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In Brief

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With the growing use of cross-sectional imaging in daily clinical practice, liver masses are incidentally detected with increasing frequency. The differential diagnosis for the finding of a liver mass is broad and includes both malignant and benign processes, which can generate significant anxiety for patients and providers alike. A thoughtful and systematic way in which to sort through this differential is necessary to allow for appropriate evaluation and management of patients with these lesions, whether this involves patient reassurance, surgical intervention, or something in between.

In this monograph, we discuss some of the most commonly encountered benign liver masses, highlighting ways in which they can be diagnosed and distinguished from one another and from malignant conditions, especially on radiographic evaluation. Still, the starting point is a thorough history and physical examination that seeks to assess for risks that the lesion may represent a cancerous process. A history of weight loss or jaundice, especially when coupled with a personal or strong family history of cancer, should elicit concern for primary or secondary liver malignancy. Likewise, patients with a history of fatty liver, chronic viral hepatitis, alcohol use, or intravenous (IV) drug use stand at risk for primary liver cancers, while patients of certain ethnic backgrounds and those with conditions such as primary sclerosing cholangitis may be at risk for gallbladder or biliary tract cancers. With regards to benign pathologies, it is important to inquire about the patient's use of oral contraceptives or anabolic steroids, as well as his/her travel and exposure-to-parasite history. Any family history of metabolic syndromes including glycogen storage disease and hemochromatosis is also important to ascertain. Finally, adjunctive blood work

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including standard chemistry panel, as well as liver function tests and tumor markers including alpha-fetoprotein, may be helpful.

Imaging of liver lesions often starts with a liver ultrasound (US), which offers the benefits of noninvasiveness and the ability to discern solid from cystic mass, assess flow, and characterize the surrounding liver parenchyma. On the other hand, ultrasound is heavily operator-dependent and limited by patient factors (e.g., body habitus). Perhaps the most useful tool in the evaluation of liver masses remains a high-quality liver protocol computed tomography (CT) scan that permits assessment of the mass across multiple phases, the patterns of which tend to be characteristic for individual pathologies. Benefits of wide availability, general ease of interpretation, and superior anatomic correlation make CT scan an attractive first-line option for providers. More recently, magnetic resonance imaging of the liver has proven to be an especially helpful tool for liver imaging, offering benefits over CT of greater soft tissue contrast, lack of radiation, and availability of hepatobiliary agents that have created a hepatobiliary imaging phase not available on CT scans. This modality, however, is less readily available and more difficult to interpret by untrained clinicians. Although imaging alone is often adequate to establish a diagnosis for most benign liver lesions with some degree of confidence, there remain some scenarios in which tissue biopsy is necessary. Indeed, even though most benign liver pathologies tend to have a characteristic set of features that help define them, some will bear atypical features and mimic malignancies. In these cases, percutaneous biopsy may be required, with best results achieved when biopsies of both the identified tumor and normal adjacent liver parenchyma are obtained.

Benign liver lesions may be solid or cystic, and uni- or multifocal. Among benign solid liver lesions, by far, the most common type is the hemangioma, a conglomeration of vascular channels supported by loose fibrous stroma that is more commonly discovered in women. Hemangiomas are typically small and present no risk for complication, although they can grow to be greater than 5 cm in size, in which case they are called giant hemangiomas. Although they tend to be asymptomatic, hemangiomas—especially the giant variant—can be associated with clinical complications, including abdominal pain, consumptive coagulopathy (Kasabach-Merritt syndrome), an intense inflammatory syndrome causing fevers, pain, and anemia (Bornman syndrome), and even high output cardiac failure. On imaging, the defining feature of hemangiomas is a discontinuous peripheral pattern of enhancement with progressive centripetal filling of the lesion from the arterial to later phases, with the contrast almost always mirroring the blood pool. There are, however, some hemangioma variants that bear atypical appearances, such as the flash-filling hemangioma or the sclerosing or hyalinized hemangioma, which will often require a tissue biopsy to rule out malignancy. As most hemangiomas are asymptomatic, there is no need to treat or follow them. In the presence of significant symptoms, surgical extirpation of the hemangioma remains the current treatment standard and may be accomplished via enucleation or resection.

Second most common among benign solid liver masses is focal nodular hyperplasia (FNH). This well-circumscribed tumor is composed of a mix of hepatocytes, Kupffer cells, bile ducts, and blood vessels, and is thought to be related to a hyperplastic reaction to an arterial malformation in the liver. FNH is most often found in women in their second to fifth decades of life, is generally asymptomatic, and bears no malignant potential. On imaging, FNH tends to have a lobulated contour and is classically associated with a central stellate scar with fibrous septa radiating outward toward the periphery, although this pathognomonic finding may be absent in as many as one-half of the lesions. Magnetic resonance imaging with hepatobiliary agents like gadoxetate may be especially helpful in distinguishing FNH from malignant processes and hepatocellular adenoma, with FNH appearing brightly hyperintense on the hepatobiliary phase. Since FNH is a benign lesion, surgical intervention is seldom necessary except in the case of atypical FNH or those causing severe symptoms.

The third major category of solid benign liver tumors to consider concerns hepatocellular adenomas (HCA). A process predominantly affecting women, HCA is stimulated by estrogen and associated with pregnancy, oral contraceptive use, as well as use of anabolic steroids. With unimpeded estrogen exposure, these tumors may grow to large sizes and rupture, with potential for significant hemorrhage. Conversely, HCA may regress with cessation of the stimulating agent.

Other risk factors for HCA include obesity, nonalcoholic steatohepatitis, and certain metabolic syndromes (e.g., glycogen storage diseases). In addition to the much greater risk for rupture that differentiates it clinically from hemangiomas and FNH and unlike those 2 pathologies, HCA does carry a significant risk for malignant transformation that is influenced by several factors, not the least of which is the molecular-pathologic HCA classification to which the tumor belongs. It is now recognized that there exist 4 subtypes of HCA based on molecular and pathologic features: hepatocyte nuclear factor 1α-inactivated HCA (HCA-H), which often demonstrates marked steatosis; inflammatory HCA (HCA-I), which is characterized by inflammatory tumor infiltration; β-catenin activated HCA (HCA-B), which carries the greatest malignant potential; and unclassified HCA (HCA-U), which lacks any of the defining features of the other 3 subtypes. Diagnosing HCA on imaging is often challenging, as is distinguishing them from malignant processes and from one another, and there may be a role for tissue biopsy. Once a diagnosis is reached, a treatment algorithm that includes surgery can be employed. Indications for HCA resection seek to eliminate risks of rupture and malignant transformation, and include male gender, HCA-B tumors, as well as large tumor size (>5 cm), presence of symptoms, and failure to regress off contraceptives.

Among benign cystic lesions of the liver, simple cysts are by far the most common entity, with a prevalence that may reach nearly 20% in the general population. They are more common in women and tend to be asymptomatic. Imaging characteristics of a round, anechoic lesion with sharply circumscribed margins with no internal nodularity or enhancement are typical for simple cysts. The exception to the rule presents when there is internal hemorrhage within the cyst, which may create debris and even calcifications over time. Simple cysts most often require no treatment, but when large and symptomatic, laparoscopic unroofing offers a safe and durable treatment option. When more than 10 or 20 cysts are present, diagnostic consideration of polycystic liver disease must be entertained. This condition may occur in isolation, but more frequently is associated with polycystic kidney disease; in both scenarios, it is autosomal dominant, although separate germline mutations have been identified. Cyst size and number may be so great as to completely replace the liver parenchyma on imaging, yet liver function is nearly always preserved. Symptoms arise with cyst hemorrhage, infection, or rupture, or when the large size of the cyst(s) and/or the entire liver causes obstruction of vascular or biliary structures or adjacent organs. Treatment options include medical therapy with somatostatin analogs that can decrease cyst fluid secretion, aspiration sclerotherapy, fenestration, hepatic resection, and liver transplantation. This last option offers the only chance for cure and may be combined with kidney transplantation for patients with autosomal dominant polycystic kidney disease.

Cystic lesions of the liver may also be related to infectious processes caused by bacteria (pyogenic), yeasts (fungal), *Entamoeba histolytica* (amebic), or echinococcal tapeworms (echinococcal). A thorough history can yield informative data to aid in the diagnosis. In particular, a travel history and assessment of exposure risk to causative organisms are critical. Pyogenic abscesses tend to occur in relatively immunosuppressed patients (e.g., those with poorly controlled diabetes mellitus) and may form directly from bacterial spread through the biliary system, as would be the case after biliary instrumentation, or indirectly after peritonitis related to viscus perforation. Amebic abscesses are endemic to certain developing countries, and form after *E. histolytica* enter the liver via the portal vein, although they may not become evident for weeks or even months. Echinococcal abscesses develop when humans are infested as part of the life cycle of tapeworms of the echinococcal family, especially *Echinococcus granulosa*. This condition is endemic to areas where sheep are raised. Pyogenic and amebic abscesses are nearly indistinguishable from each other on imaging, and the diagnosis is instead made based on the clinical picture and serologic studies. Echinococcal cysts, on the other hand, have 4 main radiographic appearances that have been described, and may be confirmed through serologic testing. Treatment of infectious abscesses differs based on the offending organism. Pyogenic abscesses are most often treated with a combination of intravenous antibiotics and abscess drainage, which can help with bacterial speciation and directed antibiotic therapy. Although aspiration may be adequate for smaller cysts, drainage catheter placement is often necessary for larger cysts. Surgical drainage is reserved for patients who fail percutaneous drainage, especially those with large gas-containing

abscesses. Amebic abscesses, unlike their pyogenic counterparts, are treated primarily with medical management with antibiotics achieving cure more than 90% of the time. Cyst aspiration is only indicated for failure of medical management. Finally, echinococcal cysts are treated with a combination of antihelminthic drugs and surgical intervention. Due to concern for spillage of the cyst content and possible anaphylaxis reaction, aspiration of the cyst content and injection of a sterilizing agent is often performed as the first step of surgical resection. Alternatively, the percutaneous aspiration-injection-reaspiration procedure has been shown to be effective and safe in treating simple echinococcal cysts. It is not a suitable option, however, for complex cysts (e.g., cysts that have eroded into the biliary tree).

Less common benign liver lesions discussed in this review include angiomyolipomas, biliary cystadenomas, and mesenchymal hamartomas. Angiomyolipomas are solid masses consisting of variable mixtures of intralesional fat, smooth muscle, and proliferating vessels (thus the name), and on imaging may be difficult to differentiate from liver metastases. Tissue biopsy is currently recommended. Although benign, these tumors do have malignant potential, especially with enlarging size, and thus should be resected if larger than 5 cm. Cystadenomas, for their part, have a somewhat distinctive radiographic appearance marked by septations that may enhance or bear calcifications. Unfortunately, this same appearance may apply to their invasive counterparts (cystadenocarcinomas), and although absence of enhancing mural nodules may support a more benign diagnosis, this is not a definitive distinguishing feature and cystadenomas therefore warrant surgical resection. Mesenchymal hamartomas are most often found in children and, because they may resemble malignant processes, are treated with surgery as well.

Although the current review does not cover all benign liver tumors (nor was it intended to), it discusses some of the most common ones and places an emphasis on their evaluation and management. With hepatic “incidentalomas” being detected with increasing frequency, and the burden they place on patients and providers alike, being able to distinguish benign from malignant liver pathologies is critical. This requires a multidisciplinary approach and must involve a radiologist specializing in liver imaging.