Hepatocellular carcinoma surveillance: A path to better effectiveness

Aarthi Parvathaneni,
Undergraduate at SMU and Researcher at UTSW Medical Center, Dallas, TX, USA.

Amit G Singal, MD, MS,
Associate Professor of Medicine,
Medical Director of Liver Tumor Program,
Clinical Chief of Hepatology,
University of Texas,
Dallas, USA.

Correspondence:
Amit G Singal, MD, MS.
Division of Digestive and Liver Diseases,
University of Texas, Southwestern
5959 Harry Hines Blvd,
POB 1, Suite 420
Dallas TX 75390-8887,
USA.
E: amit.singal@utsouthwestern.edu

Worldwide, hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality and the fifth most common malignancy [1]. The highest rates of HCC occur in East Asia and Africa, given high rates of endemic hepatitis B virus (HBV) infection. In the United States and Europe, HCC most commonly occurs in the setting of hepatitis C virus (HCV) cirrhosis, although an increasing number of HCC cases are now related to underlying non-alcoholic steatohepatitis (NASH). Although the incidence of HCC in the US and Europe is lower than Asia and Africa, its incidence in the Western World is rapidly rising [2]. In fact, HCC had the largest increase in incidence among all solid tumours during the last 10 years as assessed by Surveillance Epidemiology and End Results (SEER).

HCC Surveillance

Prognosis for HCC is primarily dependent on tumour stage at diagnosis. Patients with HCC detected at an early stage qualify for curative treatments including liver transplantation, surgical resection, and local ablative therapies, yielding 5-year survival rates of ~70% [3]. However, patients presenting with advanced stage disease are only eligible for palliative treatments, with a median survival of less than one year [4]. Given the marked difference in treatment options and overall survival between early and advanced tumour stage, early HCC detection efforts are critical. Accordingly several professional societies including the National Comprehensive Cancer Network (NCCN), American Association for the Study of Liver Diseases (AASLD) and Veterans Administration (VA) recommended HCC surveillance using abdominal ultrasound with or without alpha fetoprotein (AFP) in patients with cirrhosis [5,6].

HCC surveillance fulfills all WHO criteria for implementing a cancer screening program: 1) HCC disease burden is an important health problem, 2) there is an identifiable target population, 3) surveillance is accepted by patients and providers, 4) it is affordable, 5) it achieves an acceptable level of accuracy, 6) there are standardised recall procedures, 7) there is an advantage of treating occult HCC, and 8) surveillance reduces mortality [7]. The most compelling evidence supporting HCC surveillance comes from a randomised controlled trial (RCT) with >19,000 HBV carriers in China, in which HCC surveillance facilitated higher proportions of early tumour detection (61 vs. 0%, $p<0.001$) and lowered mortality by 37% (mortality rate ratio 0.63) [8]. There is no similar level I evidence supporting surveillance among patients with cirrhosis (the primary at-risk population in the Western World), and data from the China RCT among HBV patients cannot be directly applied to cirrhosis patients due to a greater competing risk of non-HCC mortality and a lower sensitivity of surveillance ultrasound in a nodular liver [9]. However, several cohort studies have suggested cirrhosis patients undergoing surveillance have improved survival, after adjusting for lead-time bias, compared to those not undergoing surveillance [10-12]. A recent meta-analysis of surveillance-related cohort studies concluded HCC surveillance is associated with significant improvements in early tumour detection, receipt of curative therapy, and overall survival in patients with cirrhosis [13]. While an RCT would still be the ideal study design to assess surveillance benefits and harms in patients with cirrhosis, some contend that this would be difficult, if not impossible, to conduct due to ethical concerns of a non-surveillance arm [14]. While we live in an era of evidence-based medicine, a lack of randomised data does not equate to a lack of efficacy. Currently, the preponderance of data suggests HCC surveillance can improve early detection and reduce mortality. Observing these benefits in clinical practice is dependent on HCC surveillance utilisation rates and the effectiveness of surveillance tests [15].

HCC surveillance utilisation

Currently, HCC surveillance is performed in >20% of patients with cirrhosis in the United States, with lower rates among non-Caucasians, those of low socio-economic status, and patients followed by primary care providers compared to those seen by gastroenterologists [16,17]. Underuse of HCC surveillance is associated with higher rates of advanced tumour presentation, when treatment options are limited and survival significantly worse [18]. The most common reason for surveillance not being performed is due to a lack of orders from providers [19]. This deficit can be related to several issues including difficulty with recognising at-risk patients, lack of knowledge about HCC surveillance benefits, and clinic time constraints given the myriad of competing medical issues [20]. Patients typically demonstrate high levels of knowledge about HCC surveillance and report

high levels of acceptance and willingness to participate in HCC surveillance [21]. A study conducted in a safety-net patient population suggested patient-reported barriers, such as lack of transportation and difficulty scheduling surveillance testing, may be associated with lower rates of surveillance, but it is unclear if the data can be generalised to non-safety-net settings [22].

HCC surveillance effectiveness

The primary modality for HCC surveillance is an abdominal ultrasound, which has many advantages including being: readily available, safe, inexpensive, and non-invasive with no risk of radiation or contrast exposure. Sensitivity for early stage tumours ranges from 29 to 100% in prospective cohort studies, with a meta-analysis demonstrating a pooled sensitivity of 63% (95%CI: 49-76%) in patients with cirrhosis [23]. However, data suggest its effectiveness for early detection is substantially lower, with a sensitivity of ›50% [24]. Furthermore, ultrasound can be associated with false positive or indeterminate results in over one-fourth of patients, leading to physical and financial harms from diagnostic evaluation, as well as possible psychological harms, including patient anxiety [25]. Lower effectiveness of ultrasound in clinical practice could be related to several reasons including its operator dependent nature and differences in patient populations including higher rates of obesity or more advanced fibrosis. Limitations of ultrasound sensitivity may worsen in the future as the epidemiology of HCC shifts to NASH-related, given lower image quality in patients with obesity and NASH-related cirrhosis [26]. Use of cross-sectional imaging, such as MRI, is associated with increased sensitivity and specificity for early tumour detection; however, this strategy would not be cost-effective if applied to all at-risk patients [27].

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Using biomarkers in combination wth ultrasound could potentially improve early tumour detection. In the prior meta-analysis of prospective cohort studies, using AFP with ultrasound raised sensitivity for early HCC to 69% (95%CI 53-81%), although this difference was not statistically significant [23]. Subsequent studies have been more optimistic about the potential value of adding AFP to ultrasound, demonstrating significant increases in sensitivity for HCC detection. A study among 1597 patients followed for a median of 4.8 years found the sensitivity for any-stage HCC detection increased from 92 to 99.2%, with minimal loss in specificity when adding AFP to ultrasound for surveillance [28]. Similarly, another cohort study among 442 cirrhosis patients found adding AFP increased sensitivity for any-stage HCC detection from 43.9 to 90.2% and sensitivity for early HCC detection from 31.7 to 63.4% [24]. Furthermore, most data on the benefit of adding biomarkers has evaluated their utility as a one-time test at a specific cut-off, although providers often account for changes in biomarker values when interpreting data in clinical practice. Longitudinal changes in AFP measurement can have greater accuracy for early HCC detection, but they still require further evaluation as how best to be implemented in a standardised fashion [29,30].

How can we improve?

As discussed above, HCC surveillance has the potential to improve early detection and survival in patients with chronic hepatitis B and cirrhosis; however, the full benefits of HCC surveillance are not seen in clinical practice. Fortunately, there are several ongoing efforts to optimise surveillance effectiveness in the future.

For HCC surveillance utilisation, interventions, such as provider reminder systems and mailed outreach strategies, have shown potential to significantly improve HCC surveillance rates. A quasi-experimental study evaluating a point-of-care clinical reminder for HCC surveillance targeting primary care providers within the VA health system demonstrated increased surveillance rates from 18.2 to 27.6% ($p<0.001$); however, the rate in the intervention arm still failed to reach the minimum cut-off at which HCC surveillance becomes beneficial [31]. A recent study using mailed outreach invitations in a racially diverse socio-economically disadvantaged patient population increased HCC surveillance uptake from 24 to 45% [32]. This strategy was equally effective among all subgroups of patients including Caucasians or non-Caucasians, documented or suspected cirrhosis, and those receiving or not receiving gastroenterology care. However, further follow-up is needed to determine if high repeat surveillance rates can be maintained through this strategy given prior studies suggesting possible screening fatigue over time.

For HCC surveillance test effectiveness, recent studies have also shown promise in using biomarker panels, such as the GALAD score, for improving sensitivity for early tumour detection [33]. Currently, several prospective efforts including the Early Detection Research Network (EDRN) Hepatocellular Early Detection Strategy (HEDS) study are also underway to identify and evaluate novel surveillance biomarkers to improve sensitivity for early detection [34].

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