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AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, *etc*. The *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

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RESPONSIBLE EDITORS FOR THIS ISSUE

MINIREVIEWS

Hepatocellular carcinoma surveillance: An evidence-based approach

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Abstract

Hepatocellular carcinoma (HCC) makes up 75%-85% of all primary liver cancers and is the 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. 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 and 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

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.

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% per year and the incidence is greater than 0.2% per 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 significantly 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 mm^3 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 cirrhosis 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 its use is 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 may not be generalizable to other populations as the majority of patients (74.4%) had HBV related cirrhosis and the average body mass index (BMI) was low (24.3). Given the obesity epidemic in the United States, with a prevalence of obesity (BMI > 30) in adults greater than 30%, the sensitivity of ultrasound may be reduced 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 tests 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 [53]. It has gained popularity as an affordable and accessible screening test and 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 etiologies of chronic liver disease. Among patients with chronic HCV, AFP levels may be falsely elevated due to acute inflammation and therefore the upper limit of normal may need to be adjusted in this population. This is in contrast to patients with non-HCV related cirrhosis, in which AFP levels greater than 11 ng/L have more accurate performance characteristics[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 improve the sensitivity for detection of early stage HCC when compared to annual exams. More frequent imaging (every 3 mo) has not been shown to improve survival or increase detection of small HCC lesions and is therefore not recommended at this time [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 measures 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 cirrhosis 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.

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.

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