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Approach to a Patient with a Liver Lesion



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The presence of a liver lesion undoubtedly causes significant stress and anxiety not only for the patient but also for health care providers. It is important to realize that most liver lesions can be accurately diagnosed utilizing distinguishing features on imaging, laboratory data and clinical history. In lesions that remain indeterminate, a biopsy of the lesion may be warranted. Reviewing older imaging studies can provide invaluable information regarding the stability of the lesion in question and need for additional evaluation.

Liver lesions in the setting of cirrhosis substantially alter the level of concern and clinical approach to testing. Aggregate data, including patient history, laboratory results (to calculate the the aspartate aminotransferase to platelet ratio index, or APRI), evidence of portal hypertension (pHTN) on imaging and physical signs suggestive of chronic liver disease should be used to assess patients individually.

Benign Hepatic Lesions

Hepatic hemangioma, focal nodular hyperplasia (FNH) and hepatic adenoma (HA) are the most

common benign liver lesions. The European Association for the Study of the Liver (EASL) has comprehensive guidelines on the management of benign liver lesions.¹ When considering if surgical resection is warranted in a patient with a benign liver lesion, there are key questions to consider: 1. Has there been growth of the lesion? 2. Is the lesion atypical or the diagnosis in question? 3. Is the patient having symptoms that could be attributed to the lesion? Magnetic resonance imaging (MRI) is the recommended imaging modality to most accurately characterize suspected benign liver lesions.

Hepatic hemangioma, a blood filled cavity lined by a single layer of epithelial cells that derives its blood supply from the hepatic artery, is the most common benign liver lesion. Thought to be congenital, hemangiomas are more common in woman than men. In contradistinction to other common benign liver lesions, hemangiomas can be seen in cirrhosis, however with less frequency and often diminished in size. These lesions demonstrate avid T2 enhancement on MRI. When small, they may lack the classic features such as centripetal enhancement or a “filling” in, so they must be distinguished from a malignancy in cirrhosis, particularly intrahepatic cholangiocarcinoma (iCCA). Most hemangiomas are less than 5 cm; when greater than 10 cm they are known as a

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giant hemangioma and size does not correlate with symptoms. When imaging features are consistent with a typical hemangioma, follow up imaging is not required. If a confident diagnosis cannot be made with imaging, a liver biopsy is not contraindicated, however, there must be the presence of normal liver parenchyma between the capsule and the margin of the lesion to minimize complications. Those with symptoms related to a hemangioma or a giant hemangioma should be evaluated in a multidisciplinary clinic.

Thought to occur as a result of a congenital anomaly as a result of a venous infarct, which leads to arterialization of the affected tissue, the next most common benign liver lesion is FNH. FNH is more common in females (90%), located in the right lobe and generally solitary (conditions that are associated with multiple FNHs include: Budd Chiari syndrome, obliterative portal venopathy, post treatment with oxaliplatin).² A vital feature that aids in distinguishing FNH from HA is the presence of bile ducts and kuffer cells in the former. Using a biliary agent, such as Eovist or Multihance, can help radio graphically differentiate FNH from HA. An MRI is nearly 100% specific for FNH. The hallmark radiographic sign of FNH is a central scar, which represents a corkscrew artery, however in small lesions this may not be present. In lesions less than 3 cm, a contrast enhanced ultrasound (US) may be more accurate. While there is no supporting evidence that FNH have any malignant potential, it can mimic a very rare malignancy, fibrolamellar carcinoma (approximately 200 cases per year reported worldwide) due to the presence of a calcified central scar seen in 55%. Similar to hemangioma, there is no direct correlation with symptoms and size, and resection is rarely needed.

Hepatic adenomas are the least common but most concerning (risk of bleeding and development of hepatocellular carcinoma (HCC) related to size) of the benign liver lesions. The exact incidence of HA is unknown but is 10 times less common than FNH. The classic risk factors have been use of estrogen and androgens. They are more common in females than males, 10:1, and are usually single. While the incidence of HA is declining related to oral contraceptive pill (OCP) use, it is rising due to obesity and the metabolic syndrome, often leading to multiple HA. For males, resection is

recommended for HA regardless of size. In females, lifestyle changes (discontinuation of OCP and weight loss) are recommended, with repeat imaging in six months. If the lesion decreases to less than 5 cm, repeat MRI in one year is recommended. If the lesion remains greater than 5 cm, repeat imaging in an additional six months is recommended. If the lesion increases in size by 20% or more, resection is indicated.

The risk of bleeding is highest in adenomas that are larger than 5 cm and exophytic. Additional risk factors for hemorrhage include use of OCPs in the last six months, pregnancy, and the inflammatory subtype (described below). When hemorrhage does occur with HA, embolization by interventional radiology should be performed to control bleeding. Emergent resection is associated with higher mortality rates.

A sub-classification of HAs was initially described in 2006 and updated in 2017.³ Associated with obesity and alcohol use, the lowest risk of degeneration to HCC is in the subtype HNF (inactivated hepatocyte nuclear factor). On imaging there is diffuse steatosis within the lesion. The inflammatory HA carries the highest risk of bleeding and also has a risk of HCC. The highest risk of developing HCC is seen in the beta catenin activated HA.

Pregnancy is no longer considered a contraindication in females with HA larger than 5 cm. If it is larger than 5 cm or there is a history of prior bleeding, resection prior to pregnancy should be discussed. There is currently no evidence based-algorithm for the management of HA in pregnancy. US every 6-12 weeks to monitor for growth is recommended. If a lesion is noted to be growing, embolization can be performed. The highest risk of bleeding during pregnancy is in the third trimester and carries a high mortality rate.

Malignant Hepatic Lesions

When evaluating a lesion that is concerning for malignancy, determining the presence of underlying liver disease, specifically cirrhosis, is important as cirrhosis predisposes patients to HCC as well as iCCA. Other malignant lesions are unrelated to the presence of cirrhosis.

The most common primary liver cancer is HCC, with 80 – 90% of cases occurring in patients

with cirrhosis. In 2016, data from the CDC showed a 43% increase in mortality in the United States during the period of 2000-2016. This is thought to be due to the rising incidence of HCC with fairly steady 10-year mortality rates due to HCC. HCC is the leading cause of mortality in patients with cirrhosis with an estimated 1/3 of patients developing HCC in their lifetime. The diagnosis of HCC with known cirrhosis can be made based on radiographic findings without the need for a pathologic confirmation with a biopsy. The presence of arterial enhancement with washout in the venous phase is diagnostic if HCC, regardless of the alpha-fetoprotein (AFP) level (normal in up to 30% of tumors). Arterial enhancement, due to increased hepatic artery blood flow related to angiogenesis, promotes tumor growth and spread.

The American Association for the Study of Liver Diseases (AASLD) recommends HCC surveillance in patients with cirrhosis, regardless of etiology, every six months with an US, with optional AFP level.⁴ Surveillance is not recommended in patients with Child Pugh C cirrhosis unless they are listed for transplant. The rationale is that mortality will be driven by decompensated cirrhosis and therapy for HCC, if found, is supportive in the presence of significantly impaired liver function. If a lesion on US is detected to be greater than 1 cm, contrast enhanced imaging with computed tomography (CT) or MRI is used to make a diagnosis of HCC.

The liver imaging reporting and data system (LIRADS) was developed by the American College of Radiology with the goal of standardizing the

reporting of liver lesions in patients at risk for HCC. There are 5 categories ranging from definitely benign (LI-RADS 1) to definitely malignant (LI-RADS 5). A LI-RADS 5 lesion is subdivided based on size: 5A is ≥ 1 cm & < 2 cm and 5B is ≥ 2 cm & ≤ 5 cm. For both of these, a diagnosis of HCC requires the presence of non-rim arterial phase hyperenhancement (APHE) and non-peripheral washout and/or 50% increase or more in size in six months.⁵ The probability of HCC being present is shown based on the respective LI-RADS category (Table 1).

Liver transplant (LT) provides the best chance for long term overall survival by removing not only the carcinoma but also the cirrhotic liver. Unfortunately, there remains a shortage of organs to allow transplant in all that are listed. Additionally, patients with HCC tend to have preserved liver function and thus a low model for end-stage liver disease (MELD) score. In order to overcome a disadvantage in patients with HCC and a low MELD score, patients with HCC are given a “boost”, or MELD upgrade. While a lesion 1 cm or larger can be diagnosed as HCC based on characteristics seen on contrast enhanced imaging, unless a lesion is a 5A, there is not an MELD HCC upgrade. Once a lesion is 2 cm (T2 lesion), an HCC MELD upgrade is awarded. The prioritization for HCC meeting T2 criteria has evolved since the inception of the MELD allocation system with a lowering in prioritization for HCC with each reiteration in order to make access to an organ more equitable between patients with HCC and

Table 1.

	Average Probability of HCC (%)	Cumulative Incidence of Progression to HCC or Other Malignancy (%)*
LI-RAD 1	0	0
LI-RAD 2	11	0-6
LI-RAD 3	33	6-15
LI-RAD 4	80	46-68
LI-RAD 5	96	N/A

* Based on untreated lesions followed prospectively over 24 months

those without cancer who are listed with their biological MELD. Currently patients are given an increase in MELD score after a six month waiting period to ensure that the tumor does not harbor aggressive biological behavior that would become more obvious after a period of six months. Patients must have an AFP < 1000 at the time of listing, irrespective of tumor burden. The MELD upgrade is a calculation of the average MELD at the time of LT in each respective Organ Procurement Organization – 3 points.

Cholangiocarcinoma is the second most

common primary hepatic tumor. iCCA is the least common, followed by distal CCA and perihilar CCA (most common). Similar to HCC, the incidence of iCCA has increased and shares risk factors with HCC (cirrhosis, chronic viral hepatitis, alcohol excess, diabetes, and obesity). However, in contrast to HCC, iCCA can occur in patients with a normal architectural liver. The prognosis with iCCA is poor with 5-year overall survival rates under 5%. Currently patients with cirrhosis diagnosed with iCCA are not granted a MELD upgrade for LT due to poor outcomes. It is

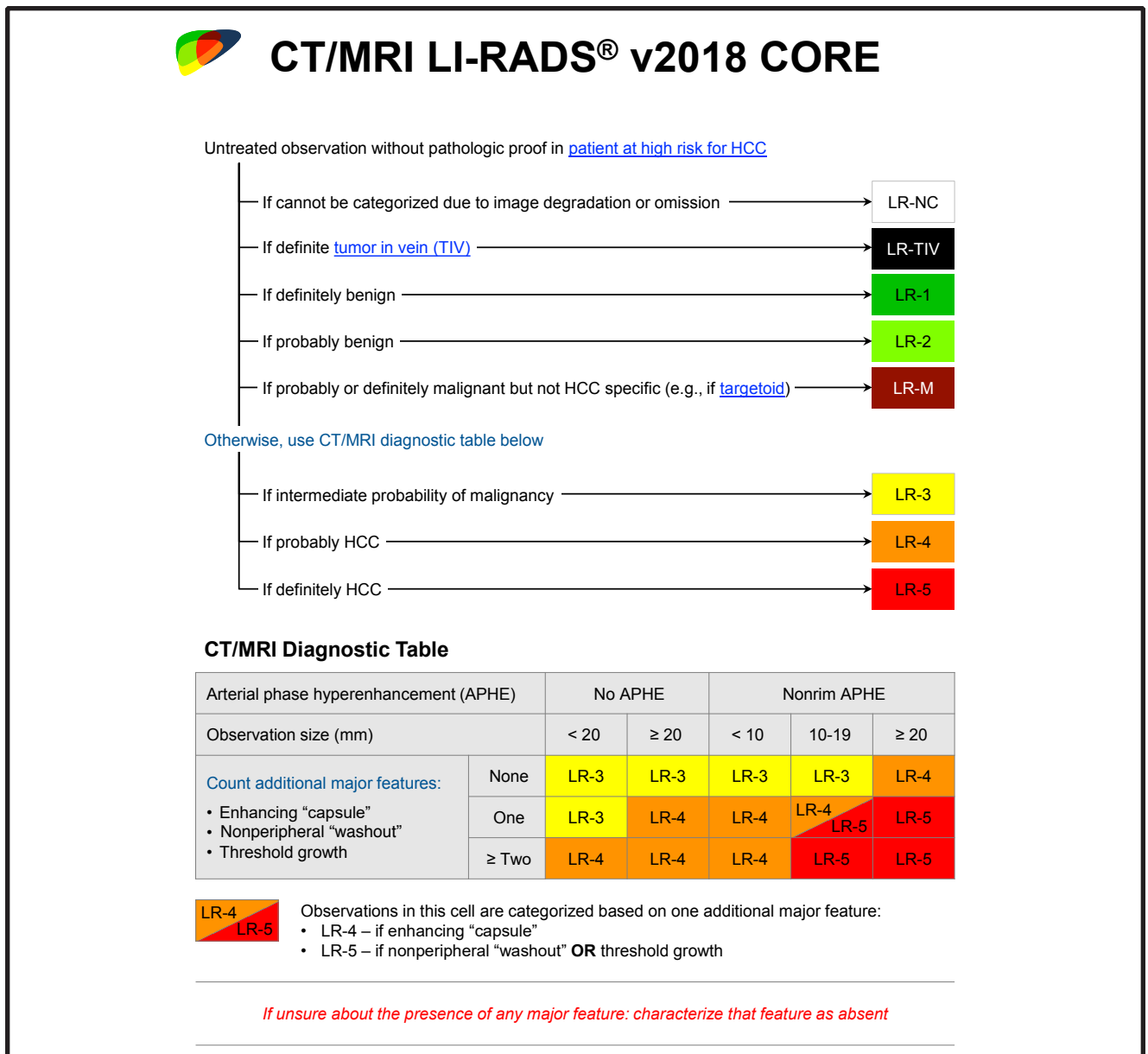


Figure 1. Risk of HCC Based on LIRADS⁶

critical to distinguish a lesion as HCC versus iCCA. Generally these two entities can be distinguished on imaging however if not, then a biopsy of the lesion is warranted. The key radiographic findings in iCCA include progressive arterial enhancement and a lack of washout; ancillary features included capsular retraction and dilated peripheral bile ducts. Surgical resection has been the mainstay of therapy.

Other malignant lesions in the liver that are not related to the presence of cirrhosis include metastatic disease, angiosarcoma and hepatic epithelioid hemangioendothelioma (HEHE). Hepatic spread of other primary malignancies is rare in cirrhosis due to alterations in portal blood flow; the exception is colorectal adenocarcinoma, which has been reported in cirrhosis. Angiosarcoma carries a dismal prognosis with two-year survival

of only 3%. Mortality is generally due to tumor rupture (high vascularity) or liver failure due to replacement of the liver with tumor. Risk factors include vinyl chloride, arsenic, cyclophosphamide, anabolic steroids, and OCP. Angiosarcoma is an absolute contraindication for LT. Treatment is resection, when possible, and chemotherapy. Lastly, HEHE is a very rare tumor of vascular origin, which is seen more commonly in middle age females. It has a more favorable prognosis compared to other hepatic malignancies, as it is generally slow growing. Treatment for HEHE includes resection, LT (>10 nodules or >4 involved hepatic segments) and anti-vascular endothelial growth factor (anti-VEGF) therapy.

CONCLUSION

Liver lesions require a careful approach to ensure correct diagnosis and therapy. It is vital to determine if a patient has cirrhosis or chronic liver disease, as this will alter the approach to a liver lesion. Fortunately, key radiographic features can help distinguish the most common benign lesion from each other and generally can be managed conservatively. ■

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