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Liver Masses: A Clinical, Radiological and Pathological Perspective For: Perspectives in Clinical Gastroenterology and Hepatology

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Abstract

Liver masses present a relatively common clinical dilemma, particularly with the increasing use of various imaging modalities in the diagnosis of abdominal and other symptoms. The accurate and reliable determination of the nature of the liver mass is critical, not only to reassure individuals with benign lesions but also, and perhaps more importantly, to ensure that malignant lesions are diagnosed correctly. This avoids the devastating consequences of missed diagnosis and the delayed treatment of malignancy or the unnecessary treatment of benign lesions. With appropriate interpretation of the clinical history and physical examination, and the judicious use of laboratory and imaging studies, the majority of liver masses can be characterized noninvasively. Accurate characterization of liver masses by cross-sectional imaging is particularly dependent on an understanding of the unique phasic vascular perfusion of the liver and the characteristic behaviors of different lesions during multiphasic contrast imaging. When non-invasive characterization is indeterminate, a liver biopsy may be necessary for definitive diagnosis. Standard histologic examination is usually complemented by immunohistochemical analysis of protein biomarkers. Accurate diagnosis allows the appropriate selection of optimal management, which is frequently reassurance or intermittent follow up for benign masses. For malignant lesions or those at risk of malignant transformation, management depends on the tumor staging, the functional status of the uninvolved liver and technical surgical considerations. Unresectable metastatic masses require oncologic consultation and therapy. The efficient characterization and management of liver

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masses therefore requires a multidisciplinary collaboration between the gastroenterologist/hepatologist, radiologist, pathologist, hepatobiliary or transplant surgeon, and medical oncologist.

Clinical Classification of Liver Mass Lesions

It is helpful to subclassify lesions into three clinical categories. 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 feasible¹.

Initial Clinical Evaluation

A careful review of the personal history and physical examination findings often helps in narrowing the differential diagnoses of liver masses. A history of chronic hepatitis or the features or complications of liver cirrhosis identifies individuals at risk for HCC and intrahepatic cholangiocarcinoma. Similarly, a history of primary sclerosing cholangitis alerts to the significant risk for cholangiocarcinoma while long-term oral contraceptive use predisposes certain women to hepatic adenoma. The family history is also of value in the initial clinical evaluation. A family history of young-onset diabetes mellitus, for example, may predispose to hepatic adenomatosis. Physical complaints such as abdominal pain are often non-specific but may be the reason to seek medical attention. Other physical symptoms are more suggestive of the underlying disease, for example the pruritus, dark urine and pale stools observed in biliary obstruction. A history of constitutional symptoms such as fever may be useful in the diagnosis of hepatic abscesses; fever can also be associated with malignancy. Constitutional features of malignancy also include anorexia, weight loss, and fatigue. The physical examination may reveal features of chronic liver disease such as spider angiomas, a periumbilical caput medusa indicative of portal hypertension, hepatomegaly or splenomegaly. Painless jaundice is highly suggestive of a malignancy such as cholangiocarcinoma or pancreatic adenocarcinoma while advanced malignant infiltration and some benign masses may be associated with palpable hepatomegaly, which may be nodular in patients with cirrhosis or focal masses.

The history and physical examination are complemented by laboratory tests which may reveal active hepatitis, a low platelet count due to chronic liver disease with cirrhosis, portal hypertension and hypersplenism, or hyperbilirubinemia. The use of the serum alpha fetoprotein (AFP) in surveillance for HCC is controversial due to low sensitivity for the detection of early stage disease^{2, 3}. The AFP is well-established as a predictor of risk of HCC in individuals with cirrhosis and can be extremely useful for HCC diagnosis in individuals with diffuse HCCs³. While one-time AFP determinations have a high false positive rate, particularly in patients with chronic hepatitis C virus, trends and patterns in AFP levels can be useful for early diagnosis of HCC⁴. A high AFP is also prognostic for the outcomes of patients with HCC⁵. The AFP-L3 and des-gamma carboxyprothrombin (DCP) also predict risk of HCC and are used extensively in Asia, particularly in Japan⁶. However, they have not as yet found widespread clinical use in Europe or the United States. The CA19-9 is helpful in the diagnosis and prognostic prediction of patients with cholangiocarcinoma⁷. In the absence of acute cholangitis, a CA19-9 greater than 1000

units/mL usually indicates the presence of extrahepatic disease⁷. 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^{8, 9}. In general, these markers are of value in determining the nature of malignant liver lesions when present, while having a relatively low specificity in the absence of detectable lesions. An elevated LDH and widespread intraabdominal lymphadenopathy may be clues to liver infiltration by lymphoma masquerading as primary liver cancer.

Radiologic Imaging Studies are Critical for Accurate Characterization of Liver Mass Lesions

The radiologic features of liver masses as assessed by liver ultrasonography (US) or by cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) are extremely helpful in diagnosis. Specialized imaging studies such as Octreotide scans, used in the diagnosis of neuroendocrine tumors, and positron emission tomography (PET) scans, used for detection of metastatic disease or cholangiocarcinoma, are also valuable adjuncts for clinical diagnosis and management.

Surveillance for Hepatocellular Carcinoma

For individuals with chronic hepatitis B virus infection or cirrhosis from any cause who are at risk for development of HCC, surveillance ultrasonography every 6 months is recommended for early identification of HCCs and is critical for achieving long-term survival (Table 2)².

The Use of Multiphasic Cross-Sectional Imaging in the Evaluation of Liver Masses

Cross-sectional imaging with CT or MRI is enhanced by the use of intravenous contrast agents and dynamic multiphasic examination techniques. The liver has three distinct phases after intravascular contrast agent is injected via a peripheral vein. The arterial phase occurs 25-35 seconds after peripheral contrast injection and is caused by the direct infusion of arterial blood with a high concentration of contrast from the heart through the hepatic artery into the liver. Next, the portal venous phase occurs 60-75 seconds after contrast injection as blood from the gastrointestinal tract is collected in the portal vein for processing in the liver. Finally, in the venous phase, blood from the liver is collected into the hepatic veins which converge to the inferior vena cava for return to the right atrium. The intravascular contrast leaks through the liver sinusoids into the extracellular space and about 3-5 minutes after injection the extracellular contrast reaches equilibrium with the concentration in the vascular system. This is known as the equilibrium phase. This unique blood supply to the liver is exploited by contrast imaging techniques, as many mass lesions have characteristic patterns of appearance in the arterial, portal venous, and equilibrium phases. Newer contrast agents that are taken up by functioning hepatocytes and excreted into bile, such as disodium gadoxetate (Gd-EOB-DTPA, Eovist) and gadobenate dimeglumine (Gd-BOPTA, MultiHance), provide further phenotypic characterization of liver masses and are particularly useful in the differentiation of adenomas from focal nodular hyperplasias and

the diagnosis of HCC and metastases. The enhancement of hepatocytes with these hepatobiliary contrast agents in the hepatocyte or parenchymal phase typically peaks 20 min to >60 min following intravenous injection. Uptake of gadoxetate and gadobenate is believed to occur mainly through cell membrane proteins in the bile canaliculi and ducts, including organic anion transporting polypeptides (OATPs) and multidrug resistance protein (MRP2)¹⁰. The expression of these proteins is usually suppressed in adenomas and HCC and lack of the hepatocyte phase enhancement is useful in differentiating them from FNH.

Imaging characteristics on MRI are useful in differentiating HCC from other hepatic lesions. The T2-weighted sequence is sensitive to alterations in water content and pathological tissues appear brighter than normal tissues. Most HCCs show high signal intensity on T2-weighted images as compared to benign lesions such as adenomas and focal nodular hyperplasias. The In- and Opposed-phase sequence in which regions of fat deposition show characteristic signal loss in the opposed phase can be useful in differentiating HCC from focal fat deposition or focal fat sparing. Diffusion weighted imaging (DWI) highlights the areas of restricted diffusion and is sensitive to focal abnormalities. Malignant lesions show restricted diffusion on DWI and appear brighter. However this finding lacks sufficient specificity to be the sole diagnostic criterion in routine clinical practice. Moreover, combining DWI with contrast enhanced MRI provides high accuracy for detection and characterization of HCCs^{11, 12}.

Recent advances in CT provide higher spatial and temporal resolution for the evaluation of liver tumor hemodynamics, while also providing three-dimensional or four-dimensional imaging for treatment planning. Perfusion CT provides quantitative information about arterial perfusion in HCC, allowing the evaluation of tumor angiogenesis and response to therapy^{13, 14}. Dual-energy CT (performed with two different energy spectra) improves detection and assessment of hypervascular tumors¹⁵. Magnetic resonance elastography (MRE) and acoustic radiation force impulse imaging (ARFI) are currently under investigation and may also be potentially useful techniques in the characterization of liver masses¹⁶⁻¹⁹.

Needle Biopsy, Histopathology and Immunohistochemical Studies

Needle biopsies combined with histopathology and immunohistochemistry can be invaluable for characterizing liver masses. For suspected malignant masses, consideration should be given to whether a biopsy is necessary. Highly-specific radiologic criteria have been established for the non-invasive diagnosis of HCC that are useful in reducing the need for biopsy in patients with cirrhosis who are eligible for liver transplantation and are at the highest risk for needle tract seeding and tumor recurrence due to the immunosuppression after liver transplantation²⁰. There is an approximately 10% false negative rate with biopsy of small liver lesions due to difficulties with accurately targeting the lesion. On the other hand, biopsy is encouraged for diagnosis of patients with advanced disease who are not surgical resection candidates, because newer molecular analyses may help determine the most appropriate chemotherapeutic agents. Overall, biopsies of malignant lesions carry a low risk of tumor seeding for suspected HCCs, however, for patients with suspected hilar cholangiocarcinomas, under consideration for potentially curative resection or liver

transplantation, transperitoneal fine needle aspiration biopsy has been shown to be associated with a higher rate of peritoneal metastases.^{21, 22}

Endoscopic, Interventional Radiologic, and Molecular Pathologic Techniques for Evaluation of Liver Mass Lesions

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 pancreatobiliary strictures or lymph nodes can further enhance the diagnostic armamentarium^{23, 24}.

Clinical and Radiologic Features of the Common Liver Mass Lesions

Cavernous Hemangioma

Epidemiology—Cavernous hemangiomas are the most common benign liver lesions. Autopsy studies show that they occur in up to 7% of individuals, more commonly in females than in males^{25, 26}.

Pathogenesis and Morphology—Hemangiomas are congenital malformations in the vascular structure of the liver and are usually solitary. They are grossly well-circumscribed and appear red-brown. Histologically they have varying sized blood-filled vascular spaces lined by flattened endothelial cells (Figure 1).

Imaging Features—Hemangiomas typically have increased echogenicity on ultrasound. Hemangiomas are typically hypo- or isodense to liver parenchyma on unenhanced CT. At MRI, they are characteristically hyperintense to liver on T2-weighted images and moderately low signal intensity on T1-weighted MR images. In multiphasic CT or MR imaging studies, they show a typical peripheral nodular enhancement in the arterial phase with progressive centripetal filling-in towards the center of the mass in the portal venous, and delayed phases²⁷⁻³² (Figure 2). The density of enhancement is similar to the contrast in aorta in all phases³³. Characteristic findings on ultrasound, CT and MRI are diagnostic of hemangiomas. Atypical hemangiomas and a significant number of small hemangiomas may show flash (immediate homogeneous) arterial phase enhancement. Large hemangiomas may be heterogeneous in appearance due to thrombosis, fibrosis or calcification²⁷⁻²⁹ especially on MRI and may not show complete filling-in³⁰⁻³². The diagnosis of atypical hemangioma can be confirmed by demonstrating stability on follow up imaging; rarely other tests or biopsy are required.

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.

Morphology—Simple cysts are lined by cuboidal to low columnar biliary epithelium and a fibrous wall.

Imaging Features—Cysts are characterized by their round or oval shape and barely visible wall on imaging³⁴. 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 signal which does not enhance during the multiphasic contrast examination³⁴(Figure 3). The clear liquid gives a bright T2 signal on MRI³⁵. Septations within simple cysts are uncommon. Thickened or nodular septa and an enhancing rim of a cystic lesion should raise the suspicion of an infected cyst or a cystic neoplasm.

Management—Simple cysts usually do not grow or cause complications. A case series of several cysts detected antenatally showed that of the 10 simple cysts that were followed postnatally, 9 remained static or regressed, suggesting that the natural history of simple cysts is benign³⁶. 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.

Polycystic Liver Disease

Epidemiology—Polycystic liver disease is diagnosed when 20 or more cysts, ranging from a few millimeters wide to several centimeters, are present. The disease is relatively rare, typically presenting as one of two phenotypes: the autosomal dominant or recessive polycystic kidney disease (ADPKD or ARPKD) or autosomal dominant polycystic liver disease (PCLD), with the former predominantly a renal disease with the possibility of liver cysts and the latter manifesting solely as a hepatic disease^{37, 38}. The disease process is thought to be due to defective bile duct formation and arrangement³⁹.

Imaging features—Imaging features are as described above for simple liver cysts, except for the multiplicity of lesions seen, which may almost completely replace the liver parenchyma.

Management—Unlike simple hepatic cysts, the multitude of cysts in this condition may interfere with liver function and are quite often symptomatic. Treatment options include aspiration, sclerotherapy or segmental liver resection. In some cases, a liver transplant may be indicated³⁷. Octreotide and related analogs are in clinical trials for treatment of polycystic liver disease⁴⁰.

Focal Nodular Hyperplasia

Epidemiology—Focal nodular hyperplasias (FNHs) are relatively common benign liver masses. They are present in the livers of approximately 4% of individuals, more commonly in females than in males⁴¹. FNH are generally solitary but can be multiple.

Pathogenesis, Morphology and Molecular Pathology—FNHs are thought to develop around a preexisting arterial malformation due to a hyperplastic growth response to parenchymal blood flow⁴². Grossly FNHs are well-circumscribed but non-encapsulated and show a central fibrous scar on cut section. They are characterized histologically by hepatic parenchyma arranged in incomplete nodules separated by fibrous tissue which contains abnormal thick-walled vessels, bile ductular proliferation and chronic inflammation (Figure 4).

Imaging Features—FNH are composed of normal hepatocytes and behave like a regenerative mass of variable size. They lack a terminal central hepatic vein and characteristically show capillarization of sinusoids derived from a feeding artery that is usually larger than normal^{43, 44}. On ultrasound, FNH may show very slight changes in echogenicity compared to the surrounding parenchyma and usually appear hypo- or isoechoic and slightly inhomogeneous due to the central scar⁴⁵. FNH are usually isodense with the surrounding liver on CT and isointense on MRI. This feature may make them undetectable on unenhanced imaging and has earned them the label “stealth lesions”. They are fairly homogeneous except for the central scar when it is present which is typically hypodense on CT and T2 bright on MRI. A central scar, when present, is quite specific^{46, 47}. 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 delayed phases. With MRI contrast agents such as gadoxetate disodium (Eovist) or gadobenate dimeglumine (MultiHance) that have both renal and biliary excretion, FNHs show active hepatocyte uptake and look similar to or brighter than the surrounding liver tissue in the hepatocyte phase of imaging^{48, 49} (Figure 4). The central scar is often absent and, rarely, FNH may contain fat or appear heterogeneous with atypical features, making the differentiation from hepatic adenomas, fibrolamellar hepatocellular carcinoma and HCCs difficult. Demonstration of the uptake of hepatocyte-specific contrast agents is most useful in such situations^{48, 49}. Biopsy may be required for a definitive diagnosis.

Management—Most FNHs do not expand or develop complications such as hemorrhage, rupture, or malignant transformation^{50, 51}. Due to their benign nature, there is no indication for therapy unless they are symptomatic from a subcapsular location in the liver.

Hepatic Adenoma and Adenomatosis

Epidemiology—Hepatic adenomas are relatively uncommon benign liver masses most commonly seen in women but also increasingly found in men, particularly those with metabolic syndrome. There are different subtypes of hepatic adenomas differentiated by their histologic, genetic, and radiologic phenotypes and by their epidemiologic characteristics. Major etiologic factors for hepatic adenomas include oral contraceptive use, anabolic steroids in males, the metabolic syndrome, and excessive alcohol use⁵²⁻⁵⁷. Newer generation contraceptive pills with lower estrogen content are likely associated with a lower risk of hepatic adenomas. Despite that, the overall incidence of hepatic adenomas has not decreased⁵⁸. This can perhaps be explained by the increasing rates of obesity worldwide and an associated increase in metabolic syndrome, with a subset of those patients being

diagnosed with hepatic adenomas, particularly the inflammatory and telangiectatic variant^{55, 59}. This suggests that obesity and metabolic syndrome increase the risk of developing adenomas. The presence of multiple hepatic adenomas in the liver, typically greater than 5 or greater than 10 adenomas, depending on the particular definition, is referred to as hepatic adenomatosis. Adenomatosis is associated with glycogenosis type Ia or III, Klinefelter syndrome, familial diabetes or familial adenomatosis⁶⁰⁻⁶². Clinically, hepatic adenomas are characterized by their responsiveness to estrogen and 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 HCCs.

Pathogenesis, Morphology and Molecular Pathology—Adenomas may be single or multifocal. They are generally round, well-circumscribed and bulge on cut section. Microscopically they show benign normal appearing hepatocytes arranged in sheets or cords with naked or unaccompanied arteries and absence of normal portal tracts. The normal cell plate architecture is preserved within the lesion and the cell plates are usually only 2 cells thick. Mitotic figures are absent or extremely rare (Figure 5). Adenomas associated with anabolic steroids show pseudogland formation with bile plugs, peliosis hepatis and nuclear atypia. Based on genetic and immunohistochemical analyses, hepatic adenomas are subclassified into (1) inflammatory hepatic adenomas, 60% of which are characterized by activating in-frame deletions of the IL-6 signal transduction protein gp130 and expression of the inflammation-associated proteins C-reactive protein and serum amyloid A protein; (2) HNF1 α -inactivated hepatic adenomas, which are steatotic and do not express liver fatty acid binding protein; HNF1 α gene mutations are also associated with familial maturity-onset diabetes of the young and hepatic adenomatosis; (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 indeterminate subgroup^{63, 64}. Characterizing the different adenoma subclasses carries prognostic significance. β -catenin-expressing adenomas have an increased risk of malignant transformation and are quite often indistinguishable from well-differentiated HCC. Similarly, inflammatory hepatic adenomas may carry β -catenin mutations and are hence at risk for malignant transformation⁶³. Phenotypic and genetic characterizations are therefore increasingly important in management of adenomas.

Imaging Features—The appearance of hepatic adenomas is variable and dependent on the composition of the adenoma. Adenomas can have variable amounts of fat and may have intra lesional hemorrhage and necrosis. 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 phases⁶⁵ (Figures 5 and 6). Larger adenomas develop intratumoral hemorrhage, necrosis, and subsequent scarring, leading to a heterogeneous appearance on imaging^{35, 65, 66}. The risk of hemorrhage is higher in lesions larger than 5 cm. The heterogeneous appearance and arterial phase enhancement of adenomas frequently mimics HCCs. Due to their preponderance of neoplastic hepatocytes and absence of biliary elements, hepatic adenomas usually show no uptake of contrast agents with hepatobiliary excretion such as gadoxetate disodium (Eovist) or gadobenate dimeglumine (MultiHance)

and consequently look darker than the surrounding liver tissue in the delayed hepatobiliary phase. This is an important feature in distinguishing hepatic adenomas from FNH (Figure 6). However, a minority of hepatic adenomas, particularly the inflammatory adenoma subtype, show uptake of Eovist^{67, 68}. Correlation with risk factors such as oral contraceptive use helps in correct diagnosis. Follow-up imaging may show interval changes of hemorrhage or necrosis in adenomas, whereas FNH generally tend to be stable over time.

Management—Hepatic adenomas are generally estrogen-responsive and can grow or suffer complications such as hemorrhage, rupture with pain or hemoperitoneum, or malignant transformation. Most adenomas have a benign natural history, with a low risk of hemorrhage or transformation. Surgical resection is recommended for high-risk adenomas, defined as lesions ≥ 5 cm in size or increasing in size over time, adenomas with evidence of internal hemorrhage, adenomas occurring in males, which have increased malignant risk, those with positive nuclear β -catenin immunohistochemical staining, and those occurring in older females with no history of use of oral contraceptives⁶⁴. For low risk adenomas less than 5 cm in size occurring in young females on oral contraceptive pills, the recommendations are to discontinue use of oral contraceptive pills, switch to alternative means of birth control, and perform intermittent surveillance imaging. Due to the high estrogen loads associated with pregnancy, females desiring pregnancy should have surgical resection of large adenomas, however small adenomas can be managed conservatively with intermittent ultrasound imaging during pregnancy⁶⁴. Adenomas that are symptomatic due to their large size or subcapsular location in the liver should be resected. Radiofrequency ablation can be used as an alternative to surgical resection in patients with high surgical risk due to medical co-morbidities.

Focal Fat Deposition or Fat-Sparing

Epidemiology—With the gradually increasing body mass index of people worldwide, particularly in North America and Europe, it is common 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 sparing⁶⁹.

Pathogenesis, Morphology and Molecular Pathology—Areas of focal fat typically show macro-vesicular steatosis affecting multiple contiguous acini that still have normal portal areas and central veins.

Imaging Features—Diffusely increased echogenicity of the fatty liver is characteristic on ultrasonography. Focal fat is also hyperechoic to the normal liver parenchyma on ultrasound⁷⁰. Fat reduces the density of the liver on CT; focal fat deposition appears hypodense to the normal liver and areas of fat sparing appear hyperdense to the surrounding fatty liver. Fatty liver classically shows loss of signal in opposed-phase MRI images compared to in-phase images (Figure 7). Focal fat deposition or fat sparing typically occur in the gallbladder fossa, adjacent to the falciform ligament and the periportal region, all of which may be supplied by aberrant systemic veins and do not receive much portal blood. Generally, these lesions do not have a well-defined border or cause any mass effect and the

normal blood vessels course through them. Nodular fat sparing can be problematic and may require biopsy for confirmation⁷¹.

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 weight⁷².

Hepatic Abscesses

Epidemiology—Hepatic abscesses can be caused by bacterial or amebic infection. 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 transarterial chemoembolization of tumor nodules. There is an increased risk of pyogenic abscess in patients with diabetes mellitus. Amebic liver abscesses occur in countries with endemic amebiasis and are decreasing in incidence in North America⁷³.

Pathogenesis, Morphology and Molecular Pathology—Abscesses related to biliary sources are usually caused by enteric gram-negative bacteria or enterococci; those from other intestinal sites frequently have mixed aerobic and anaerobic flora. Abscesses may be single or multiple and are more common in the right lobe. They range in size from microscopic to larger than 3 cm. Microscopically there is a central area of suppurative necrosis and inflammation surrounded by varying degrees of fibrosis and organizing inflammation. *Klebsiella pneumoniae* is the frequent cause of a distinct new invasive syndrome of liver abscesses in Asia and increasingly globally⁷⁴.

Imaging Features—The imaging features of hepatic abscesses are dependent on the evolution of the abscess. At earlier stages, abscesses are usually semi-solid and irregular, with areas of necrosis, and therefore show variable enhancement. Mature abscesses have a large central necrotic area and a variable rim of granulation tissue and capsule comprising hepatocytes and fibrous tissue. Imaging of early stage abscesses may show poorly-defined masses with heterogeneous enhancement; this changes to a well-defined rounded mass when the abscess is mature. By ultrasonography mature abscesses are not as completely free of echoes as simple hepatic cysts, but nevertheless do not have blood vessels or bile duct structures running through them^{75, 76}. On CT, pyogenic liver abscesses appear as loculated, single or multiple lesions with heterogeneous and variable thickness rim enhancement, whereas amoebic liver abscesses tend to be single with a thin enhancing rim and surrounding hypodensity referred to as the halo sign^{77, 78}. Mature abscesses usually do not show internal enhancement. They are bright on T2-weighted MRI and show restricted diffusion on DWI. Pyogenic liver abscesses may be associated with biliary obstruction⁷⁷. Invasive *Klebsiella pneumoniae* liver abscess syndrome is associated with metastatic infections at other sites, including the lungs, genitourinary system, and eyeball⁷⁹ (Figure 8).

Management—Suspected pyogenic liver abscesses should be aspirated for aerobic and anaerobic cultures. A drain should be left in abscesses larger than 3 cm. Empiric antibiotic therapy should be initiated and modified once culture results become available. Antibiotic therapy should be continued for at least 4-6 weeks⁸⁰. Multiple, large or loculated abscesses

may require surgical drainage. Surgery may also be required to treat the underlying cause of the abscess.

Amebic liver abscesses often do not require aspiration; aspirates have the typical appearance of “anchovy paste”. Catheter drainage is more effective for large abscesses^{81, 82}. Antiamoebic treatment is with metronidazole or tinidazole for 7-10 days, followed by a luminal agent such as paromomycin or diiodohydroxyquin⁸³.

Hepatocellular Carcinoma

Epidemiology—HCCs 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 increase in cases of HCC due to NASH. Smaller proportions of HCCs are due to hereditary hemochromatosis, primary biliary cirrhosis, and autoimmune hepatitis. Dietary exposure to fungal aflatoxins, cigarette smoking and diabetes are also important risk factors².

Pathogenesis, Morphology and Molecular 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 an inflammatory environment that leads to genetic and epigenetic aberrations. HCCs show significant molecular heterogeneity; a substantial percentage of HCCs have mutations in the p53 and CTNNB1 genes, as well as in genes regulating chromatin remodeling⁸⁴. At least 5 molecular subclasses have been 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, however they are not routinely used in clinical practice⁸⁵. Most HCCs in the United States arise within a cirrhotic liver. Microscopically HCC cells resemble normal hepatocytes to a variable extent in well to moderately differentiated tumors. The tumor is characterized by naked or unaccompanied arteries, absence of normal portal tracts, and hepatic cord thickness more than 3 cells thick which can be highlighted by a reticulin stain. Mitoses are usually present (Figure 9). Histologic patterns of HCC include trabecular (the most common pattern), acinar (pseudoglandular), solid, and scirrhous patterns. These patterns do not appear to have prognostic significance. Immunohistochemical stains such as HepPar-1, Glypican-3 and polyclonal CEA are useful for confirming the diagnosis of HCC⁸⁶.

Imaging Features—HCCs usually develop from dysplastic nodules and are characterized by increased arterial vascularization and progressive loss of the portal venous blood supply that supplies regenerative and dysplastic nodules. These features produce a characteristic pattern of arterial phase hyperenhancement followed by portal venous or delayed phase washout (washout refers to relative loss of enhancement compared to that of the surrounding liver parenchyma) on multiphasic CT or contrast MRI. In new lesions larger than 1 cm in a cirrhotic liver this pattern is diagnostic for HCC and is considered a “radiological hallmark

of HCC”⁸⁷(Figure 9). Smaller lesions often do not show high arterial phase enhancement. Distinct hypointensity in the hepatobiliary phase of imaging with Eovist is increasingly recognized as a diagnostic feature of HCC. However, a small proportion of HCCs may show uptake of Eovist and appear iso- or hyperintense to the liver in the hepatobiliary phase⁸⁸. HCCs often show decreased T1 signal, increased T2 signal, and restricted DWI on MRI; these features can be used to identify small indeterminate HCCs with atypical enhancement or washout characteristics. Hyperintensity on DWI has been proposed as a new imaging criterion for HCC¹². Other useful features are the presence of focal fat within the lesion, internal mosaic appearance; vascular invasion, particularly of the portal vein with tumor thrombus formation, and interval growth of 50% or more on serial imaging follow-up obtained at a less than 6 month interval⁸⁹. Imaging features of HCCs can vary if the lesion is previously treated and knowledge of these appearances is useful for assessment of treatment response and to detect recurrence⁹⁰. Supportive laboratory findings include a raised or increasing trend of serum AFP.

Management—Management of HCC requires a multidisciplinary approach and is dependent on the number, size and location of HCC masses, as well as, the age, performance status, comorbidities, and liver function of the patient. Of the numerous prognostic staging systems proposed, the Barcelona Clinic Liver Cancer (BCLC) system has been widely accepted, being endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD)^{2, 91}. The system incorporates tumor staging, functional status and cancer-related symptoms into a five-stage system (very early or stage 0, early or stage A, intermediate or stage B, advanced or stage C and end-stage or stage D), with therapeutic guidelines for each stage⁹². Patients with acceptable liver function who are candidates can be treated with surgical resection, if this is technically feasible⁹³. Patients with cirrhosis who meet the Milan criteria – one mass ≤ 5 cm in size or two or three lesions ≤ 3 cm in size – are listed for liver transplant. Lesions ≤ 3 cm in size that are not amenable to resection or transplant can be treated with radiofrequency ablation or percutaneous alcohol injection². Intermediate stage disease is usually treated with transarterial chemoembolization or radioembolization⁹⁴. The current standard of care for advanced stage HCC is sorafenib. Patients with poor performance status or Child Pugh class C cirrhosis have poor survival and receive symptomatic care only².

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 present with biliary obstruction at the hilum of the liver (peri-hilar cholangiocarcinomas) or within the common bile duct (distal cholangiocarcinomas)⁹⁵. The major risk factors for cholangiocarcinoma are biliary tract diseases including primary sclerosing cholangitis, liver fluke infestations with *Opisthorchis viverrini* or *Clonorchis sinensis*, and choledochal cysts, cirrhosis, diabetes, and smoking^{96, 97}. While the incidence of extrahepatic cholangiocarcinomas has remained stable over time, there has been a 7-fold increase in incidence of intrahepatic cholangiocarcinomas from 0.3 per 100,000 person years to 2.1 per 100,000 person years over the past two

decades⁹⁸. The cause of this increase is unknown, but increased exposure to environmental toxins in industrial countries has been suggested⁹⁹. 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 due in part to increasing rates of cholecystectomy for gallstone disease.

Pathogenesis, Morphology and Molecular Pathology—A common thread in the etiological factors for cholangiocarcinoma are inflammatory conditions of the liver and biliary tract, and factors such as diabetes and smoking that contribute to genomic instability through oxidative stress and faulty DNA repair mechanisms. These tumors can present as a single mass, a large mass with satellite nodules, or multiple nodules within the liver. Microscopically cholangiocarcinomas are usually well-differentiated adenocarcinomas and resemble other glandular carcinomas of extrahepatic origin. The diagnosis of cholangiocarcinoma often depends on clinical and radiological exclusion of other primary sites. Cholangiocarcinomas are often scirrhous, with islands of malignant cells surrounded by dense stroma, which can make cytological diagnosis difficult. When cholangiocarcinomas develop in bile duct strictures, the demonstration of chromosomal polysomy in cytologic specimens using fluorescence in situ hybridization has proven more sensitive than cytology, while maintaining high specificity²³. Molecular analyses of cholangiocarcinomas show mutations in the KRAS, p53, IDH1/2, BRAF, EGFR, MET, and PIK3CA genes.

Imaging Features—Intrahepatic cholangiocarcinomas usually appear as solid masses which are hypointense in precontrast images, gradually accumulating a moderate amount of contrast through the arterial, portal and venous phases of CT or MRI imaging. The accumulation of contrast in the delayed phase is heterogeneous or central related to the scirrhous tissue in the cholangiocarcinoma and distinct from hemangiomas that show complete and homogeneous filling in. A thick rim of enhancement in the delayed phase is characteristic of cholangiocarcinoma and helps in differentiating it from HCC¹⁰⁰⁻¹⁰³. 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 contralateral hepatic lobe. 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 complex¹⁰⁴. Hilar cholangiocarcinomas lead to dilatation of the intrahepatic bile ducts, while distal extrahepatic cholangiocarcinomas lead to dilatation of the entire biliary tree.

Management—The 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 for metastasis⁹⁵.

A proportion of peri-hilar or extrahepatic cholangiocarcinomas can be resected. Unresectable hilar tumors with 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 iridium-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^{105, 106}.

Liver Metastases

Epidemiology—Liver metastasis is uncommon in the cirrhotic liver. In contrast, in non-cirrhotic livers, 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, as well, as renal cell carcinoma and melanoma. Therefore, patients without liver cirrhosis should be carefully evaluated for a possible primary site. This is facilitated by special immunohistochemical stains performed on biopsies of the liver masses.

Pathogenesis, Morphology and Molecular Pathology—The pathogenesis, morphology and pathology are dependent on the primary tumor type.

Imaging Features—Metastases have variable imaging features, but are typically hypoechoic on ultrasound, hypodense on CT and hypointense on MRI during the portal venous phase, compared to the surrounding liver parenchyma. Some metastases show arterial phase rim enhancement with washout in the portal venous phase. Hypervascular metastases that show relatively homogeneous enhancement in the arterial phase typically originate from renal cell, breast, thyroid, melanoma and neuroendocrine tumors¹⁰⁷. Hypovascular metastases are usually from pancreas and gastrointestinal tract adenocarcinomas. The most specific feature of metastases is a washout in the delayed phase¹⁰⁸.

Management—The specific management of liver metastases 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.

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List of abbreviations commonly found in the text

HCC	hepatocellular carcinoma
FNH	Focal Nodular Hyperplasia

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Figure 1. Microscopic section of cavernous hemangioma (hematoxylin and eosin stain $\times 100$) showing multiple vascular spaces lined by a single layer of benign endothelial cells (arrow).

Figure 2.

MRI of a cavernous hemangioma of the liver. The hemangioma (arrow) shows typical bright signal on T2-weighted image, hypointensity on T1-weighted image and peripheral nodular enhancement in the arterial phase with centripetal filling in the portal venous phase and near complete filling in the delayed phase. GB - gall bladder.

Figure 3. Ultrasound (left panel) and contrast enhanced CT (right panel) of liver showing a simple cyst (*).

Figure 4.

Focal nodular hyperplasia (arrow) seen as isointense to hypointense liver parenchyma on T2 and T1-weighted images with a central T2 hyperintense scar. During the arterial phase there is intense homogeneous enhancement of the mass which becomes isointense in portal venous and delayed phases. Positive uptake is seen in the hepatocyte phase which is characteristic. The gross picture shows a well-circumscribed lesion exhibiting the characteristic central scar (arrow). The microscopic section (hematoxylin and eosin stain $\times 40$) shows a scar in the center (long arrow) with a few thick walled vessels subdividing the lesion into smaller nodules. There is also steatosis within the hepatocytes (short arrow).

Figure 5.

Hepatic adenoma (arrow) in the left lobe in a patient with hepatic adenomatosis. The mass is slightly heterogeneous and hyperintense to liver on T2 weighted image and iso-to hypointense on the T1 weighted image. It demonstrated arterial phase enhancement (not shown) but is nearly isointense in the portal venous phase. The gross picture shows three well-demarcated lesions within the liver (white arrows). The microscopic section (hematoxylin and eosin stain $\times 200$) shows sheets of benign hepatocytes with a naked artery (long arrow). There is also some steatosis (short arrow) within the tumor.

Figure 6.

Hepatic adenoma (arrow) in the right lobe of the liver. The adenoma is hyperintense to liver on T2 weighted image and isointense on the T1 weighted image. It is hyper-enhancing in the arterial phase but nearly isointense in the portal venous phase and does not take up Eovist in the hepatocyte phase. An adjacent simple cyst is marked on the T2 weighted image (*).

Figure 7.
Examples of focal fat sparing (upper panels) and focal fat change (lower panels) adjacent to the falciform ligament and the peri-portal region.

Figure 8. *Klebsiella* liver abscess. Contrast-enhanced CT showing a large multi-loculated hypodense rim-enhancing mass in the right lobe of the liver consistent with a liver abscess. The patient presented with fever, abdominal pain and raised serum liver enzymes.

Figure 9.

Hepatocellular carcinoma on CT. The mass appears heterogeneous due to the presence of intra-tumoral fat confirmed at histology. The mass shows arterial phase enhancement with portal venous and delayed phase washout with a thin pseudocapsule (black arrow heads). The gross picture shows a large mass within the right lobe of the liver. A separate small satellite lesion is also seen (white arrow). The microscopic section (hematoxylin and eosin stain $\times 400$) shows hepatocellular carcinoma exhibiting a trabecular architecture with thickened hepatic cords and rare mitosis (black arrow).

Figure 10.

Intrahepatic cholangiocarcinoma. The mass is iso- to hyper-intense on T2-weighted image, bright on the diffusion weighted image and hypointense on T1-weighted image. There is peripheral thin rim enhancement in the arterial phase which persists into the portal venous phase and a thick rim-like enhancement in the delayed phase without washout. Note the enhancement of the surrounding liver in arterial phase due to perfusional change caused by the tumor. The tumor shows FDG uptake on the PET scan. The gross picture shows a white lesion (white arrow). The microscopic section (hematoxylin and eosin stain $\times 400$) shows an adenocarcinoma composed of neoplastic glandular proliferation with some areas showing lumen formation (black arrow).

Table 1**Clinical Classification of Liver Mass Lesions**

A. Benign Mass Lesions for which No Treatment is Needed
Hepatic Hemangioma
Focal Nodular Hyperplasia (FNH)
Benign Liver Cyst
Focal Fat or Focal Fat Sparing
B. Benign Mass Lesions for which Treatment or Follow Up is Required
Hepatic Adenoma and Adenomatosis
Biliary Cystadenoma
Hepatic Abscess
Echinococcal Cysts
Granulomatous Inflammation
Inflammatory Pseudotumor of the Liver
C. Malignant Mass Lesions for which Treatment is Required if Feasible
Hepatocellular Carcinoma (HCC)
Cholangiocarcinoma
Liver Metastases from Other Primary Sites
Biliary Cystadenocarcinoma
Hepatic Angiosarcoma
Lymphoma

Table 2**Recommended High-Risk Population for Screening for Hepatocellular Carcinoma**

A. Patients with Chronic Hepatitis B Virus Infection (HBsAg positivity)
- Asian males over 40 years of age
- Asian females over 50 years of age
- Africans over 20 years of age
- Patients with a family history of hepatocellular carcinoma
- Patients with high HBV viral loads
- Patients with evidence of active hepatitis
B. Patients with Cirrhosis of Any Cause
- Chronic hepatitis B
- Chronic hepatitis C
- Alcoholic cirrhosis
- Non-alcoholic steatohepatitis
- Hereditary hemochromatosis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Alpha-1 antitrypsin deficiency