treatment. Lead time bias and length time bias cannot be excluded in these studies. In five retrospective studies including more than 100 patients comparing HCC detected on surveillance versus those detected without surveillance, small and potentially curable HCC were detected in the surveillance groups leading to improved patient survival.[26–29] But surveillance program did not improve prognosis in patients with advanced cirrhosis. In the surveillance groups, HCC detected are usually small and relatively uniform. HCC in the non-surveillance groups are large and varied. HCC in the non-surveillance groups are usually detected in two different manners: (i) asymptomatic but discovered outside the regular surveillance program; and (ii) symptomatic. HCC detected without symptoms in the non-surveillance group are also smaller as compared to the symptomatic group. The efficacy of the surveillance program reported will be decided on number of asymptomatic patients detected incidentally in the non-surveillance group.[30] The benefits of HCC surveillance are summarized in Table 1.

Surveillance strategies for HCC

Screening tests should have an acceptable rate of accuracy and should be affordable. The screening strategy recommended for surveillance by the majority of associations is ultrasonography with or without AFP measurement. The sensitivity and specificity of AFP for HCC is in the range of 41–65% and 80%–95%, respectively, when an AFP cut-off of 20 ng/mL is used.[19] Up to 50% of patients with HCC have AFP lower than 20 ng/mL.[20] Therefore, AFP cannot be used as the sole tool for HCC surveillance. Furthermore, it is associated with significant false-positive results related to hepatitic activities. In other words, unnecessary additional diagnostic investigations and patient anxiety may be caused by a mildly elevated AFP. AFP values greater than 400 ng/mL are more diagnostic of HCC, but only very few HCC are associated with such high AFP values at screening. Very high AFP levels are usually found in patients with massive and advanced HCC.[20]

Ultrasound is the most popular imaging method for HCC surveillance because it is simple, inexpensive, and non-invasive and allows a real-time observation. In a systematic review including 14 studies of various designs from different patient groups, the pool estimates (95% confidence interval) of sensitivity, specificity, positive likelihood ratio and negative likelihood ratio of ultrasonography (USG) to detect HCC are 60.5% (44–76%), 96.9% (95–98%), 17.7 (8.5–36.9) and 0.5 (0.4–0.6), respectively.[31] The performance of ultrasound depends on the expertise of the operator, the ultrasound equipment available and the echo-texture of the liver. The evaluation of the actual sensitivity of ultrasound is however difficult due to the lack of a definite good standard for HCC.

Combined AFP and ultrasound can increase the HCC detection rates, but it also increases the costs and the false-positive rate from 2.9% (ultrasound alone) or 5.0% (AFP alone) to 7.5% (combined).[21] Owing to the limitations of AFP and ultrasound, it is a common practice to combine these two methods for HCC surveillance. Several studies using a combined AFP and ultrasound surveillance have proven survival benefit to patients by detecting smaller and curable HCC.[22,23,30,32,33] In general, 6-monthly AFP and ultrasound surveillance is sufficient. In a longitudinal study including 1018 chronic hepatitis B patients followed up for over 4 years, there was no additional survival benefit for an intensive surveillance program including lipiodal computed tomography over a

Table 1 Survival benefit of surveillance programs for hepatocellular carcinoma (HCC) in retrospective studies (HCC)

Author reference	Location	Patient population	HCC in surveillance group (*n*)	HCC in no surveillance group (*n*)	Survival in surveillance group	Survival in no surveillance group
Chie *et al.*[25]	Taiwan	Mixed	634	156	5-year survival 35%	5-year survival 29%
Yuen *et al.*[26]	Hong Kong	Mixed	142	164	Median survival 22 months	Median survival 5 months
Trevisani *et al.*[27]	Italy	Mixed	215 (6-month surveillance) 155 (12-month surveillance)	451	Median survival 36 months (6-month surveillance) and 34 months (12-month surveillance)	Median survival 14 months
Trevisani *et al.*[28]	Italy	Mixed	158	138 (incidental) 67 (symptomatic)	Median survival 30 months	Median survival 21 months (incidental) and 7 months (symptomatic)
Wong *et al.*[29]	Hong Kong	Mixed	79	393	Median survival 22 months; 2-year survival 49%	Median survival 6.5 months; 2-year survival 21%

HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available.

Table 2 Cost-effectiveness models for hepatocellular carcinoma (HCC) surveillance

Author reference	Target population	Treatment of HCC	ICER $/QALY vs no screening (screening strategy)
Sarasin *et al.*[39]	55-year-old Child's grade A cirrhosis	Resection	26 000–284 000 (6-monthly US + AFP) 24 000–240 000 (6-monthly US)
Arguedas *et al.*[40]	> 50-year-old hepatitis C cirrhosis	Resection, loco-ablative therapy, transplant	26 689 (6-monthly US + AFP) 16 605 (6-monthly CT + AFP) 118 000 (6-monthly MRI + AFP)
Saab *et al.*[41]	Patients awaiting transplant	Loco-ablative therapy, transplant	60 300 (6-monthly US) 74 000 (6-monthly US + AFP) 110 000 (6-monthly CT)
Lin *et al.*[42]	> 40-year-old hepatitis C related Child's grade A cirrhosis	Resection, loco-ablative therapy	23 043 (12-monthly US + AFP) 33 083 (12-monthly US, 6-monthly AFP) 73 789 (6-monthly US + AFP)
Patel *et al.*[43]	45–70-year-old hepatitis C cirrhosis	Resection, transplant	26 100–58 400 (6-monthly US + AFP)
Nouso *et al.*[44]	> 45-year-old Child's A cirrhosis	Resection, loco-ablative therapy, transplant	29 900–68 800 (6-monthly US)

AFP, alpha-fetoprotein; CT, computed tomography; ICER, incremental cost-effective ratio; MRI, magnetic resonance imaging; QALY, quality adjusted life years; US, Ultrasound.

regular 6-monthly combined AFP and ultrasound surveillance program even among patients with elevated AFP (> 20 ng/mL) or abnormal ultrasound findings.[34] There is no evidence to support the use of computed tomography (CT) for routine HCC surveillance as positive and negative predictive values are unknown. There is a significant cost and radiation exposure associated with four phase-contrast CT while there may be high false-positive rates in the absence of contrast CT. The other serological tests like AFP L3 and Des-γ carboxyprothrombin (DCP) have not shown to be useful for surveillance protocol.[35]

Cost-effectiveness of surveillance strategies

The current definition of worthwhile surveillance is based on the economic situation in 1992, and surveillance is defined cost-effective if it achieves a 3-month improvement in survival at a cost of less than $US50 000/life year saved.[36,37] Efficacy of surveillance program can be determined by randomized control trials but cost-effectiveness is generally determined by modeling study. Modeling studies are based on several assumptions and may not hold true in different geographical areas, economic status and health-care delivery systems in different countries. The cost-effectiveness of a surveillance program depends critically on the rate of small HCC detected accidentally in the non-surveillance group, annual incidence of HCC in various etiologies of HCC and the availability of liver transplantation as a treatment option. The aim of HCC surveillance is to detect small tumors that allow curative treatment. In an early cost-effective analysis, HCC surveillance by yearly USG and AFP could detect an early tumor at a cost of $US11 800.[38] There are six subsequent cost-effective analyses of the surveillance program based on the computerized decision analytical models using various training tools like ultrasound, CT scan, AFP at 6-monthly or yearly intervals, treatments offered like resection or liver transplantation with reference to life saved or quality adjusted life years (QALY) (Table 2).[39–44] The incremental cost-effectiveness ratio for 6-monthly AFP and ultrasound varied between approximately $US26 000 to $US74 000/QALY. Surveillance can be effective in reducing disease-specific mortality with acceptable cost-effectiveness among selected groups of patients. The cost-effectiveness depends on the: (i) rate of incidentally detected small HCC; (ii) annual incidence of HCC; (iii) adoption of transplant as a treatment strategy; and (iv) younger age of screen population. The majority of the earlier studies were conducted before liver transplantation was considered as an effective treatment for early HCC. Long-term survival improves in patients undergoing liver transplantation for HCC as liver transplantation is not only taking care of the HCC but also the underlying cirrhosis. However, whether it is a cost-effective strategy to treat HCC with liver transplantation warrants further investigation due to the high cost of the surgery.

Surveillance strategies according to the etiology and risk factors

According to randomized controlled trials, the risk of HCC in chronic hepatitis B is 0.27%/year and HCC surveillance is cost-effective.[22] In non-HBV-related cirrhosis, the risk of HCC is more than 1.4%/year and HCC surveillance is also cost-effective.[40]

HBV

Increasing evidence suggests that persistent HBV replication as indicated by high serum HBV DNA is a predictor of HCC. A large-scaled cohort study in Taiwan (REVEAL-HBV study) has recently shown that there was a biological gradient of risk for development of HCC in subsequent years based on the viral load at the first visit.[45] This study involved more than 3700 subjects aged 30–64 years and followed over more than 10 years. Subjects who had an initial viral load below 2000 IU/mL had the lowest risk of HCC and subjects who had HBV DNA exceeding 20 000 IU/mL started to have an increased risk of HCC. A subsequent study overcame the limitation of the previous one that the risk of HCC had been reflected by one-time measurement of serum HBV DNA at the start. In a cohort of 112 patients with HBV-

Table 3 Recommended at risk population for hepatocellular carcinoma (HCC) surveillance

Chronic hepatitis B
All patients with liver cirrhosis For non-cirrhotic patients
Male above age of 40 years and female above age of 50 years
Family history of HCC
High serum hepatitis B virus DNA (> 10 000 copies/mL)
Factors under investigation
Hepatitis B virus genotype C
Basal core promoter mutations
Chronic hepatitis C
All patients with liver cirrhosis, especially aged above 40 years
Spacial caution to patients with other risk factors such as alcoholism and co-infection with hepatitis B virus or human immunodeficiency virus
Other liver diseases
All patients with liver cirrhosis (evidence not certain)

related HCC and 1031 non-HCC subjects, pre-diagnostic multiple sera were collected for HBV DNA measurement over periods of up to 16 years. Multivariate analysis showed that persistently high viral load (detected HBV DNA at ≥ 50% of the visits) was associated with higher rate of HCC development.[46] Despite some controversies in cross-sectional and case-controlled studies, HBV genotype C, particularly subgenotype Ce, HBV has been found to be an independent risk factor for HCC development in several longitudinal studies.[47–49] This observation may be related to the more aggressive disease, delayed hepatitis e antigen (HBeAg) seroconversion and high prevalence of basal core promoter mutations associated with genotype C HBV than genotype B HBV.[50,51]

Older age is another independent predictive factor for HCC development. Regarding sex effect on HCC, male sex has been consistently reported to be more susceptible than female.[31,48–52] A meta-analysis of 17 case-control and three cohort studies reported a direct trend in risk with increasing alcohol consumption.[52] In a Korean 9-year prospective study, liver cirrhosis, chronic hepatitis, HCV infection, HBV infection and age exceeding 40 years were all independently associated with the risk of HCC development.[52,53]

Therefore, in HBV-infected patients, appropriate cases for surveillance are Asian men more than 40 years and women more than 50 years (for Africans, > 20 years). Patients with cirrhosis and patients with family history of HCC mainly among Asians and Africans are appropriate candidates for surveillance. As non-cirrhotic patients with chronic hepatitis B remain at risk for HCC,[54–57] AASLD recommends surveillance for HCC among not only HBV-related cirrhotic patients but also those at an older age, with family history of HCC, or with high serum HBV DNA levels (Table 3).[2] Whether HBV genotypes and basal core promoter mutation should be considered in the HCC surveillance program remains to be studied.

HCV and other liver diseases

The HCC derived from chronic HCV infection are responsible for the majority of HCC cases in the USA, Europe and Japan.[58–61] The HCC in chronic HCV-infected patients usually have pre-existing advanced fibrosis in the liver. The reported risk factors in chronic hepatitis C-related HCC include male sex, elderly population, alcohol intake and excessive oxidative stress.[62–70] However, in Japan where the estimated life expectancy exceeds 80 years, the incidence of HCC in female patients catches up with that of male patients in the population older than 70 years old.[71] Thus, strong caution should be taken toward HCV-infected people in this generation regardless of sex. This is important because Japanese patients with HCV infections seems to be 10–15 years older than the rest of the world, thus the Japanese experience will be reproduced again 10–15 years later. The sophisticated molecular technique demonstrated when and how the HCV infections have been spread throughout the world.[72–75]

The evaluation of significant hepatic fibrosis is not uniformly agreed by hepatologists. Although liver biopsy is the gold standard to evaluate hepatic fibrosis, its invasive nature abstains hepatologists to perform it as a routine procedure for all patients with HCV infection. Instead of liver biopsy, other assessment tools for evaluating hepatic fibrosis are developed and applied to HCV infections, such as simple platelet counts, Fibrotest, aspartate transaminases to platelet ratio index (APRI), or most recently elastography (Fibroscan). The accuracy of these methods are not systematically compared, thus large-scale studies are warranted to establish the value of these methods in estimating the risk of developing HCC in chronic hepatitis C.

In all, the rational for conducting a surveillance program towards chronic HCV infected patients is obvious, because these people are at high risk for developing HCC (especially at elderly age with advanced fibrosis) and easy to identify (e.g anti-HCV antibody positive) (Table 3).[76] In patients with hepatitis C-related cirrhosis, surveillance is effective. But in other forms of cirrhosis like alcoholic cirrhosis, non-alcoholic steatohepatitis-related cirrhosis, autoimmune hepatitis or cryptogenic cirrhosis, the efficacy of surveillance remains unproven.[76]

Conclusions

In the Asia–Pacific region, HCC is a major cause of morbidity and mortality. HCC surveillance can detect early tumors that are potentially amendable to curative treatment. Six-monthly USG examination with and without AFP seems to be the most optimal and cost-effective measure for HCC surveillance. All patients at risk of developing HCC with potential curative treatment available are recommended for regular HCC surveillance. Patients with early liver cirrhosis (or non-cirrhotic HBV-infected patients) are the best candidates for HCC surveillance as hepatic resection or loco-regional therapy can be applied once early HCC is detected. Among patients with advanced liver cirrhosis, HCC surveillance should still be carried out as far as liver transplantation remains a treatment option. On the other hand, HCC surveillance should not be conducted among patients with advanced liver cirrhosis but not being a liver transplant candidate for whatever reasons. For a HCC surveillance program to be effective, an increased awareness of HBV and HCV infection is mandatory as they are the most important etiologies of HCC in the Asia–Pacific region.

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