HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Emerging Strategies for Hepatocellular Carcinoma Surveillance

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G&H What are the advantages and disadvantages of using ultrasound for hepatocellular carcinoma surveillance?

AS Ultrasound has been the mainstay of hepatocellular carcinoma (HCC) surveillance for many years, with several advantages that have led to its widespread implementation across multiple settings. Ultrasound is noninvasive, widely available, and inexpensive compared with other modalities. However, there has been increasing recognition over time that ultrasound misses many HCCs at an early stage. This limitation is particularly evident with shifting demographics of the at-risk population, including increasing proportions related to nonviral etiologies of liver disease. Indeed, ultrasound plus alpha-fetoprotein (AFP) has a pooled sensitivity of only approximately 63%, meaning that over one-third of HCCs are missed at an early stage. Consequently, there has been increasing interest in emerging modalities, whether imaging- or blood-based.

G&H Currently, when might magnetic resonance imaging or computed tomography play a role in HCC surveillance?

AS Magnetic resonance imaging (MRI) and computed tomography (CT) are the primary diagnostic modalities for HCC at this time. When a patient has an abnormal ultrasound or AFP level, dynamic contrast–enhanced MRI or multiphasic CT is recommended as a recall strategy. These tests have high sensitivity for HCC detection and diagnosis, prompting increased interest in evaluating them for surveillance. However, insufficient validation at this time as well as potential concerns about costs and adverse events preclude these modalities from being used for HCC surveillance in broad at-risk populations.

There are proposals for these modalities to be used in select populations, for example, patients in whom ultrasound has poor visualization. Guidelines from the American Association for the Study of Liver Diseases (AASLD) state that providers can consider a screening CT or MRI in these patients, given low sensitivity of ultrasound for early-stage HCC in the setting of limited visualization. Poor visualization is more likely to occur in patients with obesity or nonviral etiologies of liver disease, and MRI or CT appear to have higher test performance in these populations. The other population in whom ultrasound does not perform well is patients with Child-Pugh B or C cirrhosis, such as those awaiting liver transplantation. Some centers perform either intermittent CT or MRI alternating with ultrasound, although further data are needed to identify optimal strategies in this patient population.

G&H What research has been conducted thus far on modifications to standard CT and MRI protocols?

AS Limitations of multiphasic CT as a surveillance modality include cost, exposure to radiation, and contrast exposure. Thus, abbreviated CT protocols such as low-dose, two-phase CT have been proposed. A recent study from Korea compared low-dose, two-phase CT with ultrasound and showed that the detection of early-stage HCC was similar between the modalities. This finding provides some support to the potential use of low-dose, two-phase CT as an alternative surveillance

approach, although further validation is still needed in Western populations.

Similarly, MRI is limited by concerns about radiologic capacity and cost, and there have been proposals to use an abbreviated protocol, shortening a 45-minute diagnostic MRI examination to approximately 15 minutes by using select MRI sequences. There are several types of abbreviated MRI, including with gadolinium, gadoxetate disodium (a hepatobiliary agent), and even noncontrast MRI. There have been studies evaluating each of these abbreviated protocols. In general, across different abbreviated MRI protocols, the sensitivity and specificity for early-stage detection appears quite high, around the mid 80s to low 90s. Ongoing prospective trials, including a multicenter study in the US Department of Veterans Affairs and a multicenter study being conducted in France, are comparing abbreviated MRI vs ultrasound for early-stage HCC detection. These studies will provide better understanding of the relative benefit of abbreviated MRI vs ultrasound and potentially identify populations in whom this emerging modality can be considered.

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G&H What is the current role of serum biomarkers for HCC surveillance?

AS The only biomarker that has currently obtained sufficient validation for routine use in clinical practice is AFP. By itself, AFP has insufficient sensitivity and specificity, but it appears to be additive when used in combination with ultrasound. Data show that ultrasound alone has a sensitivity below 50% for early-stage HCC detection; however, this increases to 63% when used in combination with AFP. There is a small decrease in specificity, but it is thought to be clinically insignificant. The diagnostic odds ratio for the 2 tests in combination is higher than ultrasound alone. That is why ultrasound plus AFP is the surveillance strategy currently recommended in many guidelines, including from the AASLD.

There is interest in many other emerging biomarkers (such as Lens culinaris agglutinin-reactive AFP [AFP-L3], Des-gamma-carboxy-prothrombin [DCP], osteopontin), but most have the same limitations as AFP in that each biomarker does not perform sufficiently well enough to be used alone. Thus, there is a need to combine these biomarkers and instead consider biomarker panels, rather than use single biomarkers by themselves. Of the several biomarker panels that have been evaluated, the one that has probably been the best validated to date is GALAD, which combines gender, age, AFP, AFP-L3, and DCP into a single biomarker panel. Not only are case-control data available on this panel, but a phase 3 retrospective study of a US cohort was recently completed. The Early Detection Research Network–funded HEDS study showed promising sensitivity and specificity for GALAD, which is now moving forward in the TRACER study, an ongoing prospective clinical utility study comparing GALAD vs ultrasound in more than 5000 patients with cirrhosis.

Other panels that have been evaluated include the GAAD score and the ASAP score, which similarly leverage gender, age, AFP, and protein induced by vitamin K absence or antagonist-II; however, their evaluation has primarily been in studies outside the United States. In parallel, there has been interest in methylated DNA panels and liquid biopsy techniques. These biomarker panels also appear promising, but they have primarily been evaluated in case-control studies to date. For example, the methylated DNA panels Oncoguard Liver and HelioLiver have shown promising sensitivity and specificity in case-control studies, but data are still being awaited for prospective validation in large cohorts.

G&H In addition to HCC-specific biomarkers, has there been research on multicancer detection platforms?

AS Multicancer detection platforms have garnered interest, as they attempt to detect multiple types of cancer using a single blood sample; however, limited data are currently available for patients with liver cancer. The number of patients with liver cancer included in the initial studies was very small, and the comparison population was healthy controls without underlying liver disease. Thus, there is a need to see how these multicancer detection platforms perform in HCC-specific studies comparing larger numbers with early-stage HCC to the intended at-risk populations, including patients with cirrhosis or chronic hepatitis B.

It is also worth mentioning that multicancer detection platforms have been set to achieve a very high specificity, so their sensitivity for early cancer detection is often fairly low. Thus, it is unclear whether these platforms will have a major role in terms of HCC surveillance, in which one would want to preserve high sensitivity for early-stage tumors.

G&H Do you think HCC surveillance will be moving away from imaging-based surveillance to biomarker-based surveillance in the future?

AS I think there is a push to move toward biomarker-based surveillance, assuming we can find the right biomarker with sufficient test performance. Beyond suboptimal sensitivity for early-stage HCC, one of the limitations of ultrasound-based surveillance has been underutilization. Only approximately 1 in 4 at-risk patients with cirrhosis receive HCC surveillance owing to both patient and provider barriers, many of which are specific to imaging. Providers report limited time in clinic, with competing clinical concerns to address as well as gaps in HCC-related knowledge. Patients report difficulties with scheduling as well as transportation barriers owing to the need for a separate radiology appointment. One would hypothesize that blood-based biomarker surveillance would be easier to implement in clinical practice because it can be performed the same day as a clinic visit. Therefore, theoretically, biomarkers could not only help improve test sensitivity but also utilization, and thereby result in marked increases in surveillance effectiveness. Once there is sufficient validation of blood-based biomarkers, I believe we will see a shift in the field toward biomarker-based surveillance.

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G&H What are the next steps and future directions for non–ultrasound-based HCC surveillance?

AS Early studies have shown promising test performance for emerging modalities, and the next phase will be prospective validation to see whether that test performance translates into improved clinical outcomes, including stage migration, increases in curative therapies, and, most notably, improvements in survival. Clinical utility trials evaluating some of these emerging modalities are underway at this time. I mentioned ongoing trials that are evaluating abbreviated MRI and GALAD; these data are going to be the next big phase of research for these emerging techniques.

Additionally, most studies to date have examined a single strategy for the entire at-risk population. However, the optimal strategy is probably not one test for everyone, but rather pairing the best test for each individual patient. Similar to efforts of precision oncology treatment, we need to consider precision surveillance, in which there is a patchwork of different strategies with preferred ones for individual populations. First, we know that HCC risk varies among patients with cirrhosis or chronic hepatitis B, so there have been several efforts to validate risk stratification models to differentiate high- vs low-risk patients. Further, patients who are lean and have well-compensated liver disease may have acceptable outcomes using ultrasound-based surveillance. Conversely, individuals with obesity and nonviral liver disease are prone to ultrasound failure, so blood-based biomarkers or abbreviated MRI may be preferred. My colleagues and I recently showed that a precision surveillance strategy would be cost-effective compared with our current one-size-fits-all strategy of ultrasound in all at-risk patients. Future studies should consider how the concept of precision surveillance can be formulated and implemented.

Disclosures

Dr Singal has served as a consultant or on advisory boards for Fujifilm Medical Sciences, Exact Sciences, Roche, Abbott, Glycotest, Freenome, and GRAIL.

Suggested Reading

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