World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i40.6744

World J Gastroenterol 2013 October 28; 19(40): 6744-6756
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Surveillance for hepatocellular carcinoma in chronic liver disease: Evidence and controversies

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Received: June 8, 2013 Revised: September 2, 2013
Accepted: September 15, 2013
Published online: October 28, 2013

Abstract

Primary liver cancer is the sixth most common cancer in the world and the third cause of cancer-related death. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and generally occurs in patients with underlying chronic liver disease such as viral hepatitis, hemochromatosis, primary biliary cirrhosis and non-alcoholic steatohepatitis. Especially cirrhotic patients are at risk of HCC and regular surveillance could enable early detection and therapy, with potentially improved outcome. We here summarize existing evidence for surveillance including ultrasound, other radiological modalities and various serum biomarkers, and current international guideline recommendations for surveillance. Ultrasound and α-fetoprotein (alone or in combination) are most frequently used for surveillance, but their sensitivities and specificities are still far from perfect, and evidence for surveillance remains weak and controversial. Various other potential surveillance tools have been tested, including serum markers as des-carboxyprothrombin, lectin-bound α-fetoprotein, and (most recently) circulating TIE2-expressing monocytes, and radiological investigations such as computed tomography-scan or magnetic resonance imaging-scan. Although early results appear promising, these tools have generally been tested in diagnostic rather than surveillance setting, and in most cases, no detailed information is available on their cost-effectiveness. For the near future, it remains important to define those patients with highest risk of HCC and most benefit from surveillance, and to restrict surveillance to these categories.

Key words: Hepatocellular carcinoma; Surveillance; Chronic liver disease

Core tip: Hepatocellular carcinoma is a frequent phenomenon in cirrhotic patients. Survival is generally poor, and curative options only exist if the tumor is detected in an early stage (Barcelona Clinic Liver Cancer stage 0 or A). This review summarizes existing evidence for surveillance including ultrasound, other radiological modalities and various serum biomarkers, and current guideline recommendations for surveillance. Selection of the appropriate high risk populations remains an important tool for cost-effective surveillance.

van Meer S, de Man RA, Siersema PD, van Erpecum KJ. Surveillance for hepatocellular carcinoma in chronic liver disease: Evidence and controversies. *World J Gastroenterol* 2013; 19(40): 6744-6756 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i40/6744.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i40.6744

INTRODUCTION

Primary liver cancer is the sixth most common cancer

in the world and the third cause of cancer-related death. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers and generally occurs in patients with underlying chronic liver disease. Incidence rates are highest in East Asia and Sub-Saharan Africa, where approximately 85% of all cases occur. The high HCC risk in these regions can be explained at least in part by the high prevalence of underlying risk factors, especially chronic hepatitis B virus (HBV) infection and aflatoxin B1 in the diet[1,2].

Nevertheless, also in countries with relatively low incidence rates such as the United States, incidences have doubled over the last two decades, due to growing impact of chronic liver disease from hepatitis C virus (HCV) and non-alcoholic steatohepatitis (NASH)[3,4]. In Europe, there is a mixed pattern, with increasing or decreasing incidence rates in various countries. These geographical differences are thought to be the consequence of changing patterns of underlying risk factors for HCC, such as viral hepatitis, alcohol abuse and NASH. Although NASH conveys relatively modest risks of HCC, the burden of metabolic syndrome and insulin resistance is expected to have significant further impact on HCC incidence in the Western world in the near future. Also, coexistent metabolic syndrome and obesity further increase HCC risk in patients with other underlying liver diseases[5-7]. Smoking is another cofactor leading to increased HCC risk[7]. Interestingly, the use of cholesterol synthesis inhibitors and metformin and coffee consumption are associated with decreased HCC risk[8-11].

New local treatment options such as radiofrequency ablation (RFA) or transarterial chemo- and radioembolisation (TACE and TARE) have been introduced in recent years. Also, the multikinase inhibitor sorafenib leads to improved survival in patients with advanced stage disease[12]. Nevertheless, most patients present at relatively late stage, without options for curative treatment. Survival remains poor under these circumstances [median survival: Barcelona Clinic Liver Cancer (BCLC) stage B, 15 mo; BCLC stage C, 6 mo; BCLC stage D, < 3 mo][13]. Therefore, new strategies are urgently needed to decrease the burden of HCC. First, primary prevention of HCC can be achieved by hepatitis B vaccination, especially in endemic countries[14]. Second, antiviral therapies appear to be associated with decreased HCC risks in patients with chronic viral hepatitis. Interestingly, according to recent meta-analyses and systematic reviews, interferon-based antiviral treatment for hepatitis B is associated with only modest decrease of HCC risk (RR = 0.66, 95%CI: 0.48-0.89). Treatment with the nucleoside analog lamivudine is associated with a more substantial risk reduction (RR = 0.22, 95%CI: 0.10-0.50)[15-17]. It is reasonable to expect even better results with the currently available potent nucleos(t)ide analogs tenofovir and entecavir[18].

Third, and focus of the current review, surveillance of patients at increased risk because of underlying chronic liver disease might detect HCC at earlier stages, and could lead to better outcomes with decreased mortality (5-year survival with curative treatment in BCLC stage 0 or A: 40%-70%)[13]. Intuitively, this approach is attractive. Indeed, several international guidelines currently advise surveillance programs, defined as the repeated and systematic administration of a screening test, including registration and patient recall where applicable[19-21]. Nevertheless, surveillance remains controversial because of limited evidence for its efficiency and potential risk of side effects (for example complication from diagnostic biopsy of liver mass detected during surveillance which subsequently proves to be benign)[22,23]. This review offers an overview of current knowledge on HCC surveillance and gives a perspective on current international guidelines.

BIOMARKERS FOR HCC SURVEILLANCE

When introducing a surveillance program, applying the optimal screening modality is essential. Detection of HCC at intermediate or advanced stage [according to Barcelona Clinic Liver Cancer Staging (BCLC) system] by surveillance could have some impact, by allowing TACE or sorafenib therapy. Nevertheless, surveillance should preferably detect (very) early stage HCC (single lesion ⩽ 5 cm or ⩽ 3 lesions each ⩽ 3 cm without vascular involvement or metastasis), allowing potentially curative therapy. Serological biomarkers can be used at relatively low costs, without burden for the patient. Several biomarkers have been investigated for HCC detection, generally in diagnostic setting rather than in surveillance studies.

α-fetoprotein (AFP) is the most frequently used biomarker for HCC worldwide. AFP is a glycoprotein expressed by fetal hepatocytes or poorly differentiated HCC cells. Nevertheless, not all HCC cells secrete AFP into the circulation. Also, serum AFP levels may be elevated in patients with chronic liver disease in the absence of HCC (related to height of transaminases) and in patients with other malignancies[24]. Gupta *et al*[25] published a systematic review with five included studies on diagnostic value of AFP for detecting HCC (all stages combined) in cirrhotic and non-cirrhotic HCV patients. They concluded that even if one assumes best-case estimates of sensitivity and specificity, the case for surveillance by AFP remains weak. By using the usual cut-off point of 20 ng/mL, sensitivities and specificities for detecting all stages of HCC were 41%-65% and 80%-94%, respectively. Positive and negative likelihood ratios ranged from 3.1 to 6.8 and from 0.4 to 0.6, respectively. In a recent large case-control study with 419 included HCC patients and 417 cirrhotic controls (with various underlying etiologies of liver disease), the performance of AFP in early stage HCC was compared with other biomarkers, such as des-carboxyprothrombin (DCP) and lectin-bound AFP, with more encouraging results[26]. In this study, diagnosis of HCC was based on current criteria for diagnosis, with appropriate blinding and 6-mo post-enrollment follow-

up for controls to eliminate false negatives. Sensitivity and specificity of AFP for detecting early stage HCC were 53% and 90%, respectively, using the currently recommended clinical cut-off point of 20 ng/mL. When the point in the receiver operating characteristics (ROC) curve with optimal sensitivity and specificity was used as cut off (10.9 ng/mL), sensitivity was 66% and specificity 82%. This finding would suggest that the usual cut off of 20 ng/mL is too high for optimal performance of AFP surveillance. In a previous small case-control study with 170 HCC patients (68 early stage HCC) and 170 matched cirrhotic controls, the cut off of 20 ng/mL appeared to exhibit optimal sensitivities and specificities[27]. Nevertheless, at this cut off, sensitivities and/or specificities were often insufficient in other studies[28,29].

DCP is an abnormal protein generated as a result of an acquired defect in the posttranslational carboxylation of the prothrombin precursor in malignant liver cells[30]. Several studies investigated the performance of DCP as biomarker for early HCC, with inconclusive results[26,31-34]. For example, in a case-control study with 39 HCC patients and 77 matched controls, DCP had a greater accuracy than AFP[34]. DCP testing alone had a sensitivity and specificity of 74% and 86%, respectively, using a cutoff value of 40 mAU/mL. Another study reported much lower sensitivities for DCP with the best performance in chronic viral hepatitis[26].

Another potential biomarker for HCC is lectin-bound AFP: One of the three glycoforms of AFP, based on its reactivity in lectin affinity electrophoresis[35]. In a multicenter prospective study, the diagnostic accuracy of lectin-bound AFP *vs* AFP was compared in patients with HCV-related cirrhosis[36]. The prevalence of HCC at baseline and during the two years of follow-up was significantly higher in patients with elevated lectin-bound AFP than in those with elevated AFP. The relatively high prognostic value of lectin-bound AFP was even higher in patients with concomitantly elevated AFP levels. This suggests that lectin-bound AFP has some clinical utility as secondary test in HCV patients with mildly elevated AFP levels, by identifying a subgroup with a relatively high likelihood of HCC. Nevertheless, this study has important limitations, such as a relatively short follow-up and potential selection bias. Also, other investigators report less encouraging results. For example, in the previously mentioned case-control study of Marrero *et al*[26], sensitivity of lectin-bound AFP for detecting early HCC was only 37%. Several studies investigated the diagnostic performance of a combination of serum biomarkers. Nevertheless, when combining AFP and DCP, there appeared to be only little or no improvement in sensitivity rates for detecting early stage HCC[26,33,34].

Recently, new serum biomarkers for HCC have been suggested. Tyrosine kinase with Ig and EGF homology domains 2 (TIE2) is a receptor of angiopoietins. TIE2-expressing monocytes (TEMs) were recently reported to be enriched in HCC and other tumors where angiogenesis is known to be important for tumor progression. In a recent publication on 168 HCV infected patients (89 with HCC), frequency of circulating TEMs in peripheral blood was significantly higher in case of HCC, and independent of tumor stage[37]. TEMs were also increased in a separate group of non-HCV HCC patients. Performance of TEMs in discriminating HCC from chronic hepatitis or cirrhosis was superior to AFP or DCP (sensitivities 86% and 71% respectively; specificities 81% and 90% respectively. Nevertheless, another study found increased circulating and intrahepatic TEMs in HCV patients without HCC[38]. Although these findings relate to a relatively small cohort of HCV-infected patients, they raise concern that mobilization and expansion of TEMs may not be strictly HCC-driven, but more generally associated with chronic liver infection[39]. Several other studies investigated the performance of Glypican-3 (GPC3). GPC3 is a surface protein expressed in high percentages of HCCs, whereas it is not detectable in hepatocytes from normal subjects or patients with benign liver disease[40-42]. Another potential marker is Golgi protein 73 (GP73): An amino acid that normally remains in the Golgi complex. Marrero *et al*[43] reported that levels of GP73 are increased in serum of patients with HCC. In this study, sensitivity of GP73 for detecting early HCC was 62%. Also, interleukin-6 (IL-6) has been studied as potential marker for HCC. IL-6 is a cytokine involved in cell growth and differentiation. Serum IL-6 concentrations appeared to be increased in HCC patients (all stages combined) compared to controls[44,45]. Sensitivities of IL-6 for discrimination between HCC patients (all stages combined) and controls ranged from 46% to 73% and specificities from 87% to 95%. Also, levels of squamous cell carcinoma antigen (SCCA: A component of serine protease inhibitors) appeared to be significantly higher in HCC patients than in controls[46,47]. It remains to be seen, whether these new serum biomarkers will provide satisfactory results in the setting of surveillance in clinical practice.

ULTRASONOGRAPHY FOR HCC SURVEILLANCE

Currently, ultrasonography (US) is the most widely used method for HCC surveillance. US is not invasive, but time-consuming, relatively expensive and operator-dependent. Also, this investigation is often not suitable in case of overweight. According to a recent meta-analysis with 13 included studies by Singal *et al*[48], pooled sensitivities and specificities for detecting HCC at any stage were both 94%. However, US was less effective for detecting early stage -potentially curable- HCC, with a pooled sensitivity of 63% (95%CI: 49%-76%).

Another systematic review concluded that US is insufficiently sensitive for HCC surveillance[49]. Sensitivities for detecting HCC (all stages combined) of the 14 included studies ranged from 30% to 100% and specificities from 73% to 100%. Possible explanations for the large variability between studies are differences in opera-

tor skills and experience, in tested populations and/or in tumor size.

The potential benefit of combining US with AFP for detection of early stage HCC was also explored in the previously mentioned meta-analysis by Singal *et al*[48]. The pooled sensitivities increased from 63% to 69% (95%CI: 53%-81%), but this was not statistically significant (P = 0.65). This result suggests that adding AFP to ultrasound is not very useful for HCC surveillance.

The optimal interval for ultrasonographic surveillance is not known. It should be based on rate of tumor growth up to the limit of its detectability: Available evidence on tumor growth suggests that the interval from undetectable to a two cm diameter lesion ranges from 4-12 mo[50]. According to the meta-analysis by Singal *et al*[48] mentioned above, US sensitivities for detecting early-HCC may be improved by US at 6-mo intervals compared to surveillance intervals between 6-12 mo (pooled sensitivities: 70% *vs* 50%, P = 0.001). However, confidence intervals of pooled sensitivities were overlapping (95%CI: 55.6-84.6 *vs* 40.0-59.2).

Two recent retrospective cohort studies from Italy and South Korea report that HCC is detected at earlier stage, with curative therapy more often applied and better survival in case of surveillance interval ⩽ 6 mo compared to longer surveillance intervals, even after correction for lead time bias[51,52].

A recent randomized control trial investigated whether a 3-mo interval of US surveillance was more effective than a 6-mo interval[53]. More focal lesions < 10 mm were found in the group with 3-mo surveillance (5-year cumulative incidence: 41% *vs* 28%, P = 0.002). Nevertheless, 44% of all focal liver lesions detected during surveillance remained indeterminate. No differences in detection rates of small HCCs eligible for curative treatment were observed between the two randomized groups. Inadequate compliance occurred in approximately 10% of both groups. Also, overall 5-year survival rates were similar in both groups (85% *vs* 86%, P = 0.38).

Finally, a recent cluster-randomized trial from Taiwan compared 4- and 12-mo intervals in chronic HBV or HCV patients with thrombopenia. Although tumors were smaller in the group with 4-mo intervals, and curative treatment modalities more often applied, 4-year overall survival did not differ[54].

OTHER IMAGING TECHNIQUES FOR HCC SURVEILLANCE

Computed tomography (CT) and magnetic resonance (MR) imaging are potential tools for HCC surveillance. Until now, these imaging modalities are mainly used for further evaluation in case of abnormal findings with ultrasonographic surveillance and to determine extent of disease. Test characteristics of CT and MR imaging reported below are therefore all based on diagnostic studies rather than in a setting of surveillance. According to a systematic review of Colli *et al*[49] (studies in the period: 1996-2004 included), spiral CT imaging appeared to offer comparable sensitivities and specificities as US for detecting HCC (all stages) in patients with chronic liver disease. The pooled sensitivities for US and spiral CT imaging were 60% *vs* 68% and the pooled specificities 97% *vs* 93%. In the same systematic review, the reported pooled sensitivities (81%) and specificities (85%) of magnetic resonance imaging (MRI)-scan were, respectively, higher and lower than those obtained with US or CT imaging.

However, diagnostic accuracies of CT-scan and MRI-scan have increased in the past decade due to improvement of techniques[55-58]. For example, according to a recent retrospective study, the overall sensitivities of triple-phase multidetector CT (MDCT) imaging for detecting HCC (all stages combined) ranged between various observers from 78% to 81%[57]. Sensitivity improved with increasing HCC diameter. Also, in another recent study with prospective design, the diagnostic performances of US, MDCT imaging and contrast-enhanced MRI-scan were compared in a population of cirrhotic candidates for liver transplantation[58]. Dynamic MRI-scan with inclusion of the hepatobiliary phase had the highest accuracy with sensitivities for detecting early stage HCC, ranging from 59% to 85%. In contrast to CT imaging, MRI-scan is not associated with radiation exposure. However, MRI-scan is costly and there are no data from clinical practice to support the use of MRI-scan for surveillance.

SURVEILLANCE EFFICIENCY

The aim of surveillance is to decrease HCC-related mortality. Unfortunately, high-level evidence is limited in this respect. A recent Cochrane review[59] identified only one study with data on mortality: Zhang *et al*[60] performed a large cluster randomized controlled trial in which a policy of surveillance *vs* no surveillance was compared in 18816 patients with current or prior HBV infection or a history of chronic hepatitis. There proved to be a survival benefit for the strategy of a 6-monthly surveillance with combined AFP and US compared to the no surveillance strategy. Despite poor adherence to surveillance (58%), HCC-related mortality rates were significantly lower in the surveillance group than in the disease control group (83.2/100000 and 131.5/100000, respectively, OR = 0.63). Since this study was performed in chronic HBV patients in China, it is not clear whether its results can be extrapolated to the Western World. Also, according to the Cochrane review, there are some discrepancies between this publication and earlier publications about the same trial[61-63]. For example, numbers of disease controls and total numbers of participants dropped from 9711 and 19144, respectively, in the initial preliminary publication in 1997[62] to 9443 and 18816, respectively, in two later publications in 1999 and 2004, after completion of the trial[60,61]. Also, confidence intervals were computed as if cohorts had been randomly assigned for each individual patient, without taking the cluster randomization into account and statistical significance

was claimed with a 95%CI that was only borderline significant (95%CI: 0.41-0.98)[22]. In another large randomized controlled trial from China, the effectiveness of surveillance by 6-monthly AFP measurement in 5581 HBV carriers was investigated[29]. HCC-related mortality rates were not significantly different in the surveillance group compared to the control group (1138/100000 and 1114/100000, respectively, $P = 0.86$).

At lower evidence level, several cohort studies suggest that survival is improved with HCC surveillance[64,65]. In a population-based study of Alaska natives, 1487 HBV carriers had surveillance with AFP at 6-mo intervals[64]. In case of elevated AFP, US was performed. The long-term survival rate for patients whose HCCs were detected by the surveillance program was compared with a historical disease control group of patients with HCC: Survival rates were significantly higher for patients with HCC detected by surveillance (5-year survival rates: 42% and 0%, respectively, $P = 0.008$; 10-year survival rates: 30% and 0%, respectively, $P = 0.07$). Similar results were found in the study of Wong *et al*[65]. In this study, 56 HCC patients were retrospectively divided in three groups according to their initial presentation: Symptomatic patients presenting with abdominal pain, mass, bleeding, or weight loss; asymptomatic patients who had ultrasound for abnormal liver enzyme levels or other (unrelated) indications; and asymptomatic patients with underlying chronic liver diseases in a surveillance program. Patients in the surveillance group survived significantly longer than those in the symptomatic group (median survival of 1300 d *vs* 234 d, $P = 0.009$). Median survival of the asymptomatic group without surveillance did not differ significantly from the other groups. However, lead time bias due to disease detection in an early stage could have affected the results of the two previously mentioned studies. Also, length time bias could have biased results by preferential detection of slowly growing lesions that are more likely to remain asymptomatic until late in disease course.

Several studies indicate that surveillance programs could lead to more frequent detection of HCC at early stages, when curative treatment is still possible[60,61,66,67]. In the previously mentioned large randomized controlled trial by Yang *et al*[61], more resectable HCC cases were detected in the surveillance group than in the disease control group during five years follow-up (OR = 7.14; 95%CI: 3.53-14.43). In the later publication about the same trial, Zhang *et al*[60] reported similar results. Again, detection rates of small HCC (defined as a tumor diameter < 5 cm) were higher in the surveillance group than in the disease control group (45% *vs* 0%, $P < 0.01$).

In the systematic review by Gebo *et al*[66] covering publications in the period: 1996-2002, one prospective cohort study was identified that investigated HCC surveillance in HCV patients. This study by Solmi *et al*[67], compared 360 patients in the surveillance group (combined US and AFP measurements at 6-mo intervals) with a disease control group of 2170 patients who received usual care in other hepatology clinics. During a mean follow-up of 56 mo, the incidence of HCC in the surveillance group was 6.7% and 5.5% in the disease control group. Of note, in the surveillance group, 75% of the HCC's was unifocal and ≤ 3 cm in diameter compared to only 16% in the disease control group ($P = 0.000$).

Success of a surveillance program depends in general not only on the surveillance modality or target population. Recall strategy and adherence to follow-up are also important factors. In a large retrospective cohort study in the United States, 1873 HCC patients with a prior diagnosis of cirrhosis were identified in the period: 1994-2002[68]. In the three years before HCC diagnosis, 17% received regular surveillance, 38% received inconsistent surveillance and 45% no surveillance. In the regular surveillance group, 52% received both US and AFP, 46% AFP only and 2% US only. In a subset of 541 patients in whom cirrhosis was diagnosed at least three years prior to HCC, 29% received regular surveillance and 33% inconsistent surveillance. In another prospective cohort study, 1005 HCV patients were included in a surveillance program with combined US and AFP at 6- to 12-mo intervals[69]. During a mean follow-up of 6.1 years, 83 HCC cases were detected: 28% of those were tumors outside Milan criteria. 70% of patients with HCCs outside Milan criteria had experienced consistent surveillance and follow-up, which was not different from the total study group. Only in a minority of patients, absence of surveillance (13%) or follow-up (17%) could explain failure to detect patients at earlier stages. On multivariate analysis, study site was a strong independent predictor of consistent surveillance ($P < 0.001$). After correction for study site, also platelet counts > 150 × 10^6/mL and complete clinic visit adherence were positively associated with consistent surveillance.

TARGET POPULATIONS FOR SURVEILLANCE

Most HCCs develop in patients with chronic liver diseases. The decision to start surveillance should depend on the chance of developing HCC, *i.e.*, the incidence of HCC in specific populations. Especially high risk patients should be included in surveillance programs. However, selection of these patients remains a subject of debate. Also, it is important to decide, prior to surveillance, whether the clinical condition of the patient would allow any therapy in case of HCC detection.

Computer analyses in hypothetical cirrhotic patients

Several studies have investigated cost-effectiveness of HCC surveillance in cirrhotic patients based on computer analyses of theoretical models. In general, surveillance is considered cost-effective, if costs are less than $50000 per life-year or quality-adjusted life-year (QALY) gained. According to Sarasin *et al*[70], surveillance with combined US and AFP measurements at 6-mo intervals in patients with compensated cirrhosis results in an increase of life

expectancy of 3 mo when HCC incidence is 1.5%/year. However, in this case cost-effectiveness ratio of $55264 per life year gained exceeds the generally accepted threshold of $50000 per life year gained. When HCC incidence rates are higher, increase of life expectancy will be even more substantial. Cost-effectiveness ratios of systematic surveillance range between $26000 (HCC incidence: 6%/year) and $55000 (HCC incidence: 1.5%/year) for each additional life-year gained, in best case scenarios. Another study, using similar analyses in HCV cirrhotics, suggested that HCC surveillance with combined three-phase CT-scans and AFP measurements at 6-mo intervals was more cost-effective than other surveillance strategies[71]. This strategy was associated with an incremental cost-utility ratio of $25232/QALY compared to no surveillance. These results are based on estimated HCC incidences of 1.4%/year in patients with compensated cirrhosis and 4%/year in patients with decompensated cirrhosis.

Lin *et al*[72] suggested that combined US and AFP measurements at 6-mo intervals was the most effective surveillance strategy in HCV patients with compensated cirrhosis compared to other surveillance strategies (estimated annual HCC incidence: 0.02%-0.1%). However, this strategy entailed higher additional cost per QALY or life-year gained compared to a strategy of annual US and AFP measurements (incremental cost-effectiveness ratio: $106871/QALY) or no surveillance (incremental cost-effectiveness ratio: $129915/QALY). In this computerized decision model, surveillance with US at 12-mo intervals and AFP measurements at 6-mo intervals offered the greatest gain in life-expectancy, while still maintaining a cost-effectiveness ratio < $50000/QALY or life-year gained, regardless of HCC incidence.

Another study in a hypothetical mixed-etiology cohort of compensated cirrhotic patients suggested that combined AFP measurement and US imaging on a 6-monthly basis is the most effective surveillance strategy[73]. Compared to no surveillance, this strategy is estimated to increase the numbers of HCCs resectable at time of diagnosis more than three-fold with 50% decrease of HCC-related deaths. Significantly more small and medium-sized HCCs (diameter < 2 cm or diameter 2-5 cm, respectively) would be identified by surveillance. However, when costs were taken into account, it was doubtful whether US should be routinely offered to those with serum AFP levels ⩽ 20 ng/mL (> $45000/QALY). Also, cost-effectiveness varied considerably depending on type of underlying chronic liver disease. In this computerized decision model, annual HCC incidence ranged from 1.2% to 4.1%.

HCC incidence in cirrhotic patients

Annual incidence rates of HCC in specific populations with cirrhosis have been investigated extensively. Cirrhotic HBV patients have an increased risk for developing HCC. Studies that included only East Asian cirrhotic HBV patients showed HCC incidence rates around 3.2 per 100 person-years and 5-year cumulative HCC incidence of 15%[74,75]. Studies in European HBV cirrhotics reported lower incidence rates: 2.2 per 100 persons-years and 5-year cumulative HCC incidence of 9%[76-79].

Several studies have investigated the risk of developing HCC in HCV patients[76,80-83]. In a large prospective study of 12008 Taiwanese males, anti-HCV positive subjects had a 20-fold increased risk of developing HCC in comparison with anti-HCV negative subjects[81]. In this study, the presence or absence of cirrhosis was not evaluated. Other studies reported that especially cirrhotic HCV patients are at increased risk for developing HCC[76,80,83]. In a retrospective cohort study, the annual HCC incidence was 1.4% in European cirrhotic HCV patients[76]. Also, Degos *et al*[83] reported HCC incidence rates of 13.4% after five years follow-up in a cohort of French patients with compensated HCV-related cirrhosis. In another study from Germany, 17 of 838 HCV patients (2%) developed HCC during a mean follow-up of 50 mo[80]. All HCCs occurred in cirrhotic livers. Cirrhotic patients had a 20-fold higher risk of developing HCC than HCV patients without cirrhosis at study entry (RR = 20.2, 95%CI: 2.4-170.9). Also, Lok *et al*[82] reported that HCC incidence was higher in HCV patients with cirrhosis than in those with bridging fibrosis (annual HCC incidence rates: 1.45% *vs* 0.8%, P_{trend} = 0.08). This study was performed in the United States.

In patients with cirrhosis due to causes other than viral hepatitis, HCC incidence rates are generally not precisely known. Nevertheless, alcoholic liver disease is a clear risk factor for HCC. In a meta-analysis of Bagnardi *et al*[84], the consumption of alcohol was associated with an increased risk for developing liver cancer (RR = 1.86, 95%CI: 1.53-2.27 for alcohol consumption of 100 g/d compared to no alcohol). The presence or absence of cirrhosis was not evaluated in this meta-analysis. In a Danish nationwide cohort study, 169 (2%) of 8482 patients with alcoholic cirrhosis developed HCC during a median follow-up of 4.1 years[85]. Five-years cumulative HCC risk was 1.0% (95%CI: 0.8-1.3). Kuper *et al*[86] reported a relative risk of HCC of 2.4 for alcoholism alone and 22.4 for alcoholic cirrhosis compared to the general population. Several other studies also reported increased HCC risk in cirrhotic patients with alcohol as primary cause[87-91]. In a case-control study, heavy alcohol consumption contributed to a significant part of the 115 included HCC cases (32%), independent of other known risk factors[92].

Patients with cirrhosis due to genetic hemochromatosis also are at increased risk of developing HCC. According to a meta-analysis, patients with genetic hemochromatosis who are homozygous for the C282Y mutation have a 11-fold increased HCC risk compared to controls (OR = 11, 95%CI: 3.7-34)[93]. In a Swedish population-based cohort study, patients with genetic hemochromatosis had a 20-fold increased risk for developing primary liver cancer compared to the general population (standardized incidence ratio: 21, 95%CI: 17-28)[94]. In both studies, the presence or absence of cirrhosis was not evaluated. Several other studies reported similar results[95-98].

Table 1 Characteristics and results of studies on risk of hepatocellular carcinoma in patients with autoimmune hepatitis, α 1-antitrypsin deficiency and Wilson's disease

Ref.	Study design	Study period	Patient No.	Duration follow-up	Results
Autoimmune hepatitis					
Yeoman *et al*[110]	Prospective cohort study	1971-2007	243	median: 11 yr (range 1-36)	Annual HCC incidence: 1.1% HCC occurred more often in cirrhotic patients (9.3% *vs* 3.4%, $P = 0.048$)
Wang *et al*[111]	Prospective cohort study	Unknown	124	mean: 111 ± 6 mo	HCC incidence: 1 per 350 patient-year HCC incidence in cirrhotics: 1 per 182 patient-year
Werner *et al*[112]	Retrospective cohort study	1990-2003	473	median: 8.8 yr (range 1-45)	23-fold increased HCC risk compared to the general population. Only HCC in cirrhotics
Wong *et al*[113]	Retrospective cohort study	1999-2009	322	mean: 6.25 yr	HCC incidence all patients: 459 per 100000 patient-year (0.5%/yr) In cirrhotics: 1920 per 100000 patient-year (1.9%/yr)
Park *et al*[114]	Retrospective cohort study	Unknown	212 (88 cirrhotics)	mean: 123 ± 9 mo	HCC incidence in cirrhotics: 1 per 1002 patient-year. (0.1%/yr)
Teufel *et al*[115]	Retrospective cohort study	1970-2009	278 (89 cirrhotics)	mean: 4.8 yr (in cirrhotic pts)	No HCC observed in 431 cirrhotic patient-year
α 1-antitrypsin deficiency					
Eriksson *et al*[116]	Autopsy study	1963-1982	38250 (17 pts with A1AD)	NA	Increased HCC risk in patients with A1AD compared to controls. (OR = 20, 95%CI: 3.5-114.3)
Elzouki *et al*[117]	Autopsy study	1963-1994	50333 (31 pts with A1AD)	NA	Increased HCC risk in patients with A1AD compared to controls (OR = 5.0, 95%CI: 1.6-15.8; $P = 0.008$). Only significant in males
Propst *et al*[118]	Retrospective cohort study	1990-1992	Group 1: 240 cirrhotics with different etiologies (25% A1AD) Group 2: 130 non-cirrhotic A1AD pts	Unknown	No significant differences in HCC prevalence between cirrhotic A1AD patients and cirrhotic subjects due to other causes No HCC in non-cirrhotic A1AD patients
Wilson's disease					
Walshe *et al*[119]	Retrospective cohort study	1955-1987 1987-2000 1966-2002	159	range: 10-45 yr	9 patients (6%) developed abdominal malignancies (2 × HCC). Higher incidence compared to the general population
Thattil *et al*[120]	Case report and review	No limitation	NA	NA	19 published case reports of HCC in patients with Wilson's disease

HCC: Hepatocellular carcinoma; A1AD: α 1-antitrypsin deficiency; NA: Not applicable; pts: Patients.

Primary biliary cirrhosis (PBC) is another important risk factor for HCC development. In a recent meta-analysis, PBC patients had a 19-fold higher risk to develop HCC compared to the general population[99]. In a large Japanese cohort of PBC patients, HCC incidence was 2.4% during a mean follow up of 80 mo. HCC incidence was higher in males than in females (5.1% *vs* 2.0%)[100]. Caballeria *et al*[101] compared HCC incidence in 140 PBC patients and a group of cirrhotic HCV patients. Cumulative HCC incidence in PBC patients was 3.6% during a mean follow-up of 5.6 years. Incidence rates were much higher (11.1%), when considering only those patients with late stages of disease. PBC patients in stages Ⅲ and Ⅳ appeared to have comparable risks for HCC as cirrhotic HCV patients. Other studies reported similar results[102-105].

The exact incidence of HCC in patients with cirrhosis due to non-alcoholic fatty liver disease (NAFLD) is not known. Nevertheless, a recent systematic review of White *et al*[106] reported that patients with NASH-cirrhosis had a consistently higher risk of HCC. Cumulative incidence rates ranged from 2.4% over 7 years to 12.8% over 3 years. In cohorts with non-cirrhotic patients with NAFLD and NASH the risk of developing HCC was minimal: cumulative HCC mortality ranged from 0%-3% for study periods ranging from 6 to 21 years. Ascha *et al*[107] reported that annual cumulative HCC incidence in patients with NASH-cirrhosis was 2.6%, compared to 4.0% in patients with HCV cirrhosis ($P = 0.09$). Besides, in several studies features suggestive of NAFLD were occasionally observed in HCC patients without a well-defined other cause of chronic liver disease[108,109].

Cirrhotics patients with autoimmune hepatitis (AIH)[110-115] or α 1-antitrypsin deficiency[116-118] seem to have an increased HCC risk. However, the HCC incidence is lower than in cirrhotics with viral hepatitis. HCC in patients with Wilson's disease seems to be rare[119,120] (Table 1). Only case-reports are available for HCC in patients with cystic fibrosis[121-123].

HCC incidence in non-cirrhotic patients

The previously mentioned cost-effectiveness analyses were all restricted to cirrhotic patients and cannot be extrapolated to non-cirrhotic patients. However, also in some subgroups of HBV carriers without cirrhosis, HCC surveillance with US and AFP could be cost-effective[19]. HCC incidence should exceed 0.2%/year under these circumstances to allow cost-effective surveillance.

Table 2 Comparison of recommendations regarding hepatocellular carcinoma surveillance in guidelines

Characteristics	AASLD guideline[19]	EASL guideline[20]	APASL guideline[21]
Recommended target population	Cirrhotic HBV and HCV patients Alcoholic cirrhosis Stage 4 primary biliary cirrhosis Cirrhosis due to genetic hemochromatosis Cirrhosis due to α 1-antitrypsin deficiency HBV carriers of Asian origin (male > 40 yr, female > 50 yr) African/North American Blacks with hepatitis B HBV carriers with family history of HCC	Cirrhotic patients with Child-Pugh stage A and B Cirrhotic patients with Child-Pugh stage C awaiting liver transplantation Non-cirrhotic HBV carriers with active hepatitis or family history of HCC Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3	Cirrhotic HBV and HCV patients
Surveillance benefit uncertain	HBV carriers younger than 40 (males) or 50 (females) Hepatitis C and stage 3 fibrosis Non-cirrhotic NAFLD		
Surveillance modality	US	US	US and AFP
Interval (mo)	6	6	6

AASLD: American Association for Study of Liver Disease; APASL: Asian Pacific Association for the Study of the Liver; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Non-alcoholic fatty liver disease; US: Ultrasound, AFP: α-fetoprotein; HCC: Hepatocellular carcinoma; EASL: European Association for the Study of the Liver.

A prospective population study in 22707 Taiwanese male HBV carriers without cirrhosis showed that annual HCC incidence rate was 0.5%[124]. Annual rates increased with age. A Japanese study also reported a relatively high incidence of HCC in HBV carriers (0.4%/year)[125]. Both studies only included East Asian patients. In this population, with in general early HBV infection through vertical transmission, annual HCC incidence in non-cirrhotic carriers depends on age and starts to exceed the threshold of 0.2% per year around the age of 40 years[126]. In two large community-based prospective cohort studies from Taiwan, predictors of progressive disease in chronic hepatitis B were evaluated[127,128]. High transaminases, HBeAg positive status and high serum HBV DNA levels were risk factors for developing HCC. Nevertheless, non-Western HBV carriers remain at significant risk for developing HCC, regardless viral replication status[127,129,130]. Although HBsAg loss leads to a pronounced reduction of HCC risk, incidence remains higher that in the general population due to HBV DNA integration in the liver cell[124,131,132].

In contrast, uncontrolled prospective cohort studies in North America have indicated that the HCC incidence in HBV carriers could vary considerably[133,134]. Annual HCC incidence rates ranged between 0.06% and 0.46%. Non-Asian HBV carriers without cirrhosis are generally infected in adulthood by horizontal transmission and often exhibit low level of viral replication. They appear to be at limited risk of developing HCC[135-137]. However, HBV carriers with HCV or HIV co-infection or with a first degree relative with HCC are at increased risk for developing HCC[138-140]. Chronic HBV patients from sub-Saharan Africa often develop HCC at young age[129,141].

The HCC incidence in HCV patients without cirrhosis is not clear. A Japanese study investigated HCC incidence in HCV patients and reported that annual HCC incidences ranged from 0.5% to 7.9% in untreated chronic HCV patients with mild fibrosis and cirrhosis, respectively[142]. However, Lok *et al*[82] reported that annual HCC incidence in HCV patients with bridging fibrosis was only 0.8%. The risk of developing HCC in non-cirrhotic patients with chronic liver disease due to other causes than viral hepatitis, is not exactly known.

RECOMMENDATIONS OF GUIDELINES

In the last decade, several guidelines for management of HCC have been published worldwide. Most relevant are the practice guidelines of the American Association for Study of Liver Disease (AASLD)[19], the EASL-EORTC Clinical Practice Guidelines on the management of hepatocellular carcinoma[20] and the Asian Pacific Association for the Study of the Liver (APASL) consensus recommendations on hepatocellular carcinoma[21] (Table 2). The AASLD guideline recommends surveillance for selected groups of cirrhotics (viral hepatitis, alcohol, PBC, genetic hemochromatosis, α-1 antitrypsin deficiency) and high risk HBV patients without cirrhosis[19]. It is stated that there is insufficient evidence to recommend surveillance in HCV patients with advanced fibrosis or non-cirrhotic NAFLD. The EASL guideline advises surveillance in cirrhotics (regardless underlying cause)[20]. Also for HCV patients with advanced fibrosis and non-cirrhotic HBV carriers with active hepatitis or family history of HCC, surveillance is recommended. Of note, according to the EASL guideline, the presence of advanced (Child-Pugh C) cirrhosis prevents potentially curative therapies to be employed, and surveillance is not cost-effective under these circumstances, except for patients on the waiting list for transplantation. In fact, Child-Pugh C cirrhosis will also exclude radiologic interventions or sorafenib in palliative setting. According

to the APASL recommendations, cirrhotic patients with HBV and/or HCV should undergo surveillance[21]. Regarding modality of surveillance, the AASLD and EASL guidelines both recommend surveillance by US[19,20]. According to the APASL guideline, surveillance should be performed by combined US and AFP measurements[21]. All three guidelines recommend a surveillance interval of 6 mo[19-21].

CONCLUSION

In the last decade, there has been a marked increase in therapeutic options for HCC. Nevertheless, curative options are only feasible in case of early detection. Although regular surveillance could be beneficial in this respect, there is only limited evidence for its effectiveness in clinical practice. US at 6-mo intervals appears the most promising tool for surveillance, but the debate on serum tumor markers such as AFP has not yet ended. Defining those high risk subgroups who will benefit most from surveillance remains an important research goal for the near future.

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ISSN 1007-9327