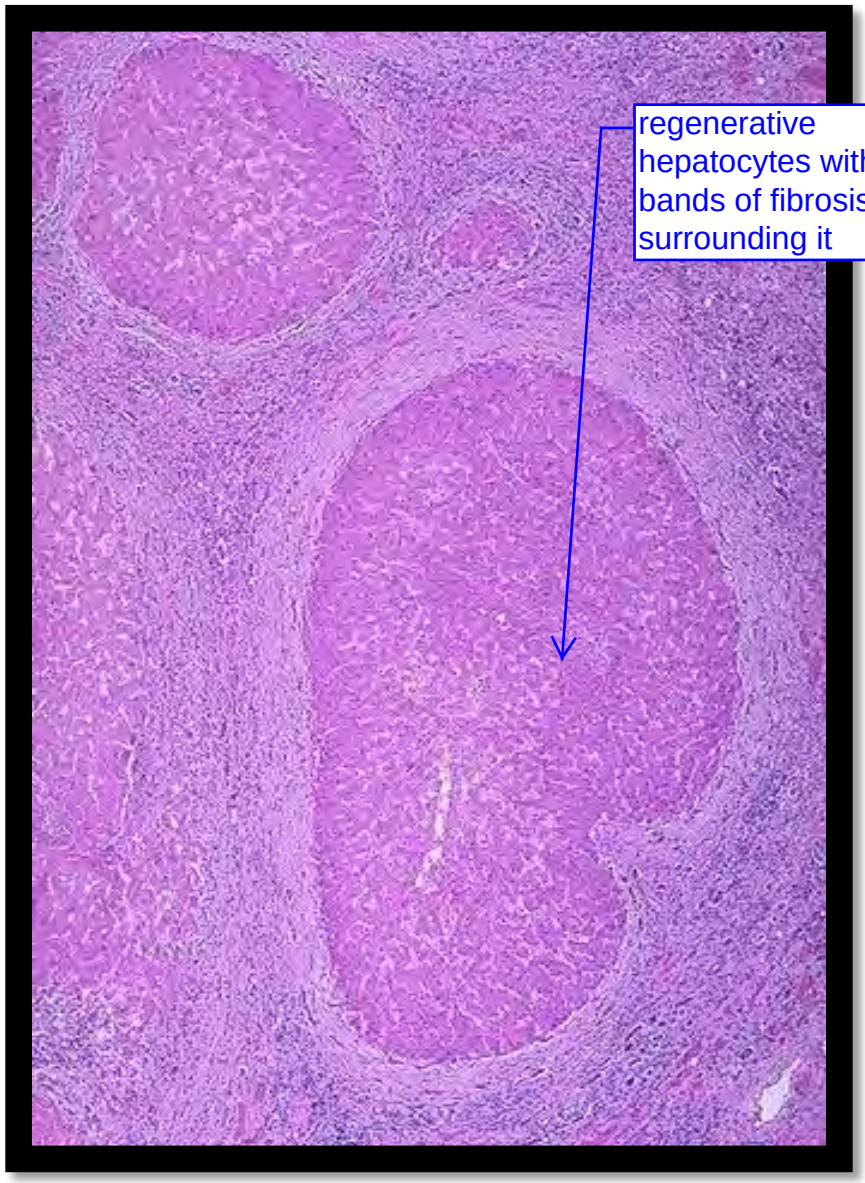
Micronodular Cirrhosis

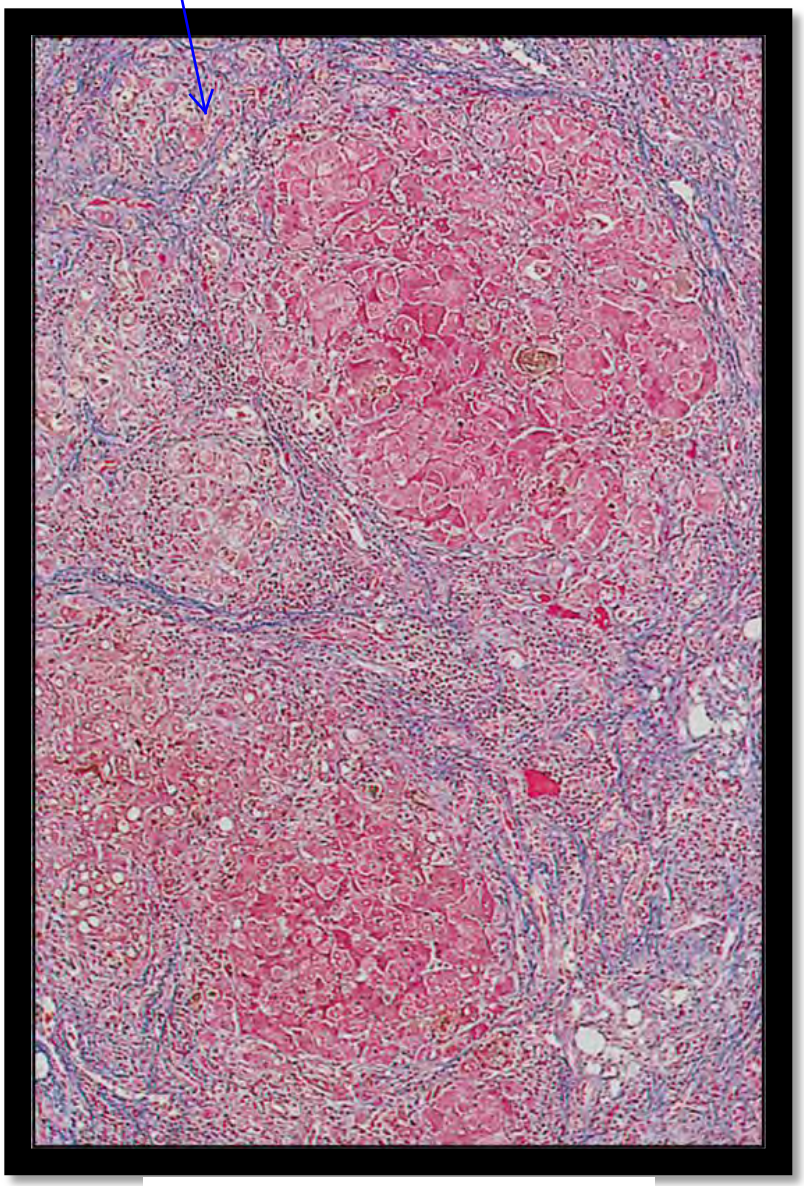
much smaller nodules throughout the parenchyma



Micronodular cirrhosis has nodules <3mm, uniform size. Often due to metabolic insult (ie alcohol, hemochromatosis, Wilson's disease).

Cirrhosis





See page at the end for a chart comparing the major ddx for some of these tumors

Liver Tumors

only going through ones in bold

Benign

- Bile Duct Hamartoma
- Bile Duct Adenoma
- Cysts
- Focal Nodular Hyperplasia
- Hepatic Adenoma
- *Regenerative Nodules*
- *Angiomyolipoma*
- *Vascular Tumors*
- *Psuedotumors*

Malignant

- Hepatocellular carcinoma
- Cholangiocarcinoma
- Hepatoblastoma
- Metastatic cancer
- *Mucinous Cyst*
- *Mesenchymal tumors*
- *Lymphoma*
- *Sarcoma*

Bile Duct Hamartoma

benign

hamartoma - = abnormal proliferation of normal tissue

- Due to a malformation of the ductal plate

ductal plate = limiting plate (area of transformation of bile duct to canals of Hering to canalicular spaces)
From Wiki: The ring of hepatocytes abutting the connective tissue of the triad is called the limiting plate.

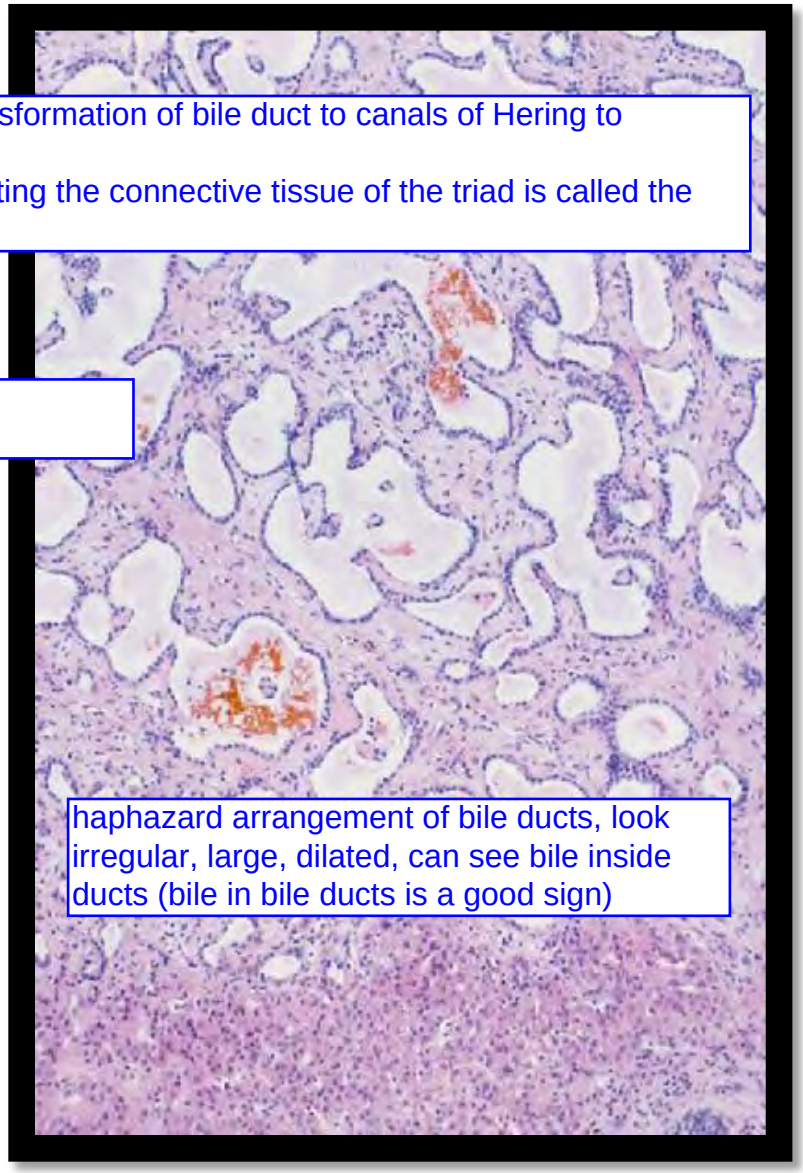
  - AKA- von Meyenburg complex
  - Spectrum of polycystic disease versus sporadic

part of polycystic liver, kidney, pancreatic

  - Usually incidental lesions that are small (< 0.5 cm) and commonly multifocal

asymptomatic

- Consist of small-medium sized bile ductules, variably dilated with inspisated bile and dense collagen



haphazard arrangement of bile ducts, look irregular, large, dilated, can see bile inside ducts (bile in bile ducts is a good sign)

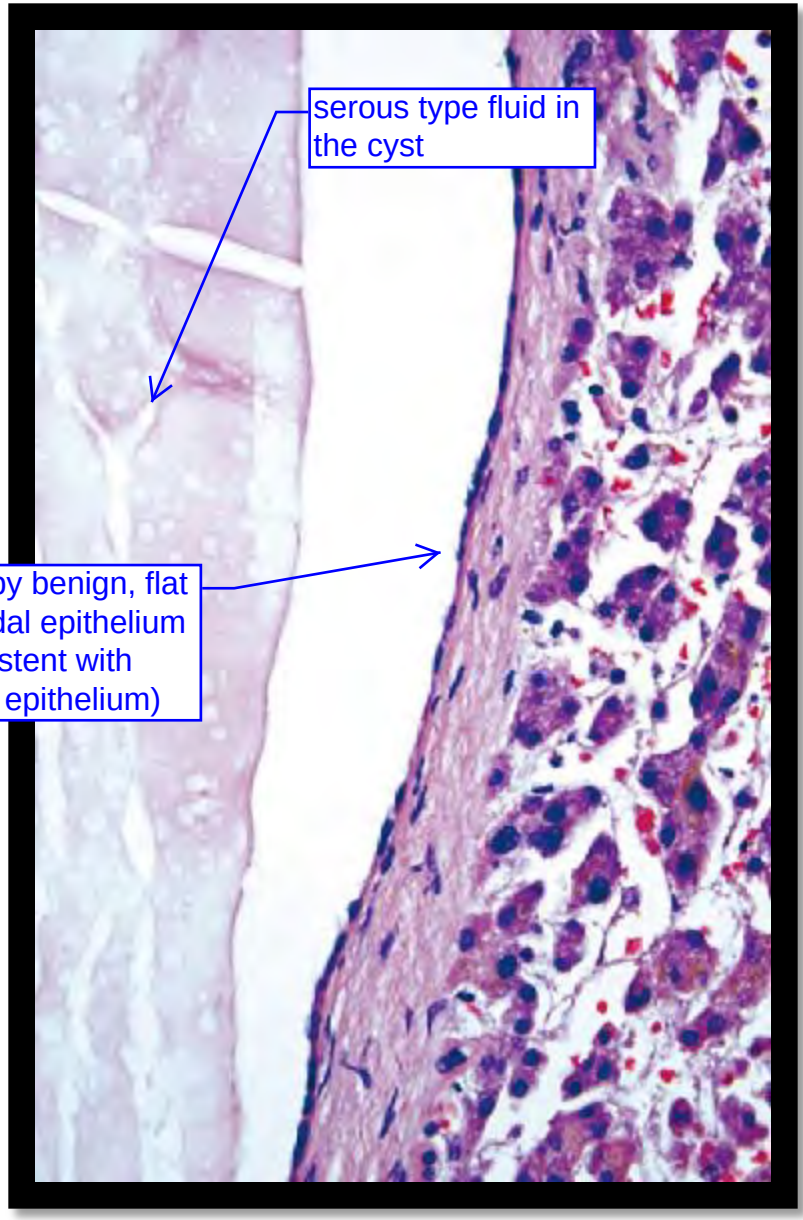
Biliary Cysts

hamartoma can be so dilated that they become biliary cysts

- Cystic dilatation of the biliary system
  - Usually an incidental finding found in adults (>40 y/o)
  - When multiple, likely a component of polycystic disease
  - Typically subcapsular
- Cysts are lined by cuboidal epithelium and have a fibrous wall

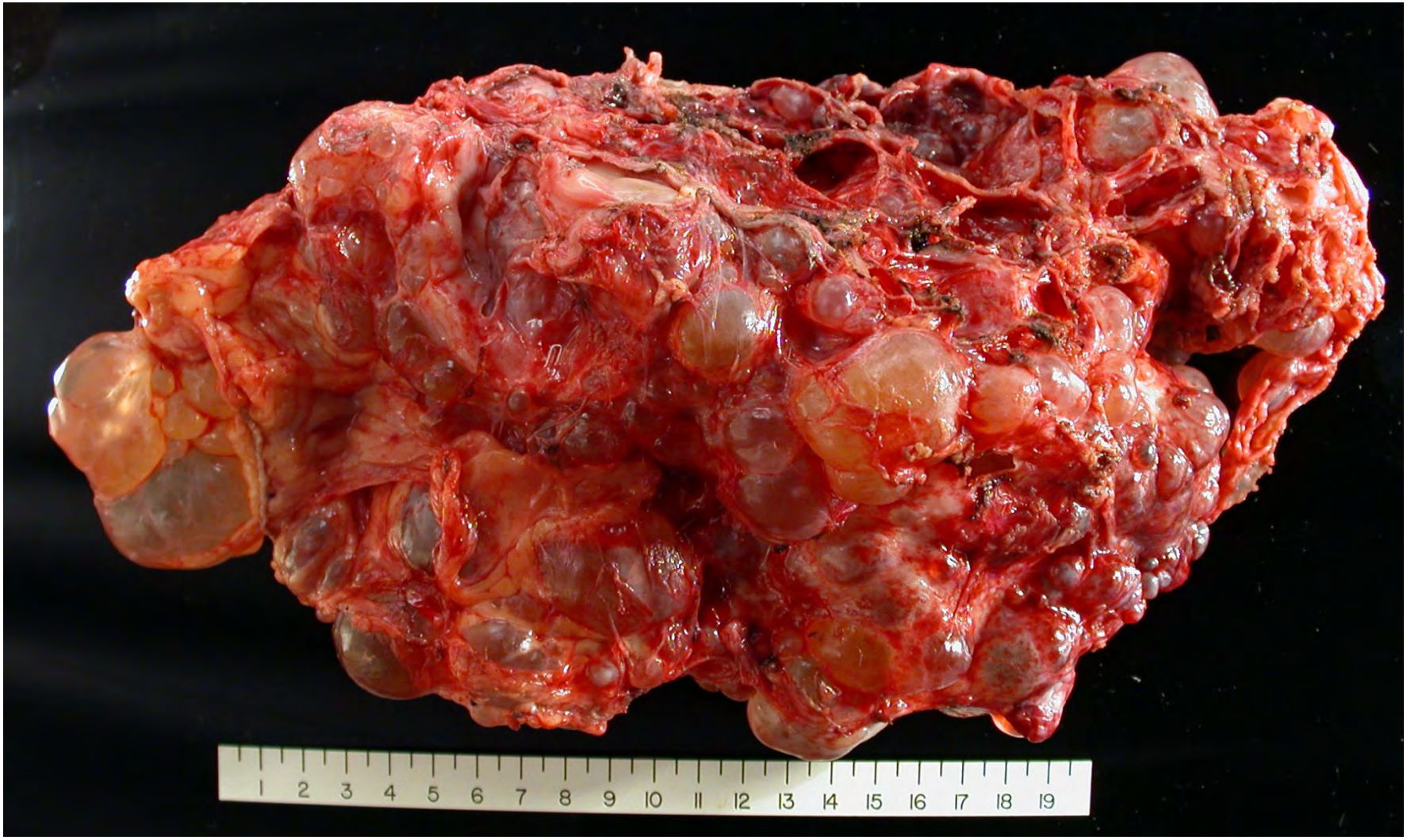
major ddx for biliary cyst is mucinous cystadenoma. Biliary cyst will not have ovarian stroma

  - Contain clear, light yellow fluid
  - No ovarian stroma is present



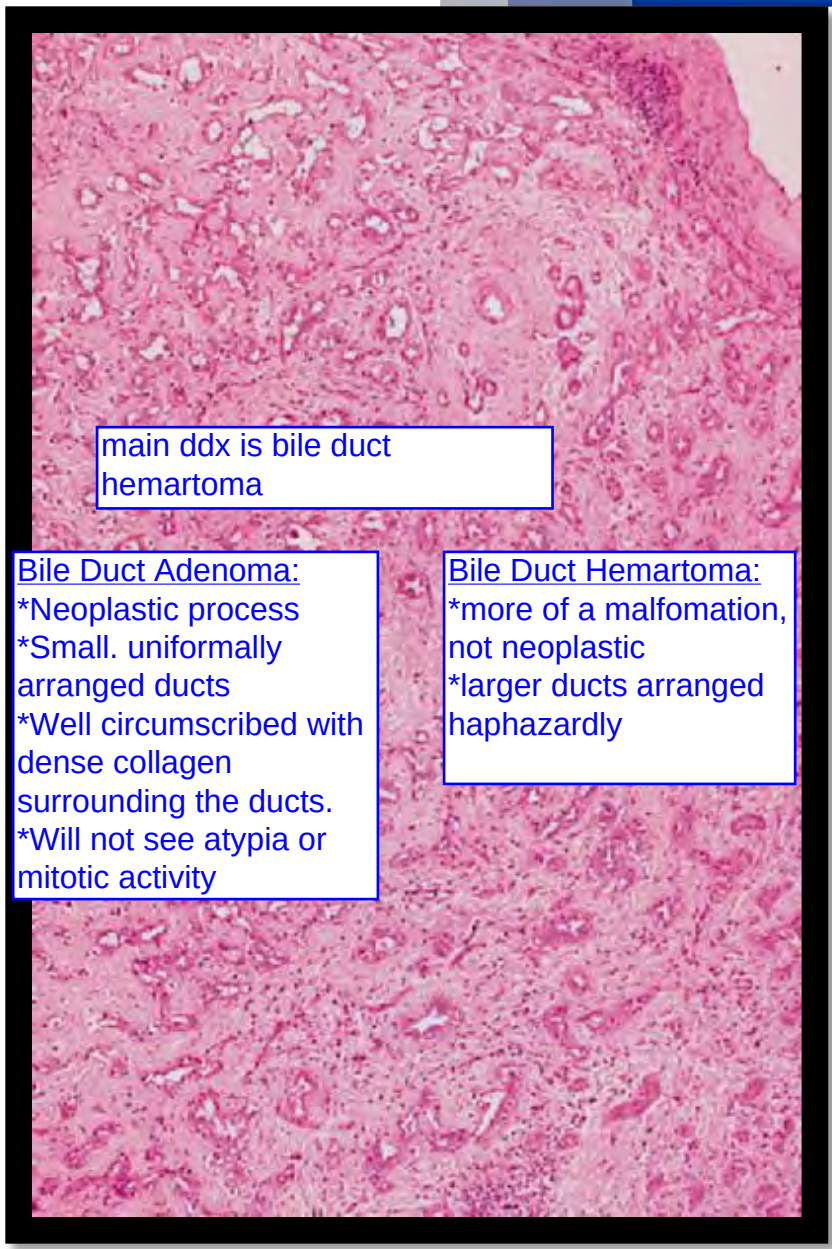
Polycystic Liver Disease

exaggerated form of biliary cyst



Bile Duct Adenoma

- Benign proliferation of bile ductules
  - Typically an incidental finding
  - Less common than BDH
  - Commonly subcapsular, < 2.0 cm and well circumscribed
- Ductules are uniform in size and appearance with less dense stroma and bland cytology
  - Main differential is metastatic adenocarcinoma



Focal Nodular Hyperplasia

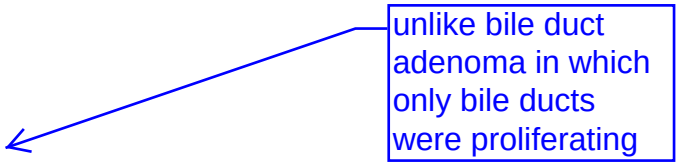
tumor that is considered reactive to vascular insult

- Considered non-neoplastic
  - Occurs in both men and women of all ages.
  - Usually asymptomatic.
- Potential causes:
  - Reactive/reparative process likely due to localized vascular abnormalities
  - Malformation
  - P450 1A1 polymorphism may lead to abnormal steroid metabolism increasing risk of FNH

Focal Nodular Hyperplasia

Gross:

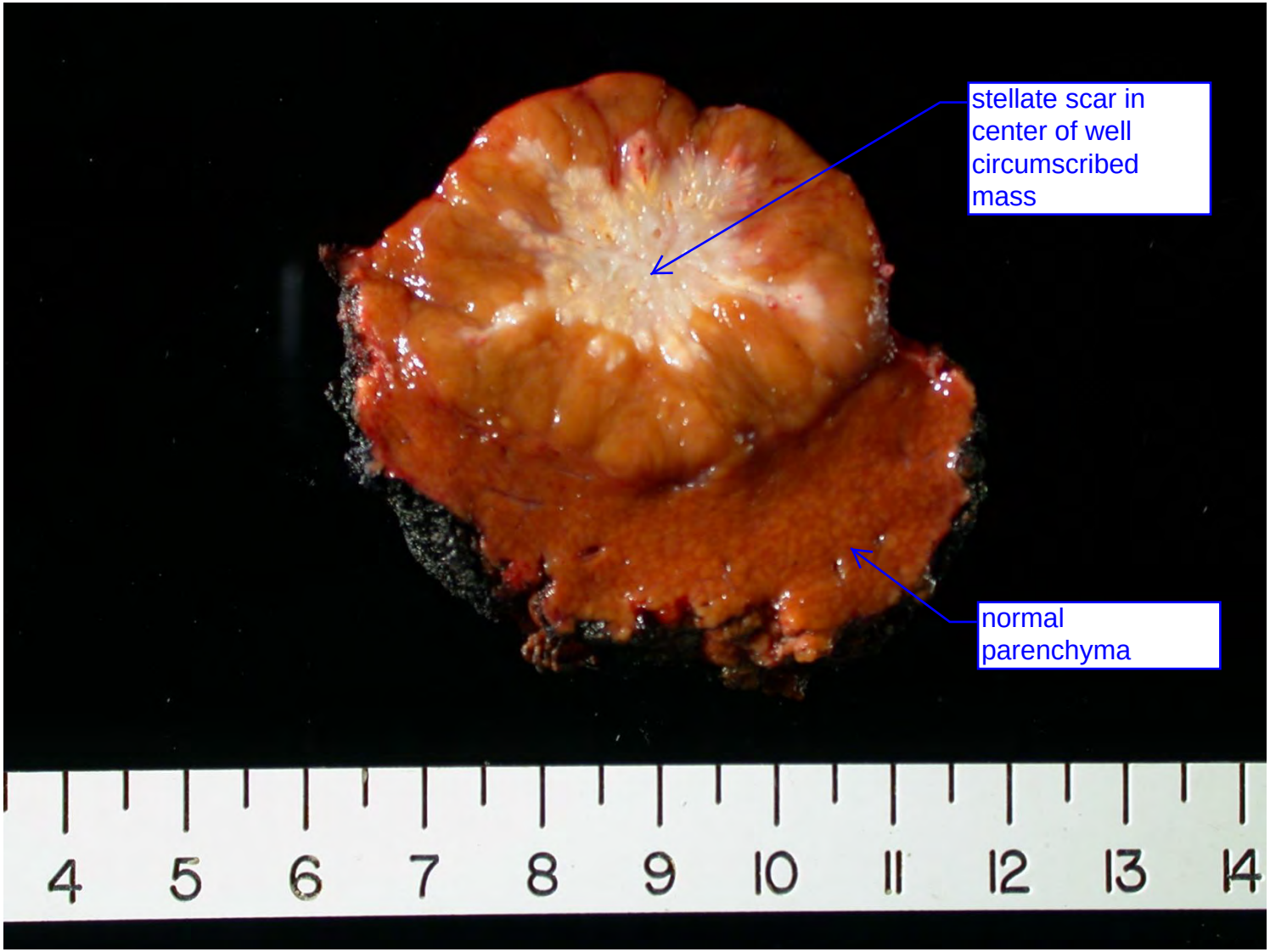
- Ill-defined area with a cirrhosis–like appearance and typically has a characteristic central stellate scar.



Microscopic:

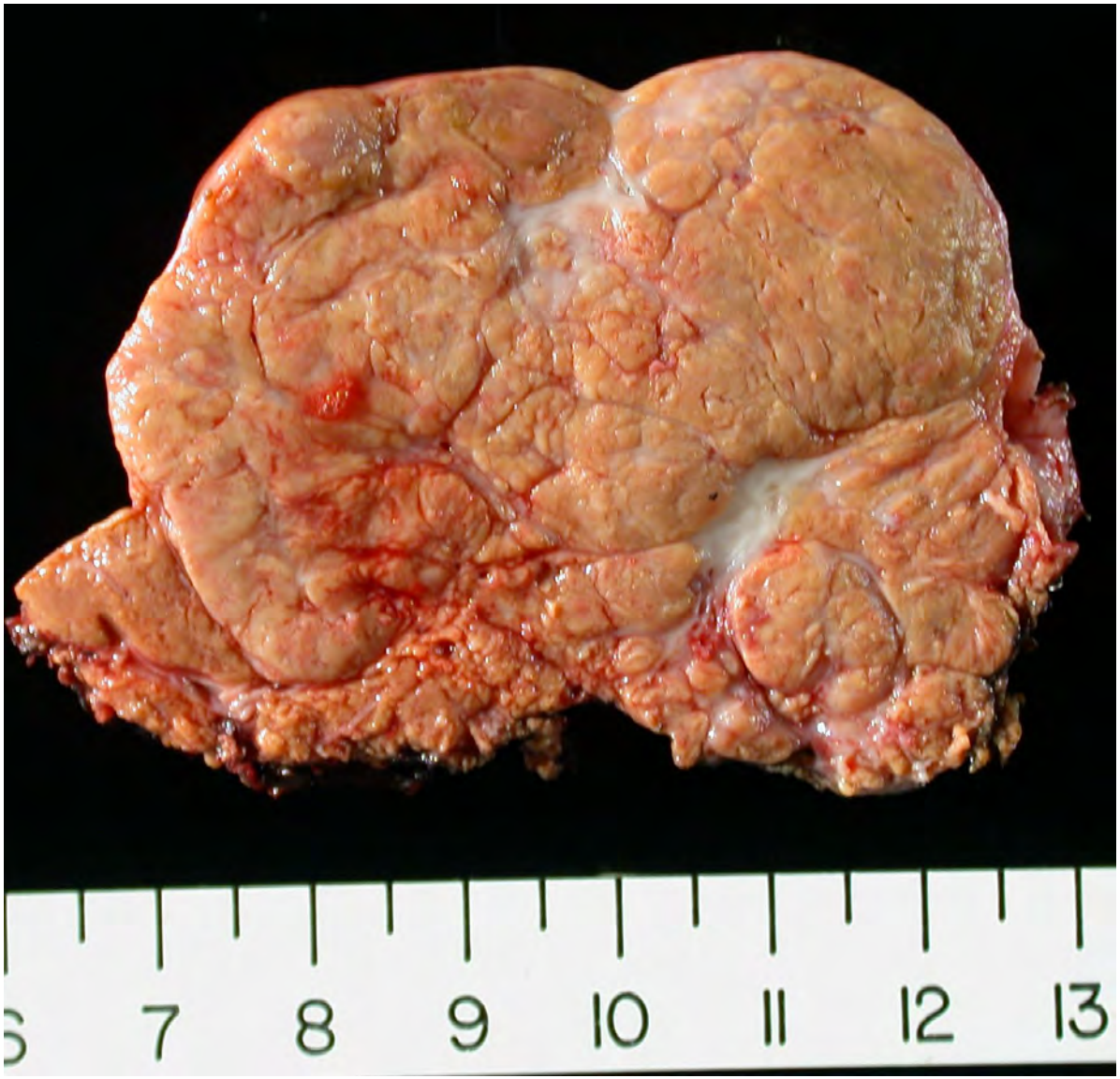
- Proliferation of all 3 elements- Cords of benign hepatocytes (< 3 cells thick plates), fibrous septa containing inflammatory cells, bile ductules, and prominent (thick walled) arteries

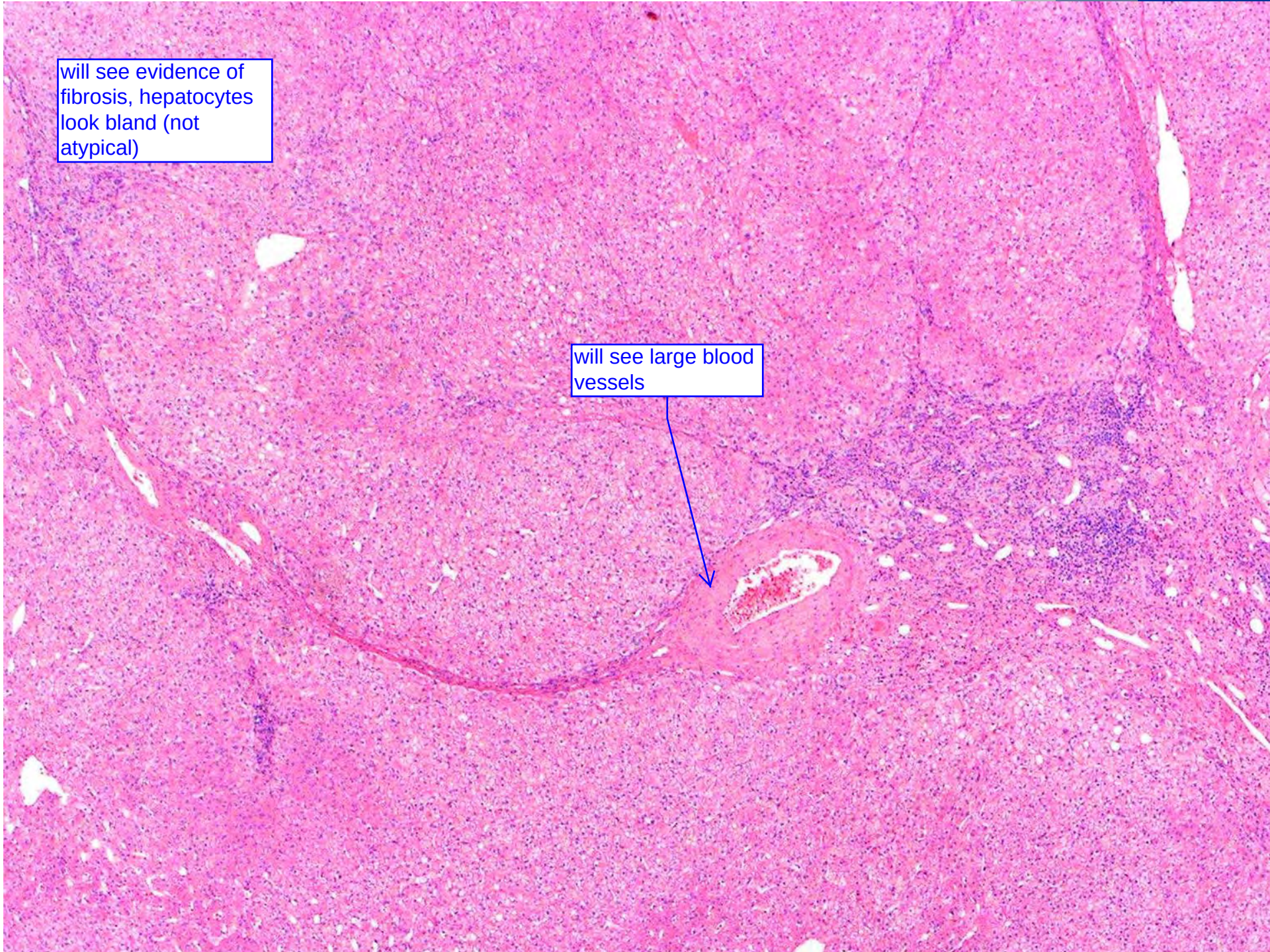
Focal Nodular Hyperplasia

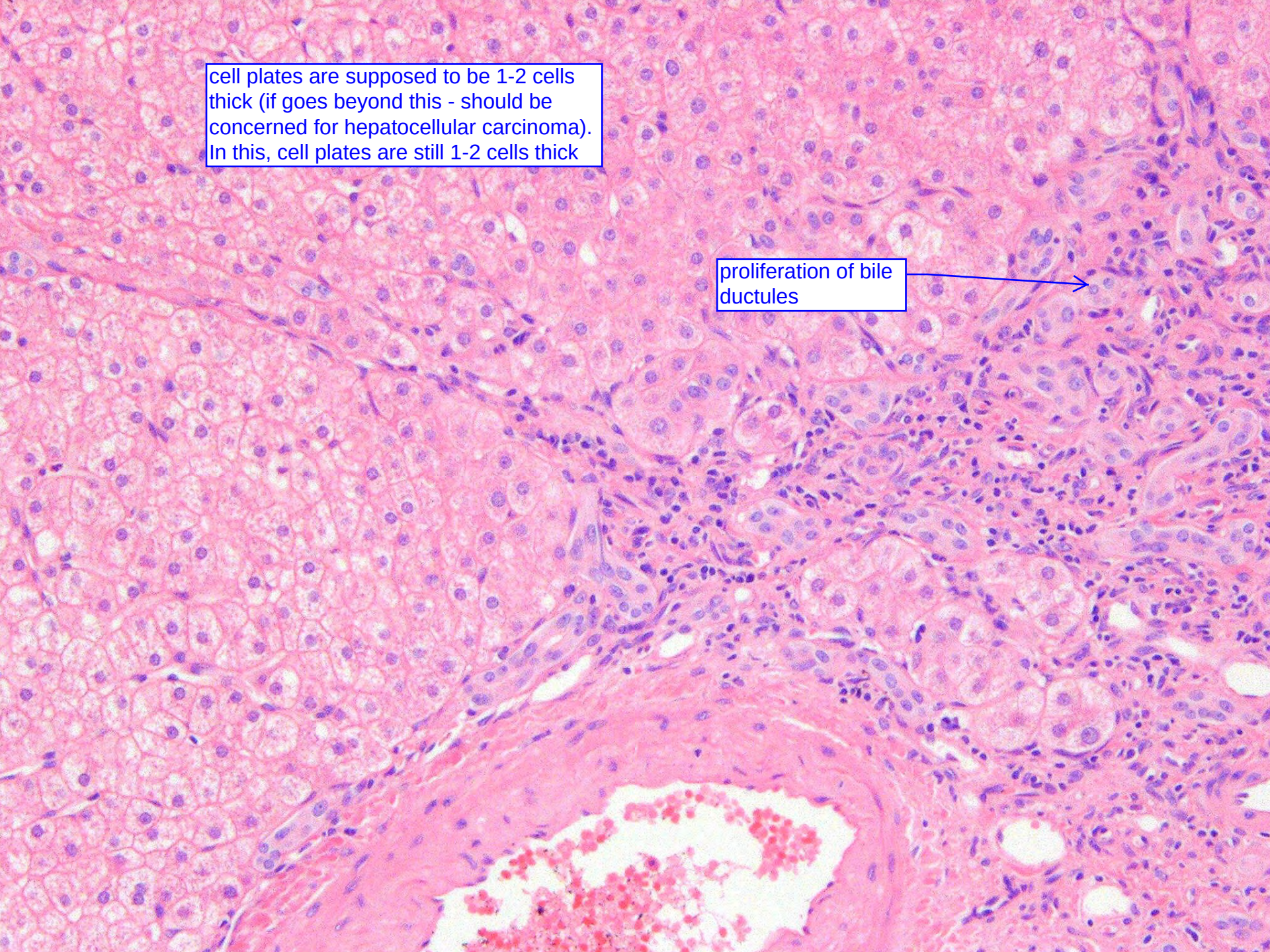


Focal Nodular Hyperplasia

very cirrhotic looking liver




will see evidence of fibrosis, hepatocytes look bland (not atypical)
will see large blood vessels


cell plates are supposed to be 1-2 cells thick (if goes beyond this - should be concerned for hepatocellular carcinoma). In this, cell plates are still 1-2 cells thick
proliferation of bile ductules

Hepatic Adenoma

main ddx for FNH is hepatic adenoma

- Benign neoplasm of hepatocytes
- Most commonly occurs in young women
- Risk factors:
  - Oral contraceptives/anabolic steroids
  - Homozygous HNF1 mutations (TCF1 gene; 12q).
    - Sporadic or associated with MODY3
  - Glycogen storage diseases
    - i.e. Von Gierke's disease, type Ia.
  - Mutation of the Wnt/β-catenin pathway
    - Increased of malignant transformation

#1 risk factor

hepatocyte nuclear factor 1

diabetes

these pts have higher risk of developing adenomatosis - greater than 10 adenomas

von Gierke's disease: glucose 6-phosphatase deficiency. Would present with severe fasting hypoglycemia, increased glycogen in the liver, increased blood lactate, hepatomegaly

Hepatic Adenoma

hepatocellular carcinoma would have a capsule

Gross:

- Usually solitary and ill-defined (no capsule)
  - >10 lesions = “adenomatosis”

Microscopic:

- Proliferation of bland hepatocytes, plates ≤3-cells thick.
  - Steatosis is common
- Isolated („naked“) arteries
  - Leads to a risk of hemorrhage, especially with large size
- No bile duct differentiation

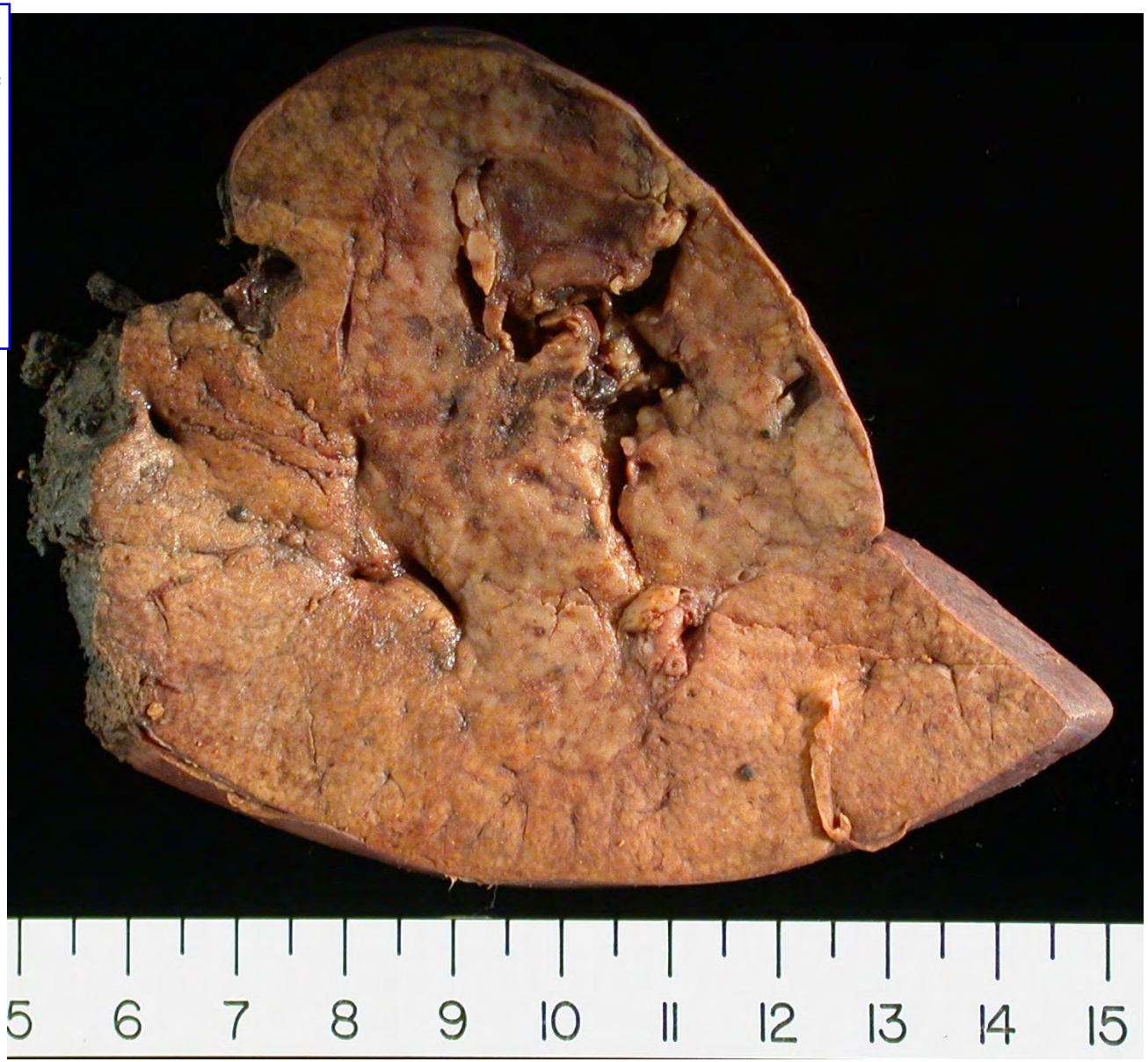
arteries not associated with veins or bile ducts

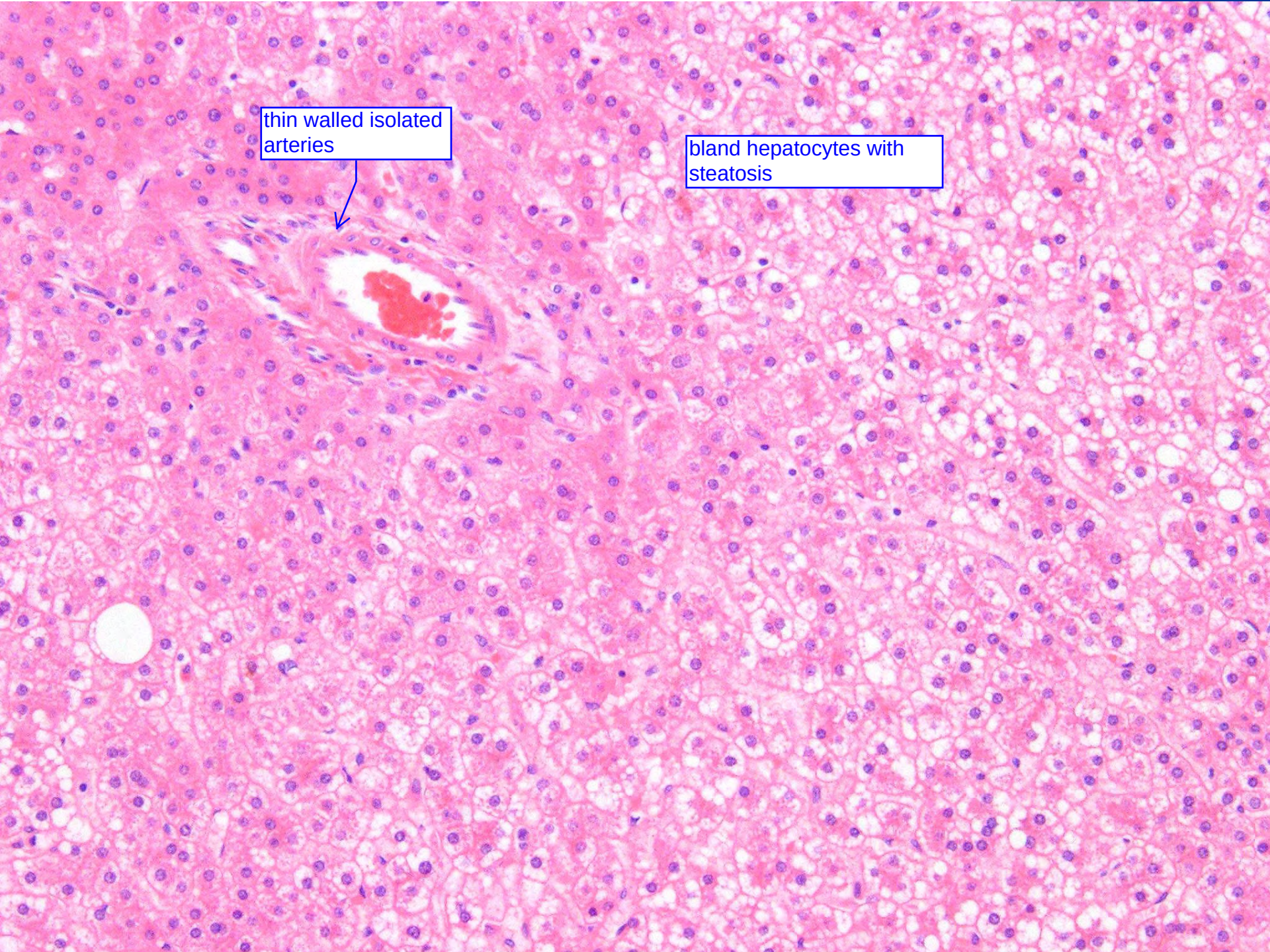
in FNH, you would see bile duct differentiation

Hepatic Adenoma

ill defined - hard to say where lesion ends and begins

they are taken out when >5 cm because high risk of hemorrhaging and rupturing (due to lots of thin walled vessels)




thin walled isolated arteries
bland hepatocytes with steatosis

MALIGNANT TUMORS

Hepatocellular Carcinoma

most common malignant primary tumor of the liver

- Globally
  - ~600,000 cases per year
  - Fifth most common cancer and third leading cause of cancer-related death worldwide .
  - M:F is as high as 8:1

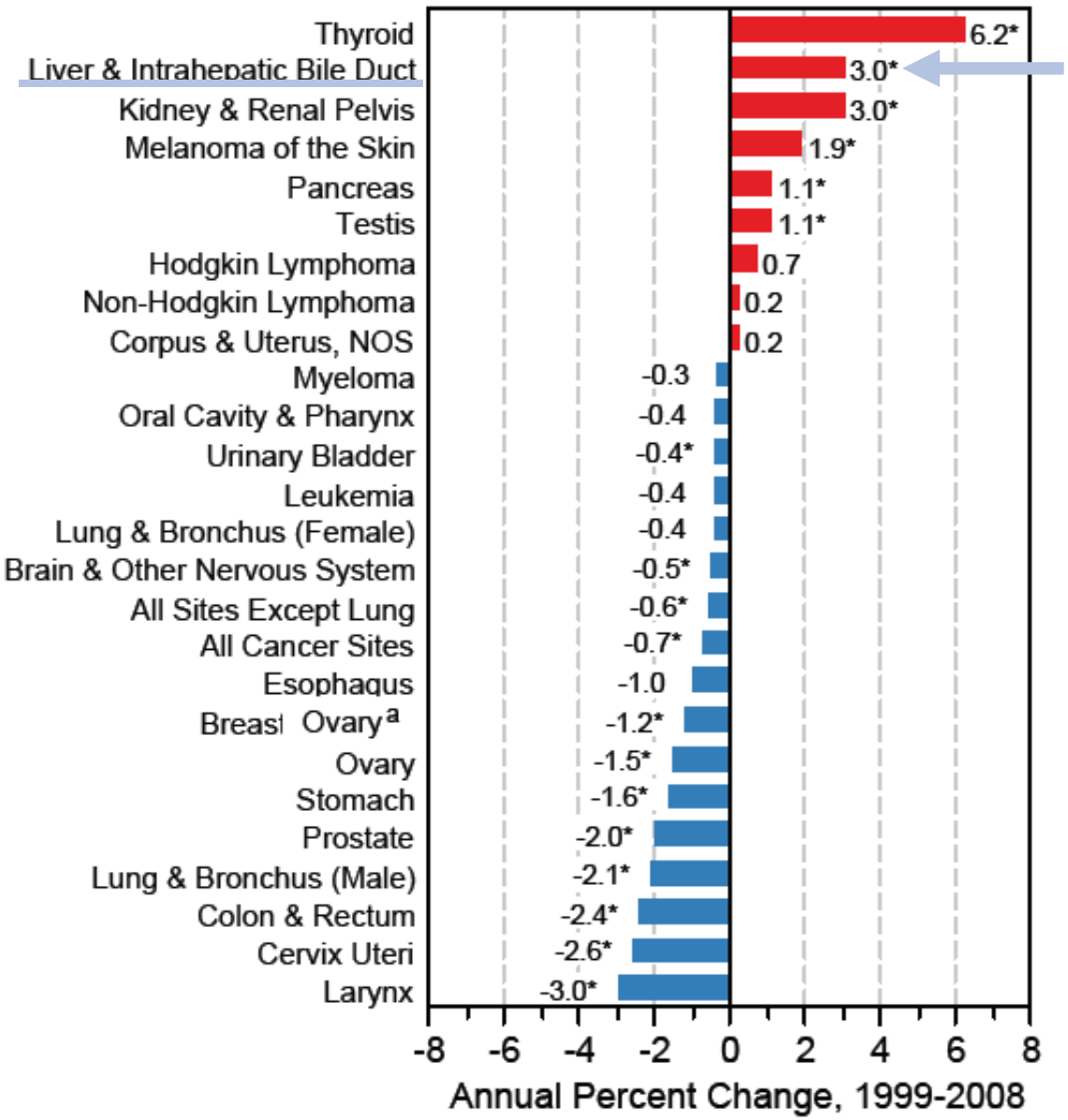
b/c men have higher risk of cirrhosis, alcoholism

- United States
  - Liver cancer is one of most rapidly increasing cancers
  - ~24,000 new cases in 2010
  - 80%-90% occurring in cirrhotic livers.

McGlynn et al. *Cancer Epidemiol Biomarkers Prev* 2006;15:1198-1203

El-Serag. *Gastroenterology* 2004;127:1372-80

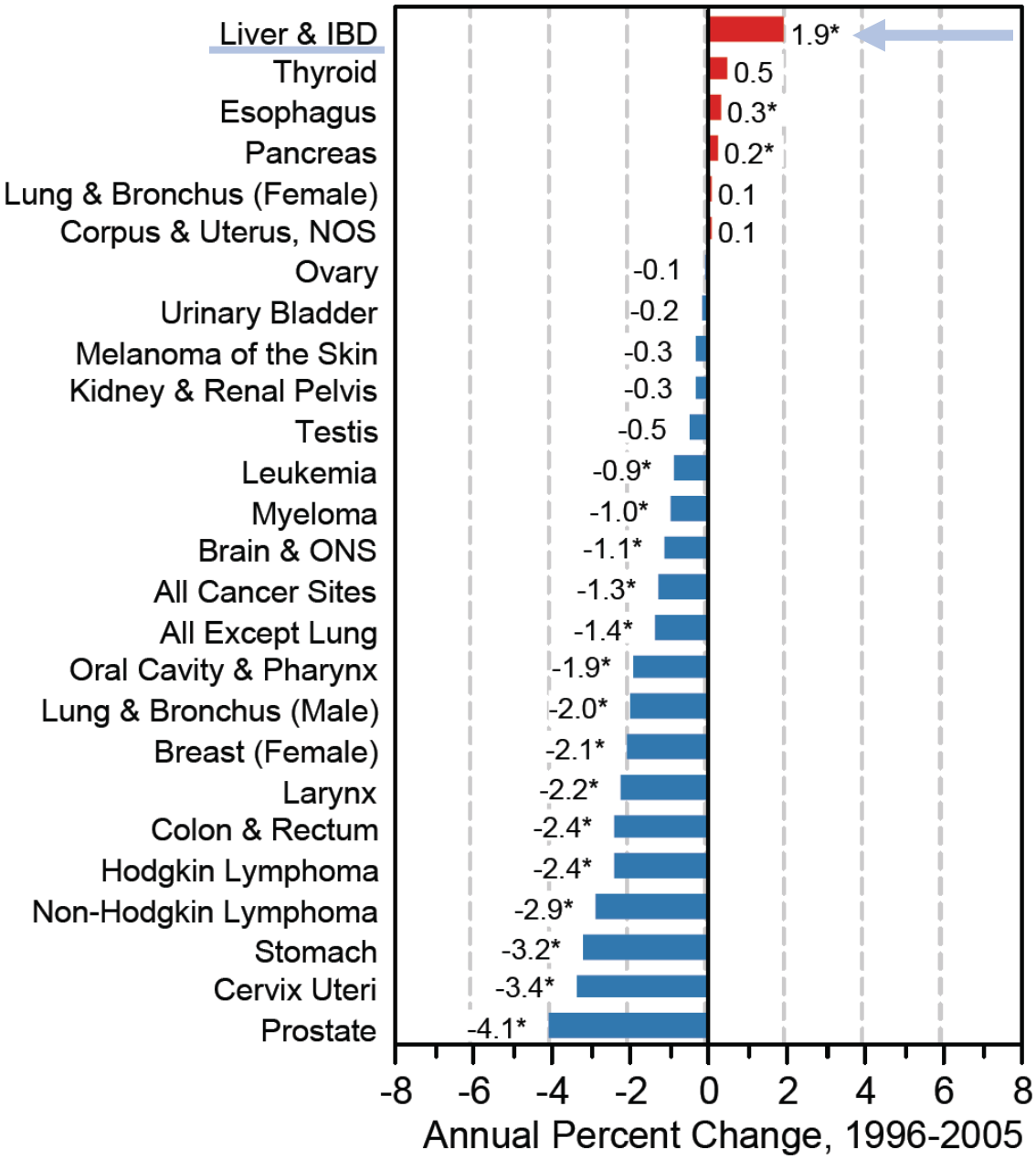
Trends in SEER Incidence Rates



hepatocellular carcinoma and cholangiocarcinoma incidence increased by 3%

http://seer.cancer.gov/csr/1975_2008/results_merged/topic_graph_trends.pdf

Trends in US Cancer Death Rates



#1 growth of death rate due to 1) incidence increasing 2) treatment has not improved while treatments for other cancers have improved

http://seer.cancer.gov/csr/1975_2005/results_merged/topic_graph_trends.pdf

Risk Factors

for hepatocellular carcinoma

- **Cirrhosis**

#1 risk factor

  - Viral Hepatitis (HCV, HBV)

even if you're not cirrhotic, HBV alone is a risk factor

  - Alcoholic steatohepatitis
  - Non-alcoholic steatohepatitis

increasing with obesity epidemic

  - Autoimmune hepatitis
  - Hemochromatosis, Alpha-1-Antitrypsin deficiency

these are hereditary

- Thorotrast, aflatoxins and anabolic steroid exposure.

toxins

Surveillance should be with ultrasound or CT/MRI at 6 to 12 month intervals *(AFP is not adequate).*

El-Serag HB. *Gastroenterology* 2004;127:13
Bruix J and Sherman M. *Hepatology* 2005;4

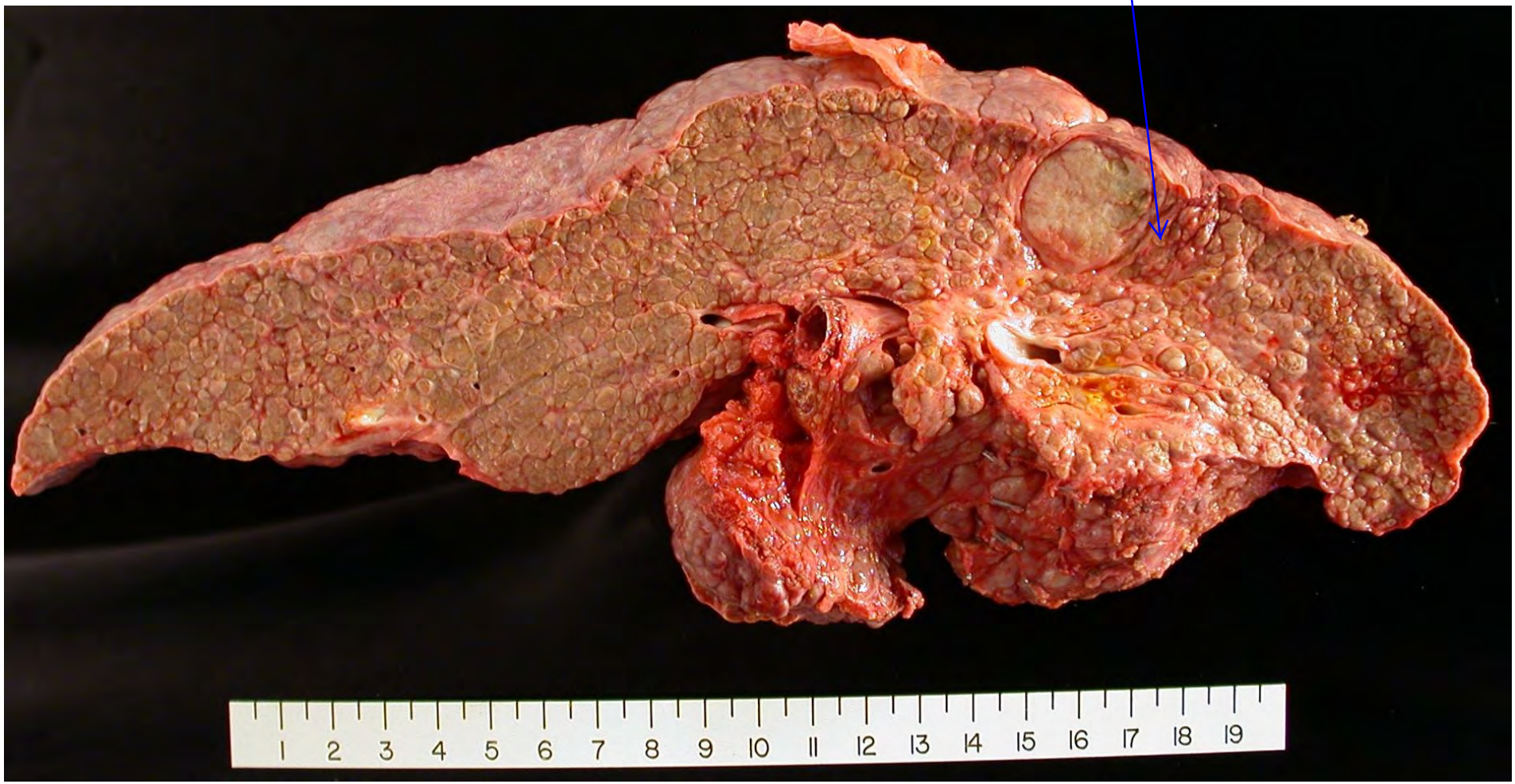
also increased incidence of HCC with Wilson's disease. Findings of HCC: jaundice, tender hepatomegaly, ascites, polycythemia, hypoglycemia. Commonly spread by hematogenous disseminiation. Increase in alpha fetoprotein. HCC may lead to Budd-Chiari syndrome

Hepatocellular Carcinoma

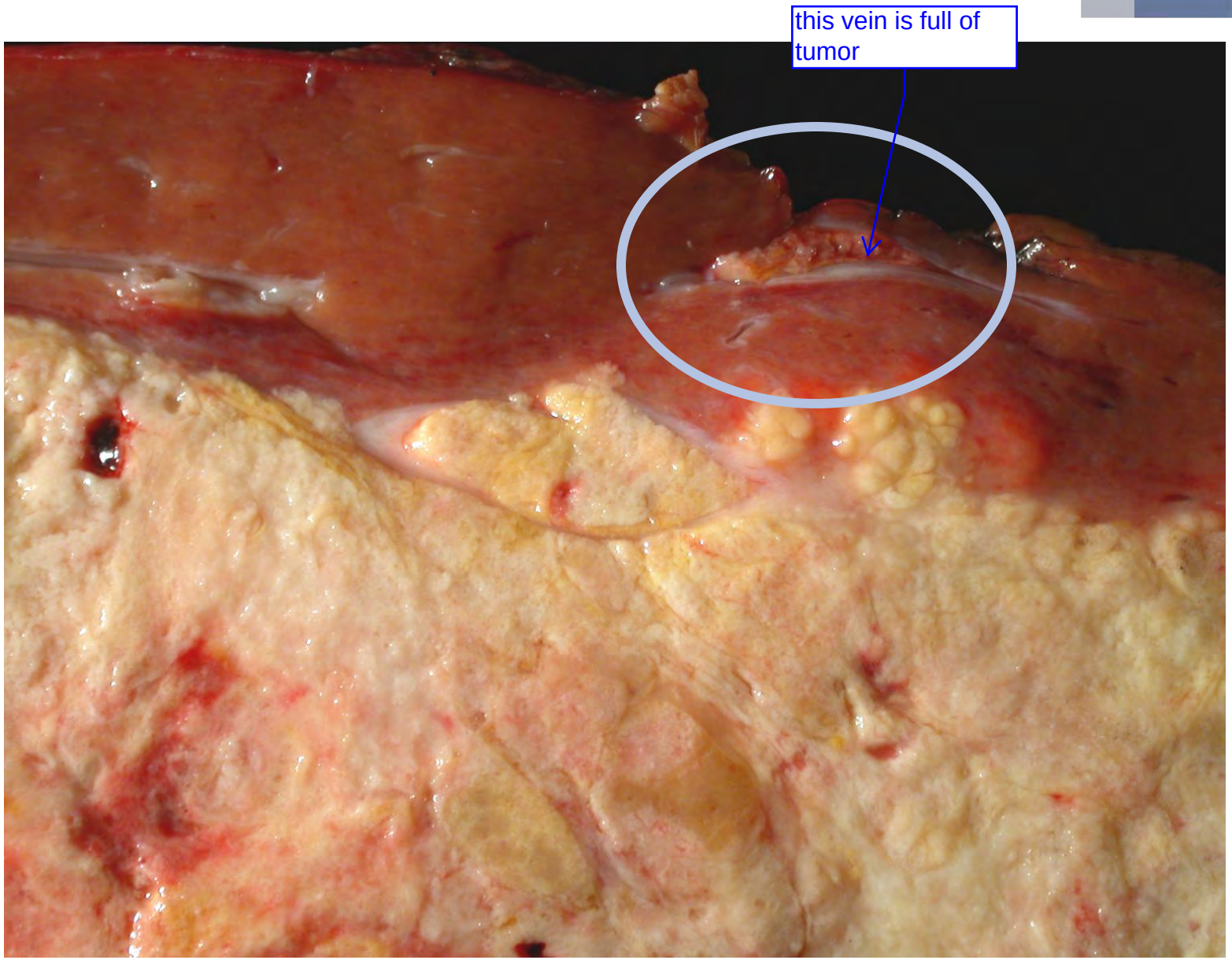
Gross:

- Solitary/ multiple nodules that typically arise in a background of cirrhosis
  - Bile stained or paler than surrounding liver
  - Can have well-circumscribed or irregular borders, but tend to have a capsule
- Satellite nodules and venous invasion is common.
  - Worse prognostic features

Hepatocellular Carcinoma



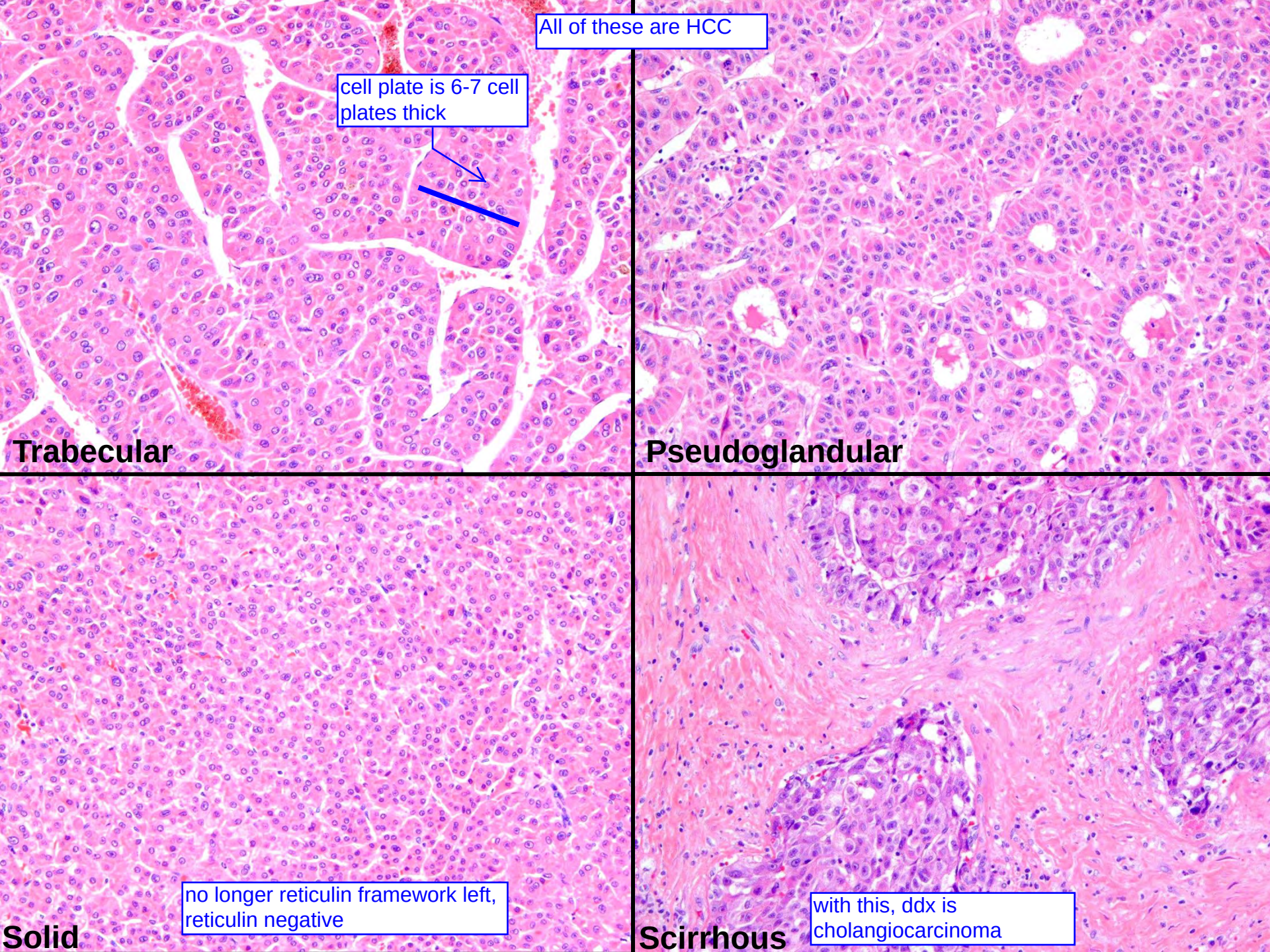
Hepatocellular Carcinoma

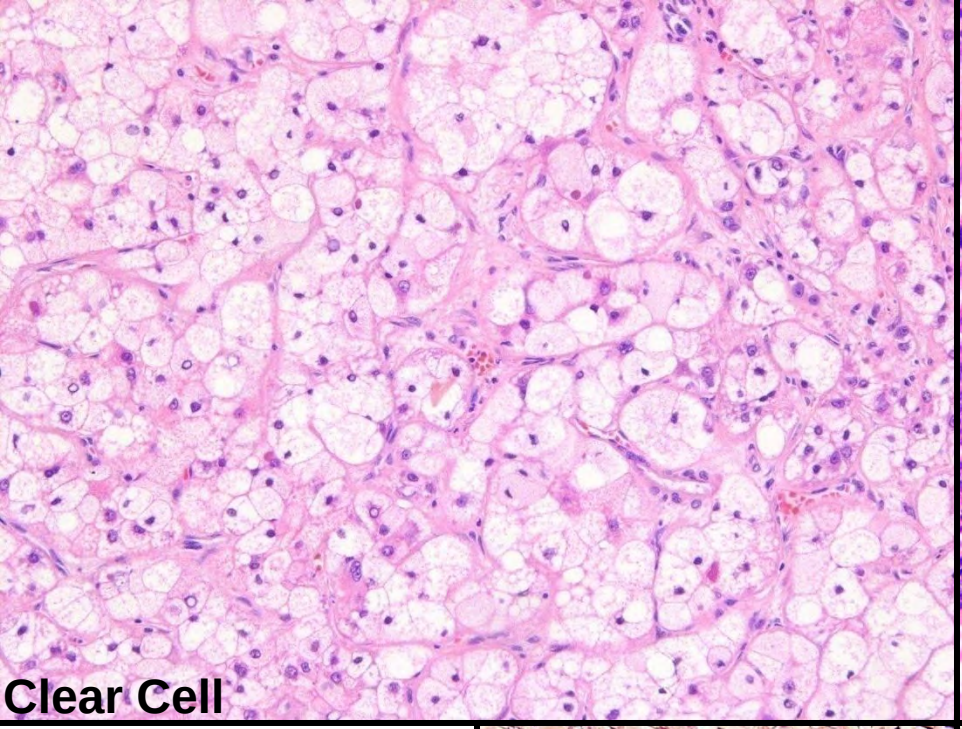


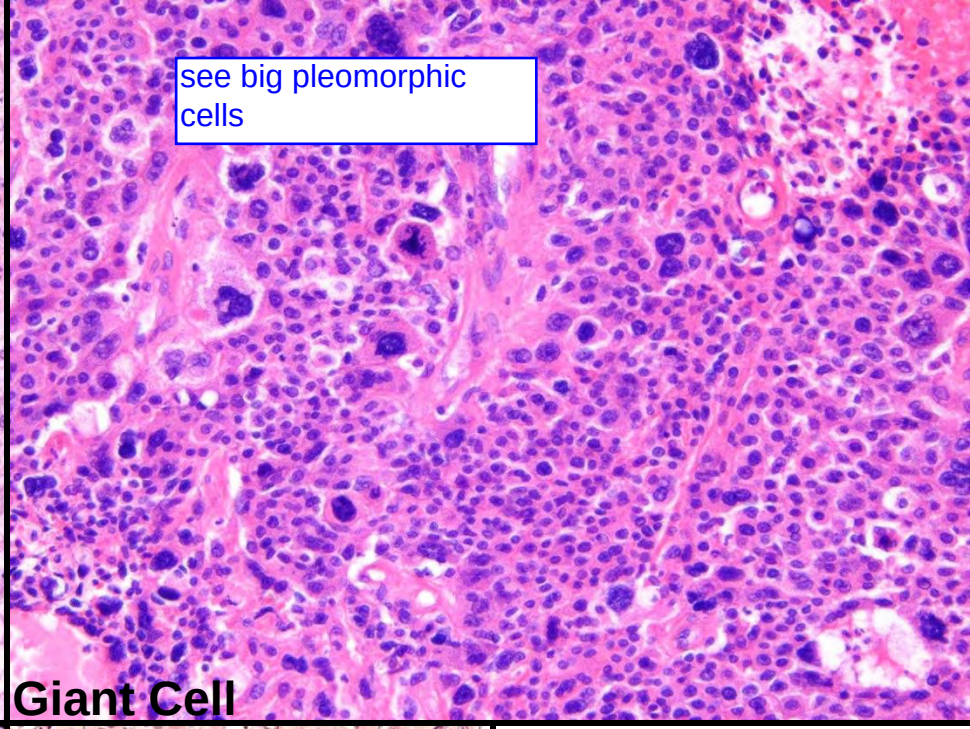
Hepatocellular Carcinoma

Histology:

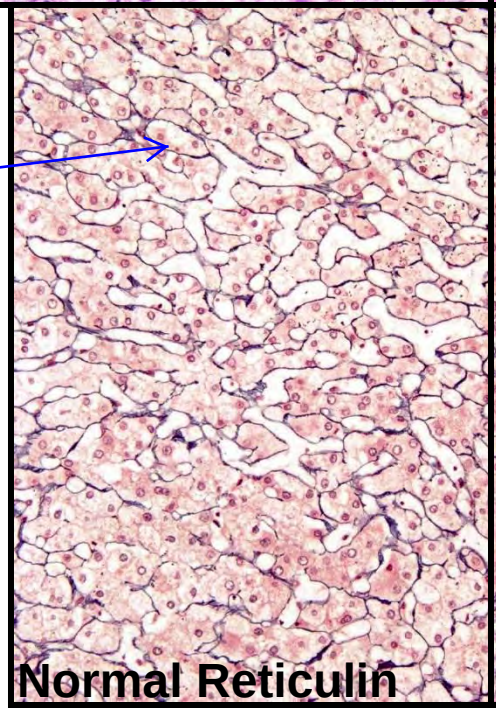
- Hepatocytes with increased nuclear:cytoplasmic, atypia, and thickened liver cell plates (>3)
  - Reticulin stain maybe helpful
- Variable Patterns/Subtypes:
  - Trabecular
  - Acinar/Pseudoglandular
  - Solid
  - Scirrhous
  - Giant cell
  - Clear cell
  - *Fibrolamellar*

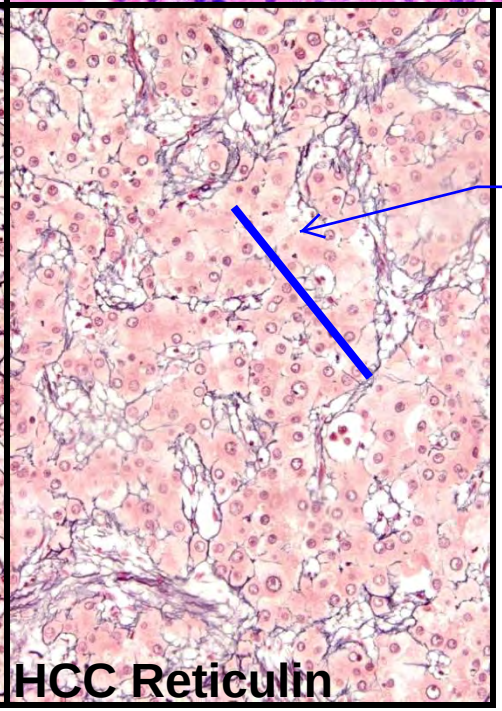

All of these are HCC
cell plate is 6-7 cell plates thick
Trabecular
Pseudoglandular
no longer reticulin framework left, reticulin negative
Solid
with this, ddx is cholangiocarcinoma
Scirrhous





highlighting thin cell plates





6-7 cells inbetween

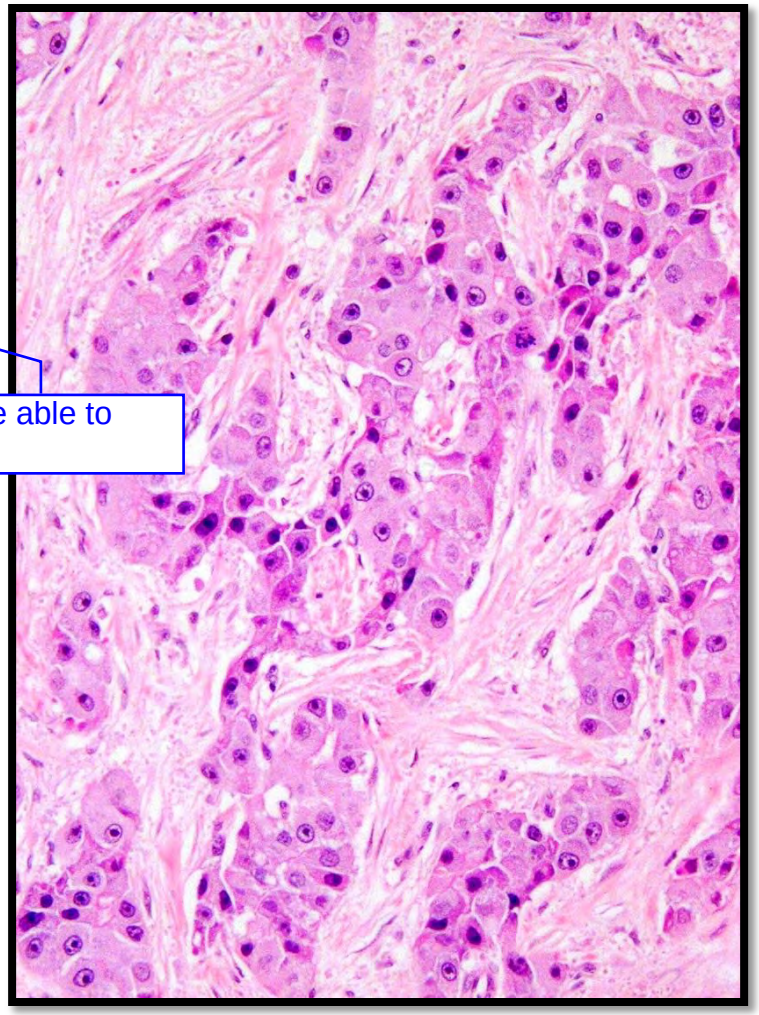
Fibrolamellar Variant

of HCC

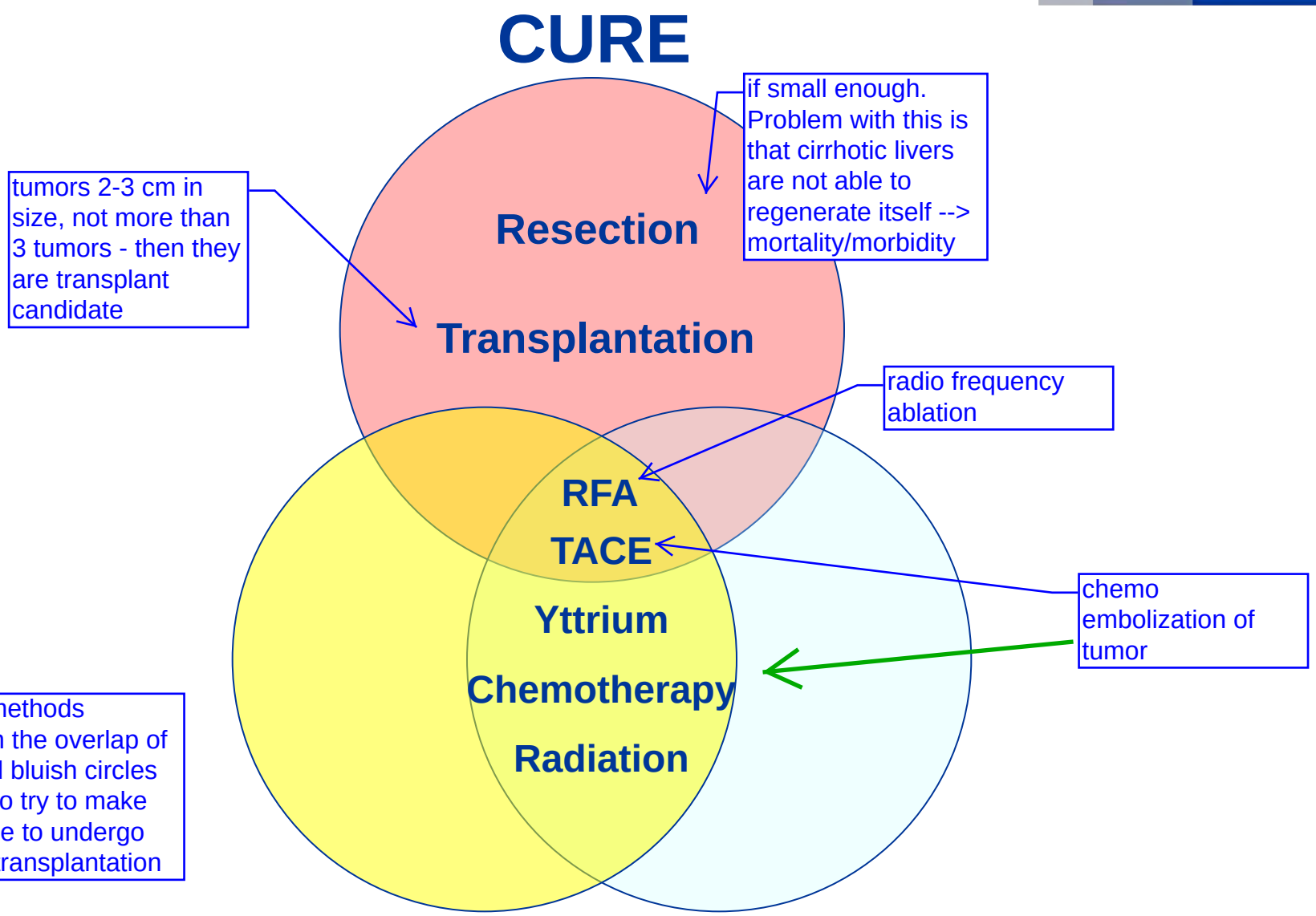
other HCC affect older individuals

- Young adults (20 – 40 y/o)
- No association with viral hepatitis or cirrhosis
- Better prognosis than HCC
- Gross:
  - Single firm sclerotic mass
- Microscopic:
  - Well differentiated, eosinophilic cytoplasm, commonly nested or in cords, separated by parallel lamellae of dense collagenous connective tissue; +/- pale bodies

may be able to resect



Potential Treatments



Hepatoblastoma

HCC in kids
*malignancy of hepatocytes

- #1 liver tumor in children (90% <5 y/o and 70% <2 y/o)
  - Patients present with an enlarging abdomen
  - Paraneoplastic syndromes- anemia/thrombocytopenia
  - 90% present with elevated AFP (negative = more aggressive)

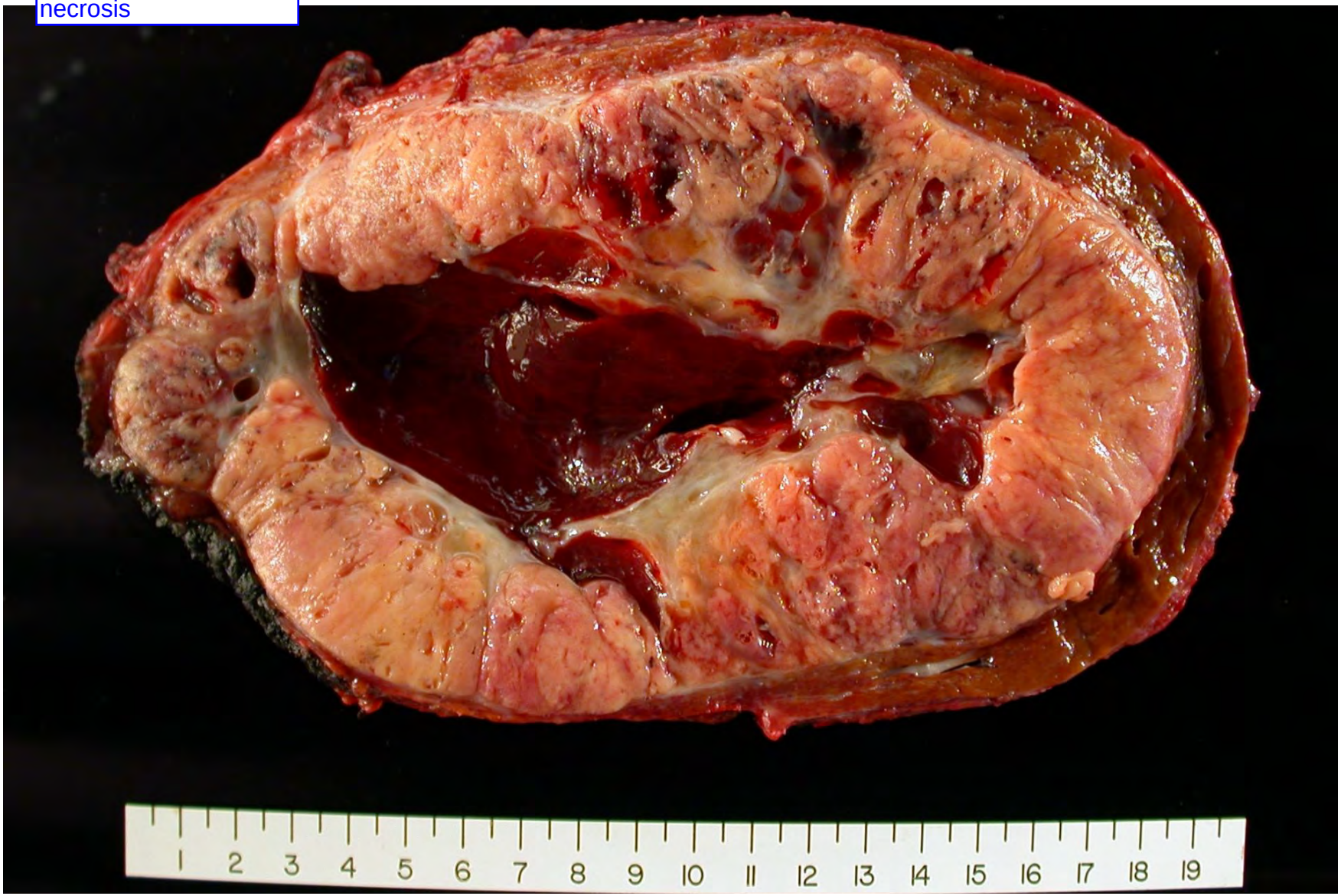
Gross:

- Single/multiple heterogeneous mass(es) most commonly involving the right or both lobes (75%)

*right lobe is the largest lobe
*can cross into left lobe if tumor is very large

Hepatoblastoma

a lot of central hemorrhage and necrosis



Hepatoblastoma

Microscopic:

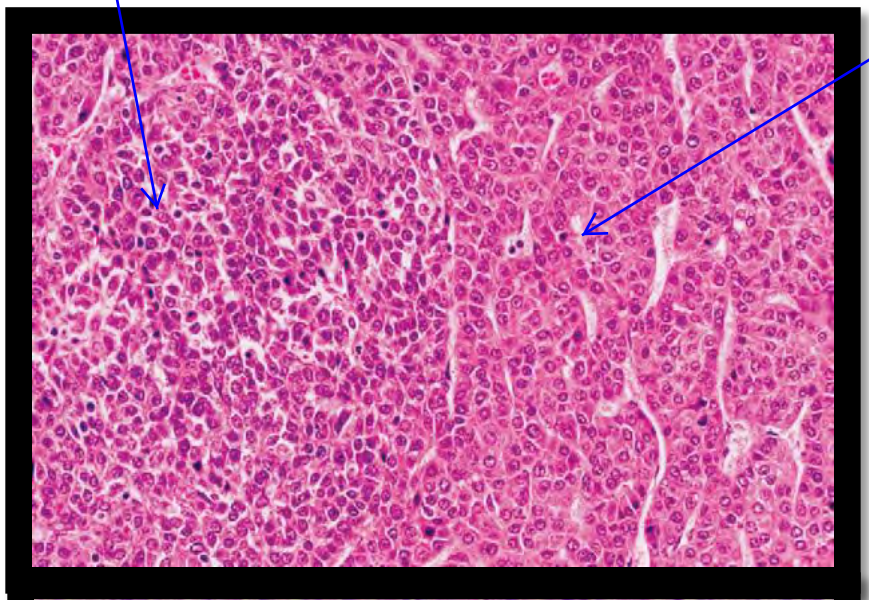
- Epithelial Type
  - Fetal
    - Most reminiscent of mature hepatocytes
    - Good prognosis
  - Mixed fetal and embryonal
    - Embryonal- small, hyperchromatic cells with increase N:C
  - Macrotrabecular
    - Similar to HCC
  - Small cell undifferentiated
- Mixed Epithelial and Mesenchymal Type
  - With or without teratoid features
- Hepatoblastoma, NOS

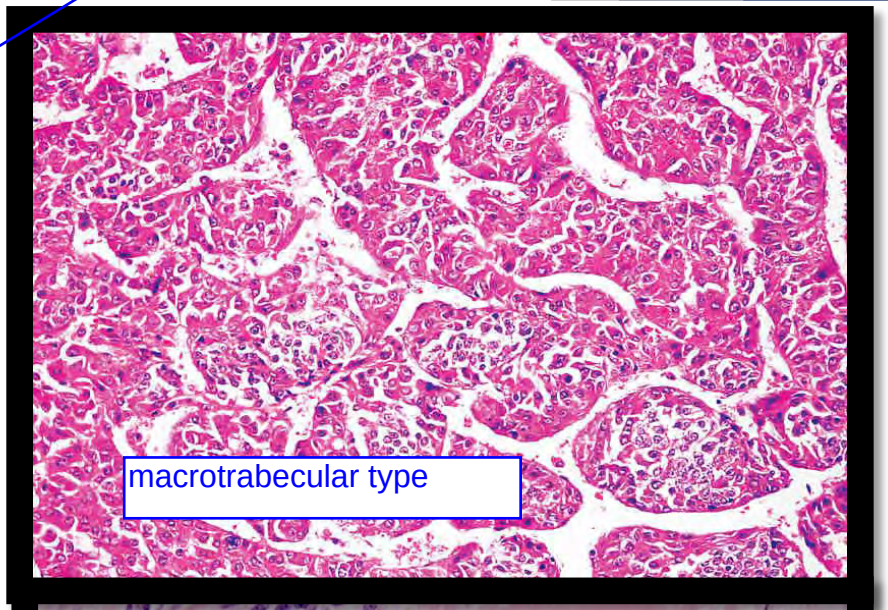
embryonal is small round blue cell tumor

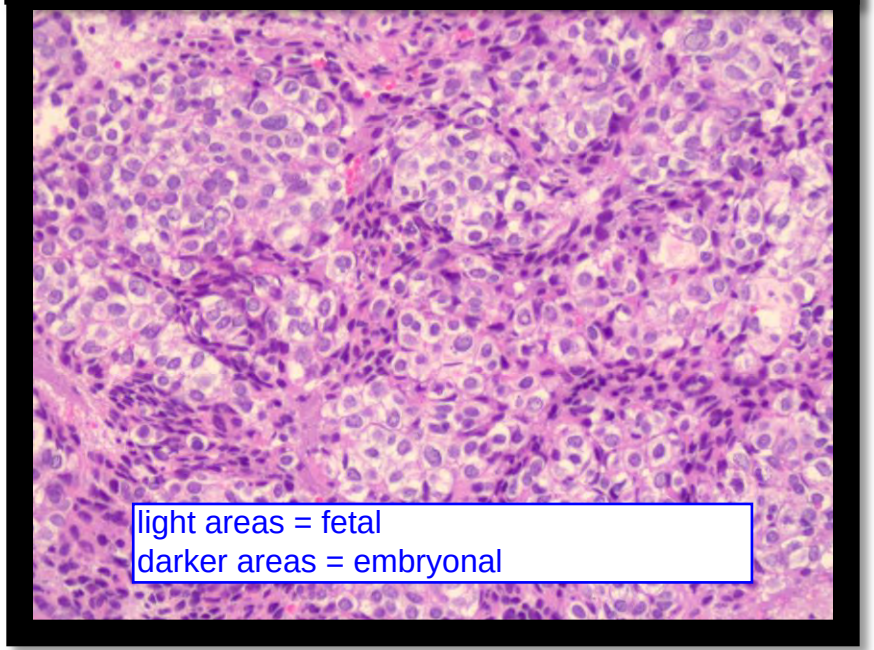
fetal type looks pale, and embryonal type looks dark

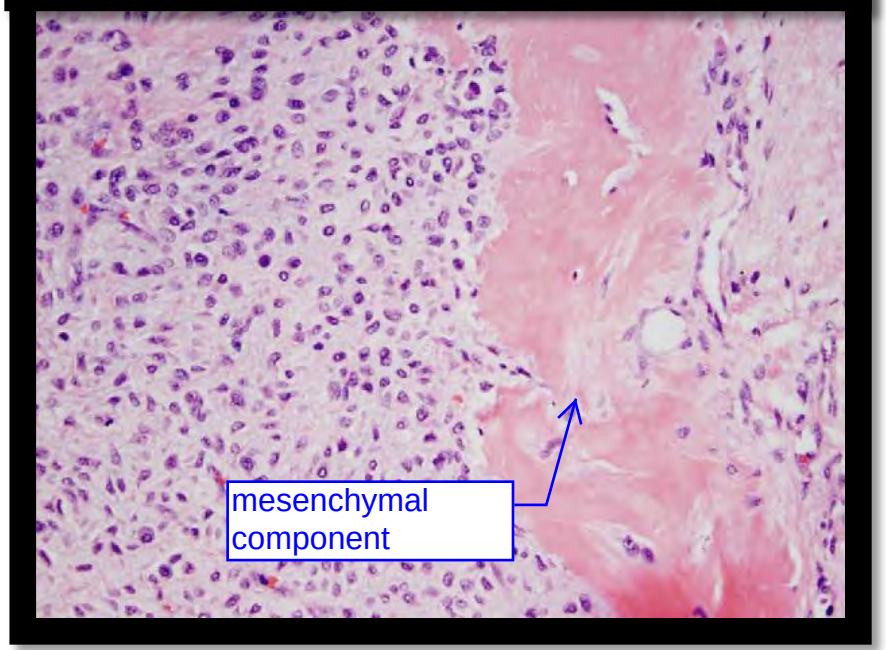
can also have malignant osteoid, cartilage, muscle

Hepatoblastoma









Hepatoblastoma

Treatment:

if small enough. good treatment

- Surgical excision with adjuvant chemotherapy is the treatment of choice
  - Neoadjuvant chemo may allow for surgical resection of previously „unresectable“ tumor

to shrink down tumor

- Liver transplantation is another option

- Prognosis is mainly dependent on tumor stage

look at morphology, size of tumor, metastasis

Cholangiocarcinoma

- Intrahepatic malignant proliferation of bile ducts
- Older adults; M=F
- Patients typically have non-cirrhotic livers and present with obstructive symptoms or pain

if occur more toward hilum, can present with pancreatitis

- Associations:
  - Caroli‟s disease, parasitic infection (clonorchis), Thorotrast, PSC

primary sclerosing cholangitis

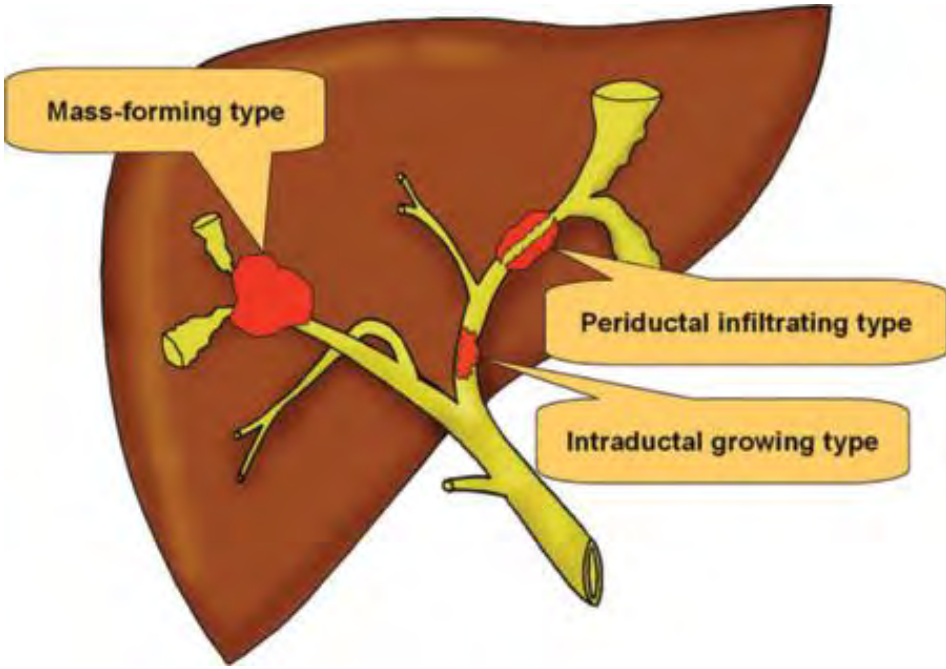
spectrum of polycystic disease

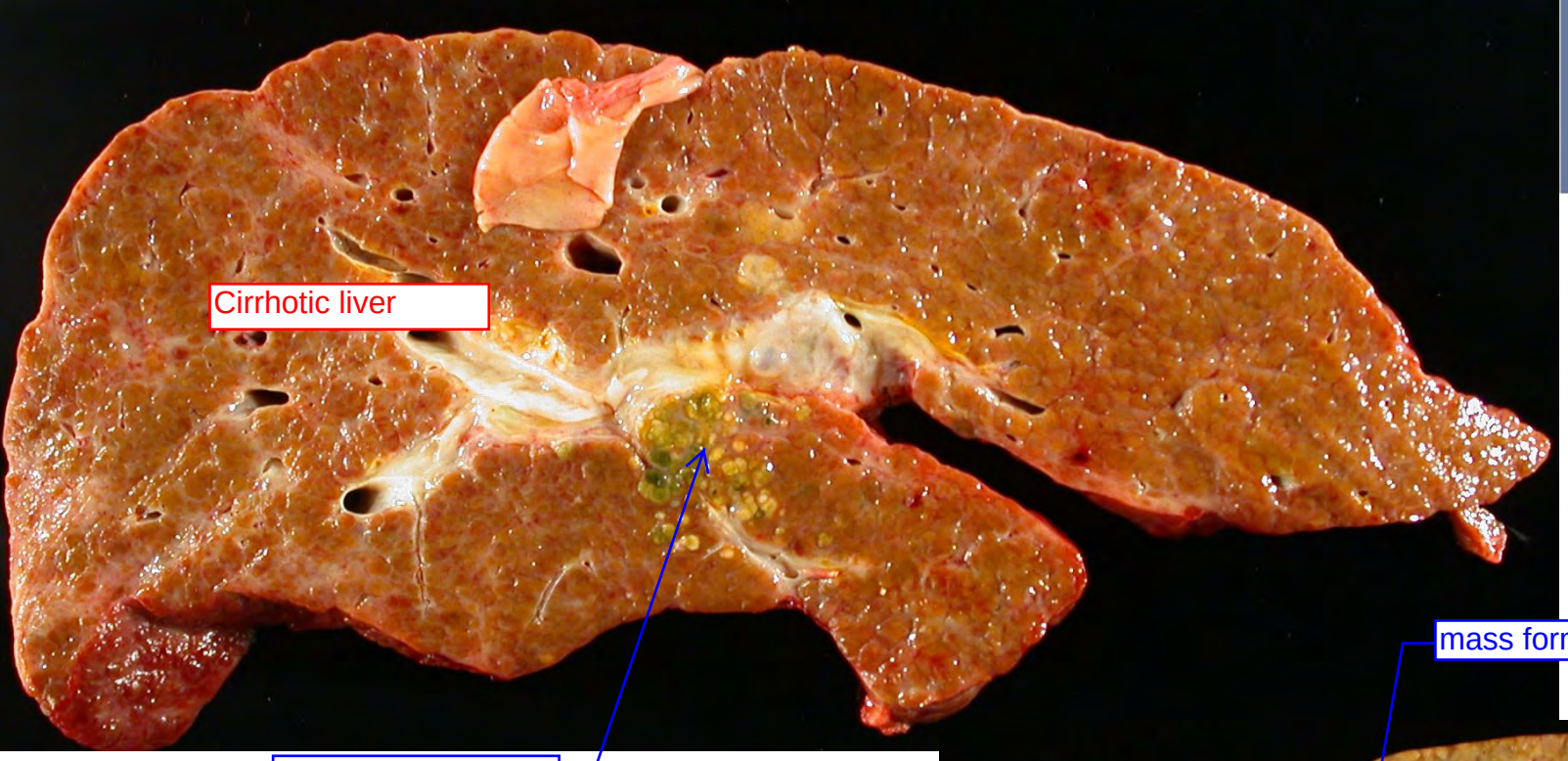
Cholangiocarcinoma

- Gross

can have variety of growth appearances - see diagram on right

  - Firm, sclerotic mass with various growth patterns and +/- pigment
  - Hilum = Klatskin tumor
- Histology
  - Proliferation of malignant glands with dense fibrosis
- Treatment
  - Surgical excision and/or chemotherapy
- Prognosis is mainly dependent on tumor stage

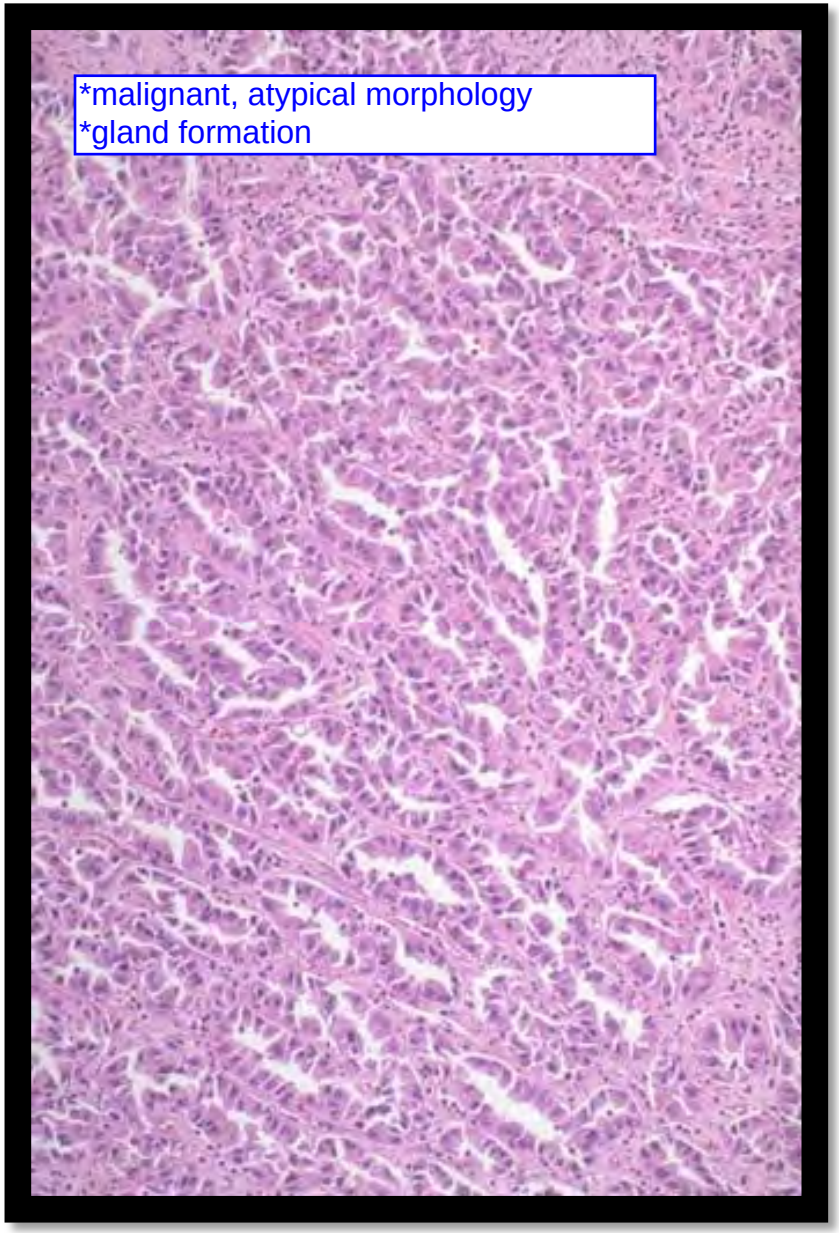


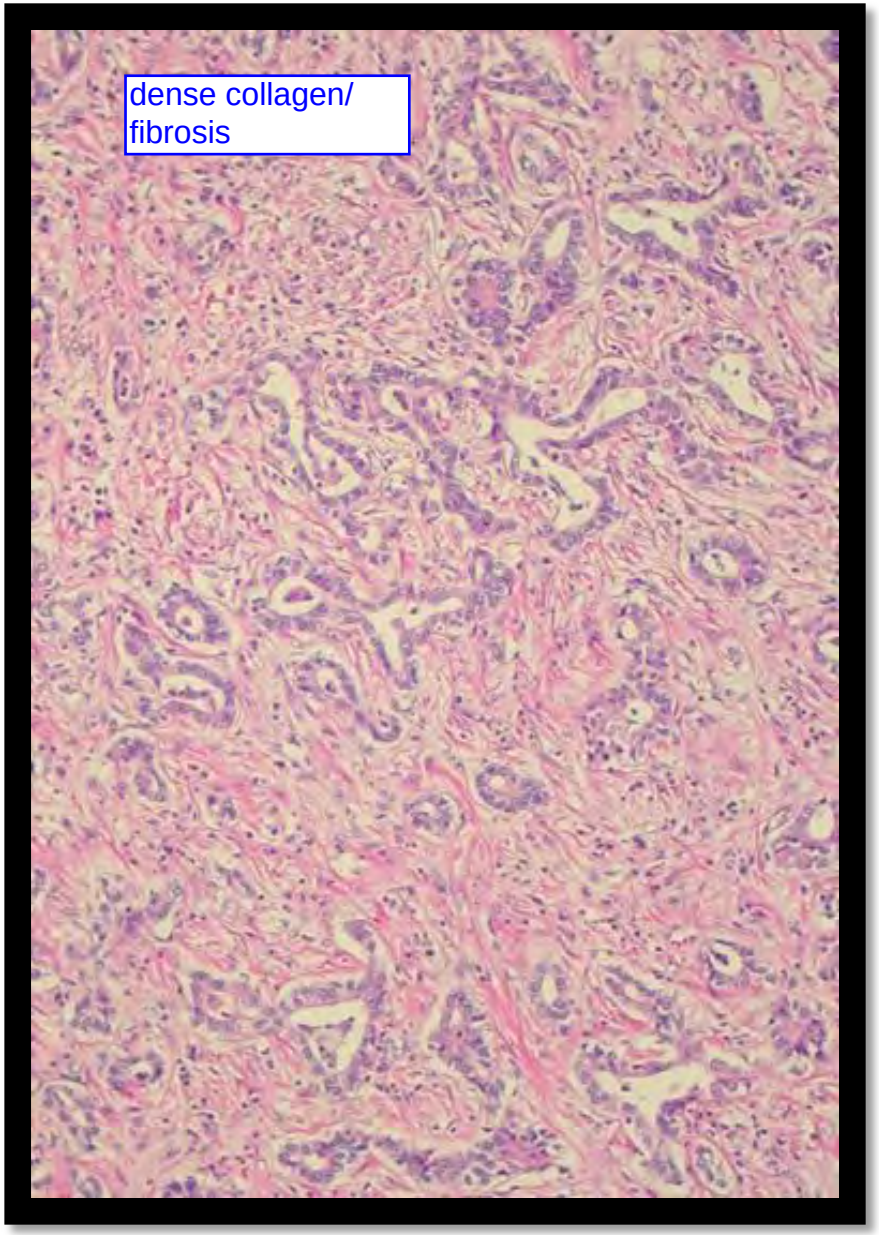


tumor with satellite nodules, involving portal area

mass forming type

Cholangiocarcinoma

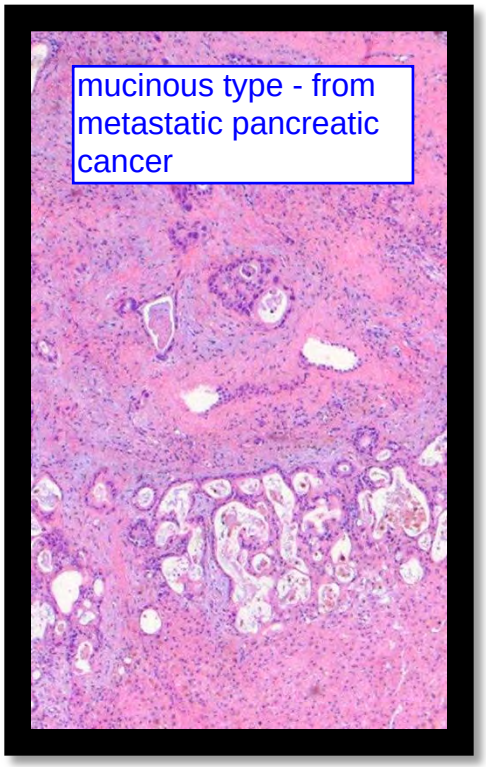




Metastatic Carcinoma

- The most common malignancy in the liver
  - Occurs in 50% of all metastasizing tumors.
  - Form mass(es) but can also be diffuse (sinusoidal)
- Most common origins:
  - Intra-abdominal malignancy (CRC, pancreas, NET, GIST, etc.), breast, lung, melanoma, lymphoma,/leukemia

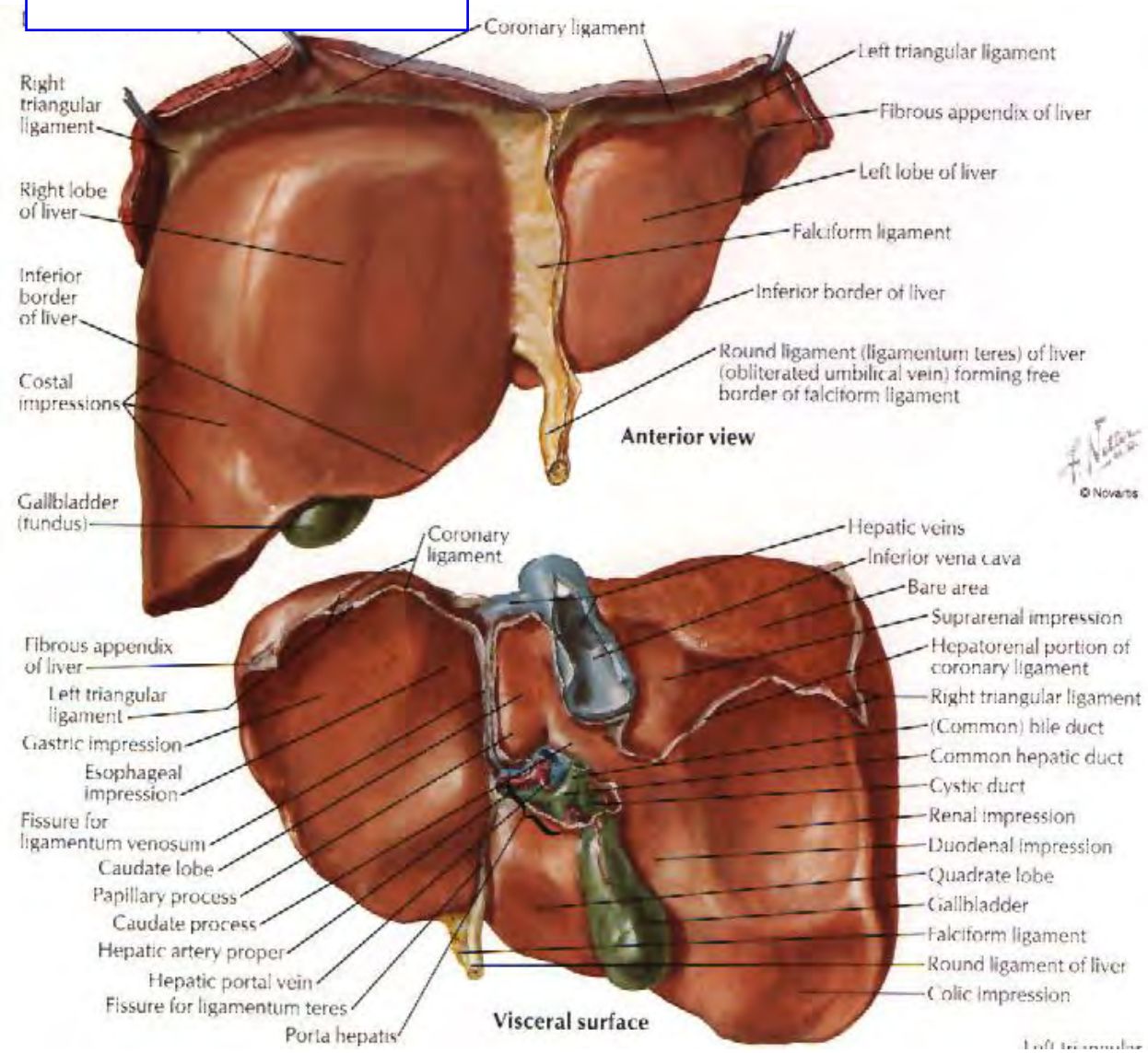
most common metastasis will be from intra-abdminal malignancy

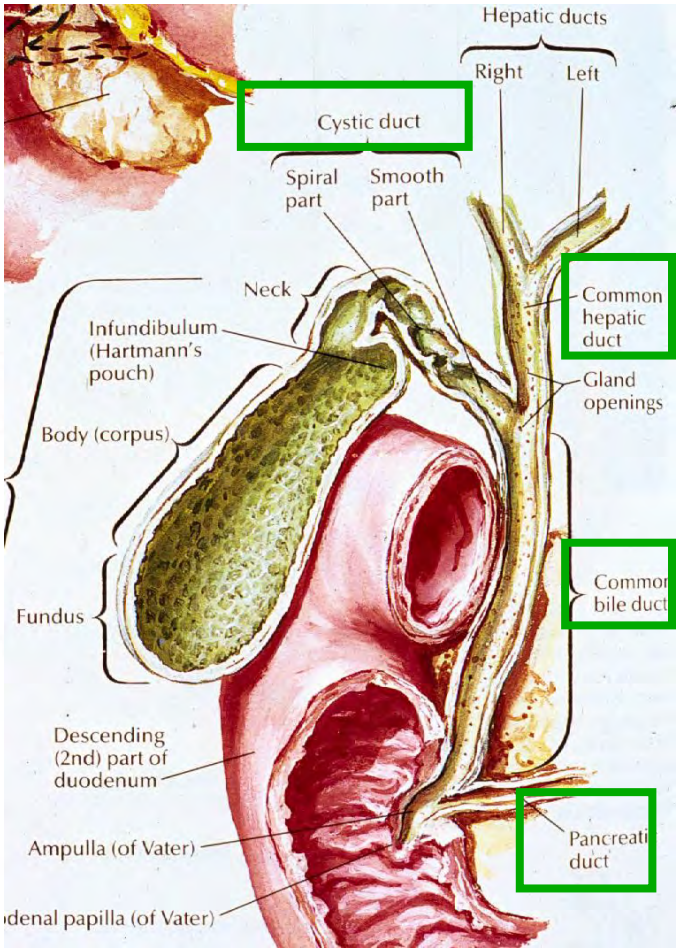


cystic duct leaves gallbladder --> drains into common bile duct -->common bile duct meets up with pancreatic duct -->ampulla of Vater -->duodenum

Gallbladder

located under right lobe of liver (under segments 5, 6)





Disorders of the Gallbladder

gallstones form when solubilizing bile acids and lecithin are overwhelmed by increased cholesterol and/or bilirubin or gallbaldder stasis

more from First Aid

- Cholelithiasis (Gallstones)
  - In general afflicts over 10% of adults in northern hemisphere
    - Prevalence rates are higher in Latin American countries (20 – 40%) and lower in Asian countries (3 – 4%)
  - 2 main types
    - Cholesterol stones (80%)
    - Bilirubin calcium salts (pigment stones)
      - i.e. Sickle cell patients

radiolucent. Associated with obesity, Crohns, CF, advanced age, clofibrate, estrogens, multiparity, rapid weight loss,Native American origin

due to buildup of bilirubin calcium salts

if kids have gallstones, more likely have pigment stones

radiopaque. Associated with chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infection

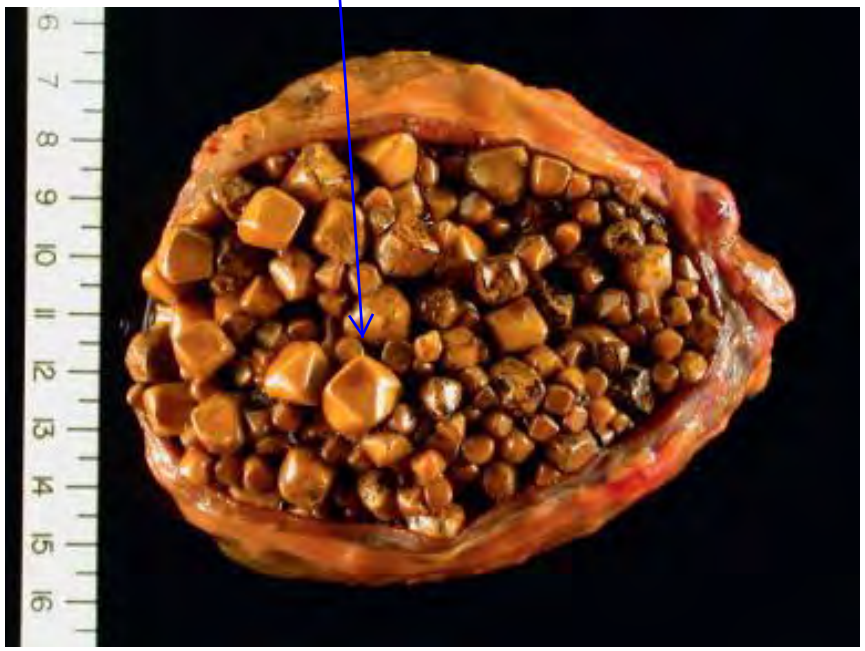
More common in women

- 4^+ „F"s(female, fat, forties, fertile, +family (hereditary))

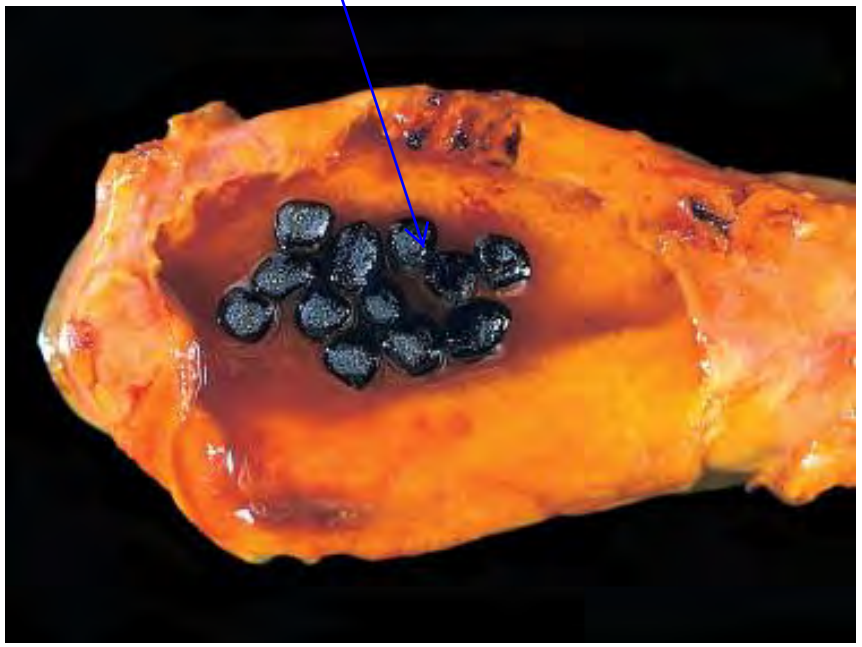
Most common cause of extrahepatic bile duct obstruction

gallstones lodged in cystic duct or common bile duct -->everything backed up in liver

Gallstones



Cholesterol Stones



Pigment Stones

Cholecystitis

rarely occurs due to ischemia or infectious (CMV)

there would be an increase in alkaline phosphatase if bile duct becomes involved (ie ascending cholangitis)

- Inflammation of the gallbladder wall
  - Frequently occurs in association with gallstones
- Acute cholecystitis
  - Sudden onset
  - Inflammation (PMNs), edema, and hemorrhage of the gallbladder wall
- Chronic cholecystitis
  - More common
  - Inflammation, thickening, and fibrosis of the gallbladder wall, and Rokitansky-Aschoff Sinuses

ab pain can radiate to back/shoulder on right side

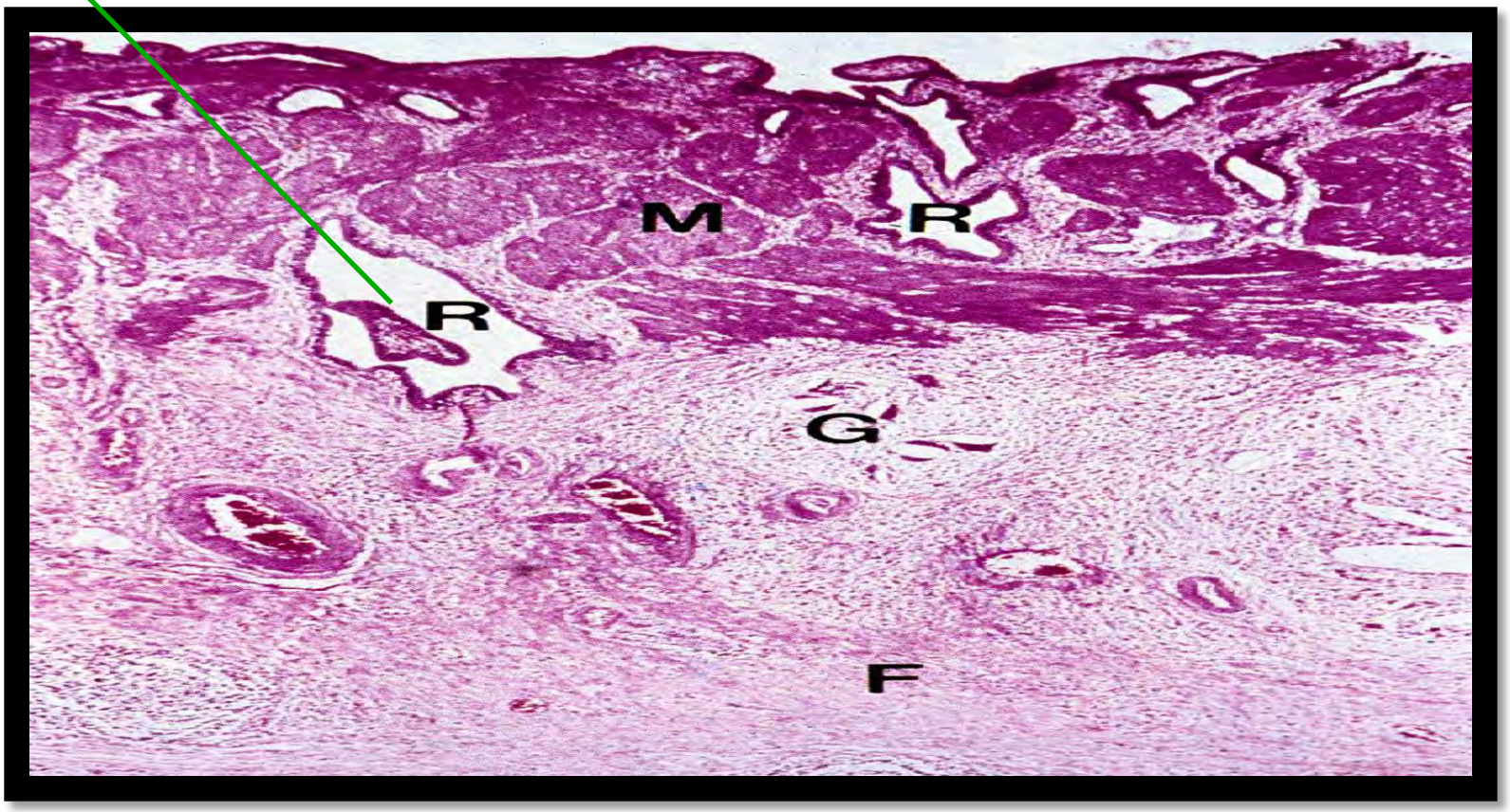
acute cholecystitis not operated on often because risk of rupture is higher -->peritonitis. Usually give some antibiotics/pain meds first until inflammation goes down and then go to surgery

lymphocytes, plasma cells

glands invaginate into wall of gall bladder

Chronic Cholecystitis

- Thickened, inflamed, and fibrotic gallbladder wall
- Rokitansky-Aschoff Sinuses
  - Dilated outpouchings of the mucosal glands into the wall



Gallbladder Tumors

most are primary

extrahepatic adenocarcinoma (outside liver)

- Most are adenocarcinoma
  - Rarely discovered at a resectable stage
    - Poor prognosis
  - Slightly more common in women
  - Most common in the elderly (60 – 70 years of age)
  - Gallstones are present in 60 – 90% of the cases
- Gross morphology
  - Exophytic mass
  - Diffusely infiltrating mass
- Morphology
  - Malignant infiltrating glands

look identical to intrahepatic cholangiocarcinoma (within liver)

both adenocarcinoma and cholangiocarcinoma involve malignant gland formation in biliary system

invade liver

chronic injury, inflammation, fibrosis (fibrosis increases risk of cancer just like in cirrhosis of liver)

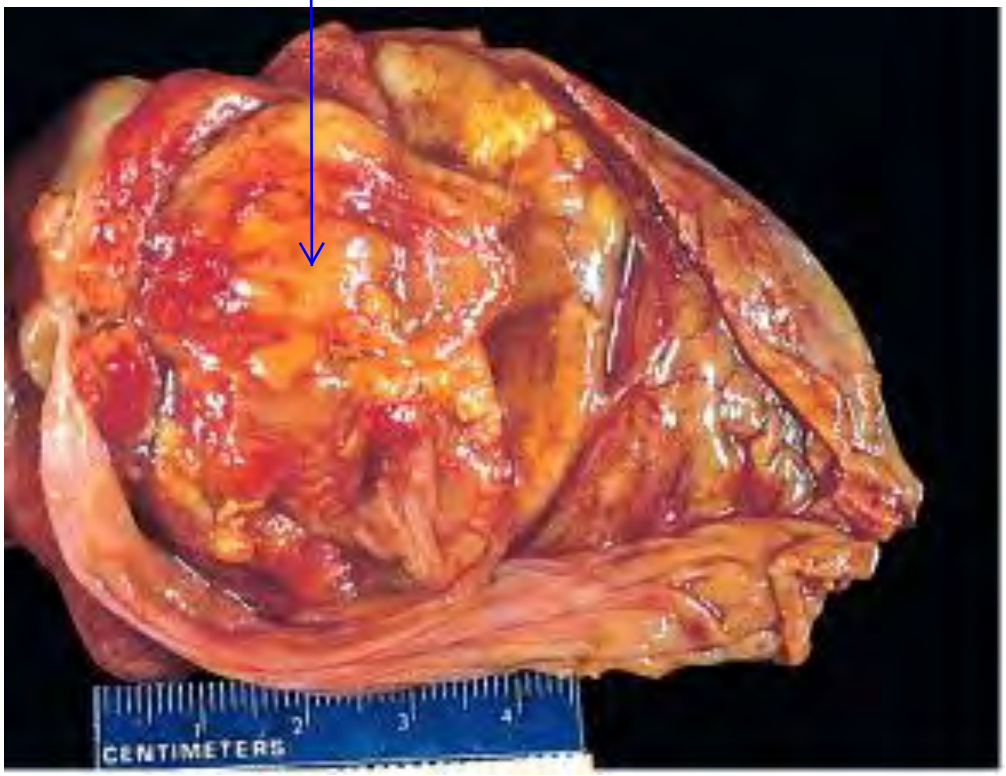
intraluminal

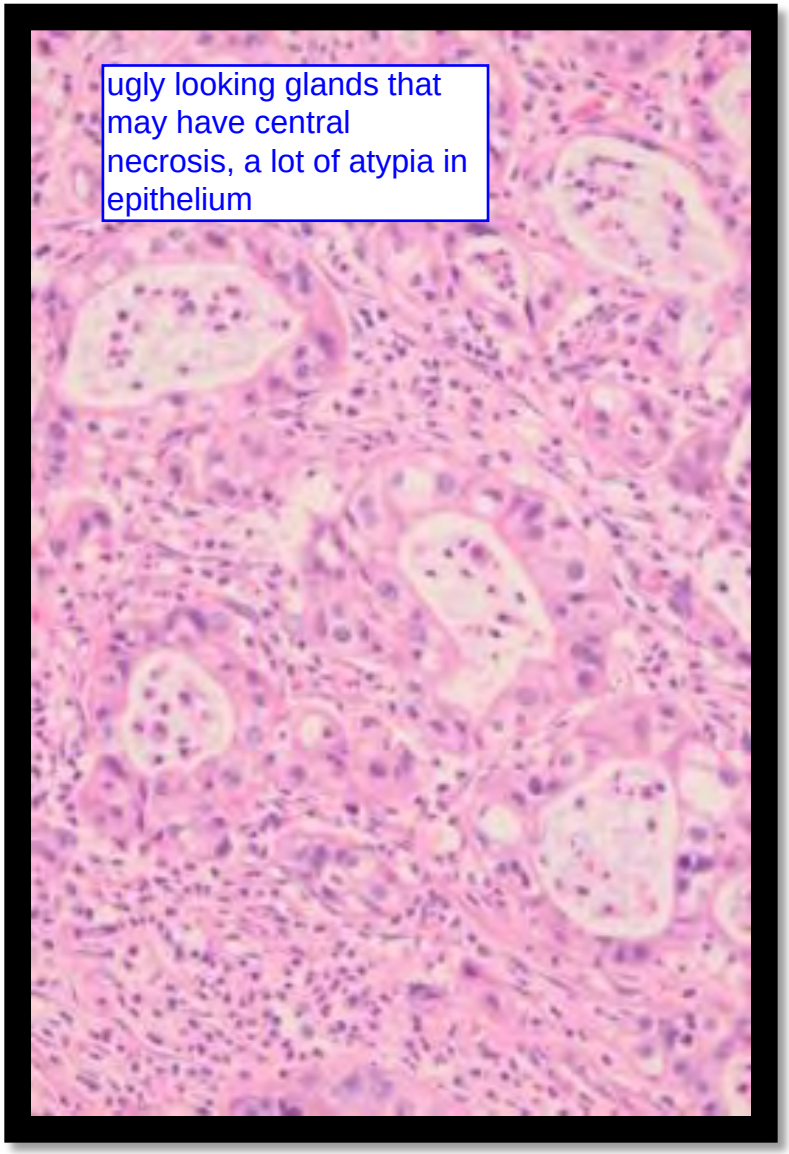
throughout wall of gall bladder into liver

Adenocarcinoma of the Gallbladder

Questions on stickies

exophytic





Bile Duct Hamartoma	*More of a malformation, not neoplastic *Larger ducts *Variable size *Haphazard arrangement of bile ducts
Bile Duct Adenoma	*Neoplastic process *Small ducts *Uniformally arranged ducts *Proliferation of bile ducts
Biliary Cyst	*No ovarian stroma *Lined by benign, flat cuboidal epithelium *Contain serous type fluid in cyst
Mucinous cystadenoma	*Ovarian stroma
Focal Nodular Hyperplasia	*Non-neoplastic/reactive process *Characteristic central stellate scar *Proliferation of all 3 elements (hepatocytes, fibrous stroma with bile ducts, arteries) *See bile duct differentiation
Hepatic Adenoma	*Neoplasm *Benign *Proliferation of hepatocytes *No capsule *Isolated arteries *No bile duct differentiation *Cell plates <3 cells thick
Hepatocellular Carcinoma	*Malignant *Capsule *Cell plates >3 cells thick