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Tailored algorithms for hepatocellular carcinoma surveillance: Is one-size-fits-all strategy outdated?

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Abstract

Purpose of review—Current clinical practice guidelines recommend regular hepatocellular carcinoma (HCC) surveillance with biannual ultrasound with or without serum alpha-fetoprotein uniformly applied to all patients with cirrhosis. However, clinical implementation of this one-size-fits-all strategy has been challenging as evidenced by very low application rate below 20% due to various reasons, including suboptimal performance of the surveillance modalities.

Recent findings—Newly emerging imaging techniques such as abbreviated MRI (AMRI) and molecular HCC risk biomarkers have increasingly become available for clinical evaluation and implementation. These technologies may have a potential to reshape HCC surveillance by enabling tailored strategies. This would involve performing optimized surveillance tests according to individual HCC risk, and allocating limited medical resources for HCC surveillance based on cost-effectiveness.

Summary—Tailored HCC surveillance could lead to achievement of precision HCC care and substantial improvement of the current dismal patient prognosis.

Keywords

Hepatocellular carcinoma; surveillance; precision medicine; molecular risk stratification

Introduction

Liver cancer, mainly hepatocellular carcinoma (HCC), is the second leading cause of cancer death worldwide, and its prognosis is still dismal with a 5-year survival rate below 15% [1].

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Compliance with Ethical Standards

Conflict of Interest

Nicolas Goossens, C. Billie Bian, and Yujin Hoshida each declare no potential conflicts of interest.

Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

In the United States, the incidence of HCC has significantly increased over the past 30 years and it is currently the fastest rising cause of cancer-related deaths [2]. The incidence of HCC is expected to continue to climb in the next decades, due to the increase of subjects with non-alcoholic fatty liver disease (NAFLD) and the increase of HCV-induced HCC despite the development of highly efficacious direct-acting antivirals [3].

Given an identifiable at-risk population, such as those with chronic viral hepatitis and/or cirrhosis, HCC surveillance using biannual ultrasound has been shown, in cohort studies and their meta-analyses, to be associated with improved survival, improved tumor detection at earlier stage, and improved curative treatment rates [4, 5]. These findings support the recommendation for biannual HCC surveillance with ultrasound with or without serum alpha-fetoprotein (AFP) in subjects at sufficient risk for HCC [6–8]. Although the strength of evidence supporting survival benefit of surveillance is not strong [9], it is ethically difficult to conduct randomized controlled studies with a ‘no surveillance arm’ to determine the magnitude of benefit [10]. Model-based simulation studies have demonstrated that biannual ultrasound for all cirrhotic patients is cost-effective compared to no surveillance, although average survival extension was less than 6 months [11]. The major limitations include suboptimal performance of the currently available surveillance modalities and the one-size-fits-all strategy recommended in the practice guidelines [12, 13], which may be substantially improved by tailored approaches discussed in this review.

Limitation of HCC surveillance modalities

Ultrasound and AFP have been the main HCC surveillance modalities widely used in clinical practice despite their suboptimal performance. The sensitivity of ultrasound detecting early-stage HCC tumor is only 63% in a meta-analysis of 13 studies [14], which somewhat exceeds suggested minimal sensitivity for a screening test to be cost-effective, 42%, assuming an access to surveillance of 34% [15]. However, the sensitivities hugely vary across institutions and could be as low as 32% for early-stage HCC detection, highlighting considerable operator dependency of its performance [16]. Serum alpha-fetoprotein (AFP) level has been widely used for HCC surveillance and diagnosis, although its clinical utility as a surveillance modality has been a matter of debate [17]. The sensitivity of AFP to detect early-stage HCC tumor is approximately 60%, but serum levels may rise in non-malignant conditions such as hepatic regeneration following an inflammation flare in patients with chronic hepatitis or cirrhosis [18].

Limitation of one-size-fits-all HCC surveillance strategy

HCC risk is approximately defined according to etiologies and stages of chronic liver diseases. For instance, 5-year cumulative HCC risks in HCV cirrhosis, hemochromatosis, alcoholic cirrhosis, and biliary cirrhosis collected from epidemiological studies are 17–30%, 21%, 8–12%, and 4%, respectively [19–21]. Based on the gross estimate for the underlying liver disease condition, a uniform regular HCC surveillance strategy, i.e., biannual assessment with ultrasound with or without AFP, is recommended when estimated overall HCC risk in the population exceeds a certain threshold of annual HCC incidence, e.g., 1.5% in cirrhotics and 0.2% in chronic hepatitis B in the American guideline [6]. However, this

one-size-fits-all strategy is practically challenging to implement in clinical practice, even in developed countries, as evidenced by the extremely low utilization rate. Patients' access to the surveillance program is a critical factor affecting its effectiveness [2]. A Markov model-based analysis revealed that the access rate should be at least 34% (with 42% effectiveness) for HCC surveillance to be associated with a survival benefit [15]. In a population-based cohort study of cirrhotic subjects over 65 years old in the U.S., only 17% of the patients received regular HCC surveillance prior to HCC diagnosis [22]. A systematic review among American patients reported a pooled rate of 18.4% [23], confirming the low surveillance rate below 20%. A European study (22%) and a Japanese study (26% in non-viral cirrhosis) found similar numbers with some exceptions (57% in Japanese viral cirrhosis), suggesting that HCC surveillance is applied only in one-fourth to half of cirrhosis patients globally [24, 25]. The poor application rate was not linked to patient adherence, as only 3% of patients with HCC in one study failed to complete surveillance despite orders [26]. Instead, provider-related factors, including failure to recognize liver disease or cirrhosis, failure to order surveillance, and time constraints, were identified as more influential factors [26, 27]. Hepatologists were more likely order surveillance compared to non-specialists (odds ratio of 6.1), and patients with alcohol abuse were less likely to have surveillance (odds ratio 0.14) [26]. Population-based interventions, such as mailed outreach invitations, nearly doubled surveillance rates, although still less than half (approximately 45%) of the patients received surveillance [28].

Experimental HCC surveillance modalities

As alternatives to the current HCC surveillance modalities, several imaging techniques and molecular biomarkers have been proposed to potentially replace ultrasound and/or AFP (Table 1). Computed tomography (CT) and magnetic resonance imaging (MRI) have been widely used for HCC diagnosis, and are less affected by the limitations of ultrasound, e.g., inter-operator variation, and likely yield better performance [13, 29]. However, these modalities have been deemed unsuitable as tools for surveillance due to the high costs and irradiation (for CT) [6]. Nevertheless, several studies assessed CT and MRI in an HCC surveillance setting (as opposed to a diagnostic setting). One study tested the diagnostic performance of a one-time screening by CT or MRI compared with ultrasound alone to detect HCC in 638 consecutive patients within 6 months before liver transplantation in a tertiary care institution comparing to findings of pathology at the time of transplantation [30]. Lesion-based sensitivity for HCC tumors smaller than 2 cm were 21%, 40% and 47% for ultrasound, CT and MRI, respectively, suggesting that although all 3 surveillance modalities had relatively low sensitivities for small tumors, CT and MRI provided substantial improvements doubling the sensitivity of ultrasound [30]. In another study, randomizing 163 subjects with compensated cirrhosis to biannual ultrasound or yearly CT, overall sensitivity for HCC detection was 71% and 67% for ultrasound and CT, respectively, with a similar proportion of early stage HCC detected (56% versus 63%) [31]. Although performance was similar, cost was higher in the CT-based surveillance strategy ($17,000 versus $57,000 for ultrasound and CT, respectively) [31]. A recent prospective study performed 3 rounds of paired ultrasound and MRI in 407 cirrhotic subjects and found an overall sensitivity for HCC detection of 85% for MRI but only 27% for ultrasound, whereas

sensitivity for early HCC was 86% and 26% for MRI and ultrasound respectively [32]. Although encouraging, the authors themselves highlighted that the cost effectiveness of this approach has yet to be assessed. To circumvent the issue of higher cost, simplified protocols have been explored to identify modalities that could replace ultrasound in the context of surveillance.

Abbreviated contrast enhanced MRI (AMRI) was retrospectively tested in 298 patients enrolled in a gadoxetic acid–enhanced MRI-based HCC surveillance program [33]. Analysis of a simulated AMRI protocol from the complete image set yielded a mean per-patient sensitivity of 83% for HCC detection, with reduced cost compared to the standard. Another retrospective single-center study reported a per-patient sensitivity of 81% and per-lesion sensitivity of 78%, confirming the maintained sensitivity in the simplified protocol [34]. The estimated range of cost saving with AMRI was 31–49%. Although these findings need prospective validation, AMRI and similar strategies could be promising options for improved performance with acceptable costs for HCC surveillance.

In parallel, to overcome the limitations of AFP, i.e., low sensitivity and specificity, there have been long-standing efforts to identify and develop serum molecular biomarkers for HCC detection (Table 1). Reported performance of detection varies, and these tests need validation in the setting of HCC surveillance in comparison with AFP.

From one-size-fits-all to tailored HCC surveillance strategy

Studies have indicated that HCC risk is not uniform across all patients with the same clinical condition, e.g., HCV cirrhosis, and therefore the current one-size-fits-all approach likely results in over- or under-estimated HCC risk for each individual [2]. In addition, the magnitude of HCC risk is not yet completely understood in emerging populations, i.e., non-alcoholic fatty liver disease (NAFLD) without cirrhosis and chronic hepatitis C after viral cure especially by direct-acting antivirals [35–39]. More precise individual HCC risk determination will address the heterogeneous HCC risk among patients and enable optimal allocation of limited resources and capability of HCC surveillance to the subset of patients who have higher risk and may benefit more from regular surveillance. Tailored surveillance strategies after prior determination of cancer risk have been successfully implemented in other disease settings, such as colorectal cancer screening, where clinical and genetic risk factors drive screening modalities and frequency, and breast cancer screening, where risk prediction models are available to determine cancer risk based on a number of variables [40–42].

HCC risk prediction has been attempted to identify a subset of patients at higher risk of HCC development using risk scores based on clinical variables such as older age, male sex, viral etiology of liver disease, Child-Pugh B/C cirrhosis, diabetes, and obesity, although their risk-predictive performance is limited especially in the sizable population of patients with earlier stage liver diseases in whom there is an unmet need for clinical prognostic factors (Table 2) [43]. Nevertheless, these studies clearly demonstrate feasibility to risk-stratify patients with chronic liver disease according to future HCC risk.

To supplement/complement these imperfect clinical scores, molecular biomarkers have been actively explored in parallel with the advent of high-throughput molecular profiling technologies (Table 2) [43]. Several germline single nucleotide polymorphisms (SNPs) have been reported as indicators of elevated HCC risk. The *EGF* 61*G allele was associated with HCC risk in a prospective cohort of patients with HCV-related advanced fibrosis (39% cirrhotic) and a prediction model including the *EGF* G/G genotype stratified subjects into 3 risk groups with increasing 6-year HCC incidence [44, 45]. A SNP in *MPO* encoding an antioxidant enzyme was associated with HCC risk in a prospective cohort of HCV cirrhotics [46]. A transcriptomic signature in diseased liver, now available as a Laboratory Developed Test (LDT), has been validated as a pan-etiology HCC risk predictor in patients with chronic hepatitis B/C, alcohol abuse, or non-alcoholic steatohepatitis (NASH) [47–50].

Prior to its diagnosis, HCC tumor is assumed to undergo subclinical growth phase with a tumor volume doubling time estimated at approximately 3–6 months, based on which the surveillance interval could be optimized [51, 52]. Given that high-risk patients are at risk of increased multicentric tumor occurrence, altering HCC surveillance interval according to estimated HCC risk may be a rational strategy. To date, uniformly longer or shorter surveillance interval has been clinically evaluated irrespective of individual HCC risk. An Italian study found that reducing surveillance to once a year led to a decrease in the detection of very early HCC and increased the number of advanced tumors detected, suggesting that this was a suboptimal strategy at least in the setting of Child-Pugh class A or B cirrhosis patients enrolled in the study [53]. Shortening surveillance interval to 3 months was tested in a randomized controlled trial, enrolling 1,278 French patients with mostly alcohol- or HCV-related liver diseases [54]. Although an increased incidence of lesions smaller than 10mm were identified in the 3-month surveillance group, this did not lead to an increase in HCC incidence or in prevalence of tumors smaller than 30mm diameter leading the authors to conclude that 3-monthly ultrasound surveillance detects more small focal lesions than biannual ultrasound, but does not improve detection of small HCC tumors at 5-year cumulative incidence of 10–12% in this study population [54]. It is still an unanswered question whether personalizing surveillance interval according to individual HCC risk leads to improved early HCC tumor detection and prognostic benefit for the patients.

With the new candidate surveillance modalities and tools for individual HCC risk assessment, one may consider tailored HCC surveillance choosing an optimal surveillance modality based on each patient's HCC risk status. However, it is challenging to ethically justify and logistically carry out prospective clinical trials assessing new HCC surveillance strategies. One viable alternative is to quantitatively evaluate tailored surveillance strategies in Markov model-based simulation studies, similarly to the evidence based underlying current clinical recommendations, based on the generally adopted criteria of cost-effectiveness, i.e., increased survival by 3 months or more and incremental cost-effectiveness ratio (ICER) below $50,000 / quality adjusted life year gained [6, 55, 56]. Indeed, a comprehensive survey of theoretically possible combinations of tailored HCC surveillance following clinical and molecular HCC risk assessment and patient stratification has revealed superior cost-effectiveness of personalized surveillance strategies compared to the current standard of care, biannual ultrasound uniformly applied to all patients with cirrhosis [57]. Although this result needs to be clinically verified, testing of such strategies is now

technically feasible given the clinical availability of the new surveillance modalities and molecular risk assessment assays.

Conclusion

Clinical implementation of HCC surveillance programs recommended in current practice guidelines, i.e., uniform biannual ultrasound HCC surveillance in all patients with cirrhosis, is practically infeasible due to multiple reasons and results in inefficient and wasteful distribution of limited medical resources for surveillance. It is now a prime time to consider tailored surveillance strategies with the rapid development of clinically available new imaging techniques and molecular assays, guided by the measure of net cost-effectiveness, which will eventually lead to achievement of precision clinical care for patients with chronic liver disease and substantial improvement of the still dismal HCC prognosis.

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Abbreviations

AFP	α-fetoprotein
ALD	alcoholic liver disease
CT	computed tomography
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
SNP	single nucleotide polymorphism

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Table 1

Experimental HCC surveillance modalities.

Modality	Reference
Imaging	
CT-based screening	[30, 31]
Abbreviated MRI	[34, 33]
Biomarker	
Lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3%)	[58–60]
Des-gamma carboxy prothrombin (DCP)	[58, 59, 61]
Golgi Protein 73 (GP73)	[62–64]
Osteopontin	[65, 66]
Glypican-3 (GPC-3)	[67]
Squamous cell carcinoma antigen (SCCA)	[68]
Dickkopf-1(DKK1)	[69]
Micro-RNAs	[70, 71]
Branch alpha(1,3)-fucosylated glycan (GlycoHCC test)	[72]

Table 2

Clinical and molecular HCC risk indicators.

Risk score	Etiology of liver disease	Outcome assessed	Variables / molecular marker	Reference
Clinical scores				
Biselli *et al*	HBV, HCV, alcohol, other	Presence of HCC	Baseline AFP and change over time	[73]
El-Serag *et al*	HCV	HCC incidence	AFP, ALT, platelets, and age	[74]
Hung *et al*	HBV	10-year HCC risk	Sex, Age, ALT, previous liver disease, history of HCC, smoking, status of HBV/HCV infection	[75]
ADRESS-HCC	HCV, Alcohol, NASH, HBV, Other	1-year HCC risk	Age, diabetes, race, etiology of cirrhosis, sex, and severity of liver dysfunction (Child-Pugh score)	[76]
Velazquez *et al*	Alcohol, HCV, HBV, Other	4-year HCC risk	Age, anti-HCV positive, prothrombin time and platelet count	[77]
UM regression model	HCV, Cryptogenic, Alcohol, Other	3 and 5-year HCC risk	AFP and gender	[78]
GAG-HCC	HBV	5 and 10-year HCC risk	Age, gender, HBV DNA, core promoter mutations, cirrhosis	[79]
CU-HCC	HBV	5-year HCC risk	Age, albumin, bilirubin, HBV DNA, and cirrhosis	[80]
LSM-HCC	HBV	3 and 5-year HCC risk	Liver stiffness, age, albumin, HBV DNA	[81]
REACH-B	HBV	3, 5 and 10-year HCC risk	Sex, age, ALT, HBeAg status, and serum HBV DNA level	[82]
Risk index	HCV after SVR	Incidence of HCC	Age, AST, platelet count	[83]
$score_{HCC}$	HCV after SVR	Incidence of HCC	Age, AFP level, low platelets and advanced fibrosis	[84]
Chang *et al*	HCV after therapy	5-year HCC risk	Age, male sex, AFP level, low platelet, advanced fibrosis, HCV genotype 1b and non SVR	[85]
El-Serag *et al*	HCV	Incidence of HCC	AFP, ALT, platelets, interaction terms, and age	[74]
HALT-C model	HCV	5-year HCC risk	Age, race, Alkaline phosphatase, esophageal varices, ever smoked, and platelet count	[86]
REVEAL-HCV	HCV	5-year HCC risk	Age, ALT, AST/ALT ratio, HCV RNA, cirrhosis and HCV genotype	[87]
Liver stiffness measurement	HBV	5-year HCC risk	Liver stiffness measurement	[88]
FIB-4	HBV	Incidence of HCC	FIB-4 (AST, ALT, platelets, age)	[89]
Molecular scores				
186-gene signature	HCV	Overall death, Progression to advanced	186-gene signature	[47,48]

Risk score	Etiology of liver disease	Outcome assessed	Variables / molecular marker	Reference
		cirrhosis, HCC		
HIR gene signature 65-gene signature	HBV	223-gene sig: late HCC recurrence, 65-gene sig: early HCC recurrence	223 (HIR) & 65-gene signature	[90]
Activated HSC gene signature	HBV	HCC recurrence and survival	37-gene signature	[91]
EGF SNP	HCV	6-year HCC risk	*EGF* 61*G (rs4444903)	[45]
PNPLA3 SNP	Alcohol, HCV	6-year HCC risk	*PNPLA3* 444*G (rs738409)	[92]
MPO SNP	HCV	HCC risk	*MPO* -463*G (rs2333227)	[46]
CAT SNP	HCV	HCC risk	*CAT* -262*C (rs1001179)	[46]
HFE SNP	Alcohol, HCV	HCC risk	*HFE* C282Y (rs1800562)	[93]

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIR, hepatic injury and regeneration; HSC, hepatic stellate cell; SNP, single nucleotide polymorphism; SVR, sustained virological response