Surveillance and Diagnosis of Hepatocellular Carcinoma

Paul Fitzmorris, MD, and Ashwani K. Singal, MD, MS

Dr Fitzmorris is a resident in the Department of Medicine and Dr Singal is a professor in the Division of Gastroenterology and Hepatology at UAB School of Medicine in Birmingham, Alabama.

Address correspondence to:
Dr Ashwani K. Singal
Division of Gastroenterology and Hepatology
UAB School of Medicine
Birmingham, AL 35294-0012
Tel: 205-975-9698
Fax: 205-975-0961
E-mail: ashwanisingal.com@gmail.com

Abstract: Hepatocellular carcinoma (HCC) is an important cause of cancer-related death worldwide. If the disease is detected early, the treatment is more likely to be curative. This article discusses the current evidence regarding the surveillance and diagnosis of HCC, focusing on recent articles and the recommendations of the American Association for the Study of Liver Diseases (AASLD), which are briefly compared with the recommendations of other liver disease organizations. HCC surveillance aims to detect disease at an early stage in order to augment the likelihood of curative treatment. According to AASLD recommendations, patients who have cirrhosis and those who do not have cirrhosis but are at high risk for HCC should be screened. Ultrasonography (USG) at 6-month intervals is recommended. The available serologic markers, including serum alpha-fetoprotein, are inadequate for surveillance, even when combined with USG. Despite achievements in HCC management, physicians continue to underutilize surveillance. Quadruple-phase, contrast-enhanced computed tomography scans or magnetic resonance images with characteristic radiologic findings are commonly used to diagnose HCC in suspicious cases. The available surveillance and diagnostic tests effectively identify HCC at an early stage, and as a result, the chances of cure are increased. Physicians caring for patients who have cirrhosis and chronic liver disease should be familiar with HCC surveillance recommendations and the prognostic importance of early diagnosis.

Keywords
Screening, liver cancer, cirrhosis, chronic liver disease, hepatitis B virus

Hepatocellular carcinoma (HCC) is a significant cause of morbidity and mortality worldwide. The detection of HCC at an early stage improves survival and allows the use of potentially curative treatments.[1,2] For this reason, the detection of early disease by surveillance and the use of accurate diagnostic methods are paramount to the management of HCC. Physicians caring for patients who have cirrhosis and chronic liver disease should be familiar with HCC surveillance and diagnostic guidelines.

Table 1. HCC Surveillance Guidelines of Various Professional Organizations[4,5,15,61,62]

Organization	Target Population	Surveillance Method and Interval
AASLD	Cirrhotic patients, noncirrhotic HBV carriers with a family history of HCC, noncirrhotic Africans and African Americans with HBV, noncirrhotic Asian male HBV carriers past the age of 40 years, noncirrhotic Asian female HBV carriers past the age of 50 years	USG every 6 months
EASL	Cirrhotic patients, noncirrhotic HBV carriers with a family history of HCC, noncirrhotic HBV carriers with active hepatitis, noncirrhotic patients with chronic HCV and advanced liver fibrosis (F3)	USG every 6 months
APASL	Cirrhotic patients with HBV or HCV infection	USG plus AFP every 6 months
JSH	Cirrhotic patients, noncirrhotic patients with chronic HBV infection, noncirrhotic patients with chronic HCV infection	USG plus AFP/AFP-L3%/DCP every 3 to 6 months

AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; AFP-L3%, Lens culinaris agglutinin A-reactive fraction of AFP; APASL, Asian Pacific Association for the Study of the Liver; DCP, serum des-carboxy prothrombin; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; JSH, Japan Society of Hepatology; USG, ultrasonography.

Screening and Surveillance

Screening is a secondary form of prevention that seeks to detect subclinical disease. When screening is repeated at given intervals, it is called surveillance.

An ideal method of screening would accurately detect disease at an early stage; however, such a screening method does not currently exist for HCC. Therefore, physicians choose surveillance tests with relatively high rates of sensitivity (true-positive rates) and relatively low rates of specificity (true-negative rates) to ensure that they do not overlook disease. The result is a higher likelihood of false-positive results, with the accompanying risk for patient burdens (physical, psychological, and financial) due to unnecessary follow-up tests. The intrinsic sensitivity of a test depends on the test itself, the individual who administers the test, and the individual who interprets the test results. The survival benefit of a surveillance test can be difficult to determine because of lead-time bias. Finally, surveillance strategies are often established without strong evidence that an intervention is actually improving outcomes because of the ethical issues involved in conducting large, randomized studies once an apparent benefit of an intervention has been noted. Despite the belief that physicians are mitigating patient suffering and decreasing financial burden, they may not be improving clinically significant outcomes and, in fact, may be doing the opposite at times.[3]

The American Association for the Study of Liver Diseases (AASLD) recommends that patients who have cirrhosis and some patients who have chronic liver disease without cirrhosis undergo surveillance for HCC with ultrasonography (USG) every 6 months.[4,5] The AASLD surveillance guidelines are compared with those of other professional organizations in Table 1. The National Cancer Society and the US Preventive Services Task Force do not currently have guidelines for HCC surveillance. HCC surveillance should be put into practice because all of the criteria for effective surveillance testing are met: (1) HCC has a major impact on public health, (2) the detection of HCC at an early stage improves outcomes, (3) there are known groups at high risk for HCC, (4) tests are available for surveillance, (5) these tests can detect HCC at an early stage, (6) the tests are cost-effective and acceptable to physicians and patients, (7) an algorithmic approach to recall and diagnosis after the detection of findings is available, and (8) there are effective treatments for confirmed cases of HCC. The evidence for these criteria is examined one by one in the subsequent sections.

Hepatocellular Carcinoma Is a Major Public Health Problem

The incidence of HCC increased from 2.1 per 100,000 persons in 2001 to 3.2 per 100,000 persons in 2006.[6-10] HCC is the third leading cause of cancer-related death worldwide and the ninth leading cause in the United States.[6,11]

Detection of Hepatocellular Carcinoma at an Early Stage Improves Outcomes

The goal of HCC surveillance is to detect disease early in its development in order to initiate potentially curative interventions and reduce overall morbidity, mortality, and the financial burden on the health care system. The 5-year survival rate of patients in whom HCC is diagnosed after the onset of symptoms is 0% to 10%. In contrast, when HCC is detected at an early stage, the 5-year survival rate is higher than 50%.[1,2] In a recently published meta-analysis that pooled data from 47 studies with 15,158 patients, HCC surveillance was associated with higher rates of early-stage detection (odds ratio [OR], 2.08; 95% CI, 1.8-2.37), higher rates of curative treatment (OR, 2.24; 95% CI, 1.99-2.52), and improved survival

after adjustment for lead-time bias (OR, 1.9; 95% CI, 1.67-2.17).[12] A 2014 Italian study analyzed the effect of lead-time bias on survival rates among 1380 patients with Child-Pugh stage A or B cirrhosis and a diagnosis of HCC. The study compared survival rates of 3 groups of patients: those in whom HCC was detected during semi-annual surveillance (n=850), those in whom HCC was detected during annual surveillance (n=234), and those in whom HCC was detected after the onset of symptoms (n=296). The 5-year survival rates for the 3 groups were 32.7%, 25.2%, and 12.2%, respectively (P<.001). After 10 years of follow-up, the median lead time calculated for the patients with HCC detected by surveillance was 6.5 months. The long-term survival benefit of HCC surveillance was not attributed to lead-time bias.[13]

The detection of early-stage disease is possible. The nationwide implementation of HCC surveillance in Japan has led to a particularly high rate of detection of early disease. In a study reported from Japan, 62% of cases of HCC in Japan were diagnosed at an early stage, compared with 30% in Western countries.[14]

Target Populations and High-Risk Groups

Surveillance is effective for populations with a high incidence of a disease. HCC surveillance is thought to be beneficial if the annual incidence of HCC is 1.5% or higher in persons with cirrhosis or is higher than 0.2% in those with chronic hepatitis B virus (HBV) infection. Table 1 summarizes the target populations of the AASLD and those of other professional organizations.

Patients who have nonalcoholic fatty liver disease without cirrhosis may also benefit from surveillance; however, more data are needed before this strategy can be implemented in routine practice.[4,5,15] It is generally agreed that patients with stage 3 fibrosis or advanced/bridging fibrosis should undergo surveillance similar to that of patients with cirrhosis. However, the data behind this guideline are limited and not strong. In a recently published, retrospective study of 149 patients (82 with stage 4 fibrosis), the HCC event rate at follow-up was much lower in patients with stage 3 fibrosis than in those with cirrhosis or stage 4 fibrosis (0.3% vs 4% per person-year).[16] Because it is often impossible to determine at follow-up when stage 3 fibrosis becomes compensated cirrhosis, it is recommended that HCC surveillance be continued for patients with stage 3 disease. However, given the data from this study, these patients probably require less frequent follow-up than patients with stage 4 fibrosis or cirrhosis. Finally, some data are emerging regarding the certainty of the benefits of screening patients who have alcoholic cirrhosis. In a recently published national registry–based cohort study of 8482 Danish patients with alcohol-related cirrhosis, the authors showed that the risk for HCC may be much lower than is currently reported and that surveillance among these patients may not be cost-effective.[17] Further studies are needed to verify these findings.

Surveillance Using Radiographic Tests

In a meta-analysis of 19 studies evaluating the accuracy of USG for HCC surveillance, the pooled data showed that USG had a sensitivity of 94% for identifying HCC at all stages and 63% for detecting HCC at an early stage. The meta-analysis also emphasized that the results cannot be accurately generalized to all patients with cirrhosis and/or chronic HBV carriers because of the heterogeneity of the study populations, surveillance intervals, and HCC verification tests.[18] Another, more recent meta-analysis reiterated the poor quality of the evidence derived from existing research on the accuracy of USG.[19]

In terms of the utility of quadruple-phase, contrast-enhanced computed tomography (CT) vs that of USG, a prospective, randomized trial in 2013 examined 163 patients at a US Veterans Affairs hospital who had compensated cirrhosis. The patients underwent either biannual USG plus serum alpha-fetoprotein (AFP) testing or annual CT plus biannual AFP testing. Biannual USG was just as good at detecting HCC as annual CT (sensitivity of 71.4% and specificity of 97.5% vs sensitivity of 66.7% and specificity of 94.4%, respectively) and was more cost-effective. Although CT did detect HCC at an earlier stage than USG, this difference was not statistically significant.[20]

Advantages of USG include its simplicity, non-invasiveness, low cost, and lack of radiation exposure. However, it also has disadvantages: operator dependence and the potential for decreased sensitivity in the setting of advanced liver fibrosis, obesity, or ascites.[4,5]

In summary, despite the moderate sensitivity of USG and the poor quality of the evidence supporting its use, USG is currently the best available radiologic surveillance method for detecting HCC.

Surveillance Using Serum Biomarkers

The AASLD does not currently recommend the measurement of AFP or other serum biomarkers alone or in combination with USG for surveillance. There is reasonable evidence to suggest that USG alone is insufficient for HCC surveillance.[21] AFP has been widely studied for HCC surveillance. An AFP level higher than 20 ng/mL results in an optimal balance between sensitivity and specificity for HCC (60% and 90%, respectively).[22] Lowering this cutoff value improves the sensitivity of AFP but increases the false-positive rate.

In the 2009 meta-analysis of 19 studies, the pooled data showed that the combination of AFP measurement and USG vs USG alone was (1) no better at detecting subclinical HCC; (2) less specific, with an increased false-

positive rate; and (3) not cost-effective. Although the combination of AFP measurement and USG increased the overall sensitivity of USG from 63% to 69%, this result was not statistically significant (*P*=.65).[18] In contrast, a prospective cohort study of 446 patients who underwent USG, AFP measurement, or a combination of these every 6 to 12 months suggested that the combination of USG and AFP measurement was superior to either method alone. Surveillance USG and AFP measurement had sensitivity rates of 44% and 66%, respectively, and specificity rates of 92% and 91%, respectively. Sensitivity significantly improved, to 90%, with a slightly lower specificity (83%) when these tests were combined.[23]

Lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3%), which is an isomer of AFP, and des-gamma carboxy prothrombin (DCP) are biomarkers cleared by the US Food and Drug Administration for use in assessing risk for HCC. The elevation of AFP-L3% is associated with the presence of HCC and a shorter tumor doubling time.[24] HCC cells lack carboxylase, which converts DCP to prothrombin. Therefore, HCC is associated with elevated serum levels of DCP. Specifically, elevated serum DCP levels may be a marker of microinvasion of HCC.[25] In combination, imaging and the measurement of AFP, AFP-L3%, and DCP may improve the ability to detect HCC at an early stage. Various studies have investigated these serum biomarkers (alone and in combination) as indicators of the risk for HCC; the results have been promising but controversial.[26-28] For example, a post hoc analysis of the HALT-C (Hepatitis C Antiviral Long-term Treatment Against Cirrhosis) prospective trial examined the DCP and AFP levels of 39 patients with HCC at the time of HCC diagnosis and at 12 months before diagnosis. The study found that neither test alone was adequate for HCC surveillance, nor was the combination of the 2 tests, because the sensitivity of these markers alone or in combination was too low for testing to be efficacious and cost-effective in detecting early-stage HCC.[29] The results of studies evaluating the role of AFP-L3% levels in HCC surveillance were similar.[30]

Many recent studies have looked at the utility of microRNAs for the early detection of HBV-related HCC. In a cohort study of 934 patients (some healthy, some with chronic HBV infection, some with cirrhosis, and some with HBV-related HCC), microRNA panels accurately identified patients who had HCC, regardless of the stage of disease, with a sensitivity of 82% and a specificity of 84%.[31,32]

In summary, the available serum biomarkers are inadequate for HCC surveillance, both in combination with one another and in combination with USG. MicroRNA biomarkers may have a role in the future, but further validation is needed before they can be included in management guidelines.

Surveillance Interval

The HCC surveillance interval is based on the expected tumor growth rate in cirrhosis.[4,5] The median doubling time of an HCC lesion is reported to be 117 days (range, 29-398 days).[33] The limitation of basing a surveillance interval on tumor growth rates is that growth rates of cancer are not necessarily the same as growth rates of subclinical lesions. The surveillance interval need not be adjusted for associated factors, such as HBV or hepatitis C virus (HCV) infection, type of cirrhosis, hepatic decompensation, diabetes mellitus, and family history of HCC.[4,5] A retrospective study of 821 patients with cirrhosis and known HCC (215 detected during semiannual surveillance, 155 during annual surveillance, and 451 after the onset of symptoms) showed the 5-year survival rates to be equivalent for 6- and 12-month surveillance intervals.[34] Pooled data from the 19 studies evaluating USG for HCC surveillance showed the sensitivity of USG with a 6-month surveillance interval to be higher than the sensitivity of USG with a 12-month surveillance interval (70.1% vs 50.1%; *P*=.001).[18] In another randomized, controlled trial involving 1278 patients with compensated cirrhosis, no difference was shown in the rates of detection of HCC with USG every 3 or 6 months (*P*=.300).[35]

In summary, the available evidence suggests that 6 months is the optimal HCC surveillance interval.

Cost-Effectiveness of Surveillance Tests

The AASLD recommends USG as a cost-effective HCC surveillance test. In one study, a computer-based Markov model showed that the incremental cost-effectiveness ratio (ICER)—the ratio of the cost of a test in US dollars to quality-adjusted life-years gained—of semiannual USG and that of combined USG and AFP was $30,700 and $73,500, respectively. The ICERs for semiannual CT and annual magnetic resonance (MR) imaging were consistently greater than $100,000.[36]

Acceptability of Surveillance Tests to Patients and Physicians

Current data show that despite evidence for the benefits of surveillance, HCC surveillance remains underutilized in the United States. A large study of 13,002 patients from Veterans Affairs medical centers showed that only 42% of patients with HCV-related cirrhosis received 1 or 2 surveillance tests during the first year after a diagnosis of cirrhosis, and only 12% of these patients received surveillance during 2 to 4 years of follow-up.[37]

A lack of patient adherence is not the predominant barrier to HCC surveillance. Approximately 95% of patients complete HCC surveillance if it is ordered by a physician.[38] Patients at risk for HCC understand the importance of HCC surveillance, and their rate of acceptance of the tests

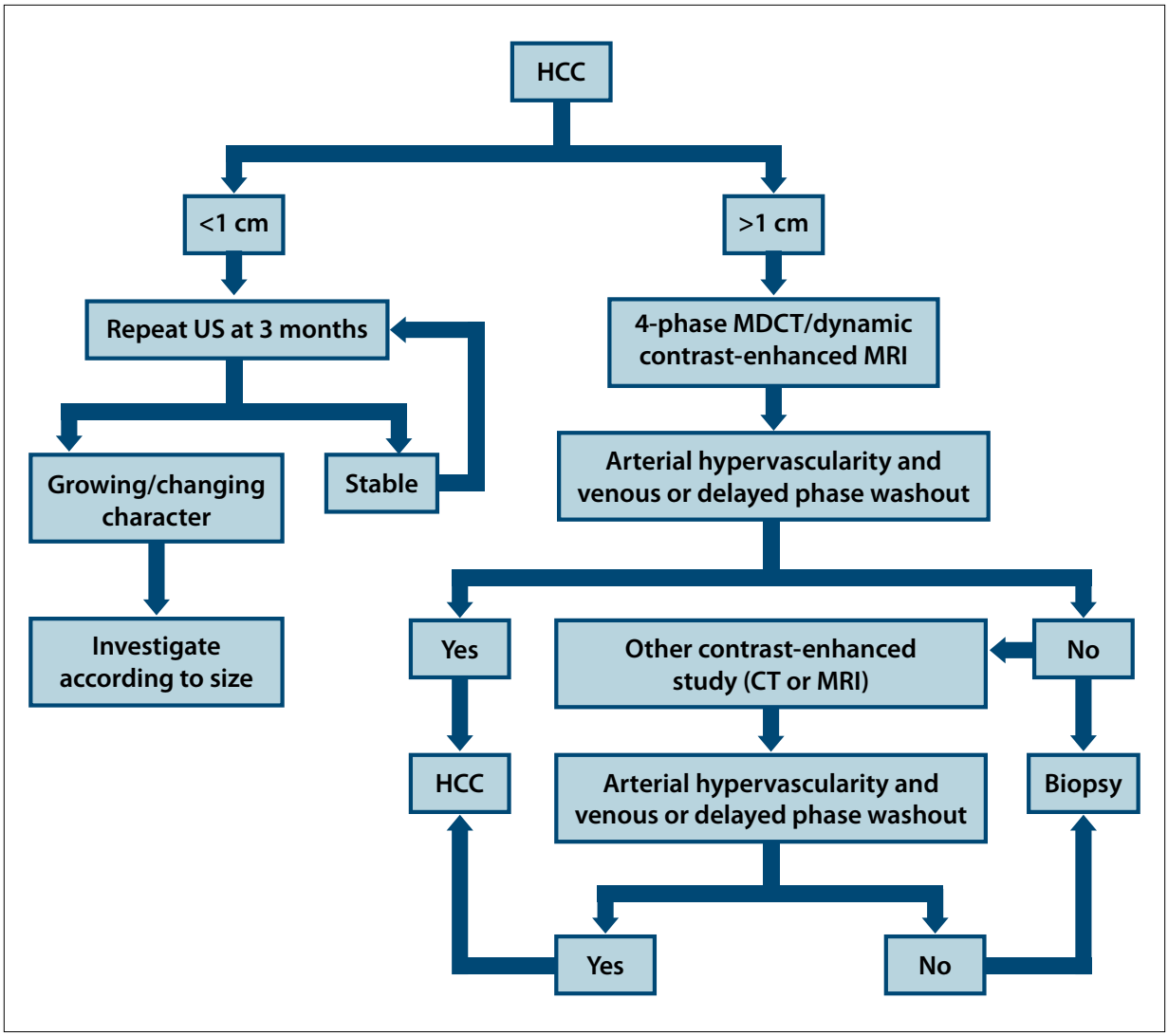

Figure 1. An algorithm from the American Association for the Study of Liver Diseases for the surveillance and diagnosis of hepatocellular carcinoma.[5]

CT, computed tomography; HCC, hepatocellular carcinoma; MDCT, multidetector computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

is high.[39] Compliance with surveillance guidelines has been shown to be strongly related to provider-related factors.[40] Surveillance rates are highest among patients seen or followed by a subspecialist. However, in the United States, only 20% to 40% of patients with cirrhosis are followed by a hepatologist or gastroenterologist.[41] Studies are needed to develop strategies aiming to overcome barriers to HCC surveillance referrals. These strategies include, but are not limited to, provider education, provider feedback on compliance with surveillance guidelines, and clinical reminders.[42]

Recall Guidelines

A recall strategy is a defined algorithm that is followed when a surveillance test detects an abnormal result. For a surveillance test to be useful and acceptable, the provider should understand how the test is interpreted and should know what needs to be done if a patient's test results are abnormal. Studies of HCC pathology suggest that the majority of hepatic nodules smaller than 1 cm are dysplastic nodules, not definite HCC.[4,5,15,43] Therefore, the AASLD guidelines recommend that patients who have tumors smaller than 1 cm be monitored with a USG examination every 3 months (Figure 1). Tumors larger than 1 cm are investigated further with quadruple-phase, contrast-enhanced CT or MR imaging. If the first contrast study does not display the characteristic HCC imaging findings (discussed in the next section), the options are to use a different imaging modality or to obtain a biopsy specimen to confirm the diagnosis (Figure 2). Patients

Table 2. Strategies for the Diagnosis of Hepatocellular Carcinoma Recommended by Various Professional Organizations[4,5,15,61,62]

Organization	Recall Strategy and Diagnostic Algorithm	Imaging Modality	Serum Biomarker
AASLD	According to tumor size (<1 cm or >1 cm), as in Figure 1	Quadruple-phase, contrast-enhanced CT or MR imaging	None
EASL	According to tumor size (<1 cm, 1-2 cm, or >2 cm)	Quadruple-phase, contrast-enhanced CT or MR imaging	None
APASL	According to tumor vascularity (hypovascular vs hypervascular)	Quadruple-phase, contrast-enhanced CT or MR imaging	AFP, DCP
JSH	According to tumor vascularity (hypovascular vs hypervascular)	Quadruple-phase, contrast-enhanced CT or MR imaging	AFP, AFP-L3%, DCP

AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; AFP-L3%, Lens culinaris agglutinin A-reactive fraction of AFP; APASL, Asian Pacific Association for the Study of the Liver; CT, computed tomography; DCP, serum des-carboxy prothrombin; EASL, European Association for the Study of the Liver; JSH, Japan Society of Hepatology; MR, magnetic resonance.

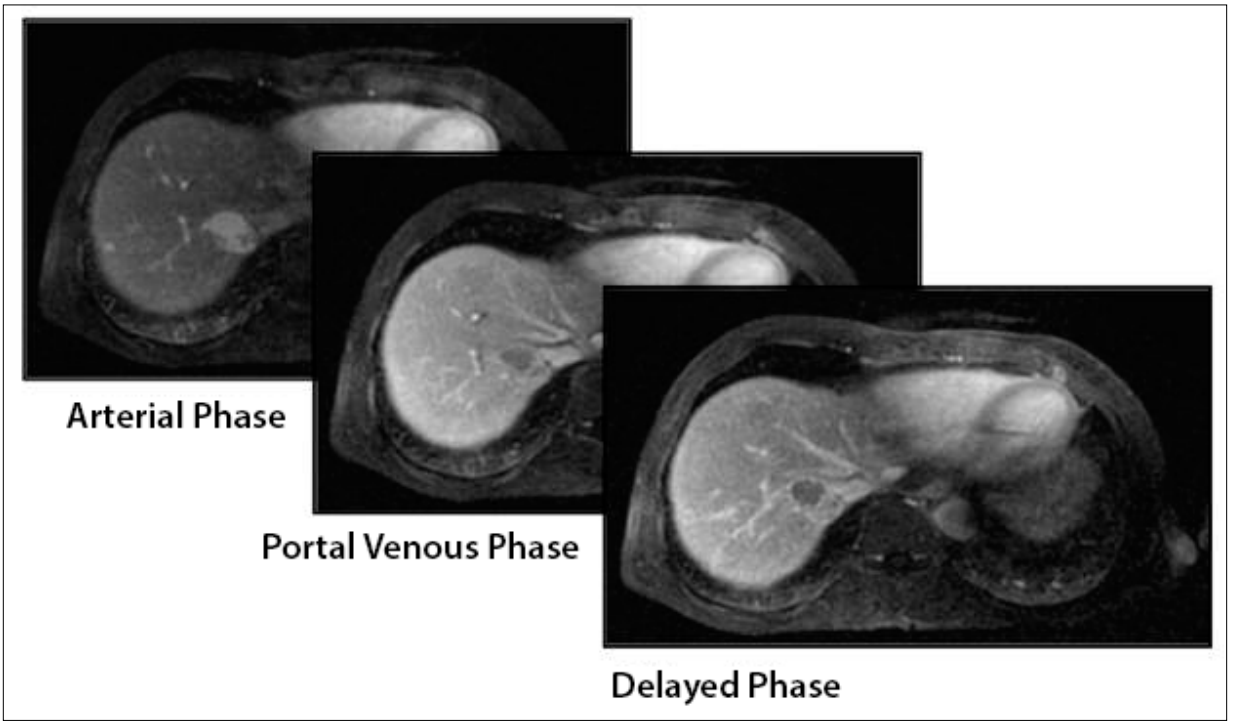

Figure 2. Classic radiologic imaging findings of hepatocellular carcinoma on a dynamic 4-phase computed tomography scan.

who have inconclusive biopsy results should be followed with serial imaging, with a low threshold to undergo biopsy again if radiographic changes are noted.[4,5,15] The AASLD approach to abnormal results (<1 cm and >1 cm) differs from that of other organizations (Table 2).

Diagnosis of Hepatocellular Carcinoma

HCC is suspected in a patient with cirrhosis in the following circumstances: (1) identification of a liver lesion in a patient with cirrhosis during routine surveillance; (2) development of symptoms, such as right upper quadrant pain and loss of weight; (3) the new onset of portal vein thrombosis in a patient with cirrhosis; and (4) the onset of hepatic decompensation (hepatic encephalopathy, jaundice, or manifestations of portal hypertension) without any clear explanation. It is important to make the diagnosis because tumors detected and confirmed early can potentially be managed with curative treatment options.[4,5,15]

Criteria for Diagnosis

Noninvasive, contrast-enhanced imaging is the method of choice for the diagnosis of HCC. This revolutionary change was brought about by good evidence that HCC can be diagnosed accurately with noninvasive imaging if the typical imaging findings are present, which would allow physicians to avoid obtaining multiple biopsies, as

often required in the past.[44-47] The AASLD recommendations for the diagnosis of HCC are compared with those of other professional organizations in Table 2.

Normal liver parenchyma receives a dual blood supply, from the hepatic artery and portal vein. The development of HCC leads to collateral arterialization, loss of the portal venous blood supply, and eventual dependence on the arterial blood supply. When intravenous contrast is introduced, the altered blood flow manifests as a robust arterial enhancement phase followed by a delayed venous "washout" phase (Figure 2).[44,48] This characteristic pattern on contrast imaging is the hallmark for the diagnosis of HCC. Specifically, the diagnostic criteria require the following sequence: (1) an unenhanced phase (before contrast), (2) an arterial phase (upon injection of a bolus of contrast), (3) a portal venous phase (35-55 seconds after initiation of the arterial phase), and (4) a delayed phase (>120 seconds after the injection of contrast). The diagnostic accuracy of this characteristic radiographic pattern has been verified.[15,49,50]

Quadruple-phase, contrast-enhanced imaging of the liver is accomplished with CT and MR imaging. In pooled data from 10 studies on CT and 9 studies on MR imaging, CT had better sensitivity than MR imaging (81% vs 68%) and MR imaging had better specificity than CT (93% vs 85%).[21] The use of diffusion-weighted imaging or a hepatobiliary contrast agent, such as gadoxetic acid (Eovist, Bayer HealthCare Pharmaceuticals), improves the sensitivity of MR imaging.[51] In terms of HCC lesions larger than 2 cm, CT and MR imaging have approximately 95% accuracy. MR imaging was slightly more accurate than CT for lesions smaller than 2 cm.[47]

The advantages of CT include lower cost, shorter time required for the actual test, patient acceptance, quicker interpretation of films, fewer radiographic artifacts, and lack of contraindications to use with metal. In contrast, the advantages of MR include the use of a thinner cannula for contrast injection, use of less contrast, safety in the setting of moderate or severe renal insufficiency (glomerular filtration rate of 30-60 mL/min), and lack of radiation exposure. The choice of test in routine practice varies depending on the preferences of liver centers and individual physicians.

Contrast-enhanced USG is not recommended for the diagnosis of HCC because of its inability to detect the extravasation of microbubbles into the extracellular space, which is characteristic of the hallmark pattern of HCC, and because of false-positive results in patients with biopsy-proven intrahepatic cholangiocarcinoma.[52]

The American College of Radiology has developed the Liver Imaging Reporting and Data System (LI-RADS) as a standardized way to interpret and report liver findings in any patient at high risk for HCC. It can be used for CT or MR imaging with extracellular and hepatobiliary contrast agents. LI-RADS stratifies radiology readings into 8 main groups corresponding to the likelihood of the presence of HCC. The advantage of LI-RADS is that it can be used by both community and academic radiologists.[53]

Role of Serum Biomarkers in the Diagnosis of Hepatocellular Carcinoma

According to the AASLD recommendations, there is no role for biomarkers in the diagnosis of HCC; rather, biomarkers, such as AFP in combination with AFP-L3%, are used as markers of the risk for HCC, as previously discussed. However, other professional organizations use serum biomarkers in the diagnosis of HCC (Table 2).[4]

Role of Liver Biopsy

The sensitivity of liver biopsy in detecting HCC is approximately 90%, and its accuracy is affected by the location of the nodule.[54] Patients with a negative biopsy result require increased surveillance. In terms of complications, the incidence of tumor seeding in a needle track is thought to be 0.9% per year and 2.7% overall, and the rate of hemorrhage due to biopsy is thought to be no different from that for liver biopsy in general.[55,56]

Role of Special Stains

It is not always possible to distinguish HCC from high-grade dysplastic nodules or other disease processes. Staining the liver tissue with vascular endothelium markers (CD34) and biliary epithelium markers (CK7 and CK19) may be useful. Staining for glypican 3, heat shock protein 70, and glutamine synthetase is also useful; studies indicate that positivity for 2 of these 3 stains may confirm the presence of HCC.[57-60]

Treatment of Hepatocellular Carcinoma

Many options are available for the effective treatment of HCC. As mentioned previously, early diagnosis is associated with better treatment outcomes. Treatments may be curative (eg, tumor resection, ablation, or liver transplant) or palliative (eg, transarterial chemoembolization, radioembolization, or sorafenib [Nexavar, Bayer HealthCare Pharmaceuticals and Onyx Pharmaceuticals], which is the only targeted therapy approved by the US Food and Drug Administration). Curative treatments are associated with 5-year survival rates above 50% among candidates for whom these modalities are appropriate. Palliative treatments are associated with variable decreases in morbidity and mortality. Details on the available treatment options are the subject of other articles.[1,4,5]

Areas for Future Research

Investigations should continue to delineate the populations at high risk for HCC and the patients for whom surveil-

lance is beneficial. Barriers to the use of surveillance should be further identified and addressed. Research should continue to elucidate the pathogenesis of HCC and to identify serum biomarkers that can be used alone or in combination with radiography for surveillance and diagnosis.

Summary

HCC is a major cause of morbidity and mortality worldwide. HCC surveillance aims to detect disease at an early stage. Patients at risk for HCC, including those with cirrhosis, should undergo surveillance. USG every 6 months is the most validated surveillance strategy. Surveillance with CT is just as good as surveillance with USG but is less cost-effective. An algorithmic approach is used to guide recall strategies for patients with abnormal test results. Quadruple-phase, contrast-enhanced CT or MR imaging is the test of choice for the diagnosis of HCC. Effective, curative options are available for treating established HCC.

The authors have no relevant conflicts of interest to disclose.

References

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med*. 2011;365(12):1118-1127.
2. El-Serag HB, Davila JA. Surveillance for hepatocellular carcinoma: in whom and how? *Ther Adv Gastroenterol*. 2011;4(1):5-10.
3. Dawson B, Trapp R. Methods of evidence-based medicine and decision analysis. In: *Basic & Clinical Biostatistics*. 4th ed. New York, NY: McGraw-Hill; 2004.
4. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022.
5. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005;42(5):1208-1236.
6. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin*. 2005;55(2):74-108.
7. El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. *J Clin Gastroenterol*. 2002;35(5 suppl 2):S72-S78.
8. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*. 2004;127(5 suppl 1):S27-S34.
9. El-Serag HB. Epidemiology of hepatocellular carcinoma. *Clin Liver Dis*. 2001;5(1):87-107, vi.
10. Jepsen P, Vilstrup H, Tarone RE, Friis S, Sorensen HT. Incidence rates of hepatocellular carcinoma in the U.S. and Denmark: recent trends. *Int J Cancer*. 2007;121(7):1624-1626.
11. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009;27(9):1485-1491.
12. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. *PLoS Med*. 2014;11(4):e1001624.
13. Cucchetti A, Trevisani F, Pecorelli A, et al; Italian Liver Cancer Group. Estimation of lead-time bias and its impact on the outcome of surveillance for the early diagnosis of hepatocellular carcinoma. *J Hepatol*. 2014;61(2):333-341.
14. Kudo M. Japan's successful model of nationwide hepatocellular carcinoma surveillance highlighting the urgent need for global surveillance. *Liver Cancer*. 2012;1(3-4):141-143.
15. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-943.
16. Sarker S, Shoreibah M, Mudumbi S, et al. Patients with stage 3 fibrosis need different and less frequent surveillance compared to stage 4 fibrosis. *Am J Gastroenterol*. 2014;109(12):S165. Abstract P236.
17. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nationwide cohort study. *Ann Intern Med*. 2012;156(12):841-847, W295.
18. Singal AG, 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(1):37-47.
19. Kansagara D, Papak J, Pasha AS, et al. Screening for hepatocellular carcinoma in chronic liver disease: a systematic review. *Ann Intern Med*. 2014;161(4):261-269.
20. Pocha C, Dieperink E, McMaken KA, Knott A, Thuras P, Ho SB. Surveillance for hepatocellular cancer with ultrasonography vs. computed tomography—a randomised study. *Aliment Pharmacol Ther*. 2013;38(3):303-312.
21. 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(3):513-523.
22. Trevisani F, D'Intino PE, Morselli-Labate AM, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. *J Hepatol*. 2001;34(4):570-575.
23. Singal AG, Conjeevaram HS, Volk ML, et al. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):793-799.
24. Kumada T, Nakano S, Takeda I, et al. Clinical utility of Lens culinaris agglutinin-reactive alpha-fetoprotein in small hepatocellular carcinoma: special reference to imaging diagnosis. *J Hepatol*. 1999;30(1):125-130.
25. Koike Y, Shiratori Y, Sato S, et al. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer*. 2001;91(3):561-569.
26. Shimauchi Y, Tanaka M, Kuromatsu R, et al. A simultaneous monitoring of Lens culinaris agglutinin A-reactive alpha-fetoprotein and des-gamma-carboxy prothrombin as an early diagnosis of hepatocellular carcinoma in the follow-up of cirrhotic patients. *Oncol Rep*. 2000;7(2):249-256.
27. Toyoda H, Kumada T, Kiriyama S, et al. Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2006;4(1):111-117.
28. Volk ML, Hernandez JC, Su GL, Lok AS, Marrero JA. Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: a comparison of AFP, DCP, and AFP-L3. *Cancer Biomark*. 2007;3(2):79-87.
29. Lok AS, Sterling RK, Everhart JE, et al; HALT-C Trial Group. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. *Gastroenterology*. 2010;138(2):493-502.
30. Sterling RK, Jeffers L, Gordon F, et al. Clinical utility of AFP-L3% measurement in North American patients with HCV-related cirrhosis. *Am J Gastroenterol*. 2007;102(10):2196-2205.
31. Zhou J, Yu L, Gao X, et al. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. *J Clin Oncol*. 2011;29(36):4781-4788.
32. Zhang ZQ, Meng H, Wang N, et al. Serum microRNA 143 and microRNA 215 as potential biomarkers for the diagnosis of chronic hepatitis and hepatocellular carcinoma. *Diagn Pathol*. 2014;9(1):135.
33. Sheu JC, Sung JL, Chen DS, et al. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology*. 1985;89(2):259-266.
34. Trevisani F, De Notariis S, Rapaccini G, et al; Italian Liver Cancer Group. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). *Am J Gastroenterol*. 2002;97(3):734-744.
35. Trinchet JC, Chaffaut C, Bourcier V, et al; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire (GRETCH). Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. *Hepatology*. 2011;54(6):1987-1997.
36. Andersson K, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2008;6(12):1418-1424.
37. Davila JA, Henderson L, Kramer JR, et al. Utilization of surveillance for hepatocellular carcinoma among hepatitis C virus-infected veterans in the United States. *Ann Intern Med*. 2011;154(2):85-93.
38. Singal AG, Yopp AC, Gupta S, et al. Failure rates in the hepatocellular carcinoma surveillance process. *Cancer Prev Res (Phila)*. 2012;5(9):1124-1130.
39. Singal AG, Volk ML, Rakoski MO, et al. Patient involvement in healthcare is associated with higher rates of surveillance for hepatocellular carcinoma. *J Clin Gastroenterol*. 2011;45(8):727-732.
40. Singal A, Nehra M, Huet B, Marrero J, Lok AS, Lee WM. Failure rates in a surveillance program for hepatocellular carcinoma among patients in the HALT-C Trial. *Gastroenterology*. 2012;142(suppl 1):S1008.

41. Stravitz RT, Heuman DM, Chand N, et al. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. *Am J Med*. 2008;121(2):119-126.
42. Singal AG, Tiro JA, Gupta S. Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. *Clin Gastroenterol Hepatol*. 2013;11(5):472-477.
43. Roskams T. Anatomic pathology of hepatocellular carcinoma: impact on prognosis and response to therapy. *Clin Liver Dis*. 2011;15(2):245-259, vii-x.
44. Levy I, Greig PD, Gallinger S, Langer B, Sherman M. Resection of hepatocellular carcinoma without preoperative tumor biopsy. *Ann Surg*. 2001;234(2):206-209.
45. Burrel M, Llovet JM, Ayuso C, et al; Barcelona Clínic Liver Cancer Group. MRI angiography is superior to helical CT for detection of HCC prior to liver transplantation: an explant correlation. *Hepatology*. 2003;38(4):1034-1042.
46. Yu JS, Kim KW, Kim EK, Lee JT, Yoo HS. Contrast enhancement of small hepatocellular carcinoma: usefulness of three successive early image acquisitions during multiphase dynamic MR imaging. *AJR Am J Roentgenol*. 1999;173(3):597-604.
47. Mueller GC, Hussain HK, Carlos RC, Nghiem HV, Francis IR. Effectiveness of MR imaging in characterizing small hepatic lesions: routine versus expert interpretation. *AJR Am J Roentgenol*. 2003;180(3):673-680.
48. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. *Hepatology*. 2008;47(1):97-104.
49. Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK, 1979-94. *Lancet*. 1997;350(9085):1142-1143.
50. Umemura T, Ichijo T, Yoshizawa K, Tanaka E, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol*. 2009;44(suppl 19):102-107.
51. Lee JM, Yoon JH, Kim KW. Diagnosis of hepatocellular carcinoma: newer radiological tools. *Semin Oncol*. 2012;39(4):399-409.
52. Rimola J, Forner A, Reig M, et al. Cholangiocarcinoma in cirrhosis: absence of contrast washout in delayed phases by magnetic resonance imaging avoids misdiagnosis of hepatocellular carcinoma. *Hepatology*. 2009;50(3):791-798.
53. ACR American College of Radiology. Liver Imaging Reporting and Data System (LI-RADS). v2014. Reston, VA: American College of Radiology; 2014.
54. Sala M, Fuster J, Llovet JM, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. *Liver Transpl*. 2004;10(10):1294-1300.
55. Silva MA, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut*. 2008;57(11):1592-1596.
56. Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK. Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. *Cancer Treat Rev*. 2007;33(5):437-447.
57. Park YN, Kojiro M, Di Tommaso L, et al. Ductular reaction is helpful in defining early stromal invasion, small hepatocellular carcinomas, and dysplastic nodules. *Cancer*. 2007;109(5):915-923.
58. Kandil D, Leiman G, Allegretta M, et al. Glypican-3 immunocytochemistry in liver fine-needle aspirates: a novel stain to assist in the differentiation of benign and malignant liver lesions. *Cancer*. 2007;111(5):316-322.
59. Wang XY, Degos F, Dubois S, et al. Glypican-3 expression in hepatocellular tumors: diagnostic value for preneoplastic lesions and hepatocellular carcinomas. *Hum Pathol*. 2006;37(11):1435-1441.
60. Di Tommaso L, Franchi G, Park YN, et al. Diagnostic value of HSP70, glypican 3, and glutamine synthetase in hepatocellular nodules in cirrhosis. *Hepatology*. 2007;45(3):725-734.
61. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int*. 2010;4(2):439-474.
62. Clinical Practice Guidelines for Hepatocellular Carcinoma – The Japan Society of Hepatology 2009 update. *Hepatol Res*. 2010;40(suppl 1):2-144.