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Liver Masses: Work up and When to Worry

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Liver lesions are common. A nodule found on ultrasound could be benign without the need for follow-up or malignant requiring urgent attention. This review examines the differential diagnosis, epidemiology, and management of common liver lesions. We review the imaging (particularly contrast-enhanced magnetic resonance imaging) characteristics and management considerations for cystic lesions, hemangiomas, adenomas, and focal nodular hyperplasia. We also review the diagnostic approach to solid lesions in patients with cirrhosis where hepatocellular carcinoma is more common.

Epidemiology

Liver lesions are common. The best data on population-based prevalence comes from incidental findings in scans ordered for reasons unrelated to the risk of liver lesions. For example, among 17,309 people receiving cross-sectional imaging ordered for lung cancer screening, 6.1% had liver lesions. Of these 1,064 lesions, one in three were potentially significant and 8 (0.8% of lesions) were found to be malignant.[1] Among 4,691 patients who received abdominal imaging during a trauma evaluation, 93 (3%) had liver cysts and 10 (0.3%) had potentially significant lesions requiring further evaluation.[2] There is variation depending on the population and the imaging modality selected. In general, when examining ultrasounds of the abdomen, cysts are detected in 6-8%, hemangiomas in 3-5%, focal nodular hyperplasia in 0.2-0.8%, and adenoma in 0.04%.[3]

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Cystic Liver Lesions

Cystic lesions range from simple cysts which have no malignant potential to complex pre-malignant lesions. Simple cysts contain clear fluid, do not communicate with the biliary tree, and are smooth but occasionally contain septations, particularly if they have been complicated by hemorrhage (often after trauma). On ultrasound, there is often acoustic shadowing in the parenchyma distal to the cyst. Occasionally, when very large, simple cysts can cause abdominal symptoms and can be treated surgically.[4] Hydatid cysts have thicker, frequently calcified walls with hypoechoic contents. On cross-sectional imaging, daughter cysts can be observed in the periphery.

Cystadenomas are cystic structures that have the potential for malignancy. Cross-sectional imaging is indicated when the cyst is irregular, with multiple septations, or very large. These have thick or irregular linings with papillary projections that often enhance during contrast phases, septations, and frequently contain heterogeneous fluid. Cystadenomas require monitoring or intervention given the risk of cystadenocarcinoma.

Solid liver lesions

General principles

If a patient has a small (<3cm), smooth, and stable (if prior imaging is available) lesion, it is likely to be benign. Many such lesions can be fully characterized by ultrasound, but cross-sectional imaging is usually definitive. Patients with cirrhosis (or hepatitis B) or known (or suspected) extrahepatic malignancy, and those with new or enlarging lesions (if prior imaging is available) require cross-sectional imaging for evaluation.

Understanding the biology across the differential diagnosis of solid liver lesions is key to ensuring accurate assessment and management. There are three central factors to consider: vascular supply, cellular components, and hormone sensitivity. (**Table 1**)

Benign lesions

Hemangioma

A hemangioma is mass consisting of septate clusters of vascular endothelium fed with hepatic arterial supply. The classic ultrasound appearance is homogenously hyperechoic and sharp margins. On MRI, hemangiomas display strong signal intensity on T2-weighted sequences and enhance strongly with contrast.[5] The pattern of enhancement is early/arterial enhancement in the periphery with progressive opacification through the portal and delayed phases. They are more common among women, can be large (>5cm), but do not grow or transform into malignancy.[6] There is no need for further monitoring on oral contraceptives or during pregnancy.[7] Rarely, the so-called 'cavernous hemangioma' (>5-10cm) can cause symptoms or rupture. Abdominal symptoms are common irrespective of the presence of liver lesions and attribution of abdominal symptoms to hemangiomas is therefore challenging and must be done carefully. Surgical resection or embolization is successful in highly selected cases. Among patients with hemangiomas >20cm, there have been case reports of Kasabach-Merrit Syndrome, a consumptive coagulopathy that improves with resection of the lesion.[8]

Focal Nodular Hyperplasia (FNH)

The vast majority of FNH occur in females. It is generally a solitary lesion. FNH consists of a proliferation of hyperplastic hepatocytes surrounding a central stellate scar with abnormal biliary drainage. There is no portal veinous supply and enlarged arterial branches are presented, coursing through the central fibrosis toward the lesion's rim. To distinguish FNH from adenomas, contrast-enhanced cross-sectional imaging may be required. Specifically, multiphasic MRI with a contrast agent that is readily taken up by hepatocytes such as Eovist is useful.[9] The enhancement is significant during the arterial phase and it persists through the delayed phase because the hepatocytes are functional but the biliary drainage is abnormal. FNH are not hormone sensitive and need no additional monitoring during pregnancy or when patients receive oral contraceptives.[7]

Adenomas

Hepatocellular or hepatic adenomas are mostly benign but understanding several key features is needed to discern benign from risky lesions. Adenomas are clusters of nonfunctional hepatocytes without portal tracts – they are fed by arteries and lack portal venules or bile ducts

Table 1. Liver Lesion Basics

Lesion	Biology	Imaging Features	What to Do	When to Worry	What it Could Be	Next Step
Cyst	Clear fluid.	Smooth, occasional septations. Acoustic shadow on ultrasound.	No monitoring needed for simple cysts.	Ultrasound with nodular cyst wall, heterogeneous fluid, multiple septations, or calcifications.	Cystadenoma can transform into malignancy. Hydatid cysts may require therapy.	MRI with contrast.
Hemangioma	Septate clusters of vascular endothelium fed with hepatic arterial supply.	Ultrasound: hyperechoic with sharp margins. MRI: strong signal intensity on T2-weighted sequences and early peripheral arterial contrast enhancement with progressive centripetal filling on later phases.	No monitoring needed.	If >10 cm, can cause abdominal symptoms. If >20cm, rarely can cause coagulopathy.	Cavernous (large) hemangiomas can cause pain or, very rarely, Kasabach-Merrit Syndrome.	Multidisciplinary management with a surgeon and liver tumor board.
Focal nodular hyperplasia (FNH)	Proliferative hepatocytes with intact portal triads surrounding a central scar.	Ultrasound: subtle, if any differences from surrounding tissue. Doppler may see 'spoke-wheel' arterial flow. Cross-sectional: arterial enhancement, isointensity in later phases. Scar will appear hypointense on T1, hyperintense on T2, and hyperintense on delayed contrast-enhanced phases.	No monitoring needed after diagnosis by MRI.	If Gadolinium-Eovist enhanced MRI is not conclusive.	Without conclusive imaging features, biopsy may be needed to exclude adenoma.	Biopsy or multidisciplinary management at liver tumor board.
Adenoma	Hepatocytes that are less functional than those in FNH. They lack portal tracts and are fed by arteries. When caused by HNF1-A mutations, there is significant fatty infiltration. B-catenin mutations do not cause specific features. Inflammatory subtypes have vessel clusters and dilated sinusoids.	Variable by subtype. Dilated vascular structures can be seen on ultrasound if present. If fatty infiltration, signal dropout on T1-weighted MRI sequences. HNF1a: arterial enhancement which fades on delayed phases. Inflammatory lesions with telangiectatic arteries are hyperintense on T2 with persistent enhancement on delayed phases. B-catenin lesions often appear the same. Noninflammatory lesions are isointense on T1 and T2 with arterial enhancement and delayed washout.	Stop oral contraceptives. Consider 6 or 12 month follow up to determine growth pattern.	Men, pregnancy, >5cm or growing.	Large lesions can rupture and bleed or transform into hepatocellular carcinoma. Lesions with b-catenin mutations are more likely to transform into malignancy.	Biopsy if lesion is inconclusive or needed for decision making. Resection for high-risk lesions (men, >5cm, growing, b-catenin mutation). Monitor each trimester in pregnancy and 12-weeks post-partum. Bland embolization if >5cm and pregnant.
Hepatocellular Carcinoma (HCC)	Malignant transformation of hepatocytes with preference for arterial blood supply. Arises in patients with cirrhosis, hepatitis B, and rarely in non-cirrhotic livers.	Solitary or multi-nodular lesions. Ultrasound cannot distinguish from other lesions. Arterial hyperenhancement with 'washout' on portal veinous phases.	Refer for multidisciplinary tumor board review.	All patients require urgent evaluation.	HCC is fatal if untreated.	Multidisciplinary selection of therapeutic modalities.

MRI = magnetic resonance imaging

– and often are diffusely infiltrated with steatosis. These features often lead to accurate diagnoses by MRI. When infiltrated by steatosis, there will be signal dropout on T1-weighted sequences. Many adenomas, particularly the common inflammatory subtype which has telangiectatic arteries, possess a strong hypersignal on T2-weighted images and display persistent enhancement on delayed phases. Notably, adenomas do not take up the MRI contrast agent Eovist because it is selective for (functional) hepatocytes.

Adenomas can arise and grow in association with estrogen exposure. The epidemiology of adenomas is derived from case-control studies and suggest that the lower doses of estrogen in modern contraceptives are linked to a lower risk of adenoma development. Discontinuation of contraceptives results in regression or stability of the lesion.[10] Of note, intrauterine devices, depoprogestin injections, and progestin-only pills are considered safe. Given the risk of growth during high estrogen states, pregnancy is a high-risk period for patients with adenomas. Women with adenomas should undergo ultrasound surveillance each trimester and at week 12 post-partum. The risk of hemorrhage and rupture is highest for lesions >5cm and therefore to prevent complications, bland transarterial embolization is indicated when lesions reach this size. Adenomas will also grow when exposed to and regress after discontinuation of anabolic steroids taken by men.[11] Finally, adenomas arise in those with obesity and the metabolic syndrome. There is limited evidence to suggest that some adenoma will stabilize or shrink in response to weight loss.[12]

Two key features characterize the risk of complications, namely hemorrhage and malignancy. First, lesions >5cm, particularly those in men or those which do not regress with discontinuation of estrogen, are high risk. Second, there are multiple histological subtypes of adenomas, and one is more likely to become cancer. The most common adenoma subtypes are the inflammatory, HNF1A mutated, and, comprising 10%, the beta-catenin mutated adenoma. Beta-catenin mutations pose the greatest risk of malignancy, are more common among men, and therefore molecular diagnostics from lesional biopsies can inform decision making. Specifically, this information guides the frequency of follow-up imaging and the benefit of early treatment particularly when size is <5cm or when patient is unsure of their next steps. Generally, resection is indicated when adenomas are growing during surveillance, when beta-catenin is detected, and for men. Surveillance can be short-term (6 months) when observing following cessation of estrogen therapy or at 1-year when tracking progression for lesions <5cm.

Hepatocellular Carcinoma

Cirrhosis is the primary risk factor for HCC, according for 80-90% of HCC with an annual incidence of 2-4%.[13,14] The highest incidence are among people with uncured/viremic hepatitis C and uncontrolled hepatitis B infections.[15, 16] Hepatitis B can cause HCC in the absence of cirrhosis. As such, people with cirrhosis should undergo screening for HCC. Among those with HBV, men >40 years old, females >50 years old, and those with a family history of HCC should be screened.[17] Screening should involve liver ultrasounds and AFP testing semiannually, however cross-sectional imaging can be used. When a liver mass is detected in someone with cirrhosis or HBV, prompt diagnostic evaluation is needed to improve outcomes.[18] Although it is a cancer, HCC can be diagnosed by imaging without the need for biopsy. When a suspicious lesion is found, patients should undergo cross-sectional diagnostic imaging with a multiphasic CT or MRI. Owing to the differential blood supply of the liver (primarily portal veinous blood) and HCC (primary arterial), the timing of contrast phase can identify lesions as HCC or not. Liver lesions are categorized and interpreted according to the American College of Radiology criteria for Liver Imaging Reporting and data system (LI-RADS).[19] Lesions are classified from definitely benign (LI-RADS 1) to definitely HCC (LI-RADS 5), as well as non-HCC malignancy (LI-RADS M) and noncategorizable (LI-RADS NC). For LI-RADS 4 lesions and above, the AASLD recommends a multidisciplinary discussion, with biopsy in select cases, or follow up imaging in 3 months.

Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is a rare (9 per 1,000,000 people) lesion with poor survival. Risk factors are poorly defined but there are some high-risk groups: primary sclerosing cholangitis, recurrent pyogenic cholangitis, liver flukes, Caroli's disease, and age >65 years. Though often diagnosed when symptomatic and advanced, cholangiocarcinoma can be diagnosed as a solitary lesion. On ultrasound, they can be indistinguishable from other lesions but are occasionally irregular with associated capsular retraction. Cross-sectional contrast-enhanced imaging displays slow centripetal enhancement and the draining bile ducts are frequently dilated.

CONCLUSION

Liver lesions are frequently encountered incidentally. We review approaches in **Table 1**. The key principles guiding their diagnosis are fourfold. First, all decisions must be considered in the context of whether the patient has underlying chronic liver disease such as cirrhosis or sclerosing cholangitis. Second, many lesions can be diagnosed by ultrasound if cystic or small and smooth. Third, most lesions will require an MRI with contrast which provides the greatest detail based on the underlying physiology of the lesion. Fourth, where doubt remains following an MRI, follow-up imaging or discussion at a multidisciplinary tumor board are reasonable approaches. Following a diagnosis, management is often conservative apart from hepatic adenomas and lesions in patients with chronic liver disease. ■

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