Review

Hepatocellular carcinoma surveillance

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Surveillance of hepatocellular carcinoma in cirrhotic patients: Current knowledge and future directions

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Abstract

Patients with cirrhosis are at the highest risk to develop hepatocellular carcinoma (HCC), with a variable annual risk of 1–8%. Currently, biannual abdominal ultrasound (USG) with or without alpha fetoprotein (AFP) is the recommended HCC surveillance strategy of major professional liver societies for all cirrhotic patients. However, the effectiveness of USG and AFP has been a sprawling subject of debate due to conflicting results and the low quality of the evidence. The role of cross-sectional imaging is controversial due to potential harm and cost-effectiveness concerns. Several novel serum biomarkers have been introduced for HCC screening, but have yet to be validated for various geographic regions. A risk-stratified algorithm is needed to increase the yield of HCC surveillance by distinguishing a high-risk group that requires more intense screening with cross-sectional imaging and serum biomarkers, and a low-risk group, where the standard surveillance strategy is continued. In this review, the strengths and concerns related to standard USG-based surveillance strategy are discussed, as well as efforts to increase the effectiveness of surveillance.

Keywords: Cirrhosis complications; hepatocellular carcinoma; surveillance.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related deaths globally.[1] The most commonly established etiologies for the development of HCC are chronic hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, excessive alcohol consumption, and non-alcoholic fatty liver disease. In 90% of cases, these risk factors lead to cirrhosis before HCC development, but there is a small proportion (≈10%) of cases of HCC that occur in a non-cirrhotic liver.[2] Patients with cirrhosis are at the highest risk of developing HCC, with a variable annual risk of 1–8%.[3]

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Several observational cohort studies in patients with cirrhosis, and two large, randomized, controlled trials in patients with HBV have demonstrated that HCC surveillance can lead to discovery of HCC at an earlier stage, potentially curative treatment, and improved survival compared with patients who present symptomatically or are diagnosed incidentally.[4–6] Based on these data, the European Association for the Study of the Liver (EASL), the American Association for the Study of the Liver (AASLD), the Asian Pacific Association for the Study of the Liver (APASL), and the National Comprehensive Cancer Network (NCCN) recommend surveillance for at-risk individuals, including all cirrhotic patients, regardless of etiology, and selected subgroups of chronic HBV patients[7–10] (Table 1).

Currently, a biannual abdominal ultrasound (USG), with or without alpha fetoprotein (AFP), is the recommended HCC surveillance strategy of major professional liver societies for at-risk individuals (Table 2). A biannual USG with AFP is also recommended for at-risk individuals in the Turkey Hepatitis B Road Map, which was proposed by the Turkish Association for the Study of the Liver (TASL) in 2009.[11] However, the effectiveness of USG has been a subject of broad debate, due to conflicting results and the low quality of the evidence. The main reasons for the enquiry about USG are due to patient-related factors, such as obesity and the ability to view nodules on the liver in cases of cirrhosis, as well as operator dependency, which results in huge variations in the success of USG across institutions. The addition of AFP to surveillance seems to have been withdrawn from some recommendations and left to the physician's preference. This review is a discussion of the strengths and concerns of this standard of care surveillance strategy, in addition to efforts to increase the yield of surveillance and diminish cost-effectiveness concerns.

What do we gain from standard biannual USG±AFP surveillance?

The direct aim of any cancer surveillance program is clear: to detect cancer at an early, curable stage (Barcelona Clinic Liver Cancer [BCLC] stage 0 or A), which results in a favorable survival expectancy. Therefore, when a lesion is caught at a stage beyond eligibility for curative treatments (BCLC stage B, C, or D), USG is not considered to have a surveillance-related benefit as it would not have any influence on survival. The sensitivity and specificity of USG for any stage of HCC detection has been reported to exceed 90%. On the other hand, a recent meta-analysis found that USG alone detected early-stage HCC with only a 47% sensitivity rate, and the addition of AFP increased the sensitivity rate to 63%.[12] This may be explained by the higher rate of omission of small lesions in a cirrhotic liver due to the limitations of USG. A prior meta-analysis of 13 prospective

Table 1. Patients for whom surveillance for hepatocellular carcinoma is recommended according to society guidelines

Cirrhotic patients regardless of etiology, Child-Pugh stage A-B[7–9]
Cirrhotic patients regardless of etiology, Child-Pugh stage C awaiting liver transplantation[7–9]
Asian male hepatitis B carriers over the age of 40[8,9]
Asian female hepatitis B carriers over the age of 50[8,9]
Hepatitis B carriers with a family history of HCC[8,9]
Non-cirrhotic F3 patients, regardless of etiology may be considered for surveillance based on an individual risk assessment.[7]

Table 2. Guideline suggestions for hepatocellular carcinoma surveillance

Society guidelines	Surveillance recommendation
EASL[7]-2018	Ultrasound every 6 months
AASLD[8]-2018	Ultrasound with or without AFP every 6 months
APASL[9]-2017	Ultrasound and AFP every 6 months
NCCN[10]-2018	Ultrasound with or without AFP every 6 months
TASL[11]-2009	Ultrasound with AFP every 6 months

AASLD: American Association for the Study of the Liver; AFP: Alpha-fetoprotein; APASL: Asian Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; NCCN: National Comprehensive Cancer Network; TASL: Turkish Association for the Study of the Liver.

cohort studies concluded that AFP had no additional value compared with USG alone.[13] The demonstrated contribution of AFP in the literature may be due to higher advanced-stage HCC detection rates under USG-based surveillance.

The indirect, but actual goal of surveillance is to decrease cancer-related mortality in patients with cirrhosis. A recently published case-control study has demonstrated that neither USG nor AFP decreased HCC-related mortality.[14] The suboptimal performance of USG in reaching the direct and indirect goals of HCC surveillance highlights the need for alternative surveillance strategies. The global acceptance of USG in surveillance relies on the absence of risks, non-invasiveness, and lower costs, which is understandable. Model-based simulation studies have demonstrated that a biannual USG for all cirrhotic patients is cost-effective compared with no surveillance, although the average survival extension was less than 6 months.[15] Despite the contradictions, there is still evidence to suggest the use of AFP in combination with USG for patients with cirrhosis until better surveillance strategies are available. The only subgroup of patients with cirrhosis who are not recommended to undergo a standard surveillance program are those with Child-Pugh Class C cirrhosis, unless they are awaiting liver transplantation, given the low probability of treatment eligibility when HCC occurs.

What is the potential harm?

HCC surveillance with USG±AFP cannot constitute a direct physical harm; however, there is potential downstream harm associated with the diagnostic evaluation process. False negative results are common in USG-based surveillance. Suspicious liver lesions typically undergo subsequent computed tomography (CT) and/or magnetic resonance imaging (MRI), and are followed-up in shorter intervals, which adds radiation exposure, possible contrast injury, and financial burden.[16–18] A biopsy may be performed when the lesion cannot be characterized with these cross-sectional imaging techniques; however, biopsy is associated with risks of bleeding, tumor seeding, and injury to nearby organs.[19] In addition, this process and the follow-up period may entail a significant psychosocial burden for the patient. A recent report has revealed that 75% of patients under surveillance are concerned that they will die from the disease. While not specifically questioning the effect of routine intervals of surveillance, the impact on quality of life is apparent.[20] The potential harm has been weighted in a cirrhosis cohort, and 27.5% of patients were exposed to surveillance-related physical harm, of which 22.8% was USG-related and 11.4% was AFP-related.[21] In our Turkish cirrhotic cohort, we demonstrated that an annual, MRI-based surveillance strategy had a lower (6.5%) physical harm rate, without investigating the financial and psychosocial burden.

Is there any place for cross-sectional imaging?

The role of cross-sectional imaging is controversial. Several studies and meta-analyses have investigated the performance of MRI and CT.[22,23] Generally, there is a trend toward greater success in MRI compared with CT. In a randomized trial, an annual CT had a 62.5% sensitivity rate for the detection of early-stage HCC in the surveillance of patients with cirrhosis, which did not significantly differ from a biannual USG.[24] In addition to the lack of demonstrated benefits, CT-based surveillance is restricted due to its physical risks, including radiation exposure and contrast-induced nephrotoxicity.[16,17] Another study conducted to compare biannual, liver-specific, contrast-enhanced MRI and USG has shown that a biannual MRI had a sensitivity of 83.7% in the detection of early-stage HCC, whereas it was only 25.6% in the biannual USG arm.[25] Although a biannual MRI has demonstrated satisfactory results in the literature, the main barriers for MRI use in surveillance programs have been concerns with regard to cost-effectiveness, contraindications, long scan times, and limited availability.[18] Abbreviated-protocol screening MRI, which was proposed as a shorter version of conventional MRI screening, has shown comparable results to complete-protocol diagnostic MRI and made MRI a more assertive and cost-effective tool as a candidate for HCC surveillance.[26,27] Furthermore, the cost-effectiveness of a biannual MRI in the HCC surveillance of patients with cirrhosis has recently been proven using a cohort-based Markov model.[28] The Liver Imaging Reporting and Data System (LI-RADS) was developed to standardize the reporting and increase the diagnostic specificity of HCC using CT or MRI. The latest (2018) version of LI-RADS, which was first supported and endorsed by the American College of Radiology in 2011 and was integrated into the latest HCC guidelines of AASLD in 2018, helps radiologists to standardize the reporting of liver lesions and helps clinicians to optimize the management of liver lesions detected during surveillance.[8,29] In a recent study conducted by our group, we evaluated the efficacy of an annual contrast-enhanced MRI as an HCC-surveillance tool. In our cirrhotic cohort of 294 patients with consistent annual surveillance with MRI, we demonstrated satisfactory performance of MRI in the surveillance of HCC in terms of detect-

ing most of the lesions at earlier, curable stages (85.8%), and observed high sensitivity and specificity (sensitivity: 83.3% and 80%; specificity: 95.4% and 91.4%, respectively for detecting early and very early-stage HCC) with no additional benefit from biannual AFP.[30]

Contrast-enhanced ultrasound (CEUS) has been proposed in the last decade as another advantageous radiological tool for surveillance. The examination is performed by injecting intravenous, microbubble contrast agents without renal excretion and has the advantage of real-time, dynamic imaging. The CEUS technique is generally considered safe and well-tolerated, and may even be used in renal failure patients. Use in clinical practice is suggested by the latest version of the EASL guidelines on the management of HCC as part of a work-up of focal liver lesions and as a diagnostic tool for HCC, where available.[7] CEUS demonstrated superior performance to conventional USG in detecting early HCC in a head-to-head, prospective, multicenter, randomized, controlled trial, and has a sensitivity rate of 85% and a specificity of 91% for HCC detected in a cirrhotic liver.[31,32] CEUS appears to be a more sensitive tool than non-contrast USG for HCC screening, where available. However, it still has several limitations, such as a lack of specificity on differentiation between HCC and intrahepatic cholangiocarcinoma, which occurs in 2–5% of all new nodules in cirrhosis.[33,34] For this reason, a dedicated Contrast Enhanced Ultrasound Liver Imaging Reporting and Data System (CEUS LI-RADS) was developed in 2016, which uses the size, type, presence of washout, degree of arterial phase enhancement, and the timing and degree of washout to categorize focal liver lesions in patients at high risk for HCC.[35] The CEUS LI-RADS algorithm has been reported to be highly specific for the diagnosis of HCC, and may help CEUS take the lead in the race among radiological tools for HCC surveillance.[36]

Considering all of the limitations with standard, non-contrast USG, a better radiological surveillance tool is needed. In order to overcome the financial burden and increase the yield, the inclusion of advanced imaging tools to surveillance can be narrowed to selected patients with a higher risk of HCC development.

Are there any promising serological biomarkers to be used in HCC surveillance?

Novel biomarkers, such as biochemical metabolites, proteins, and RNA, have been introduced in the screening of many cancer types for early detection and prognosis determination. AFP has been widely accepted and used in combination with USG for HCC surveillance. However, AFP is not able to detect early HCC in 80% of cases, which made its usage in surveillance controversial. Another criticism of current biomarkers, especially AFP, appears to be drawn from its inconsistent performance characteristics across various etiologies of chronic liver disease and different regions. Thus, there has been interest in developing novel biomarkers with more success in early detection that could be used in different regions. The future of biomarker screening is promising, with numerous other molecules under research, such as osteopontin, alfa fetoprotein-L3 (AFP-L3), des-gamma-carboxy prothrombin (DCP), glypican-3 (GCP3), and alpha-L-fucosidase 1.

Since the conventional liver tissue biopsy is an invasive procedure and representative of only a small portion of the tumor, it is unable to represent tumor heterogeneity. Over the years, a new diagnostic method, liquid biopsy, has emerged as a promising tool for both detecting early HCC and determining prognosis and molecular profiling. Liquid biopsy has the advantages of being quick, easy obtainable, minimally invasive, and representative of a comprehensive tissue profile.[37] Liquid biopsy techniques are primarily based on detecting circulating tumor cells, micro RNA, tumor cell-free DNA, tumor-derived/associated extracellular vesicles, and metabolites and proteins.[38] A large number of liquid biopsy biomarkers have been studied in the early detection of HCC, and there is a suggestion that they could be promising biomarkers and an attractive option for AFP-negative early HCC; however, these candidate biomarkers must be internationally validated using methodologies easily transferable to clinical settings.

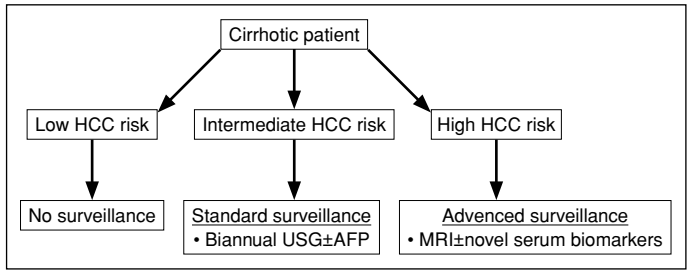

Figure 1. An illustrated risk-stratified hepatocellular carcinoma surveillance algorithm.

AFP: Alpha fetoprotein; HCC: Hepatocellular carcinoma; MRI: Magnetic resonance imaging; USG: Ultrasound.

Is a one-size-fits-all strategy practical for surveillance of HCC in cirrhotic patients?

The risk of developing HCC is not uniform, and may increase due to underlying parameters. However, despite our increasing awareness of prognostic and etiological risk factors, most patients present with advanced stages at the time of diagnosis, and fewer than 20% are eligible for curative treatment options.[39] The most critical game-changer intervention for the course of HCC remains improving the rate of detection at an early stage. To achieve this goal, the most accurate approach may be to optimize screening strategies and better reveal the higher risk patients who require more intense surveillance with better imaging modalities and/or serum biomarkers. This opinion is supported by a recent report examining the cost-effectiveness of risk-stratified HCC surveillance in which the method outperformed the currently recommended non-stratified, biannual USG for all patients, according to Markov decision-analytic modeling.[40] Our risk-stratified algorithm for the surveillance of HCC among cirrhotic patients in whom status has yet to be determined is illustrated in Figure 1.

A number of scoring systems have been developed to predict the risk of HCC, mainly focusing on chronic HBV[41–48] and HCV;[49–53] only a few have targeted all cirrhotic patients, regardless of etiology[54–56] (Table 3). Among them, the REACH-B (Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B), the PAGE-B (Platelets, Age, Gender in Chronic Hepatitis B), and the HALT-C (Hepatitis C Antiviral Long-Term Treatment against Cirrhosis) are the most popular and externally validated. In 2014, the ADRESS (age, diabetes, race, etiology of cirrhosis, sex, and severity) risk model, which uses variables of liver dysfunction, was developed to predict the 1-year HCC risk. ADRESS-HCC only categorized etiologies into three groups (autoimmune, alcohol/metabolic, viral), which proved unsatisfactory to weigh the different etiologies and treatment response status. In 2017, THRI (Toronto Hepatocellular Carcinoma Risk Index) was developed to predict the 10-year HCC risk using simple clinical and laboratory parameters (age, gender, etiology, platelets).[56] THRI weighed etiologies in more detail, including the sustained virological response status of HCV-related cirrhosis. The performance of THRI has been demonstrated in three

Table 3. Hepatocellular carcinoma prediction risk scores

Risk scores	Study population	Target group	Variables	External validation
Yuen et al.[41] (GAG-HCC)	Asian (Hong Kong)	HBV	-Age -Gender -HBV DNA -Cirrhosis	Yes (Asian)
Wong et al.[42] (CU-HCC)	Asian (Hong Kong)	HBV	-Age -Albumin -Bilirubin -Radiological cirrhosis	Yes (Asian)
Papatheodoridis[43] (PAGE-B)	Caucasians (Europe)	HBV	-Age -Gender -Platelet count	Yes (Asian)
Kim et al.[44] (mPAGE-B)	Asian (South Korea)	HBV	-Age -Gender -Platelet count -Albumin	Yes (Asian)
Wong et al.[45] (LSM-HCC)	Asian (Hong Kong)	HBV	-Age -Albumin -HBV DNA concentration -LSM value	No
Yang et al.[46] (REACH-B)	Asian (Taiwan)	HBV	-Age -Gender -ALT -HBeAg status -HBV DNA concentration	
Lee et al.[47] (REVEAL)	Asian (Taiwan)	HBV	-Age -Gender -ALT -HBeAg/HBV DNA/HBsAg/ genotype status	No
Lee et al.[48] (mREACH-B)	Asian (South Korea)	HBV	-Gender -ALT -HBeAg status -LSM value	Yes (Asian)
Lok et al.[49]	USA (HALT-C cohort)	HCV	-Age -Race (Black) -ALP -Esophageal varices -History of cigarette use -Platelet count	No
El Serag et al.[50]	USA	HCV	-Age -ALT -Platelet count -AFP	No
Chang et al.[51]	Asian (Taiwan)	HCV	-Age -Platelet count -AFP -Fibrosis stage	No
Matsuzaki et al.[52]	Asian (Japan)	HCV	-LSM	No
Ganne-Carrié et al.[53]	French (France)	HCV	-Age -Past excessive alcohol consumption -Platelet count -GGT -SVR status	No
Flemming et al.[34] (ADRESS-HCC)	USA	All cirrhotics	-Age -Diabetes -Race -Etiology of liver disease -Sex -Child-Pugh Score	Yes (USA)
Sharma et al.[36] (THRI)	Canada	All cirrhotics	-Age -Sex -Etiology of liver disease -Platelet count	Yes (Netherlands, China, Turkey)
Liang et al.[35]	Asian (Taiwan)	All cirrhotics	-Platelet count -HDL -Sugar/insulin ratio -LNR	Yes (South Korea)

AFP: Alpha-feto protein; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; HBeAg: Hepatitis B e-antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDL: High-density lipoprotein; LNR: Lymphocyte/neutrophil ratio; LSM: Liver stiffness measurement; SVR: Sustained virological response.

cohorts from different regions (Canada, Netherlands, and China).[56,57] THRI showed similar efficacy to predict HCC development in these three cohorts. We recently validated the efficacy of THRI in our Turkish cirrhotic cohort and found a similar area under the receiver operating characteristic (AUROC) curve value to the Canadian, Dutch, and Chinese cohorts, and very interestingly, determined the same optimal cut-off value of 240 to distinguish the high-risk HCC group.[58] This emerging evidence encourages the use of THRI and/or other validated scoring systems that apply the combination of clinical and laboratory variables to the risk-stratified surveillance algorithm.

In recent years, combinations of available clinical and laboratory variables have been evaluated to develop HCC risk-predictive scores, although the performance is somewhat limited and has yet to be adopted in clinical practice. To further adjust HCC prediction, the combination of three biomarkers (AFP, AFP-L3, and DCP) with sex and age was proposed as a diagnostic model (GALAD),[59] and later had better results when combined with USG (presence of solid lesion on surveillance) (GALADUS).[60] The GALAD score demonstrated remarkable performance in surveillance with an AUROC value of 0.95 (95% confidence interval [CI]: 0.93–97), a sensitivity of 92% and a specificity of 85%. The performance of GALAD for early HCC detection remained high as well (AUROC: 0.92; 95% CI: 0.88–0.96; sensitivity 92%, specificity 79%). Another risk score, the Doylestown algorithm, incorporates biomarkers (AFP and fucosylated biomarkers) and relevant clinical variables (age, gender, and ALT).[61] To supplement inadequate clinical scores, new molecular biomarkers have been investigated. Several germline single-nucleotide polymorphisms in epidermal growth factor and myeloperoxidase have been identified and validated as an HCC risk predictor, and a liver-derived 186-gene signature has been proposed as a prognostic parameter.[62–67] Although they have been considered for patients with cirrhosis in most need of surveillance, all are far from being in widespread use due to heterogeneity in etiological and differential characteristics of HCC globally. Validation studies from different geographic regions are required before further affirmative comments can be made for these combined clinical and serological prediction models.

Conclusion

Our knowledge of the cost-effectiveness of performing HCC surveillance is founded on model-based studies. Since follow-up without surveillance is not an option for trials, surveillance has become the worldwide standard of care. Despite the questionable quality of evidence, the literature suggests performing surveillance. A standard of care with a biannual USG±AFP is premature, and it is not rational to implement the same strategy for every cirrhotic patient. The key to increasing the yield and cost-effectiveness lies in risk-stratified surveillance strategy. There is growing evidence for and progress in the integration of cross-sectional imaging modalities and serum biomarkers to HCC surveillance. The evolving HCC-risk stratification models may help us to tailor a surveillance strategy and integrate costly tools in selected patients. Further studies are needed to better stratify the risk for HCC and to determine improved surveillance strategies, including imaging and biomarkers.

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