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INVITED PAPER

# Surveillance Strategies for Hepatocellular Carcinoma: Recent Advances and the Shifting Paradigm

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## Abstract

Currently, international liver societies recommend screening at-risk individuals for HCC (patients with cirrhosis regardless of etiology, and/or chronic hepatitis B virus, and/or advanced liver fibrosis) with biannual abdominal ultrasound (USG) with or without alpha-fetoprotein (AFP). The global acceptance of USG in surveillance relies on the absence of risks, non-invasiveness, and lower costs. However, the suboptimal performance of USG ± AFP in reaching direct and indirect goals of HCC surveillance highlights the need for alternative surveillance strategies. Several studies targeted contrast-enhanced magnetic resonance imaging techniques, but the main barriers for their entrance to surveillance programs have been concerns about cost-effectivity and long scan times. Overall, the HCC risk stratification appears at hand by several validated multiple score systems, but their optimal performance is obtained only in populations who show highly homogenous clinical, pathological, epidemiologic, etiologic, and therapeutic characteristics, and this limitation poses a major drawback to their sustainable use in clinical practice. We need globally validated and molecular integrated risk stratification tools to shape the future tailored HCC surveillance decision algorithms. A dynamic process for HCC surveillance algorithms awaits us owing to the expected further prospective studies focusing on risk-stratified screening strategy.

**Keywords** Hepatocellular carcinoma · Surveillance · Risk assessment · Ultrasound · Magnetic resonance imaging

## Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer and the second leading cause of cancer-related deaths, and the incidence is on the rise globally [1]. Owing to this epidemiological scenario, prognosis and mortality of HCC can reasonably be ameliorated with preventive measures, mainly with surveillance of the population at risk to identify at earlier curable stages. Currently, international liver societies recommend screening at-risk individuals for HCC (patients with cirrhosis regardless of etiology, and/or chronic hepatitis B virus, and/or advanced liver fibrosis) with biannual abdominal ultrasound (USG) with or without alpha-fetoprotein (AFP) [2, 3]. However, the effectiveness of USG has been a sprawling subject of debate, due to the conflicting results and the low quality of the evidence. The main reasons for the inquiry on USG are owing to its patient-related factors such as obesity and nodular view liver in cirrhosis and operator dependency which results in huge variations in the success of USG across institutions. Nevertheless, the global acceptance of USG in surveillance relies on the absence of risks, non-invasiveness, and lower costs, which is comprehensible. Besides, model-based simulation studies have demonstrated that biannual USG for all cirrhotic patients is cost-effective compared to no surveillance, although the average survival extension was less than 6 months [4].

The addition of AFP to surveillance seems to be withdrawn from recommendations and left to physician's preference based on the evidence that USG alone detects early-stage HCC with only a 45% sensitivity rate, and the addition of AFP increased the sensitivity rate to 63% [5]. Most recent evidence concluded that AFP has no additional value compared with USG alone [6]. Despite its low efficacy in detecting tumors in early stages, AFP is still frequently used for HCC surveillance in real-world clinical practice due to its low cost and easy accessibility. The suboptimal performance of USG ± AFP in reaching direct and indirect goals of HCC surveillance highlights the need for alternative surveillance strategies.

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## Recent Advances in HCC Surveillance

The diagnosis of HCC is typically performed with contrast-enhanced cross-sectional imaging techniques (computed tomography [CT] or magnetic resonance imaging [MRI]), which provide reasonable sensitivity (depending on tumor size) and high specificity. Despite favorable accuracy and availability, conventional CT and MRI have not been considered ideal for HCC surveillance due to radiation exposure for CT and long examination duration and cost for MRI. Several studies and meta-analyses have investigated the performance of CT and MRI in HCC surveillance. In a randomized trial, annual CT exhibited a 62.5% sensitivity rate in the surveillance of patients with cirrhosis to detect an early-stage HCC, which did not significantly differ from biannual USG [7]. Another study conducted to compare biannual liver-specific contrast-enhanced MRI and USG showed that biannual MRI had a sensitivity of 83.7% in detecting early-stage HCC, whereas it was only 25.6% in the biannual USG arm [8]. In general, there is a trend towards higher success in MRI compared to CT. Although biannual MRI exhibits satisfactory results in the literature, the main barriers for MRI to enter the surveillance programs have been concerns about cost-effectivity and long scan times.

Recently, we evaluated the performance and potential of an annual contrast-enhanced MRI plus biannual AFP strategy as a HCC surveillance tool in our Turkish cohort of 294 patients with cirrhosis [9]. We aimed to incorporate a more improved screening tool with extended intervals to see whether we can still reach similar efficacy with lower cost and loss of time. In our cirrhotic cohort of 294 patients with consistent annual surveillance with MRI, we demonstrated the satisfactory performance of MRI in the surveillance of HCC, in terms of detecting most of the lesions in earlier curable stages (85.8%) and indicating high sensitivity and specificity (sensitivity, 83.3% and 80%, and specificity, 95.4% and 91.4, for detecting early and very early-stage HCC, respectively) with no additional benefit of biannual AFP. Several issues still should be concerned despite our satisfactory results. First, the biannual strategy is globally accepted based on the knowledge on the mean HCC volume doubling time and the goal of prolonging survival [10–12]. While retrospective studies identified a better performance of the 6-month screening interval in terms of the detection of early-stage HCC, cohort comparisons of biannual vs. annual USG-based schemes provided similar results in terms of survival improvement [13, 14]. Moreover, we were not able to measure the potential harms due to extended intervals MRI strategy. Thus, the annual MRI strategy should still be considered for tertiary centers with experienced radiologists until validated globally, proven cost-effective, and safe in larger prospective series. Abbreviated MRI, which emerged as a promising alternative tool for HCC surveillance, may further increase the plausibility of integrating cross-sectional imaging [15].

Considering all limitations, a better-improved surveillance strategy is required for patients at risk for HCC. There is a global doubt that the application of the standard surveillance strategy to all patients with chronic liver diseases at risk of HCC imposes major sustainability and economic burdens on healthcare systems. In other words, a one-size-fits-all strategy is probably not suitable for HCC surveillance. To overcome the financial burden and increase the yield, narrowing the inclusion of advanced imaging tools only to selected patients with a higher risk of HCC development is a rationale idea. The projected future HCC algorithm is illustrated in Fig. 1. At this point, the issue is how to stratify patients for HCC development risk. Several scoring systems were developed to predict the risk of HCC, mainly from Asian cohorts, to stratify the HCC prediction in patients with CHB. Similarly, even if less than for CHB, a few scoring systems were developed for CHC patients or cirrhotic patients with chronic liver diseases of different etiologies [16].

We recently validated the efficacy of the Toronto Hepatocellular Carcinoma Risk Index (THRI), one of the most comprehensive HCC risk stratification tool that was proposed in 2017, in our Turkish cirrhotic cohort [17]. THRI was developed to predict 10-year HCC risk, using simple clinical and laboratory parameters (age, gender, etiology, platelet) [18]. Moreover, THRI weighed etiologies in more detail, including the sustained virological response status of HCV-related cirrhosis. The performance of THRI has been illustrated in three different cohorts from different regions (Canada, the Netherlands, and China) [18, 19]. These three cohorts showed similar efficacy of THRI to predict HCC development. In our Turkish cirrhotic cohort, we found a similar AUC value to the Canadian, Dutch, and Chinese cohorts, very interestingly with the same optimal cut-off value of 240 to distinguish high-risk HCC group.

## The Shifting Paradigm in HCC Surveillance and the Road Ahead

Overall, the HCC risk stratification appears at hand by several validated multiple score systems, but their optimal performance is obtained only in populations who show highly homogenous clinical, pathological, epidemiologic, etiologic, and therapeutic characteristics, and this limitation poses a major drawback to their sustainable use in clinical practice. In this regard, the result from our recent study encourages the usage of THRI in the risk-stratified surveillance algorithm. Recently, a few newsworthy HCC risk algorithms were developed for patients with cirrhosis using the combination of serologic HCC markers and clinical parameters.

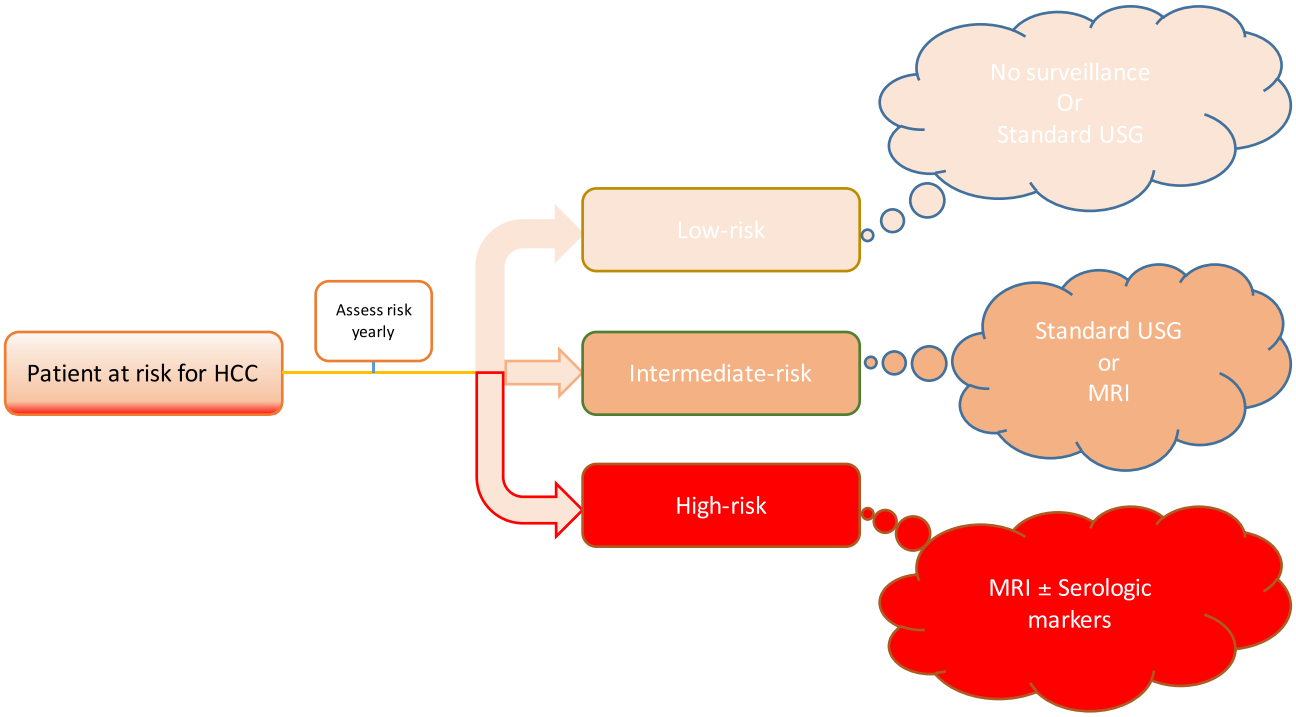


**Fig. 1** Projected HCC screening algorithm. HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; USG, Ultrasonography

All HCC markers so far identified have a highly dis-homogeneous prevalence in patients with different etiology of CLD that imposes their use in multiple markers panels. Furthermore, the serum levels of HCC biomarkers change over time, and the detection of this velocity might improve their specificity. A better understanding of the dynamic process driving the progression from chronic liver disease to HCC derived from studies based on molecular approaches and genetics, epigenetics, and liquid biopsy will enable the identification of new biomarkers to define the individual risk of HCC in the near future, with the possibility to achieve a real and cost/effective personalization of surveillance.

Currently, there is a strong recommendation to perform surveillance in patients with cirrhosis regardless of their liver disease etiology, origin, age, and sex. The proposed HCC risk scores are not yet standardized to be incorporated into sustainable HCC surveillance decision algorithms, and more efforts should be made to personalize HCC surveillance. The question remains as to whether the time intervals of ultrasound screening can be safely reduced or completely eliminated in lower risk cirrhotic patients, but the introduction of MRI seems reasonable for intermediate and/or high-risk patients. However, a globally acknowledged HCC risk stratification tool is still lacking which prevents us from implementing a tailored surveillance strategy in clinical practice. We need an ideal risk scoring system that would define optimal cut-off values to discriminate high-risk HCCs with high annual HCC incidence (> 3–5%) and high PPV and low-risk HCCs with high NPV (> 99%). Until then, we will keep performing the standard surveillance strategy recommended by CPGs, and the illustrated algorithm in Fig. 1 will only be subject to clinical trials. Other than the traditional risk factors, several overlooked carcinogenic metabolic conditions such as diabetes, co-existing NASH, and its additive fibrotic impact should be taken into account to increase the efficacy of HCC risk assessment. Most importantly, the risk stratification tool must be validated in the planned country or at least geographic area before its utilization. Individual molecular profiling will provide a crucial integration of HCC surveillance decision algorithms and help identify high-risk target populations in the future, but they are currently not widely available. Thus, we can conclude that a dynamic process for HCC surveillance algorithms awaits us owing to the expected further prospective studies focusing on risk-stratified screening strategy.

**Author Contribution** COD designed and prepared the draft and made literature search; OCO and FG performed critical review and final approval of the manuscript.

**Data Availability** Not applicable.

## Declarations

**Ethics Approval and Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Conflict of Interests** The authors declare no competing interests.

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