



# Is hepatocellular carcinoma surveillance in high-risk populations effective?

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Several professional societies recommend hepatocellular carcinoma (HCC) surveillance in high-risk patients including patients with cirrhosis from any etiology and subsets of noncirrhotic chronic hepatitis B virus infection. The efficacy of HCC surveillance to increase early detection and improve survival has been demonstrated in a large randomized controlled trial among hepatitis B virus patients and several cohort studies among those with cirrhosis. However, the effectiveness on HCC surveillance, when applied in clinical practice, is lower due to low utilization of HCC surveillance among at-risk patients, poorer test performance given operator dependency and differences in patient characteristics, and downstream process failures such as treatment delays. Interventions to increase surveillance utilization and improve surveillance test performance should improve surveillance effectiveness in the future.

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Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide [1]. The highest burden of HCC resides in East Asia and Africa related to high rates of endemic hepatitis B virus (HBV) infection in those areas [2]. However, implementation of HBV vaccination programs has started to decrease HCC incidence in some parts of Asia [3]. Although HCC is less common in the USA and Europe, the incidence and mortality are rising [4]. Over the past 10-year period assessed by Surveillance Epidemiology and End Results, HCC had the largest increase in mortality among all solid tumors [2]. If these trends continue, HCC is projected to become the third leading cause of cancer-related death in the USA by 2030 [5].

The strongest risk factor for HCC is the presence of cirrhosis from any etiology. Patients with cirrhosis have an annual risk of 2–6%, and over 90% of HCC occur in patients with underlying cirrhosis [6]. The most common underlying liver diseases include hepatitis C, hepatitis B, alcohol-related liver disease, nonalcoholic steatohepatitis (NASH) and metabolic causes of liver disease [7]. Historically, the most common underlying liver disease in the Western world was hepatitis C with active viremia, but contemporary cirrhosis cohorts have substantially higher proportions of patients with NASH, alcohol-related liver disease and hepatitis C after sustained viral response [8].

Prognosis for HCC is largely related to three factors – tumor burden, degree of liver dysfunction and patient performance status [9]. Although the 5-year survival for HCC has improved over time, it remains less than 20% among all patients – related to many patients presenting with advanced tumor burden and/or poor liver function. Patients who present with early-stage HCC are amenable to curative therapies such as surgical resection or liver transplantation and can achieve 5-year survival exceeding 70% [10]. In contrast, patients presenting with more advanced tumor burden are only amenable to palliative therapies and have a median survival of approximately 2 years [10]. Those with significant liver dysfunction or poor performance status are often not amenable to any HCC-directed therapy and have a median survival below 1 year.

Given the strong association between tumor stage and survival, professional societies including the American Association for the Study of Liver Diseases, European Association for the Study of the Liver and Asian Pacific Association for the Study of the Liver recommend HCC surveillance in at-risk patients, including subsets of patients with chronic HBV and those with cirrhosis [10,11]. Although there is some variation in society recommendations for surveillance modalities, most recommend semi-annual abdominal ultrasound with or without the serum biomarker,

alpha-fetoprotein (AFP). This strategy has been shown to increase early detection and improve survival in a large randomized controlled trial (RCT) in HBV patients and several cohort studies in patients with cirrhosis [12,13].

In this article, we discuss the efficacy and effectiveness of HCC surveillance in patients with cirrhosis, including factors that may contribute to a gap between efficacy and effectiveness.

### Efficacy versus effectiveness

Efficacy studies investigate the benefits and harms of an intervention under highly controlled conditions, evaluating how well the intervention can work [14]. Efficacy studies have clear methodologic advantages and have high internal validity; however, they often highly select patients (e.g., minimal comorbidity and adherent), providers (e.g., highly knowledgeable and skilled) and tools (e.g., most recent ultrasound technology), and use more intensive protocols than routine practice (e.g., patient navigation to complete screening and follow-up). The ideal study design to evaluate efficacy is a placebo-controlled RCT because it minimizes confounding and other sources of bias, although this can also be done in prospective cohort studies as well.

In contrast, effectiveness studies examine interventions under circumstances that more closely approach real-world practice and evaluate how well an intervention does work in clinical practice [14]. Effectiveness studies include more heterogeneous patient and provider populations and less-standardized treatment protocols as part of routine clinical practice. Although effectiveness studies sacrifice internal validity, they have higher external validity than efficacy studies. A gap between efficacy and effectiveness can be explained by ineffective intervention, poor implementation, lack of provider recommendation or lack of patient adherence [15].

### Efficacy of HCC surveillance

The efficacy of HCC surveillance has been evaluated in a large RCT among patients with chronic HBV and prospective cohort studies in patients with cirrhosis [12,13]. The RCT from China used block randomization in > 18,000 patients with HBV infection who were allocated to surveillance or no surveillance. Patients randomized to surveillance had significantly higher proportion of early-stage HCC detection (60.5 vs 0%) and curative treatment receipt (46.5 vs 7.5%), resulting in significantly reduced HCC-related mortality (83.2 vs 131.5 per 100,000 persons; hazard ratio (HR): 0.63; 95% CI: 0.41–0.98). Although this study provides level I data supporting HCC surveillance, there have been concerns that the analysis failed to adhere to intention-to-treat principles and did not account from block randomization [16].

These data cannot be extrapolated to patients with cirrhosis given increased nodularity and heterogeneity potentially impacting ultrasound sensitivity and increased risk of liver-related mortality. When a large randomized trial was attempted in patients with cirrhosis, it had to be terminated given poor enrollment and authors concluded an RCT may not be feasible in light of patient and provider preferences [17]. However, several cohort studies provide level II data supporting HCC surveillance in patients with cirrhosis [18–20]. A systematic review of 47 studies demonstrated that surveillance was associated with increased tumor detection odds ratio (OR): 2.08; 95% CI: 1.80–2.37), increased curative treatment receipt (OR: 2.24; 95% CI: 1.99–2.52) and improved 3-year survival (OR: 1.90; 95% CI: 1.67–2.17) [13]. Surveillance remained associated with improved survival in the subset of studies adjusting for lead time bias and length time bias, although studies were still prone to other biases inherent in cohort studies such as selection bias and residual confounding [18]. Overall, we believe these data provide strong, albeit imperfect, data supporting HCC surveillance as efficacious in patients with chronic HBV or cirrhosis.

### Effectiveness of HCC surveillance

The potential gap between surveillance efficacy and effectiveness was highlighted by a recent case–control study from the Veterans Affairs (VA) Health System, which failed to find an association between surveillance receipt and improved survival [21]. The authors found surveillance receipt did not significantly differ between patients who died of HCC and a matched group of cirrhosis patients who had not died of HCC. As above, it is unclear if these results are related to surveillance being an ineffective strategy when implemented in clinical practice or if this were related to poor implementation with the VA health system. Most notably, a decision analysis found surveillance utilization and test performance are two of the most important determinants of HCC surveillance effectiveness and ability to afford a survival benefit [22].

### Surveillance utilization

Several large studies have demonstrated HCC surveillance is underused in clinical practice. The first large studies to demonstrate underuse of surveillance were large population-based studies from the Surveillance Epidemiology and End Results–Medicare and national VA databases, with both studies showing less than 20% of patients had received an ultrasound or AFP in 2 of the 3 years prior to HCC diagnosis [23,24]. Since that time, several cohort studies have similarly shown HCC surveillance is underused, with a recent meta-analysis finding a pooled surveillance utilization of 24.0% (95% CI: 18.4–30.1%) [25]. In subgroup analyses, the highest surveillance receipt was reported in studies including patients from subspecialty gastroenterology clinics and the lowest surveillance receipt in studies using population-based cohorts (73.7 vs 8.8%). Lower surveillance receipt was also observed among patients with nonviral etiologies such as alcohol-related and metabolic-associated fatty liver disease. Finally, surveillance utilization was significantly lower in US-based studies compared with those from Europe or Asia (17.8 vs 43.2 and 34.6%). These figures pale in comparison with screening utilization observed in other evidence-based cancer screening programs, such as those for colorectal cancer, breast cancer and cervical cancer, which typically report surveillance receipt exceeding 60% among at-risk patients [26].

HCC surveillance implementation can be broken down into several discrete steps: patients must be engaged in healthcare and have a clinic visit, providers must accurately identify at-risk patients, providers must order appropriate surveillance tests; surveillance tests must be scheduled and the patient must adhere with the surveillance recommendations. There appears to be breakdowns at each of these steps in clinical practice, although the most common issues are lack of engagement in healthcare/clinic visits and lack of provider recommendation for surveillance testing in patients with known cirrhosis [27]. Patients' nonadherence to surveillance testing can occur but appears to be relatively rare.

Survey studies have been conducted among both providers and patients to gain further insight into potential barriers for surveillance completion. Primary care providers appear to believe HCC surveillance is efficacious for early tumor detection and reducing mortality; however, they had some important misconceptions about surveillance logistics including some believing physical examination or liver enzymes levels were useful for detecting HCC [28,29]. Providers also reported several barriers to performing surveillance including not being up-to-date with surveillance recommendations, considering surveillance outside of scope of primary care, and limited time in clinic with competing clinical concerns. Patients demonstrate high levels of HCC-related knowledge but similarly believed eating a healthy diet could preclude the need for HCC surveillance and that surveillance was not needed in the setting of a normal physical exam and labs [30,31]. Patients expressed worry about developing HCC and desire to complete HCC surveillance but reported barriers including difficulty with scheduling, costs of the tests and transportation difficulties. Surveillance receipt was significantly lower in patients who reported barriers to HCC surveillance.

Several studies have evaluated interventions to increase HCC surveillance utilization. Studies have reported significant increases with inreach efforts including primary care provider education or an electronic medical record reminder. For example, Del and colleagues reported an increase in surveillance-detected HCC after primary care provider education (55.3 vs 34.8%), compared with no significant change among a control group without education (39.2 vs 25.9%) [32]. In the largest study evaluating an electronic medical record reminder, Beste and colleagues reported increased adequate HCC surveillance ( $\geq 2$  imaging studies within 18 months) from 18.2 to 27.6%, whereas control sites without the intervention had no appreciable change in surveillance (16.1 vs 17.5%) [33]. Recently, a large pragmatic RCT has evaluated a population health outreach strategy to increase HCC surveillance. One-time screening within 6 months was significantly higher in the mailed outreach arm than usual care arm (44.5 vs 24.3%); the addition of patient navigation did not significantly increase one-time screening completion (47.2%) compared with outreach alone [34]. In a follow-up study, the team found continued benefits of outreach and navigation over longer periods of time; semi-annual surveillance over an 18-month period was performed in 23.3% of outreach/navigation patients, 17.8% of outreach-alone patients and 7.3% of usual care patients ( $p < 0.001$  for both vs usual care and  $p = 0.02$  for outreach  $\pm$  navigation) [35]. Although the trial demonstrated a benefit of these interventions, surveillance receipt among those who received mailed outreach and patient navigation was disappointingly low. Some of this may relate to the difficult-to-reach patient population, although these results may also imply the need for more intensive interventions in the future. Overall, these studies provide a roadmap to start addressing surveillance barriers, increase surveillance utilization and thereby improve surveillance effectiveness.

### Surveillance test effectiveness

Abdominal ultrasound has been the cornerstone of HCC surveillance for many years because it is readily available, noninvasive, inexpensive and safe with no risk of radiation or contrast exposure. Ultrasound has a high sensitivity of 84% (95% CI: 76–92%) for detecting HCC at any stage; however, it only has a sensitivity of 47% (95% CI: 33–61%) for early-stage HCC detection [36]. Further, its effectiveness can be affected by operator expertise and patient-level factors such as obesity and liver disease severity, leading to wide center-to-center and patient-to-patient variation in sensitivity [37,38]. A retrospective cohort study found 20% of ultrasound exams were of suboptimal quality for HCC surveillance, with this being significantly more likely in obese patients and those with NASH cirrhosis [39]. The lower sensitivity of ultrasound in patients with obesity and nonviral cirrhosis is concerning, given an increasing proportion of HCC related to NASH [40].

Surveillance value not only depends on potential benefits, in other words, sensitivity for early detection and improved survival, but also potential harms. Screening-related harms can be categorized as physical, financial or psychological. Data on harms of HCC surveillance have been limited to date, with only two studies quantifying physical harms and no studies examining financial or psychological harms. Both studies examining physical harms found 20–30% of cirrhosis patients experience a false-positive or indeterminate surveillance result that prompts diagnostic evaluation with computed tomography (CT) or MRI [41,42]. Moderate–severe harm, defined as repeated imaging or invasive evaluation such as biopsy, was observed in 10%. While some harms were related to suboptimal test specificity, there were patients who experienced harm related to nonguideline concordant management of indeterminate results, for example, subcentimeter liver lesion [41]. The latter category may increase the gap between surveillance value in efficacy and effectiveness settings.

There has been an increasing use of surveillance CT or MRI in clinical practice; however, there are limited data supporting routine use of cross-sectional imaging for this indication. A small single-center RCT comparing CT and ultrasound-based surveillance failed to find a significant difference in early detection (62.5 vs 55.5%;  $p = 0.93$ ) or HCC-related mortality (8.8 vs 6.0%;  $p = 0.46$ ) despite higher costs in the CT arm [43]. In a prospective cohort study comparing MRI- and ultrasound-based surveillance among 407 cirrhosis patients, Kim and colleagues found MRI-based surveillance had higher sensitivity for early HCC detection than ultrasound (83.7 vs 25.6%) [44]. However, data about MRI performance in non-HBV patients and its cost–effectiveness are needed prior to routine use of MRI for surveillance. Studies would also likely need to evaluate other potential concerns such as physical harms (radiation and contrast exposure), costs and limited radiologic capacity. A decision analysis suggested MRI may be particularly useful among patients at the highest risk of HCC; however, accurate risk stratification models are not yet available for routine use in practice [45]. Although MRI-based surveillance may increase surveillance effectiveness in the future, further data evaluating these novel imaging techniques in larger cohorts are still needed.

In parallel, there has been an increasing interest in serum biomarkers that may improve sensitivity for early HCC detection. The potential for novel biomarkers to improve surveillance effectiveness is supported when comparing outcomes in the Western world to those in countries like Japan, where biomarkers are incorporated into the routine surveillance recommendations and most patients are found at an early stage [46]. AFP remains the best studied biomarker but has poor sensitivity for HCC when used alone [47]. A meta-analysis found use of combination ultrasound and AFP improved early HCC detection compared with ultrasound alone, with sensitivities of 63%, (95% CI: 48–75%) and 45%, (95% CI: 30–62%), respectively [36]. Although this was associated with decreased specificity (84 vs 92%), the diagnostic odds ratio of the two in combination was higher than that of ultrasound alone. Recent data suggest using longitudinal changes in AFP values, rather than a single threshold, may also more accurately identify patients with early-stage HCC [48,49].

Other emerging biomarkers have similarly failed to achieve high sensitivity for early detection when used alone, so there is an increasing interest in combinations of biomarkers. For example, GALAD, which includes gender, age, AFP-L3%, AFP and des-gamma-carboxy prothrombin (DCP), has been evaluated in a large case-control study with 6834 patients (2430 HCC and 4404 chronic liver disease) and achieved sensitivities ranging from 60 to 80% for early HCC detection [50,51]. A methylated DNA marker panel was also recently shown to have promising performance in a large case-control study with sensitivity exceeding 70% for early HCC detection with specificity of approximately 90% [52]. Although these data for emerging biomarkers are promising, they still require validation in large Phase III cohort biomarker studies [53].

### Downstream process failures

Surveillance and early detection is part of the larger screening continuum and is dependent on timely diagnostic evaluation and appropriate treatment to translate into a survival benefit [15,54]. Some studies have suggested diagnostic and therapeutic delays may be associated with worse outcomes including stage migration, lower receipt of curative treatment and worse survival for other cancers including colorectal and breast cancer [55–58]. Although few studies have examined these issues among HCC patients, existing literature suggests failures in these downstream processes. In a retrospective single-center study, nearly one in five patients experienced diagnostic delays, defined as time from presentation to diagnosis exceeding 3 months [59]. Diagnostic delays may be related to providers missing or misinterpreting abnormal screening results, inefficient system-level workflows and scheduling processes, patients missing appointments or inaccurate diagnostic tests with suboptimal sensitivity [60]. Given an expected tumor doubling time of approximately 4–6 months, diagnostic delays of >3 months could allow for substantial tumor growth; however, studies have not yet demonstrated stage migration or worse survival with diagnostic delays in HCC [61,62]. Similarly, a single-center retrospective study also demonstrated a median time-to-treatment of 1.7 months, with nearly a third of patients experiencing therapeutic delays, defined as time from diagnosis to treatment exceeding 3 months [63]. In multivariable analysis, treatment delays were associated with significantly worse survival. Beyond therapeutic delays, several studies have highlighted underuse of HCC therapy in treatment-eligible patients, including low receipt of curative treatment among patients diagnosed at an early stage [64]. Treatment patterns are also notable for significant disparities with lower curative treatment receipt among racial/ethnic minorities and those of low socio-economic status. Multidisciplinary care and being seen in high-volume centers have both been shown to improve timely treatment and appropriate treatment receipt, which result in improved stage-by-stage survival [65–68].

### Conclusion

There is level I data in HBV patients and level II data in patients with cirrhosis suggesting HCC surveillance is efficacious for both early HCC detection and improving survival. However, effectiveness of HCC surveillance may be substantially lower given low utilization, poor test performance given operator dependency and differences in patient characteristics, and downstream process failures such as treatment delays.

### Future perspective

Ongoing interventions to increase surveillance utilization and evaluate novel imaging- and blood-based surveillance strategies should improve surveillance effectiveness in the future. We believe blood-based biomarkers have the greatest potential to address both surveillance underuse and test effectiveness over the next 5–10 years. By doing so, this would significantly increase the proportion of tumors detected at an early stage and thereby reduce HCC-related mortality.

#### Executive summary

- Hepatocellular carcinoma (HCC) surveillance should be performed in all patients with cirrhosis and high-risk subgroups of patients with chronic hepatitis B virus infection.
- Surveillance should be performed with high-quality ultrasound examinations and the serum biomarker, alpha-fetoprotein, every six months.
- Patients with subcentimeter liver lesions on ultrasound have a low risk of HCC and can be followed with short interval ultrasound.
- Patients with a liver lesion exceeding 1 cm should undergo timely diagnostic evaluation with multiphase computed tomography or contrast-enhanced MRI to evaluate for HCC.
- Patients with HCC should be referred for treatment evaluation, preferably in a setting offering multidisciplinary care.

### Author contributions

AG Singal takes responsibility for integrity and accuracy of the manuscript. AG Singal contributed toward concept and design; K Onyirioha and AG Mittal, contributed toward drafting of the manuscript. All authors contributed toward critical revision of the manuscript for important intellectual content. AG Singal provided administrative, technical and material support as well as study supervision.

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