# Surveillance for Hepatocellular Carcinoma

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**KEYWORDS**

• Surveillance • Alpha-fetoprotein • Ultrasound • Cirrhosis

**KEY POINTS**

- Patients with cirrhosis are at the highest risk for hepatocellular carcinoma and should undergo surveillance.
- Surveillance improves overall survival in patients with cirrhosis.
- Alpha-fetoprotein and ultrasound is the best strategy for the early detection of hepatocellular carcinoma.

## INTRODUCTION

The decision to screen a population at risk for a specific cancer is based on well-established criteria.[1] Although the overall goal of surveillance for cancer is the reduction of overall cancer-specific mortality, the objective of surveillance is the application of a reliable and reproducible test in a large number of at-risk individuals to determine whether or not they are likely to develop the cancer for which they are being screened. Screening is the one-time application of an examination that allows detection of a disease at a curable stable and, thereby, reducing mortality, whereas surveillance refers to the continuous monitoring for disease occurrence in a population at risk with the same goals as those of screening. Surveillance is the best strategy that applies to the early detection of hepatocellular carcinoma (HCC).

The World Health Organization developed criteria to assess whether surveillance should be performed for a specific disease.[2] The criteria are as follows: (1) the disease in question should be an important health issue and a significant health burden, (2) there should be an identifiable target population, (3) treatment of disease before onset of symptoms (ie, early stage) should offer advantages compared with the treatment of symptomatic disease, (4) the surveillance examination should be affordable and provide benefits to justify its cost, (5) the surveillance examination should be acceptable to both patients and health care professionals, and (6) surveillance examinations should have an acceptable level of accuracy, and surveillance should result in

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reductions in mortality from the disease. HCC meets all criteria for surveillance and it is recommended to be performed in patients at risk to improve outcomes.[3] We review several of the important aspects for the surveillance of HCC.

## AT-RISK POPULATION

Cirrhosis is found in more than 90% of individuals diagnosed with HCC.[4] Thus, any cause of chronic liver disease and ultimately cirrhosis should be considered as the main risk factor for HCC. The major causes of cirrhosis, and hence HCC, are chronic hepatitis B (HBV) infection, chronic hepatitis C (HCV), alcohol liver disease, and nonalcoholic fatty liver disease (NAFLD), but less prevalent conditions such as hereditary hemochromatosis, primary biliary cholangitis, and Wilson disease have also been associated with HCC development.

The decision to enter a patient into a surveillance program is determined by the level of risk for HCC while also taking into account the patient's age, overall health, functional status, and willingness and ability to comply with surveillance requirements. The level of HCC risk, in turn, is indicated by the estimated incidence of HCC. However, there are no experimental data to indicate the threshold incidence of HCC to trigger surveillance. Instead, decision analysis has been used to provide some guidelines as to the incidence of HCC at which surveillance may become effective. In general, an intervention is considered effective if it provides an increase in longevity of approximately 100 days, that is, approximately 3 months.[5] Interventions that can be achieved at a cost of less than approximately USD 50,000/y of life gained are considered cost-effective.[6] Several published decision analysis/cost-effectiveness models for HCC surveillance have reported that surveillance is cost-effective, although in some cases only marginally so, and most find that the effectiveness of surveillance depends on the incidence of HCC. For example, in a theoretic cohort of patients with Child-Pugh A cirrhosis, Sarasin and colleagues[7] reported that surveillance increased longevity by approximately 3 months if the incidence of HCC was 1.5%/year; if the incidence was lower, surveillance did not prolong survival. Conversely, Lin and colleagues[8] found that surveillance with alfa-fetoprotein (AFP) and ultrasound was cost-effective regardless of HCC incidence. Thus, although there is some disagreement between published models, surveillance should be offered for patients with cirrhosis of varying etiologies when the risk of HCC is 1.5%/year or greater. The preceding cost-effectiveness analyses, which were restricted to cirrhotic populations, cannot be applied to hepatitis B carriers without cirrhosis. A cost-effectiveness analysis of surveillance for hepatitis B carriers using ultrasound and AFP levels suggested that surveillance became cost-effective once the incidence of HCC exceeded 0.2%/year.[4] **Table 1** shows the populations at risk for HCC that should undergo surveillance. We will review the most common causes of cirrhosis.

### *Hepatitis B Virus*

The evidence linking HBV with HCC is unquestioned.[9] Active viral replication is associated with higher risk of HCC and longstanding active infection with inflammation resulting in cirrhosis is the major event resulting in increased risk.[10,11] The incidence of HCC in inactive HBV carriers without liver cirrhosis is less than 0.3% per year. The role of specific HBV genotypes or mutations in hepatocarcinogenesis is not well established, especially outside Asia. HBV DNA integrates into the host cellular genome in most cases of chronic hepatitis B and induces genetic damage. DNA integration in nontumoral cells in patients with HCC suggests that genomic integration and damage precede the development of tumor. Thus, infection with HBV may be

**Table 1**
**Patients at the highest risk for HCC**

| Population Group | Incidence of HCC |
|---|---|
| Asian male hepatitis B carriers older than 40 | 0.4%–0.6% per y |
| Asian female hepatitis B carriers older than 50 | 0.3%–0.6% per y |
| Hepatitis B carrier with family history of HCC | Incidence higher than without family history |
| HBV cirrhosis | 3%–8% per y |
| HCV cirrhosis | 1%–3% per y |
| Hepatitis C cirrhosis | 1%–3% per y |
| NAFLD cirrhosis | 1%–3% per y |
| Alcohol-related cirrhosis | 1%–3% per y |
| Genetic hemochromatosis and cirrhosis | 1%–2% per y |
| Alpha-1 antitrypsin deficiency and cirrhosis | ~1% per y |
| Primary biliary cholangitis cirrhosis | 2%–5% per y |
| Autoimmune hepatitis cirrhosis | 2%–3% per y |

*Abbreviations:* HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; NAFLD, nonalcoholic fatty liver disease.

correlated with the emergence of HCC even in the absence of liver cirrhosis. However, most studies show that the risk of HCC increases markedly in those with cirrhosis.[12] The HCC incidence among patients without cirrhosis ranged from 0.1 to 0.8 per 100 person-years, whereas the incidence in cirrhosis ranged from 2.2 to 4.3 per 100 person-years. There is strong evidence from prospective cohort studies that persistent HBV e antigen (HBeAg) and high levels of HBV serum DNA increase the risk of HCC. There is a multiplicative effect of heavy smoking and alcohol drinking in those with HBV infection, increasing the risk of HCC ninefold. The implementation of vaccination against HBV, as well as antiviral treatment of HBV infection has resulted in a significant decrease of HCC incidence.[13] Family history of HCC in patients with chronic HBV are at a significantly higher risk for developing HCC, and should undergo surveillance.[14]

### *Hepatitis C Virus*

HCV is the most common cause of HCC in Western countries and fueled the increase in HCC in the United States. The prevalence of HCV in HCC cohorts varies according to the prevalence of HCV within each geographic area. HCC risk sharply increases after cirrhosis develops, with annual incidence ranging between 2% and 8%.[15] In addition, in patients with cirrhosis, the risk of HCC decreases but is not completely eliminated even after a sustained response to antiviral therapy.

Currently, well-tolerated combinations of direct-acting antivirals (DAAs) have replaced interferon-based therapy. The rates of sustained virological response (SVR) with combinations of DAAs exceed 95%.[16] Importantly, DAA therapy may lead to decreases in portal hypertension and change the natural history of patients with cirrhosis.[17] Successful DAA therapy is associated with a 71% reduction in HCC risk.[18] However, patients with cirrhosis continue to have a significantly elevated risk of HCC despite achieving SVR, with HCC being reported even 10 years after SVR. It is of critical importance to continue HCC surveillance in those with cirrhosis who have achieved SVR. DAA therapies have led to a significant reduction in HCC incidence from 3.6% per year to 1.8% per year,.[19]

An important question is whether those without cirrhosis should undergo surveillance. Those without cirrhosis have a lower HCC incidence of 1% per year and, therefore, would not warrant surveillance.[20] Another large study showed that those without cirrhosis but with a fibrosis-4 (Fib-4) score >3.25 had an incidence rate for HCC of 0.9% per 100 person-years (confidence interval [CI] 0.54–1.43).[19] Therefore, at this time, those without cirrhosis should not undergo surveillance for HCC because the incidence rate is too low for a survival benefit.

### *Nonalcoholic Fatty Liver Disease*

It has been estimated that the worldwide prevalence of NAFLD is approximately 25%, and it is likely to continue to increase.[21] An association between NAFLD and HCC is well established.[22] In a study comparing the incidence of HCC among patients with HCV infection and NAFLD, 315 patients with cirrhosis secondary to HCV and 195 with cirrhosis due to NAFLD were followed for a median of 3.2 years.[23] The cumulative incidence of HCC was 2.6% in the NAFLD group compared with 4% in the HCV group ($P = .09$). The annual HCC incidence rate among patients with cirrhosis from NAFLD is approximately 1.8% per 100,000.[24]

The population attributable fraction (PAF) is the quantifiable contribution of a risk factor to a disease such as HCC. It is important for pursuing prevention of disease or interventions that may reduce disease burdens. A population-based study of 6991 patients with HCC older than 68 years evaluated the PAF.[25] The study showed that eliminating diabetes and obesity has the potential for a 40% reduction in the incidence of HCC and the impact would be higher than eliminating other factors including HCV. Therefore, the presence of the metabolic syndrome could be an important area for the prevention of HCC and a target for future interventions.

HCC does occur in patients without cirrhosis. HCC has been observed in patients with NAFLD without cirrhosis but incidence rates at lower than 1% a year.[26] Additional high-quality prospective studies are needed to confirm these observations, but at this time surveillance is not recommended in patients without cirrhosis. A recent review recommended surveillance for HCC among those with NAFLD with advanced fibrosis based on the difficulty of the available tools to distinguish cirrhosis from those with advanced fibrosis.[27]

### *Other Etiologies of Liver Disease*

Alcohol-related cirrhosis is also associated with the development of HCC. The proportion of HCC attributed to alcoholic liver disease has been constant between 20% to 25%.[28] The risk of HCC among patients with alcoholic cirrhosis ranges from 1.3% to 3.0% annually.[29] The PAF for alcoholic liver disease is estimated to be between 13% and 23%, but this effect is modified by race and gender. Importantly, the effect of alcohol as an independent risk factor for HCC is potentiated by the presence of concurrent factors, especially viral hepatitis. Therefore, cirrhosis related to alcoholic liver disease remains an important risk factor for developing HCC.

Other causes of cirrhosis can also increase the risk of HCC. In a population-based cohort of patients with hereditary hemochromatosis and 5973 of their first-degree relatives, the authors found 62 patients developed HCC with a standardized incidence ratio of 21 (95% CI: 16–22).[30] Men were at higher risk than women, and there was no increased risk for development of nonhepatic malignancies. Cirrhosis from primary biliary cholangitis is also an important risk factor. In a study of 273 patients with cirrhosis from primary biliary cholangitis followed for 3 years, the incidence rate was 5.9%.[31] In a systematic review, a total of 6528 patients with autoimmune hepatitis with a median follow-up of 8 years were evaluated for HCC incidence.[32] The pooled

incidence rate in the study was 3.1 per 1000 person-years, indicating that autoimmune hepatitis-related cirrhosis is a risk factor for HCC. In a prospective study of patients with cirrhosis due to alpha-1 antitrypsin deficiency, the annual incidence rate of HCC was 0.9% after a median follow-up time of 5.2 years.[33]

### *Liver Function and Hepatocellular Carcinoma Surveillance*

Given the goal of HCC surveillance is to improve survival, this should be performed in patients who are eligible for HCC-related treatments. Therefore, prior studies have suggested HCC surveillance should be performed in patients with Child A or B cirrhosis but is not beneficial in Child C patients outside of liver transplant eligibility.[3,4] Moreover, if a patient's age, medical comorbidities, and poor performance status (ie, wheelchair bound) are clinically significant, then it is unlikely that these patients would have a survival benefit from surveillance for HCC, and palliative treatment should be considered. There are no studies that have indicated the best surveillance strategy for those on the liver transplant waiting list, although clearly surveillance for HCC is indicated given the increased priority these patients have for liver transplantation and the potential for curative therapy with this modality.

## RISK STRATIFICATION FOR HEPATOCELLULAR CARCINOMA

The incidence rates for HCC among cirrhosis ranges from 1% to 3% per year, which means that the patients with cirrhosis are a group at a very high risk for developing HCC. However, the risk of developing HCC is not homogeneous among the patients with cirrhosis. For example, men have more than a 2:1 risk of developing HCC compared with women. The ability to stratify the risk of HCC is urgently needed to maximize the surveillance tests to those at the high risk. Unfortunately, prior predictive algorithms based on typical clinical risk factors such as age, gender, and degree of liver dysfunction have suboptimal performance when externally validated.[34] Recently, a tissue-based gene expression profile that predicts clinical progression in persons with HCV-induced cirrhosis and the development of HCC in individuals with cirrhosis has been developed. For the 186-gene expression panel that predicts clinical progression, classification in the high-risk group was associated with significantly increased risks of hepatic decompensation (hazard ratio [HR] 7.36, $P<.001$), overall death (HR 3.57, $P = .002$), liver-related death (HR 6.49, $P<.001$) and all liver-related adverse events (HR 4.98, $P<.001$).[35] For prediction of HCC development, the 186-gene panel was reduced to a 32-gene signature implemented on the Nanostring platform. In an independent cohort of 263 surgically treated patients with early-stage HCC, the probability of developing HCC was nearly fourfold higher in patients with a high-risk prediction score (41%/year) compared with those with a low-risk prediction score (11%/year).[36] Using these data, a recent Markov model was performed with an initial strategy of stratifying the risk HCC into a high-risk, intermediate-risk, or low-risk group using the molecular signature.[37] Once stratified into a risk group, a surveillance modality was for each group. Compared with biannual ultrasound and AFP, risk-stratified approach was more cost-effective. The surveillance of the high-risk group with MRI or abbreviated MRI was cost-effective with no surveillance of the low-risk group. Although this study needs prospective validation, it shows that surveillance strategies tailored to HCC risk are cost-effective and may improve overall utilization of surveillance. This panel looks promising to better define which of those with cirrhosis are at risk for development of HCC; however, it needs validation in serum as well as in different racial/ethnic groups and in different etiologies of liver disease before

widespread use. It is likely that the ability to stratify the risk of HCC among patients with cirrhosis will ultimately be a combination of demographic, clinical, and genetic data.

## SURVEILLANCE TESTS

At this time, HCC surveillance should be performed for all individuals with cirrhosis.[3] The modalities recommended for surveillance are liver ultrasound with or without AFP every 6 months. Ultrasound, with or without AFP, is recommended for surveillance because most of the studies showed a benefit of the combination of ultrasound and AFP in improving overall survival with a pooled sensitivity of 65% and specificity of 90%.[38]

Recently, guidelines have been developed for how surveillance ultrasound examinations should be performed, interpreted, and reported.[39] An ultrasound examination is considered negative if there are no focal abnormalities or if only definitely benign lesions such as cysts are identified. An examination is considered nondiagnostic if there are lesions measuring smaller than 10 mm that are not definitely benign. An examination is considered positive if there are lesions measuring $\geq$10 mm. A 10-mm threshold is used because lesions smaller than 10 mm are rarely malignant. Even if malignant, such nodules are difficult to diagnose reliably because of their small size and, so long as the patient is in regular surveillance, they may be followed safely. By comparison, lesion(s) $\geq$10 mm have a substantial likelihood of being malignant,[40] they are easier to diagnose reliably, and there is greater risk of harm from delaying the diagnosis.

AFP is considered positive if its value is >20 ng/mL, and negative if lower. Based on receiver operating curve analysis, this threshold provides a sensitivity of approximately 60% and a specificity of approximately 90%.[41] Assuming a 5% prevalence of HCC (approximately that expected in the HCC surveillance population), this is expected to provide 25% positive predictive value for HCC. Moreover, the addition of AFP is expected to increase the sensitivity of surveillance ultrasound, although the magnitude of the incremental gain is not yet known. More recent data suggest longitudinal changes in AFP may increase sensitivity and specificity than AFP interpreted at a single threshold of 20 ng/mL.[42] Other suggested strategies to increase AFP accuracy have included use of different cutoffs by cirrhosis etiology and AFP-adjusted algorithms but needs further validation.

In addition to AFP, a number of other biomarkers have been evaluated for surveillance. These include the *Lens culinaris* lectin binding sub-fraction of the AFP, or AFP-L3%, which measures a sub-fraction of AFP shown to be more specific although generally less sensitive than the AFP,[43] and des gamma carboxy prothrombin (DCP), also called protein induced by vitamin K absence/antagonist-II (PIVKA-II), a variant of prothrombin that is also specifically produced at high levels by a proportion of HCC.[44] These biomarkers are approved by the Food and Drug Administration for risk stratification but not HCC surveillance in the United States. In the past few years, a diagnostic model has been proposed that incorporates the levels of each of the 3 biomarkers AFP, AFP-L3%, and DCP, along with patient gender and age, into the Gender, Age, AFP-L3%, AFP, and DCP (GALAD) model.[45] GALAD has been shown to be promising in phase II (case-control) biomarker studies but still requires phase III and phase IV studies to evaluate its performance in large cohort studies.

There is also active development of novel cancer biomarker assays, including assays for cancer-specific DNA mutations, differentially methylated regions of DNA, microRNAs, long non-coding RNAs, native and posttranslationally modified proteins,

and biochemical metabolites. Recent results suggest that there is differential expression of many biomolecules in exosomes released from tumor cells compared with those from normal cells.[46]

Despite their high diagnostic performance, cross-sectional multiphase contrast-enhanced computed tomography (CT) or MRI are not recommended for HCC surveillance given the paucity of data on its efficacy and cost-effectiveness. However, a recent cohort study of 407 patients with cirrhosis compared ultrasound with MRI (liver-specific contrast) for the surveillance of HCC.[47] A total of 43 patients developed HCC, with 1 detected by ultrasound only, 26 by MRI alone, 11 by both, and 5 missed by both modalities. MRI had a lower false-positive rate compared with ultrasound (3.0% vs 5.6%, $P = .004$). This is a provocative study that requires further validation as the primary surveillance test. Future studies should evaluate whether surveillance MRI may be better suited in those in whom the performance of ultrasound will be suboptimal due to body habitus or other criteria. To maximize the value of cross-sectional MRI while minimizing contrast exposure, scanning time, and cost, abbreviated MRI (AMRI) examination protocols have been developed and are being tested.[48] The abbreviated protocols typically include T1-weighted imaging obtained in the hepatobiliary phase post gadoxetate disodium injection, often supplemented with T2-weighted imaging and diffusion-weighted imaging. These protocols achieve sensitivities of 80% to 90% and specificities of 91% to 98% in small cohort studies. Ongoing studies may clarify the most appropriate niche for cost-effective and safe use of CT and MRI, AMRI protocols, perhaps particularly in those settings in which ultrasound performs the least reliably, such as in individuals with truncal obesity or marked parenchymal heterogeneity due to cirrhosis.

The surveillance strategy of biannual ultrasound versus MRI in patients with cirrhosis was shown to be cost-effective.[49] The study showed that MRI leads to increase in life-years and quality adjusted life years despite an increase in costs of >$5000; however, the importance of this study is that the annual HCC incidence was the most influential factor on determining the cost-effectiveness of this strategy. When the HCC incidence rate was greater than 1.81%, the strategy of using MRI was cost-effective; however, the surveillance strategy with MRI was not cost-effective at lower incidence rates, again further evidence that risk stratification is urgently needed. As reviewed previously, the HCC incidence rates in NAFLD, alcohol, and treated HCV cirrhosis, the most common chronic liver disease, have lower incidence rates than what this study shows to be cost-effective and therefore, this strategy of obtaining MRI every 6 months is not be feasible at this time. This study confirms the need and the importance for stratifying the risk of HCC among patients with cirrhosis to use MRI for those at the highest risk.

## SURVEILLANCE UTILIZATION AND HARMS

An important limitation of the effectiveness of HCC surveillance in patients with cirrhosis has been the low utilization of this strategy in patients with cirrhosis.[50] In this systematic review, 29 studies with a total of 118,799 patients were evaluated and found to have a pooled estimate for surveillance utilization of 24.0% (95% CI 18.4–30.1). In subgroup analyses, the highest surveillance receipt was reported in studies with patients enrolled from subspecialty gastroenterology/hepatology clinics and lowest in studies characterizing surveillance in population-based cohorts. Commonly reported correlates of surveillance included higher receipt among patients followed by subspecialists and lower receipt among those with alcohol-related or nonalcoholic steatohepatitis–related cirrhosis. Modeling studies have shown that

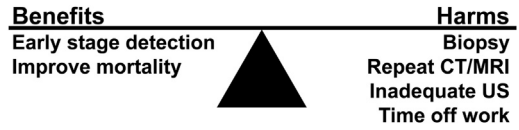


**Fig. 1.** The balance of benefits and harms of surveillance for HCC. US, ultrasound of the liver.

the minimal utilization of surveillance in patients with cirrhosis should be 34% of the population to improve outcomes.[51] The overall utilization of surveillance remains too low and is an important reason for the overall poor outcomes seen with this HCC.

Interventions to improve utilization of surveillance have been performed with outreach invitations, patient/provider educations, mailed/call reminders, and nurse navigators have resulted in an increase of surveillance utilization between 9% and 64%.[50] Unfortunately, these interventions proven to increase surveillance utilization have not been implemented in medical centers, so there is an opportunity to potentially improve outcomes if these interventions are applied. HCC surveillance utilization needs to markedly increase to improve overall impact of early detection for these patients.

The harms of surveillance are being recognized as an important aspect of early detection of cancer, and a balance between the benefits (early detection of the tumor) and harms is the best desired effect as shown in **Fig. 1**. The harms of surveillance were evaluated in a cohort of patients with cirrhosis undergoing surveillance, and it showed that the harms of surveillance (mostly related to false-positives and indeterminate tests) were more often associated with ultrasound when compared with AFP.[52] The harms were mostly physical related to follow-up imaging tests (CT, MRI, or angiogram) or performing a liver biopsy. There are also indirect harms related to potential loss of income by taking the time off to perform these tests or time off from family duties that also needs to be taken into account. Moreover, it has been estimated that 20% of ultrasounds are classified as inadequate for surveillance, and alternative surveillance modalities may be needed in those with inadequate surveillance ultrasound such as in obesity, alcohol, and NAFLD-related cirrhosis.[53] A recent model showed that accounting for both harms and benefits of ultrasound and AFP surveillance for HCC results in the best cost-effective strategy at this time.[54] Therefore, when assessing the surveillance strategy for the early detection of HCC, a balance between the benefits and harms is critically important, and overall AFP plus ultrasound is the best strategy.

## SUMMARY

Patients with cirrhosis should undergo surveillance with AFP in combination with ultrasound. Harms and benefits of surveillance should be taken into account when deciding whether to start surveillance for a patient. Better tools for risk stratification and new surveillance strategies are being developed that may further improve the benefits of surveillance for HCC.

## DISCLOSURE

Consultant Glycotest.

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