

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Advances in Hepatocellular Carcinoma Surveillance



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G&H What is the current status of abbreviated magnetic resonance imaging in hepatocellular carcinoma surveillance?

NR Abbreviated magnetic resonance imaging (aMRI) is one of the most promising alternatives to ultrasound-based hepatocellular carcinoma (HCC) surveillance, particularly for patients with poor ultrasound visualization, such as those with obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), or advanced cirrhosis with very nodular livers. aMRI uses a shortened protocol, reducing scan time from approximately 45 minutes to 15 or 20 minutes while eliminating nonessential sequences. This reduces cost and burden on the patient compared with a full diagnostic MRI. Recent meta-analyses report pooled sensitivities of approximately 85% to 86% and specificities of 92% to 93% for HCC detection. Although performance varies by protocol and study population, aMRI consistently outperforms ultrasound for early-stage HCC detection. In a meta-analysis my colleagues and I published in *Gastroenterology* in 2018, ultrasound alone had a pooled sensitivity of approximately 45%, increasing to 62% with the addition of alpha-fetoprotein (AFP).

Despite these advantages, aMRI availability remains limited because MRI scanner capacity is constrained in many health systems, especially outside of academic and tertiary referral centers. In addition, aMRI protocols and follow-up pathways vary considerably across studies. Therefore, aMRI remains an emerging alternative for selected patients rather than a universal replacement for ultrasound. Current American Association for the Study of Liver Diseases (AASLD) practice guidance continues to recommend semiannual ultrasound plus AFP as the standard surveillance strategy, while acknowledging that computed tomography (CT) or MRI may be appropriate when ultrasound visualization is inadequate.

G&H Is there a role for contrast-enhanced CT or low-dose CT in HCC surveillance?

NR Contrast-enhanced CT is not recommended as a routine first-line surveillance modality. Because surveillance is performed every 6 months, repeated CT raises concerns about cumulative radiation exposure, contrast-associated nephrotoxicity, and cost. Unlike ultrasound-based surveillance, there are currently no prospective data demonstrating that CT-based surveillance improves survival. The primary role of multiphasic contrast-enhanced CT is diagnostic rather than for surveillance, particularly for characterization of lesions detected on ultrasound or when MRI is contraindicated or not available.

Low-dose CT is an attractive concept because it is faster and more widely available than MRI. Although radiation exposure is reduced compared with conventional CT, cumulative radiation exposure is still a concern and this strategy remains investigational. Key unanswered questions include its sensitivity for early-stage HCC, long-term safety, and cost-effectiveness.

G&H What is the current use of the Liver Imaging Reporting and Data System nationally and globally?

NR The Liver Imaging Reporting and Data System (LI-RADS) is a standardized system developed by the American College of Radiology to improve the acquisition, interpretation, reporting, and management of liver imaging in patients at risk for HCC. It includes algorithms for surveillance ultrasound as well as diagnostic CT and MRI, providing a common language for radiologists and clinicians to describe liver observations and guide management. LI-RADS is most embedded in North America, especially the United States, where it is closely integrated

into radiology reporting workflows. It has also been incorporated into recent AASLD guidance and was recently further aligned with United Network for Organ Sharing/Organ Procurement and Transplantation Network criteria for liver transplant. Internationally, LI-RADS is increasingly being adopted in clinical practice and research, particularly at academic centers, but its use remains variable as some regions rely on local or society-specific imaging

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criteria. One of the most important recent advances was the 2024 update to the ultrasound LI-RADS algorithm, which aligns closely with the updated AASLD guidance and emphasizes standardized assessment of ultrasound visualization quality. By identifying patients with inadequate ultrasound visualization, clinicians can better determine when alternative surveillance strategies, such as MRI-based surveillance, may be more appropriate.

G&H Could you discuss the potential for using blood-based biomarker panels in HCC surveillance?

NR Blood-based biomarker panels are among the most promising advances in HCC surveillance, but they are not yet part of routine clinical practice. One reason there is so much interest in these tests is that ultrasound surveillance is underutilized both globally and in the United States. Despite guideline recommendations, only approximately 1 in 5 patients with cirrhosis or chronic hepatitis B who are eligible for surveillance receive recommended imaging at 6-month intervals. Ultrasound surveillance requires multiple steps to occur successfully: clinicians must remember to order the test; patients must schedule and attend the appointment; and they must overcome logistical, financial, and transportation barriers. Blood-based biomarkers have the potential to simplify surveillance by making it easier to identify high-risk patients during routine clinic visits or laboratory testing.

The biomarker panel that has been studied most

extensively is GALAD, which combines AFP, Lens culinaris agglutinin-reactive AFP (AFP-L3), and Des-gamma-carboxy-prothrombin (DCP) with the demographic factors of age and sex. Because these laboratory tests are routinely available, GALAD has the potential to be implemented broadly if ongoing studies demonstrate clinical benefit. The National Institutes of Health–funded TRACER trial, a large randomized study comparing standard surveillance with ultrasound plus AFP vs GALAD-based surveillance, should provide important prospective evidence over the next several years. GAAD is a simplified version that incorporates only age, sex, AFP, and DCP.

These biomarker panels consistently outperform AFP alone and have shown improved performance for early-stage HCC detection, particularly when combined with imaging or used in patients with poor ultrasound visualization. However, an important unanswered question is how these panels will be implemented in clinical practice—as an adjunct to ultrasound, an alternative strategy for selected patients, or part of a broader risk-stratified surveillance approach. Additional work is needed to optimize cutoff values and improve specificity because false-positive results may lead to unnecessary imaging, increased health care costs, and patient anxiety. Overall, blood-based biomarker panels are an exciting, rapidly evolving area of HCC surveillance, but additional prospective validation is needed before they can be incorporated into routine clinical practice or guideline recommendations.

G&H How much promise do cell-free DNA methylation assays show for HCC surveillance?

NR Cell-free DNA methylation assays are a promising emerging approach for HCC surveillance. The premise is that tumor-associated DNA methylation changes can be detected in circulating cell-free DNA before a lesion is visible on conventional imaging, potentially allowing for earlier cancer detection. Several phase 2 studies have demonstrated encouraging diagnostic performance, raising the possibility that methylation-based assays could complement existing blood-based biomarkers such as AFP, AFP-L3, and DCP.

However, these assays are not yet ready for routine clinical practice. Most studies to date have been case-control studies enriched with patients who already have known HCC, which may overestimate diagnostic performance compared with a true surveillance population of patients with cirrhosis. Before these assays can be adopted into clinical practice, prospective validation is needed in real-world surveillance cohorts to demonstrate both high sensitivity for early-stage HCC detection and adequate specificity in distinguishing cancer from benign

liver inflammation or regeneration. Additionally, studies evaluating cost-effectiveness, implementation, and appropriate clinical management of abnormal test results will be essential before these assays can be incorporated into surveillance guidelines.

G&H How is artificial intelligence being integrated into HCC surveillance?

NR There are two major ways that artificial intelligence (AI) is being integrated into HCC surveillance. The first is through imaging analysis, including radiomics and other AI-based image interpretation techniques. These approaches extract quantitative imaging features that are not readily appreciated by visual interpretation alone, and may improve classification of focal liver lesions, assess ultrasound quality, and potentially increase diagnostic accuracy. The second involves predictive AI models that integrate imaging findings with longitudinal electronic health record data such as laboratory values, liver disease etiology, fibrosis severity, demographics, and other clinical variables to estimate an individual's future risk of developing HCC.

Although there has been considerable discussion about AI replacing radiologists, I do not think that is the most important near-term application. Instead, AI will serve as a clinical-decision support tool that helps optimize surveillance. For example, AI could help identify patients whose ultrasound examinations are unlikely to

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provide adequate visualization, determine which patients should be transitioned to MRI-based surveillance, and prioritize patients at the highest risk for more-intensive surveillance strategies. Ultimately, the greatest value of AI may be helping clinicians deliver the right surveillance strategy to the right patient at the right time.

G&H Might there be a role for polygenic risk scores in this area?

NR There has been growing interest in using polygenic risk scores to refine HCC risk stratification, especially in

patients with MASLD and mixed-etiology chronic liver disease. These scores combine the effects of multiple common genetic variants that are associated with hepatic steatosis, fibrosis progression, and HCC risk with the goal of identifying individuals whose risk differs substantially from what would be predicted based on traditional clinical factors alone. This approach is particularly attractive in patients with MASLD because the disease affects such a large proportion of the population, yet only a small minority of patients will ultimately develop HCC.

Several studies have shown that polygenic risk scores provide incremental prognostic information beyond conventional clinical risk factors, and a recent US study found that a hepatic fat polygenic risk score was associated with future HCC risk. However, the improvements in risk prediction have generally been modest, and it remains unclear whether these gains are sufficient to justify routine clinical testing or meaningfully change surveillance recommendations. Importantly, there is no prospective data demonstrating that polygenic risk score-guided surveillance improves early detection, treatment, or survival, and questions regarding implementation and cost-effectiveness remain. For these reasons, polygenic risk scores are not yet ready for routine clinical decision-making but are an important area of ongoing investigation.

G&H Could you discuss the recent shift toward risk-based surveillance?

NR This is probably the biggest conceptual shift occurring in HCC surveillance today. Historically, surveillance has followed a one-size-fits-all approach, with ultrasound plus AFP every 6 months for nearly all eligible patients. Increasingly, however, the field is moving toward precision surveillance, in which the surveillance strategy is tailored to an individual's underlying risk of HCC as well as the expected performance of the surveillance test. For example, lower-risk patients may ultimately continue standard surveillance or, in carefully selected cases, undergo less-intensive surveillance, whereas those at higher risk or with consistently poor ultrasound visualization may benefit from abbreviated or full MRI, blood-based biomarker-enhanced surveillance, or other more-intensive surveillance strategies (eg, every 3 months instead of every 6 months).

Although this is the direction where the field is moving, current AASLD and other international society guidelines continue to recommend semiannual ultrasound plus AFP as the standard surveillance strategy for most patients with cirrhosis. Importantly, however, both the recent AASLD guidance and the updated LI-RADS algorithm recognize that ultrasound quality matters. By incorporating standardized assessment of ultrasound

visualization, clinicians can better identify patients in whom alternative surveillance strategies may be more appropriate.

This evolution has been driven in large part by the changing epidemiology of chronic liver disease. As hepatitis C has declined following widespread, effective antiviral therapy, MASLD has emerged as one of the leading causes of HCC. Because MASLD affects nearly one-third of adults worldwide, universal surveillance is neither practical nor cost-effective, particularly since the absolute risk of HCC remains low for most individuals with cirrhosis. Although approximately 20% to 30% of MASLD-related HCC occurs in patients without cirrhosis, the denominator of patients with MASLD is so large that better methods are needed to identify those at highest risk. Risk-based surveillance also offers a potential solution by matching surveillance modality and intensity to an individual's predicted HCC risk. The European Association for the Study of the Liver has similarly highlighted risk-adapted surveillance as an important future direction to improve efficiency while maintaining clinical effectiveness.

G&H What are the biggest remaining needs in HCC surveillance?

NR The biggest remaining needs are improving the sensitivity for early-stage HCC detection and developing better surveillance strategies for patients with MASLD, obesity, and others who consistently have poor ultrasound visualization. We need prospective studies validating aMRI and blood-based biomarker strategies, as well as head-to-head comparisons to determine which approaches provide the greatest clinical benefit for different patient populations. We also need robust cost-effectiveness analyses and implementation studies to understand how these strategies can be incorporated into routine clinical practice.

One of the unique challenges in HCC surveillance is that, unlike many other cancers, we already know who the highest-risk population is—patients with cirrhosis and selected patients with chronic hepatitis B. In theory, this should make surveillance straightforward, yet we continue to see disappointingly low surveillance utilization in real-world practice. Therefore, developing better tests alone is not enough; rather, we also need strategies that improve surveillance delivery and adherence.

Importantly, future studies must demonstrate not

only improved diagnostic accuracy, but also meaningful improvements in patient outcomes, including earlier-stage detection, greater receipt of curative therapy, and ultimately improved survival. Those data are beginning to emerge, particularly through prospective studies such as the TRACER trial evaluating GALAD-based surveillance.

Another important unmet need is developing practical clinical algorithms for managing increasingly complex surveillance scenarios, such as patients with positive blood-based biomarkers but negative imaging, persistently poor ultrasound visualization, or discordant test results. I think the next major advance will not be a single test that replaces ultrasound. Instead, it will be a risk-adapted surveillance pathway that integrates an individual's clinical risk, ultrasound visualization quality, blood-based biomarkers, and advanced imaging to deliver the right surveillance strategy to the right patient. This paradigm was recently highlighted in an American Gastroenterological Association Clinical Practice Update, which emphasized moving beyond a one-size-fits-all approach and toward truly personalized HCC surveillance. I think that is where the field will see its greatest advances over the next decade.

Disclosures

Dr Rich has served as a consultant or on advisory boards for AstraZeneca, Eisai, Exelixis, Genentech, and Madrigal.

Suggested Reading

- Gu W, de Lédinghen V, Aubé C, et al. Hepatocellular cancer surveillance in patients with advanced chronic liver disease. *NEJM Evid.* 2024;3(11):EVIDo2400062.
- Gupta P, Singh S, Gulati A, et al. Noncontrast abbreviated MRI demonstrates superior diagnostic accuracy compared to ultrasound for hepatocellular carcinoma detection: interim results from a prospective surveillance trial [published online May 11, 2026]. *Hepatology.* doi:10.1097/HEP.0000000000001788.
- Rich NE, Villanueva A, Marrero JA, Kanwal F. AGA clinical practice update on risk stratification and emerging surveillance strategies for hepatocellular carcinoma: expert review. *Gastroenterology.* 2026;170(7):1606-1615.
- Singal AG, Llovet JM, Yarchoan M, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. *Hepatology.* 2023;78(6):1922-1965.
- Thrift AP, Kanwal F, Liu Y, et al. Risk stratification for hepatocellular cancer among patients with cirrhosis using a hepatic fat polygenic risk score. *PLoS One.* 2023;18(2):e0282309.
- Tzartzeva K, Obi J, Rich NE, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. *Gastroenterology.* 2018;154(6):1706-1718.e1.
- Wolf E, Rich NE, Marrero JA, Parikh ND, Singal AG. Use of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis. *Hepatology.* 2021;73(2):713-725.