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Surveillance for hepatocellular carcinoma in adults

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INTRODUCTION

Almost all adult patients with cirrhosis and some patients with chronic hepatitis B virus (HBV) are at sufficiently high risk for developing hepatocellular carcinoma (HCC), so they should be enrolled in a screening and surveillance program. The goal of screening is to detect subclinical disease, and when screening is performed at regular intervals, it is called surveillance. Surveillance of at-risk patients with imaging results in detection of HCC at an earlier stage, which has a favorable effect on outcomes. The development of effective treatments for early-stage HCC has provided additional rationale for surveillance. (See "Overview of treatment approaches for hepatocellular carcinoma".)

This topic will review the approach to surveillance for HCC in high-risk patients and follow-up testing for lesions found during surveillance. The clinical features and additional testing to confirm the diagnosis of HCC, the treatment of HCC, and the prognosis of patients with HCC are discussed separately.

- (See "Clinical features and diagnosis of hepatocellular carcinoma".)
- (See "Overview of treatment approaches for hepatocellular carcinoma".)
- (See "Staging and prognostic factors in hepatocellular carcinoma".)

An overview of the approach to solid liver lesions is also discussed separately. (See "Approach to the adult patient with an incidental solid liver lesion".)

EFFECT OF HCC SURVEILLANCE ON OUTCOMES

The goal of HCC surveillance is to reduce mortality, and groups at risk for HCC that are candidates for surveillance are generally well defined. The recommendation for HCC surveillance in high-risk patients is based on a trial that found a 37 percent reduction in mortality after surveillance in patients with chronic hepatitis B virus (HBV) infection, with or without cirrhosis [1]. In this trial of 19,200 Chinese patients with chronic HBV and five-year follow-up, the mortality rate due to HCC was lower in patients undergoing surveillance (ultrasound and alpha-fetoprotein level every six months) compared with patients with no surveillance (83 versus 132 per 100,000, mortality rate ratio of 0.63, 95% CI 0.41-0.98).

A large randomized trial that validates this result in patients with cirrhosis is unlikely to happen because surveillance is part of routine care for these patients [2]. However, observational studies show that surveillance is associated with both early tumor detection and improved survival [3,4]. In a meta-analysis of 59 studies including over 140,000 patients with HCC, patients in whom HCC was detected by surveillance had lower risk of mortality compared with patients who did not undergo surveillance (hazard ratio [HR] 0.67, 95% CI 0.61-0.72) [4]. In addition, surveillance was associated with a greater likelihood of early-stage tumor detection (OR 1.86, 95% CI 1.78-1.98) and of receiving curative treatment (OR 1.83, 95% CI 1.69-1.97).

HIGH-RISK GROUPS

Society guidelines on surveillance for HCC vary somewhat in the patient populations specified. However, most identify the following high-risk groups [5-8]:

- Patients with cirrhosis, Child-Pugh class A and B
- Patients with cirrhosis, Child-Pugh class C, only if awaiting liver transplantation
- Noncirrhotic patients with hepatitis B virus (HBV) infection with any of the following characteristics:
 - Active hepatitis (elevated serum alanine aminotransferase [ALT] and/or high viral load)
 - Family history of HCC
 - Africans and African Americans
 - Asian males over 40 years of age
 - Asian females over 50 years of age

Additionally, some societies recommend surveillance in patients with chronic hepatitis C virus and advanced liver fibrosis (stage F3) [6].

Our recommendations are generally consistent with guidelines issued by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer (EASL-EORTC) [6,7], although we limit surveillance to patients who are treatment candidates if HCC is discovered at a potentially curable stage.

Patients with nonalcoholic steatohepatitis do not undergo surveillance until they progress to cirrhosis.

Patients with cirrhosis — We recommend HCC surveillance in all patients with cirrhosis (from any cause) who are treatment candidates, which includes the following groups [7]:

- Patients with Child-Pugh class A or B
- Patients with Child-Pugh class C, only if they are waitlisted for transplantation

The annual incidence of HCC in these populations exceeds 1.5 percent, a threshold above which surveillance for HCC is thought to be cost effective in the identified subgroups [2]. Surveillance is not recommended in patients with Child-Pugh class C due to their limited expected lifespan and low hepatic functional reserve to tolerate treatment for detected cancer.

Patients with hepatitis B without cirrhosis — We agree with most guidelines that suggest surveillance in patients with chronic HBV without cirrhosis with any of the following characteristics [6,7,9-11] (see "Hepatitis B virus: Screening and diagnosis in adults", section on 'Serum HBV DNA assays'):

- Active hepatitis (eg, elevated serum ALT) and/or high viral load (ie, >100,000 copies/mL [20,000 international units/mL])
- Family history of HCC
- Asian males over the age of 40 years
- Asian females over the age of 50 years
- Africans and African Americans

The annual incidence of HCC exceeds 0.2 percent in these populations, a threshold above which surveillance for HCC is cost effective in the identified subgroups.

Patients of Asian descent — We suggest HCC surveillance for patients of Asian descent who have HBV infection and no cirrhosis at age 40 years for males and at age 50 years for females. The incidence of HCC in Asian patients with HBV is higher than that seen in White patients (0.4

to 0.6 percent per year compared with less than 0.2 percent per year) [12,13]. The incidence in male HBV carriers from Southeast Asia starts to exceed 0.2 percent around the age of 40 years and is the basis for the recommendation that surveillance start in Asian men at age 40 years [14]. The incidence in Asian women is lower, but it is not well-defined.

Patients of African descent — We recommend beginning surveillance for adults of African descent at the time of HBV diagnosis. Patients with HBV who are of African descent tend to develop HCC at a younger age than other carriers [15,16].

Patients with a family history of HCC — We suggest HCC surveillance for adults with HBV infection and no cirrhosis if they have family history (ie, first degree relative) of HCC. HCC is more common in HBV carriers with a family history of HCC [17]. In a study of 5238 HBV carriers (553 with HCC and 4685 without HCC), the risk of HCC was significantly higher in those with a family history of HCC (adjusted rate ratio [ARR] 2.4) [17]. If the carrier had two or more affected family members, the risk was even higher (ARR 5.6). By the age of 70 years, the cumulative risk of HCC was significantly higher among those with an affected family member compared with patients without an affected family member (23.6 versus 8.9 percent). However, there are no data regarding the optimal age to begin surveillance in such patients. In the absence of such evidence, we suggest that such patients begin surveillance after the age of 18 years at the time of HBV diagnosis.

Patients with active HBV — We suggest HCC surveillance for all patients with evidence of active HBV (ie, elevated serum ALT and/or high HBV DNA levels), even if they do not fulfill any of the demographic criteria listed above. There is no clear definition of what constitutes a high viral load, although a viral load >100,000 copies/mL (20,000 international units/mL) is a risk factor for disease progression and HCC in Asian patients [9,10], and it is the cutoff value suggested by the National Institutes of Health to define active chronic HBV infection [11]. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Serum HBV DNA assays'.)

Therefore, we suggest HCC surveillance for all patients with viral load >100,000 copies/mL (20,000 international units/mL).

In contrast, the incidence of HCC is low for treatment-naïve patients with inactive hepatitis (long-term normal ALT and HBV DNA levels less than 2000 international units/mL) [18,19]. As a result, surveillance for such patients without cirrhosis and without an additional risk factor is not recommended [7].

Patients successfully treated for HBV — We continue to perform surveillance for patients who have been successfully treated for chronic HBV infection and who are hepatitis B surface antigen seropositive, although the risk of HCC appears to be decreased among these patients

[6,7]. Treatment of chronic HBV is discussed elsewhere. (See "Hepatitis B virus: Overview of management".)

The risk of HCC following treatment for HBV was examined in a meta-analysis of 17 studies with 5031 patients [20]. Twelve of the studies looked at treatment with interferon. Compared with controls, patients treated with interferon had a 34 percent reduction in the risk of HCC (relative risk [RR] 0.66, 95% CI 0.48-0.89). Five of the studies looked at patients treated with a nucleos(t)ide analog and found a 78 percent reduction in the risk of HCC compared with controls (RR 0.22, 95% CI 0.10-0.50).

Risk scores based on a combination of patient and disease characteristics have been proposed to prioritize patients for HCC screening including those with pharmacologically suppressed HBV [21-23]. For example, HCC screening for patients with Platelet count, Age, Gender, hepatitis B score ≥10 has been recommended by society guidelines [6]. (See 'Individualizing surveillance based on risk' below.)

Patients with hepatitis C and advanced fibrosis — We suggest surveillance for patients with chronic hepatitis C virus and advanced liver fibrosis (stage F3) in the absence of cirrhosis [6], although the cost effectiveness of surveillance in such patients has not been verified, and some guidelines, such as those by the AASLD, do not advocate surveillance in these patients. In patients who have been treated for chronic hepatitis C virus and have achieved sustained viral response, the risk of HCC persists and surveillance should be continued. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

Porphyria — Surveillance for HCC is warranted for some patients with neurovisceral porphyrias such as acute intermittent porphyria, hereditary coproporphyria, or variegate porphyria because they are at risk for HCC, independent of the severity of liver disease. The frequency and modality for screening may differ from other populations. This is described in more detail separately. (See "Acute intermittent porphyria: Management", section on 'Monitoring for disease complications' and "Hereditary coproporphyria", section on 'Screening and interventions for long-term complications' and "Variegate porphyria", section on 'Screening for long-term complications'.)

OUR APPROACH TO SURVEILLANCE

Ultrasound — For HCC surveillance in most at-risk patients, we recommend abdominal ultrasound at six-month intervals, in accordance with a number of consensus guidelines [6,7,24]. Abdominal ultrasound performed for HCC surveillance is usually focused on the liver

alone with added evaluation of the spleen in some cases. However, dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) or abbreviated MRI exams of the abdomen are included in surveillance at many practices and applied to some eligible patients. These advanced imaging exams demonstrate higher sensitivity, but no trials have been performed to test their impact on survival. (See 'Alternatives to surveillance with ultrasound alone' below.)

In general, we do not suggest dynamic contrast-enhanced CT or MRI of the abdomen as the primary modality for routine surveillance; instead, we suggest the use of these modalities to further characterize lesions ≥1 cm identified during surveillance. (See 'Lesions measuring ≥1 cm' below.)

Among the options for liver imaging, ultrasound is the least sensitive for detection of HCC [25,26]. However, unlike the other modalities, semi-annual (twice a year) ultrasound surveillance has been shown to improve the survival of patients with chronic hepatitis B virus [1]. (See 'High-risk groups' above.)

Sensitivity of ultrasound for detecting HCC varies widely and is subject to patient habitus, the presence of cirrhosis, the imaging technique, and reference standard used for HCC diagnosis. Sensitivity decreases in patients with cirrhosis because parenchymal heterogeneity obscures small lesions. The sensitivity of ultrasound alone for detecting HCC at any stage is 78 percent (95% CI 67-86 percent) and for early-stage HCC is 45 percent (95% CI, 30-62 percent) [25,27]. In one study, sensitivity decreased with lesion size and was 85, 62, and 21 percent for lesions >4 cm, 2 to 4 cm, and <2 cm, respectively [26]. Reported specificity is uniformly high at >90 percent.

Six-month interval — The recommendation for surveillance at six-month intervals was initially based on the expected tumor growth rate (median doubling time for HCC is 117 days [range, 29 to 398 days]), while this time interval has subsequently been supported by observational data [7,28-31]. Because the surveillance interval is a function of the tumor growth rate and not the degree of risk of developing HCC, the interval is not shortened for patients at higher risk for HCC.

The following studies support the six-month interval for surveillance [30-32]:

 In a retrospective study of 649 patients with cirrhosis and HCC detected with surveillance, the median survival rate was higher in patients undergoing ultrasound at six-month intervals compared with patients undergoing annual surveillance (45 versus 30 months) [31].

- In a pooled analysis of 19 studies, the sensitivity of ultrasound applied in a surveillance context to detect tumors before clinical presentation was higher in patients assigned to a six-month surveillance interval compared with patients receiving annual surveillance (70 versus 50 percent) [30].
- In a trial of 1278 patients with cirrhosis, patients assigned to a three-month interval for surveillance ultrasound had similar rates of detection of HCC compared with patients in a six-month interval group [32].

Alternatives to surveillance with ultrasound alone — An alternative approach to HCC surveillance is to obtain ultrasound and alpha-fetoprotein (AFP) at six-month intervals. This approach has not been directly compared with ultrasound alone. However, the sensitivity of ultrasound is lower compared with ultrasound plus AFP for detecting HCC at any stage (78 versus 97 percent, relative risk [RR] 0.88, 95% CI 0.83-0.93) and for detecting early stage HCC (45 versus 63 percent, RR 0.81, 95% CI 0.71-0.93) [25,27].

Although dynamic contrast-enhanced CT or MRI of the abdomen are other tools that could be used for surveillance, the American Association for the Study of Liver Diseases does not recommend them for routine use [7]. Nevertheless, some practitioners use CT or MRI in conjunction with or instead of ultrasound for surveillance, especially for patients in whom ultrasound visualization of the liver is limited by body habitus, hepatic steatosis, or severe parenchymal heterogeneity from advanced cirrhosis. Both CT and MRI are more sensitive than ultrasound for detecting HCC <2 cm and thus more likely to identify candidates for liver transplantation therapy. AFP testing alone is not an acceptable alternative for surveillance. The use of contrast-enhanced ultrasound for surveillance is investigational and is not recommended for general clinical practice.

- Computed tomography Contrast-enhanced CT of the abdomen is not recommended as the primary imaging modality for surveillance, except for patients in whom ultrasound is limited as described above. Once ultrasound detects a nodule, CT is used to determine the likelihood that it is an HCC. CT is more sensitive than ultrasound and has a specificity of >90 percent [25]. CT involves iodinated contrast administration, and repeated scanning would result in cumulative exposure to radiation. (See 'Patients with a lesion detected by ultrasound' below.)
- Magnetic resonance imaging Contrast-enhanced MRI of the abdomen is not recommended as the primary imaging modality for surveillance, except for patients in whom ultrasound is limited as described above. When ultrasound detects a nodule, a complete contrast-enhanced MRI is used to determine the likelihood that it is an HCC. MRI

is more sensitive than ultrasound and has a specificity of >90 percent [25]. MRI requires that a patient lie still in an enclosed magnet for up to 30 minutes and cooperate with breath-holding instructions. Its use in surveillance would require repeated administration of gadolinium contrast. Non-contrast abbreviated MRI has shown promise as a screening test for HCC in preliminary studies in some patient populations, but not in others [33-35]. As an example, a modelling study suggested that surveillance with contrast-enhanced, abbreviated MRI was cost effective for adults with cirrhosis and an annual HCC risk exceeding 3 percent compared with ultrasound alone [35]. Additional studies are needed to validate abbreviated MRI as a screening tool and to determine the optimal imaging method (eg, non-contrast or contrast-enhanced). (See 'Patients with a lesion detected by ultrasound' below.)

- Alpha-fetoprotein We do not recommend serum AFP alone for surveillance. Because of its poor sensitivity and specificity [30,36], AFP testing alone should **not** be used unless imaging is unavailable [37]. Since the combined use of AFP and abdominal ultrasound increases detection rates compared with ultrasound alone [27,38], AFP may be added to ultrasound for surveillance, although this increases false-positive rates [30,36,37].
- Contrast-enhanced ultrasound Ultrasound of the abdomen with contrast in the delayed phase permits detection of HCC nodules. Contrast-enhanced ultrasound is not recommended for surveillance, however, as its use in this context has not been validated. Practitioners should also be aware that the entire liver cannot be imaged with ultrasound during the dynamic phase of contrast administration to characterize all detected nodules [39]. Instead, contrast-enhanced ultrasound permits characterization of one or a limited number of identified nodules.

Other tests have been proposed for surveillance, such as the ratio of the L3 fraction of AFP to total AFP, des-gamma-carboxy prothrombin, and other serum proteins or RNA molecules. However, none of these has been adequately studied as a surveillance test, and they cannot be recommended. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Alpha-fetoprotein'.)

PATIENTS WITH A LESION DETECTED BY ULTRASOUND

For patients at risk for HCC who have a lesion detected by surveillance ultrasound, the subsequent work-up depends upon the size of the lesion [2,7]. Our approach is described in the following sections.

Lesions measuring <1 cm — Lesions measuring <1 cm in diameter are too small to be definitively diagnosed by further imaging or biopsy. They are likely to be benign. We monitor them at short intervals (eg, every three to six months) for up to two years. If the lesion disappears or remains smaller than 1 cm, the patient may return to routine surveillance at sixmonth intervals. If the lesion grows beyond 1 cm, or if a new \geq 1 cm lesion develops, or if the alpha-fetoprotein level rises, we obtain dynamic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the liver tailored for liver lesion characterization. Contrast-enhanced ultrasound, if available, can also be used instead of CT or MRI, with the caveat that if the lesion proves to be malignant, a contrast-enhanced CT or MRI will be needed to stage the tumor burden in the liver (algorithm 1).

Lesions measuring ≥1 cm — Lesions measuring ≥1 cm in diameter should be further evaluated with other liver imaging that incorporates intravenous contrast [7]. Further evaluation and diagnosis of HCC using these imaging exams is described elsewhere. (See "Clinical features and diagnosis of hepatocellular carcinoma", section on 'Imaging'.)

Diagnosis of HCC can be made either with imaging alone or by biopsy. Imaging features include nodule size, kinetics and pattern of contrast enhancement, and growth on serial imaging. Imaging can also diagnose some lesions (eg, cyst, hemangioma) as definitively benign based on imaging features or as probably benign based on imaging features and/or if they remain unchanged in long-term (eg, >24 month) follow-up.

INDIVIDUALIZING SURVEILLANCE BASED ON RISK

If the risk of developing HCC could be accurately predicted based on patient characteristics, surveillance recommendations could then be tailored to individual patient risk (precision surveillance) [8]. A number of risk factors for HCC have been identified and some have been incorporated into risk scores, although none have been extensively validated [9,40-52]. (See 'High-risk groups' above.)

One study proposed a nomogram that predicted individual risk in patients with chronic hepatitis B virus ([HBV]; genotypes B and C) [53]. Preliminary data supporting this algorithm have been published, and a 17-point risk score that accurately predicts risk of HCC in patients with HBV is available [52]. Components of the score include sex, age, serum alanine aminotransferase concentration, hepatitis B e antigen (HBeAg) status, and serum HBV DNA level. Patients may score between 0 and 17 points. A score of 0 corresponds to a 10-year risk of HCC of 0 percent, a score of 8 corresponds to a risk of 2 percent, and a score of 17 corresponds to a risk of 82 percent. The major drawback is that the score was developed in Asia and has been validated in Asia, where more patients are infected with hepatitis B genotypes B and C. Although the relationship probably also holds for other genotypes, the cut-off points have not been determined, so this score may only be useful in an Asian population.

The platelet count, Age, Gender, hepatitis B (PAGE B) score for predicting risk of HCC includes patient age, sex, and platelet count, and it has been validated in White European patients and Asian patients with HBV who have been treated with antiviral therapy and are HBeAg negative [21-23,54]. However, the PAGE B score has not been validated in patients of African descent, HBeAg positive patients with pharmacologically suppressed HBV, and White patients with untreated HBV. CAGE-B and SAGE-B scores consisting of age and fibrotic burden as cirrhosis (CAGE-B) and/or liver stiffness (SAGE-B) have been proposed to predict HCC risk among White patients and Asian patients with chronic hepatitis B infection on long-term antiviral therapy [23,55].

The individual risk factors for developing HCC that are unique to patients with chronic HBV, including viral load, HBeAg, and hepatitis B surface antigen status, are discussed separately. (See "Clinical significance of hepatitis B virus genotypes" and "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Hepatitis B virus'.)

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: Hepatocellular carcinoma".)

SUMMARY AND RECOMMENDATIONS

- Our approach to surveillance for hepatocellular carcinoma (HCC) is generally consistent with most society guidelines that recommend surveillance for subsets of adult patients with chronic hepatitis B virus (HBV) infection and for all adult patients with cirrhosis who are candidates for treatment (**Grade 2C**) (see 'High-risk groups' above):
 - Patients with Child-Pugh class A or B
 - Patients with Child-Pugh class C, only if they are waitlisted for transplantation

We suggest that subsets of patients with chronic HBV infection undergo surveillance (**Grade 2C**). Patients with chronic HBV at sufficiently high risk to warrant surveillance for HCC include:

- Patients with a family history of HCC
- Asian males over the age of 40 years
- Asian females over the age of 50 years
- Africans and African Americans
- For patients with evidence of active hepatitis B (eg, elevated serum alanine aminotransferase) and/or high viral load (ie, >100,000 copies/mL [20,000 international units/mL]), we suggest performing surveillance (Grade 2C). (See 'Patients with active HBV' above.)
- For high-risk patients who require HCC surveillance, we suggest abdominal ultrasound as the primary modality. Abdominal ultrasound performed for HCC surveillance is usually focused on the liver alone with added evaluation of the spleen in some cases. (See 'Ultrasound' above.)
- For high-risk patients who require HCC surveillance, the abdominal ultrasound is performed every six months. (See 'Our approach to surveillance' above.)
- In patients in whom ultrasound evaluation of the liver is technically suboptimal (eg, body habitus, hepatic steatosis, advanced cirrhosis), other modalities such as computed tomography or magnetic resonance imaging with contrast may be appropriate. (See 'Alternatives to surveillance with ultrasound alone' above.)
- The addition of serum alpha-fetoprotein (AFP) to ultrasound for surveillance is optional. The combined use of AFP and ultrasound increases detection rates but also increases false-positive rates. (See 'Alternatives to surveillance with ultrasound alone' above.)
- For patients with lesions detected with surveillance ultrasound, follow-up testing depends upon the size of the lesion (see 'Patients with a lesion detected by ultrasound' above and "Clinical features and diagnosis of hepatocellular carcinoma"):
 - Lesions <1 cm are too small to be definitively diagnosed by further imaging or biopsy. They are likely to be benign. We monitor them at short intervals (eg, every three to six months) for up to two years. If the lesion disappears or remains smaller than 1 cm, the patient may return to routine surveillance at six-month intervals.
 - Lesions measuring ≥1 cm in diameter should be further evaluated with other liver imaging that incorporates intravenous contrast.

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REFERENCES

- 1. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130:417.
- 2. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018; 391:1301.
- 3. Singal AG, Mittal S, Yerokun OA, et al. Hepatocellular Carcinoma Screening Associated with Early Tumor Detection and Improved Survival Among Patients with Cirrhosis in the US. Am J Med 2017; 130:1099.
- 4. Singal AG, Zhang E, Narasimman M, et al. HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol 2022; 77:128.
- 5. Clinical Practice Guidelines for Hepatocellular Carcinoma The Japan Society of Hepatology 2009 update. Hepatol Res 2010; 40 Suppl 1:2.
- 6. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018; 69:182.
- Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018; 68:723.
- 8. Kanwal F, Singal AG. Surveillance for Hepatocellular Carcinoma: Current Best Practice and Future Direction. Gastroenterology 2019; 157:54.
- 9. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006; 295:65.
- 10. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006; 130:678.
- 11. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000--summary of a workshop. Gastroenterology 2001; 120:1828.
- 12. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. Pathol Biol (Paris) 2010; 58:273.
- 13. Sakuma K, Saitoh N, Kasai M, et al. Relative risks of death due to liver disease among Japanese male adults having various statuses for hepatitis B s and e antigen/antibody in serum: a prospective study. Hepatology 1988; 8:1642.
- 14. Beasly R. Hepatitis B virus as the etiologic agent in hepatocellular carcinoma. Hepatology 1982; 2:21S.

- 15. Kew MC, Marcus R, Geddes EW. Some characteristics of Mozambican Shangaans with primary hepatocellular cancer. S Afr Med J 1977; 51:306.
- 16. Kew MC, Macerollo P. Effect of age on the etiologic role of the hepatitis B virus in hepatocellular carcinoma in blacks. Gastroenterology 1988; 94:439.
- 17. Yu MW, Chang HC, Liaw YF, et al. Familial risk of hepatocellular carcinoma among chronic hepatitis B carriers and their relatives. J Natl Cancer Inst 2000; 92:1159.
- 18. Manno M, Cammà C, Schepis F, et al. Natural history of chronic HBV carriers in northern Italy: morbidity and mortality after 30 years. Gastroenterology 2004; 127:756.
- 19. Bellentani S, Miglioli L, Croce L, et al. Natural history of HBV infection: A nine years followup of the Dionysius cohort. J Hepatol 2002; 36:228S.
- 20. Sung JJ, Tsoi KK, Wong VW, et al. Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2008; 28:1067.
- 21. Zeng G, Gill US, Kennedy PTF. Prioritisation and the initiation of HCC surveillance in CHB patients: lessons to learn from the COVID-19 crisis. Gut 2020; 69:1907.
- 22. Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV. Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int 2020; 40:484.
- 23. Papatheodoridis GV, Sypsa V, Dalekos GN, et al. Hepatocellular carcinoma prediction beyond year 5 of oral therapy in a large cohort of Caucasian patients with chronic hepatitis
 B. J Hepatol 2020; 72:1088.
- 24. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. Lancet 2022; 400:1345.
- 25. Colli A, Fraquelli M, Casazza G, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. Am J Gastroenterol 2006; 101:513.
- 26. Yu NC, Chaudhari V, Raman SS, et al. CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol 2011; 9:161.
- 27. Tzartzeva K, Obi J, Rich NE, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology 2018; 154:1706.
- 28. Trevisani F, De Notariis S, Rapaccini G, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002; 97:734.
- 29. Sheu JC, Sung JL, Chen DS, et al. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. Gastroenterology 1985; 89:259.

- **30.** Singal A, Volk ML, Waljee A, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009; 30:37.
- 31. Santi V, Trevisani F, Gramenzi A, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010; 53:291.
- Trinchet JC, Chaffaut C, Bourcier V, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011; 54:1987.
- **33.** Vietti Violi N, Lewis S, Liao J, et al. Gadoxetate-enhanced abbreviated MRI is highly accurate for hepatocellular carcinoma screening. Eur Radiol 2020; 30:6003.
- 34. Whang S, Choi MH, Choi JI, et al. Comparison of diagnostic performance of non-contrast MRI and abbreviated MRI using gadoxetic acid in initially diagnosed hepatocellular carcinoma patients: a simulation study of surveillance for hepatocellular carcinomas. Eur Radiol 2020; 30:4150.
- 35. Nahon P, Najean M, Layese R, et al. Early hepatocellular carcinoma detection using magnetic resonance imaging is costeffective in high-risk patients with cirrhosis. JHEP Rep 2021.
- **36.** Lok AS, Sterling RK, Everhart JE, et al. Des-gamma-carboxy prothrombin and alphafetoprotein as biomarkers for the early detection of hepatocellular carcinoma. Gastroenterology 2010; 138:493.
- 37. Chronic hepatitis B: Update 2009. Lok AS, McMahon BJ. Available at: http://publish.aasld.or g/Pages/Default.aspx (Accessed on September 08, 2009).
- **38**. Chang TS, Wu YC, Tung SY, et al. Alpha-Fetoprotein Measurement Benefits Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. Am J Gastroenterol 2015; 110:836.
- 39. Claudon M, Dietrich CF, Choi BI, et al. Guidelines and good clinical practice recommendations for Contrast Enhanced Ultrasound (CEUS) in the liver - update 2012: A WFUMB-EFSUMB initiative in cooperation with representatives of AFSUMB, AIUM, ASUM, FLAUS and ICUS. Ultrasound Med Biol 2013; 39:187.
- 40. Serfaty L, Aumaître H, Chazouillères O, et al. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. Hepatology 1998; 27:1435.
- 41. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112:463.
- **42.** Bonis PA, Tong MJ, Blatt LM, et al. A predictive model for the development of hepatocellular carcinoma, liver failure, or liver transplantation for patients presenting to clinic with chronic

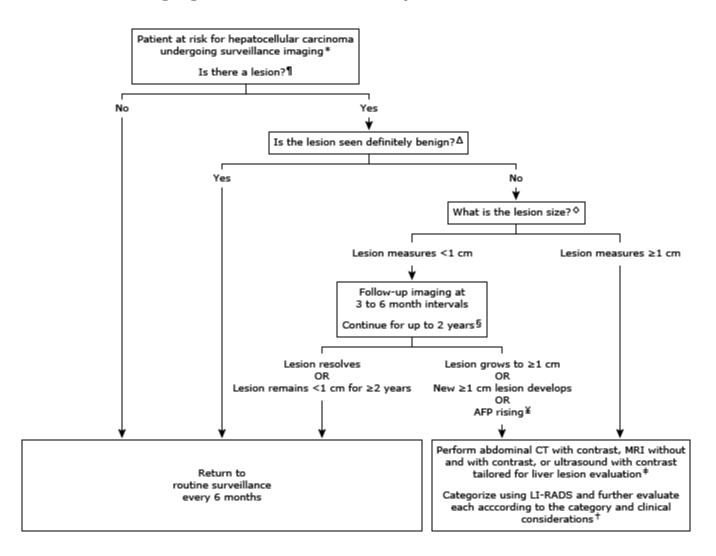
hepatitis C. Am J Gastroenterol 1999; 94:1605.

- **43.** Velázquez RF, Rodríguez M, Navascués CA, et al. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. Hepatology 2003; 37:520.
- 44. de Jongh FE, Janssen HL, de Man RA, et al. Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver. Gastroenterology 1992; 103:1630.
- **45.** Realdi G, Fattovich G, Hadziyannis S, et al. Survival and prognostic factors in 366 patients with compensated cirrhosis type B: a multicenter study. The Investigators of the European Concerted Action on Viral Hepatitis (EUROHEP). J Hepatol 1994; 21:656.
- 46. Di Marco V, Lo Iacono O, Cammà C, et al. The long-term course of chronic hepatitis B. Hepatology 1999; 30:257.
- 47. Yang HI, Lu SN, Liaw YF, et al. Hepatitis B e antigen and the risk of hepatocellular carcinoma. N Engl J Med 2002; 347:168.
- **48.** Yu MW, Yeh SH, Chen PJ, et al. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. J Natl Cancer Inst 2005; 97:265.
- 49. Chen CJ, Yang HI, Iloeje UH, et al. A risk function nomogram for predicting HCC in patients with chronic hepatitis B: The REVEAL-HBV study. J Hepatol 2007; 46(Suppl 1):S180.
- 50. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009; 50:80.
- 51. Lok AS, Seeff LB, Morgan TR, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009; 136:138.
- Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 2011; 12:568.
- 53. Yang HI, Sherman M, Su J, et al. Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 2010; 28:2437.
- 54. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016; 64:800.
- 55. Ji JH, Park SY, Son WJ, et al. External validation of CAGE-B and SAGE-B scores for Asian chronic hepatitis B patients with well-controlled viremia by antivirals. J Viral Hepat 2021; 28:951.

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GRAPHICS

Surveillance imaging in adults at risk for hepatocellular carcinoma



AFP: alpha-fetoprotein; CT: computed tomography; MRI: magnetic resonance imaging; LI-RADS: Liver Imaging Reporting and Data System.

* Abdominal ultrasound is recommended in most patients. However, surveillance modalities (eg, addition of serum alpha fetal protein, abdominal CT, or MRI with intravenous contrast rather than ultrasound) are sometimes individualized as described elsewhere in UpToDate.

¶ If there are multiple lesions, this algorithm can be applied to each lesion. However, management choice is driven by the lesion that is the most suspicious (eg, largest and not definitely benign, growing).

Δ Examples of definitely benign lesions include simple cysts or those previously characterized on contrast-enhanced liver imaging or biopsy as definitely benign (eg, hemangioma).

♦ Size is defined as the maximum cross-section diameter measured on the image where the lesion is most clearly seen.

§ Same imaging modality should be used for initial follow-up, but subsequent imaging may involve a change in modality. While the two-year follow-up represents our practice, stability over that time does

not confirm that a lesion is benign. For these patients, we resume routine surveillance imaging every six months.

¥ Practice varies on whether serum AFP is measured in this setting.

[‡] Imaging technology and performance should adhere to standards required for liver lesion characterization which are more stringent than those for routine abdominal imaging and requires multiphase post-contrast imaging¹. Modality choice depends on available scanner technology, imaging expertise, and patient contraindications. Contrast-enhanced CT and MRI demonstrate comparable accuracy. Contrast-enhanced ultrasound is more limited in availability and its diagnostic performance is not as well characterized.

[†] Liver Imaging Reporting and Data System (LI-RADS) system to categorize, further evaluate, and diagnose liver lesions is described elsewhere in UpToDate. LI-RADS evaluation can involve biopsy or follow-up imaging with contrast-enhanced CT, MRI, or ultrasound.

Reference

1. American College of Radiology. Liver Reporting & Data System v2017. https://www.acr.org/Clinical-Resources/Reportingand-Data-Systems/LI-RADS (Accessed on December 20, 2017)

Graphic 117489 Version 2.0

Contributor Disclosures

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Conflict of interest policy

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