COMMENTARY

For reprint orders, please contact: reprints@futuremedicine.com

Surveillance for hepatocellular carcinoma in chronic hepatitis B virus infection: for whom

Jihyun An¹ & Han Chu Lee*¹

Many authors continue to use the terms ‘screening’ and ‘surveillance’ indiscriminately. Screening is the application of a test to detect a disease in a population that has no signs or symptoms of that disease, while surveillance is the periodic repetition of the screening test in an at-risk population [1]. Surveillance for hepatocellular carcinoma (HCC) in patients with liver disease, who are at risk of developing this cancer, is conducted to identify malignancies at early stages and to improve patient survival [1,2].

There are many guidelines for the surveillance of various cancers, but these procedures need be carried out in accordance with the disease prevalence, the socioeconomic and cultural backgrounds of the population, and the medical resources of individual countries [3]. Surveillance also should be cost effective, and one crucial determinant of this is the disease incidence in the target population [3]. The American Association for the Study of Liver Disease guidelines have suggested that an intervention is considered cost effective if 1 life-year can be saved at a cost of less than US\$20,000–50,000, depending on the economic situation and the HCC burden of the particular country [1]. Based on this

calculation, the incidence threshold that should trigger surveillance in patients with cirrhosis is 1.5% per year, while for patients with chronic hepatitis this drops to 0.2% per year since the prognosis is much poorer for cirrhosis [1,4,5].

Cirrhosis is a well-established risk factor for HCC. The annual incidence of HCC in patients with known hepatitis B virus (HBV) cirrhosis ranges from 2 to 8% [6,7]. Considering the above mentioned thresholds, patients with cirrhosis are appropriate candidates for cost-effective surveillance [1,2]. Patients with liver cirrhosis who achieve a virologic response on long-term effective oral antiviral treatment still show a higher annual incidence of HCC up to 3% [8–11]. A recent study has also reported that the risk of HCC in antiviral-treated cirrhotics appears to decrease after 3 years of antiviral treatment compared with the predicted risk of HCC [12]. Similarly, if spontaneous or treatment-induced hepatitis B surface antigen (HBsAg) loss is occurred in cirrhotic patients, the prognosis could be improved. However, HCC has been reported years after clearance of HBsAg, especially in patients with genotype C, which is known as a high-risk factor

“Hepatocellular carcinoma risk prediction derived from the identification of major risk factors is necessary for providing adequate surveillance strategies to high-risk individuals.”

Hepatic Oncology

KEYWORDS

• chronic hepatitis B
• hepatocellular carcinoma • risk prediction • surveillance

“...there have been several studies targeted at identifying these at-risk individuals using risk prediction scores more precisely so that those with a lower risk could be excluded from surveillance.”

¹Asan Liver Center, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 86, Asanbyeongwon-gil, Songpa-gu, Seoul 138-736, Korea

*Author for correspondence: Tel.: +82 2 3010 3915; Fax: +82 2 2485 5782; hch@amc.seoul.kr

“...we recommend cirrhotic patients with hepatitis B virus as candidates for surveillance regardless of age and antiviral treatment.”

for HCC. These patients should continue to undergo surveillance, since the estimated annual incidence of HCC even after HBsAg loss is up to 2.85% [13]. In summarizing the findings of these studies, we recommend cirrhotic patients with HBV as candidates for surveillance regardless of age and antiviral treatment. However, from the perspective of the benefit of surveillance in terms of patient survival, the anticipated survival benefit from early detection of HCC might be minimal in Child-Pugh class C patients compared with the patients with Child-Pugh class A or B, because of the poor survival outcomes that are expected for those patients [6].

Subjects with chronic hepatitis B (CHB) are also at risk of HCC development in the absence of cirrhosis. Previous studies have indicated that the incidence of HCC in CHB patients varies widely [14,15]. Whereas the HCC incidence ranges 0.1–0.4%/year in western CHB patients, that in adult Asian HBV carriers may exceed this level regardless of replication status; the estimated annual incidence of HCC is 1.2% in hepatitis e antigen (HBeAg)-positive carriers and 0.3% in those with negative HBeAg [16–18]. Since some of these HBeAg-negative carriers may have active hepatic inflammation due to precore or core promoter mutations, which are considered viral variants related with increased risk of HCC [19], the exact risk of HCC in these patients might be higher than that of HBeAg-negative subjects with persistently normal ALT levels.

However, a common experience is that only a minority of patients with CHB ever develop HCC. HCC risk prediction derived from the identification of major risk factors is necessary for providing adequate surveillance strategies to high-risk individuals. Therefore, there have been several studies targeted at identifying these at-risk individuals using risk prediction scores more precisely so that those with a lower risk could be excluded from surveillance.

Yang *et al.* have derived and validated REVEAL-HBV nomograms incorporating risk predictors, including age, gender, family history of HCC, alcohol consumption, HBeAg sero-status, HBV genotype and serum levels of ALT and HBV DNA from a prospective community-based cohort that did not receive antiviral treatment [20]. None of the included patients had cirrhosis, which was defined by ultrasonographic (USG) findings at the time of recruitment, and these cases remained treatment naive throughout the follow-up period. The REACH-B score

was also developed from this Taiwanese community-based cohort [21], and then validated in three hospital cohorts in Hong Kong and South Korea. In contrast to the training cohort, 18.4% of patients in the validation cohort had cirrhosis. The 17-point REACH-B score includes only five risk predictors, which are sex, age, HBeAg status and serum levels of ALT and HBV DNA, because data on the family history of HCC, alcohol consumption and HBV genotype were not available in the three hospital cohorts. According to the REACH-B risk score, the probability of developing HCC is 2.0% at 10 years at the score of 8, which is equal to the threshold incidence of HCC (0.2%/year) for the initiation of surveillance recommended by American Association for the Study of Liver Disease guidelines. The area under the receiver operating characteristic curves (AUROCs) to predict risk were 0.81, 0.80 and 0.77, respectively, at 3, 5 and 10 years in the validation cohort; the scores increased to 0.90, 0.78 and 0.81, respectively, after exclusion of cirrhotic patients from the validation cohort. However, in patients with cirrhosis, the AUROCs to predict risk for HCC were relatively low, 0.67, 0.70 and 0.65, respectively.

The CU-HCC score was derived from a clinic-based cohort of Chinese CHB patients including cirrhotics from tertiary referral centers [22]. The CU-HCC score is composed of five parameters: age, albumin, bilirubin, HBV DNA and cirrhosis. Two cut-off values (5 and 20) that best discriminated HCC risk into three categories were identified. At the score of 5, the AUROCs of the prediction for HCC at 5 and 10 years were 0.76 and 0.78, respectively. Of note, this score has a high negative predictive value of 98.3% to exclude future HCC development.

The GAG-HCC score was also developed from a clinic-based cohort of 820 Chinese CHB treatment-naïve patients [23]. The original GAG-HCC score is composed of gender, age, HBV DNA level, cirrhosis and core promoter mutations. There is a simplified version that omits core promoter mutations, because they may not be easily available in some centers. A cutoff value of 101 was found to have a good negative predictive value up to 98.3–100%. The sensitivity and specificity were also high, 84.1 and 76.2% for the 5-year prediction and 88.0 and 78.7% for the 10-year prediction, respectively.

Recent advances in therapy have led to relatively high rates of HBV suppression, which modifies the natural history of the disease and

reduces the risk of HCC [10]. Nonetheless, there is still a low, but clinically relevant risk of HCC in patients receiving antiviral therapy, even after a complete virologic response is achieved and maintained [24]. Thus, surveillance should be offered to treated patients with CHB who remain at risk of HCC development. However, all of the previous risk scores were developed in cohorts of patients with viral hepatitis not treated with antiviral agents. Treatment of chronic viral hepatitis may lower both viral load and serum ALT levels, which may result in the regression of fibrosis and the prevention of HCC. This leads to a question about the clinical significance of dynamic changes in the risk scores during longitudinal follow-up. In a recent cohort study of CHB patients with entecavir treatment, the baseline all of three scores before antiviral treatment could predict HCC development in 5 years with AUROCs ranging from 0.71 to 0.80. [10]. After antiviral therapy, the risk scores of patients would have decreased due to lower levels of HBV DNA and ALT, HBeAg-seroconversion, and improvements in liver function including change of albumin or bilirubin levels. The change of category from high to low risk is observed in 14.0, 8.2 and 38.3% of patients defined by the CU-HCC, GAG-HCC and REACH-B scores, respectively. Patients persistently in the low-risk category had the lowest risk of HCC; those downgraded in risk group showed a lower risk of HCC than those in the high-risk category. Therefore, these risk scores still seem to be useful in patients receiving antiviral therapy.

These HCC risk scores have several advantages and limitations. The major limitation of these scores is that all three studies only involved Asian patients with genotype B or C; the validity and applicability to other populations where the viral genotype, host genetics, or environmental exposure profile remains uncertain. The comparative advantage of the REACH-B score is that the model is derived from a community-based cohort, which may reflect the risk of developing HCC in persons with relatively mild disease more accurately than other models do. Therefore, it is appropriate to use this model to determine the target population for HCC surveillance in the community setting. Another important aspect of the REACH-B score is that the risk can be calculated easily and accurately according to each score; therefore, modifying the threshold score for the initiation of HCC surveillance in a country with a different

socioeconomic status is available. However, the strengths mentioned above could be weak points of the REACH-B score. To date, most surveillance programs for HCC have been conducted for clinic-based patients in most countries. The REVEAL cohort predominantly included non-cirrhotic HBeAg-negative persons with normal ALT who might have a low possibility for developing HCC [25]. Approximately 34% of patients in the training cohorts and 44% in the validation cohorts were younger than 40 years old [21], and 47% of patients in the REACH-B training cohort had genotype B, which has been shown to be associated with a lower risk of HCC than genotype C [25]. Although the REACH-B score was validated by external hospital-based cohorts, these patients were also untreated patients with mild disease activity, similar with those of the REACH-B training cohort [21]. A recent hospital cohort study from Hong Kong showed that the risk of HCC based on the baseline REACH-B score before antiviral therapy is very likely overestimated in clinic-based settings, with only 16.5% of specificity at a cutoff value of 8 in patients undergoing antiviral therapy [10]. For example, a 35-year-old male who has 90 IU/ml of ALT, HBV DNA $>10^5$ copies/ml, and a positive HBeAg is classified into the high-risk group according to his REACH-B score regardless of the antiviral treatment that he should receive. Therefore, the REACH-B score could be useful for identifying persons who need regular surveillance in the community setting or with mild disease activity, but has a less discriminative power among patients undergoing antiviral therapy. Further analysis incorporating alcohol consumption, aflatoxin exposure, or family history of HCC – which were excluded in the validation cohort due to lack of information – into the REACH-B score is expected to provide more precise risk prediction.

The CU-HCC score stratifies the patients into three groups according to their HCC risk and could not provide a more refined and systemic stratification of HCC risk by each risk score of an individual [22]. Therefore, the application of the CU-HCC score to determine patients who need HCC surveillance is limited in an individual country with a different socio-economic status. For example, the negative predictive value of CU-HCC in the 5-year prediction of HCC was 98.3%; therefore, the estimated incidence of HCC in the low-risk group was higher than the recommended threshold incidence of 0.2%/year

“The threshold incidence of hepatocellular carcinoma for surveillance should be determined individually based on the economic situation of each country.”

for initiating HCC surveillance by Western guidelines, but modifying the cut-off score is difficult. Another point of CU-HCC score is that heavy weighting is assigned to the presence of cirrhosis. Notably, the CU-HCC score is composed mostly of cirrhosis-related parameters such as the presence of cirrhosis, decreased level of albumin, or increased level of bilirubin. Thus, the CU-HCC score may not be very suitable to stratify HCC risk precisely in noncirrhotic patients with CHB or HBV carrier state.

As we mentioned above, all CHB patients with liver cirrhosis should be considered for HCC surveillance. Despite the importance of cirrhosis, the definition of liver cirrhosis has been inconsistent between the risk scores and cohorts. The presence of cirrhosis in the training cohort of REACH-B score and the cohort of CU-HCC score was only evaluated by USG; whereas, clinical and serological data including ascites, varices, hypersplenism, hypoalbuminemia and the ratio of aspartate aminotransferase to platelet count combined USG was used to define patients with cirrhosis in the GAG-HCC score cohort and REACH-B score validation cohort [21–23]. The predicted risk of HCC may suffer from substantial error, since early liver cirrhosis may be missed on USG [26]. Liver stiffness measurement (LSM) with transient elastography, which one of the most widely used non-invasive tools to detect early cirrhosis, may be useful to refine the presence of cirrhosis as a component in the risk score.

Recently, Wong *et al.* modified their CU-HCC score with LSM (LSM-HCC score) [27], and the AUROCs and 5-year negative predictive value of the LSM-HCC score were higher than those of the CU-HCC score.

Surveillance for HCC is recommended in high-risk populations with chronic HBV infection. The threshold incidence of HCC for surveillance should be determined individually based on the economic situation of each country. Current HCC risk scores could accurately predict subsequent HCC development in both treatment-naïve patients and in those receiving antiviral therapy. Nevertheless, each risk score should be carefully applied to the patients depending on the real-world settings. Risk calculators also can be further upgraded continuously with newly identified independent risk predictors. Different levels of HCC surveillance should be offered according to the risk profile of the patients.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

- Bruix J, Sherman M. American Association for the Study of Liver Disease. Management of hepatocellular carcinoma: an update. *Hepatology* 53(3), 1020–1022 (2011).
- European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J. Hepatol.* 56(4), 908–943 (2012).
- Prorok PC. Epidemiologic approach for cancer screening. Problems in design and analysis of trials. *Am. J. Pediatr. Hematol. Oncol.* 14(2), 117–128 (1992).
- Sarasin FP, Giostra E, Hadengue A. Cost-effectiveness of screening for detection of small hepatocellular carcinoma in western patients with Child-Pugh class A cirrhosis. *Am. J. Med.* 101(4), 422–434 (1996).
- Di Bisceglie AM. Issues in screening and surveillance for hepatocellular carcinoma. *Gastroenterology* 127(5 Suppl. 1), S104–107 (2004).
- Trevisani F, Santi V, Gramenzi A *et al.* Surveillance for early diagnosis of hepatocellular carcinoma: is it effective in intermediate/advanced cirrhosis? *Am. J. Gastroenterol.* 102(11), 2448–2457 (2007).
- Sangiovanni A, Del Ninno E, Fasani P *et al.* Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. *Gastroenterology* 126(4), 1005–1014 (2004).
- Cho JY, Paik YH, Sohn W *et al.* Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. *Gut* 63(12), 1943–1950 (2014).
- Papatheodoridis GV, Manolakopoulos S, Touloumi G *et al.* Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide hepnec. Greece cohort study. *Gut* 60(8), 1109–1116 (2011).
- Wong GL, Chan HL, Mak CW *et al.* Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology* 58(5), 1537–1547 (2013).
- Singal AK, Salameh H, Kuo YF, Fontana RJ. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. *Aliment. Pharmacol. Ther.* 38(2), 98–106 (2013).
- Kim WR, Berg T, Loomba R *et al.* 43 long term tenofovir disoproxil fumarate (tdf) therapy and the risk of hepatocellular carcinoma. *J. Hepatol.* 58(Suppl. 1), S19 (2013).
- Kim GA, Lee HC, Kim MJ *et al.* Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. *J. Hepatol.* 62(5), 1092–1099 (2014).

- 14 Villeneuve JP, Desrochers M, Infante-Rivard C *et al.* A long-term follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in montreal. *Gastroenterology* 106(4), 1000–1005 (1994).
- 15 Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. *Hepatology* 22(2), 432–438 (1995).
- 16 Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J. Hepatol.* 48(2), 335–352 (2008).
- 17 Yang HI, Lu SN, Liaw YF *et al.* Hepatitis B e antigen and the risk of hepatocellular carcinoma. *N. Engl. J. Med.* 347(3), 168–174 (2002).
- 18 Hsu YS, Chien RN, Yeh CT *et al.* Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 35(6), 1522–1527 (2002).
- 19 Chou YC, Yu MW, Wu CF *et al.* Temporal relationship between hepatitis B virus enhancer II/basal core promoter sequence variation and risk of hepatocellular carcinoma. *Gut* 57(1), 91–97 (2008).
- 20 Yang HI, Sherman M, Su J *et al.* Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. *J. Clin. Oncol.* 28(14), 2437–2444 (2010).
- 21 Yang HI, Yuen MF, Chan HL *et al.* Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol.* 12(6), 568–574 (2011).
- 22 Wong VW, Chan SL, Mo F *et al.* Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. *J. Clin. Oncol.* 28(10), 1660–1665 (2010).
- 23 Yuen MF, Tanaka Y, Fong DY *et al.* Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J. Hepatol.* 50(1), 80–88 (2009).
- 24 Lim YS, Han S, Heo NY, Shim JH, Lee HC, Suh DJ. Mortality, liver transplantation, and hepatocellular carcinoma among patients with chronic hepatitis B treated with entecavir vs lamivudine. *Gastroenterology* 147(1), 152–161 (2014).
- 25 Chen CJ, Yang HI, Su J *et al.* Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 295(1), 65–73 (2006).
- 26 Chan HL. Identifying hepatitis B carriers at low risk for hepatocellular carcinoma. *Gastroenterology* 142(5), 1057–1060 (2012).
- 27 Wong GL, Chan HL, Wong CK *et al.* Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. *J. Hepatol.* 60(2), 339–345 (2014).