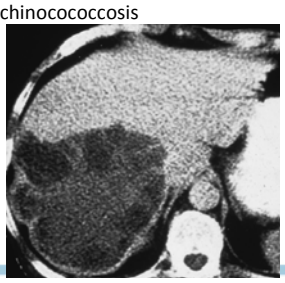
Approach

- 1st Duplex US → Cystic/Solid Lesion
- 2nd if solid lesion then H&P, Labs, Advanced Imaging (if cystic then usually don't do anything unless some unusual features)
    - H&P: RFs (for malignancy), S/S (proceed w/ caution, must r/o other processes to confirm that mass is truly causing Sx)
    - Lab: LFTs, AFP
    - Imaging: US can never firmly make diagnosis, CT w/ Multiphase Contrast provides greater characterization of solid lesion but confirmation and dx of equivocal cases requires MRI w/ Gadolinium Contrast
    - What about Bx?
        - Rarely done w/ only 5% of cases still equivocal after w/u and thus undergo biopsy but many these days opt for close f/u vs biopsy
        - Why?
            - (1) radiology is advancing very quickly obviating the need for invasive diagnosis w/ Bx
            - (2) difficult b/c can miss lesions → false negatives
            - (3) risk of needle tract seeding and tumor spread into circulation if cancer
            - (4) risk of bleeding
- 3rd: Solid Lesion is Malignant vs Benign ("Incidentaloma")
    - Malignant Lesion = aggressive management
    - Benign Lesion = conservative management w/ f/u interval H&P and Imaging (Hz is controversial) → any interval changes require further work-up

Liver Cysts

- **False: trauma, infarction**
- **Fibrocystic Dz**
    - **Simple Hepatic Cyst**
        - Pathophysiology: congenital defect of intrahepatic bile ducts resulting in the formation of cysts lined by biliary epithelium but do not connect with the biliary tree
        - Epidemiology: 2.5% of general population, F>M, increases w/ age
        - Definition: ≤3 simple cysts, <5cm, no FHx, no renal cyst (if any different then consider PCLD or cystadenoma)
        - S/S: asymptomatic discovered incidentally sometimes pain if large, bleeding, get infected, rupture, compress adjacent organs
        - Dx: US (anechoic structures, "simple" = NO septations, papillary projections, calcifications, NB hemorrhage can make hepatic cysts look complex)
        - Tx: nothing unless Sx then lap fenestration, partial hepatic resection or percutaneous aspiration w/ ethanolamine/alcohol/doxycyline sclerosis but recurrence is frequent
    - **PolyCystic Liver Disease (PCLD)**
        - Precursor: Von Meyenburg Complexes aka Biliary Microhamartomas
        - Pathophysiology: in isolation (2/2 PRKCSH mutation which produces hepatocystin which regulates protein folding) or associated w/ ADPKD (50% of pts w/ ADPKD have PCLD)
        - Complications: cholestasis, portal HTN, hepatic venous outflow obstruction or cyst infection occurs (NB surprisingly there is normal hepatocyte volume therefore liver function is usually preserved)
        - S/S/Dx/Tx: similar to simple hepatic cysts except transplants are sometimes done
    - **Von Meyenburg Complexes aka Biliary Microhamartomas**
        - Epidemiology: 1-5% of autopsies
        - Etiology: incidental in normal livers or in pts w/ cystic diseases of the liver
        - Pathophysiology: 2/2 developmental arrest of the primitive ductal plate
        - Bx: incidental small, multiple, asymptomatic congenital collections of cystically dilated ectatic bile ducts embedded in fibrous stroma, ducts contain inspissated bile concretions and polypoid projections into the lumen
        - Complication: cholangiocarcinoma (rare) and PCLD
    - **Type IV/V Choledochal Cyst** (refer)
- **Hepatobiliary Cystadenoma (HBCA)**
    - Epidemiology: adult, F>M
    - Etiology: derived from intrahepatic ovarian heterotopia or ectopic intrahepatic gallbladder rests
    - Subtypes: mucinous (most common) or serous, presence or absence of ovarian like mesenchymal stroma
    - Description: large (~>10cm) single complex cyst w/ thick walls, septation, nodularity, calcifications and papillary projections (not connected w/ normal biliary system)
    - S/S: pain, palpable mass, compressive Sx on biliary tree or other adjacent structures
    - Labs: elevated CA19-9 and CEA (higher compared to other cysts)
    - Bx (mucinous fluid w/in an epithelial lined cyst surrounded by spindle cell stroma surrounded by connective tissue)
    - Complication: sepsis, hemorrhage, rupture, malignant transformation to cystadenocarcinoma (25% risk)
    - Tx: surgical resection b/c of cancer risk
- **Hydatid Liver Cyst**
    - Epidemiology: Southwestern Europe, North Africa, Middle East, South/Central America, North Asia

- Etiology: *Echinococcus granulosus/multicoularis*
- Mechanism**:** fecal-oral transmission of eggs from coyote/wolf/dog/fox/sheep/rodent feces to human mouth (human is an accidental host), eggs penetrate mucosa and migrate to various organs via veins, resulting in cysts that can develop anywhere in the body but 2/3 of pts have liver involvement (other organs include lung, brain, kidneys, spleen, bone, heart)
- Description: 1-20cm, ~cystadenoma but also calcifications and daughter cysts
- S/S: RUQ pain, constitutional Sx
- Dx: high index of suspicion, eosinophilia, serum serology (90% sensitive, variable specificity), Casoni Skin Test
- Complications: can rupture and cause anaphylactic shock or blockage of bile duct, bacterial superinfection
- Tx: controversial, some say if small/non-superficial/asymptomatic then watch others say Tx all cysts b/c of complications, pre-op benzimidazole/mebendazole/albendazole → surgical resection → peel off ectocyst →sterilize space w/ scoliocide, 0.5% EtOH, silver nitrate, hypertonic saline → ensure no bile leakage (caution to avoid spilling the contents of the cyst into the peritoneal cavity b/c highly infectious and will form cysts in other organs, hence never aspirate/Bx) →post-op flagyl x2yrs to prevent alveolar echinocococcosis

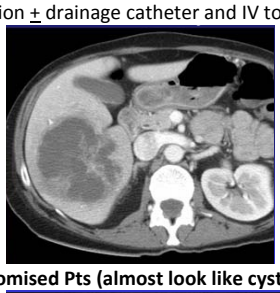


Confluent Granulomatous Disease (refer)

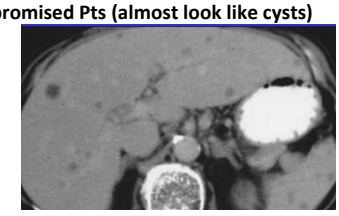
Hematoma

Abscess (refer)

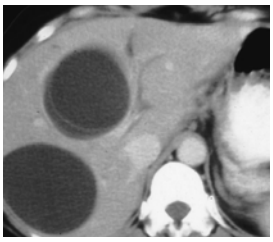
- **Pyogenic Liver Abscess**
  - Mechanism
    - Ascending Cholangitis (monobacterial GN aerobes: *E.coli, Klebsiella, Proteus, Psuedomonas, Strept milleri*, *Proteus* spp.)
    - Systemic Infection via Hepatic Artery (monomicrobial GP aerobes)
    - Intra-Abdominal Infection (Appendicitis, Diverticulitis, IBD, Bowel Perforation) via Portal Vein (polymicrobial and anaerobes)
    - Liver or Gallbladder Cancer
    - Direct Trauma
    - Cryptogenic (most common, 40%)
  - S/S (often non-specific and subtle and may be dominated by the underlying cause eg. appendicitis)
    - F, malaise, anorexia, weight loss, N/V, RUQ pain, jaundice, hemobilia, pts are very ill, fatal if untreated
  - Dx
    - BCx (50% sensitive), Aspirate Cx (90% sensitive)
    - multiple small bilobed abscesses if ascending cholangitis otherwise usually solitary right sided abscess
  - Tx
    - percutaneous aspiration ± drainage catheter and IV to PO BS Abx x4-6wks



- **Candida Microabscesses in Immunocompromised Pts (almost look like cysts)**

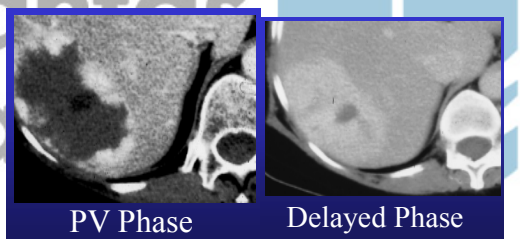


- ***Entamoeba histolytica* Liver Abscess (refer to diarrhea notes, unlike above usually more acute S/S, more jaundice and single abscess)**

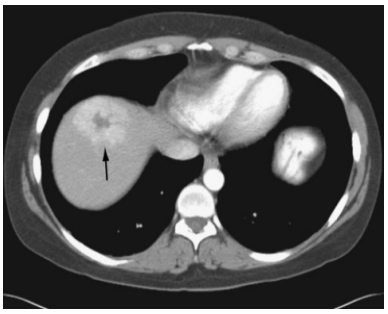


Benign Liver Masses

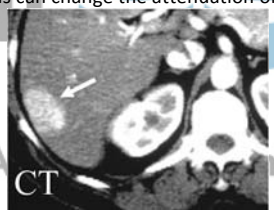
- **Regenerative Nodules (refer)**
- **Cavernous Hepatic Hemangioma (CHH)**
  - Epidemiology: 1% of the population (most common benign solid mass of the liver), F>M (role of estrogen in growth is unclear but some cases grow during pregnancy and w/ OCP use), 20-40yos
  - Pathogenesis: congenital vascular malformation
  - S/S: rarely symptomatic unless complications or increase in size (pain, compression of bile ducts, gastric outlet, etc)
  - Description: 1-5cm (when >5cm then termed "giant") single (10% multiple) blue-red soft subcapsular mass
  - US: hyperechoic mass (NB despite highly vascular lesion blood flow is unimpressive on Doppler b/c very slow)
  - CT: Pre-Contrast Phase (hypodense) → Arterial Phase (contrast has not made its way to the lesion so it still remains hypodense) → Portal-Venous Phase (contrast begins to make its way into the lesion from periphery to center creating a peripherally only hyperdense lesion) → Delayed Phase (contrast finally makes its way through out the entire lesion from periphery to center creating a completely hyperdense lesion)
  - MRI: T1 (hypointense mass) vs T2 (hyperintense mass)
  - Bx: contraindicated b/c r/o bleeding but if done it will show multiple blood filled vascular sinusoids occasionally w/ thrombi and calcifications separated by connective tissue septae
  - Tagged RBC Scintigraphy: rarely done but can be helpful if diagnosis unclear
  - Complications: Rupture/Infarction/Bleeding/Thrombosis (acute Sx of pain, shock, etc, higher risk in pregnancy and w/ OCP use), Kasabach-Merritt Syndrome (consumptive coagulopathy w/ DIC), hemangiomas in other organs
  - Tx: no Tx UNLESS Sx, complications or dramatic increase in size w/ either surgical resection or chemoembolization ("most pts die with it and not from it")



- **Focal Nodular Hyperplasia (FNH)**
  - Epidemiology: 0.4% of population (2nd most common benign solid mass of the liver), adult, female (FALSELY believed to be associated w/ OCP use but not estrogen sensitive rather it is a local hyperplastic response to an underlying congenital AVM)
  - S/S: rarely symptomatic unless complications or increase in size (pain, compression of bile ducts, gastric outlet, etc)
  - Description: 1mm-20cm (average ~5cm) single (25% multiple) subcapsular mass w/ a central stellate scar characterized by radiating hypervascular fibrous septa (NB sometimes HCC can have central stellate scar appearance)
  - US: isoechoic mass
  - CT: Pre-Contrast Phase (iso/hypodense w/ no apparent scar 80% of the time) → Arterial Phase (hyperdense lesion w/ hypodense scar, NB unlike hemangiomas) → Portal-Venous Phase (slow washout w/ lesion becoming isodense, peripheral enhancement may be seen) → Delayed Phase
  - MRI: T1 (iso/hypointense mass) vs T2 (iso/hyperintense mass)
  - Sulfur Colloid Scan will light up this lesion b/c this mass contains Kupffer cells which pick up sulfur colloid unlike any other mass
  - Bx: "focal area of cirrhosis" = fibrotic septa w/ intervening parenchyma that has distorted architecture
  - Complications: hemorrhage/necrosis (rare), metachronous HCA/CHH
  - Tx: conservative observation w/ imaging and not Tx UNLESS Sx, complications or dramatic increase in size then resection



- **HepatoCellular Adenoma (HCA)**
  - Epidemiology: 0.004% of population, F>M, adult
  - Pathogenesis (NB many pts have no identifiable risk factor)
    - OCP/Pregnancy (2/2 estrogens which have a trophic effect, before the advent of OCPs in the 1960s these tumors were very rare, there is increase in size during pregnancy and regression after pregnancy)
    - Anabolic Androgen Steroids
    - Type Ia/III Glycogen Storage Diseases (GSDs)
    - Antiepileptic Drugs (new)
    - Hepatic Hemosiderosis (new)
    - NAFLD (new)
  - Subtype (new concept, ability to differentiate on MRI is emerging making non-invasive dx possible, each subtype seem to have variable risk for HCC conversion, presented at DDW Post Graduate Course by Dr. K Rajender Reddy)
    - Hepatocyte Nuclear Factor 1-Alpha (HNF1-α) Inactivating Mutation
    - Inflammatory (IHCA) aka "Telangiectatic HCA"
    - Beta-Catenin (β-catenin) Activating Mutation
  - S/S: 75% asymptomatic vs 25% symptomatic w/ RUQ pain, N/V, anorexia, variable LFTs
  - Description: 1-15cm, single (25% multiple, "adenomatosis" if >10 lesions, seen in GSDs/NAFLD, higher r/o complications) yellow subcapsular mass
  - US: hyperechoic mass
  - CT: Pre-Contrast Phase (isodense) → Arterial Phase (hyperdense) → Portal-Venous Phase (rapid washout w/ lesion becoming isodense)
    - NB occasionally rim enhancement will be seen if a capsule is present
    - NB hemorrhage and calcifications can change the attenuation of these lesions



  - MRI: T1 (hypointense mass) vs T2 (hyperintense mass)
    - NB various hepatocyte-selective MRI contrasts (eg., Eovist) have been used to differentiate b/t FNH (hyperintense) and HCA (hypointense)
  - Technitium-99m Sulfur Colloid Scintigraphy: tracer taken up by Kupffer cells which are low in number in HCA and high in number in FNH hence cold defect in HCA vs hot uptake in FNH
  - Bx: contraindicated b/c r/o bleeding but if done will show strikingly normal appearing liver tissue except for some subtle changes including thick plates, slightly atypical hepatocytes, dilated sinusoids, absence or abnormal bile ducts / portal vein / central vein
  - Complications
    - Hemorrhage ± Rupture & Hemoperitoneum (20% risk)
      - S/S: acute Sx of pain, shock, etc
      - RF: adenoma (multiple/large/rapidly-growing/superficial), pt (concurrent OCP use, after menstruating or pregnant at that time)
      - Tx: emergent surgery vs embolization
    - HCC (5% risk)
      - S/S: any change in symptoms, size, LFTS, AFP
      - RFs: >5cm, beta-catenin mutation, GSD
      - Tx: resection
  - Tx (controversial)
    - 1st Reverse Etiology (HCA may decrease in size or disappear) and advise female pts to avoid pregnancy

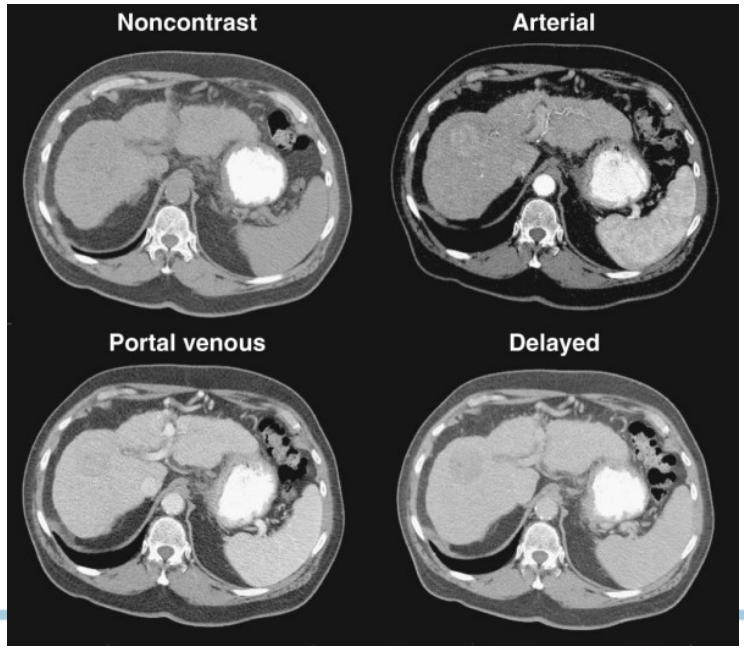
        - 2nd Conservative Tx if asymptomatic, <5cm and HNF1-α/IHCA subtype vs Resection if symptomatic OR >5cm OR β-Catenin subytpe
            - Why? these are the most well defined RFs for complications
            - NB there are recent reports of complications occurring in adenomas that are small or that have decreased in size
- **Nodular Regenerative Hyperplasia (NRH)**
    - Epidemiology: rare
    - Pathogenesis: non-specific tissue adaptation to heterogeneous distribution of blood flow with subsequent atrophy of affected areas (Zone 3) and compensatory hyperplasia (Zone 1) occurring in areas with adequate blood supply
        - Vascular (BCS, PVT)
        - Toxins (Azathioprine, various chemo)
        - CVD (SLE, SSc, RA, Felty's)
        - Liver Dz (PBC, s/p Liver Tx)
        - Cancer (MPD, NHL, s/p BM Tx)
        - Immunodeficiency (HIV)
        - Heme (hypercoaguable)
    - S/S: asymptomatic and typically benign
    - Description: diffuse fine (1-2mm) nodularity distributed throughout the liver in the absence of fibrous septa between the nodules, sometimes very subtle on Bx
    - Bx: often needed to confirm Dx, thick liver plates w/o fibrosis, often confused for cirrhosis and there have been many cases of pts inappropriately undergoing transplant
    - Complications: portal hypertension however subsequent complications are unusual
    - Tx: treat underlying condition
    - NB **"Partial Nodular Transformation of the Liver"** (essentially NRH restricted to the hilum)
- **Infantile Hemangioendothelioma**
    - Epidemiology: F>M, children (most common liver tumor of infants)
    - Pathogenesis: vascular tumor derived from endothelial cells
    - S/S: solitary/multifocal, often large (2mm-20cm) mass resulting in hepatomegaly, LFTs (hyperbilirubinemia)
    - Dx: US (variable echoic mass), CT/MRI (hyponense dense w/ dilated, irregular vascular lakes whose enhancement persists beyond the arterial phase), Bx (contraindicated, multiple small vessels lined by plump endothelial cells surrounded by fibrous stroma w/ calcifications)
    - Complications: problems form hepatomegaly, high output CHF (these tumors act as a AV shunt), coexist w/ hemangiomas in other organs esp skin, rupture, Kasabach-Merritt Syndrome, other abnormalities including ASD, PDA, myelomeningocele, renal agenesis, etc, rare conversion into angiosarcoma
    - Tx: tumor grows during the first 6mo of life followed by involution depending on size, if significant tumor exists then Tx w/ medical Tx (steroids, Cyclophosphamide, IFN-2apha), hepatic artery ligation, radiation, etc, if CHF is managed pts generally do well, transplantation
- **Intrahepatic Bile Duct Adenoma** (rare, M>F, adults, solitary subcapsular mass, Bx (numerous normal appearing bile ducts surrounded by fibrous stroma), different than cholangiocarcinoma which has cellular atypia, mitotic activity, vascular invasion, etc, believed to be a reactive process to focal injury)
- **Mesenchymal Hamartoma** (rare, tumor, childhood, M>F, solitary large cystic mass, Bx (tissue contains hepatic cells with vascular proliferation interspersed w/ cystic spaces, resection if large and symptomatic)
- **Focal Fatty Change** (localized steatosis, US (hyperechoic area), CT (well-defined geometric hypodense areas w/ no vessel displacement or mass effect despite looking like a non-spherical "mass", generally there is rapid change over time (days-weeks), MRI (T1 hyperintensity)) believed to be 2/2 altered venous blood flow to the liver, tissue hypoxia and lipoprotein malabsorption
- **Psuedolipoma** (lipocytes detaching from adherent epiploic appendices)
- **Inflammatory Psuedotumor** (localized area of hepatic mass, usually seen in young men who have an extrahepatic infection though rarely are microorganisms identified in the "tumor", usually symptomatic w/ fever and ab pain, leukocytosis abnl LFTs, US (heterogenous lesion w/ mosaic pattern), CT (irregular heterogenous hypodense mass), must differentiate from abscess, Bx is usually needed to make dx, Bx (fibrous tissue infiltrated by plasma cells), may regress spontaneously but some cases require antibiotics or steroids or even surgery)
- **Angiomyolipoma** (collection of adipose tissue, smooth muscle, vessels)

Malignant Liver Masses

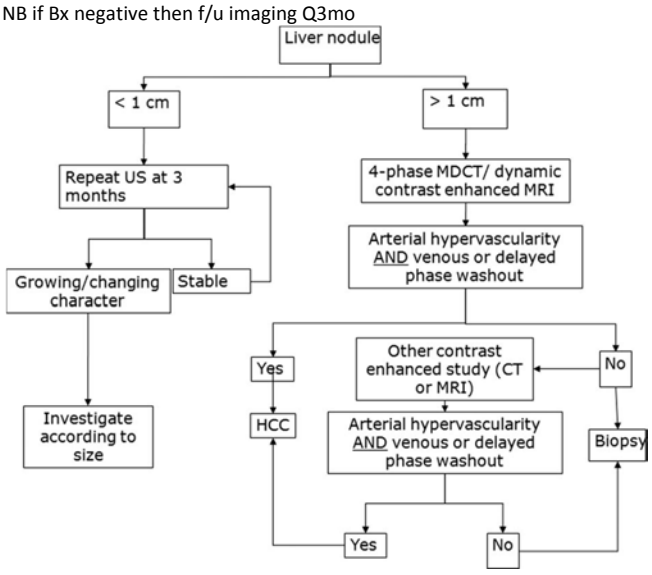
- **Mets**
    - 2nd most common site for metastasis!!! (first are LNs)
    - Only 2% have a single nodule vs 98% multiple nodules
    - Why? 2/2 immense blood flow to liver and the presence of fenestrations in the sinusoidal epithelium that facilitates malignant cell penetration into hepatic parenchyma
    - Originate from organs w/ portal venous return (GI w/ 1° CRC) but also others (breast, lung, pancreas, stomach)
    - CT (mets can look like anything!!!)
        - Non-Enhancing w/ Contrast ake Hypovascular: GI, Lung, Breast, Lymphoma
        - Enhancing w/ Contrast aka Hypervascular: Breast, Neuroendocrine, Renal, Thyroid, Melanoma, Sarcoma
    - Can be expansive w/ discrete masses or infiltrative
    - Tx: treat underlying cancer, consider regional therapy for liver mets similar to that used in HCC

- **Intrahepatic Cholangiocarcinoma** (refer, 15% of all primary liver cancers and 25% of cholangiocarcinomas)
- **Cystadenocarcinoma** (refer above)
- **Hemangiosarcoma**
    - Epidemiology: elderly, M>F
    - RFs
        - Vinyl Chloride Monomer – VCM (old inhalational anesthetic and aerosol propellant but when polymerized it forms non toxic PVC used to make pipes)
        - Thorium Dioxide aka Thorotrast (old IV contrast)
    - Features: 15% can rupture, rapidly growing multicentric mass w/ blood filled cyst, Kasabach-Merritt Syndrome (platelets entrapped w/in tumor), DIC, microangoipathic hemolytic anemia
    - Tx: very poor prognosis even when surgery is attempted
- **Hepatoblastoma**
    - Epidemiology: 1-3yo, M>F, sporadic (no clear environmental RF) or in association w/ Beckwith-Weidmann Syndrome and FAP, 3rd most common malignant tumor in children and 1st most common hepatic malignant tumor in children
    - Features: p/w a large well-circumscribed solitary rapidly progressive ab mass, paraneoplastic syndrome of precocity in boys 2/2 human chorionic gonadotropin and thrombocytosis 2/2 thrombopoietin, +AFP
    - Tx: very poor prognosis, neo-adjuvant chemo followed surgery
- **Epithelioid Hemangioendothelioma**
    - Epidemiology: very rare w/ only 137 cases reported, F>M, adults
    - Features: multiple highly vascular masses which may infiltrate throughout the liver
    - Tx: good prognosis and thus must be distinguished from hemangiosarcoma
- **Hepato Cellular Carcinoma (HCC) aka Hepatoma**
    - Epidemiology
        - Incidence: 5 cases / 100,000 / year, increasing since 2000 worldwide, 5th / 4th most common annual incidence/mortality cancer in the US, highest incidence in Sub-Saharan Africa and China
        - AA/Asians>Hispanics>Whites
        - M>F
    - Pathology/Etiology
        - Non-Fibrolamellar (more common, multiple lesions, usually unresectable and thus shorter survival times, usually has elevated AFP, typically occurs in older pts w/ h/o cirrhosis)
            - HepB/C
                - HBV: risk is 2.5%/yr if cirrhosis
                    - Theory: b/c DNA virus HBV genome randomly integrates into human genome resulting in cis-activation of oncogenes and (possibly) the T&T of carcinogenic HBV hence HCC can occur in pts w/o cirrhosis
                    - Prevention: anti-viral Tx does NOT reduce risk (therefore continue surveillance regardless sero-conversion)
                - HCV: risk is 2%/yr if cirrhosis
                    - Theory: HCC occurs mainly in cirrhotic livers w/ higher incidence than would be expected for cirrhosis alone suggesting that additional chronic inflammation is likely a contributing cause
                    - Prevention: anti-viral Tx does reduce risk BUT risk is not eliminated (therefore continue surveillance regardless of SVR)
            - Cirrhosis of Any Type
                - chronic cycles of hepatocyte necrosis followed by regeneration eventually leads to the selection of autonomous cell lines leading to cancer
                - RFs: metabolic syndrome, macro/irregular regenerative nodules, higher AFP, male gender, increasing age
                - Anytime you see multiple masses in a cirrhotic liver it is uniformly HCC and NOT mets (think about this way it is hard for cancer to infiltrate a scarred liver in addition to the fact that blood flow thru the liver is impaired)
            - Cryptogenic
        - Fibrolamellar (less common, single lesion in left lobe, usually resectable and thus longer survival time, usually has normal AFP, typically occurs in younger pts w/o h/o cirrhosis, cells are uniquely plump, deeply eosinophilic and encompassed by abundant fibrous stroma composed of thin, parallel fibrous bands that separate the cells into trabeculae or nodules, cytoplasm is packed w/ swollen mitochondria and hyaline bodies w/ prominent nuclei)
            - Carcinogens: Smoking, Androgenic Steroids, OCP
            - Genetic: Hemochromatosis, Alpha-1 Antitrypsin Deficiency, Ataxia Telangiectasia, Inborn Errors of Metabolism (all of these can occur prior to cirrhosis)
            - Membranous Obstruction of the IVC
            - Hepatic Adenomas
            - Infections: *Aspergillus flavus/parasiticus* (mold infecting corn/nuts/beans/grains stored in warm moist conditions) → dietary intake of Aflatoxin B1 → acute consumption leads to hepatitis → chronic consumption leads to an inactivating mutation of the p53 tumor suppressor gene

- Clinical Features
  - Variable LFTs
  - Constitutional Sx
  - Decompensating Cirrhosis (eg. worsening ascites, encephalopathy, et al)
  - Interval increase in liver size instead of the natural slow decrease in size seen in cirrhosis
  - Non-Specific GI Sx
    - RUQ Pain (stretches capsule and impinges on diaphragm w/ referred R shoulder pain)
    - Ascites (reflecting peritoneal metastasis or hepatic/portal vein invasion causing portal HTN)
    - Smooth to Nodular HM w/ Arterial Bruit
    - Jaundice
    - Intra-abdominal bleeding from rupture of liver capsule
  - Paraneoplastic Syndrome (uncommon)
    - Erythrocytosis 2/2 Erythropoeitin (10%)
    - Hypoglycemia 2/2 ILGF (5%)
    - Hypercalcemia 2/2 PTHrP (rare)
  - Pityriasis Rotunda Circumscripta (distinct, circular, scaly, patches on the torso)
- Diagnosis (diagnosis can now be made by clinical picture and imaging alone)
  - Alpha Feto Protein (AFP)
    - Other Markers: Des-Gamma-Carboxy-Prothrombin (abnormal prothrombin produced by HCC cells), glypican-3, golgi protein-73, hepatocyte growth factor, et al
    - Sensitivity
      - Variable depending on the ethnicity (higher AA), age (higher the younger), underlying cause of liver dz (higher in non-fibrolamellar form), stage (higher in higher stages)
      - Depends on what the cut-off is for positivity (60% if >20ng/mL to 22% if >200ng/mL, in most liver clinic settings w/ a prevalence of 5% the PPV is 41% if >20ng/mL to 60% if >200ng/mL)
      - HCC levels can range anywhere from 1,000 to 1,000,000
    - Specificity
      - also produced by normal fetal liver (alpha-globulin normally found in [high] in fetal serum but thereafter at [low]), regeneration following acute liver injury/failure, adult cancers adult mesodermal tumors (germ cell tumors), intrahepatic cholangiocarcinomas!!!, CRC mets!!!, pediatric endodermal tumors (teratomas, hepatoblastoma, yolk sac carcinoma, neuroblastoma), pregnancy
      - Rapid doubling time and a value >400ng/mL is highly specific
      - AFP secreted by HCC has an unusual complex sugar side chain (L3) which can be detected increasing specificity
    - Not used in surveillance algorithms b/c neither sensitive nor specific
    - Can be used to monitor response to therapy
  - Imaging
    - Sometimes difficult to distinguish from background nodularity
    - US (48% sens 97% spec, variable in appearance from hypo to hyperechoic)
    - Contrast enhanced CT or MRI
      - multiphase (non-contrast (variable) → arterial (enhancement) → venous (central-to-peripheral washout) → delayed (full washout))
      - Sens: 61-75% Spec: 66-76% (CT-MRI therefore MRI is better)
      - MRI provides better anatomy of the tumor than just CT
      - Why enhancement? liver is less enhanced b/c it contains both contrast arterial blood and non-contrast venous blood while HCC only gets contrast arterial blood and during the venous phase the HCC is less enhanced compared to liver b/c it contains no contrasted portal blood
      - low sensitivity also b/c some HCC are more infiltrative and not a distinct mass
      - important to note that CT and MRI are complementary in that some lesions not seen on MRI are seen on CT and vice versa
    - NB only 50% are PET active
    - HCC can be multiple nodules (esp in cirrhotic livers), single large mass w/ satellite nodules (esp in non-cirrhotic livers), infiltrating (rare)



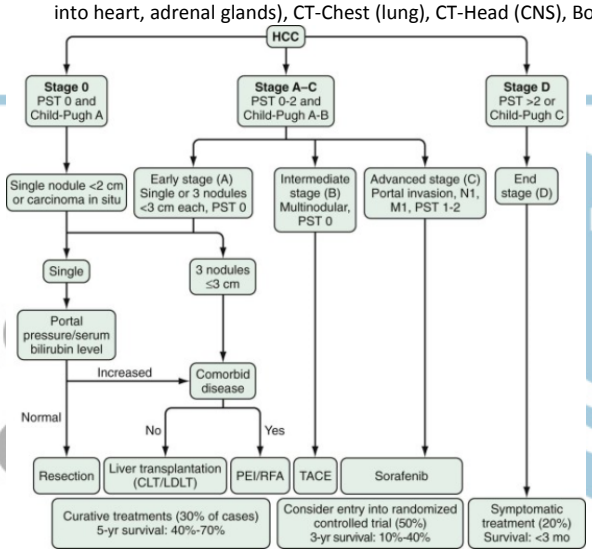
- US/CT Guided Percutaneous Liver Bx/FNA (Gold Standard)
  - Only do if imaging is equivocal otherwise don't do b/c (1) 20% false negative b/c you have to stick a needle thru dense cirrhotic tissue while trying to hit a small lesion, (2) you need a lot of tissue to accurately make a dx, (3) r/o bleeding, (4) r/o seeding
  - Stains: CD34, CK7, glypican 3, HSP-70, glutamine synthetase
- HCC Screening/Surveillance
  - Why? once Sx develop HCC is seldom amenable to surgical cure
  - Screening of Populations w/ High Incidence: not cost-effective or have significant impact on overall survival
  - Surveillance of Pts w/ High Risk (>1.5% risk/yr): US Q6mo (some alternate US w/ CT/MRI and add AFP and increase to Q12mo)
    - Who?
      - Cirrhotics
      - Chronic HBV Carriers w/o Cirrhosis but are AA >20yo, Asian male >40yo, Asian female >50yo, +FHx or acquired HBV perinatal or during childhood
      - It appears that pts w/o cirrhosis but w/ hemochromatosis and A1AT may have increased risk of HCC
- Approach (algorithm) 1cm
  - NB if a <1cm lesion is stable after 2yrs of Q3mo US f/u then go back to Q6mo
  - NB if Bx negative then f/u imaging Q3mo



- Tx (algorithm)
  - Barcelona Clinic Liver Cancer (BCLC) System (most common system used and currently adopted by the AASLD)
    - Based on Stage (TNM, vascular invasion) + Performance Status (0 good, 1 moderate, 2 poor) + Child Score

Stage		T	N	M
I		1 (solitary lesion w/o vascular invasion)	0	0
II		2 (solitary lesion w/ vascular invasion or multiple tumors none >5cm)	0	0
III	**A**	3a (multiple tumors >5cm)	0	0
	B	3b (any numbers of tumors involving major branch of portal/hepatic vein)	0	0
	C	4 (direct invasion of adjacent organs other than GB)	0	0
IV	**A**	#	1	0
	B	#	#	1

    - Metastasis: CT-Ab w/ contrast (portal vein as these tumors often spread hematogenously even up into heart, adrenal glands), CT-Chest (lung), CT-Head (CNS), Bone Scan (bone)



    - **Resection**
      - Consider if single <2cm lesion
      - Use of neoadjuvant therapy is controversial
    - **Transplant**
      - the decision for transplantation in the BCLC algorithm is based on the original Milan Criteria (≤5cm or ≤3 lesions and each ≤3cm w/ total tumor burden of ≤9cm and no vascular invasion) NB there is a lot of debate about expanding these criteria (particularly at UCSF and BUMC) to include single lesions ≥6cm and multiple lesions ≤5cm)
      - Provides the best chance for cure, better results compared to any other Tx modality, also addresses the underlying insult to the liver
      - MELD poorly predicts mortality in HCC pts hence UNOS changes the point system for HCC pts giving them 22 points if HCC >2cm or >1 nodule, in addition a 10% point increase is given Q3mo on waiting list (importantly HCC transplanted pts vs non-HCC transplanted pts w/ equivalent MELD have worse prognosis)
      - NB some use Tx below as a bridge to resection/transplant (controversial) as pts can fall off the transplant list if the wait is long
    - **Local Ablative Therapy**
      - Done if lesions meet Milan criteria but pt has comorbid conditions prohibiting transplant
      - US guided Percutaneous **Radiofrequency Ablation (RFA)** preferred over **Percutaneous Ethanol Injection (PEI)** b/c more effective, can Tx larger tumors, requires fewer sessions BUT higher costs and adverse events (NB PEI is generally used for tumors adjacent to large vessels/ducts)
      - New: Cryo/Microwave/Laser Ablation, Acetic Acid/Boiling Saline Injection
      - Effectiveness of Tx is assessed by CT Q3-4mo demonstrating lack of vascular enhancement

- **Chemoembolization**
  - Done if pts does NOT meet Milan criteria
  - **TransArterial ChemoEmbolization (TACE)** initially w/ chemo (eg. adriamycin, cisplatin) followed by a thrombotic agent (eg. gelfoam, coils)
  - HCC uniquely gets its blood supply by neo-angiogenesis from the hepatic artery w/ no blood from the portal system while normal liver tissue gets blood supply from both portal vein and hepatic artery
  - New: Yttrium90-labeled glass beads
- **Chemotherapy**
  - radiation has very little activity against HCC w/ high toxicity and no change in survival
  - Done if pt has Stage IV cancer
  - **Sorafenib (Nexavar)**
    - Inhibitor of Raf/VEGF/PDGF/c-kit kinases
    - SEs: hand-foot rash, diarrhea
    - SHARP Trial (NEJM 2008) Multicenter Phase III RCT: 602 pts, hazard ratio 0.69 (95% CI: 0.55-0.86, P = 0.0006) w/ a median survival for sorafenib arm of 10.7 months vs 7.9 months for placebo (NB Criticisms: studied in Child A, ECOG 0, BCLC C)