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A PRACTICAL GUIDELINE FOR HCC SCREENING IN PATIENTS AT RISK

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SELECTED HIGHLIGHTS

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BACKGROUND

- Several professional societies recommend screening patients at risk for HCC, including: [1-4]
  - All patients with cirrhosis
  - Subgroups of patients with chronic HBV infections
- In spite of these recommendations, HCC screening programmes across the world are limited by low utilization rates[5-10]
  - Fewer than 1 in 5 high-risk patients are regularly screened
  - Guideline-adherent screening rates in the US are under 2%
  - Patients followed by gastroenterologists are screened more regularly

- **The purpose of this review is to discuss the value of HCC screening in at-risk patients with chronic liver disease**

HBV, hepatitis B virus; HCC, hepatocellular carcinoma

1. Heimbach J, et al. Hepatology. 2018;67:358-380. 2. European Association For The Study Of The Liver. J Hepatol. 2018;69:182-236. 3. Omata M, et al. Hepatol Int. 2017;11:317-370. 4. Kokudo N, et al. Hepatol Res. 2015;45. 5. Hirata A, et al. Hepatol Res. 2017;47:283-292. 6. Singal AG, et al. Am J Med. 2015;128:90.e1-7. 7. Edenvik P, et al. Liver Int. 2015;35:1862-1871. 8. Davila JA, et al. Ann Intern Med. 2011;154:85-93. 9. Davila JA, et al. Hepatology. 2010;52:132-141. 10. Singal AG, et al. J Gen Intern Med. 2012;27:861-867.

RECOMMENDED SCREENING POLICIES FROM INTERNATIONAL GUIDELINES

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Guideline	EASL[1]	AASLD[2]	JSH[3]	APASL[4]
Definition of high-risk population	• Pts with cirrhosis, Child-Pugh stage A and B • Pts with cirrhosis, Child-Pugh stage C awaiting liver transplantation • Pts without cirrhosis with HBV and an intermediate or high risk of HCC (PAGE-B score ⩾ 10a) • Pts without cirrhosis with chronic HCV and bridging fibrosis	• Pts with cirrhosis, Child-Pugh stage A and B • Pts with cirrhosis, Child-Pugh stage C awaiting liver transplantation • Pts without cirrhosis with HBV	• Extremely high-risk pts: ○ Pts with cirrhosis and HBV or HCV • High-risk pts: ○ Non-viral cirrhosis ○ Pts without cirrhosis with HBV or HCV	• Pts with cirrhosis • Pts without cirrhosis with HBV: ○ Asian females > 50 yrs ○ Asian males > 40 yrs ○ Africans > 20 yrs ○ Family history of HCC
Screening interval	• Every 6 months	• Every 4-8 months	• Every 3-4 months in extremely high-risk pts • Every 6 months in high-risk pts	• Every 6 months
Imaging modality	• US (performed by experienced personnel)	• US	• US • CT/MRI optional every 6–12 months in extremely high-risk pts	• US
Biomarkers	• Not recommended	• At discretion of provider	• AFP • AFP-L3 fractions • DCP	• AFP (+ US)

AASLD, American Association for the Study of Liver Disease; AFP, alpha-fetoprotein; APASL, Asian Pacific Association for the Study of the Liver; CT, computed tomography; DCP, des-gamma carboxyprothrombin; EASL, European Association for the Study of the Liver; HBV, hepatitis-B virus; HCC, hepatocellular carcinoma; HCV, hepatitis-C virus; JSH, Japan Society of Hepatology; MRI, magnetic-resonance imaging; PAGE-B, platelet, age, gender, hepatitis B; pts, patients; US, ultrasound; yrs, years

1. European Association For The Study Of The Liver. J Hepatol. 2018;69:182-236. 2. Heimbach J, et al. Hepatology. 2018;67:358-380. 3. Omata M, et al. Hepatol Int. 2017;11:317-370. 4. Kokudo N, et al. Hepatol Res. 2015;45.

THE BENEFITS OF HCC SCREENING LIKELY OUTWEIGH POTENTIAL HARMS

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Benefits

- **Patients with chronic HBV**
  - A randomised trial showed screening improves early tumour detection, receipt of curative treatment and OS vs not screening (HR 0.63)[1]
- **Patients with cirrhosis**
  - Level I data are lacking
  - Cohort studies showed a strong and consistent association with improved survival[2, 3]

Harms

- Up to one-third of patients with cirrhosis may experience physical harms related to false-positive and indeterminate screening results[4]
  - Most harms consist of additional diagnostic exams
  - Severe physical harm (e.g. invasive procedures or procedure-related complications) is rare

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratio; OR, odds ratio; OS, overall survival

1. Zhang B-H, et al. J Cancer Res Clin Oncol. 2004;130:417-422. 2. Singal AG, et al. PLoS Med. 2014;11:e1001624. 3. Johnson P, et al. Br J Cancer. 2017;116:441-417. 4. Atiq O, et al. Hepatology. 2017;65:1196-1205.

PATIENT SELECTION FOR SCREENING

PATIENTS WITH CIRRHOSIS

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- Patients with cirrhosis have an annual risk of 2-4% of developing HCC[1]
- All international professional society guidelines recommend HCC screening patients with cirrhosis, independent of liver disease aetiology[2-5]
  - The benefits of screening are generally limited to patients with compensated cirrhosis (Child-Pugh class A or B)

Risk factors for cirrhosis

Viral infections

- In Africa and East Asia, **HBV** infections cause approximately 70% of HCC cases[1]
- In the Western world and Japan most HCC cases are related to **HCV** infections[1]
- SVR significantly reduces the risk of HCC, but patients with cirrhosis remain at risk[6]

Non-alcoholic fatty liver disease (NAFLD)

- NAFLD-related cirrhosis is anticipated to soon become the most common cause of HCC in the Western world

Alcohol

- Heavy drinking increases the risk of liver cancer, with a linear relationship between the risk and the amount of alcohol intake[7]

HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; SVR, sustained viral response

1. El-Serag HB. 2012;142:1264-1273.e1. 2. Heimbach J, et al. Hepatology. 2018;67:358-380. 3. European Association For The Study Of The Liver. J Hepatol. 2018;69:182-236. 4. Omata M, et al. Hepatol Int. 2017;11:317-370. 5. Kokudo N, et al. Hepatol Res. 2015;45. 6. Jacobson IM, et al. Gastroenterology. 2017;152:1578-1587. 7. Turati F, et al. Ann Oncol. 2014;25:1526-1535

PATIENT SELECTION FOR SCREENING

PATIENTS WITHOUT CIRRHOSIS

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Advanced Fibrosis

- Debate on the value of HCC screening in patients with significant fibrosis without cirrhosis
- European guidelines recommend screening, American guidelines do not[1,2]

Non-cirrhotic chronic HBV

- Most guidelines, including AASLD, restrict screening to selected subgroups with chronic HBV[1-4]
- Anti-viral treatment reduces, but does not eliminate the risk of HCC in patients with chronic HBV infections[5,6]

Non-cirrhotic NAFLD

- Despite data suggesting non-cirrhotic NAFLD may be a risk factor for the development of HCC, no guideline recommends screening these patients[1-4]

AASLD, American Association for the Study of Liver Disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease

1. Heimbach J, et al. Hepatology. 2018;67:358-380. 2. European Association For The Study Of The Liver. J Hepatol. 2018;69:182-236. 3. Omata M, et al. Hepatol Int. 2017;11:317-370. 4. Kokudo N, et al. Hepatol Res. 2015;45. 5. Papatheodoridis GV, et al. J Hepatol. 2015;62:956-967. 6. Cho JY, et al. Gut. 2014;63:1943-1950.

HCC SCREENING METHODS

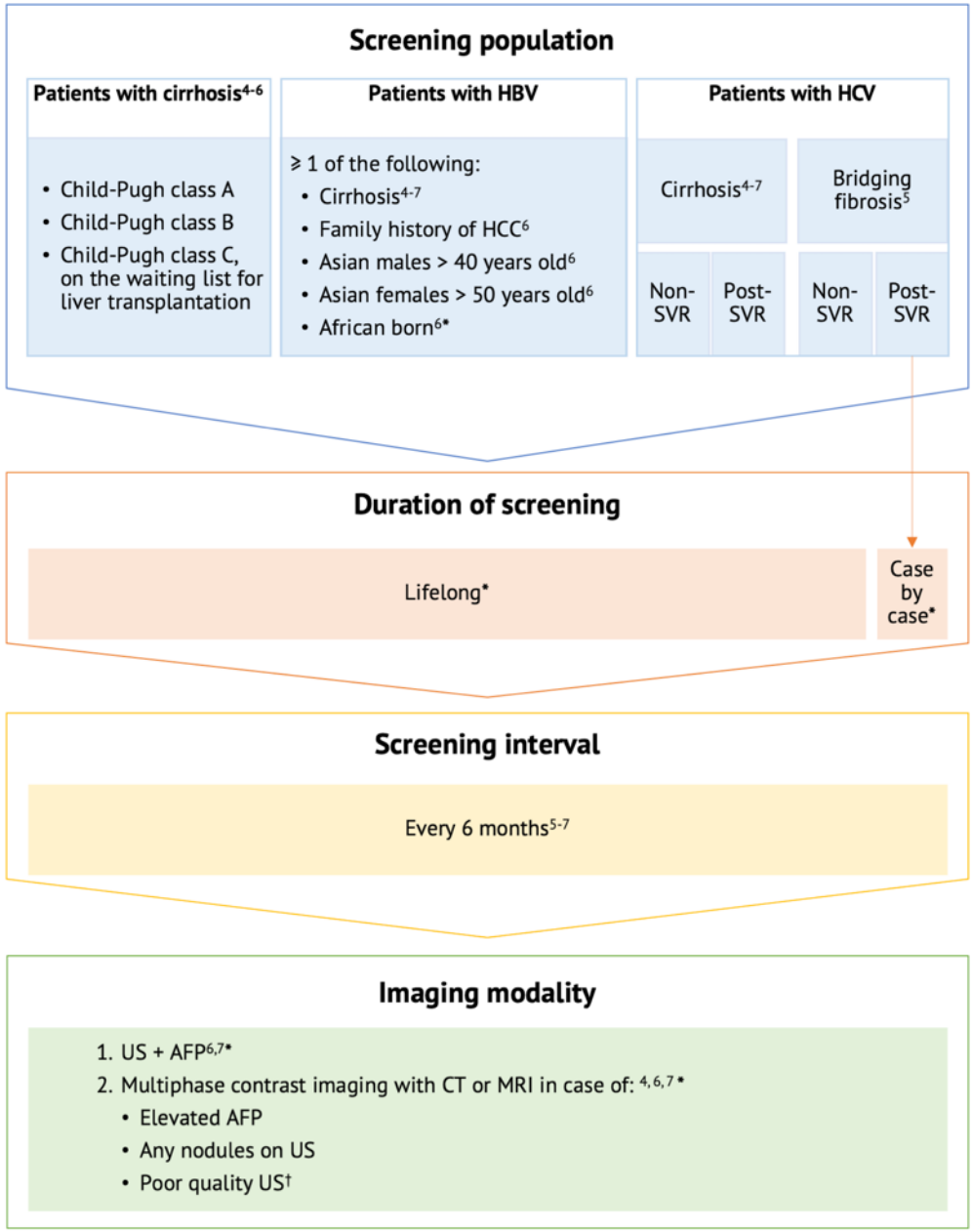
- Most guidelines recommend **ultrasound** screening **every 6 months**[1-4]
  - Inexpensive, non-invasive, readily available, fairly accurate and well tolerated
    - Ultrasound sensitivity is affected by technology, operator experience and patient characteristics
  - In populations in whom ultrasound imaging is inadequate (e.g. obesity, multinodular cirrhosis), MRI and CT may be potential alternatives[4-7]

- **Alpha-fetoprotein (AFP)** best studied serum biomarker for screening[8]
  - Inexpensive, readily available and easy to perform
  - Although the sensitivity and specificity of AFP alone are suboptimal, it may add benefit to ultrasound by improving early tumour detection[9-11]
    - This improvement in sensitivity must be weighed against a decrease in specificity

CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic-resonance imaging

1. Heimbach J, et al. Hepatology. 2018;67:358-380. 2. European Association For The Study Of The Liver. J Hepatol. 2018;69:182-236. 3. Omata M, et al. Hepatol Int. 2017;11:317-370. 4. Kokudo N, et al. Hepatol Res. 2015;45. 5. Pocha C, et al. Aliment Pharmacol Ther. 2013;38:303-312. 6. Kim SY, et al. JAMA Oncol. 2017;3:456-463. 7. Andersson KL, et al. Clin Gastroenterol Hepatol. 2008;6:1418-1424. 8. Harding JJ, et al. Dig Dis Sci. 2019. [Epub ahead of print]. 9. Lok AS, et al. Gastroenterology. 2010;138:493-502. 10. Singal A, et al. Aliment Pharmacol Ther. 2009;30:37-47. 11. Singal AG, et al. Cancer Epidemiol Biomarkers Prev. 2012;21:793-799.

PROPOSED SCREENING ALGORITHM FOR PATIENTS AT RISK FOR HCC



Based on the American[4], European[5], Asia-Pacific[6] and Japanese[7] guidelines and expert opinion (*).

† Situations in which it could be worthwhile to perform cross-sectional imaging include unavailability of experienced personnel, obese patients, patients who are unable to hold their breath, and patients with an excessively nodular liver.

A clear protocol for the **diagnostic evaluation** of abnormal screening results is key

- In patients with a **positive screening result** (ultrasound mass > 1 cm or AFP > 20 ng/mL) further evaluation with multiphase contrast imaging (CT or MRI) is required to evaluate for potential HCC
- For **lesions < 1 cm**, close follow-up with repeat short-interval ultrasound and AFP is required

AFP, alpha-fetoprotein; CT, computed tomography; HBV, hepatitis-B virus; HCC, hepatocellular carcinoma; HCV, hepatitis-C virus; MRI, magnetic-resonance imaging; SVR, sustained virologic response; US, ultrasound

CONCLUSION

- Global guidelines recommend screening high-risk populations to allow for early detection of HCC, but adherence is low
- Increased awareness about the need for screening is crucial to allow more patients to qualify for curative treatment options
- Lifelong, biannual screening using ultrasound and AFP is recommended for patients with cirrhosis and select patients without cirrhosis with HBV infection

AFP, alpha-fetoprotein; HBV, hepatitis-B virus; HCC, hepatocellular carcinoma

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