EVALUATION OF LIVER MASS LESIONS
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Clinical Classification of Liver Mass Lesions
It is helpful to subclassify lesions into three clinical subcategories. First are benign mass lesions for which no treatment is needed; second are benign mass lesions for which treatment is required; and third are malignant mass lesions for which treatment is always required if feasible.1

Clinical Evaluation
The clinical evaluation of liver mass lesions begins with a careful history and physical examination. Historical features will often give clues to the underlying diagnosis. For example a history of chronic hepatitis or the features or complications of liver cirrhosis is helpful in determining if individuals are at risk for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. A history of primary sclerosing cholangitis is helpful for determining if an individual is at risk for cholangiocarcinoma and a history of long term contraceptive use is helpful in identifying those women at risk for hepatic adenoma. Similarly, individuals with a family history of young onset diabetes mellitus may be at risk for hepatic adenomatosis. In general a history of abdominal pain tends to be nonspecific and unhelpful but pain caused by non-intra-abdominal causes such as abdominal wall pain is sometimes the reason that a patient with a liver mass will initially present for evaluation. Individuals with biliary obstruction will typically present with jaundice with associated pruritus, dark urine and pale stools. A history of constitutional symptoms such as fever may be useful in the diagnosis of hepatic abscesses; fever can also be associated with malignancy. Other features of malignancy include anorexia, weight loss, and fatigue. The history is complemented by the results of the physical examination. The physical examination can reveal features of chronic liver disease such as spider angiomas, a periumbilical caput medusa indicative of portal hypertension, hepatomegaly or splenomegaly. The finding of jaundice in a patient with no history of pain is highly suggestive of the development of a malignancy such as cholangiocarcinoma or pancreatic adenocarcinoma. Advanced malignant infiltration and some benign masses may be associated with palpable hepatomegaly, which may be nodular in the presence of cirrhosis or focal masses. History and physical examination findings are complemented by the results of laboratory tests which can indicate or reveal whether the patient has active hepatitis, chronic liver disease with cirrhosis, portal hypertension and hypersplenism resulting in a low platelet count, or hyperbilirubinemia. The use of the serum alpha fetoprotein (AFP) test as a surveillance test for hepatocellular carcinoma is controversial due to its low sensitivity for the detection of early stage disease. The AFP test is well-established as a predictor of risk of development of HCC in individuals with cirrhosis and can be extremely useful for diagnosis of HCC in those individuals with diffuse HCCs who do not have focal liver lesions on imaging studies. While one-time determinations of the AFP have a high false positive rate, particularly in patients with chronic hepatitis C virus infection, careful attention to trends in AFP levels can prove invaluable in the early diagnosis of HCC. The AFP-L3 isoform and des-gamma carboxyprothrombin (DCP) are also predictors of risk of HCC. The CA19-9 test is helpful in the diagnosis and prognostic prediction of patients with cholangiocarcinoma. In the absence of acute cholangitis, a CA19-9 value greater than a 1000 units/mL is almost always associated with the presence of extrahepatic disease. The CEA is valuable in assessing colorectal cancer metastatic to the liver and the chromogranin A and 24-hour urine 5-HIAA are useful for assessing neuroendocrine carcinomas metastatic to the liver.

Radiologic Imaging Studies Are Critical for Accurate Characterization of Liver Mass Lesions
Careful examination of the radiologic features of the liver mass as assessed by liver ultrasonography (US) or by cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) can be extremely helpful in determining the nature of the mass. In particular, for those individuals with chronic hepatitis B virus infection or cirrhosis from other causes who are at risk for development of hepatocellular carcinoma, regular surveillance ultrasonography performed every six months is recommended for early identification of newly developed hepatocellular carcinomas and is the most critical clinical tool for achieving long term survival of patients with hepatocellular carcinoma.

The Importance of Multiphasic Cross-sectional Imaging in the Evaluation of Liver Masses
Cross-sectional imaging methods such CT and MRI are substantially enhanced by the use of intravenous contrast agents for multiphasic examination techniques. The liver is unique in having three phases to its blood supply. First is the arterial phase that is caused by the direct infusion of arterial blood from the heart through the hepatic artery into the liver; second is the portal venous phase which is composed of the collection of arterial blood which has gone through the mesenteric and splenic arteries into the gastrointestinal tract and spleen and is now collected with the absorbed nutrients from the
gastrointestinal tract and brought to the liver for processing. The portal venous supply, which still has a high arterial oxygen concentration, provides approximately 80% of the blood supply to the normal liver tissue. The remaining 20% of the blood supply to the liver is provided by the hepatic artery. The blood coursing through the liver is collected into the hepatic vein branches which converge to the inferior vena cava and is returned to the right side of the heart. This phasic blood supply to the liver is exploited by contrast imaging techniques for the characterization of mass lesions which have characteristic or typical patterns of appearance in the arterial, portal venous, hepatic venous and equilibrium phases of contrast imaging. In addition to the information gained by the use of standard intravenous contrast agents, newer contrast agents that are excreted into the biliary system in the delayed phase of multiphasic examination, such as disodium gadoxetate and gadobenate dimeglumine, provide further information on the phenotypic characteristics of liver masses and are particularly useful in the differentiation of adenomas from focal nodular hyperplasias and the diagnosis of hepatocellular carcinomas. MRI sequences such as T2 imaging, diffusion weighted imaging, and in- and out-of-phase imaging can also be extremely helpful in differentiating benign from malignant lesions and distinguishing normal liver from focal fat or focal fat sparing.

**Diagnostic Needle Biopsies**

Diagnostic needle biopsies combined with histopathology and immunohistochemistry can be invaluable for characterizing liver masses. For suspected malignant masses, consideration should be given to whether biopsy is necessary. Highly specific radiologic criteria have been established for the non-invasive diagnosis of hepatocellular carcinoma that are most useful in reducing the need for biopsy in those patients who are eligible for liver transplantation and who are at the highest risk for needle tract seeding and tumor recurrence due to the immunosuppression required after liver transplantation. It is important to recognize that there is an approximately 10% false negative rate with attempted biopsy of small liver lesions due to technical difficulties with accurately targeting the lesion. On the other hand, biopsy should be encouraged for confirmation of the diagnosis in patients with more advanced disease who are not candidates for surgical resection, because newer methods of molecular analysis may help to determine the most appropriate chemotherapeutic agents for treatment.

**Combined Endoscopic, Interventional Radiologic, and Pathologic Techniques for the Evaluation of Liver Mass Lesions**

The techniques of endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and endoscopic ultrasonography (EUS) allow access to detailed imaging of the biliary system and the hepatic hilum, pancreas and associated lymph nodes. Ancillary techniques such as cholangioscopy, bile duct biopsy and brushing, lymph node sampling by fine needle aspiration, and cytologic and fluorescence in situ hybridization (FISH) examination of cells obtained from biliary strictures or lymph nodes can further enhance the diagnostic capabilities of these procedures.
Clinical and Radiologic Features of the Common Liver Mass Lesions

Cavernous Hemangioma

*Epidemiology* – Cavernous hemangiomas are among the most common liver lesions. Autopsy studies have shown that they are present in the livers of approximately 7% of individuals, more commonly in females than in males.

*Pathogenesis and Pathology* – Hemangiomas are congenital malformations in the vascular structure of the liver. They are characterized histologically by a sponge-like arrangement of blood filled spaces.

*Imaging Features* – Hemangiomas typically have increased echogenicity on liver ultrasound. In multiphasic CT or MR imaging studies, they show a typical peripheral nodular enhancement in the early arterial phase with slow fill in towards the center of the mass in the portal venous, hepatic venous and delayed phases (Figure 1).

*Management* – Hemangiomas do not generally grow or suffer complications such as hemorrhage, rupture, or malignant transformation. Due to their benign nature, there is no indication for therapy unless they are symptomatic, causing pain from a subcapsular location in the liver or are so large that they compromise liver synthetic function.

Simple Hepatic Cyst

*Epidemiology* – Simple liver cysts are also very common in the liver, occurring in about 5% of individuals. They are also more common in females than males.

*Pathogenesis and Pathology* – Simple cysts are fluid filled sacs lined by benign biliary epithelium.

*Imaging Features* – Cysts typically show through transmission with no echoes and a sharp distant border with shadowing on liver ultrasound. In multiphasic CT or MR imaging studies, they show a water density which does not change during the multiphasic contrast examination. The clear liquid gives a bright T2 signal on MRI.

*Management* – Simple cysts generally do not grow or cause complications. Rarely a large cyst will cause biliary obstruction, which can be treated by alcohol sclerosis, or if needed, by laparoscopic or open surgical cyst fenestration.

Focal Nodular Hyperplasia

*Epidemiology* – Focal nodular hyperplasias (FNHs) are relatively common benign liver masses. Autopsy studies have shown that they are present in the livers of approximately 4% of individuals, more commonly in females than in males.

*Pathogenesis and Pathology* – FNHs are thought to develop within an area of the liver with a congenital anomaly of the vascular structure that leads to an abnormal configuration of the liver parenchyma. They are characterized histologically by a central stellate scar and the presence of normal biliary elements.

*Imaging Features* – In multiphasic CT or MR imaging studies, FNHs typically show rapid homogeneous uptake of contrast in the early arterial phase with rapid return to near-normal enhancement in the portal venous and venous phases. In imaging studies with contrast agents such as gadoxetate disodium or gadobenate dimeglumine that have both renal and biliary excretion, FNHs show delayed biliary excretion and consequently look equivalent to or brighter than the surrounding liver tissue in the delayed phase of imaging (Figure 2).

*Management* – FNHs typically do not grow or suffer complications such as hemorrhage, rupture, or malignant transformation. Due to their benign nature, there is no indication for therapy unless they are symptomatic from a subcapsular location in the liver.
Focal Fat or Fat-sparing

Epidemiology – With the gradually increasing body mass index of people worldwide, but particularly in North America and Europe, it is now not uncommon for individuals to develop regions of focal fatty infiltration in the liver, or alternatively, a liver that is diffusely infiltrated with fat except for regions of focal fat sparing.

Pathogenesis and Pathology – Areas of focal fat typically show micro-vesicular or macro-vesicular steatosis; this is typically also seen in diffusely fatty livers, except for the regions of focal fat sparing.

Imaging Features – Fat is characteristically hyperechoic on ultrasound imaging, and this is often the first sign that a mass may represent focal fat. Diffusely increased echogenicity of the liver is characteristic on liver ultrasonography. Fat has a classical appearance on in- and out-of-phase MRI imaging of the liver.

Management – There is no specific treatment needed for focal fat or focal fat sparing, unless the patient has steatohepatitis. Focal fat will often resolve if the patient loses weight.

Hepatic Adenoma and Adenomatosis

Epidemiology – Hepatic adenomas are relatively uncommon benign liver masses that are most commonly seen in women but are increasingly also found in men, particularly those with metabolic syndrome. There appear to be several different subtypes of hepatic adenomas that are differentiated by their histologic, genetic, and radiologic phenotypes as well as by their epidemiologic characteristics. Major etiologic factors for the development of hepatic adenomas include oral contraceptive use, the metabolic syndrome, and excessive alcohol use. The presence of multiple hepatic adenomas in the liver, typically greater than five or greater than ten adenomas, depending on the particular definition, is referred to as hepatic adenomatosis, and is associated with a markedly induced tendency to adenoma formation within the liver. Clinically, hepatic adenomas are characterized by their responsiveness to estrogen and by their tendency towards intratumoral hemorrhage with scarring and rarely hepatic rupture with hemoperitoneum. Adenomas also have a small but real risk of malignant transformation into hepatocellular carcinomas.

Pathogenesis and Pathology – Adenomas consist of a benign mass of proliferated hepatocytes. They are subclassified into (1) inflammatory hepatocellular adenomas, 60% of which are characterized by activating in-frame deletions of the IL-6 signal transduction protein gp130 and express the inflammation associated proteins C-reactive protein and serum amyloid A protein; (2) HNF1α-inactivated hepatic adenoma, which are steatotic and do not express liver fatty acid bind-
ing protein; HNF1α gene mutations are also associated with familial young onset diabetes and hepatic adenomatosi.s; (3) β-catenin-activated hepatic adenomas, which overexpress glutamine synthetase in the cytoplasm and show aberrant expression of β-catenin in the nucleus; and (4) an unclassified subgroup. Hepatic adenomas typically do not have biliary elements.2

**Imaging Features** – Small adenomas are frequently mistaken for FNHs, as they typically show rapid homogeneous uptake of contrast in the early arterial phase of multiphasic CT or MR imaging studies with rapid return to near-normal enhancement in the portal venous and venous phases. Larger adenomas develop intratumoral hemorrhage, necrosis, and subsequent scarring, leading to a heterogeneous appearance on imaging. Due to their absence of biliary elements, hepatic adenomas show no excretion with the use of contrast agents with biliary excretion such as gadoxetate disodium or gado-benate dimeglumine and consequently look darker than the surrounding liver tissue in the delayed hepatobiliary phase of imaging. This feature is an important tool in distinguishing hepatic adenomas from focal nodular hyperplasia (Figure 3).

**Management** – Hepatic adenomas are generally estrogen-responsive and can grow or suffer complications such as hemorrhage, rupture with pain or hemoperitoneum, or malignant transformation. Due to their benign nature, there is no indication for therapy unless they are symptomatic from a subcapsular location in the liver.

Hepatic Abscesses

**Epidemiology** – Hepatic abscesses can be caused by bacterial or amebic infection of the liver. Pyogenic bacterial liver abscesses are usually caused by rupture or leak of the bile duct or bowel. They may be associated with biliary stenting, biliary instrumentation, or transcatheter chemoembolization of tumor nodules. There is an increased risk of pyogenic abscess in patients with diabetes mellitus.

**Pathogenesis and Pathology** – Abscesses related to biliary sources are usually caused by enteric gram negative bacteria or enterococci; those from other intestinal sites will frequently have mixed aerobic and anaerobic flora.

**Imaging Features** – Ultrasonography shows liver lesions that are not as completely free of echoes as simple hepatic cysts, but which nevertheless do not have any blood vessels or bile duct structures running through them.

**Management** – Suspected pyogenic liver abscesses should be aspirated for aerobic and anaerobic cultures. A drain should be left in abscesses greater than 3 cm in size. Empiric antibiotic therapy based on the likely organisms should be initiated and modified once culture results are available. Antibiotic therapy should be continued for at least 4–6 weeks. Multiple, large or loculated abscesses may require surgical drainage. Surgery may also be required to treat the underlying cause of the abscess.

**Figure 3:** Adenoma of the liver discovered during evaluation of lower abdominal pain. A, Contrast MRI with gadoxetate disodium showing heterogeneous intense hyperenhancement in the arterial phase. B, Rapid return to near isoenhancement of the tumor with the surrounding normal liver in the portal venous phase. C, Inability of the tumor to concentrate contrast in the delayed hepatobiliary phase.
Amebic liver abscesses often do not require aspiration; if aspiration is performed the typical appearance is of "anchovy paste." Antiamebic treatment is with metronidazole or tinidazole for 7-10 days, followed by a luminal agent such as paromomycin or diiodohydroxyquin.

Hepatocellular Carcinoma

**Epidemiology** – Hepatocellular carcinomas (HCC) usually develop in the context of liver cirrhosis due to chronic hepatitis B (HBV) or hepatitis C virus (HCV) infection, alcohol, or non-alcoholic steatohepatitis (NASH). There are over 700,000 cases of HCC worldwide each year, and it is the third most common cause of death from cancer. Although the prevalence of chronic HBV and HCV infection are expected to peak and begin decreasing in the next several years due to improvements in prevention, diagnosis and treatment, it is anticipated that there will be an increasing number of cases of HCC due to NASH. A smaller proportion of cases are due to less common causes of chronic liver disease such as hereditary hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis. Dietary exposure to fungal aflatoxins, cigarette smoking and diabetes are also important risk factors.

**Pathogenesis and Pathology** – HCCs are thought to arise as a consequence of premature hepatocyte senescence caused by repeated cycles of cell injury, regeneration and repair, occurring in the context of a genotoxic inflammatory environment that increases the propensity to oncogenic genetic and epigenetic aberrations. HCCs show significant molecular heterogeneity; a substantial percentage of HCCs have mutations in the p53 gene, in addition, there are at least five molecular subclasses identified thus far, including a proliferative subclass characterized by PI3 kinase/Akt kinase activation, a β-catenin mutated subclass, interferon related, polysomy 7, and undefined classes.

**Imaging Features** – Arterial phase enhancement followed by portal venous washout on multiphasic CT or standard gadolinium contrast MRI in new lesions developing in the cirrhotic liver has been shown to be diagnostic for HCCs above 1 cm in size. Distinct hypointensity in the hepatobiliary phase of imaging with disodium gadoxetate is increasingly recognized as a diagnostic feature of HCC. HCCs also often show decreased T1 signal and increased T2 signal on MRI and diffusion weighted imaging, and these features are increasingly being used to discriminate those small indeterminate HCCs that have atypical enhancement or washout characteristics.

**Management** – The management of HCC requires a multidisciplinary approach and is dependent on the number, size and location of HCC masses, as well as the age, co-morbidities, and liver function of the patient. Patients with normal liver function who are candidates can be treated with surgical resection, as long as this is technically feasible. Patients with cirrhosis who meet the Milan criteria – one mass no greater than 5 cm in size or two or three lesions with the largest being no more than 3 cm in size – meet criteria for listing for liver transplantation. Lesions up to 3 cm in size that are not amenable to resection or transplantation can be treated with radiofrequency ablation or percutaneous alcohol injection. Intermediate stage disease is usually treated with transarterial chemoembolization or radioembolization. The current standard of care for advanced stage disease is the multikinase inhibitor sorafenib.

**Biliary Tract Cancers**

**Epidemiology** – Biliary tract cancers include cholangiocarcinoma and gallbladder cancers. Cholangiocarcinomas are malignancies of the intra- or extra-hepatic biliary tract. Intrahepatic cholangiocarcinomas usually present as mass lesions within the liver, while extrahepatic cholangiocarcinomas...
frequently present with biliary obstruction at the hilum of the liver or within the common hepatic duct or the common bile duct. The major risk factors for cholangiocarcinoma include biliary tract diseases including primary sclerosing cholangitis, liver fluke infestations with Opisthorchis viverrini or Clonorchis sinensis, and cholecodochal cysts, cirrhosis, diabetes, and smoking. While the incidence of extrahepatic cholangiocarcinomas appears to have remained stable over time, there has been an approximately 7-fold increase in the incidence of intrahepatic cholangiocarcinomas from 0.3 per 100,000 person years to 2.1 per 100,000 person years over the past two decades. The cause of this increase is unknown. Concomitantly, the incidence of gallbladder cancer has decreased by approximately 50% from 4.0 per 100,000 person years to 2.2 per 100,000 person years, perhaps in part due to increasing rates of cholecystectomy for gallstone disease in women.

Pathogenesis and Pathology – A common thread in the etiological factors for cholangiocarcinoma are inflammatory conditions of the biliary tract, or factors such as diabetes and smoking that contribute to genomic instability through oxidative stress and impaired DNA repair mechanisms.

Imaging Features – Intrahepatic cholangiocarcinomas usually appear as solid masses on multiphasic cross-sectional CT or MRI imaging which are hypointense in precontrast images and gradually accumulate a moderate amount of contrast through the arterial, portal and venous phases. Characteristically, hilar cholangiocarcinomas will initially occlude the bile duct to one lobe of the liver and encase the portal vein supplying that lobe. This leads to lobar atrophy and compensatory hypertrophy of the hepatic lobe on the other side. Progression of the tumor across the hilar bifurcation then results in occlusion of both the right and left bile ducts, resulting in the typical atrophy-hypertrophy complex. Hilar cholangiocarcinomas lead to dilatation of the intrahepatic bile ducts, while distal extrahepatic cholangiocarcinomas lead to dilatation of the entire biliary tree.

Management – The preferred management of intrahepatic cholangiocarcinomas is surgical resection if technically feasible. Unfortunately, because intrahepatic cholangiocarcinomas typically occur in patients without known risk factors, they are often large and unresectable at the time of diagnosis. Palliative chemo- or radioembolization and/or chemotherapy are the most frequent treatments used. Patients with intrahepatic cholangiocarcinomas are not candidates for liver transplantation due to their high propensity to metastasize. Hilar or extrahepatic cholangiocarcinomas can be resected in a proportion of cases. If resection is not feasible, a select subset of patients with hilar tumors having a radial diameter of up to 3 cm and no evidence of extrahepatic spread qualify for a protocol of external beam radiotherapy combined with radiosensitizing chemotherapy, brachytherapy with endoscopically placed iodium-192 beads, maintenance chemotherapy, staging laparoscopic surgery to rule out the interval development of metastases, and orthotopic liver transplantation. This protocol has been shown to achieve a 53% 5-year survival.

Liver Metastases
Epidemiology – Liver metastases from other primary sites are the most common malignant liver masses and are most frequently from colorectal, gastric, pancreatic, or intestinal primary sites, including neuroendocrine tumors. Particularly in patients without liver cirrhosis, there should be a careful evaluation for a potential primary site. This can be facilitated by special immunohistochemical stains performed on biopsies of the liver masses.

Pathogenesis and Pathology – The pathogenesis and pathology are dependent on the primary tumor type.

Imaging Features – Metastases can have variable imaging features, but are typically hypodense on non-contrast cross sectional imaging and show gradually increasing enhancement during the arterial, portal venous and venous phases of contrast imaging.

Management – The specific management is dependent on the primary tumor type and the extent of metastatic disease. Appropriate therapies may include systemic therapy, surgical resection, local ablation, or loco-regional radioembolization, chemoembolization, or bland embolization.
REFERENCES

