Hepatocellular adenoma

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INTRODUCTION

Hepatocellular adenoma (HCA; also termed hepatic adenoma) is an uncommon solid, benign liver lesion that develops in an otherwise normal-appearing liver. Typically, HCAs are solitary and are found in young women in association with use of estrogen-containing medications. In addition, patients with glycogen storage disease or metabolic syndrome are at higher risk for developing HCA.

This topic will focus on the risk factors, clinical features, diagnosis, and management of HCA. The approach to patients with other benign, solid liver lesions is discussed separately. (See "Focal nodular hyperplasia" and "Hepatic hemangioma".)

The approach to patients with cystic liver lesions is discussed separately. (See "Diagnosis and management of cystic lesions of the liver".)

The clinical features, diagnosis and management of hepatocellular carcinoma are discussed separately:

- (See "Clinical features and diagnosis of hepatocellular carcinoma".)
- (See "Overview of treatment approaches for hepatocellular carcinoma".)
- (See "Surveillance for hepatocellular carcinoma in adults".)

EPIDEMIOLOGY AND RISK FACTORS

Exposure to estrogens — Use of estrogens (eg, oral contraceptives [OC]) is a risk factor for developing HCA. The annual incidence of HCA in users of OCs is approximately 30 to 40 cases per million OC users in comparison with one case per million nonusers [1,2]. Observational studies have demonstrated a dose-dependent association between estrogen therapy and developing HCA [1,3,4]. Cases of HCA were rarely reported before the advent of OCs in the 1960s [5]. The introduction of low-dose estrogen contraceptives may have reduced the incidence of HCA, although there have been no large epidemiologic studies [6,7]. Finally, HCA regression has been observed after discontinuation of OCs with recurrence during drug rechallenge or pregnancy [1,8-11].

Anabolic androgen use — The development of HCA has been associated with the use of anabolic androgenic steroids for the treatment of aplastic anemia, Fanconi anemia, hereditary angioedema, and for muscle mass development in body builders [12-15]. (See "Management and prognosis of Fanconi anemia", section on 'Androgens'.)

Genetic syndromes — Genetic syndromes including glycogen storage diseases (GSD) and familial adenomatous polyposis are associated with HCA. The lifetime incidence of HCA is up to 75 percent in patients with GSD type Ia, and HCAs are more common in males with GSD who typically have multiple lesions [16-18]. (See 'Multiple hepatocellular adenomas' below.)

The mechanism by which GSD promotes the development of HCA is unknown. (See "Overview of inherited disorders of glucose and glycogen metabolism".)

Obesity and metabolic syndrome — Obesity and metabolic syndrome are associated with the development of HCA, particularly in men [19-21]. The mechanism by which obesity and metabolic syndrome may increase an individual's risk for developing HCA is unclear. (See "Metabolic syndrome (insulin resistance syndrome or syndrome X)".)

PATHOLOGIC FEATURES

HCAs are typically solitary lesions with a clear margin, and size ranges from a few millimeters to several centimeters. HCAs with pedunculated morphology are seen less frequently [22]. Lesions are often located in the right lobe of the liver, and they are soft and smooth with a tan appearance (picture 1). Complications such as hemorrhage and necrosis occur because the hepatic sinusoids are supplied by a prominent arterial system, and the lack of a fibrous capsule contributes to lesion rupture and free intraperitoneal bleeding.

Microscopically, HCAs are composed of large plates of adenoma cells, which are typically larger than normal hepatocytes and contain glycogen and lipid (picture 2). The nuclei are small and

regular, and mitoses are almost never seen. The adenoma cells are arranged in normal or thickened trabeculae interspersed with prominent arteries and thin-walled blood vessels and sinusoids. A small number of Kupffer cells may also be present. There is notable absence of normal hepatic architecture (ie portal tracts, bile ductules), and this feature helps distinguish HCA from focal nodular hyperplasia [23]. (See 'Differential diagnosis' below and "Hepatic hemangioma", section on 'Differential diagnosis'.)

However, inflammatory HCA is an exception because it does contain ductular structures [24]. (See 'Classification' below.)

CLASSIFICATION

HCA can be classified on the basis of genotypic and phenotypic features, and while all subtypes show arterial phase enhancement on magnetic resonance imaging (MRI), the enhancement patterns in the subsequent phases vary by lesion subtype [25-28]. If the subtype cannot be determined on the basis of MRI, a biopsy may be helpful for identifying the subtype based on histology. However, lesion biopsy is not frequently performed for this purpose in clinical practice. (See 'Diagnostic approach' below.)

The HCA subtypes are [22,25,29,30]:

- **HCA with hepatocyte nuclear factor (HNF)-1 alpha mutation** – HCAs with HNF-1 alpha mutation occur almost exclusively in women, comprise 35 to 50 percent of HCAs, and are characterized by diffuse steatosis and a lack of cytologic abnormalities or inflammatory infiltrates. On MRI, HCAs with HNF-1 alpha mutation demonstrate moderate arterial enhancement that does not extend into the portal venous phase. This subtype is associated with a low risk of complications for lesions <5 cm.

- **Inflammatory HCA** – Inflammatory HCA are predominantly seen in women and comprise 40 to 55 percent of HCAs. The histologic appearance is characterized by inflammatory infiltrates, sinusoidal dilation, tortuous blood vessels, and hemorrhage. MRI demonstrates intense arterial enhancement persisting into the portal venous and delayed phases.

- **HCA with beta-catenin activation** – HCA with beta-catenin activation are observed less often than the other subtypes (10 to 15 percent of patients) and are more frequently found in males. They are associated with use of androgens and display no specific characteristic features on contrast-enhanced, multiphasic MRI [22,25]. Morphologically, the beta-catenin subtype is characterized by cellular atypia, cholestasis, and pseudoglandular formation [31].

HCAs with mutations in beta-catenin are associated with increased risk for malignant transformation. In a series of 96 patients with HCA, HCAs associated with hepatocellular carcinoma (or having histologic features bordering on hepatocellular carcinoma) were observed almost exclusively in the beta-catenin group [25].

CLINICAL FEATURES

Patterns of clinical presentation — The spectrum of presentation of HCA ranges from asymptomatic individuals with incidental imaging findings to patients with acute, life-threatening hemorrhage resulting from adenoma rupture and intraabdominal bleeding [32]. Most HCAs are seen in women of reproductive age who have a history of oral contraceptive (OC) use [33]. (See 'Exposure to estrogens' above.)

When symptoms are present, the most common symptom is episodic abdominal pain that may be localized to the epigastrium or right upper quadrant and may reflect an enlarged liver, bleeding into the lesion, or necrosis [34]. The development of sudden, severe pain associated with hypotension reflects rupture into the peritoneum, an event associated with a mortality of up to 20 percent if not identified and treated emergently [17,35,36]. (See 'Bleeding' below.)

Physical examination may be normal or may demonstrate an abdominal mass (up to 30 percent of patients) or hepatomegaly (in approximately 25 percent of patients) [37]. Jaundice is rare but has been described and may reflect compression of the intrahepatic bile ducts by the lesion [38,39].

Laboratory studies — Liver biochemical and function test abnormalities are uncommon but may occur in patients with a large (>5 cm) HCA including elevated alkaline phosphatase and gamma-glutamyl transpeptidase (GGT), particularly in patients with HCA complicated by bleeding or more than one lesion. Serum biomarkers of inflammation (eg, C-reactive protein) are usually increased, particularly in patients with inflammatory HCA [40]. Alpha fetoprotein (AFP) is normal in patients with HCA in the absence of malignant transformation. (See 'Malignant transformation' below.)

Imaging studies — The imaging appearance of HCA depends on the specific imaging modality, use of contrast enhancement and multiphasic techniques, lesion size, lesion subtype, and presence of hemorrhage or necrosis [22]:

- Ultrasound – On noncontrast ultrasound, the appearance of HCA is often nonspecific. HCA may appear well-demarcated and hyperechoic because of the high lipid content of hepatocytes, but can also be heterogeneous because of intralesional bleeding. Bleeding

may also appear as calcification, while lesion necrosis may appear as hyperechoic areas with acoustic shadows [41]. Doppler studies can demonstrate intralesional vessels in the absence of a central arterial signal [42].

Contrast-enhanced ultrasound (CEUS) of HCA typically shows rapid arterial hyperenhancement that progresses from the periphery to the center. In the late phase, there is gradual washout due to missing portal veins. The use of CEUS for evaluating liver lesions is discussed separately. (See "Contrast-enhanced ultrasound for the evaluation of liver lesions", section on 'Findings associated with specific lesions'.)

- Computed tomography (CT) – On noncontrast-enhanced CT of the liver, HCAs are typically well-demarcated and have low attenuation or are isodense. On contrast-enhanced, multiphase (arterial and venous) CT, the lesion may demonstrate peripheral enhancement during the early phase with subsequent centripetal flow during the portal venous phase, which is characteristic of HCA [43]. During the late phase of the contrast-enhanced CT, the lesion may become isodense and then hypodense (image 1). In addition, HCAs often have areas of hemorrhage, necrosis, or fibrosis, giving them a heterogeneous appearance. HCA with recent bleeding appears as a high-attenuating lesion.

- Magnetic resonance imaging (MRI) – HCAs are usually well-demarcated on contrast-enhanced MRI because of the fat or glycogen content of the hepatocytes [44,45]. HCAs show arterial phase enhancement on MRI, while enhancement patterns in the subsequent phases vary depending upon the lesion subtype. (See 'Classification' above.)

  MRI using gadolinium-based contrast and multiphasic enhancement can help differentiate between HCA from other solid liver lesions (eg, focal nodular hyperplasia), and the use of gadolinium-based magnetic resonance (MR) contrast agents for evaluating liver lesions is discussed separately [46]. (See "Patient evaluation before gadolinium contrast administration for magnetic resonance imaging".)

DIAGNOSTIC APPROACH

The diagnosis of HCA may be suspected in a patient without cirrhosis who is found to have a solid liver lesion on imaging. If the diagnosis is suspected based on ultrasound or computed tomography (CT) findings, contrast-enhanced, cross-sectional imaging using multiphase magnetic resonance imaging (MRI) is performed. The general approach to incidental liver lesions identified by ultrasound or CT is discussed separately. (See "Approach to the adult patient with an incidental solid liver lesion".)

The diagnostic approach depends on whether the patient is female or male:

- For female patients, the diagnosis of HCA is made with contrast-enhanced, cross-sectional imaging using multiphase MRI [22,47]. (See 'Imaging studies' above.)

  Core needle biopsy or fine needle aspiration of the lesion is usually not indicated because the tissue obtained is frequently insufficient to establish a diagnosis and because HCA may be difficult to distinguish microscopically from normal hepatocytes.

- For male patients, the diagnosis is made with cross-sectional, contrast-enhanced imaging using multiphase MRI and is generally confirmed with histology obtained at the time of surgical resection. (See 'Male patients' below.)

DIFFERENTIAL DIAGNOSIS

If cross–sectional imaging of the liver lesion is not specific, additional evaluation for an alternative diagnosis may be required. The differential diagnosis includes:

- **Focal nodular hyperplasia** – Although contrast-enhanced multiphasic imaging (ie, magnetic resonance imaging [MRI]) can often distinguish between focal nodular hyperplasia and HCA, further evaluation and/or intervention (eg, surgical resection) may be required for definitive diagnosis. (See "Focal nodular hyperplasia".)

- **Hepatocellular carcinoma** – HCA with beta-catenin activation are not characterized by any specific features on contrast-enhanced MRI and may mimic hepatocellular carcinoma with arterial enhancement and portal venous washout; however, patients with hepatocellular carcinoma often have history of cirrhosis. The risk factors for and diagnosis of hepatocellular carcinoma are discussed in detail separately. (See "Clinical features and diagnosis of hepatocellular carcinoma" and "Surveillance for hepatocellular carcinoma in adults", section on 'High-risk groups'.)

- **Metastatic disease** – Metastases to the liver are a likely cause of a solid liver lesion in patients with a history of extrahepatic malignancy. In such patients, the evaluation should start with imaging to search for metastatic disease in other organs, and this is discussed separately. (See "Approach to the adult patient with an incidental solid liver lesion".)

MANAGEMENT

Management of HCA depends upon the presence of symptoms, patient sex, lesion size, and pattern of lesion progression.

General measures for all patients — General measures for patients with HCA include (see 'Epidemiology and risk factors' above and "Management of nonalcoholic fatty liver disease in adults", section on 'Weight loss'):

- Discontinue and avoid estrogen-containing medications (eg, oral contraceptives [OCs]). Regression of HCA ≤5 cm has been observed after discontinuing OCs [8,48].
- Maintain an ideal body weight, including diet modification and exercise for patients with body mass index (BMI) >25 kg/m^2 [31]. Lifestyle interventions to promote weight loss are discussed separately. (See "Obesity in adults: Overview of management".)

Asymptomatic women with lesions ≤5 cm — We observe asymptomatic women with HCA ≤5 cm and perform surveillance contrast-enhanced magnetic resonance imaging (MRI) in six months (algorithm 1). (See 'General measures for all patients' above.)

If the lesion's size does not increase on surveillance imaging at six months, we typically obtain contrast-enhanced MRI in one year and then annually thereafter. However, if the lesion appears to be growing (ie, ≥20 percent increase in diameter) or if the lesion becomes >5 cm, intervention (eg, surgical resection) is typically performed because of the risk of hemorrhage with larger lesions [31,49]. (See 'Women with symptoms or lesions >5 cm' below.)

In an observational study of 32 women with HCA <5 cm who were managed with observation, no patients had increase in lesion size, bleeding, or malignant degeneration after a median follow-up interval of two years [50].

Women with symptoms or lesions >5 cm — For most women who have symptoms attributable to the lesion (eg, persistent abdominal pain) or who have a lesion >5 cm in size, surgical resection with minimal margins is typically performed because larger lesions are associated with higher bleeding risk (algorithm 1) [34]. (See 'Bleeding' below.)

Surgical resection of the liver and complications of liver resection are discussed separately. (See "Overview of hepatic resection".)

For asymptomatic women with lesions >5 cm in the setting of OC use, discontinuing OC and obtaining follow-up contrast-enhanced MRI in 6 to 12 months is a reasonable option. If the lesion remains >5 cm or if symptoms develop, surgical resection is typically performed.

If the patient does not desire or is not a candidate for operative management, alternative management strategies include nonsurgical intervention or observation with imaging surveillance:

- **Transarterial embolization (TAE)** – TAE has been used primarily for HCA complicated by bleeding, but TAE can also be used as an elective intervention for patients with symptomatic or large (>5 cm) lesions. TAE is associated with lesion regression. In a systematic review of 40 studies, including 851 patients with HCA, TAE was performed in 151 patients (17 percent), and surgical resection was avoided in 68 of these patients (45 percent). Lesion regression was seen in 75 percent of cases, and complete resolution was seen in 10 percent of cases [51]. (See 'Management' below.)

- **Radiofrequency ablation** – Radiofrequency ablation is a nonoperative intervention for symptomatic HCAs that are <3 cm; however, many patients require multiple treatment sessions to achieve complete ablation [52,53]. Radiofrequency ablation for other liver lesions (hepatocellular carcinoma) is discussed separately. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation", section on 'RFA'.)

- **Observation and surveillance** – While most patients with symptomatic lesions or lesions >5 cm (in the absence of estrogen-containing medications) undergo procedural intervention, some patients prefer an initial period of observation and surveillance. For these patients, we obtain repeat contrast-enhanced MRI of the liver in 6 to 12 months, and if the lesion has not regressed to ≤5 cm, either surgical resection or TAE is performed.

  Limited data suggest that some lesions >5 cm will regress without intervention. In an observational study of 86 patients with HCA >5 cm who were observed without intervention, surveillance imaging demonstrated that 15 percent of the lesions regressed to <5 cm after six months, 25 percent of the lesions regressed after one year, and approximately 60 percent of the lesions regressed after two years. [54].

Male patients — Male patients who are found to have HCA should undergo surgical resection, irrespective of the size of the lesion because of an increased risk of malignant transformation and risks associated with development of hepatocellular carcinoma [31,55]. (See "Overview of treatment approaches for hepatocellular carcinoma".)

This approach is consistent with guidelines from the European Association for Study of the Liver (EASL) that advocate for resection of HCA in males regardless of the size of the tumor or molecular classification [31]. In a cohort study of 218 patients with HCA, the rate of malignant transformation was higher in males compared with females (47 versus 4 percent) [55]. In a

study including 20 males with HCA without malignant features based on expert pathologist review, special staining, and next generation sequencing, 15 patients had treatment with curative intent (eg, surgical resection, liver transplantation). None of the patients in this cohort had HCA recurrence or tumor-related death after a mean of 45 months [56]. These data suggest that a subgroup of males with low risk for malignant transformation may exist. However, caution should be used in interpreting these findings due to small sample size, the possibility of biopsy sampling error, and the need for expert review and immunohistochemical testing that may not be routinely available.

COMPLICATIONS

Bleeding

Incidence and risk factors — The risk of bleeding is difficult to establish since incidence estimates have been derived mostly from studies of predominantly symptomatic patients in whom the risk of bleeding ranges from 25 to 64 percent [57,58]. Risk factors for bleeding include larger lesion size (>5 cm), recent hormone use, pregnancy, exophytic morphology, and inflammatory subtype [57-59]. (See 'Pathologic features' above and 'Classification' above.)

Clinical presentation — Patients with HCA complicated by bleeding may present with severe abdominal pain with or without hemodynamic instability [36,60]. Bleeding related to HCA is often confined to the lesion, but in some cases, bleeding may lead to lesion rupture resulting in hypotension and acute hemoperitoneum [22]. Computed tomography (CT) is typically performed if bleeding is suspected because CT images can be obtained quickly to confirm lesion hemorrhage and to facilitate management.

Management — Therapeutic interventions for HCA complicated by hemorrhage include emergent surgical resection, transarterial embolization (TAE) with or without subsequent surgery, or supportive care alone with subsequent surgery. Selection of initial therapy depends on severity of bleeding, the hemodynamic status of the patient, local expertise, and clinician preference. Subsequent therapy depends on lesion residual or recurrence following initial treatment (eg, TAE).

Management typically requires a multidisciplinary approach (ie, critical care medicine, hepatobiliary surgery, interventional radiology) [34,58,60].

We perform TAE as the initial therapy for most patients with HCA complicated by bleeding and then monitor the patient for residual or recurrent HCA with imaging studies. Patients who

undergo TAE may develop abdominal pain and/or fever within 24 hours after the procedure, but symptoms usually resolve within one week [22].

After approximately six months following TAE (when the postprocedure hematoma has been resorbed), we perform follow-up imaging with contrast-enhanced magnetic resonance imaging (MRI). Most patients with any residual HCA on imaging are referred for elective surgical resection [34,61,62]. For patients who have no residual lesion, monitoring for recurrence with surveillance imaging (ie, contrast-enhanced MRI) is performed in six months and then annually thereafter [22].

TAE for liver tumors such as hepatocellular carcinoma is discussed separately. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates not eligible for local thermal ablation", section on 'Arterial embolization'.)

For patients with bleeding HCA, TAE is preferred for initial intervention because emergency surgery is associated with greater blood loss and complication risk compared with delayed resection [17,34,58,62]. In an observational study of 26 patients with HCA and bleeding, patients who underwent emergency surgery had higher blood transfusion requirements (mean number of units: 6 versus 1 unit) and had higher rates of postoperative complications (83 versus 5 percent) compared with patients who had elective surgery in three to six months after the bleeding episode [34].

In addition, for some patients, embolization of the bleeding HCA may obviate the need for subsequent surgery. In a systematic review of cohort studies including 73 patients with HCA and bleeding who were treated with TAE, 22 patients (30 percent) did not require subsequent surgical intervention [51].

Malignant transformation — The risk of malignant transformation from HCA to hepatocellular carcinoma is approximately 5 percent, and risk factors include male sex, lesion size >5 cm, and beta-catenin activation subtype [25,34,55,58]. An increase in size on sequential imaging studies should raise concern that malignant transformation has occurred. The long-term prognosis for patients with HCA with malignant transformation who undergo surgical resection is good, and recurrence is uncommon [34]. (See 'Classification' above.)

PROGNOSIS

The prognosis for patients with HCA is not well established. While some lesions may regress or resolve (particularly after discontinuation of oral contraceptives [OCs]), HCAs have been

associated with spontaneous hemorrhage and rupture and with malignant transformation. (See 'General measures for all patients' above and 'Complications' above.)

PREGNANCY

We do not advise against pregnancy for female patients with known HCA ≤5 cm who wish to conceive; however, pregnant women with HCA are managed by a multidisciplinary team including clinicians with expertise in high-risk obstetrics and hepatology.

For pregnant women with HCA, we perform imaging surveillance and intervene if the lesion becomes symptomatic or large. Specifically, we obtain liver ultrasound every 6 to 12 weeks to monitor the size of the lesion. For lesions that are growing (ie, ≥20 percent increase in diameter), large (>5 cm), or symptomatic, we generally intervene (eg, surgical resection) because of the increased risk of lesion bleeding and rupture [63,64]. Resection should ideally be performed during the second trimester, during which the risks to the mother and the fetus are minimized [65]. (See "Pregnancy in women with pre-existing chronic liver disease", section on 'Hepatocellular adenoma' and "Anesthesia for nonobstetric surgery during pregnancy".)

Pregnant women with HCA require close monitoring because of the potential for hormone-induced lesion growth and rupture; however, the majority of HCA remain stable during pregnancy [34,63]. In an observational series of 12 patients with HCA who had 17 pregnancies, no intervention was required in 14 pregnancies; two pregnancies were delivered by cesarean section at weeks 34 and 36 (because of the estimated risk of HCA rupture); and one patient underwent a radiofrequency ablation in the first trimester to prevent further lesion growth [63].

MULTIPLE HEPATOCELLULAR ADENOMAS

The presence of more than ten HCAs is referred to as multiple HCAs (also termed liver adenomatosis) and is associated with obesity, hepatic steatosis, and metabolic syndrome [19,40,66]. Our approach to managing patients with multiple HCAs is generally based on the size of the largest lesion because the risk of complications (eg, bleeding) appears to be related to the size of the largest lesion rather than the total number of lesions [31,32,34,67-69]. Patients with HCAs confined to one lobe of the liver and with at least one lesion >5 cm (or symptomatic lesions) are referred for surgical resection. For patients with disease affecting both lobes of the liver, options include surgical resection of the largest HCA while liver transplantation has been performed for treatment of liver adenomatosis [70,71]. (See 'Management' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Focal liver lesions".)

SUMMARY AND RECOMMENDATIONS

- Hepatocellular adenoma (HCA; also termed hepatic adenoma) is an uncommon, solid benign liver lesion. The spectrum of clinical presentation of HCA ranges from asymptomatic individuals with incidental imaging findings to patients with acute, life-threatening hemorrhage resulting from lesion hemorrhage, rupture, and intraabdominal bleeding. (See 'Clinical features' above.)

- HCA has been associated with the use of estrogen-containing medications or anabolic androgens; additional risk factors include obesity, metabolic syndrome, or glycogen storage disease. (See 'Epidemiology and risk factors' above.)

- HCAs are typically solitary lesions with a well-defined margin, and they range in size from a few millimeters to several centimeters. Lesions are often located in the right lobe of the liver, and they are soft and smooth with a tan appearance (picture 1). (See 'Pathologic features' above.)

- HCAs are classified on the basis of genotypic and phenotypic features, and the subtypes are (see 'Classification' above):

  - HCA with hepatocyte nuclear factor (HNF)-1 alpha mutation
  - Inflammatory HCA
  - HCA with beta-catenin activation

- To diagnose HCA, the approach depends on whether the patient is female or male (see 'Diagnostic approach' above):

  - For female patients, the diagnosis is made with contrast-enhanced, cross-sectional imaging using multiphase magnetic resonance imaging (MRI).

  - For male patients, the diagnosis is made with cross-sectional, contrast-enhanced MRI and is generally confirmed with histology obtained at the time of surgical resection.

- General measures for all patients with HCA include (see 'General measures for all patients' above):
  - Discontinue and avoid estrogen-containing medications (eg, oral contraceptives [OCs])
  - Maintain an ideal body weight, including diet modification and exercise for patients with body mass index (BMI) >25 kg/m^2
- For asymptomatic women with HCA ≤5 cm, we suggest surveillance imaging rather than procedural intervention because the risk of bleeding or malignant transformation is low (**Grade 2C**). We perform contrast-enhanced MRI in six months and monitor for symptoms. If the lesion is growing or symptomatic, we proceed with procedural intervention. (See 'Asymptomatic women with lesions ≤5 cm' above.)
- For most women with HCA >5 cm or with a symptomatic lesion, we suggest surgical resection over other procedural interventions because such lesions are more likely to bleed (algorithm 1) (**Grade 2C**). Transarterial embolization (TAE) is an alternative intervention, while observation with imaging surveillance is also an option. (See 'Women with symptoms or lesions >5 cm' above.)

  For asymptomatic women with lesions >5 cm in the setting of OCs, discontinuing OC and performing surveillance contrast-enhanced MRI in 6 to 12 months is an acceptable alternative.
- For male patients with HCA of any size, we suggest surgical resection rather than surveillance because of the risk of malignant transformation and the risks associated with hepatocellular carcinoma (**Grade 2C**). (See 'Male patients' above.)
- The prognosis for patients with HCA is not well established. While some lesions may regress or resolve (particularly after discontinuation of OCs), HCAs have been associated with spontaneous hemorrhage and rupture or malignant transformation. (See 'Complications' above.)
- We do not advise against pregnancy for female patients with HCA ≤5 cm who wish to conceive; however, pregnant women with HCA are managed by a multidisciplinary team including clinicians with expertise in high-risk obstetrics and hepatology. We typically monitor pregnant women with HCA by performing noncontrast liver ultrasound every 6 to 12 weeks. (See 'Pregnancy' above.)

REFERENCES

1. Rooks JB, Ory HW, Ishak KG, et al. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. JAMA 1979; 242:644.
2. Reddy KR, Schiff ER. Approach to a liver mass. Semin Liver Dis 1993; 13:423.
3. Rosenberg L. The risk of liver neoplasia in relation to combined oral contraceptive use. Contraception 1991; 43:643.
4. Giannitrapani L, Soresi M, La Spada E, et al. Sex hormones and risk of liver tumor. Ann N Y Acad Sci 2006; 1089:228.
5. Edmondson HA. Tumors of the liver and intrahepatic bile ducts. In: Atlas of tumor patholog y, Edmondson HA (Ed), Armed Forces Institute of Pathology, Washington, D.C. 1958. Vol Fas cicle 25.
6. Cherqui D, Rahmouni A, Charlotte F, et al. Management of focal nodular hyperplasia and hepatocellular adenoma in young women: a series of 41 patients with clinical, radiological, and pathological correlations. Hepatology 1995; 22:1674.
7. Benhamou JP. Diagnostic approach to a liver mass: diagnosis of an asymptomatic liver tumor in a young woman. J Hepatol 1996; 25 Suppl 1:30.
8. Edmondson HA, Reynolds TB, Henderson B, Benton B. Regression of liver cell adenomas associated with oral contraceptives. Ann Intern Med 1977; 86:180.
9. Kawakatsu M, Vilgrain V, Erlinger S, Nahum H. Disappearance of liver cell adenoma: CT and MR imaging. Abdom Imaging 1997; 22:274.
10. Aseni P, Sansalone CV, Sammartino C, et al. Rapid disappearance of hepatic adenoma after contraceptive withdrawal. J Clin Gastroenterol 2001; 33:234.
11. Norris S. Drug- and Toxin-Induced Liver Injury. In: Comprehensive Clinical Hepatology, O'Gr ady J, Lake J, Howdle P (Eds), Harcourt Publishers Limited, London 2000. p.1.
12. Nakao A, Sakagami K, Nakata Y, et al. Multiple hepatic adenomas caused by long-term administration of androgenic steroids for aplastic anemia in association with familial adenomatous polyposis. J Gastroenterol 2000; 35:557.
13. Resnick MB, Kozakewich HP, Perez-Atayde AR. Hepatic adenoma in the pediatric age group. Clinicopathological observations and assessment of cell proliferative activity. Am J Surg Pathol 1995; 19:1181.
14. Velazquez I, Alter BP. Androgens and liver tumors: Fanconi's anemia and non-Fanconi's conditions. Am J Hematol 2004; 77:257.
15. Socas L, Zumbado M, Pérez-Luzardo O, et al. Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of

the literature. Br J Sports Med 2005; 39:e27.

16. Labrune P, Trioche P, Duvaltier I, et al. Hepatocellular adenomas in glycogen storage disease type I and III: a series of 43 patients and review of the literature. J Pediatr Gastroenterol Nutr 1997; 24:276.
17. Leese T, Farges O, Bismuth H. Liver cell adenomas. A 12-year surgical experience from a specialist hepato-biliary unit. Ann Surg 1988; 208:558.
18. Talente GM, Coleman RA, Alter C, et al. Glycogen storage disease in adults. Ann Intern Med 1994; 120:218.
19. Bioulac-Sage P, Taouji S, Possenti L, Balabaud C. Hepatocellular adenoma subtypes: the impact of overweight and obesity. Liver Int 2012; 32:1217.
20. Chang CY, Hernandez-Prera JC, Roayaie S, et al. Changing epidemiology of hepatocellular adenoma in the United States: review of the literature. Int J Hepatol 2013; 2013:604860.
21. Bunchorntavakul C, Bahirwani R, Drazek D, et al. Clinical features and natural history of hepatocellular adenomas: the impact of obesity. Aliment Pharmacol Ther 2011; 34:664.
22. Agrawal S, Agarwal S, Arnason T, et al. Management of Hepatocellular Adenoma: Recent Advances. Clin Gastroenterol Hepatol 2015; 13:1221.
23. Maillette de Buy Wenniger L, Terpstra V, Beuers U. Focal nodular hyperplasia and hepatic adenoma: epidemiology and pathology. Dig Surg 2010; 27:24.
24. Paradis V, Benzekri A, Dargère D, et al. Telangiectatic focal nodular hyperplasia: a variant of hepatocellular adenoma. Gastroenterology 2004; 126:1323.
25. Zucman-Rossi J, Jeannot E, Nhieu JT, et al. Genotype-phenotype correlation in hepatocellular adenoma: new classification and relationship with HCC. Hepatology 2006; 43:515.
26. Laumonier H, Bioulac-Sage P, Laurent C, et al. Hepatocellular adenomas: magnetic resonance imaging features as a function of molecular pathological classification. Hepatology 2008; 48:808.
27. Ronot M, Bahrami S, Calderaro J, et al. Hepatocellular adenomas: accuracy of magnetic resonance imaging and liver biopsy in subtype classification. Hepatology 2011; 53:1182.
28. Gore RM, Pickhardt PJ, Mortele KJ, et al. Management of Incidental Liver Lesions on CT: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol 2017; 14:1429.
29. Bioulac-Sage P, Balabaud C, Zucman-Rossi J. Subtype classification of hepatocellular adenoma. Dig Surg 2010; 27:39.
30. van Aalten SM, Verheij J, Terkivatan T, et al. Validation of a liver adenoma classification system in a tertiary referral centre: implications for clinical practice. J Hepatol 2011; 55:120.

31. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on the management of benign liver tumours. J Hepatol 2016; 65:386.
32. Bioulac-Sage P, Laumonier H, Couchy G, et al. Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. Hepatology 2009; 50:481.
33. Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenoma: Classification, variants and clinical relevance. Semin Diagn Pathol 2017; 34:112.
34. Dokmak S, Paradis V, Vilgrain V, et al. A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. Gastroenterology 2009; 137:1698.
35. Nagorney DM. Benign hepatic tumors: focal nodular hyperplasia and hepatocellular adenoma. World J Surg 1995; 19:13.
36. van Aalten SM, de Man RA, IJzermans JN, Terkivatan T. Systematic review of haemorrhage and rupture of hepatocellular adenomas. Br J Surg 2012; 99:911.
37. Molina, E, Schiff, E. Benign solid lesions of the liver. In: Schiff's Diseases of the Liver, 8th edit ion, Schiff, E, Sorrell, M, Maddrey, W (Eds), Lippincott-Raven, Philadelphia 1999. p.1245.
38. Sturvetant, F. Oral contraceptives and liver tumors. In: Controversies in contraception, Mog hissi, K (Eds), Williams and Wilkins, Baltimore 1979. p.93.
39. Neuberger J, Davis M, Williams R. Clinical aspects of oral contraceptive-associated liver tum ors. In: Drug reactions and the liver, Davis M, Tredger J, Williams R (Eds), Pittman Medical, B ath, UK 1981. p.271.
40. Paradis V, Champault A, Ronot M, et al. Telangiectatic adenoma: an entity associated with increased body mass index and inflammation. Hepatology 2007; 46:140.
41. Sandler MA, Petrocelli RD, Marks DS, Lopez R. Ultrasonic features and radionuclide correlation in liver cell adenoma and focal nodular hyperlasia. Radiology 1980; 135:393.
42. Golli M, Van Nhieu JT, Mathieu D, et al. Hepatocellular adenoma: color Doppler US and pathologic correlations. Radiology 1994; 190:741.
43. Grazioli L, Federle MP, Brancatelli G, et al. Hepatic adenomas: imaging and pathologic findings. Radiographics 2001; 21:877.
44. Paulson EK, McClellan JS, Washington K, et al. Hepatic adenoma: MR characteristics and correlation with pathologic findings. AJR Am J Roentgenol 1994; 163:113.
45. Arrivé L, Fléjou JF, Vilgrain V, et al. Hepatic adenoma: MR findings in 51 pathologically proved lesions. Radiology 1994; 193:507.
46. McInnes MD, Hibbert RM, Inácio JR, Schieda N. Focal Nodular Hyperplasia and Hepatocellular Adenoma: Accuracy of Gadoxetic Acid-enhanced MR Imaging-A Systematic

Review. Radiology 2015; 277:927.

47. van Aalten SM, Terkivatan T, de Man RA, et al. Diagnosis and treatment of hepatocellular adenoma in the Netherlands: similarities and differences. Dig Surg 2010; 27:61.
48. Ault GT, Wren SM, Ralls PW, et al. Selective management of hepatic adenomas. Am Surg 1996; 62:825.
49. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228.
50. van der Windt DJ, Kok NF, Hussain SM, et al. Case-orientated approach to the management of hepatocellular adenoma. Br J Surg 2006; 93:1495.
51. van Rosmalen BV, Coelen RJS, Bieze M, et al. Systematic review of transarterial embolization for hepatocellular adenomas. Br J Surg 2017; 104:823.
52. van Vledder MG, van Aalten SM, Terkivatan T, et al. Safety and efficacy of radiofrequency ablation for hepatocellular adenoma. J Vasc Interv Radiol 2011; 22:787.
53. van der Sluis FJ, Bosch JL, Terkivatan T, et al. Hepatocellular adenoma: cost-effectiveness of different treatment strategies. Radiology 2009; 252:737.
54. Klompenhouwer AJ, Bröker MEE, Thomeer MGJ, et al. Retrospective study on timing of resection of hepatocellular adenoma. Br J Surg 2017; 104:1695.
55. Farges O, Ferreira N, Dokmak S, et al. Changing trends in malignant transformation of hepatocellular adenoma. Gut 2011; 60:85.
56. van Rosmalen BV, Furumaya A, Klompenhouwer AJ, et al. Hepatocellular adenoma in men: A nationwide assessment of pathology and correlation with clinical course. Liver Int 2021; 41:2474.
57. Bieze M, Phoa SS, Verheij J, et al. Risk factors for bleeding in hepatocellular adenoma. Br J Surg 2014; 101:847.
58. Deneve JL, Pawlik TM, Cunningham S, et al. Liver cell adenoma: a multicenter analysis of risk factors for rupture and malignancy. Ann Surg Oncol 2009; 16:640.
59. Bioulac-Sage P, Rebouissou S, Thomas C, et al. Hepatocellular adenoma subtype classification using molecular markers and immunohistochemistry. Hepatology 2007; 46:740.
60. Marini P, Vilgrain V, Belghiti J. Management of spontaneous rupture of liver tumours. Dig Surg 2002; 19:109.
61. Huurman VA, Schaapherder AF. Management of ruptured hepatocellular adenoma. Dig Surg 2010; 27:56.

62. Erdogan D, Busch OR, van Delden OM, et al. Management of spontaneous haemorrhage and rupture of hepatocellular adenomas. A single centre experience. Liver Int 2006; 26:433.
63. Noels JE, van Aalten SM, van der Windt DJ, et al. Management of hepatocellular adenoma during pregnancy. J Hepatol 2011; 54:553.
64. Lazarus E, Mayo-Smith WW, Mainiero MB, Spencer PK. CT in the evaluation of nontraumatic abdominal pain in pregnant women. Radiology 2007; 244:784.
65. Terkivatan T, de Wilt JH, de Man RA, Ijzermans JN. Management of hepatocellular adenoma during pregnancy. Liver 2000; 20:186.
66. Furlan A, van der Windt DJ, Nalesnik MA, et al. Multiple hepatic adenomas associated with liver steatosis at CT and MRI: a case-control study. AJR Am J Roentgenol 2008; 191:1430.
67. Ribeiro A, Burgart LJ, Nagorney DM, Gores GJ. Management of liver adenomatosis: results with a conservative surgical approach. Liver Transpl Surg 1998; 4:388.
68. Flejou JF, Barge J, Menu Y, et al. Liver adenomatosis. An entity distinct from liver adenoma? Gastroenterology 1985; 89:1132.
69. Grazioli L, Federle MP, Ichikawa T, et al. Liver adenomatosis: clinical, histopathologic, and imaging findings in 15 patients. Radiology 2000; 216:395.
70. Yoshidome H, McMasters KM, Edwards MJ. Management issues regarding hepatic adenomatosis. Am Surg 1999; 65:1070.
71. Wellen JR, Anderson CD, Doyle M, et al. The role of liver transplantation for hepatic adenomatosis in the pediatric population: case report and review of the literature. Pediatr Transplant 2010; 14:E16.

Topic 3590 Version 23.0

GRAPHICS

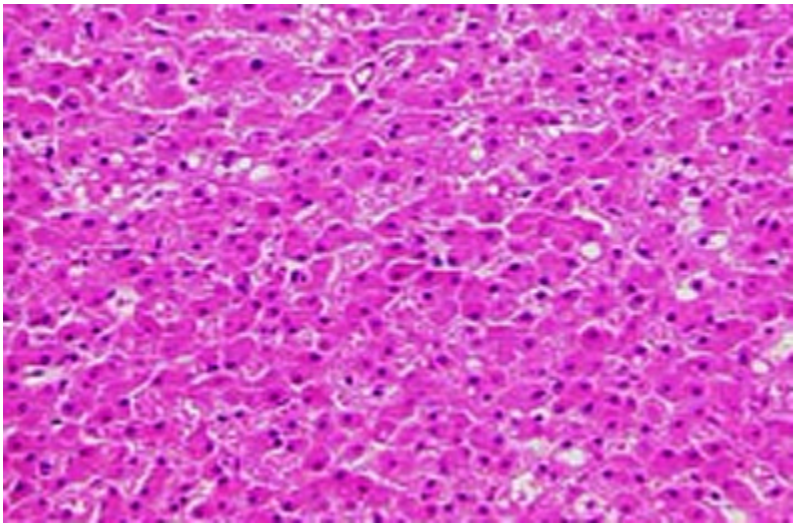
Hepatocellular adenoma

Gross sectioned pathological specimen of a resected pedunculated hepatocellular adenoma measuring >6 cm in diameter. The adenoma shows the typically tan fleshy appearance of an adenoma with no capsule. There is no evidence of hemorrhage or necrosis.

Courtesy of Imad Nasser, MD.

Graphic 72131 Version 2.0

Hepatocellular adenoma

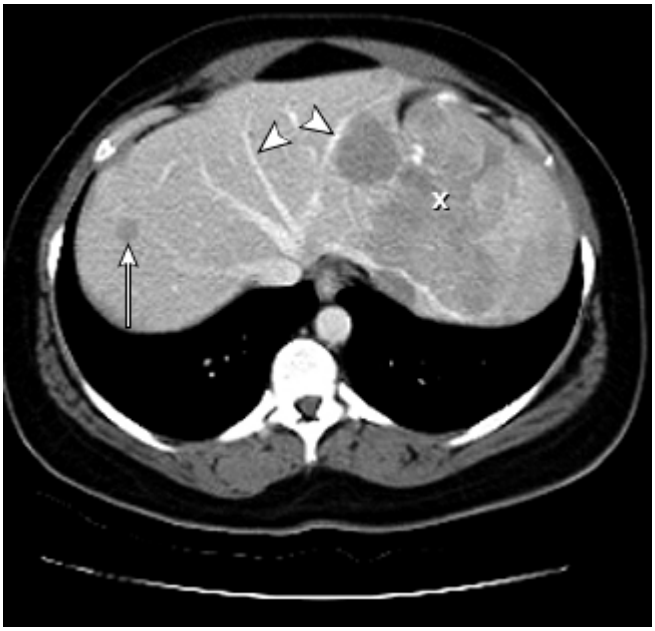


Hematoxylin and eosin slide of hepatocellular adenoma. Adenoma cells resemble normal hepatocytes but have small regular nuclei and some fat vacuoles and are arranged in thickened trabeculae. There is a characteristic absence of portal tracts.

Courtesy of Sanjiv Chopra, MD.

Graphic 51149 Version 2.0

Large hepatocellular adenomas



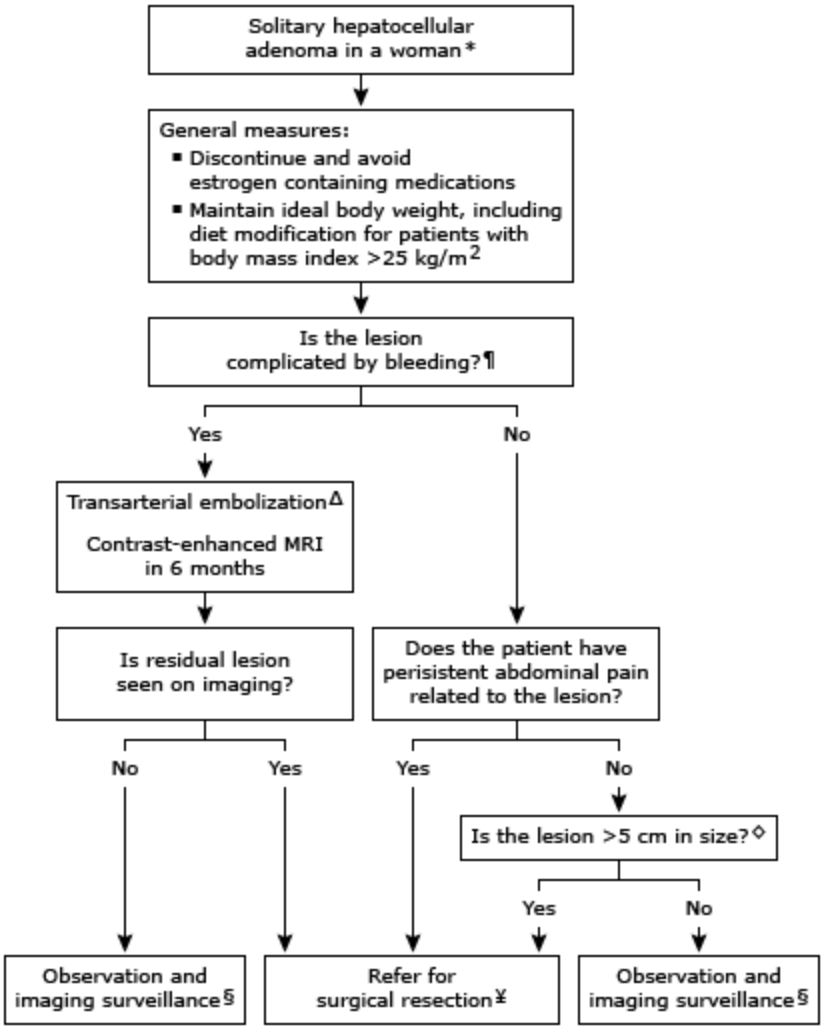
This contrast-enhanced CT scan demonstrates a large complex enhancing mass (X) in the left lobe of the liver displacing vessels (arrowheads). A smaller, low attenuation mass is also noted in the right lobe of the right lobe of the liver (arrow).

CT: computed tomography.

Courtesy of Jonathan Kruskal, MD.

Graphic 68931 Version 6.0

Management of hepatocellular adenoma in women



Refer to UpToDate content on the management of hepatocellular adenoma.

HCA: hepatocellular adenoma; MRI: magnetic resonance imaging.

* Male patients with HCA are referred for surgical intervention regardless of the size of the lesion.

¶ Patients with HCA complicated by bleeding may present with acute abdominal pain with or without hemodynamic instability; the diagnosis is confirmed on imaging.

Δ Transarterial embolization is performed as initial therapy for most patients with HCA complicated by bleeding.

◇ For asymptomatic women with a lesion >5 cm in the setting of oral contraceptives, discontinuing oral contraceptives and obtaining repeat imaging in 6 to 12 months is a reasonable option. If lesion size remains >5 cm, surgical resection is typically performed.

§ We obtain contrast–enhanced MRI in 6 months and then annually thereafter, provided that the lesion is not growing (ie, ≥20% increase in diameter) and is not >5 cm in size.

¥ Alternatives to surgical resection include transarterial embolization and radiofrequency ablation.

Graphic 126065 Version 2.0

Contributor Disclosures

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Conflict of interest policy

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