

Review

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# Screening for hepatocellular carcinoma: summary of current guidelines up to 2018

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## Abstract

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer related to worldwide death with a great geographical variation. To be eligible for curative therapy at the time of diagnosis is important. However, the majority of cases are diagnosed at late stages. This can be achieved with applicable screening modalities. Until now, many organizations around the world have developed guidelines according to their own evidence-based data for screening of HCC. The purpose of this article is to review the screening modalities of HCC to assist gastroenterologists and providers involved in the management of HCC.

**Keywords:** Hepatocellular carcinoma, screening, guidelines, surveillance

## INTRODUCTION

As emphasized in publications, liver cancer is the second most common cause of worldwide cancer deaths with the fifth most common cancer in men and the ninth in women in 2012<sup>[1]</sup>. Hepatocellular carcinoma (HCC) represents the major histological sub-type up to 90% of primary liver cancers<sup>[2-5]</sup>.

The first HCC cases in hepatitis-associated cirrhosis have been reported in the 1940s<sup>[6]</sup>. Following the dis-



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covery of alpha-fetoprotein (AFP) in HCC by the Russian scientist, screening HCC is widely recommended for patients who are under risk for more than 40 years<sup>[7,8]</sup>.

Over the time, the underlying etiologies, incidence, and HCC outcomes are changed according to the countries. While the incidence of HCC is rising in the west, attributed to the past HCV epidemic (baby-boomers) and trends of metabolic disorders, it is decreasing in the East<sup>[9-11]</sup>. In despite of receiving regular HCC surveillance, nearly 40% of patients still died in 5 years<sup>[12,13]</sup>. These changes are accommodating the new research on and development of new guidelines for HCC management.

Guidelines mean “rules or instructions about the best way to do something”<sup>[14]</sup>. They assist health care providers in the decision-making process according to evidence-based data, with guiding clinical practice in circumstances where all possible resources and therapies are available<sup>[15]</sup>. International scientific societies have issued recommendations for establishing a common standardized approach in the management of HCC.

Although these organizations are international, the recommendation-guidelines mostly directed to their own cases. It is essential for gastroenterologist to be familiar with these organizations and their proposed guidelines. As recommended in the guidelines, it is more appropriate to follow the guidelines but to adapt on the patient basis. In this article, you will find a summary of the current screening guidelines for HCC of three different continents.

## CURRENT GUIDELINES

The success of the screening is influenced by the availability of effective treatment with the identification of the target population and the selection of appropriate screening tests. The cost-effectiveness should also be taken into consideration. In this review, the target group is divided into cirrhotic and non-cirrhotic patient group.

### Screening recommendations for cirrhotic adults

Cirrhosis is the strongest predisposing factor for HCC formation. Nearly 85%-95% of HCC is developed on the cirrhotic liver<sup>[16-18]</sup>. These patients have a lifetime risk of developing HCC by 30% with leading cause of liver related death in compensated cirrhosis<sup>[2,19,20]</sup>. The risk varies with the underlying condition; the highest 5-year cumulative risks are reported in HCV cirrhosis (17% in the west, 30% in Japan), hemochromatosis (21%), HBV cirrhosis (10% in high endemic areas, 15% in the west), alcoholic cirrhosis (8%-12%), and biliary cirrhosis (4%). Also, the presence of co-infection (HCV/HBV or HBV/HCV) or alcohol abuse increases the risk by at least 200%<sup>[21]</sup>. In addition to underlying etiology, other patient-related factors influence the risk of HCC. In general, low platelet count of less than  $100 \times 10^9/L$ , presence of esophageal varices in addition to older age and male gender correlate with development of HCC among patients with cirrhosis<sup>[22-24]</sup>. However, current guidelines do not incorporate with the risk of stratification models (RSM) for cirrhotic that may be useful in the future for excluding some patients from screening.

Screening modalities consist of the periodic application of diagnostic tools with cost effectiveness which is generally taken into consideration based on the gain of life expectancy and guidelines indicating that an incidence of  $\geq 1.5\%$  year would warrant surveillance of HCC in cirrhosis<sup>[25,26]</sup>. Guidelines including the last updated screening section with data-supported recommendations were selected for the review; recommendations are as follows.

#### *From North America*

The American Association for the Study of Liver Diseases (AASLD-2017): routine screening is recommended for HCC in adults with cirrhosis. The initial screening is performed with ultrasound (US) with or without

alpha-fetoprotein (AFP) every 6 months. AASLD does not suggest performing surveillance of patients with Child-Pugh class C cirrhosis unless they are on the transplant waiting list, given the low anticipated survival for these patients. They pointed out some technical remarks regarding screening modalities (US alone or plus AFP), interval (4-8 months) and modification in screening strategy based on etiology of liver diseases or risk stratification models<sup>[26]</sup>. In the previous guideline (AASLD-2011), ultrasound scanning alone was recommended<sup>[27]</sup>.

The Canadian Association for the Study of the Liver (CASL 2014): this report is from consensus conference updated of the existing consensus - CASL 2011. The current statements for cirrhosis are similar with AASLD except they recommend US alone in every 6 months. The committee does not recommend AFP either alone or combined with US due to less sensitivity of AFP (67% sensitivity). They also do not recommend other biomarkers (AFP) lectin fraction (AFP-L3) and des-gamma-carboxy prothrombin (DCP) due to less validation<sup>[28,29]</sup>.

#### *From Asia*

The Asian Pacific Association for the Study of the Liver (APASL-2017): their recommendation is using combination of US and serum AFP measurement in every 6 months. The cut-off value of AFP should be set at 200 ng/mL for the cirrhotics. They do not suggest screening to cirrhotics not ineligible for treatments due to severe liver disease or other comorbidities which is similar with North America groups<sup>[30]</sup>.

CHINESE-2017: updated from 2011. Their recommendation for cirrhosis is identical with APASL. The only difference is that there is no excluding criteria for severe liver diseases<sup>[31]</sup>.

The Japan Society of Hepatology (JSH-2015): updated from 2013. Modalities and screening intervals mostly differ from the other countries and Asia. Besides AFP, a protein induced by vitamin K absence or antagonist-II (PIVKA-II) and AFP-L3 measurements are also recommended by the JSH to increase sensitivity. The JSH evidence-based clinical practice guidelines for HCC divided patients into an extremely high-risk group (hepatitis B or C cirrhosis) and a high-risk group (patients with chronic hepatitis B, chronic hepatitis C, or non-viral cirrhosis). Their recommendations for extremely high-risk patients are periodic imaging screening by US every 3-4 months along with three tumour markers (AFP, PIVKA-II and AFP-L3). Additionally, they recommend multi-detector computed tomography (MDCT) or MRI examinations in every 6-12 months as the first step of screening (optional) method even there is no evidence of tumour on US, because of poor visualization capability<sup>[32,33]</sup>. The recommendations for the high-risk group cirrhosis are more cost effective and included periodic screening by US along with three tumour markers, every 6 months. MDCT and MRI are not recommended for high-risk patients<sup>[32,33]</sup>.

Japan Society of Hepatology- Liver Cancer Study Group (JSH-LCSG 2014): consensus-based guidelines. The JSH-LCSG practice guidelines use identical definitions for the extremely high-risk group and high-risk group. However, JSH-LCSG recommends EOB-MRI (gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid-enhanced magnetic resonance imaging) instead of dynamic MDCT which has higher detection sensitivity than CT, as the first-line modality for surveillance every 6-12 months, even if no tumour is detected on US<sup>[33,34]</sup>.

#### *From Europe*

The European Association for the Study of the Liver (EASL-2018): the guideline is in press, their screening recommendations for Child-Pugh stage A and B patients are used by abdominal ultrasound every six months. AFP or other tumour biomarkers (AFP, AFP-L3 and DCP) are not recommended due to less accuracy for early detection of HCC. Stage C cirrhosis is excluded from screening except for transplant candidates<sup>[2]</sup>.

**Table 1. Recommendations for cirrhotic adults**

Continent	Guidelines	Modality	Time interval (months)	Exceptions
North America	AASLD-2017	US with or without AFP	6	Child-Pugh stage C unless awaiting liver transplantation
Asia	CASL-2014	US	6	Same as AASLD
	APASL-2017	US and AFP	6	Severe liver diseases/other co-morbidities (ineligible for curative therapy)
Europe	CHINESE-2017	US and AFP	6	NS
	JSH-2015*	Extremely-high risk patients: (HBV/HCV cirrhosis) - US and three Tm markers (AFP/PIVKA-II/ AFP-L3) - CT or MRI (optional)	3-4 6-12	NS
	JSH-LCSG-2014	High risk patients: (cirrhosis of another etiology) US and three tumor markers (AFP/PIVKA-II, AFP-L3)	6	NS
	EASL-2018**	Recommend EOB-MRI instead of CT or MR	Same as JSH	NS
	SPANISH-2016 (AEEH, SEOM, SERAM, SERVEI and SETH)	US	6	Same as AASLD
	SEOM-2015	US	6	Same as AASLD
ESMO-ESDO-2012	US	6	NS	

\*3rd JSH-HCC guidelines, 2013 update; \*\*in press. HBV: hepatitis B virus; HCV: hepatitis C virus; AFP: alpha-fetoprotein; NS: not specified; US: ultrasound; PIVKA-II: proteins induced by vitamin K absence; CT: computed tomography; MRI: magnetic resonance imaging; EOP-MRI: gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging

Selected guidelines from Spain (consensus document from The Spanish Association for the Study of the Liver (AEEH), Spanish Society of Medical Oncology (SEOM), The Spanish Society of Medical Radiology (SERAM), The Spanish Society of Vascular and International Radiology (SERVEI), The Spanish Society of Liver Transplantation (SETH)-2016 and European Society for Medical Oncology (ESMO)/European Society of Digestive Oncology (ESDO)-2012 recommend every 6 months US examination to patients with or without cirrhosis, and specify the theory behind this recommendation<sup>[35,36]</sup>. However; SEOM-2015 guideline excluded Child C patients from screening (unless awaiting for liver transplantation) like EASL<sup>[37]</sup>.

This section was summarized in [Table 1](#).

### Recommendations for non-cirrhotic adults

A small proportion of patients with HCC is diagnosed in the non-cirrhotic liver (NCL) with the risk of being less than 1% annually in patients with chronic hepatitis without significant fibrosis, in contrast to 3%-7% annually when the patient develops cirrhosis<sup>[26,35,38]</sup>. HCC in NCL ranges widely from 7% to 54% according to the etiology of the liver disease and varies of the geographic areas<sup>[39]</sup>. While viral hepatitis is pre-screened with decrease in the east as known, metabolic causes predominate in the west.

As compared to cirrhotic HCC, it has lower prevalence of the three main risk factors (hepatitis B and C virus infections and alcohol abuse), with an increased prevalence of other etiological factors, such as non-alcoholic fatty liver diseases, obesity and type 2 diabetes mellitus, exposure to genotoxic substances-aflatoxin, tobacco, sex hormones, inherited diseases and genetic mutations<sup>[2,3,11,26,30,36,38-40]</sup>.

In contrast to cirrhotic, NCL-HCC are more suitable for surgical treatments even in more advanced tumour stage at the time of diagnosis, since it is generally detected at a symptomatic stage due to unsettled scheduled screening program in these groups<sup>[2,38,39]</sup>.

There is also a risk stratification model for non-cirrhotic HCCs. PAGE-B (platelet, age, gender, hepatitis B) that is developed for HBV is recommended for non-cirrhotic HBV patients by EASL-2018<sup>[2,24,41]</sup>.

Recommendations from guidelines are as follows.

#### *From North America*

AASLD-2017: there is no proposal for non-cirrhotic patients in the current guideline. The previous AASLD guideline (2010), described the high-risk HBV carriers for HCC [Table 2] and the recommendation for screening was US in every 6 months<sup>[26,27]</sup>.

CASL-2014: identical with AASLD-2010, the CASL recommends HCC screening for the following high-risk groups by using US in every 6 months: Asian male hepatitis B carriers over the age of 40, Asian female hepatitis B carriers over the age of 50, hepatitis B carriers with a family history of HCC, Africans and African Americans with hepatitis B<sup>[29]</sup>.

#### *From Asia*

APASL-2017: recommendations for non-cirrhotic group similar to CASL. Differently, they recommend screening in Africans older than 20 years old. The surveillance strategy is combination of US and serum AFP, every 6 months, recommending that the cut-off value of AFP can be set at a lower value in a population with hepatitis virus suppression or eradication<sup>[30]</sup>.

CHINESE-2017: recommendations for non-cirrhotic-chronic liver diseases (any etiology) are AFP with ultrasonography in every 6 months for surveillance<sup>[31]</sup>.

JSH-2015 and JSH-LCSG 2014: for the high-risk non-cirrhotic (patients with chronic hepatitis B, chronic hepatitis C), they recommend an US examination along with measurement of three tumour markers (AFP/PIVKA-II, AFP-L3) in every 6 months [Table 2]<sup>[32-34]</sup>.

#### *From Europe*

EASL-2018: categorized the non-cirrhotic HBV patients at intermediate or high risk of HCC according to PAGE-B classes for Caucasian subjects, respectively 10-17 and  $\geq 18$  score points<sup>[2,41]</sup>.

To this group and non-cirrhotic F3 patients, regardless of etiology screening based on an individual, risk assessment is recommended for patients in the low HCC risk class (PAGE-B score  $\leq 9$ ), who do not reach the 0.2%/year threshold for starting screening. The PAGE-B score has not yet been validated in Asia due to Caucasian subjects. They recommend an US examination in every 6 months<sup>[2]</sup>.

The consensus document from the AEEH, SEOM, SERAM, SERVEI and SETH -2016 has not specified the screening for non-cirrhotic subjects<sup>[35]</sup>. However, SEOM-2015 recommended screening for high-risk HBV chronic hepatitis patients (higher viral load, viral genotype or Asian or African ancestry) and non-cirrhotic patients with chronic hepatitis C and advanced fibrosis (F3)<sup>[37]</sup>.

ESMO-ESDO-2012 recommendations are similar to SEOM-2015, which suggests to non-cirrhotic HBV carriers with high viral load ( $> 10.000$  copy/mL) and non-cirrhotic patients with chronic hepatitis C and advanced cirrhosis<sup>[36]</sup>.

This section was summarized in Table 2.

**Table 2. Recommendations for non-cirrhotic adults**

Continent	Guidelines	Target population	Modality	Time interval (months)
North America	AASLD-2017	No recommendation for surveillance of non-cirrhotics at this time		
	AASLD-2010	HBV carriers: - Asian female > 50 years - Asian male > 40 years - Family history of HCC - African/North American Blacks	US	6
Asia	CASL-2014	Same as AASLD-2010	US	6
	APASL-2017	Non-cirrhotic (HBsAg positive): - Asian females > 50 years - Asian males > 40 years - Africans aged > 20 years - History of HCC in the family	US and AFP	6
	CHINESE-2017	Chronic liver diseases of any etiology	US and AFP	6
	JSH-2015 and JSH-LCSG-2014	High risk patients (chronic hepatitis B or C)	US and three tumor markers AFP/PIVKA-II/AFP-L3	6
Europe	EASL-2018	Non-cirrhotic HBV patients at intermediate or high risk of HCC* Non-cirrhotic F3 patients regardless of etiology**	US	6
	SPANISH-2016 (AEEH, SEOM, SERAM, SERVEI and SETH)	No recommendation for surveillance of non-cirrhotics at this time		
	SEOM-2015	High-risk HBV chronic hepatitis patients (higher viral load, viral genotype or Asian or African ancestry) Non-cirrhotic patients with chronic hepatitis C and advanced fibrosis (F3)	US	6
	ESMO-ESDO-2012	Non-cirrhotic HBV carriers with high viral load (> 10,000 copy/mL) Non-cirrhotic patients with chronic hepatitis C and advanced fibrosis (F3)	US	6

\*According to PAGE-B classes for Caucasian subjects, intermediate or high risk of HCC (10-17 and U 18 score points, respectively);

\*\*considered for surveillance based on an individual risk assessment. HCC: hepatocellular carcinoma; F3: bridging fibrosis; HBV: hepatitis B virus; AFP: alpha-fetoprotein; US: ultrasound

## REMARKS FROM GUIDELINES & COMMENTS

All three continents propose a 6-month screening interval using ultrasonography with or without AFP, regardless of cirrhosis, except Japan. Japanese guidelines suggest a shorter interval (3-4 months) for extremely high-risk cirrhotic patients, the three tumour markers (AFP/PIVKA-II, /AFP-L3) along with ultrasound and EOB-MRI with 6-12 months interval, or dynamic CT.

Based on the tumour doubling time (range 29 to 398 days), the 6-month interval represents a reasonable choice<sup>[42]</sup>, since shorter interval detects more small lesions, but does not improve detection of small HCC<sup>[43]</sup>. The incidence of HCC in the target population and available facilities may affect the screening interval. However, there is still a question about optimal interval for screening ranging from 4 to 8 months<sup>[2,26,30]</sup>.

Sensitivity of ultra-sonogram is ranging from 58% to 89% with specificity greater than 90% when used as a screening test before they presented clinically, other than that it seems to be less effective for detecting early-stage HCC (sensitivity of only 63%)<sup>[2,26,44,45]</sup>.

AFP is not recommended along with ultrasound in North America and Europe because the present studies were not directed to determine an improvement in survival. AFP is usually elevated in cirrhosis intermittently, but markedly elevation in small tumour is rare<sup>[2,16,26,30]</sup>. Therefore, APASL suggests cut-off value (set at 200 ng/mL) of AFP for screening programs when used in combination with US. Combined with US, AFP provides additional detection in 6%-8% of cases not previously identified by US, confirmed more recently<sup>[2,46]</sup>.

Serological tests that are under investigation for early diagnosis of HCC include (PIVKA II) AFP-L3, alpha-fucosidase, and glypican. These markers have been tested mostly for diagnosis and prognosis, but need to be



studied in screening set-up<sup>[2,26,30]</sup>.

As imaging modality, Japanese guidelines recommend EOB-MRI or dynamic CT to be performed in every 6-12 months for screening for extremely high-risk of cirrhotic patients since small nodules may not be detected on ultrasound alone<sup>[32,34]</sup>.

HCC risk stratification models for cirrhotics have not yet been included in the guidelines and the majority of the presented guidelines exclude Child C cirrhosis from screening protocols unless they are eligible for curative therapy.

Screening guidelines for non-cirrhotics differ from countries, mainly in selection of the target population. Whereas AASLD-2017 does not specify, APASL-2017 and EASL-2018 describe the target population in the guidelines.

EASL-2018 made a breakthrough and used the PAGE B score system for non-cirrhotic HBV patients. The score system is intended to determine unnecessary screening for Caucasian patients with chronic HBV. However, the PAGE-B score has not yet been validated in Asia<sup>[2]</sup>.

Overall F3 (bridging fibrosis) patients regardless of aetiology were also included in the screening protocol at first time by EASL-2018 developers.

CHINESE-2017 recommends screening for patients with chronic liver diseases regardless of aetiology. In contrast, Japan guidelines suggest screening for patients with only chronic HBV and HCV.

In general, the screening modalities for non-cirrhotics are almost identical with cirrhotics except Japan guidelines. The Japan guidelines recommend the three tumour markers additional to ultra-sonogram, for every 6 months.

Final question is: do the screening modalities really work? Japan and Hong Kong HCC screening methods were compared in that particular context. In Hong Kong, where there was no formal surveillance program, 20% of HCC were detected only in the pre-symptomatic period with low survival rate (17.8 months) whereas in Japan over 75% of cases were detected by surveillance. The median survival was 52 months in Japan and the stage of HCC at presentation was the most important factor influencing survival according to the cohort<sup>[47]</sup>.

## CONCLUSION

Recommendations from the three continents are mostly influenced in the prevalence of HCC and availability of resources. It may be necessary to modify the screening methods according to the condition of patients. This situation is more evident in those countries with no national guidelines and/or heterogeneous patient population. Hence, developing countries should be encouraged to issue their own guidelines. The common point is that, cost-effectiveness is universal and screening modality is one of the factors that influence the variation in survival.

## DECLARATIONS

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