

CME

ACG Clinical Guideline: Focal Liver Lesions

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Focal liver lesions (FLLs) have become an increasingly common finding on abdominal imaging, especially asymptomatic and incidental liver lesions. Gastroenterologists and hepatologists often see these patients in consultation and make recommendations for management of multiple types of liver lesions, including hepatocellular adenoma, focal nodular hyperplasia, hemangioma, and hepatic cystic lesions including polycystic liver disease. Malignancy is important to consider in the differential diagnosis of FLLs, and healthcare providers must be familiar with the diagnosis and management of FLLs. This American College of Gastroenterology practice guideline uses the best evidence available to make diagnosis and management recommendations for the most common FLLs.

KEYWORDS: liver lesion; liver mass; adenoma; liver cyst; focal nodular hyperplasia; hemangioma; choledochal cysts; cystic liver lesions; cystic neoplasms

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PREAMBLE

The guideline is structured in the format of statements that were considered to be clinically important by the content authors. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used to assess the quality of evidence for each statement (1) (Table 1). The quality of evidence is expressed as high (we are confident in the effect estimate to support a particular recommendation), moderate, low, or very low (we have very little confidence in the effect estimate to support a particular recommendation) based on the risk of bias of the studies, evidence of publication bias, heterogeneity among studies, directness of the evidence, and precision of the estimate of effect (2). A strength of recommendation is given as either strong (recommendations) or conditional (suggestions) based on the quality of evidence, risks vs benefits, feasibility, and costs taking into account perceived patient and population-based factors (3). Furthermore, a narrative evidence summary for each section provides important details for the data supporting the statements.

This writing group was invited by the American College of Gastroenterology to update existing guidelines to the diagnostic approach and management of focal liver lesions (FLLs). Regular meetings were conducted among this writing group throughout the guideline development process to formulate Problem, Intervention, Comparison, Outcome (PICO) questions that guided the subsequent literature search, development of recommendation statements and key concepts, GRADE assessments, and the preparation of the full guideline document.

We conducted an electronic search using Embase and Ovid MEDLINE through September 2022. We limited the search to English language and included Epub Ahead of Print, In-Process, In-Data-Review, & Other Non-Indexed Citations. For each PICO question developed, we comprehensively reviewed the existing literature, with a focus on studies of the highest quality of evidence (e.g., when available, systematic reviews and meta-analyses, followed by randomized controlled trials, followed by observational studies).

In addition to guideline recommendations, the authors have highlighted key concept statements that were not included in the GRADE assessment. Key concepts are statements that the GRADE process has not been applied to and can include both expert opinion recommendations and definitions/epidemiological statements. Table 2 is a summary of recommendations, whereas Table 3 summarizes the key concept statements.

These guidelines are established to support clinical practice and suggest preferable approaches to a typical patient with a particular medical problem based on the currently available published literature. When exercising clinical judgment, particularly when treatments pose significant risks, healthcare providers should incorporate this guideline in addition to patient-specific medical comorbidities, health status, and preferences to arrive at a patient-centered care approach.

FLLs are solid or cystic lesions, which are identified as an abnormality in the liver. For the purposes of this update, the term “lesion” will be used instead of “mass” because first, the term

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Table 1. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Strength of recommendations, quality of evidence, and implications for the patients and clinicians

Strength of recommendation	Criteria
Factors influencing the strength of the recommendation include the quality of the evidence, clinical and patient-reported outcomes, risk of harm, and costs/healthcare resource utilization	
Strong	Strong recommendation is offered when the desirable effects of an intervention clearly outweigh the undesirable effects Implications from a patient and clinician perspective: Patients: Most individuals in this situation would prefer the recommended course of action, and only a small proportion would choose an alternative Clinicians: Most patients should receive the recommended course of action or an alternative with similar strength of recommendation
Conditional	Conditional recommendation is offered when trade-offs are less certain—either because of low quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced Implications from a patient and clinician perspective: Patients: Some individuals would want the suggested course of action, whereas others may not. A discussion regarding pros, cons, and available alternatives is appropriate to reach an individualized patient-specific decision Clinicians: A shared decision-making model through a discussion regarding the available evidence and alternative options is appropriate, taking into consideration the values and preferences of the patient
Quality of evidence	Criteria
High	We are very confident that the true effect closely aligns with that of the estimate of the effect
Moderate	We have a moderate level of confidence in the estimate of effect. It is likely that the true effect is close to the estimate of the effect
Low	Our confidence in the effect estimate is limited. The true effect could differ from the estimate of effect
Very low	We have very little confidence in the effect estimate. The true effect may be substantially different from the estimate of effect

lesion can be used to describe a solid or cystic mass, and second, it is in keeping with the updated Liver Imaging Reporting and Data System lexicon (4). This guideline will be focused predominantly on the diagnosis and management of FLLs in people without known liver disease.

INTRODUCTION

With the continued dramatic rise in the widespread role of imaging in diagnosis and management of patients, there is a resultant rise in detection of asymptomatic incidental liver lesions. Common imaging modalities in which incidental liver lesions are detected include ultrasonography (US) with or without contrast agent (CEUS), computed tomography (CT), and magnetic resonance imaging (MRI) for abdominal or nonabdominal indications (breast and spine). Studies show a continued upward trend in utilization of CT/MRI/US imaging in adults in the United States and Canada, inevitably resulting in increased detection of incidental FLLs within the liver (5). In fact, some studies show that up to 52% of patients without cancer have a benign liver lesion at autopsy (6). The American College of Radiology reports that up to 15% of patients have an incidental liver lesion detected on routine nonsurveillance imaging (7). Therefore, it is critical to understand appropriate management of incidentally detected benign FLLs because they have differing clinical implications from malignant lesions such as hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA), and metastatic disease.

Initial evaluation and management of incidental FLLs

Incidental liver lesions can be defined as unsuspected findings within the liver, which are often identified on outpatient or emergency department imaging performed to investigate an

unrelated clinical symptom such as pain, weight loss, or trauma. Imaging studies performed under these circumstances are usually either an abdominal ultrasound or contrast-enhanced single portal venous phase CT. Although these modalities will detect an FLL, they cannot adequately characterize the lesion itself. Because most patients with incidentally detected FLL are asymptomatic, the question then arises whether further workup is necessary, and if so, what is the management recommendation for an incidentally detected FLL?

Given the extensive categories of benign and malignant pathologies of FLLs, as well as differences in management, liver-directed imaging is often needed for adequate clarification (8,9). There are a few instances where further workup of incidental FLLs is not necessary, specifically if the imaging appearance on abdominal ultrasound or single-phase CT is characteristic for a hemangioma or benign uncomplicated cyst. The imaging appearances of these 2 lesions will be discussed later in these clinical guidelines.

In most instances, characterization of liver lesions requires careful investigation of the medical history, clinical symptomatology, physical examination, laboratory workup, and imaging. History should include any medical history and current clinical symptoms and should determine whether the individual has any predisposing condition, which would be associated with the development of liver lesions. Possible histories that would suggest the increased risk of FLLs include history of previous cancer, presence of constitutional symptoms (anorexia, weight loss, night sweats, or fever), history of foreign travel, medications (oral contraceptive pills [OCPs], hormone supplementation, or steroids), and perhaps most important is identifying risk factors for chronic liver disease. The latter is critical to adequately characterize FLLs on imaging

Table 2. Summary and strength of recommendations

Statement	GRADE quality	Strength of recommendation
General		
1. In patients with a focal liver lesion of uncertain etiology, we recommend multiphasic contrast-enhanced imaging, preferably MRI or CT performed with late arterial, portal venous, and delayed phases	Strong	Low
Hepatic adenoma		
2. We recommend discontinuation of oral contraceptives or intrauterine devices that are hormone-impregnated in patients with hepatic adenomas	Strong	Low
3. We suggest encouraging weight loss in overweight or obese patients with hepatic adenomas	Conditional	Very low
4. We suggest using multiphasic liver imaging (preferable MRI) over standard cross-sectional imaging modalities to accurately distinguish hepatic adenomas from other benign or malignant liver lesions	Conditional	Very low
5. In women with hepatic adenomas <5 cm, we suggest discontinuation of exogenous hormones and advise weight loss, if applicable, for overweight or obese individuals	Conditional	Very low
6. In women with hepatic adenomas <5 cm, we suggest surveillance with contrast-enhanced imaging modalities every 6 months for 2 years, then annually thereafter	Conditional	Low
7. In patients with hepatic adenomas requiring treatment who are unable to undergo surgical resection, we suggest embolization or ablation as alternative treatment approaches	Conditional	Low
8. In patients with ruptured hepatic adenomas, we suggest hemodynamic stabilization followed by embolization and/or surgical resection	Conditional	Very low
Focal nodular hyperplasia		
9. We suggest evaluating patients with focal liver lesions that are suspicious for focal nodular hyperplasia using multiphase MRI with hepatobiliary-specific contrast agents to distinguish focal nodular hyperplasia from hepatocellular adenoma	Conditional	Low
10. We do not suggest routinely discontinuing oral contraceptives in patients diagnosed with focal nodular hyperplasia	Conditional	Very low
Hemangioma		
11. In patients with cirrhosis or chronic hepatitis B who meet criteria for hepatocellular carcinoma surveillance and have a suspected hemangioma, we recommend continued imaging surveillance every 3–6 months for at least 1 year	Strong	Low
Simple hepatic cysts		
12. In patients with asymptomatic simple hepatic cysts, regardless of size, we recommend expectant management without need for routine surveillance or intervention	Strong	Low
13. In patients with simple hepatic cysts with specific high-risk features seen on ultrasound (e.g., septations, fenestrations, calcifications, mural thickening or nodularity, heterogeneity, and presence of daughter cysts), we recommend further investigation with CT or MRI.	Strong	Low
14. We suggest surgical cyst fenestration or aspiration with sclerotherapy for management of patients with symptomatic simple hepatic cysts	Conditional	Low
Polycystic liver disease		
15. We suggest discontinuation of exogenous estrogen use in women with polycystic liver disease	Conditional	Very low
16. For patients with PCLD with numerous small- to medium-sized cysts throughout the liver not amenable to surgical resection, cyst fenestration, or aspiration sclerotherapy, or for patients with symptomatic ADPKD with concurrent PCLD, we recommend medical management using somatostatin analogs	Strong	Moderate
Hydatid/echinococcal cysts		
17. We suggest surgical management in patients with complicated hydatid cysts (i.e., those with biliary fistulas or cysts communicating with the biliary tree, multiseptated cysts, rupture or hemorrhage, secondary infection, or percutaneously inaccessible cysts) provided there is no contraindication to surgery	Conditional	Very low
18. In patients with uncomplicated hydatid cysts in whom surgery is not an option, we suggest percutaneous treatment with PAIR with adjunct antihelminthic therapy	Conditional	Low
CT, computed tomography; MRI, magnetic resonance imaging; PCLD, polycystic liver disease; ADPKD, autosomal dominant polycystic kidney disease; PAIR, puncture, aspiration, injection of scolicidal agent, and reaspiration.		

Table 3. Key concepts

General

- 1. In an asymptomatic patient without known liver disease and an incidentally detected liver lesion, workup includes a thorough patient history (history of previous cancer), constitutional symptoms (weight loss, loss of appetite, and fevers), medication history (oral contraceptives and steroids), risk factors for chronic liver disease (viral hepatitis, transfusion history, tattoos, intravenous drug use, and alcohol excess), features of metabolic syndrome (obesity, dyslipidemia, insulin resistance, hypertension, and cardiovascular disease) blood tests (liver enzymes, tumor markers, and viral hepatitis panel), and contrast-enhanced imaging (CEUS, MRI, and CT)
- 2. Inadequately characterized and/or atypical focal liver lesions should be reviewed at a multidisciplinary liver tumor board
- 3. Multiphasic postcontrast MRI and CT have shown no statistically significant difference in diagnostic accuracy for focal liver lesions, although MRI confers many advantages
- 4. Most solid focal liver lesions in patients with no associated risk factors will be benign, including hemangioma, adenoma, or focal nodular hyperplasia

Hepatic adenoma

- 5. The use of anabolic steroids in men, obesity, polycystic ovarian syndrome, glycogen storage disease, and possibly exogenous hormonal therapy in men, women, and transgender individuals are risk factors for development of hepatic adenomas
- 6. Hepatic adenomas are generally benign but can be associated with an increased risk of hemorrhage and/or malignant transformation
- 7. When a solid hepatic mass is incidentally discovered in a patient with no known risk factors, appropriate multiphasic contrast-enhanced imaging (CT or MRI) should be the first step in management and is often a sufficient test for diagnosis and subtyping of hepatic adenomas
- 8. Biopsy should be performed when a hepatic adenoma has an uncharacteristic appearance on imaging or change in imaging features that are concerning for malignant transformation
- 9. MRI features are beneficial for subtyping inflammatory-type adenomas and HNF-1 α mutated adenomas, but are not specific for subtyping β -catenin mutated, sonic hedgehog, and unclassified adenomas
- 10. Risk factors for development of inflammatory HCAs include obesity and/or metabolic syndrome risk factors, heavy alcohol consumption, and/or glycogen storage disease
- 11. β -catenin mutated HCAs are at a higher risk of malignant transformation compared with other clinical subtypes and should be resected regardless of size
- 12. Hepatic adenomas that develop in men are commonly β -catenin mutated and associated with a higher risk of malignant transformation
- 13. Women with hepatic adenomas $\geq$ 5 cm should modify risk factors, undergo observation for 6–12 months, and undergo resection if the lesion does not regress to $<$ 5 cm
- 14. Men with hepatic adenomas should undergo surgical resection regardless of lesion size because of elevated risk of malignant transformation
- 15. Hepatic adenomas should be monitored regularly during pregnancy and should be treated if there is growth to $>$ 6.5 cm or with high-risk features for hemorrhagic rupture
- 16. Hepatic adenomas of any size that have imaging features concerning for malignant transformation should be treated as a hepatocellular carcinoma, with consideration to surgical resection, locoregional therapies, and/or liver transplantation
- 17. Hepatic adenomatosis is a variant of HCA characterized by 10 or more hepatic adenomas, more commonly associated with background steatosis, or glycogen storage disease
- 18. Consideration for liver transplantation should be given to patients who meet the OPTN policy for transplantation, especially those with glycogen storage disease, unresectable β -catenin positive adenoma, or unresectable with complications of hemorrhagic or malignant transformation of hepatic adenomas

Focal nodular hyperplasia

- 19. Advanced imaging techniques (e.g., contrast-enhanced multiphase MRI with hepatobiliary-specific contrast) can accurately diagnose focal nodular hyperplasia in most cases, and biopsy is not routinely needed
- 20. In a patient with a focal nodular hyperplasia confirmed on imaging, no further follow-up is required
- 21. If the diagnosis of focal nodular hyperplasia is confirmed, then even in the case of growth, resection is not required. If resection is being considered because of symptoms, then patients must be counseled that their symptoms may not improve after surgery as FNH rarely causes symptoms
- 22. If focal nodular hyperplasia lesions are symptomatic and surgery is not an option because of comorbidities or anatomic considerations, then transarterial embolization with or without bleomycin may be considered to decrease size
- 23. Men with focal nodular hyperplasia do not need to have any different evaluation, monitoring, or treatment compared with women

Hemangioma

- 24a. Small echogenic avascular lesions less than 2 cm with well-defined borders in a patient with a normal liver and no underlying medical history or risk factors for liver disease or malignancy can be diagnosed as hemangioma on ultrasound
- 24b. In patients with a lesion that does not meet the above criteria, multiphasic contrast-enhanced imaging should be performed to confirm the diagnosis
- 25. If a suspected hemangioma cannot be confirmed on cross-sectional imaging, then the next step is to monitor and to review the case at a multidisciplinary tumor board

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Table 3. (continued)

26. Biopsy of a suspected hemangioma should be avoided when possible because of the risk of bleeding
27a. Once the diagnosis of hemangioma is confirmed, no further follow-up is needed unless the patient has cirrhosis or other risk of malignancy such as hepatitis B
27b. Patients who are pregnant do not need to have monitoring of the hemangioma even in the case of large, cavernous hemangiomas
28. Even in patients with asymptomatic large, cavernous hemangiomas (generally >10 cm), surgical resection is not indicated. No further follow-up is required
29. Indications for resection of a hemangioma are complications related to the lesion, such as rupture, intralesional hemorrhage, consumptive coagulopathy, or organ or vessel compression. These complications are rare. Resection may be performed through open or laparoscopic approach
30. If surgery is not an option for a patient with complications related to the lesion, other treatments may be considered such as ablation (microwave or radiofrequency), radiation therapy, transarterial embolization, or in the very rare instance, liver transplantation. Treatment options in these instances should be discussed at a multidisciplinary tumor board
Solid liver lesions of malignant potential
31. Patients with hepatocellular carcinoma, cholangiocarcinoma, neuroendocrine tumor, and metastatic colon cancer that are within guidance and consensus recommendations for liver transplant should be referred early in their course to a liver transplant center experienced in that disease process
32. For lesions that are suspected to be metastatic to the liver, MRI with hepatobiliary contrast enhancement and diffusion-weighted imaging is the recommended modality
Hepatic endothelial hemangioendothelioma
33. If resection is planned because of imaging being very suspicious for hepatic endothelial hemangioendothelioma, a needle biopsy does not necessarily need to be performed before surgery
34. Patients with diagnosed hepatic endothelial hemangioendothelioma should undergo imaging for staging of disease with whole-body contrast enhanced CT or whole-body contrast-enhanced MRI. PET-CT or PET-MRI may be considered with the understanding that hepatic endothelial hemangioendothelioma is generally only mild or moderately PET avid
35. Hepatic endothelial hemangioendothelioma should be resected whenever possible. If resection is not feasible, then liver transplantation offers the best survival, even in the setting of extrahepatic disease
36. In the setting of nonresectable and nontransplantable hepatic endothelial hemangioendothelioma, there are very little data to guide treatment choices and patients should be referred to a specialty center whenever possible. Ablative therapies and stereotactic body radiotherapy have shown some response in small studies. There is no systemic therapy that can be recommended from published evidence, given the small numbers of patients
Fibrolamellar hepatocellular carcinoma
37. In patients with fibrolamellar hepatocellular carcinoma, surgical resection is the treatment of choice. In patients who have limited liver-localized disease that is unresectable, liver transplant may be considered on a case-by-case basis
38. Neoadjuvant or adjuvant systemic therapy is not recommended for fibrolamellar hepatocellular carcinoma except in the setting of a clinical trial
39. In patients with fibrolamellar hepatocellular carcinoma, biopsy should be performed to confirm the diagnosis, but molecular analysis of the biopsy for guidance of systemic therapy is not beneficial
Hepatic angiosarcoma
40. In patients with primary hepatic angiosarcoma, surgical resection should be performed whenever feasible
Hepatic cystic lesions
41. In patients with asymptomatic complex hepatic cysts, regardless of size, we recommend discussion at a multidisciplinary tumor board and consideration of surveillance imaging in 6–12 months
Polycystic liver disease
42. Treatment goals for polycystic liver disease should be aimed at symptom relief and preservation of quality of life
43. Treatment options for polycystic liver disease including cyst aspiration with sclerotherapy, surgical cyst fenestration, or resection of dominant cyst(s) should be based on cyst characteristics, underlying hepatic reserve and center expertise
44. Liver transplantation with or without simultaneous kidney transplantation should be considered as a curative option in patients with polycystic liver disease with refractory symptoms because of significant cyst burden
Mucinous cystic neoplasms of the liver
45. Fluid aspiration or biopsy of mucinous cystic neoplasms of the liver is not recommended to distinguish between benign vs malignant cysts because of low sensitivity
46a. Mucinous cystic neoplasms of the liver with imaging characteristics consisting of thick septations, fenestrations, nodularity, calcifications, or mixed solid and cystic components require prompt evaluation for complete surgical resection
46b. For patients who are not surgical candidates, surveillance imaging should be implemented, although a specific interval cannot be recommended. Changes suggestive of malignant degeneration should be discussed at a multidisciplinary tumor board for consideration for nonsurgical options

Table 3. (continued)

Biliary hamartomas and peribiliary cysts

- 47. Biliary hamartomas and peribiliary cysts are benign malformations and do not require surveillance imaging
- 48. Intraductal papillary neoplasm of the bile ducts are premalignant biliary lesions with a high risk of malignant transformation, and thus, continued surveillance imaging is recommended even after surgical resection

Intrahepatic choledochal cysts

- 49a. Management and treatment of choledochal cysts is based on type of cyst and risk of malignant transformation
- 49b. Type I or IV choledochal cysts are most commonly associated with malignancy and should undergo surveillance imaging, although a specific interval cannot be recommended
- 50. In both type IV and V choledochal cysts, when resection is not feasible, liver transplantation should be considered

Hydatid/echinococcal cysts

- 51a. Medical therapy of hydatid cysts with antihelminthic drugs is indicated before surgery or cyst puncture in patients with symptomatic or active hydatid cysts to prevent risk of recurrence, secondary seeding, or to decrease cyst pressure or in inoperable cases
- 51b. Medical therapy alone is not recommended because of ineffective treatment unless percutaneous aspiration or surgery is contraindicated

CEUS, contrast-enhanced ultrasound; MRI, magnetic resonance imaging; CT, computed tomography; HNF-1 α , hepatocyte nuclear factor-1 α ; HCA, hepatocellular adenoma; OPTN, Organ Procurement and Transplant Network; FNH, focal nodular hyperplasia; PET, positron emission tomography.

because some benign and malignant lesions may have overlap in imaging features, and history is key to categorize lesions. Pertinent questions regarding risk factors for chronic liver disease include history of viral hepatitis or cirrhosis, history of blood product transfusions, tattoos, intravenous drug use, alcohol use, and features of the metabolic syndrome (obesity, type 2 diabetes mellitus, hypertension, hyperlipidemia, and/or cardiovascular disease). Often, imaging findings of a nodular liver morphology, hepatic steatosis, or imaging features of portal hypertension can be obtained from the incidental imaging study in which the FLL was discovered.

Although history and laboratory data are an important part of the workup for FLLs, proper imaging workup is critical. Studies suggest that up to 95% of FLLs detected on grayscale ultrasound can be diagnosed with proper contrast-enhanced imaging without the need for biopsy (10,11). In addition, 97% of lesions detected in patients with known risk factors for chronic liver disease with characteristic imaging features for HCC based on Liver Imaging Reporting and Data System diagnostic categorization and American Association for the Study of Liver Diseases (AASLD) guidelines do not need pathologic confirmation for diagnosis and management. However, discussion on FLL in patients with chronic liver disease is not the intent of this review (12–14). Diagnostic imaging can be performed with CEUS, multiphasic contrast-enhanced CT, or multiphasic dynamic postcontrast MRI.

Standardization of the technical specifications of postcontrast imaging is important to ensure appropriate characterization of FLLs. Liver transplant consensus recommendations provide specifications for postcontrast CT and MRI, and although the report focuses on HCC diagnosis, the same technical aspects can be applied in the evaluation of benign FLLs (15). Key elements to diagnostic imaging include the need for intravenous contrast agents and multiple postcontrast phases of imaging, specifically late arterial, portal venous, and delayed phase of imaging. Of note, on CT, this is ordered as a triple-phase liver protocol (in contradistinction to a routine abdominal CT, which includes only a single portal venous phase of imaging), and on MRI, it is a

dynamic postcontrast liver MRI. CEUS has been shown to have high sensitivity, specificity, and positive predictive values of 97.8%, 83.9%, and 82.2%, for benign FLL characterization (16).

One challenge for clinicians is understanding which imaging modality should be used for workup of FLLs. A review of literature has shown no statistically significant difference between CT and MRI in diagnosis of FLLs (17). However, advanced MRI techniques have improved the detection and differentiation of different FLLs, and thus in general, MRI is favored for characterization of suspected benign FLLs (18–22). In addition, the lack of ionizing radiation makes MRI a more attractive study for younger individuals without risk factors when ongoing surveillance imaging is required.

A frequent clinical dilemma is understanding whether to order an MRI with extracellular vs hepatobiliary contrast agent. Because hepatobiliary agents are partially excreted by the biliary system, lesions with biliary pathology (focal nodular hyperplasia [FNH]) will be hyperintense on hepatobiliary phase (HBP) of imaging, allowing for imaging-based diagnosis requiring no further workup. On the other hand, most other lesions will be hypointense on HBP of imaging. Therefore, in a young patient with no known risk factors for malignancy, MRI with hepatobiliary agent allows for diagnosis of FNH vs adenoma, both of which have different management recommendations (23). Follow-up thereafter can be with extracellular or hepatobiliary contrast agent because the diagnosis has already been confirmed. In other clinical scenarios where FNH may not be a consideration, there is no consensus on use of extracellular vs hepatobiliary contrast agent as first line for imaging diagnosis. Based on expert opinion, extracellular contrast agent is favored because hepatobiliary agent-induced respiratory motion (acute transient dyspnea) and lack of adequate dynamic-phase enhancement are limitations of hepatobiliary agents (24,25).

When a diagnosis cannot be definitively made on imaging, a multidisciplinary discussion and core biopsy should be considered (26). In FLLs that cannot be characterized with contrast-enhanced cross-sectional imaging and are not amenable to biopsy (secondary to technical challenges), surveillance imaging is

recommended to detect changes in lesion size, lesion appearance, and development of new lesions. Surveillance intervals are individualized and depend on the suspected diagnosis, patient risk factors, and often multidisciplinary discussion and generally range from 3 to 6 months.

The remainder of this document will discuss specific solid and cystic liver lesions, with recommendations on appropriate diagnosis and management. Figure 1 summarizes the guidance document in a flowchart form.

Key concepts

1. In an asymptomatic patient without known liver disease and an incidentally detected liver lesion, workup includes a thorough patient history (history of previous cancer), constitutional symptoms (weight loss, loss of appetite, and fevers), medication history (OCPs and steroids), risk factors for chronic liver disease (viral hepatitis, transfusion history, tattoos, intravenous drug use, and alcohol excess), features of metabolic syndrome (obesity, dyslipidemia, insulin resistance, hypertension, and cardiovascular disease), blood tests (liver enzymes, tumor markers, and viral hepatitis panel), and contrast-enhanced imaging (CEUS, MRI, and CT).
2. Inadequately characterized and/or atypical FLLs should be reviewed at a multidisciplinary liver tumor board.
3. Multiphasic postcontrast MRI and CT have shown no statistically significant difference in diagnostic accuracy for FLLs, although MRI confers many advantages.
4. Most solid FLLs in patients with no associated risk factors will be benign, including hemangioma, adenoma, or FNH.

Recommendation

1. In patients with an FLL of uncertain etiology, we recommend multiphasic contrast-enhanced imaging, preferably MRI or CT performed with late arterial, portal venous, and delayed phases (strong recommendation, low level of evidence).

SOLID LIVER LESIONS

Hepatocellular adenoma

Epidemiology and risk factors. Hepatocellular adenoma (HCA) is a benign frequently asymptomatic neoplasm of the liver, with limited prevalence data, reported to be around 0.007%–0.012% (27). Risk factors include females taking OCPs, anabolic steroid use, obesity, glycogen storage disease, and polycystic ovarian syndrome (PCOS).

Females taking OCPs have an incidence of 3–4 per 100,000 users compared with 0.13–1.0 per 100,000 in nonusers, with modern-era OCPs having markedly decreased concentration of estrogen and progesterone compared with the 1960s (27–29). Discontinuation of OCPs or estrogen-impregnated intrauterine devices has been associated with regression of adenomas in many cases (30,31).

Males and females taking anabolic androgenic steroids are also at an increased risk of the development of hepatic adenomas (32,33). The incidence of HCA in men is believed to have increased because of the use of anabolic steroids particularly in the setting of weightlifting, although these can be used for treatment of medical conditions such as aplastic anemia or paroxysmal nocturnal hemoglobinuria (34). There are limited data currently

suggesting the use of exogenous hormonal or steroid therapy in transgender individuals increases risk of hepatic adenoma development (35).

Obesity has emerged as a notable risk factor for hepatic adenoma development, likely owing to the endogenous estrogen production through activation of aromatase in adipose tissue. Patients with metabolic syndrome and particularly hepatic steatosis are also at risk of development of adenomas; many of these patients having overlapping risk factors of obesity, OCP use (often because of concomitant PCOS), and other risk factors of metabolic syndrome, also promoting disease progression (33,36). In lean patients with HCA, weight gain is also discouraged owing to the association of HCA growth with increased body mass index. A future study is planned looking at the impact of a low-calorie ketogenic diet on weight reduction and HCA size (37).

Glycogen storage disease, particularly types Ia and III, carries a particularly high lifetime incidence of adenoma development, including a risk of hepatic adenomatosis. This particular group of patients is noted to have a male predominance (2:1) and often present at a younger age, as early as the second or third decades of life (38–40). Cases of HCA have also been noted in patients with PCOS and other sex hormone imbalance conditions, although it is unclear whether this establishes causality.

Key concept

5. The use of anabolic steroids, obesity, PCOS, glycogen storage disease, and possibly exogenous hormonal therapy in men, women, and transgender individuals are risk factors for development of hepatic adenomas.

Recommendations

2. We recommend discontinuation of OCPs or intrauterine devices that are hormone-impregnated in patients with hepatic adenomas (strong recommendation, low quality of evidence).
3. We suggest encouraging weight loss in overweight or obese patients with hepatic adenomas (conditional recommendation, very low quality of evidence).

Pathophysiology and natural history. HCAs represent a benign proliferation of mature hepatocytes, which can develop in a background of an otherwise normal liver, or one affected by steatosis or glycogenosis. This tumor is usually well-defined but rarely encapsulated, highly vascular, variable in size, and solitary or multifocal. The presence of multifocal (>10) nodules has been defined as adenomatosis (41,42).

The initial diagnosis is often made incidentally during abdominal imaging. Alternatively, patients can present with abdominal pain. Currently, there is no formal recommendation for HCA screening with metabolic risk factors or duration of OCP exposure.

Most hepatic adenomas are benign and asymptomatic. However, different from other benign liver lesions, hepatic adenomas are associated with a risk of hemorrhage (up to 15%) and/or malignant transformation (up to 5%) (42,43). The risk of hemorrhagic complications is associated with the clinical subtype of HCA as well as the size and rate of growth of the lesion. Similarly, the likelihood of malignant transformation, although rare,

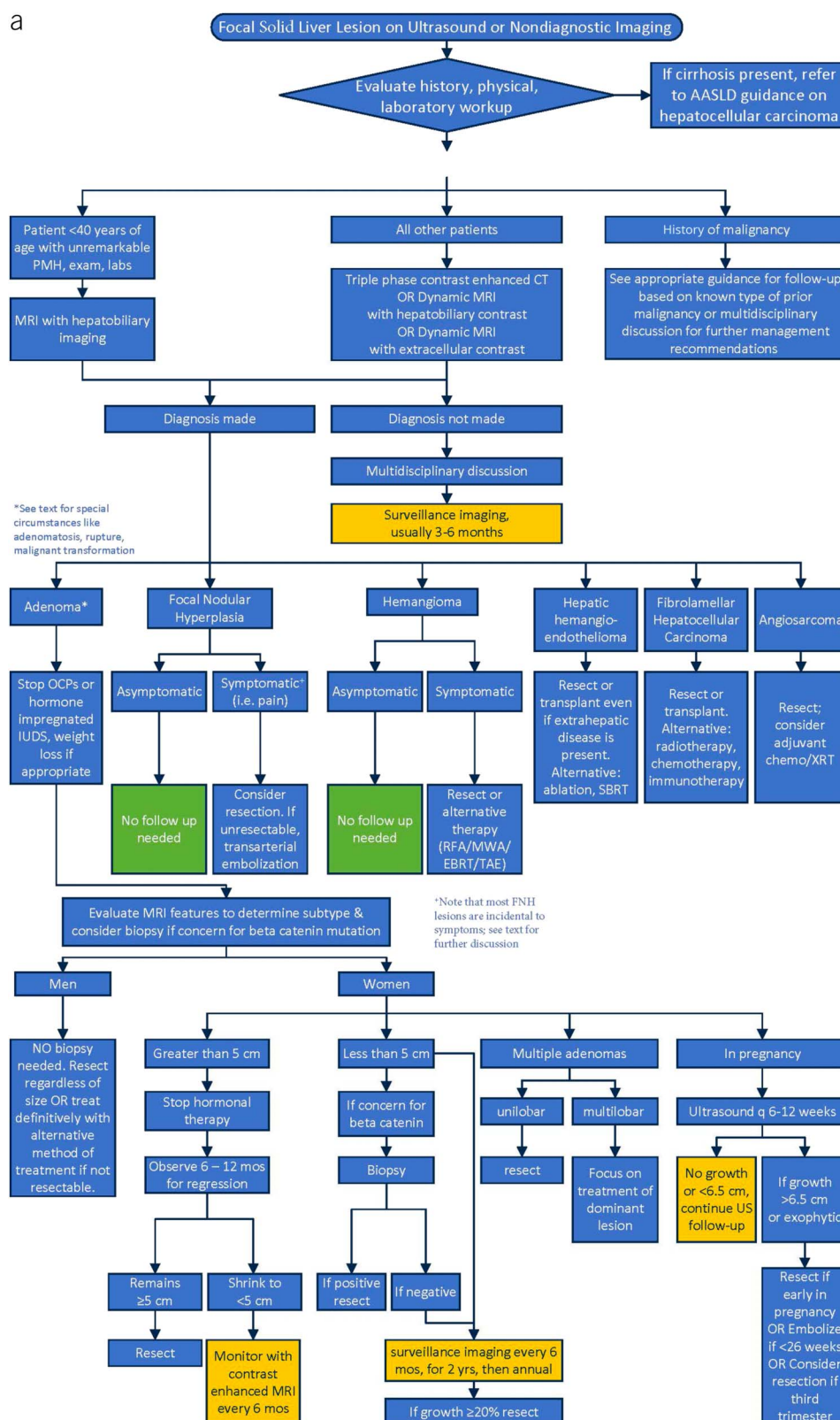


Figure 1. This flowchart is a diagram outline of the recommendations made within this guidance document. Further details of each recommendation made can be found within the text. Figure 1a outlines recommendations for solid focal liver lesions. Figure 1b outlines recommendations for cystic focal liver lesions. For any situation that is not included in this flowchart, please refer to the text for further discussion.

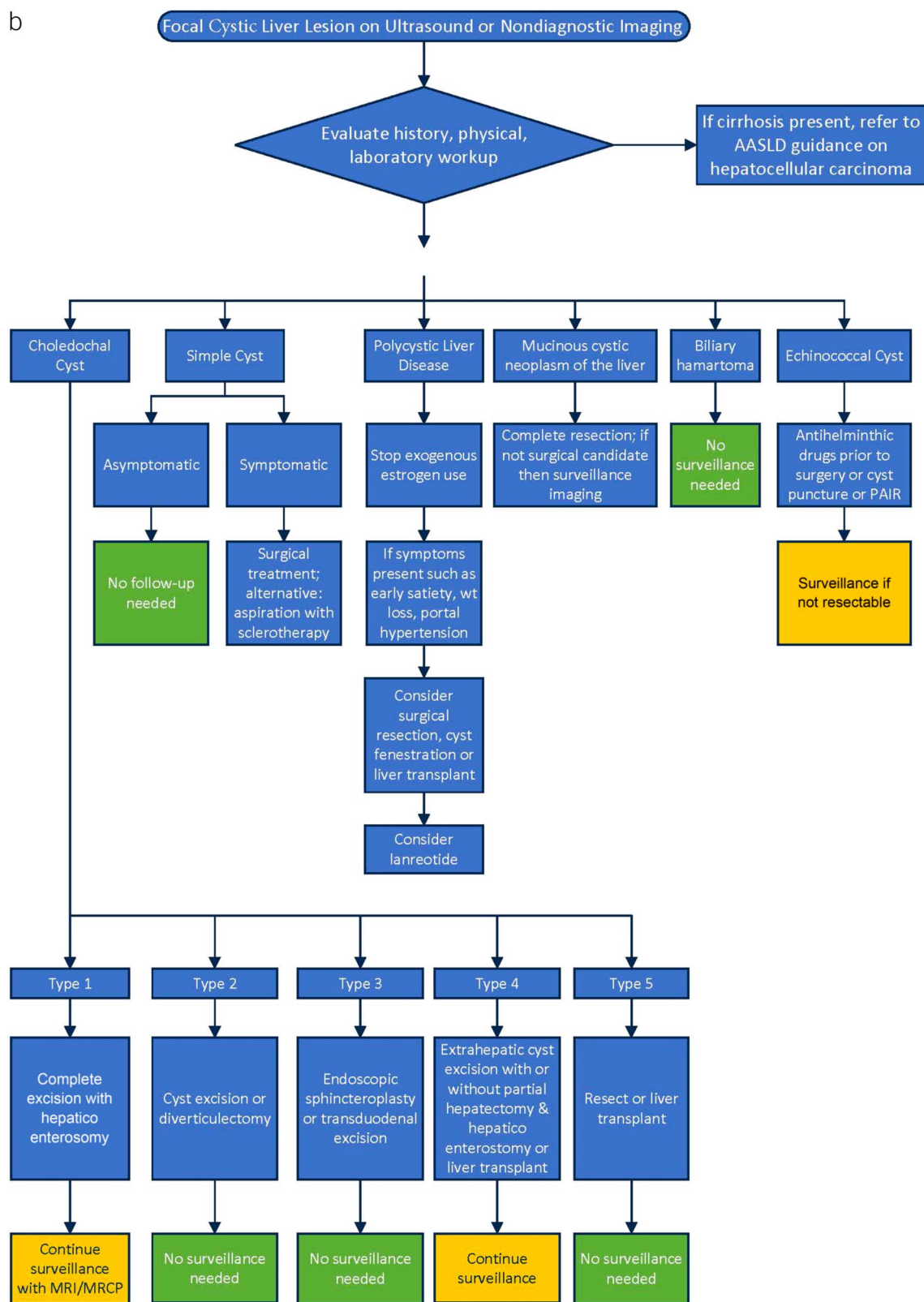


Figure 1. (Continued)

Table 4. Hepatic adenoma subtype clinical characteristics

	Inflammatory	HNF-1 α	β -Catenin activated	Sonic hedgehog	Unclassified
Epidemiology	~35%–45%	~35%–40%	Exon 3 mutation ~ 10%, male predominant (CTNN β 1 exon 7/8 mutation <10%)	<5%	5%–10%
Risk factors	Excess estrogen stimulus (moderate association), obesity, hepatic steatosis, excess alcohol, and glycogen storage disease	Excess estrogen stimulus (strong association; OCP use, excess estrogen, and anabolic steroids) and MODY3	Anabolic steroid use, androgen therapy, male sex with adenoma, and glycogen storage disease	Exogenous hormonal stimuli and obesity	
Biochemical/molecular analysis	Activated JAK/STAT pathway; elevated alkaline phosphatase, CRP, +/- fibrinogen	Inactivation of the HNF-1 α transcription factor	β -catenin mutation leads to increased glutamine synthase, Wnt/ β -catenin pathway simulation	Sonic hedgehog pathway activation; INH β E/GLI1 fusion	
Histology	Inflammatory infiltrates, sinusoidal dilatation, dystrophic vessels, IHC: CRP+ and amyloid A+, liver FABP+	Significant intralesional fat; IHC: loss of liver FABP staining (FABP–)	Increase in nuclear atypia, β -catenin positive nuclear and cytoplasmic staining; IHC for glutamine synthase is heterogeneous	Liver FABP+	Liver FABP+
Complications	Hemorrhage: Low Malignancy: Moderate	Hemorrhage: Low Malignancy: Low	Hemorrhage: Low Malignancy: High, up to 46% (exon 3)	Hemorrhage: High Malignancy: Low	

CRP, C-reactive protein; CTNN β 1, cadherin-associated protein β 1; FABP, fatty acid-binding protein; GLI1, glioma-associated oncogene homolog 1; HNF-1 α , hepatocyte nuclear factor-1 α ; IHC, immunohistochemistry; INH β E, inhibin β E chain; JAK/STAT, Janus kinase/signal transducer and activation transcription; MODY, maturity-onset diabetes of the young; OCP, oral contraceptive pills.

is associated with specific HCA subtypes, sex, size, and growth patterns. Men carry a higher risk of malignant transformation because they are more commonly diagnosed with the β -catenin mutated variant. As further described below, this molecular subtyping can risk-stratify patients (44,45) (Table 4). Recommendations for surveillance and management are mainly based on the presence of symptoms (i.e., abdominal pain), risk factor modification, clinical subtype, adenoma size, and number. Typically, adenomas that are associated with these complications are >5 cm in size, although complications can arise in smaller lesions (46,47). A patient presenting with adenoma rupture and associated hemorrhage may present with signs and symptoms of acute abdominal pain, anemia, and/or hemorrhagic shock. Emergent cross-sectional imaging is essential to assess for hemorrhagic rupture of HCA, followed by angiography for potential embolization of active extravasation.

Because of the benign nature of most hepatic adenomas, treatment is often unnecessary. Stabilization or regression of HCA lesions has been noted with elimination of hormonal stimuli and can be seen with aggressive management of metabolic risk factors (48–50).

Key concept

6. Hepatic adenomas are generally benign but can be associated with an increased risk of hemorrhage and/or malignant transformation.

Imaging and diagnosis. The initial diagnosis of hepatic adenoma is often made through abdominal imaging, including US or cross-sectional imaging. Patients with metabolic risk factors or glycogen storage disease may have evidence of hepatic steatosis, or metabolic dysfunction-associated steatotic liver disease. Although adenomas may form in a cirrhotic liver, it is less common to see benign liver lesions form *de novo* in the presence of cirrhosis, and any lesion in a patient with cirrhosis must be considered HCC until proven otherwise. The presence of a solid liver lesion on ultrasound should lead to further evaluation with contrast-enhanced multiphase CT, MRI, or CEUS. The imaging appearance of HCAs can vary depending on the molecular subtype, which can allow for imaging-based diagnosis of the subtype, particularly when using MRI for evaluation. On postcontrast CT or MRI with extracellular agent, HCA will demonstrate arterial phase hyperenhancement that becomes isoenhancing on the portal venous and equilibrium phases. On MRI, the lesion will generally demonstrate mild T2 hyperintensity and T1 hypointense-to-isointense signal. There may be intralesional lipid. On HBP MRI, HCAs are usually devoid of signal, in contradistinction to FNH (discussed below). However, in some atypical inflammatory and β -catenin mutated HCAs, the presence of the biliary transporter, OATP1B1/B3 (organic anion transporter polypeptide 1B1/B3), results in increased retention of gadoteric acid in the HBP and thus hyperintense signal (51,52). These lesions remain a diagnostic dilemma because they do not have imaging characteristics definitive for FNH or HCA; thus, these lesions may be biopsied, followed, and/or discussed at

Table 5. Hepatic adenoma subtypes: radiographic characteristics

	Inflammatory adenoma	HNF-1 α mutated adenoma	β -catenin mutated adenoma
T2 signal	Marked hyperintense Atoll sign ^a	Isointense/mildly hyperintense	Heterogeneously hyperintense
Presence of intralesional lipid	–/+ (17%)	– (78%)	+ / –
Arterial phase enhancement	++	+	++
PV/delayed phase enhancement	++	+ / –	—
HBP enhancement	11% are isointense to hyperintense (secondary to OATP1B3 receptor expression)	Hypointense	59% are isointense to hyperintense (secondary to OATP1B3 receptor expression)
HNF-1 α , hepatocyte nuclear factor-1 α ; PV, portal vein; HBP, hepatobiliary phase; OATP1B3, organic anion transporting polypeptide 1B3.			
^a Atoll sign: T2-hyperintense rim with central isointensity.			

multidisciplinary liver tumor board (53). If there has been previous hemorrhage in an adenoma, the appearance can be hyperdense on noncontrast CT or hyperintense on T1 precontrast MRI. CEUS can be used to aid in the diagnosis of HCA, although it is not specific enough to subtype the adenoma.

Changes in imaging appearance over time can be suggestive of malignant transformation and include rapid increase in size, subsequent development of intralesional lipid, or new washout on portal venous or delayed phase of imaging. In these cases, biopsy should be considered. One common diagnostic dilemma, however, is that pathology of adenomas often returns as well-differentiated HCC. Pathologic features that favor HCC over HCA include more than patchy cytological atypia, thickened hepatocyte trabeculae, pseudoglandular structures, cholestasis, small cell change, and loss of reticulin staining (54). Furthermore, the 3-marker panel of glypican-3, heat shock protein 70, and GS can help distinguish HCC from HCA (55). In cases where pathology is indeterminate and a confident diagnosis of HCA vs HCC cannot be made, new pathological terms “atypical hepatocellular neoplasm” and “hepatocellular neoplasm of uncertain malignant potential” have been used (54,56). When biopsy is inconclusive, multidisciplinary discussion is warranted to determine management such as resection or close imaging surveillance.

There are no specific serum biomarkers that are diagnostic of HCA. If there is concern for possible malignant transformation, it is recommended to order an α -fetoprotein level (AFP), although this has low sensitivity for detection of HCC alone in this setting.

Key concepts

- When a solid hepatic mass is incidentally discovered in a patient with no known risk factors, appropriate multiphasic contrast-enhanced imaging (CT or MRI) should be the first step in management and is often a sufficient test for diagnosis and subtyping of hepatic adenomas.
- Biopsy should be performed when a hepatic adenoma has an uncharacteristic appearance on imaging or change in imaging features that are concerning for malignant transformation.

Recommendation

- We suggest using multiphasic liver imaging (preferable MRI) over standard cross-sectional imaging modalities to accurately distinguish hepatic adenomas from other benign or malignant liver lesions (conditional recommendation, very low quality of evidence).

Clinical and molecular subtypes. An enhanced understanding of hepatic adenomas has led to clinical and molecular subtyping into 3 main categories (inflammatory, hepatocyte nuclear factor-1 α , and β -catenin activated) and 2 less well-understood subtypes, which include the sonic hedgehog and the unclassified cohorts (Table 4). Improved imaging techniques and histologic studies allow for subtyping of up to 90% of HCAs. Subtyping has had increased relevance for understanding risks of complications of hemorrhage, malignant transformation, and risk factor modification. The currently accepted clinical and molecular subtypes are presented below by order of prevalence, of which there are characteristic imaging features, which can allow for improved imaging-based diagnosis of subtype, as described in Table 5.

Inflammatory adenomas. Inflammatory-type adenomas (I-HCAs) account for up to 44% of cases and are represented molecularly by the activation of the Janus kinase signal transducer and the activation transcription pathway (57). Laboratory changes can include elevations in serum alkaline phosphatase in cases of larger or multiple adenomas or elevated systemic inflammatory markers such as C-reactive protein and fibrinogen levels, although presently, there is insufficient evidence to support routinely checking CRP or fibrinogen in these cases (58). Risk factors for development of I-HCAs include those that also result in increased risk of hepatic steatosis, such as obesity, metabolic syndrome, heavy alcohol consumption, and glycogen storage disease. Because of their often larger size, subcapsular location, and high vascularity, these can be prone to hemorrhage. The risk of malignant transformation is low unless there is concomitant presence of the β -catenin mutation (59). Figure 2 shows an example of an inflammatory adenoma on imaging.

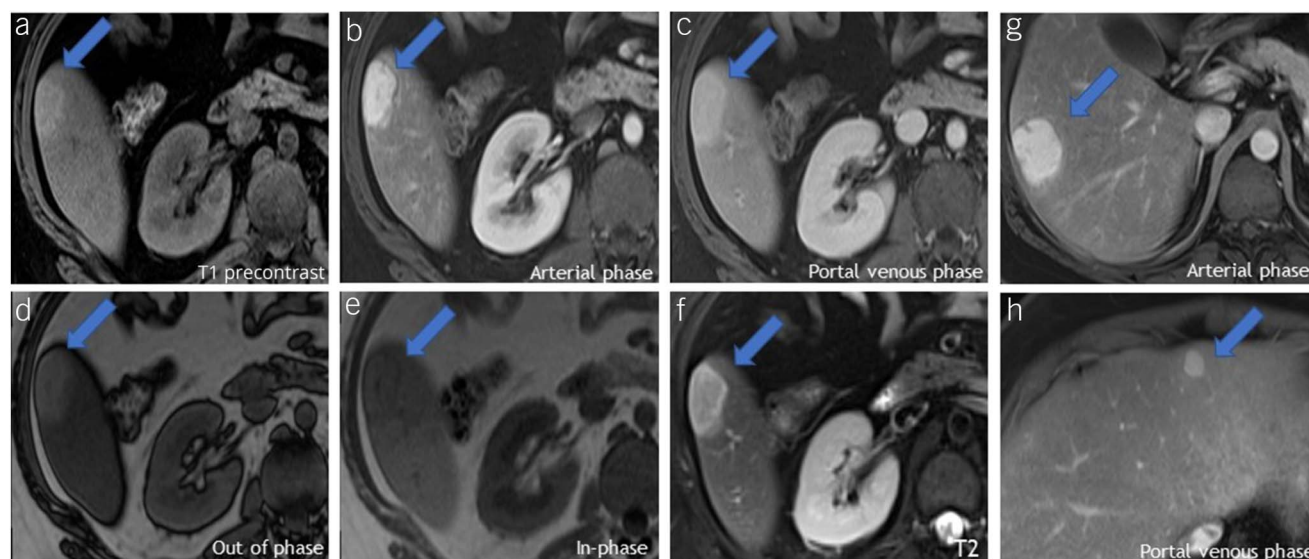


Figure 2. Inflammatory adenoma. A 35-year-old woman with severe hepatic steatosis presented with incidentally discovered liver lesions seen during imaging for right upper-quadrant pain. MRI with an extracellular MRI contrast agent (gadobenate dimeglumine) shows a segment 5 mass, which demonstrates intrinsic T1-hyperintense signal (a), homogeneous arterial phase hyperenhancement (b), which persists on portal venous phase of imaging (c), with T2-hyperintense signal (d), without intracellular lipid (out-of-phase and in-phase images) (e, f). Note the atoll sign on T2-weighted imaging (d), with central isointensity to the parenchyma and a rim of hyperintense signal. Imaging shows additional lesions with similar characteristics (g, h). This lesion is characteristic for inflammatory variant adenomas. MRI, magnetic resonance imaging.

Hepatocyte nuclear factor-1 α . Up to 40% of HCAs are classified by inactivation of hepatocyte nuclear factor-1 α , known as H-HCA (58). There is a strong association noted with OCP use or excess estrogen exposure and a lesser association with maturity-onset diabetes of the young 3 diabetes (60). Because of the impairment of fatty acid mobilization because of the mutated HNF-1 α , there is a varying but often prominent degree of steatosis observed in H-HCAs. Compared with the other subtypes, the risk of hemorrhage and malignant transformation is among the lowest for H-HCAs (58). Figure 3 shows a representative case of an HNF-1 α adenoma in a young woman.

β -catenin activated HCA. The β -catenin mutated HCA (β -HCA) in exon 3 accounts for up to 10% of HCAs and is most prevalent in men and among individuals with risk factors such as glycogen storage disease or anabolic steroid use. When present, these tend to develop at a young age and are often large at presentation. This subtype is associated with the highest risk of transformation to HCC. As such, β -catenin mutated HCAs are at a higher risk of malignant transformation compared with other clinical subtypes and should be resected regardless of size. Recent studies have noted that the cadherin-associated protein β 1 (CTNNB1, the gene that encodes for the β -catenin protein) exon 3 mutation is

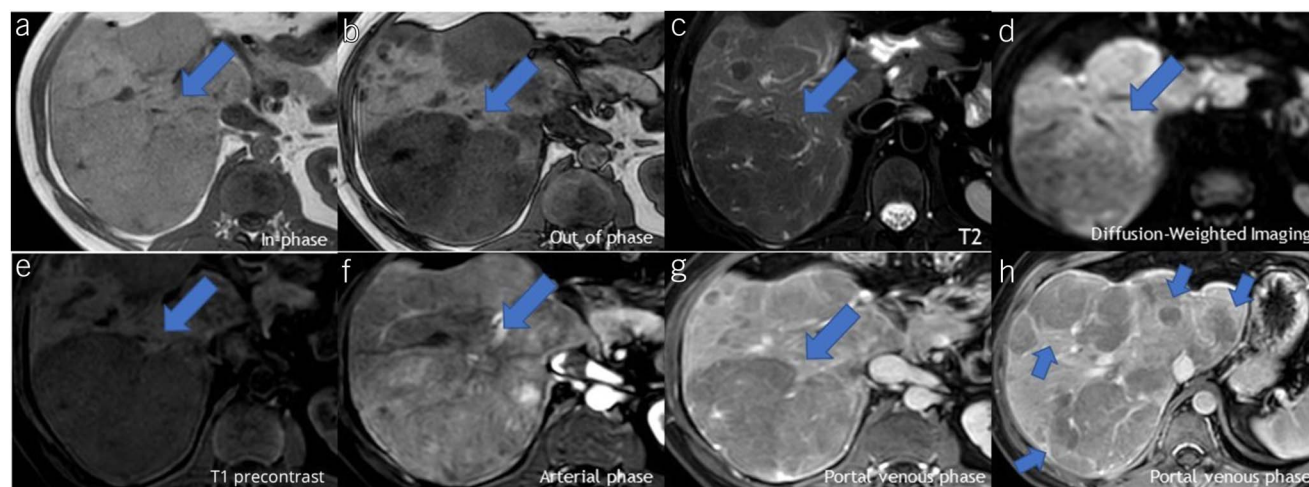


Figure 3. HNF-1 α adenoma. A 34-year-old woman with incidentally discovered liver lesion during imaging for abdominal pain. MRI with an extracellular MRI contrast agent (gadobenate dimeglumine) shows a large mass demonstrating loss of signal as seen on out-of-phase images (a, b), which is T2-hypointense (c), no restricted diffusion (d), T1 precontrast hypointense (e) with arterial phase enhancement (f) and washout (g). This was compatible with a biopsy-proven HNF-1 α subtype hepatic adenoma. Of note, this patient has multiple adenomas (h), compatible with hepatic adenomatosis. MRI, magnetic resonance imaging; HNF-1 α , hepatocyte nuclear factor-1 α .

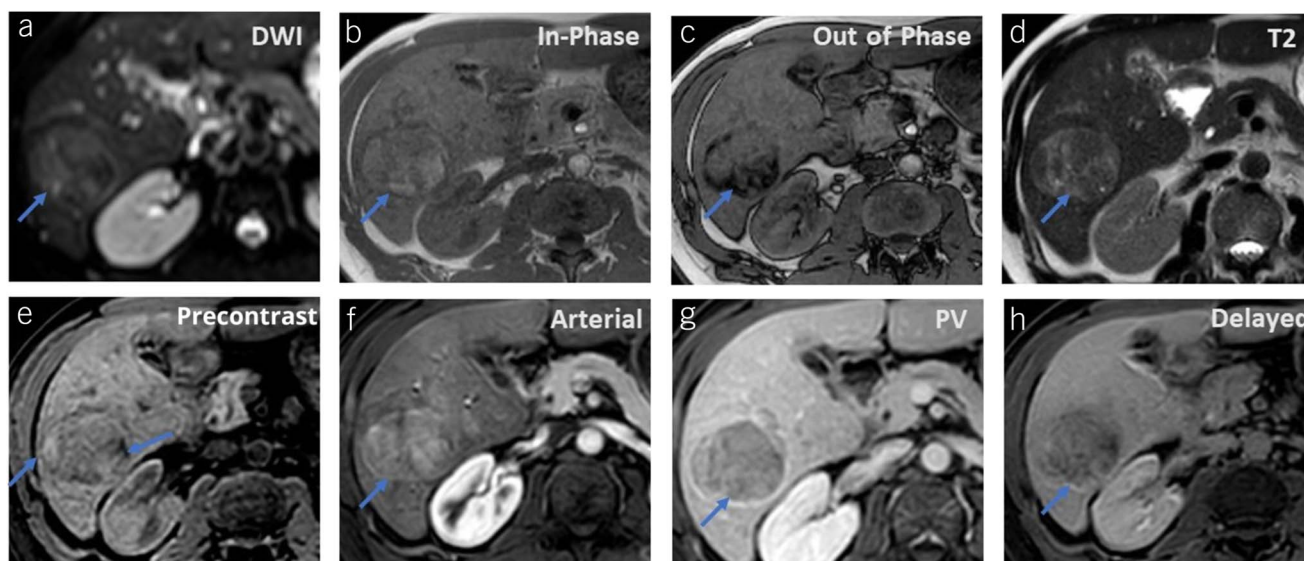


Figure 4. β -catenin mutated adenoma. A 48-year-old man with no underlying medical history presented with right upper-quadrant pain. CT showed a solitary hemorrhagic mass (not shown). MRI was obtained for further characterization and demonstrates a large mass with areas of restricted diffusion (a), intracellular lipid (loss of signal on out-of-phase images) (b, c), and mild heterogeneous T2-hyperintense signal (d). There are areas of intrinsic T1 precontrast hyperintense signal (e), consistent with intralesional hemorrhage. On multiphase postcontrast images, the mass demonstrates arterial phase hyperenhancement (f) and washout and capsule on portal venous and delayed phase of imaging (g, h). Imaging characteristics are suggestive of β -catenin mutated adenoma vs HCC; however, in the absence of cirrhosis, adenoma is more likely. This patient was diagnosed with a β -catenin mutated adenoma on resection pathology. CT, computed tomography; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma.

associated with approximately 10% or greater risk of malignant potential, compared with no significant increased risk of malignancy when there is a mutation in CTNN β 1 exon 7 and 8, which is present in <10% of β -catenin mutated HCAs (44,58). Next-generation sequencing has also been proposed to enhance the histopathological diagnosis and subtyping of HCAs when enough tissue is available and subtyping may influence management (61).

MRI cannot reliably distinguish this variant from the other subtypes and is not specific enough to differentiate β -catenin mutated activated HCA from well-differentiated HCC, given similar imaging appearance of arterial phase hyperenhancement, washout, and capsule (Figure 4). Even on pathology, distinguishing β -catenin mutated activated HCA from HCC is challenging. Although imaging of β -catenin HCA and well-differentiated HCC overlaps, the lack of risk factors for chronic hepatocellular disease renders the former the more likely diagnosis.

Key concepts

9. MRI features are beneficial for subtyping I-HCAs and HNF-1 α mutated adenomas but are not specific for subtyping β -catenin mutated, sonic hedgehog, and unclassified adenomas.
10. Risk factors for development of I-HCAs include obesity and/or metabolic syndrome risk factors, heavy alcohol consumption, and/or glycogen storage disease.
11. β -catenin mutated HCAs are at a higher risk of malignant transformation compared with other clinical subtypes and should be resected regardless of size.
12. Hepatic adenomas that develop in men are commonly β -catenin mutated and associated with a higher risk of malignant transformation.

Management. The management of patients with HCAs can be conservative for patients with small, asymptomatic lesions, with an overall low-risk profile. Patients with a more complicated HCA presentation or higher-risk profile can benefit from discussion with a multidisciplinary team. It has become increasingly recognized that the factors influencing risk of complications include size of the lesion, sex, and the clinical and molecular subtype. Treatment is generally more nuanced and aggressive than other benign liver lesions because of the risk of possible hemorrhage or malignant transformation. The association with endogenous and exogenous hormonal stimuli also results in potential for growth at a young age, during pregnancy, and/or with weight gain. Most patients requiring intervention should undergo surgical resection, although there are increasing reports of less invasive treatment options through interventional radiology. A meta-analysis from 2019 reviewed over 219 articles on treatment options for adenomas, and very few patients were treated with embolization or ablation. Reports of elective locoregional therapy for the treatment of HA are limited to case reports and small institutional series (62). Until further research is available, locoregional therapy with ablation or embolization cannot be recommended routinely. Ultimately given some of the uncertainty of long-term outcomes, shared decision-making will allow for patients to be engaged in their management options.

Females with adenomas <5 cm. Females with asymptomatic HCAs diagnosed at <5 cm in size can be monitored and initially managed conservatively unless imaging prompts concerns for β -catenin mutated subtype. These are far less commonly associated with complications of hemorrhage and/or malignancy (63). The use of exogenous hormonal therapy should be discontinued (30,31). In the case of an elevated body mass index, weight loss should be encouraged, although there is no specific

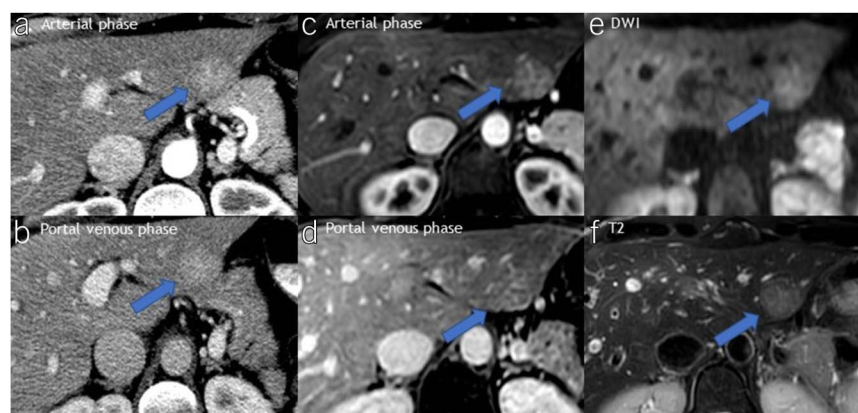


Figure 5. Malignant degeneration of inflammatory variant hepatic adenoma. A 45-year-old woman with history of multiple adenomas presented for 1-year follow-up imaging. CT demonstrates a 2.5-cm mass with arterial phase hyperenhancement (a) that persists on delayed phase of imaging (b), likely inflammatory variant adenoma. One year later, the mass has increased in size, now measuring 2.9 cm with change in imaging appearance. There is arterial hyperenhancement (c) and new capsule and isoenhancement on portal venous phase of imaging (d), with new restricted diffusion (e) and mild T2 hyperintense signal (f). The patient underwent biopsy, and pathology revealed well-differentiated hepatocellular carcinoma. CT, computed tomography.

established weight loss target for adenoma regression (33,48). Repeat contrast-enhanced MRI should be performed after 6 months to assess for stability or regression of the adenoma, regardless of subtype. In cases that are indeterminate by imaging for HCA, or those that warrant further evaluation for malignancy, a biopsy should be performed. Cases where biopsy is positive for β -catenin mutation in exon 3 or that have transformed to HCC should proceed with resection. If the patient is not a candidate for resection, then locoregional therapy should be considered. If biopsy confirms H-HCA, I-HCA, or a low-risk HCA profile, continued surveillance is warranted. Routine biopsy for purposes of subtyping is not recommended for lesions <5 cm in female patients until there are prospective data supporting this approach.

During surveillance, if there is growth of the lesion, suggested as $\geq 20\%$ as extrapolated from RECIST criteria for malignant liver tumors, resection or definitive treatment should be considered (64–66). This is also reasonable to consider for patients who prefer treatment over surveillance alone. Although regression of HCAs is possible, it is far more common for lipid-rich lesions to show stability. Ongoing surveillance every 6 months with contrast-enhanced imaging is recommended for 2 years, and then, it is reasonable to continue surveillance imaging annually. The modality of imaging can be adjusted over time to minimize radiation exposure and cost, noting that many patients when diagnosed are young and will require long-term continued follow-up (67). After 2 years, ultrasound could be considered for follow-up, and if there is any change in the adenomas, contrast-enhanced CT or MRI would be indicated. Presently, there remain insufficient data to determine whether and when to discontinue imaging surveillance, although it has been recently suggested that these patients may no longer need monitoring after menopause (68).

Females with adenomas ≥ 5 cm. For females with HCAs that are 5 cm or larger, a period of 6 months of observation is reasonable with cessation of exogenous hormone use (OCPs, hormonal intrauterine devices, and anabolic steroids) and, if applicable, a recommendation for weight loss (69). In non- β -catenin mutated HCAs, it is reasonable to observe at 6-month intervals noting the greater period for regression of lesions in response to lifestyle

changes (70). Any imaging features concerning for malignancy should lead to immediate treatment without a period of observation. In cases where the adenoma remains ≥ 5 cm after observation, definitive treatment should be pursued with surgical resection to minimize the risk of hemorrhage or malignancy. If the patient is not a resection candidate, other treatment options should be considered such as embolization. If during the observation period, the adenoma has regressed to <5 cm, continued observation with contrast-enhanced MRI is recommended. Similar to female patients with adenomas <5 cm, these patients should continue to have long-term follow-up surveillance imaging initially every 6 months, with the interval adjusted over time based on risk factors for age, premenopausal state, and stability (71,72). Although malignancy is unlikely with HCA regression to <5 cm, it has been infrequently reported to occur at this size (73). A biopsy to stratify risk based on subtype has not been shown to be beneficial in this cohort with HCA regression because the prevalence of β -catenin mutations is overall low and most reported cases proceed to definitive management. An ongoing prospective cohort study aims to study the patient-reported outcomes for interventional treatments of large adenomas compared with untreated lesions (74). Residual HCA after resection has shown varying patterns including regression, stabilization, and progression, warranting ongoing imaging surveillance and consideration to retreatment if progression is seen (75).

Males with adenomas. For males, regardless of size or subtype, adenomas should be surgically resected or treated definitively because of the higher incidence of malignancy (45). They should also be encouraged to eliminate anabolic steroid or exogenous steroid use and recommended weight loss. The recommendation for resection is present regardless of the size of the lesion, noting the high risk of β -catenin subtype, but this recommendation is irrespective of subtype. A biopsy is not advised before surgical resection but should be performed if the patient is not a surgical candidate and will require nonsurgical therapies such as ablation (based on size of lesion) or embolization. Laparoscopic liver resection is strongly preferred over nonsurgical modalities (76,77). Ablation can have limited success in larger lesions, and

embolization is associated with a risk of incomplete eradication with possible need for retreatment (78–80). These could be considered as a bridge to future more definitive therapy. After resection, embolization, or ablation, it is recommended to continue surveillance imaging every 6–12 months, although the frequency and duration of monitoring are not well established.

Pregnancy. In the setting of pregnancy, HCAs may exhibit growth and progression. The greatest risk of complications (such as hemorrhage) is in the third trimester because of the increased hepatic vascularity and hyperdynamic circulation. This requires close monitoring, although there is no single validated approach. Repeat imaging with ultrasound every 6–12 weeks is a recommended strategy. Adenomas that remain <5 cm in size, non-exophytic, and without growth during pregnancy can be safely monitored and do not impact the modality of delivery (81). A recent prospective study of 51 pregnant women with <5-cm HCA noted a quarter of patients with HCA growth, a quarter with HCA regression, and no instances of hemorrhage (81). Adenomas that exhibit growth during pregnancy particularly to >6.5 cm in size or have high-risk features for hemorrhagic rupture including exophytic lesions should be treated with resection if early in the pregnancy or embolization before 26 weeks' gestation (82). During the third trimester, emergent surgery is recommended for hemorrhagic rupture from HCA. This should be performed in concert with obstetrics and balancing harms and benefits. Larger lesions (>6.5 cm) have demonstrated risk of hemorrhage both during pregnancy, delivery, and immediately postpartum. Preconception counseling should include a discussion of risk and optimal management strategy for patients with previously diagnosed HCAs. Pre-emptive treatment during pregnancy for HCAs that do not exhibit high-risk features is not recommended because of added risks in pregnancy (82). Before planned conception, HCAs smaller than 5 cm should be considered for resection or embolization if they are at particularly high risk of growth or hemorrhage (i.e., has exhibited growth previously with hormonal stimulation or is exophytic), and HCAs ≥ 5 cm should be treated to minimize need for treatment during pregnancy. Larger registry data are needed to understand the behavior of HCA during pregnancy.

Ruptured adenoma. Because of the rich vascularity of this lesion, spontaneous rupture of HCAs is a known complication that requires emergent attention in the case of hemodynamic instability. Intralesional hemorrhage is of less significance compared with tumor rupture because of the risk of hemoperitoneum. Established risk factors include HCAs ≥ 5 cm, growth of the lesion, and/or exophytic location of the lesion. Management includes initial supportive care with hemodynamic stabilization and transfusion (83). If instability remains, emergent transarterial embolization (TAE) should be pursued to achieve hemodynamic stability until surgical resection can be performed (84–86). After hemorrhage with spontaneous cessation of bleeding, the treatment course for patients is not well defined. Many proceed to definitive surgery, although others have been noted to have regression of their adenoma. If the patient is a surgical candidate, residual HCA should be laparoscopically resected, minimizing risk of future recurrent hemorrhage. Post-treatment monitoring is recommended as the risk of recurrent hemorrhage or growth of residual HCA remains. There are insufficient data to show a

correlation between the HCA subtype and future risk of hemorrhage. A history of HCA rupture has not been consistently associated with an increased risk of malignant transformation, although case reports have suggested coexistence of HCA rupture and malignant transformation (66,87).

Malignant transformation. The risk of malignant transformation of HCA is reported to be <5%, although challenges remain in determining an accurate incidence. The highest risk cohort includes males with HCA (10 $\times$ greater than females), β -catenin mutated HCA in exon 3, and lesions ≥ 5 cm (45). Patients with glycogen storage disease are also believed to be at a higher risk of malignant transformation. Diagnosis of malignant transformation can be challenging, given overlap in imaging features; however, a change in imaging characteristics and rapid growth are concerning features (Figure 5). In cases where concern exists, management is variable, as described in the above sections. However, in general, multidisciplinary discussion and biopsy may be warranted, as well as surgical resection in males with HCA. Next-generation sequencing can be helpful to identify malignant transformation, in which AFP levels are not reliable (61). Patients who are not candidates for surgical resection can be treated with other modalities used for HCC treatment including ablation, embolization, radiation therapy, and/or liver transplantation.

Hepatic adenomatosis. Hepatic adenomatosis is a variant of HCA characterized by 10 or more hepatic adenomas (41,85). This often develops in a background of hepatic steatosis and metabolic risk factors, often with the molecular subtype of HNF-1 α HCAs (42). It is not uncommon to see coexisting hepatic hemangiomas or FNH in this setting. Adenomatosis can also develop in the setting of glycogen storage disease, which if previously undiagnosed should have further evaluation with genetic testing. The variant of adenomatosis is an important distinct clinical entity because these patients are at substantially higher risk of complications and thus require more aggressive treatment considerations. The risk of bleeding is substantially higher in these patients (up to 46% in some case series), and development of malignancy has been reported in up to 7% of cases (88). Unilobar disease can be managed with surgical resection or resection of a dominant larger adenoma. In the setting of bilobar involvement, management is best focused on treating the largest or dominant lesion or any that raise suspicion for complications such as hemorrhage or malignant transformation. Ongoing monitoring by imaging is recommended, at least annually. As explained below, liver transplantation is reserved for select patients with multiple HCAs (89). Lifestyle modification including removal of exogenous hormone therapy, and metabolic risk factor management, has been shown to reduce the overall burden and size of multiple HCAs (33).

Liver transplantation. Liver transplantation has a select role for patients with HCAs. Specifically, this should be considered for patients with evidence of HCA hemorrhage or malignant transformation who are not candidates for surgical resection or other curative-intent therapy. The Organ Procurement and Transplant Network policy establishes that HCA should be a rare indication for liver transplantation and should be considered an option for patients with HCA in the background of glycogen storage disease, those with unresectable β -catenin positive adenoma, or in the

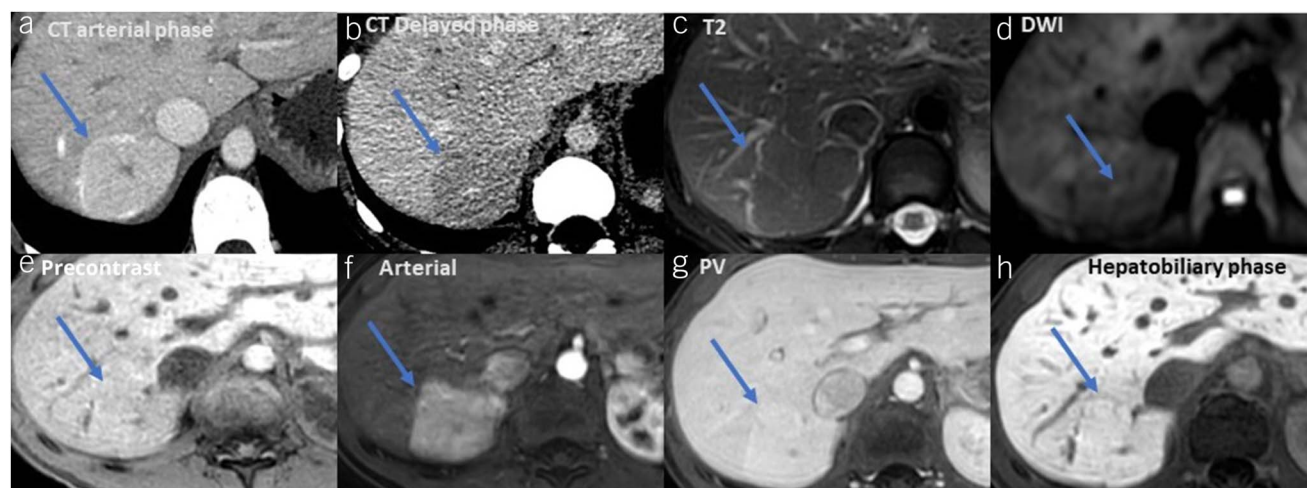


Figure 6. Focal nodular hyperplasia. A 42-year-old woman with no underlying medical history had incidentally discovered liver mass. CT shows a solitary mass demonstrating arterial phase hyperenhancement, capsule, and central hypoenhancing scar on arterial phase (a), with delayed enhancement of the central scar (b). MRI was obtained for definitive characterization and demonstrates a T2-isointense mass (c) with focal restricted diffusion of the central scar (d), isointense on T1 precontrast (e), and homogeneous APHE (f), which is isoenhancing on portal venous phase of imaging (g). The mass is isointense on 20-minute hepatobiliary phase of imaging (h). These imaging findings are characteristic for focal nodular hyperplasia. APHE, arterial phase hyperenhancement; CT, computed tomography; MRI, magnetic resonance imaging.

case of an unresectable progressive HCA, despite medical management and/or with complications of hemorrhagic or malignant transformation (90–93). Patients meeting this highly select criteria may be offered a priority score for transplantation. The overall outcome for these patients is similar to other indications for liver transplantation; however, the strict selection criteria are essential, given the overall indolent disease course and discordance between imaging concerns and explant findings of malignancy (94).

Key concepts

13. Women with hepatic adenomas ≥ 5 cm should modify risk factors, undergo observation for 6–12 months, and undergo resection if the lesion does not regress to < 5 cm.
14. Men with hepatic adenomas should consider surgical resection regardless of lesion size because of elevated risk of malignant transformation.
15. Hepatic adenomas should be monitored regularly during pregnancy and should be treated if there is growth to > 6.5 cm or with high-risk features for hemorrhagic rupture.
16. Hepatic adenomas of any size that have imaging features concerning for malignant transformation should be treated as an HCC, with consideration to surgical resection, locoregional therapies, and/or liver transplantation.
17. Hepatic adenomatosis is a variant of HCA characterized by 10 or more hepatic adenomas, more commonly associated with background steatosis or glycogen storage disease.
18. Consideration for liver transplantation should be given to patients who meet the Organ Procurement and Transplant Network policy for transplantation, especially those with glycogen storage disease, unresectable β -catenin positive adenoma, or unresectable with complications of hemorrhagic or malignant transformation of hepatic adenomas.

Recommendations

5. In women with hepatic adenomas < 5 cm, we suggest discontinuation of exogenous hormones and advise weight loss, if applicable, for overweight or obese individuals (conditional recommendation, very low level of evidence).
6. In women with hepatic adenomas < 5 cm, we suggest surveillance with contrast-enhanced imaging modalities every 6 months for 2 years, then annually thereafter (conditional recommendation, low level of evidence).
7. In patients with hepatic adenomas requiring treatment who are unable to undergo surgical resection, we suggest embolization or ablation as alternative treatment approaches (conditional recommendation, low level of evidence).
8. In patients with ruptured hepatic adenomas, we suggest hemodynamic stabilization followed by embolization and/or surgical resection (conditional recommendation, very low level of evidence).

Focal nodular hyperplasia

FNH is the second most common solid liver lesion, with 0.3%–3% of people having FNH on autopsy (95). FNH is favored to arise as a local reaction to vascular abnormalities, specifically aberrant hemodynamics within the liver, usually secondary to an aberrant dystrophic artery or a vascular injury, resulting in a disturbance of local blood flow, which can result in hyperperfusion, oxidative stress from hypoxia, and hepatic stellate cell response, all of which result in a hyperplastic microenvironment and FNH development (96). This is further corroborated by cases of FNH-like lesions such as nodular regenerative hyperplasia that are seen in patients with abnormal vascular flow to the liver in cases of cardiac etiologies of cirrhosis (97).

Most FNHs are discovered incidentally, and up to 20% of patients with FNH will also have a hepatic hemangioma present (95).

There is a known female preponderance, and compared with men, women tend to develop larger FNH lesions that present earlier (95). Because of these epidemiologic characteristics, it has been believed that there may be a causative role for sex hormones in FNH development; however, over time, this has been disproven because of lack of correlation between OCP use and FNH growth or prevalence and lack of evidence of change in FNH during pregnancy (98,99). Importantly, unlike adenomas, FNH do not need to be treated differently in men as compared to women and do not require monitoring during pregnancy.

Imaging most often allows the definitive diagnosis of FNH vs adenoma, which is important because management differs between the 2 lesions. An MRI with a hepatobiliary contrast agent, such as gadoxetic acid, is the preferred imaging modality of choice because it can correctly classify FNH from adenoma with an accuracy of over 90% (100–102). MRI has a specificity of almost 100% for diagnosis of an FNH (103). If the patient has a contraindication to MRI, then multiphase CT can be performed. CEUS can be used for diagnosis of FNH, with increased diagnostic accuracy in lesions measuring <3 cm in size (104–107).

On postcontrast CT or MRI, FNH usually appears as a well-circumscribed homogeneously arterial hyperenhancing mass, which becomes isoenhancing on portal venous and delayed phase of imaging (Figure 6) (108). Classically, there is a central scar, which is usually hypodense/hypointense on noncontrast imaging CT/MRI, respectively, demonstrates delayed enhancement on portal venous and delayed phase of imaging, and is isointense to hyperintense on T2-weighted imaging.

Because FNH contains hepatocyte-specific membrane transport proteins, they almost always show hyperintense signal on the 20-minute HBP of imaging, rendering the diagnosis of FNH with nearly 100% confidence (108,109) (Figure 6). In fact, studies show that only 2% of FNH are hypointense on 20-minute HBP of imaging (110).

Of note, with increasing use of biopsy for hepatic adenomas and newer stains allowing improved subtype classification, there is emerging evidence that 11% of inflammatory and 59% of β -catenin mutated adenomas demonstrate OETP1B3 receptor expression and therefore can demonstrate hyperintense signal on HBP of imaging. Therefore, any lesion that has atypical imaging appearance for FNH on dynamic imaging that demonstrates HBP hyperintense signal should be closely followed (111).

In the rare case that a diagnosis of FNH cannot be made by imaging, then a biopsy may be considered after discussion at multidisciplinary tumor board. Biopsy can sometimes be difficult to interpret, with some case series reporting diagnosis as low as 58%, although the interpretation can be aided with the addition of immunohistochemistry (112,113).

Once the diagnosis of FNH is confidently made, a conservative approach with no further follow-up is recommended. Given the little to no change over time in most cases, there is no benefit to continued imaging, and those lesions that do grow do not cause life-threatening complications (114). Current evidence suggests no indication that patients should avoid or discontinue OCPs or hormonal therapy, and that FNH does not need to be followed during pregnancy (115,116).

In the rare case of symptoms such as pain, surgical resection may be considered, but most FNH lesions are incidental to symptoms rather than the cause of symptoms and patients should be educated that their symptoms may not improve after surgery (117). Even in the setting of growth of an FNH, there is an

extremely slim chance of malignancy, and therefore, resection is not recommended (117). Because FNH is usually supplied by a single artery, TAE seems like a logical minimally invasive method for treatment in cases that require treatment. There remains much debate, however, as to which embolic agent is best used for TAE of FNH. A few small case series suggest that TAE with bleomycin for symptomatic FNH can result in decrease in tumor size by 50%, but bland embolization is often used (80,118,119).

Key concepts

19. Advanced imaging techniques (e.g., contrast-enhanced multiphase MRI with hepatobiliary-specific contrast) can accurately diagnose FNH in most cases, and biopsy is not routinely needed.
20. In a patient with an FNH confirmed on imaging, no further follow-up is required.
21. If the diagnosis of FNH is confirmed, then even in the case of growth, resection is not required. If resection is being considered because of symptoms, then patients must be counseled that their symptoms may not improve after surgery as FNH rarely causes symptoms.
22. If FNH lesions are symptomatic and surgery is not an option because of comorbidities or anatomic considerations, then TAE with or without bleomycin may be considered to decrease size.
23. Men with FNH do not need to have any different evaluation, monitoring, or treatment compared with women.

Recommendations

9. We suggest evaluating patients with FLLs that are suspicious for FNH using multiphase MRI with hepatobiliary-specific contrast agents to distinguish FNH from HCA (conditional recommendation, low quality of evidence).
10. We do not suggest routinely discontinuing OCPs in patients diagnosed with FNH (conditional recommendation, very low quality of evidence).

Hemangioma

Hemangiomas are the most common benign noncystic liver lesions, occurring in up to 20% of the population, with a reported preponderance in women at a 4:1 ratio (120). They are benign mesenchymal vascular lesions consisting of clusters of blood-filled cavities lined by endothelial cells, ranging in size from a few millimeters to greater than 20 cm (121). Hemangiomas are believed to arise from a congenital abnormality in vasculogenesis, growing slowly from birth. Increase in size of hemangiomas can occur and is favored to be due to progressive ectasia of the vasculature and not related to hypertrophy of the lesion (122). Hemangiomas are usually asymptomatic lesions, which are incidentally detected on imaging studies, although larger lesions can result in pain, poor appetite, or abdominal fullness (122). Rarely, hemangiomas can result in a consumptive coagulopathy known as Kasabach–Merritt syndrome, which can present as thrombocytopenia, systemic bleeding, and disseminated intravascular coagulation, usually seen in giant cavernous hemangiomas (123,124).

There has been no clear causative link between hemangiomas and female sex hormones, and thus, it is not recommended to avoid OCP or pregnancy in patients with hemangiomas

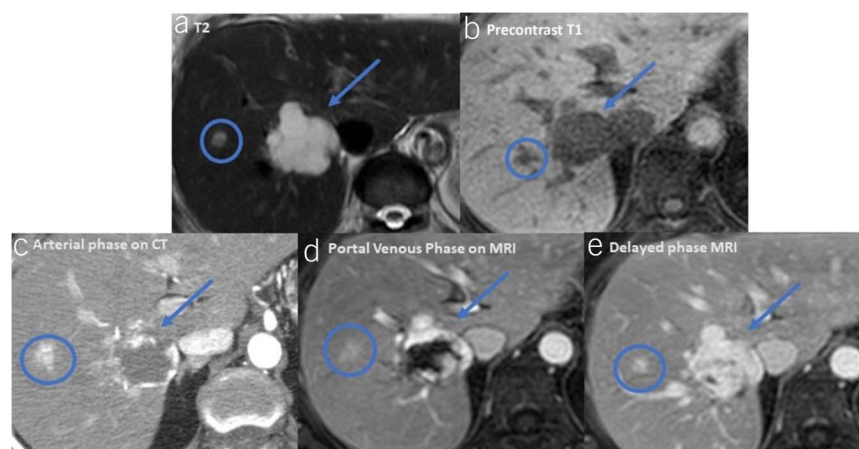


Figure 7. Hemangioma. A 56-year-old woman with no underlying medical history had incidentally discovered liver mass. MRI showed 2 lesions. The first in the circle demonstrates T2-hyperintense signal (a), T1 precontrast hypointense signal (b), and homogeneous arterial phase hyperenhancement (c), which persists on portal venous (d) and delayed phase of imaging (e). This is compatible with a flash-filling hemangioma. The second (marked with the arrow) demonstrates the more classic appearance of lightbulb bright appearance on T2 (a), hypointense on T1 precontrast (b), and peripheral nodular enhancement with progressive centripetal fill on dynamic postcontrast images (c–e). This is a classic hemangioma. MRI, magnetic resonance imaging.

(125,126). There are 3 classic types of hemangiomas: *cavernous*, *capillary*, and *sclerosed*.

Ultrasound is often the first imaging modality to detect an incidental hemangioma and can sometimes be diagnostic enough not to require further evaluation (127). However, in most instances, further evaluation with cross-sectional imaging is necessary for diagnosis confirmation, especially when a suspected hemangioma is seen in a patient with hepatitis B, cirrhosis, or underlying history of malignancy. MRI has the best sensitivity and specificity (92%–100% and 85.7%–99.4%, respectively), followed by CT (sensitivity 98.3% and specificity 55.0%) and CEUS (accuracy 97.3%) (128,129).

The typical sonographic appearance of a cavernous hemangioma is a homogeneous hyperechoic observation with posterior acoustic enhancement, usually seen in hemangiomas less than 3 cm in size. Hemangiomas tend to be “avascular” on color Doppler imaging, which is related to slow flow within the large vascular spaces within the tumor (127,130,131).

If ultrasound imaging is atypical or nondiagnostic, or in a lesion that is greater than 2 cm, further evaluation CEUS, CT, or MRI should be obtained. A recent study showed high diagnostic utility of

CEUS with an accuracy of 92.7%, demonstrating classic imaging features of peripheral nodular enhancement (132). Another study evaluating 103 patients with hemangiomas showed a diagnostic rate of 90.2% for hemangiomas when using CEUS (133).

Classic CT/MRI features of a cavernous hemangioma include hypodensity or hypointensity on noncontrast CT or T1 precontrast MRI, respectively, and peripheral nodular enhancement on early postcontrast imaging with progressive centripetal enhancement on portal venous and delayed phase of imaging, which follows arterial blood pool (134) (Figure 7). Hemangiomas are light bulb bright on T2-weighted sequences. One unique imaging feature that is helpful in atypical lesions is that hemangiomas are hyperintense on low b-value diffusion-weighted images and decrease in signal with increasing b-value (135–137). Giant cavernous hemangiomas are a subtype of hemangiomas, which measure over 10 cm in size (although some authors define these as over 4–5 cm in size) and can demonstrate similar imaging appearance as mentioned above. However, they can also demonstrate areas of calcification, large areas of central nonenhancement, and can have heterogeneous postcontrast enhancement.

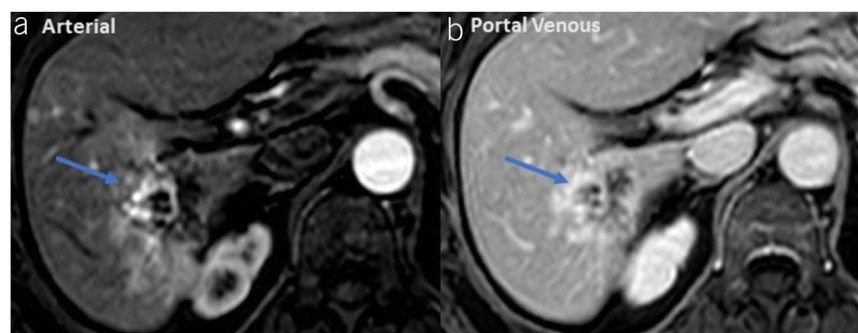


Figure 8. Sclerosed hemangioma. A 58-year-old man with no underlying medical history had incidentally discovered liver mass. MRI showed a mass that demonstrated thick peripheral rim enhancement on arterial phase (a) with progressive enhancement on delayed phase of imaging (b). This mass does not have classic imaging appearance of any benign lesion, and differential diagnosis is cholangiocarcinoma, metastasis, or sclerosing hemangioma. This was a pathology-proven sclerosing hemangioma. MRI, magnetic resonance imaging.

Capillary hemangiomas, also known as flash-filling hemangiomas, tend to be under 1 cm in size and demonstrate rapid homogenous arterial phase enhancement on postcontrast CT or MRI (120). On ultrasound, these small lesions may demonstrate vascular flow, unlike the cavernous hemangiomas, because the vascular spaces are smaller (138).

A sclerosed hemangioma, also known as a thrombosed or hyalinized hemangioma, usually occurring secondary to degeneration of a cavernous hemangioma and contain large amounts of fibrosis. Sclerosed hemangiomas are a diagnostic dilemma because they do not have typical imaging appearances as mentioned above. In fact, this subtype presents as areas of thick peripheral rim enhancement on early postcontrast phases with progressive enhancement of the lesion in a noncentripetal and non-nodular fashion. Unlike cavernous hemangiomas, they are heterogeneous on T2-weighted imaging and demonstrate increasing restricted diffusion on high b-value images. In addition, they can cause upstream capsular retraction (139,140) (Figure 8). These imaging features are also characteristic of iCCA or hypovascular metastasis. Thus, in these instances, careful comparison with previous imaging revealing a stable lesion or a typical hemangioma in the same location is required. In some instance, a biopsy may be required.

In general, hemangiomas are considered “do not touch lesions” because imaging is sufficient to make the diagnosis with near-complete certainty. However, if an FLL cannot be confirmed as a hemangioma, multidisciplinary review could be performed (26,141). Biopsy is generally avoided, given the vascular nature of hemangiomas, although reports have indicated that risk of bleeding with biopsy of hemangiomas is low (0.15%) if small needles are used (142). Once the diagnosis of hemangioma is confirmed, no further follow-up imaging is needed, except for patients with underlying cirrhosis or risk of HCC, because lesions can mimic hemangioma early in the course of malignancy development (143,144). These patients should undergo follow-up imaging as recommended for FLL in the AASLD Hepatocellular Carcinoma Guidance (145).

Surgical treatment of hemangiomas, including giant cavernous hemangiomas, should be avoided if the main indication is discomfort and anxiety because these symptoms nearly always recur (128,146–150). The clearest indications for treatment of a hemangioma remain complications related to the tumor, such as rupture, intratumoral hemorrhage, consumptive coagulopathy, and organ or vessel compression. Thankfully, spontaneous rupture of hepatic hemangiomas is an exceedingly rare event (151). Surgical treatment can be performed through the open approach or laparoscopically; the most common surgery is enucleation, and the second most common is nonanatomical resection (152). Larger hemangiomas (>15 cm) are more likely to have complications with surgery such as blood loss and blood transfusion or prolonged recovery (153). In patients who are not surgical candidates either because of anatomic concerns or comorbidities, other interventions can be considered such as ablation for lesions smaller than 3.5 cm (radiofrequency or microwave), radiation therapy, TAE, and in the case of life threatening Kasabach–Merritt syndrome, even a few reports of liver transplantation after discussion at multidisciplinary tumor board (128,154). Patients with asymptomatic hemangiomas do not require intervention or follow-up regardless of the size (155).

Key concepts

- 24a. Small echogenic avascular lesions less than 2 cm with well-defined borders in a patient with a normal liver and no underlying medical history or risk factors for liver disease or malignancy can be diagnosed as hemangioma on ultrasound.
- 24b. In patients with a lesion that does not meet the above criteria, multiphasic contrast-enhanced imaging should be performed to confirm the diagnosis.
25. If a suspected hemangioma cannot be confirmed on cross-sectional imaging, then the next step is to monitor and to review the case at a multidisciplinary tumor board.
26. Biopsy of a suspected hemangioma should be avoided when possible because of the risk of bleeding.
- 27a. Once the diagnosis of hemangioma is confirmed, no further follow-up is needed unless the patient has cirrhosis or other risk of malignancy such as hepatitis B.
- 27b. Patients who are pregnant do not need to have monitoring of the hemangioma even in the case of large, cavernous hemangiomas.
28. Even in patients with asymptomatic large, cavernous hemangiomas (generally >10 cm), surgical resection is not indicated. No further follow-up is required.
29. Indications for resection of a hemangioma are complications related to the lesion, such as rupture, intralesional hemorrhage, consumptive coagulopathy, or organ or vessel compression. These complications are rare. Resection may be performed through open or laparoscopic approach.
30. If surgery is not an option for a patient with complications related to the lesion, other treatments may be considered such as ablation (microwave or radiofrequency), radiation therapy, TAE, or in the very rare instance liver transplantation. Treatment options in these instances should be discussed at multidisciplinary tumor board.

Recommendation

11. In patients with cirrhosis or chronic hepatitis B who meet criteria for HCC surveillance and have a suspected hemangioma, we recommend continued imaging surveillance every 3–6 months for at least 1 year (strong recommendation, low quality of evidence).

Solid liver lesions of malignant potential

Solid liver lesions on imaging often causes concern for malignancy, and this must always be considered when determining the next step in diagnosis and management of a liver lesion. In a patient with underlying liver disease, HCC should always be on the top of the differential, and even when a solid liver lesion appears typical for another diagnosis, the patient must have ongoing surveillance to assess for growth. The AASLD recently updated the Guidance document for HCC (145). Rather than discussing HCC in more detail in this document, we encourage the reader to refer to that Guidance document.

CCA is another solid mass lesion of concern, especially when the mass appears in the hilar area, although iCCA must also be considered. Patients with primary sclerosing cholangitis and viral hepatitis are at higher risk of CCA development, and patients with underlying cirrhosis from any cause can develop mixed HCC-CCA (156,157). Again, a recent Guidance statement that is specific to CCA has recently been published, and we refer the reader to that document (158).

In patients with multiple liver lesions in the setting of symptoms suggestive of carcinoid syndrome or with concomitant mass in the pancreas or small intestine, neuroendocrine tumors (NETs) must be considered. A consensus document on pancreatic NET was published in 2020, and although this document focuses on NET of pancreatic origin, many of the same issues around imaging and therapy can be applied to NETs of other origins (159). The only area of treatment that was not addressed in this consensus statement is the role of liver transplantation in the treatment of NET. Patients with metastatic NET with the primary tumor originating in areas with portal venous drainage that is limited to the liver with the primary tumor resected and a period of disease stability seem to have long-term survival after liver transplant with a 5-year survival rate of approximately 50% and in some cases can be as high as 70%, depending on selection criteria (160). The United Network for Organ Sharing has clear guidance on who may be considered for liver transplantation, but there is no consensus on which patients should be referred and evaluated for transplant or at what time point in the disease process this should occur (93). However, given the long wait times for donor organs in many areas, it is prudent to refer patients early for evaluation and discussion of liver transplantation as a treatment option.

Metastatic liver lesions

Incidentally discovered FLLs in the setting of a previous or current malignancy should prompt a workup for rapid and accurate diagnosis, given the important prognostic and treatment implications. There are multiple imaging modalities available, and choosing the appropriate study can be difficult.

If the incidentally discovered FLL is in a patient with no history of malignancy but has an imaging appearance suspicious for extrahepatic primary, this should instigate a workup to identify the primary source. If there is a known primary extrahepatic malignancy, and an FLL is discovered on initial staging workup, then further imaging may be warranted to confirm that the incidental FLL is a liver metastasis. For most malignant liver lesions, the most sensitive and specific imaging test will be an MRI with an hepatocyte-specific MRI contrast agent in combination with diffusion-weighted imaging (161,162). A recent meta-analysis showed that the sensitivity of gadobenate (MultiHance) for detecting liver metastases on a per-lesion basis for precontrast and combined dynamic, delayed HBP imaging was 77.8%, 88.1%, and 95.1%, respectively, which is similar to that reported for gadoxetate (Primovist/Eovist) (21). Unless there is a reason for alternative imaging, we recommend MRI for evaluation of liver lesions in the setting of concurrent or previous malignancy. Contrast-enhanced CT allows for fast, accessible, and high-quality imaging with a sensitivity of 74% for detection of liver metastasis, similar to that of dynamic postcontrast MRI (163). Additional imaging modalities for the detection of hepatic metastatic disease include positron emission tomography (PET)-CT and PET-MR. One consideration is that in a patient with known primary extrahepatic malignancy, a new incidental FLL most likely represents a metastatic lesion because development of “new” benign lesions in a surveillance patient is rare. In this instance, further dedicated imaging of the liver is not indicated, and the patient can undergo repeat staging workup and/or biopsy.

For further evaluation and treatments of metastatic lesions in the liver, please refer to the appropriate guidance for the source

cancer. However, in the following sections, we will briefly review a few primary liver malignancies of importance.

Metastatic colon cancer is a special case that gastroenterologists and hepatologists must be aware of because there has now been a consensus statement and recommendations on liver transplant for colorectal liver metastases (164). Patients with nonresectable colorectal liver metastases that fulfill appropriate molecular criteria and have had a response to chemotherapy for at least 6 months may be considered, at a center with experience in liver transplantation for this indication.

Key concepts

31. Patients with HCC, CCA, NET, and metastatic colon cancer that are within guidance and consensus recommendations for liver transplant should be referred early in their course to a liver transplant center experienced in that disease process.
32. For lesions that are suspected to be metastatic to the liver, MRI with hepatobiliary contrast enhancement and diffusion-weighted imaging is the recommended modality.

Hepatic epithelioid hemangioendothelioma

Hepatic epithelioid hemangioendothelioma (HEHE) is a rare, low-to-intermediate grade tumor that derives from vascular endothelial cells. It can occur in multiple places in the body but is most commonly known to arise in the liver. It is slightly more common in women with a ratio of men to women at 3:2 and an estimated incidence of 1–2 cases of every 1 million people. Mean age at diagnosis is in the mid-40s to early 50s, and lesions are diagnosed incidentally 25% of the time (165). Unfortunately, distant metastases are present at time of diagnosis in approximately 37% of patients, with regional disease in 27.5%. Despite the presence of metastatic disease, the prognosis has shown a median survival of 182 months (165). However, patients who present with lung or multiorgan involvement, ascites with serosal metastasis, age greater than 55 years, and male gender have poor prognosis, often under 1 year (166,167).

There are 2 types of HEHE seen at different stages. Early stage disease presents with nodular type ranging from 0.5 to 12 cm in size, usually peripheral subcapsular in location. Advanced stage disease appears as diffuse disease with the nodules coalescing (168).

On ultrasound, HEHE is usually hypoechoic and heterogeneous in appearance. Capsular retraction, calcifications, and multifocal lesions may also be seen (169). A halo can be seen on US in 20% of patients (170). Imaging findings on CEUS are nonspecific; however, rim enhancement with washout of contrast on portal venous phase should clue the radiologist that it is a malignant lesion, prompting further cross-sectional imaging.

On cross-sectional imaging (CT or MRI), HEHE is often present in a subcapsular location with capsular retraction and calcifications. Enhancement can vary and present as mild homogeneous enhancement seen on all phases or thin ring-like enhancement in the arterial phase, with progressive enhancement in the portal venous phase (171) (Figure 9). The characteristic imaging sign is the “lollipop” sign, which is due to tumor spread along the portal and hepatic vein branches and sinusoids, resulting in vascular and sinusoidal narrowing and obstruction (172). As a result, there is tapering of the portal and hepatic vein branches as they approach the lesion. The narrowing and occluded vessels are like sticks on the lesion, simulating the lollipop

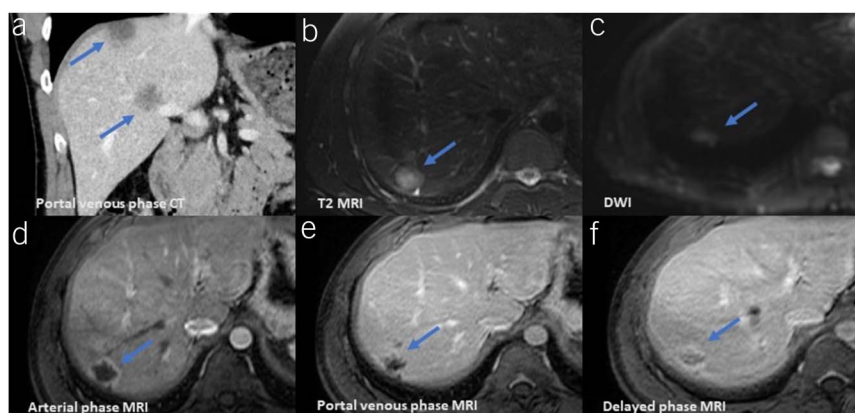


Figure 9. Hepatic epithelioid hemangioendothelioma. A 31-year-old man with multiple hypoenhancing hepatic masses detected on portal venous phase CT (a). Further workup with MRI was performed. The lesions demonstrate T2-hyperintense signal (b), restricted diffusion (c), and thin ring-like enhancement in the arterial phase (d), with progressive enhancement in the portal venous (e) and delayed phase of imaging (f). Best seen on the T2 is the “target” sign, which is an inner ring that consists of a fibrotic center, a middle ring of epithelial proliferation, and an outer ring defined by an avascular zone between the nodule and the liver parenchyma. This lesion was biopsy-proven hepatic epithelioid hemangioendothelioma. CT, computed tomography; MRI, magnetic resonance imaging.

appearance (173). Another radiographic sign of HEHE on imaging is the “target” sign, which is an inner ring that consists of a fibrotic center, a middle ring of epithelial proliferation, and an outer ring defined by an avascular zone between the nodule and the liver parenchyma (171). The presence of capsular retraction, lollipop sign, and the target sign together is fairly specific for HEHE, and the presence of these features warrants further investigation (174). HEHE is generally mildly or moderately PET avid, and PET-CT or PET-MRI may be used as part of the workup for metastatic disease, although whole-body CT or whole-body MRI is the preferred imaging modality (175,176).

Although imaging features that are highly suggestive of HEHE, they can overlap with angiosarcoma, CCA, metastatic carcinoma, and sclerosing variant of HCC, and therefore, pathology is necessary to confirm the diagnosis. If surgical resection may be considered, then the patient can proceed to resection without a biopsy beforehand, and diagnosis can be confirmed with the surgical specimen. However, if resection is not imminently planned, then core needle biopsy must be performed.

Because of the rarity of HEHE, there are few studies to inform treatment recommendations. However, it is well

accepted that surgical resection is the preferred treatment with 70%–80% cure rates after an R0 resection (177). In patients who are not able to undergo surgical resection, liver transplantation is also an accepted treatment for HEHE with 5-year survival of 77%, and the United Network for Organ Sharing has a pathway for these patients to receive model for end-stage liver disease exception points (178). Notably, the presence of extrahepatic disease has not been associated with worse outcomes after liver transplant and is not considered to be a contraindication (93). In the largest reported cohort of HEHE patients, patients who underwent liver transplant had the best survival when compared with other therapies (179). For patients who are not surgical candidates, sporadic studies and expert consensus statements recommend ablative therapies or stereotactic body radiotherapy (176). Systemic therapy is not often recommended, given the slow-growing nature of HEHE and should only be considered in patients with clear progression of disease and/or marked systemic symptoms. A variety of different systemic therapies have been reported, ranging from conventional chemotherapy to targeted therapies, but results have been disappointing, with overall survival generally less than 2 years (180).

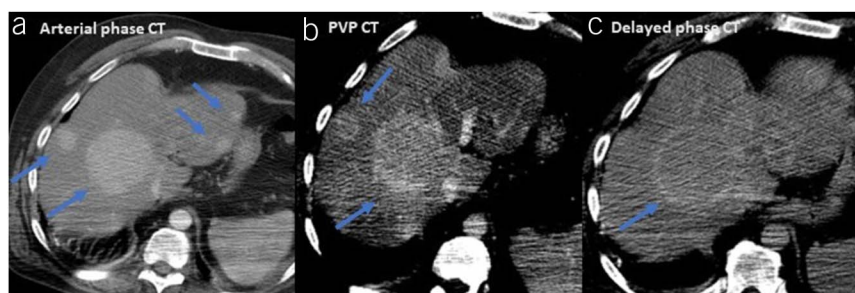


Figure 10. Fibrolamellar hepatocellular carcinoma. A 39-year-old man with multiple arterial hyperenhancing hepatic masses detected on arterial phase CT (a), with washout and capsule on portal venous (b) and delayed phase CT (c). Approximately 50% demonstrate a central scar. Note the absence of underlying chronic hepatocellular disease. Differential diagnosis could be multifocal adenomas, given the absence of risk factors, multifocal HCC, and hypervascular metastasis. This was biopsy-proven fibrolamellar HCC. CT, computed tomography; HCC, hepatocellular carcinoma.

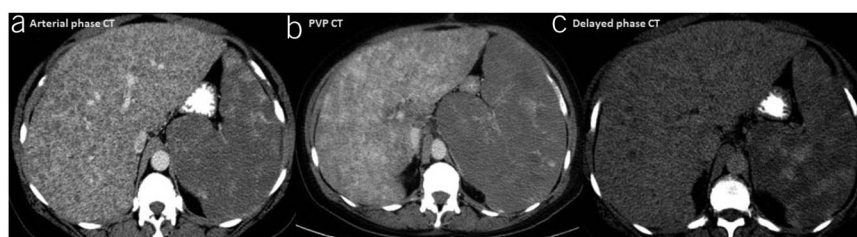


Figure 11. Hepatic angiosarcoma. A 56-year-old man with multiple arterial hypoenhancing hepatic masses, in an almost miliary pattern, on arterial phase CT (a), with persistent hypoenhancement on portal venous (b) and delayed phase CT (c). This was biopsy-proven hepatic angiosarcoma. CT, computed tomography.

Key concepts

33. If resection is planned because of imaging being highly suspicious for HEHE, a needle biopsy does not necessarily need to be performed before surgery.
34. Patients with diagnosed HEHE should undergo imaging for staging of disease with whole-body contrast-enhanced CT or whole-body contrast-enhanced MRI. PET-CT or PET-MRI may be considered with the understanding that HEHE is generally only mild or moderately PET avid.
35. HEHE should be resected whenever possible. If resection is not feasible, then liver transplantation offers the best survival, even in the setting of extrahepatic disease.
36. In the setting of nonresectable and nontransplantable HEHE, there are very little data to guide treatment choices, and patients should be referred to a specialty center whenever possible. Ablative therapies and stereotactic body radiotherapy have shown some response in small studies. There is no systemic therapy that can be recommended from published evidence, given the small numbers of patients.

Fibrolamellar HCC

Fibrolamellar HCC (FLHCC) is a rare primary liver cancer, accounting for <1% of all primary liver tumors in the United States. The highest incidence of FLHCC is in White men under the age of 40 years, although there is somewhat of a bimodal age distribution between 15 and 19 years and 70–74 years (181). Typically, it arises in a noncirrhotic liver with no specific risk factors identified. It has historically been thought of as a variant of conventional HCC, although genetic profiling has determined there is a unique mutation found in FLHCC, a *DNAJB1-PRKACA* chimeric gene fusion RNA transcript that is very rarely found in other cancers

(182,183). Typically, α -fetoprotein is not elevated in FLHCC, although the presence of elevated AFP is an independent predictor of poor survival (184).

FLHCC is most commonly presents with symptoms, such as abdominal pain, palpable mass, or rarely mental status changes from acquired ornithine transcarboxylase deficiency (185). Unlike conventional HCC, FLHCC must be diagnosed with biopsy, although imaging can be suggestive of the diagnosis. FLHCC most often presents as a large, often solitary tumor with a background normal liver. There is generally heterogeneous early contrast enhancement, and calcifications can be present (186) (Figure 10). On hepatobiliary MRI, there is hypointensity in the HBP (187). A central scar can be present in up to half of patients with FLHCC, so confusion with FNH can occur (188).

FLHCC is best treated surgically, even when lymph node metastases are present, with high recurrence rates ranging from 5% to 86% (181). There are very little data available on adjuvant or neoadjuvant therapy, although database studies suggest a worse outcome with the use of adjuvant or neoadjuvant chemotherapy (189,190). Liver transplant has also been performed, with 5-year survival rates of 48% (191). Given that the overall survival after transplant is worse than conventional HCC and slightly lower than 50% at 5 years, liver transplant should be reserved for liver-localized, unresectable disease.

In patients who are not candidates for surgical treatments or have recurrence, options are somewhat limited but include radiotherapy, traditional chemotherapy, or immunotherapy. Despite the identified genetic mutation found in patients with FLHCC, initial attempts at systemic therapy targeted to this mutation have not been successful (192). Several cases of partial responses to immunotherapy have been reported, including 1 complete response to the combination of anti-CTLA4 and anti-

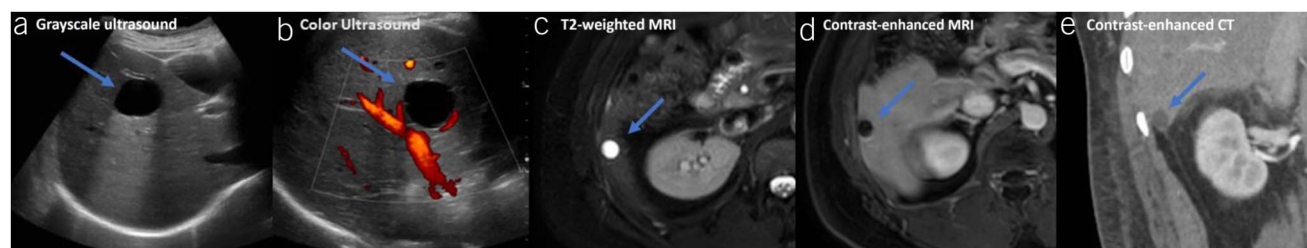


Figure 12. Simple hepatic cyst. A 32-year-old woman with right upper-quadrant pain presented with incidental anechoic lesion on grayscale ultrasound (a). Note the imperceptible wall and acoustic through transmission (increased echogenicity posterior to the cyst). No flow detected on color imaging (b). A 41-year-old man has a 1.2-cm well-circumscribed T2-hyperintense lesion in segment 6 of the liver on MRI (c), no enhancement on MRI (d), or CT (e). CT, computed tomography; MRI, magnetic resonance imaging.

PD-1 antibodies (193,194). Given the very limited data available, patients with FLHCC who require systemic therapy should be enrolled in clinical trials whenever feasible.

Key concepts

37. In patients with FLHCC, surgical resection is the treatment of choice. In patients who have limited liver-localized disease that is unresectable, liver transplant may be considered on a case-by-case basis.
38. Neoadjuvant or adjuvant systemic therapy is not recommended for FLHCC except in the setting of a clinical trial.
39. In patients with FLHCC, biopsy should be performed to confirm the diagnosis, but molecular analysis of the biopsy for guidance of systemic therapy is not beneficial.

Hepatic angiosarcoma

Angiosarcoma is a rare and aggressive cancer that can occasionally present as a primary liver lesion. Primary hepatic angiosarcoma accounts for less than 1% of primary malignant liver tumors and 1%–2% of all soft-tissue sarcomas (195). This tumor usually presents with symptoms once at an advanced stage, and the only known risk factors include exposure to thorium dioxide, vinyl chloride, arsenic, and radiation (196). There is a slight male predominance, and nearly 80% of patients are older than 50 years at the time of diagnosis.

On imaging, hepatic angiosarcomas can have a varied appearance and range from multiple masses to a single heterogeneous mass. On CT, the lesions are most frequently hypoenhancing on all postcontrast phases, unless they hemorrhage, in which case portions of the tumor are hyperdense on noncontrast imaging (Figure 11). On MRI, tumors are heterogeneous on all sequences (197).

The prognosis of primary hepatic angiosarcoma is very poor, with 1-year survival at just 12.8% (195). Studies using the National Cancer Institute's Surveillance, Epidemiology, and End Results database show that surgical resection does seem to prolong survival, although recurrence is frequent (196,198). There are some small studies to suggest that adjuvant radiation or chemotherapy may be of use, but the data are mixed, and this is not routinely recommended (199–201). Given the complexity and poor outcomes, we recommend that patients with primary hepatic angiosarcoma be referred to a sarcoma specialty center for treatment whenever possible.

Key concept

40. In patients with primary hepatic angiosarcoma, surgical resection should be performed whenever feasible.

CYSTIC LIVER LESIONS

Cystic liver lesions are an increasingly common, heterogeneous group of lesions, which are often found incidentally because of the frequent use of cross-sectional imaging studies. Early reports from laparotomy series described a prevalence of 0.2%–1%, whereas recent ultrasound and CT series report a range of 2.5%–18% (202–205). With increased use of imaging for unrelated reasons, the incidence of incidentally detected hepatic cysts rises, and thus, understanding the types of cysts and management has become increasingly important. Most cysts have an indolent course; however, it is important to differentiate benign, simple cysts from those with malignant or infectious potential

such as biliary cystadenomas/cystadenocarcinomas, choledochal cysts, and hydatid cysts. Specific high-risk features such as septations, fenestrations, calcifications, mural thickening or nodularity, heterogeneity, and the presence of daughter cysts should prompt further investigation (206). In addition, patients with multiple or large cysts can present with related symptoms, which requires further management.

Simple hepatic cysts

Hepatic cysts are thin-walled structures lined by cuboidal bile duct epithelium and filled with isotonic fluid (202). They are the result of ductal plate malformation without communication with the biliary tree (207,208). They can be solitary or multiple and often coexist with other mass lesions. They are usually asymptomatic and incidentally found, unless they are very large, in which case they can be symptomatic. There is a female predominance, although there is no established correlation with OCP use or pregnancy and cyst prevalence increases with age (208).

Simple hepatic cysts can be diagnosed on conventional gray-scale ultrasound with a sensitivity and specificity of 90% (209). Simple hepatic cysts are usually homogeneously anechoic with through transmission and smooth margins. Up to 2.5%–5% of simple cysts can have up to 2 septa within them and include congenital cysts, Caroli disease, biliary hamartomas, and polycystic liver disease (PCLD). When a simple cyst is seen on ultrasound with these characteristics, no further imaging or follow-up is required. On CT, simple cysts demonstrate no internal architecture, are hypodense with fluid attenuation (<20 Hounsfield units), and demonstrate absent postcontrast enhancement. On MRI, simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images with no enhancement. There is decreasing intensity on higher b-value diffusion-weighted imaging (209,210) (Figure 12).

There is no indication for intervention or follow-up of simple cysts, regardless of size, unless symptoms develop or there are characteristic high-risk features such as mural nodularity or enhancing septations. Symptoms can occur when cysts enlarge, rupture, or compress key structures, leading to significant abdominal pain or pressure, shortness of breath, early satiety, epigastric fullness, or lower extremity edema because of inferior vena cava compression. High-risk features seen on ultrasound (e.g., septations, fenestrations, calcifications, mural thickening or nodularity, heterogeneity, and presence of daughter cysts) should prompt further investigation with CT or MRI to rule out more significant pathology such as infected cysts, pyogenic abscess, cystic metastasis, hydatid cysts, or mucinous cystic neoplasms of the liver (MCN-L).

For symptomatic cysts, treatment options include surgical cyst fenestration, also known as derofing/marsupialization, or aspiration with sclerotherapy (206,211–213). There is a lack of robust randomized controlled trials (RCTs) and long-term outcome data comparing these methods to determine best modality for treatment. Although both are effective, surgical intervention has the lowest recurrence rate and allows for histological examination of the cyst (213). However, the decision to pursue surgical intervention, including type of surgery (open or laparoscopic), should be based on the patient's operative candidacy, individual preference, and center expertise.

Aspiration sclerotherapy can be achieved with several substances including 100% ethanol, tetracycline, or other sclerosants

and may take up to 6 months to see maximum benefit (213). Thus, repeat intervention within 6 months of sclerotherapy is not recommended. Cyst aspiration alone, although helpful to diagnose the cyst as the cause of symptoms, is not recommended for definitive treatment, given the high recurrence rate (214). There is no need for postintervention imaging. Serum CA 19-9 levels can be elevated in up to 50% of these patients and therefore may not help to differentiate between simple and malignant cysts (215,216). In addition, cyst fluid can contain CA 19-9, a finding that does not necessarily correlate with malignancy (209).

Key concept

41. In patients with asymptomatic complex hepatic cysts, regardless of size, we recommend discussion at a multidisciplinary tumor board and consideration of surveillance imaging in 6–12 months.

Recommendations

12. In patients with asymptomatic simple hepatic cysts, regardless of size, we recommend expectant management without need for routine surveillance or intervention (strong recommendation, low quality of evidence).
13. In patients with simple hepatic cysts with specific high-risk features seen on ultrasound (e.g., septations, fenestrations, calcifications, mural thickening or nodularity, heterogeneity, and presence of daughter cysts), we recommend further investigation with CT or MRI (strong recommendation, low level of evidence).
14. We suggest surgical cyst fenestration or aspiration with sclerotherapy for management of patients with symptomatic simple hepatic cysts (conditional recommendation, low level of evidence).

PCLD

Autosomal dominant PCLD is characterized by the presence of multiple hepatic cysts (at least >10–20) with characteristics similar to simple cysts with few or no kidney cysts. Cysts are not connected to the biliary system, and PCLD is believed to be part of a clinical spectrum of ciliopathies (a heterogeneous group of genetic disorders encoding defective proteins, which result in abnormal function or formation of cilia), leading to various clinical manifestations including fibrocystic diseases of the liver (206,207,217). The most common ciliopathy phenotypes are autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant PCLD. The former is a systemic disorder characterized by renal cysts leading to renal failure, with up to 60%–80% of affected patients also having hepatic cyst involvement, often diagnosed by ultrasound (218–220). Patients with ADPKD should be screened for PCLD with abdominal ultrasound. Conversely, autosomal dominant PCLD is relatively benign, often asymptomatic and with cysts restricted only to the liver (221,222). Isolated PCLD is far less common than ADPKD with a prevalence of 1–10 per million (219). However, patients with PCLD should still obtain an initial ultrasound of the kidneys to exclude ADPKD. Patients with ADPKD have a germline mutation in 1 of 2 genes (*PKD1* and *PKD2*), whereas most cases of isolated PCLD do not have a pathologic gene identified and are genetically distinct from the PCLD seen in patients with ADPKD (219). Because of this genetic heterogeneity seen in PCLD (i.e., the 6 genes identified in PCLD only account for 30%–45% of

population), genetic testing is generally not recommended in this group. However, in young patients with PCLD and few renal cysts who do not meet diagnostic criteria, genetic testing might be helpful to exclude ADPKD (223). Patients with isolated PCLD do not develop the extrarenal manifestations seen in ADPKD such as intracranial aneurysms. Overall, genetic testing does not play a significant role in PCLD.

Most patients with PCLD present later in life with a larger number and size of cysts than those with ADPKD and are often asymptomatic (224,225). PCLD has a largely female predominance (>80%), increases in prevalence with age, and has an association with pregnancy and OCP use (224,226). The role of exogenous estrogen in increasing total liver volume in these patients stems from an initial prospective study of postmenopausal patients with ADPKD who were noted to have significant increase in liver volume with hormone replacement therapy compared with controls (227). In another large cross-sectional cohort study, the use of estrogen-containing OCPs in premenopausal women worsened PCLD severity, that is, led to a 15.5% higher height adjusted total liver volume for every 10 years of use, compared with those not on therapy (228). Exogenous estrogen use should be discontinued in patients with PCLD because studies have shown an increase in cyst volume in these patients (229,230). The effect of pregnancy on cyst burden in PCLD remains unclear with older studies showing an increase in cyst burden, but more recent observational studies do not (230).

In patients who have significant cyst burden, increased cyst volume can lead to palpable hepatomegaly, early satiety, abdominal discomfort, dyspnea, lower extremity edema, and significant weight loss, leading to malnutrition, frailty, and poor quality of life factors. Patients can also have complications related to cyst rupture, infection, bleeding, compression of the inferior vena cava, portal vein, or biliary tree. Liver enzymes and synthetic function are often preserved, despite heavy cyst burden except in advanced cases. The most common elevations are seen in gamma-glutamyl transferase (GGT) and alkaline phosphatase; CA 19-9 is also elevated in ~50% of patients without evidence of malignancy (221). Rarely, patients may develop severe protein calorie malnutrition, weight loss, sarcopenia, or symptoms of portal hypertension or hepatic venous outflow obstruction because of significant cyst burden, and those who meet specific criteria can be granted exception points on the liver transplant waitlist (93,219,231) (Table 6).

Imaging appearance of cysts in PCLD is similar to that of simple cysts on all imaging modalities. The difference is that there are often numerous cysts throughout the liver, which can vary in size. Imaging surveillance of the cysts is not recommended in asymptomatic patients because there is no malignant potential (232).

Primary treatment goals for PCLD are aimed at symptom relief and improvement and preservation of quality of life. Optimal management is based on cyst location, volume, size, and number. Cyst aspiration with sclerotherapy is primarily for large cysts and, although immediately effective, has a high recurrence rate. Surgical options include surgical cyst fenestration, resection, and liver transplantation. Surgical cyst fenestration also significantly reduces cyst volume and provides immediate symptom relief. However, there is a 30% recurrence rate with this procedure, and complications can include ascites, bile leak, pleural effusion, or bleeding (221). Hepatic resection is considered when fenestration is unlikely to be successful and when liver

Table 6. Criteria to obtain MELD exception points^a for patients with PCLD who are not clinically eligible for resection/fenestration or alternative therapy (93)

Hepatic decompensation or severe portal hypertensive complications
Concurrent hemodialysis
GFR less than 20 mL/min
Patient with previous kidney transplant
Moderate to severe protein calorie malnutrition as documented by a registered dietician using any of the following:
• GLIM phenotypic criteria
• ASPEN criteria
• NFPE
• SGA-C score
Severe sarcopenia as documented with SMI (<39 cm ² /m ² in women and <50 cm ² /m ² in men) or equivalent
ASPEN, American Society for Enteral and Parenteral Nutrition; GFR, glomerular filtration rate; GLIM, Global Leadership Initiative on Malnutrition; MELD, model for end-stage liver disease; NFPE, Nutrition Focused Physical Examination; PCLD, polycystic liver disease; SGA-C, Subjective Global Assessment; SMI, skeletal muscle index.
^a Indication for exception includes those with PCLD with severe symptoms related to PCLD plus any of the above.

transplantation is not required. Outcomes are excellent, and laparoscopic approach is preferred when feasible (233). Data comparing the effectiveness of these options are limited (206). Treatment should be aimed at selecting the least invasive procedure that provides the most effective outcome. Liver transplantation with or without simultaneous kidney transplantation is the only curative option and has excellent long-term survival in patients with marked synthetic dysfunction, malnutrition, or significant impairment in quality of life (219,234). Patients with PCLD with severe symptoms who are currently on dialysis, have a GFR <20 mL/min, or require a kidney transplant should undergo liver transplant simultaneously with their kidney transplant and will be granted exception points on the transplant waitlist (93) (Table 6).

Data on medical management of PCLD are limited and include treatment with somatostatin analogs, mammalian target of rapamycin (mTOR) inhibitors, and bile acids. Medical management should be considered in patients with PCLD with numerous small- to medium-sized cysts throughout the liver not amenable to surgical

resection, cyst fenestration, or aspiration sclerotherapy or for patients with symptomatic ADPKD with concurrent PCLD. Several clinical trials and meta-analyses have confirmed the benefits of somatostatin analogs on liver cyst volume, with the biggest reductions seen within the first 6 months of treatment and lasting for up to 2–4 years (227,228,235,236). In the largest RCT assessing the role of lanreotide in decreasing cyst burden, compared with controls, the lanreotide group had a statistically significant reduction in height-adjusted liver volume (HA-LV) by almost 6% (95% CI –9.18 to –2.63; $P < 0.001$), and this effect still continued with an additional 3.87% reduction at 4 months after the last injection of lanreotide (235). The recommended dose of lanreotide long-acting release (LAR) in this trial was 120 mg intramuscularly every 4 weeks. Although this reduction in HA-LV may seem clinically insignificant, this correlates to approximately 140 mL of volume reduction in the lanreotide arm, and studies have shown symptom improvement with a decrease in liver volume of >100 mL (237,238).

Unfortunately, symptoms eventually recur after treatment discontinuation. Treatment is overall well tolerated with only a small percentage of patients discontinuing medications (<5%) because of intolerance or adverse events. Steatorrhea type symptoms are the most common with somatostatin analogs and are self-limited, often fading after the first few injections.

Data for mTOR inhibitors are not as favorable. Although a small pilot trial showed initial improvement in liver volume with sirolimus in patients with ADPKD, an RCT did not show any significant improvement in cyst volume with everolimus when added to long-acting octreotide (239,240). A multicenter randomized controlled trial investigating the effect of ursodiol on PCLD did not show any improvement in cyst volume in patients with isolated PCLD but did show some improvement in liver cyst volume in patients with ADPKD in post-hoc analysis (241).

Key concepts

42. Treatment goals for PCLD should be aimed at symptom relief and preservation of quality of life.
43. Treatment options for PCLD including cyst aspiration with sclerotherapy, surgical cyst fenestration or resection of dominant cyst(s) should be based on cyst characteristics, underlying hepatic reserve and center expertise.
44. Liver transplantation with or without simultaneous kidney transplantation should be considered as a curative option in patients with PCLD with refractory symptoms because of significant cyst burden.



Figure 13. MCN-L. A 64-year-old woman with abdominal pain presented with a large cystic mass centered in segment 4 of the liver, demonstrating thick peripheral mural calcifications (a). The cyst was resected secondary to pain and was a confirmed MCN-L. A 58-year-old woman with a large cystic lesion demonstrating hyperintense signal with thick septations on T2-weighted MRI (b). The septations demonstrate enhancement on postcontrast imaging (c). The cyst was resected and demonstrated elevated CEA with histology confirming MCN-L. Key features included multiple septations, septations arising directly from the wall, and enhancement of the septations. CEA, carcinoembryonic antigen; MCN-L, mucinous cystic neoplasm of the liver; MRI, magnetic resonance imaging.

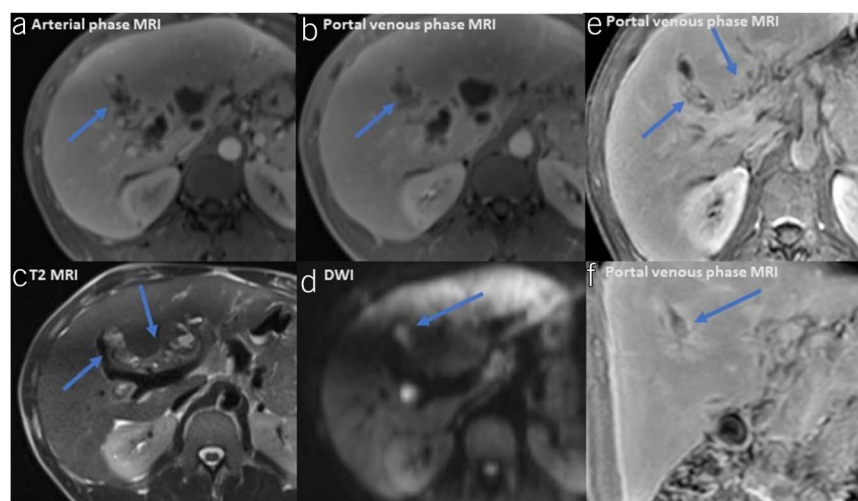


Figure 14. IPNB. A 61-year-old woman with multifocal tubular areas of frond-like soft tissue within bile ducts throughout the liver. The solid frond-like soft tissue demonstrates hypoenhancement on arterial phase (a) with mild progressive enhancement on PV phase (b). There is heterogeneous T2 signal (c) with focal areas of restricted diffusion (d). Follow-up MRI 6 months later demonstrates increase in size of the enhancing soft tissue within the bile duct (e, f). IPNB, intraductal papillary neoplasm of the bile duct; MRI, magnetic resonance imaging.

Recommendations

15. We suggest discontinuation of exogenous estrogen use in women with PCLD. (conditional recommendation, very low level of evidence).
16. For patients with PCLD with numerous small- to medium-sized cysts throughout the liver not amenable to surgical resection, cyst fenestration or aspiration sclerotherapy, or for patients with symptomatic ADPKD with concurrent PCLD, we recommend medical management using somatostatin analogs. (strong recommendation, moderate level of evidence).

Mucinous cystic neoplasms of the liver

MCN-L, previously reported as biliary cystadenoma (BC) or biliary cystadenocarcinoma, are a rare but heterogeneous group of cystic tumors within the hepatic parenchyma and account for <5% of all liver cysts. In 2019 the World Health Organization (WHO) reclassified BC into MCN-L, which is defined as an epithelial cystic neoplasm lined by cuboidal, columnar, or mucin producing epithelium and can be associated with ovarian-type subepithelial stroma (207,242). These can furthermore be classified as invasive and noninvasive subtypes (243). These cysts often have septations composed of either mucinous (95%) or serous (5%) material, can be unilocular or multilocular (90%), and do not communicate with the biliary tree; some may have papillary projection that form thick septa, or they may have enhancing septa, mural calcifications, or mural nodules (206,207). Although MCN-L account for <5% of all cystic liver lesions, historically, they were associated with up to 20%–30% malignant transformation rate to adenocarcinoma (244–247); however, with the updated WHO diagnostic criteria in 2010, recent studies suggest up to 10% risk of malignant transformation (243). There is a strong female predominance (1:4) and often manifest in the fifth or sixth decade of life; they are not clearly linked to the use of OCPs.

MCN-L can be subcategorized into those that have mesenchymal tissue resembling ovarian stroma on histology and those that do

not; the former being more common and seen in women, whereas the latter is seen equally between men and women and have a high rate of recurrence of malignancy with poor prognosis (242,248). Similar to other benign lesions, MCN-L are often asymptomatic and found incidentally on imaging, although larger lesions can cause mass effect leading to palpable abdominal mass, abdominal discomfort, early satiety, nausea, dyspepsia, anorexia, or weight loss (206,249). Although MCNs can be precursors to the development of biliary cystadenocarcinomas (BCAs), the rate of progression or factors that lead to progression are not clearly identified (247,250). CA 19-9 levels are elevated in 28%–73% of BCAs; however, serum or cystic fluid CA 19-9 levels do not discriminate between simple and malignant cysts or between MCNs and BCAs (207).

The treatment of MCN-L is surgical excision because of the risk of malignant potential; however, because of its rare presentation and overlap with simple hepatic cysts, MCN-L can be misdiagnosed, and thus, an understanding of specific imaging features is important to accurately diagnose this lesion (251,252). Up to 76% of MCN-Ls occur in the left hepatic lobe, with a predilection for segment IV (253). On ultrasound, MCN-L usually appears as a hypoechoic lesion with irregular, often thickened walls, internal septations, mural nodularity, and occasionally internal echoes, which represents debris (254,255). If a complex cyst is identified on ultrasound, cross-sectional imaging with CT or MRI should be obtained. In general, MRI is the preferred modality to evaluate cystic lesions. On CT or MRI, MCN-L is usually a large encapsulated multiloculated cystic lesion, often with internal septa of varying thickness (256,257). Both the presence and the location of septa are an important distinguishing feature of MCN-L vs simple hepatic cyst. The presence of septations has shown to be 95% sensitive in the diagnosis of MCN-Ls (256). Multiplicity of septations is also a distinguishing feature of MCN-L. Furthermore, septations that arise directly from the wall of the cyst (as opposed to being located in a lobulation of the cyst) showed 100% sensitivity and 56% specificity for MCN-L as opposed to a simple hepatic cyst (256). Finally, septations resulting in an indentation of the cyst wall and septations that demonstrate

enhancement are more likely to represent MCN-Ls (253). Mural calcifications have a 90% specificity for MCN-L and can be seen in up to 65% of cysts (253) (Figure 13).

On MRI, MCN-L are usually T2-hyperintense and T1 variable secondary to the potential of proteinaceous and less often hemorrhagic internal debris, a finding that causes the hypoechoic appearance on ultrasound (258). The presence and enhancement of septations and mural nodularity are much better characterized on MRI, and in fact a highly sensitive feature of MCN-L, nearly 100% (256). Upstream biliary ductal dilatation suggesting biliary obstruction from a cystic lesion is another feature, which is highly specific for MCN-L (259).

Imaging differential diagnosis of an MCN-L includes intra-ductal papillary mucinous neoplasm of the bile duct (IPNB), simple hepatic cysts, cystic metastasis, choledochal cyst, and abscesses. Differentiation between simple cyst and MCN-L was discussed above; differentiation between IPNB and MCN-L is that the latter does not demonstrate biliary communication, lacks intraductal masses, and does not demonstrate bile duct dilatation as a dominant feature (260,261).

Appropriate management is critical, given the increased risk of malignancy and recurrence without definitive treatment. Complete surgical resection, either by laparoscopic or open method, is the gold standard for all MCNs, given high rate of recurrence or progression to cystadenocarcinoma with incomplete resection (246,262–266). Other modalities including cyst aspiration, sclerosis, partial resection, or cyst fenestration are not recommended because of the high rate of recurrence, reported at 81% in some studies (246,267–270). Therefore, for patients who are not surgical candidates, surveillance imaging is recommended, although there are no established guidelines regarding specific intervals. In these patients, if surveillance imaging shows evidence suggestive of malignant degeneration, then the case should be discussed at a multidisciplinary tumor board for consideration of nonsurgical options.

Key concepts

45. Fluid aspiration or biopsy of MCN-L is not recommended to distinguish between benign vs malignant cysts because of low sensitivity.
- 46a. MCN-L with imaging characteristics consisting of thick septations, fenestrations, nodularity, calcifications, or mixed solid and cystic components require prompt evaluation for complete surgical resection.
- 46b. For patients who are not surgical candidates, surveillance imaging should be implemented, although a specific interval cannot be recommended. Changes suggestive of malignant degeneration should be discussed at a multidisciplinary tumor board for consideration of nonsurgical options.

Biliary hamartomas and peribiliary cysts

Biliary hamartomas or von Meyenburg complexes are benign malformations of the intrahepatic bile ducts and appear as multiple cystic lesions that do not communicate with the biliary tree and can appear anywhere in the liver, although frequently peripherally, and are usually smaller than 1.5 cm in size (271,272). They do not affect liver function tests, are largely found incidentally, and do not require specific surveillance. Malignant transformation to iCCA or HCC is rare and has been described as case reports in patients with underlying liver disease or in those with congenital hepatic fibrosis or Caroli disease (207,273–276).

Unlike biliary hamartomas, peribiliary cysts are frequently perihilar, small in size (<1 cm), and seen on both sides of the bile ducts as a “string of pearls” around hilar portal veins (272,277). They do not communicate with the biliary tree, are often found incidentally, and commonly seen in patients with underlying chronic liver disease and/or portal hypertension (272,278,279). IPNB is 1 of 3 preinvasive biliary lesions: biliary intraepithelial neoplasia, IPNB, and MCN-L.

Intraductal papillary neoplasm is a precursor to CCA and is analogous to intraductal papillary mucinous neoplasm of the pancreas, except located in bile ducts and has a much higher rate of malignant transformation, because 40%–80% of IPNB can harbor malignancy. Risk factors for IPNB include hepatolithiasis, clonorchiasis, primary sclerosing cholangitis, choledochal cysts, familial adenomatous polyposis, and Gardner syndrome (280). Median age at presentation is 60–66 years with a male-to-female ratio of 2:1. Symptoms include recurrent abdominal pain, cholangitis, and jaundice (281). Imaging can vary and depends on the size and morphology of the intraductal mass, degree of mucin secretion, and tumor location. There are 4 morphologic subtypes including an intraductal mass with proximal duct dilatation, diffuse ductal dilatation without a visible mass, intraductal mass with both proximal and distal dilatation, and focal aneurysmal dilatation of the duct with a cystic and solid intraductal mass (261) (Figure 14). Treatment is surgical resection of the bile duct with or without associated hepatectomy depending on size, extent, and invasiveness of the lesion (282,283). Imaging surveillance is recommended even after resection because of the high rate of undetected lesions remote from the main tumor, which are a source of recurrence.

Key concepts

47. Biliary hamartomas and peribiliary cysts are benign malformations and do not require surveillance imaging.
48. Intraductal papillary neoplasm of the bile ducts are premalignant biliary lesions with a high risk of malignant transformation, and thus, continued surveillance imaging is recommended even after surgical resection.

Intrahepatic choledochal cysts

Choledochal cysts are rare cystic dilatations of the intrahepatic and/or extrahepatic bile ducts, more frequently seen in women (1:4 male-to-female ratio) and more common in Asian populations compared with other ethnicities (284–288). They present predominantly in the first decade of life (80%), although incidence seems to be rising in adults. They are believed to arise from the reflux of pancreatic enzymes into the biliary tree through an anomalous pancreaticobiliary junction (APBJ) (289).

They are classified according to the Todani classification system, which is based on anatomic findings and extent of biliary involvement (290) (Figure 15). Type I cysts appear as cystic or fusiform dilation of the extrahepatic bile duct and are the most commonly seen choledochal cysts in both children and adults. Type II cysts are seen as extrahepatic (supraduodenal) diverticulum, whereas type III cysts present as intraduodenal diverticulum (choledochocoele). Unlike the others, type III cysts lack the female predominance and rarely have risk of malignant transformation. Type IV cysts appear as both extrahepatic and intrahepatic cystic dilations (type IVA) or multiple extrahepatic dilations (IVB) and are the second most common type of

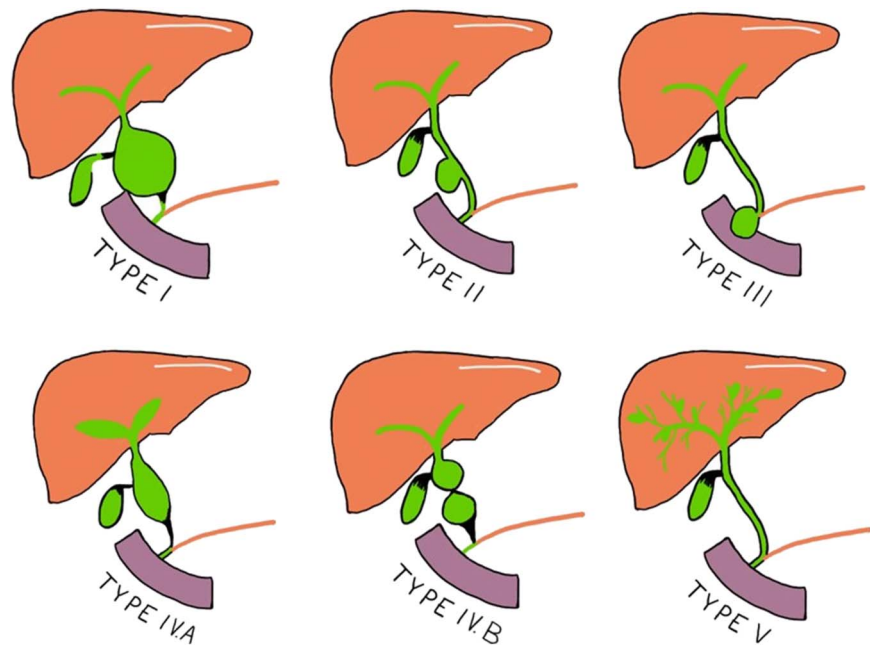


Figure 15. Todani classification of bile duct cysts.

choledochal cysts. Type V cysts (Caroli disease) involve only the intrahepatic bile ducts and are the least common type. It is important to distinguish Caroli disease from Caroli syndrome, which encompasses congenital liver fibrosis and kidney cysts in addition to type V biliary dilatations.

MRI with magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic cholangiography are the best imaging modalities to evaluate for this, although MRCP may offer the advantage of detecting an APBJ and does not contaminate the biliary tree with instrumentation. Key features on MRI with MRCP include abnormalities of the intrahepatic and/or extrahepatic bile ducts as mentioned above. One key feature distinguishing biliary ductal dilatation as a choledochal cyst from malignancy causing obstruction is that malignancy usually results in diffuse intrahepatic biliary ductal dilation as opposed to more focal areas of intrahepatic biliary ductal dilation (291).

The most common symptom in both children and adults is abdominal pain (60%) (285). The classic triad of abdominal pain, jaundice, and palpable abdominal mass is rarely seen. Other common symptoms include pancreatitis, nausea and vomiting, right upper-quadrant pain, infectious complications, and jaundice (285,292).

Management and treatment of choledochal cysts will be based on symptomatology, type of cyst, risk of malignancy, and extent of operation. The estimated risk of malignancy ranges from 7.5% to 30%, with low rates in young children (<1%) and increases significantly with each decade (30%–40% risk in those older than 50 years) (293,294). The most common malignancy is CCA (~70%), followed by gallbladder cancer (23.5%) (294). Type I or IV choledochal cysts are most commonly associated with malignancy, whereas malignant transformation is extremely rare in type II or III cysts. The presence of APBJ also seems to increase the risk of malignancy (295).

Table 7. World Health Organization-Informal Working Group on Echinococcosis classification of the hydatid cyst

Classification	Echographic aspect of cyst	Stage	Treatment
CE 1	Univesicular fluid collection/simple cyst	Active	<5 cm: albendazole >5 cm: PAIR + albendazole
CE 2	Multivesicular fluid collection with multiple daughter cysts or septae (honeycomb)	Active	Catheterization or surgery + albendazole
CE 3A	Fluid collection with membrane detached (water lily sign)	Transitional	<5 cm: albendazole >5 cm: PAIR + albendazole
CE 3B	Daughter cysts in solid matrix	Transitional	Catheterization or surgery + albendazole
CE 4	Cysts with heterogeneous matrix, no daughter cysts (“wool clew” aspect)	Inactive/degenerative	Watch and wait
CE 5	Solid matrix with calcified wall	Inactive/degenerative	Watch and wait

CE, cystic echinococcosis; PAIR, puncture, aspiration, injection of scolicidal agent, and reaspiration.

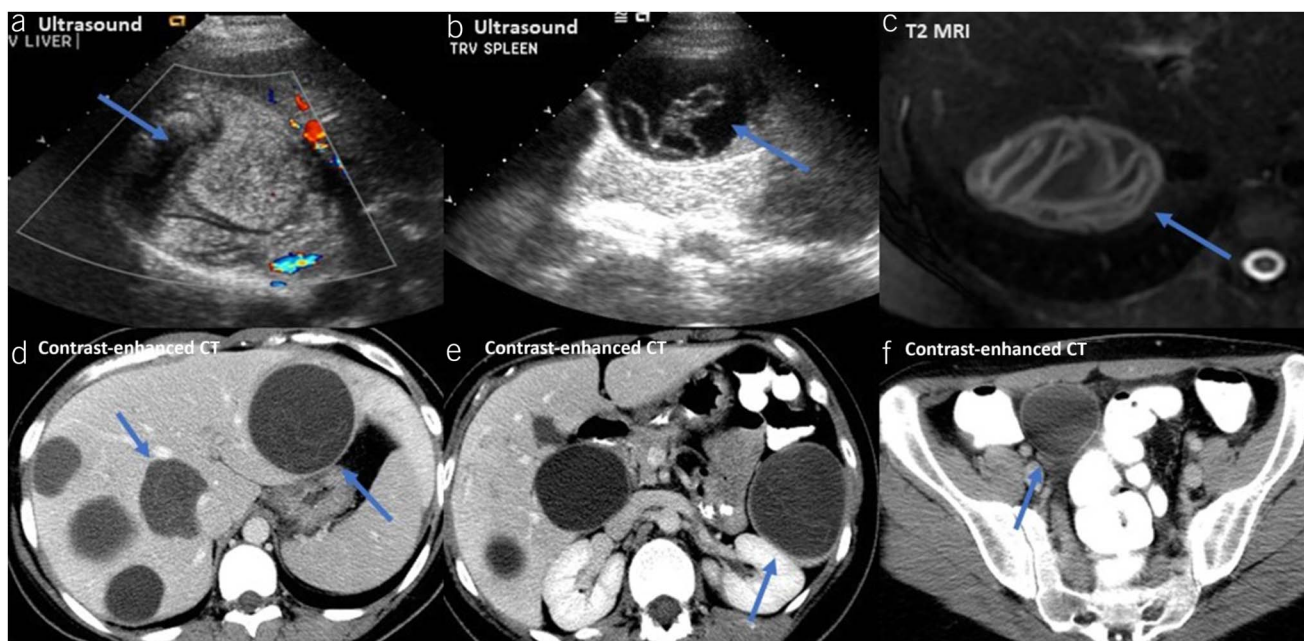


Figure 16. Echinococcal cyst. A 38-year-old man with an echogenic lesion within the liver with acoustic through transmission and septations within it (a). Anechoic lesion with through transmission and intraluminal membranes within the spleen (b). T2-weighted MRI demonstrates a cyst with floating intraluminal membranes (the waterlily sign) (c). Portal venous phase CT at multiple levels in the abdomen and pelvis reveals multiple cysts in the liver (d) with thin membranes within the cysts, lesion in the spleen (e), and peritoneum (f). CT, computed tomography; MRI, magnetic resonance imaging.

Patients with type I cysts should undergo complete cyst excision with Roux-en-Y hepaticoenterostomy. Type II cysts can undergo simple cyst excision or diverticulectomy, whereas type III cysts can be managed endoscopically by unroofing (either undergo endoscopic or transduodenal sphincteroplasty) or transduodenal excision for larger cysts (285,296). Type IV cysts are managed based on extent of intrahepatic disease and can undergo extrahepatic cyst excision with or without partial hepatectomy and hepaticoenterostomy and rarely require liver transplantation (297,298). Finally, in patients with type V cysts or Caroli disease, hepatic resection or, in select cases, liver transplantation may be necessary based on the extent of disease (299). We suggest that patients with type I and IV cysts should continue to undergo surveillance even after cyst resection because of the ongoing risk of malignancy (285).

Key concepts

- 49a. Management and treatment of choledochal cysts is based on type of cyst and risk of malignant transformation.
- 49b. Type I or IV choledochal cysts are most commonly associated with malignancy and should undergo surveillance imaging, although a specific interval cannot be recommended.
50. In both type IV and V choledochal cysts, when resection is not feasible, liver transplantation should be considered.

Hydatid/echinococcal cysts

Cystic echinococcosis or hydatid cysts are caused by an endemic helminthic disease caused by *Echinococcus granulosus* infection. Echinococcus infection is most commonly seen in rural sheep grazing areas and has a wide geographical distribution but is typically seen in South America, Eastern Europe, Russia, Middle East, Central Asia, China, Australia, and East Africa (300).

Humans serve as accidental intermediate hosts when they consume contaminated foods, water, or soil with *Echinococcus* eggs or eat organ meat from infected animals such as sheep or cows (206). The eggs hatch in the small intestine of the human host and releases a 6-hooked oncosphere, which penetrates the intestinal wall and migrates into the portal venous system and into various organs including the liver and lungs. The oncospheres develop into a thin-walled, unilocular, fluid-filled cyst. The cysts often grow slowly, usually over many years, and can grow up to 10–15 cm in diameter. Cysts most commonly occur in the liver (70%) or lungs (20%) and the remainder in other organs including spleen, heart, kidney, or brain (301). The cysts have an inner germinal layer surrounding a fluid-filled central hydatid cavity and an outer, acellular laminated layer. As the cyst enlarges, it forms a combination of protoscolices (future heads of adult worms) and daughter cysts; larger cysts may have over a liter of highly antigenic fluid and millions of protoscolices (301,302). They are often high pressured because of increased fluid production with a tendency to rupture after trauma or surgical manipulation (206).

Cysts are often asymptomatic given their slow growth. Larger cysts can cause abdominal discomfort and pain based on size and location including compression of bile ducts, leading to obstructive jaundice or cholangitis. Cyst rupture or leak can lead to abdominal pain, severe allergic reactions or anaphylaxis causing peritonitis, ascites, and septic shock. Management of hydatid cysts varies based on cyst characteristics (size, location, and number), clinical presentation, and center expertise (303).

Hydatid cysts can have varying imaging appearances. The WHO-Infomal Working Group on Echinococcosis classification details the characteristics of the cysts for staging purposes based on ultrasound features, which helps guide treatment options (304–306) (Table 7). In the initial phase of disease, hydatid cysts appear as anechoic well-defined cysts, often with small internal

echogenic foci floating within the cyst on ultrasound. In this phase, CT reveals an anechoic fluid-attenuating lesion, and MRI reveals a T2 homogeneous hyperintense, T1-hypointense non-enhancing cystic lesion. As the active phase of disease continues, the imaging appearance can vary. On ultrasound, there is often a septated cyst with internal daughter cysts. On MRI, the cyst may demonstrate intermediate T1 signal if there is internal proteinaceous debris, and the walls and septations may enhance on postcontrast imaging. The “water-lily” sign is a classic imaging feature of floating internal membranes secondary to a detached endocyst (307). Finally, the inactive phase of hydatid cysts can show a densely calcified cystic lesion, with rim calcification or internal calcifications within the septations (Figure 16). Although the diagnosis of hydatid cysts is based on imaging, serologic testing can be useful; however, these tests are often limited by laboratory availability and heterogeneity of the varying assays (308,309).

Medical therapy consists of chemotherapy with antihelminthic drugs, albendazole or mebendazole, with studies indicating the former as the superior agent (304,310). Medical therapy is indicated before surgery or cyst puncture to prevent risk of recurrence, secondary seeding, or to decrease cyst pressure or in inoperable cases (i.e., multiple cysts and peritoneal involvement or poor surgical candidate) (301,304). Furthermore, the risk of anaphylaxis with percutaneous drainage can be mitigated by initiating medical therapy first. The exact duration of medical treatment before and after surgical or percutaneous therapy varies according to experts. In general, it is recommended that medical therapy be started before the above procedures and continued for 1–6 months afterward. Asymptomatic, inactive, or calcified cysts can be observed with surveillance imaging, although this is not required in all cases. Medical therapy alone is not recommended unless percutaneous aspiration or surgery is contraindicated; a large systematic review showed that >40% of hydatid cysts remain active or reactivate after 2 years of medical monotherapy (303). An important change in medical therapy is that cyclical regimens are no longer recommended, given the parasitostatic activity of these drugs and overall safety data (306). It is important to remember the side effects of albendazole including hepatic dysfunction and agranulocytosis, and patients should be monitored regularly with white cell counts and liver function tests.

Percutaneous or surgical approaches are recommended for large cysts (>5 cm), cysts that are likely to rupture, cysts that have not previously responded to medical therapy, or in patients with contraindications to medical therapy (including those with liver or bone marrow disorders) (303). Puncture, aspiration, injection of scolical agent, and reaspiration with adjunct antihelminthic therapy is an effective alternative to surgery (311–314). However, it is contraindicated in patients with biliary fistulas or cysts communicating with the biliary tree, in patients with complex, multiseptated cysts or percutaneously inaccessible cysts. Surgical approach is with the goal of cyst removal and obliteration of the cavity and methods may vary based on cyst characteristics from simple cyst resection to radical pericystectomy (304,315–317). Hepatic resection may be warranted in some instances to remove all the hydatid disease (202). There is a lack of prospective randomized trials to compare long-term data of surgical vs medical management. It is important that the treatment of hydatid cysts occurs in centers with clinical expertise where multimodal and multidisciplinary team management including surgical and infectious disease expertise are readily available.

Key concepts

- 51a. Medical therapy of hydatid cysts with antihelminthic drugs is indicated before surgery or cyst puncture in patients with symptomatic or active hydatid cysts to prevent risk of recurrence, secondary seeding, or to decrease cyst pressure or in inoperable cases.
- 51b. Medical therapy alone is not recommended because of ineffective treatment unless percutaneous aspiration or surgery is contraindicated.

Recommendations

- 17. We suggest surgical management in patients with complicated hydatid cysts (i.e., those with biliary fistulas or cysts communicating with the biliary tree, multiseptated cysts, rupture or hemorrhage, secondary infection, or percutaneously inaccessible cysts) provided there is no contraindication to surgery (conditional recommendation, very low level of evidence).
- 18. In patients with uncomplicated hydatid cysts in whom surgery is not an option, we suggest percutaneous treatment with puncture, aspiration, injection of scolical agent, and reaspiration with adjunct antihelminthic therapy (conditional recommendation, low level of evidence).

CONCLUSIONS AND FUTURE DIRECTIONS

FLLs continue to be a frequent source of concern for providers and patients alike, and detection will likely continue to rise in incidence as an increasing volume of radiographic imaging studies are being performed. Many FLLs are benign, but it is important to understand indications for further workup, including multidisciplinary discussion, biopsy, and need for surveillance imaging to ensure that a malignancy is not missed. The clinical history, physical examination, underlying comorbidities, and laboratory workup are an important part of the evaluation of these patients, which, when combined with improved diagnostic imaging, can frequently lead to a diagnosis without the need for biopsy.

The application of artificial intelligence (AI) is being studied in many areas of medicine, including radiographic diagnostics. The detection and classification of FLLs have been studied with AI applications, deep learning systems, and neural networks, and early work seems promising for the ability of AI to aid in the differential diagnosis of FLL (318). However, AI cannot replace healthcare professionals, who can integrate the imaging characteristics and the patient history to make the diagnosis. Despite the radiographic results, patients will continue to rely on their providers to make the best recommendations for ongoing care, which in the ideal scenario is the reassurance that no further follow-up is required, especially in patients without underlying comorbidities.

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CONFLICTS OF INTEREST

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