**Name of Journal: *World Journal of Gastroenterology***

**Manuscript NO: 46747**

**Manuscript Type: MINIREVIEWS**

**Hepatocellular carcinoma surveillance: An evidence-based approach**

Harris PS *et al*. HCC surveillance

Patrick S Harris, Ross M Hansen, Meagan E Gray, Omar I Massoud, Brendan M McGuire, Mohamed G Shoreibah

**Patrick S Harris, Ross M Hansen,** Division of Internal Medicine, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States

**Meagan E Gray, Omar I Massoud, Brendan M McGuire, Mohamed G Shoreibah,** Division of Gastroenterology and Hepatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States

**ORCID number:** Patrick S Harris (0000-0002-9583-2939); Ross M Hansen ([0000-0003-4502-1377](https://orcid.org/0000-0003-4502-1377)); Meagan E Gray (0000-0001-7556-8985); Omar I Massoud (0000-0002-5093-9572); Brendan M McGuire (000-0002-15310-4112); Mohamed G Shoreibah (0000-0002-8461-3976).

**Author contributions:** Harris PS and Shoreibah MG contributed to the conception and design of the study; Harris PS and Hansen RM contributed to literature review, analysis and drafting of manuscript; Shoreibah MG, Gray ME, Massoud OI and McGuire BM contributed to critical revision and editing; all authors equally contributed to approval of the final version.

**Conflict-of-interest statement:** No potential conflicts of interest.

**Open-Access:** This is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Corresponding author:** **Mohamed G Shoreibah, MD, Attending Doctor, Doctor,** Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, 1808 7th Avenue South, BDB 391, Birmingham, AL 35294, United States. mshoreibah@uabmc.edu

**Telephone:** +1-205-9755676

**Fax:** +1-205-9759777

**Received:** February 21, 2019

**Peer-review started:** February 22, 2019

**First decision:** March 5, 2019

**Revised:** March 9, 2019

**Accepted:** March 16, 2019

**Article in press:**

**Published online:**

**Abstract**

Hepatocellular carcinoma (HCC) makes up 75%-85% of all primary liver cancers and is fourth most common cause of cancer related death worldwide. Chronic liver disease is the most significant risk factor for HCC with 80%-90% of new cases occurring in the background of cirrhosis. Studies have shown that early diagnosis of HCC through surveillance programs improve prognosis and availability of curative therapies when. All patients with cirrhosis and high-risk hepatitis B patients are at risk for HCC and should undergo surveillance. The recommended surveillance modality is abdominal ultrasound (US) given that it is cost effective, noninvasive with good sensitivity. However, US is limited in obese patients and those with non-alcoholic fatty liver disease (NAFLD). With the current obesity epidemic and rise in the prevalence of NAFLD, abdominal computed tomography or magnetic resonance imaging may be indicated as the primary screening modality in these patients. The addition of alpha-fetoprotein to a surveillance regimen is thought to improve the sensitivity of HCC detection. Further investigation of serum biomarkers is needed. Semiannual screening is the suggested surveillance interval. Surveillance for HCC is underutilized and low adherence disproportionately affects certain demographics such as non-Caucasian race and low socioeconomic status.

**Key words:** Liver cancer; Hepatocellular carcinoma; Surveillance

**© The Author(s) 2019.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Hepatocellular carcinoma (HCC) is a leading cause of cancer related death and 80%-90% of new cases occur in patients with cirrhosis. Surveillance programs have been developed on the basis that earlier detection of disease provides more curative treatment options and a better prognosis. This comprehensive review focuses on current literature regarding the utility of HCC surveillance, high-risk populations, surveillance modalities and adherence and recall.

Harris PS, Hansen RM, Gray ME, Massoud OI, McGuire BM, Shoreibah MG. Hepatocellular carcinoma surveillance: An evidence-based approach. *World J Gastroenterol* 2019; In press

**INTRODUCTION**

Primary liver cancer is projected to be the sixth most commonly diagnosed and fourth most common cause of cancer death worldwide in 2018 with hepatocellular carcinoma (HCC) making up 75%-85% of all primary liver cancers[1]. HCC has a higher incidence in developing countries with > 80% of HCC cases occurring in either sub-Saharan Africa or Eastern Asia. HCC is three times more prevalent among men than women. The mean age at diagnosis varies among geographical location depending on the local burden of disease. While the incidence of HCC is decreasing in some Chinese and Japanese populations due to vaccination and treatment programs for viral hepatitis, HCC cases are increasing in the United States. In fact, HCC is the fastest growing cause of cancer-related deaths in the United States, with a decrease in the mean age at diagnosis[2-4]. Chronic liver disease of any etiology remains the most significant risk factor, with 80% to 90% of new HCC cases occurring in this population[4-6]. Given the international burden of disease, surveillance programs have been developed for earlier detection and mortality reduction. Current guidelines recommend enrollment in surveillance programs for adults with cirrhosis and high-risk patients without cirrhosis using ultrasound (US) with or without alpha-fetoprotein (AFP) at six-month intervals. These guidelines are largely unanimous among major international societies including the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL)[7-9]. Our objective is to summarize the current literature regarding utility of HCC surveillance, high-risk populations, surveillance modalities and adherence and recall.

**LITERATURE SEARCH**

A comprehensive literature search was performed using PubMed and Google Scholar for research papers regarding HCC surveillance and related literature was analyzed to prepare this review article. We did not restrict the search to a certain period of time. Articles written in English and published in peer-reviewed journal were included.

**HCC SURVEILLANCE**

Optimal screening tests are designed to detect an asymptomatic or subclinical disease and must meet several criteria including high sensitivity, cost effectiveness and availability. Diseases suitable for screening include those that are of high burden in selected populations with a proven treatment strategy and outcomes that improve with early detection[10]. When screening tests are used at regular intervals in at-risk populations, this is considered surveillance[11].

A randomized clinical trial (RCT) is the optimal way to measure the effectiveness of cancer surveillance programs but unfortunately there is limited RCT data available to address whether HCC surveillance programs reduce disease-related mortality. A key study that is often cited was performed by Zhang *et al*[12] in China and included 18816 patients with current or previous evidence of hepatitis B infection. The selected patients were randomly assigned to surveillance group (*n* = 9373) or control group (*n* = 9443). Surveillance in this study consisted of measurement of serum AFP levels and US imaging every 6 mo. Study adherence was poor (60%) but showed a significant reduction (37%) in mortality related to HCC in the surveillance group. While this landmark study is the basis for many of the surveillance recommendations, it is not without its criticisms and limitations. Limitations of this study include lack of outcome data other than death and lack of information regarding all-cause mortality. The authors also failed to account for clustering which could produce misleading statistical significance. Additionally, the study population included only HBV patients. With these points in mind, some have argued that there is limited ability to extrapolate this data and its conclusions to Western countries[13]. However, any attempts to affirm these conclusions with an RCT in North America or Europe is largely impractical due to ethical concerns in randomizing patients at risk for HCC to a no surveillance group and the sheer difficulty of enrolling patients who are informed of the potential risks and benefits of HCC surveillance[14].

Although the RCT data is of limited quality and unable to be replicated, this does not disprove the effectiveness of HCC surveillance and there is observational data available to support a survival benefit from HCC surveillance. A 2014 meta-analysis of forty-seven cohort and case-controlled studies looked at the effect of HCC surveillance on early tumor stage detection, receipt of curative therapy and overall survival in patients with cirrhosis. Of the 15158 patients analyzed, 6284 (41.4 %) had HCC detected by surveillance while 8874 (58.6%) had HCC detected incidentally or due to presence of symptoms. Rates of HCC detected by surveillance were higher among studies in the United States (51%) and Europe (45%). Of the studies that included data on tumor stage and curative treatment, HCC surveillance was associated with improved early stage detection, curative treatment rates and prolonged survival. The pooled 3-year survival rate was 50.8% among patients undergoing surveillance compared to 27.9% among those without surveillance. Overall the data is encouraging, however, limitations include short duration of follow up and failure to adjust for liver function or lead-time bias. This data suggests that given the association of HCC surveillance with significant improvements in early tumor detection, these patients are more likely to receive curative treatment and thus overall survival benefit providing evidence to support regular HCC surveillance guidelines[15].

Given the poor 1-year and 3-year survival rates in patients with HCC (36% and 17%, respectively), early detection may provide curative treatment options including surgical resection, transplantation and percutaneous ablation. Finding late stage or advanced HCC removes these options and leaves only palliation[16-18].

HCC surveillance has also been shown to be cost effective. Both Lin *et al*[19] and Arguedas *et al*[20] found that HCC screening using either biannual AFP and annual abdominal US or triple phase computed tomography (CT) were cost effective compared to no surveillance, with cost effectiveness ratio less than $50000 quality-adjusted life year. This is comparable to other frequently used screening strategies including colonoscopy and mammography[19,20].

**HIGH RISK POPULATIONS**

The AASLD recommends offering surveillance when the risk of HCC is at least 1.5%/year and the incidence is greater than 0.2%/year, which includes patients with cirrhosis and some non-cirrhotic hepatitis B carriers[7]. The risk for HCC in chronic liver disease differs based on the underlying etiology of disease. Chronic hepatitis C virus (HCV) infection is associated with a 15- to 20-fold higher risk of HCC compared to those without HCV and patients with HCV related cirrhosis have a 3.5% annual rate of HCC development[4]. While HCC can develop in HCV infected patients in the absence of cirrhosis, the odds decrease to one fifth when elastography shows a lack of advanced fibrosis (< 10 kPa)[21]. Currently, HCC surveillance is not recommend in patients with chronic hepatitis C without cirrhosis[7]. Eradication of HCV with sustained viral response (SVR) has been shown to decrease the risk for HCC. Morgan *et al*[22] previously showed that in the interferon era, eradication of HCV with SVR resulted in a reduced risk for HCC (relative risk = 0.24).

The landscape of HCV treatment has evolved with the availability of effective direct antiviral agents (DAAs). As opposed to IFN-based therapies, DAAs are better tolerated in patients with advanced liver disease and can provide SVR rates > 95%[23-25]. Despite the utility of DAAs, there has been a debate regarding increased incidence of HCC (recurrence or *de novo*) in contrast to IFN-based treatment. There are conflicting results from various retrospective studies looking at DAA therapy and HCC. An initial small cohort study by Reig *et al*[25] suggested an increase in rates of HCC following DAA therapy, however a large meta-analysis subsequently found no difference in HCC occurrence in patients following SVR from DAA *vs* IFN-based treatment[26]. Kwong *et al*[27] recently showed that although the incidence of *de novo* HCC in patients with HCV cirrhosis has increased in the DAA era, these changes may be explained by changes in the rates of liver transplantation among HCV patients and wait list mortality. Increasing age and severity of liver disease likely contributes to a higher incidence of HCC in transplant candidates as well[23,27]. Current guidelines continue to recommend HCC surveillance in patients with cirrhosis even after eradication of HCV with DAA therapy[7].

Patients with chronic hepatitis B virus (HBV) represent a unique population who require HCC surveillance outside of the setting of cirrhosis. Specific recommendations for surveillance in patients with chronic hepatitis B without cirrhosis include Asian and black males > age 40, Asian females > age 50, African/North African blacks with hepatitis B > age 20, patients with hepatitis D co-infection, and patients with a first-degree relative with HCC[7,28]. High levels of HBV DNA are associated with a higher risk of developing HCC and worse prognosis in those with HCC[29]. It is thought that active HBV viral proliferation promotes carcinogenesis through both direct and indirect mechanisms and therefore antiviral treatment can lower the risk for HCC occurrence in these patients[30]. A previous study showed that patients with advanced fibrosis or cirrhosis who received lamivudine had a significantly lower risk (3.9%) of developing HCC compared to placebo (7.4%)[30]. Despite the reduced risk, these patients still require routine monitoring for HCC occurrence. Alanine aminotransferase (ALT) is a marker of liver injury and can be used in conjunction with other host factors such as age and duration of infection to identify high-risk HBV carriers[28,29]. Other important risk factors include environmental exposures such as alcohol, cigarettes and the mycotoxin aflatoxin[31] as well as a family history of HCC[32].

Heavy alcohol use and subsequent alcohol related liver disease has also been associated with the development of HCC. The incidence of HCC in patients with alcohol related cirrhosis (Child-Pugh A or B) has been previously reported to be 2.5%[33]. A previous review found that alcohol use greater than 80 g/d for more than 10 years led to a 5-fold increase in risk for development of HCC[34]. A synergistic effect can occur between alcohol use and other risk factors for HCC, most prominently viral hepatitis. It has been suggested that screening patients younger than age 55 with platelet counts > 125000 mm3 may not be cost effective[34], however current guidelines still recommend surveillance for all patients with cirrhosis[7].

Non-alcoholic fatty liver disease (NAFLD) and its complications are of increasing clinical significance, particularly in Western nations due to a rising burden of metabolic syndrome[35]. A prior retrospective analysis has shown that cumulative incidence of HCC is slightly lower in NAFLD related cirrhosis compared to HCV cirrhosis (2.6% *vs* 4%)[36], however surveillance is still recommended in this population. A very low incidence of HCC has been described in patients with NAFLD without cirrhosis, however incidence rates do not meet surveillance criteria at this time[37,38]. Continued investigation of these relationships is of utmost importance given the increasing prevalence and incidence of NAFLD[7].

Less common etiologies of cirrhosis that can also increase the risk for HCC include hereditary hemochromatosis (HH), primary biliary cholangitis (PBC), autoimmune hepatitis (AIH) and alpha 1-antitrypsin deficiency (A1AT). Patients with HH have been shown to have a 20-fold higher risk of HCC without an increased risk for non-hepatic malignancies in a large Swedish based population cohort study[39]. While the incidence of HCC in HH patients with cirrhosis is unknown, the AASLD endorses a surveillance benefit in these patients[7]. HCC also occurs with increased frequency in patients with cirrhosis secondary to PBC[40]. The risk of HCC in these patients has been shown to be similar to the risk of HCC in patients with HCV cirrhosis[41], and therefore the AASLD recommends routine surveillance[7]. Although there are no formal recommendations regarding surveillance in patients with cirrhosis secondary to AIH, several studies note an annual incidence rate > 1.5% and therefore it is reasonable to include these patients in standard surveillance protocols[42]. The incidence of HCC in patients with cirrhosis secondary to A1AT deficiency has been previously shown to be 0.88%/year in one small retrospective study[43], however guidelines still recommend biannual surveillance at this time[7]. Additional studies would be helpful in these less common causes of cirrhosis to more accurately determine annual incidence and suitability for surveillance programs.

As mentioned, the mortality benefit in HCC surveillance lies in the advantages of early detection so that curative therapies, including liver transplantation, can be considered. As such, patients with Childs Pugh C cirrhosis who are not eligible for HCC treatments and are not candidates for liver transplantation should not be offered surveillance programs. Liver transplant candidates should continue to undergo surveillance up until the time of transplantation[7].

**SURVEILLANCE METHODS**

The AASLD recommends surveillance using US with or without AFP every 6 mo. We will look at the evidence behind the surveillance methods including imaging techniques and biomarkers as well as the time intervals when they should be performed.

***Imaging techniques***

US is an inexpensive and noninvasive surveillance method without any risk or radiation exposure for the patient. US detection of HCC in a cirrhotic liver is limited by several factors including hepatic features such as abnormal liver texture, patient characteristics such as obesity and technical limitations such as quality of US and experience of ultrasonographer[44]. A meta-analysis looking at the performance characteristics of surveillance US to detect early HCC found a sensitivity of 94% for detecting HCC lesions at any stage and sensitivity of 63% for early stage tumors. Adding AFP measurement to the US regimen did not provide a statistically significant increase in sensitivity. Performing the surveillance every 6 mo as opposed to annually increases the sensitivity to 70% for detecting early stage HCC[45]. An additional study looking strictly at patients with Child-Pugh classes A and B found that by combining AFP to US the sensitivity increased from 32% to 65% for detecting early stage HCC[46]. Given the variation in reported sensitivity of US, one study looked at predictors of surveillance failure and found that one in five USs for HCC surveillance are classified as inadequate. This study showed that US quality is diminished in obese patients and those with cirrhosis from alcohol or NAFLD. It is thought that this deficiency is related to altered US visualization from the presence of subcutaneous fatty tissue in addition to hepatic steatosis. Consequently, this leads to under-recognition of small or early stage HCC nodules[47,48]. Pocha *et al*[49] randomized 163 patients with cirrhosis to receive either biannual US or annual triphasic CT to compare performance and costs. Biannual US was found to be more sensitive (71.4%) when compared to CT (66.7%). Overall costs were less for biannual US. In addition to lacking cost-effectiveness, CT has risks of radiation exposure and renal injury that must be kept in mind when considering imaging modalities[50]. Magnetic resonance imaging (MRI) is the most sensitive imaging modality for HCC but limited by high cost and low accessibility. A recent prospective study of 407 South Korean patients compared surveillance with MRI to US and found that MRI with liver specific contrast had a higher detection rate and a lower false-positive rate. MRI was significantly more sensitive in detecting very early stage HCC meaning a single lesion < 2 cm with a sensitivity of 84.8% compared to 27.3% detected by US. This study has limitations that limit extrapolation of data to other populations. For example, the majority of patients (74.4%) had HBV related cirrhosis. Another key point worth addressing is that the average body mass index (BMI) in this study was 24.3. The United States currently has an obesity epidemic, which would be expected to further reduce the sensitivity of US. Studies estimate that prevalence of obesity (BMI > 30) in adults is greater than 30%. This could reduce the sensitivity of US in this population[51,52]. While the AASLD practice guidelines acknowledge limited US reliability in patients with truncal obesity or marked parenchymal heterogeneity, CT or MRI is not recommended as the primary imaging technique for HCC surveillance. CT or MRI may be utilized in select patients with inadequate US visualization or at high risk for inadequate US[7].

***Serum biomarkers***

Novel biomarkers are being introduced as simple blood test with growing applications for cancer screening in patients carrying a diagnosis of cirrhosis, including early detection, prognostication, and surveillance. Biomarkers in development are variable in approach, including biochemical metabolites, proteins, and RNA. Perhaps the most promising biomarker in cirrhosis screening is AFP, which has gained favor as a supplement to US screening and was the first to make it to Phase 5 of biomarker development[53]. It has gained popularity as an affordable and accessible screening test and AFP received a ‘conditional’ recommendation to be used in conjunction with semiannual US according to AASLD guidelines[7].

As mentioned, screening US may be limited among select populations secondary to body habitus, obesity, and early HCC disease[15]. In such cases, biomarkers may supplement US in the detection of early disease. And while the combined performance characteristics of AFP in conjunction with US are not yet known in full, it is believed that AFP does improve the sensitivity of interval screening[7]. In a retrospective analysis of all etiologies of cirrhosis, the performance characteristics for serum values above 20 ng/mL approach 70% sensitivity and 90% specificity[54]. When AFP is implemented alongside US screening, one analysis found an improvement in curative treatment rates and improved 3-year overall survival rates when compared to groups that did not receive routine HCC screening[15].

Some of the largest criticisms of biomarkers, and specifically AFP, appear to be drawn from its inconsistent performance characteristics across different screening populations: HCV cirrhosis, NASH cirrhosis, alcoholic cirrhosis, and high-risk HBV infections. Among populations with chronic HCV infections, elevations in AFP are at risk of being attributed to an evolving malignancy, while in fact it may be acute inflammation driving elevations in AFP. Among these populations, a higher cut-off may be required to avoid false positives and unnecessary testing. This is in comparison to non-HCV cirrhosis, which is suspected to have more accurate performance characteristics at a threshold as low as 11 ng/L[54]. As a result, there is the possibility of confusion among clinicians wishing to screen for HCC, as multiple thresholds may be needed, depending on the sub-population.

European guidelines continue to recommend against the use of AFP despite estimated improvement of 6% to 8% detection rate, as it is met with a larger number of false positives[8]. But the future of biomarker screening is promising, with numerous other molecules under research and development: osteopontin, Midkine, AFP-L3, DCP, GPC3, and alpha-1-fucosidase. Predictive models, such as the GALAD, have also been validated as a tool to address the heterogeneity in biology among cirrhosis etiologies[53]. As alternative biomarkers progress through development, the landscape of HCC screening will assuredly change alongside it.

***Surveillance intervals***

There is evidence to support the suggested six-month surveillance interval. A study by Santi et al compared patients with semiannual surveillance to annual surveillance. The semiannual surveillance group was associated with increased detection rate of early stage HCC tumors leading to higher chance of curative therapies and overall better prognosis[55]. In the aforementioned meta-analysis by Singal *et al*[45] surveillance US every 6 mo significantly improves the sensitivity for detection of early stage HCC when compared to annual exams. Furthermore, a multicenter RCT found that US surveillance at 3 mo did not improve survival or increase the detection of small HCC tumors eligible for curative treatment when compared to 6-mo interval[56].

**ADHERENCE AND RECALL**

***Adherence***

Proper screening for HCC is a continuum of services, extending from initial patient screening, diagnosis, treatment and ultimately surveillance. As one may expect, there are numerous chances for failure in the delivery of cancer screening care. Patient adherence seems to be a major barrier in colorectal cancer screening, where nearly 40% of patients were found to have missed their first colonoscopy or flexible sigmoidoscopy appointment[57]. But in the case of HCC, one analysis suggested that only 3% of patients missed screening once ordered by a provider. The most significant barrier identified in this same retrospective cohort was the lack of surveillance orders from a provider, which neared 40% missed opportunities on behalf of the healthcare system[58]. Among referring providers, there seems to be a measurable difference in frequency of screening between primary care physician (PCP) settings and subspecialty gastroenterology clinics. The most prominent barriers perceived by PCPs are related to falling out-of-date with regards to the newest HCC screening guidelines, ineffective communication with at-risk patients and prioritizing other issues in clinic[59]. Of course, referring patients to be screened for HCC is more nuanced than a simple referral, and requires recognizing at-risk patients, establishing a diagnosis of cirrhosis, and then actively counseling the patient. A meta-analysis of 9 studies looked utilization rates and factors that affect them for HCC surveillance. Pooled utilization rates for HCC surveillance were 18.4%. Utilization rates were better in patients followed by subspecialists (51.7%) compared to primary care physicians (16.9%). This study also found other demographics associated with lower surveillance rates including non-Caucasian race and low socioeconomic status[60]. Studies have found that quality improvement measure can be used to increase the rate of HCC surveillance. By enrolling cirrhotic patients into a chronic disease management program that incorporates automatic reminders for surveillance, surveillance rates increased from 73% to 90% over 3 years[61]. Including reminders for HCC surveillance along with screening for other known complications of such as varices or ascites could be helpful as well. Overall, data on patient adherence suggests an opportunity for improvement available on the part of providers as well as systems based approach.

***Recall***

Surveillance programs need a reliable recall strategy for abnormal findings on US imaging. Lesions less than 1 cm can be followed with repeat US (with or without AFP) in 3-6 mo. Further management of abnormal surveillance imaging including lesions > 1 cm can be managed according to the Liver Imaging Reporting and Data System (LI-RADS). Diagnostic liver biopsy may be needed for indeterminate lesions that fall into LI-RADS 4 (probably HCC) or LI-RADS M categories (malignancy but not definitely HCC)[7].

**CONCLUSION**

To summarize, there is sufficient evidence to support the importance and survival benefit of HCC surveillance (Table 1). Early identification through surveillance provides more curative treatment options. Surveillance programs are indicated for all cirrhotic patients and high-risk HBV patients without cirrhosis. Surveillance for obese and NAFLD patients is of increasing interest as this population continues to rise in the United States. Semiannual US (with or without AFP) is the recommended imaging modality for surveillance but clinicians must consider alternative imaging if the US is limited. Surveillance rates are low and disproportionately affect certain populations. Clinicians must recognize the importance of adherence to surveillance and continue to explore options to improve surveillance rates through systems based approaches and awareness.

**REFERENCES**

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **El-Serag HB**, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007; **132**: 2557-2576 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]

3 **El-Serag HB**. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012; **142**: 1264-1273.e1 [PMID: 22537432 DOI: 10.1053/j.gastro.2011.12.061]

4 **El-Serag HB**, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* 2014; **60**: 1767-1775 [PMID: 24839253 DOI: 10.1002/hep.27222]

5 **Fattovich G**, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology* 2004; **127**: S35-S50 [PMID: 15508101 DOI: 10.1053/j.gastro.2004.09.014]

6 **White DL**, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. *Clin Gastroenterol Hepatol* 2012; **10**: 1342-1359.e2 [PMID: 23041539 DOI: 10.1016/j.cgh.2012.10.001]

7 **Marrero JA**, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018; **68**: 723-750 [PMID: 29624699 DOI: 10.1002/hep.29913]

8 **European Association for Study of Liver.**; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Eur J Cancer* 2012; **48**: 599-641 [PMID: 22424278 DOI: 10.1016/j.ejca.2011.12.021]

9 **Omata M**, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*2017; **11**: 317-370 [PMID: 28620797 DOI: 10.1007/s12072-017-9799-9]

10 **Wilson JM**, Jungner G. The principles and practice of screening for disease. Geneva, Switzerland: World Health Organization; 1968. Available from: http://www.who.int/bulletin/volumes/86/4/07-050112BP.pdf

11 **An J**, Lee HC. Surveillance for hepatocellular carcinoma in chronic hepatitis B virus infection: for whom. *Hepat Oncol* 2015; **2**: 225-229 [PMID: 30191004 DOI: 10.2217/hep.15.17]

12 **Zhang BH**, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130**: 417-422 [PMID: 15042359 DOI: 10.1007/s00432-004-0552-0]

13 **Lederle FA**, Pocha C. Screening for liver cancer: the rush to judgment. *Ann Intern Med* 2012; **156**: 387-389 [PMID: 22393134 DOI: 10.7326/0003-4819-156-5-201203060-00012]

14 **Poustchi H**, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J. Feasibility of conducting a randomized control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed? *Hepatology* 2011; **54**: 1998-2004 [PMID: 21800340 DOI: 10.1002/hep.24581]

15 **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**: e1001624 [PMID: 24691105 DOI: 10.1371/journal.pmed.1001624]

16 **El-Serag HB**. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; **127**: S27-S34 [PMID: 15508094 DOI: 10.1053/j.gastro.2004.09.013]

17 **Yuen MF**, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. *Hepatology* 2000; **31**: 330-335 [PMID: 10655254 DOI: 10.1002/hep.510310211]

18 **Singal AG**, Marrero JA. Recent advances in the treatment of hepatocellular carcinoma.*Curr Opin Gastroen* 2010; **26**: 189-195 [DOI: 10.1097/MOG.0b013e3283383ca5]

19 **Lin OS**, Keeffe EB, Sanders GD, Owens DK. Cost-effectiveness of screening for hepatocellular carcinoma in patients with cirrhosis due to chronic hepatitis C. *Aliment Pharmacol Ther* 2004; **19**: 1159-1172 [PMID: 15153169 DOI: 10.1111/j.1365-2036.2004.01963.x]

20 **Arguedas MR**, Chen VK, Eloubeidi MA, Fallon MB. Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis. *Am J Gastroenterol* 2003; **98**: 679-690 [PMID: 12650806 DOI: 10.1111/j.1572-0241.2003.07327.x]

21 **Masuzaki R**, Tateishi R, Yoshida H, Goto E, Sato T, Ohki T, Imamura J, Goto T, Kanai F, Kato N, Ikeda H, Shiina S, Kawabe T, Omata M. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. *Hepatology* 2009; **49**: 1954-1961 [PMID: 19434742 DOI: 10.1002/hep.22870]

22 **Morgan RL**, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med* 2013; **158**: 329-337 [PMID: 23460056 DOI: 10.7326/0003-4819-158-5-201303050-00005]

23 **Gray SH**, Shoreibah MG, Locke JE, White JA. The risk of de novo hepatocellular carcinoma still exists in the in the direct acting antiviral era. *AME Med J* 2018; **3**: 100–100 [DOI: 10.21037/amj.2018.09.09]

24 **Falade-Nwulia O**, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral Direct-Acting Agent Therapy for Hepatitis C Virus Infection: A Systematic Review. *Ann Intern Med* 2017; **166**: 637-648 [PMID: 28319996 DOI: 10.7326/M16-2575]

25 **Reig M**, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol* 2016; **65**: 719-726 [PMID: 27084592 DOI: 10.1016/j.jhep.2016.04.008]

26 **Waziry R**, Hajarizadeh B, Grebely J, Amin J, Law M, Danta M, George J, Dore GJ. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. *J Hepatol* 2017; **67**: 1204-1212 [PMID: 28802876 DOI: 10.1016/j.jhep.2017.07.025]

27 **Kwong AJ**, Kim WR, Flemming JA. De Novo Hepatocellular Carcinoma Among Liver Transplant Registrants in the Direct Acting Antiviral Era. *Hepatology* 2018; **68**: 1288-1297 [PMID: 29672886 DOI: 10.1002/hep.30045]

28 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

29 **Chen CJ**, Yang HI, Iloeje UH; REVEAL-HBV Study Group. Hepatitis B virus DNA levels and outcomes in chronic hepatitis B. *Hepatology* 2009; **49**: S72-S84 [PMID: 19399801 DOI: 10.1002/hep.22884]

30 **Liaw YF**, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, Tanwandee T, Tao QM, Shue K, Keene ON, Dixon JS, Gray DF, Sabbat J; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004; **351**: 1521-1531 [PMID: 15470215 DOI: 10.1056/NEJMoa033364]

31 **Chen CJ**, Chen DS. Interaction of hepatitis B virus, chemical carcinogen, and genetic susceptibility: multistage hepatocarcinogenesis with multifactorial etiology. *Hepatology* 2002; **36**: 1046-1049 [PMID: 12395312 DOI: 10.1053/jhep.2002.37084]

32 **Loomba R**, Liu J, Yang HI, Lee MH, Lu SN, Wang LY, Iloeje UH, You SL, Brenner D, Chen CJ; REVEAL–HBV Study Group. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. *Clin Gastroenterol Hepatol* 2013; **11**: 1636-45.e1-3 [PMID: 23669307 DOI: 10.1016/j.cgh.2013.04.043]

33 **Mancebo A**, González-Diéguez ML, Cadahía V, Varela M, Pérez R, Navascués CA, Sotorríos NG, Martínez M, Rodrigo L, Rodríguez M. Annual incidence of hepatocellular carcinoma among patients with alcoholic cirrhosis and identification of risk groups. *Clin Gastroenterol Hepatol* 2013; **11**: 95-101 [PMID: 22982095 DOI: 10.1016/j.cgh.2012.09.007]

34 **Morgan TR**, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S87-S96 [PMID: 15508108 DOI: 10.1053/j.gastro.2004.09.02]

35 **Degasperi E**, Colombo M. Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease. *Lancet Gastroenterol Hepatol* 2016; **1**: 156-164 [PMID: 28404072 DOI: 10.1016/S2468-1253(16)30018-8]

36 **Ascha MS**, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology* 2010; **51**: 1972-1978 [PMID: 20209604 DOI: 10.1002/hep.23527]

37 **Leung C**, Yeoh SW, Patrick D, Ket S, Marion K, Gow P, Angus PW. Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. *World J Gastroenterol* 2015; **21**: 1189-1196 [PMID: 25632192 DOI: 10.3748/wjg.v21.i4.1189]

38 **Perumpail RB**, Wong RJ, Ahmed A, Harrison SA. Hepatocellular Carcinoma in the Setting of Non-cirrhotic Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome: US Experience. *Dig Dis Sci* 2015; **60**: 3142-3148 [PMID: 26250831 DOI: 10.1007/s10620-015-3821-7]

39 **Elmberg M**, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, Lindgren S, Lööf L, Stål P, Wallerstedt S, Almer S, Sandberg-Gertzén H, Askling J. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003; **125**: 1733-1741 [PMID: 14724826 DOI: 10.1053/j.gastro.2003.09.035]

40 **Silveira MG**, Suzuki A, Lindor KD. Surveillance for hepatocellular carcinoma in patients with primary biliary cirrhosis. *Hepatology* 2008; **48**: 1149-1156 [PMID: 18785621 DOI: 10.1002/hep.22458]

41 **Caballería L**, Parés A, Castells A, Ginés A, Bru C, Rodés J. Hepatocellular carcinoma in primary biliary cirrhosis: similar incidence to that in hepatitis C virus-related cirrhosis. *Am J Gastroenterol* 2001; **96**: 1160-1163 [PMID: 11316164 DOI: 10.1111/j.1572-0241.2001.03695.x]

42 **Tansel A**, Katz LH, El-Serag HB, Thrift AP, Parepally M, Shakhatreh MH, Kanwal F. Incidence and Determinants of Hepatocellular Carcinoma in Autoimmune Hepatitis: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2017; **15**: 1207-1217.e4 [PMID: 28215616 DOI: 10.1016/j.cgh.2017.02.006]

43 **Antoury C**, Lopez R, Zein N, Stoller JK, Alkhouri N. Alpha-1 antitrypsin deficiency and the risk of hepatocellular carcinoma in end-stage liver disease. *World J Hepatol* 2015; **7**: 1427-1432 [PMID: 26052388 DOI: 10.4254/wjh.v7.i10.1427]

44 **Dănilă M**, Sporea I. Ultrasound screening for hepatocellular carcinoma in patients with advanced liver fibrosis. An overview. *Med Ultrason* 2014; **16**: 139-144 [PMID: 24791845 DOI: 10.11152/mu.201.3.2066.162.md1is2]

45 **Singal A**, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. *Aliment Pharmacol Ther* 2009; **30**: 37-47 [PMID: 19392863 DOI: 10.1111/j.1365-2036.2009.04014.x]

46 **Singal AG**, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS, Marrero JA. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 793-799 [PMID: 22374994 DOI: 10.1158/1055-9965.EPI-11-1005]

47 **Simmons O**, Fetzer DT, Yokoo T, Marrero JA, Yopp A, Kono Y, Parikh ND, Browning T, Singal AG. Predictors of adequate ultrasound quality for hepatocellular carcinoma surveillance in patients with cirrhosis. *Aliment Pharmacol Ther* 2017; **45**: 169-177 [PMID: 27862091 DOI: 10.1111/apt.13841]

48 **Della Corte C**, Colombo M. Surveillance for hepatocellular carcinoma. *Semin Oncol* 2012; **39**: 384-398 [PMID: 22846857 DOI: 10.1053/j.seminoncol.2012.05.002]

49 **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**: 303-312 [PMID: 23750991 DOI: 10.1111/apt.12370]

50 **Andersson KL**, Salomon JA, Goldie SJ, Chung RT. Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2008; **6**: 1418-1424 [PMID: 18848905 DOI: 10.1016/j.cgh.2008.08.005]

51 **Kim SY**, An J, Lim YS, Han S, Lee JY, Byun JH, Won HJ, Lee SJ, Lee HC, Lee YS. MRI With Liver-Specific Contrast for Surveillance of Patients With Cirrhosis at High Risk of Hepatocellular Carcinoma. *JAMA Oncol* 2017; **3**: 456-463 [PMID: 27657493 DOI: 10.1001/jamaoncol.2016.3147]

52 **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; **311**: 806-814 [PMID: 24570244 DOI: 10.1001/jama.2014.732]

53 **Sengupta S**, Parikh ND. Biomarker development for hepatocellular carcinoma early detection: current and future perspectives. *Hepat Oncol* 2017; **4**: 111-122 [PMID: 30191058 DOI: 10.2217/hep-2017-0019]

54 **Gopal P**, Yopp AC, Waljee AK, Chiang J, Nehra M, Kandunoori P, Singal AG. Factors that affect accuracy of α-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2014; **12**: 870-877 [PMID: 24095974 DOI: 10.1016/j.cgh.2013.09.053]

55 **Santi V**, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, Di Nolfo MA, Benvegnù L, Farinati F, Zoli M, Giannini EG, Borzio F, Caturelli E, Chiaramonte M, Bernardi M; Italian Liver Cancer (ITA.LI.CA) Group. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. *J Hepatol* 2010; **53**: 291-297 [PMID: 20483497 DOI: 10.1016/j.jhep.2010.03.010]

56 **Trinchet JC**, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, Roulot D, Mallat A, Hillaire S, Cales P, Ollivier I, Vinel JP, Mathurin P, Bronowicki JP, Vilgrain V, N'Kontchou G, Beaugrand M, Chevret S; 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**: 1987-1997 [PMID: 22144108 DOI: 10.1002/hep.24545]

57 **Turner BJ**, Weiner M, Yang C, TenHave T. Predicting adherence to colonoscopy or flexible sigmoidoscopy on the basis of physician appointment-keeping behavior. *Ann Intern Med* 2004; **140**: 528-532 [PMID: 15068980 DOI: 10.7326/0003-4819-140-7-200404060-00013]

58 **Singal AG**, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, Nehra M, Lee WM, Marrero JA, Tiro JA. Failure rates in the hepatocellular carcinoma surveillance process. *Cancer Prev Res* (Phila) 2012; **5**: 1124-1130 [PMID: 22846843 DOI: 10.1158/1940-6207.CAPR-12-0046]

59 **Singal AG**, Tiro JA, Gupta S. Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. *Clin Gastroenterol Hepatol* 2013; **11**: 472-477 [PMID: 23200983 DOI: 10.1016/j.cgh.2012.11.010]

60 **Singal AG**, Yopp A, S Skinner C, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. *J Gen Intern Med* 2012; **27**: 861-867 [PMID: 22215266 DOI: 10.1007/s11606-011-1952-x]

61 **Aberra FB**, Essenmacher M, Fisher N, Volk ML. Quality improvement measures lead to higher surveillance rates for hepatocellular carcinoma in patients with cirrhosis. *Dig Dis Sci* 2013; **58**: 1157-1160 [PMID: 23111632 DOI: 10.1007/s10620-012-2461-4]

62 **Shoreibah MG**, Bloomer JR, McGuire BM, Massoud OI. Surveillance for hepatocellular carcinoma: evidence, guidelines and utilization. *Am J Med Sci* 2014; **347**: 415-419 [PMID: 24759379 DOI: 10.1097/MAJ.0000000000000200]

**P-Reviewer:** Lin ZY, Tai DI

**S-Editor:** Ma RY **L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 Patients at the highest risk for hepatocellular carcinoma**

|  |  |  |
| --- | --- | --- |
| **Population group** | **Threshold incidence for efficacy of surveillance**  **(> 0.25 LYG; % per year)** | **Incidence of HCC**  **(% per year)** |
| High risk of HCC for whom surveillance benefit is indicated |  |  |
| Asian male hepatitis B carriers over age 40 | 0.2 | 0.4%-0.6% per year |
| Asian female hepatitis B carriers over age 50 | 0.2 | 0.3%-0.6% per year |
| Hepatitis B carrier with family history of HCC | 0.2 | Increased |
| African and/or North American blacks with hepatitis B | 0.2 | HCC occurs at a younger age |
| Hepatitis B carriers with cirrhosis | 0.2-1.5 | 3%-8% per year |
| Hepatitis C cirrhosis | 1.5 | 3%-5% per year |
| Stage 4 PBC | 1.5 | 3%-5% per year |
| Genetic hemochromatosis and cirrhosis | 1.5 | Probably > 1.5% per year |
| Alpha-1 antitrypsin deficiency and cirrhosis | 1.5 | Probably > 1.5% per year |
| Cirrhosis secondary to other etiologies | 1.5 | Unknown |
| High risk of HCC for whom surveillance benefit is uncertain |  |  |
| Male hepatitis B carriers younger than 40 | 0.2 | < 0.2% per year |
| Female hepatitis B carriers younger than 50 | 0.2 | < 0.2% per year |
| Hepatitis C and stage 3 fibrosis | 1.5 | < 1.5% per year |
| NAFLD without cirrhosis | 1.5 | < 1.5% per year |

Adapted with permission from AASLD guidelines on management of HCC[7] and HCC Surveillance[62]. LYG: Life-years gained; AASLD: American Association for the Study of Liver Disease; HCC: Hepatocellular carcinoma; NAFLD: Non-alcoholic fatty liver disease.