HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

Section Editor: Robert G. Gish, MD

Update on Hepatocellular Carcinoma Surveillance, Staging, and Therapy

Sheila Eswaran, MD, MS
Associate Professor
Section of Hepatology
Rush University Medical Center
Chicago, Illinois

G&H What are the latest recommendations for hepatocellular carcinoma surveillance?

SE All patients with cirrhosis from any cause and those with hepatitis B who are noncirrhotic, from an endemic country, with family history of hepatocellular carcinoma (HCC), or with a high PAGE-B score (≥10) should undergo HCC surveillance. The PAGE-B score, a new addition to surveillance recommendations, is a score based on age, gender, and platelets to predict 5-year HCC risk and has been validated in a Western population. Currently, guidelines from the American Association for the Study of Liver Diseases do not recommend surveillance for patients with noncirrhotic metabolic dysfunction-associated steatohepatitis or hepatitis C with stage 3 fibrosis, but more data are needed to identify further risk stratification or biomarkers that can be used in these populations.

Recommendations for HCC surveillance still involve obtaining alpha-fetoprotein (AFP) levels and performing ultrasound every 6 months. For a while, there was some controversy regarding whether AFP should be used because it does not have very high sensitivity. For example, AFP can be normal in approximately one-third of patients with HCC, and it can be high in the setting of active inflammation. However, fairly recent data show that the addition of AFP to ultrasound increases sensitivity for identifying early-stage cancers. This is especially important because the sensitivity of ultrasound is lower in individuals with metabolic dysfunction-associated steatotic liver disease. Especially in this patient population and patients who might have a more dense liver, ultrasound plus AFP is the recommendation for HCC surveillance.

Recently, there has been some interest in using abbreviated magnetic resonance imaging (aMRI) instead of ultrasound for HCC surveillance. Historically, computed tomography (CT) and MRI cross-sectional imaging with and without contrast have occasionally been used for HCC surveillance (eg, when there has been poor visualization with ultrasound). However, there are cost-effectiveness issues with routine use of these tools as well as limitations with CT or MRI contrast. aMRI has been considered recently because it still involves contrast MRI but is shortened, which decreases cost and potentially increases sensitivity for HCC surveillance. aMRI takes approximately 15 minutes and includes only T1-weighted precontrast and dynamic contrast-enhanced images with an extracellular gadolinium-based contrast agent. A clinical trial in a population of veterans is currently underway, and its results are awaited.

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G&H Could you discuss recent efforts for improving rates of HCC surveillance?

SE A lot of research and clinical efforts are in progress to increase HCC surveillance rates. These efforts include

increases in outreach through automated letters or telephone calls, identifying patients through electronic health records to determine who is at risk for HCC, and sending outreach points to the individuals so they can be educated about the need for surveillance every 6 months. Telemedicine has improved outreach access to remote areas, so patients can undergo surveillance if they are at risk for HCC.

Biomarkers such as Des-gamma-carboxy-prothrombin (DCP) and Lens culinaris agglutinin-reactive AFP (AFP-L3) and methylated DNA markers can be used for HCC surveillance. Ongoing clinical trials are looking at whether these or additional biomarkers might be beneficial, especially in patients in whom ultrasound and AFP might have lower sensitivity. There are also risk stratification calculators to identify patients at risk for HCC. For example, the GALAD score (based on gender, age, AFP-L3, total AFP, and DCP) can be used to help identify patients who might be at risk for HCC. Providers might use these scores through electronic health records to reach out to patients to notify them of the need for updated surveillance.

G&H Have there been any recent updates involving HCC staging?

SE There are multiple different staging systems, but the one that is most commonly used is the Barcelona Clinic Liver Cancer (BCLC) staging system, which takes into account the patient's underlying liver function, functional status, and size and number of tumors. An important concept we have come to understand is stage migration, in which the stage of HCC is not fixed. Depending on cancer treatment, a patient's cancer stage may improve and thus be downstaged and moved to an earlier stage. Or, if a patient has liver dysfunction or experiences progression of their cancer, the stage might progress to a later one. Therefore, the stage is no longer considered fixed, and with all of the new therapies currently available for HCC, there can be migration to an earlier stage. This is particularly important in the context of liver transplantation, as patients who are beyond transplant criteria can potentially be downstaged to be considered for this curative option.

Another update involves subclassification of intermediate-stage HCC. BCLC stage B can now be separated into 3 subclasses. Typically, for BCLC stage B, the treatment recommendation is locoregional therapy, but now for patients with diffuse, infiltrative, bilobar cancer, the recommendation might be more systemic treatment. If there are well-defined nodules or preserved portal flow, then liver-directed therapy is more appropriate. There has been a change in the understanding of intermediate-stage cancers; not all are the same.

G&H How has the treatment landscape for HCC evolved recently in terms of nonsystemic therapy?

SE The biggest recent advances in HCC have involved the treatment realm. Treatment is still based on a multidisciplinary approach. Because there are many different treatment options, the multidisciplinary team should review patient cases to determine their underlying liver function, and then, based on the stage, treatment options are discussed with the patient.

Locoregional therapy delivered by interventional radiology includes radiofrequency ablation, transarterial chemoembolization, and transarterial radioembolization, which are used for early and intermediate stages of HCC or for downstaging in advanced-stage HCC. A new liver-directed therapy is histotripsy, which is a noninvasive ablation technique that uses ultrasound waves to form a cavity at the site of the liver tumor. There are upcoming trials looking at this new method, which just started being used clinically within the past year.

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There are also recent and ongoing studies on stereotactic body radiation therapy (SBRT) alone and in combination with locoregional therapy. The phase 3 trial NRG/RTOG 1112 compared SBRT followed by sorafenib, an oral tyrosine kinase inhibitor, with sorafenib alone in patients with advanced HCC. The study showed that the combination of SBRT followed by sorafenib improved overall survival, progression-free survival, and time to progression without a significant increase in adverse events. The addition of SBRT to immunotherapy is currently under investigation.

There has also been expansion of surgical candidacy for resection using different radiologic techniques. With the help of interventional radiology to increase the liver remnant through ablative techniques, surgeons have been able to push the envelope in terms of surgical resection, which was once more restrictive and conservative. In

addition, neoadjuvant immunotherapy or chemotherapy is being considered to offer the possibility for resection at later stages.

As for liver transplant, in addition to the opportunity for downstaging with a multimodal approach, there is an ongoing discussion about whether patients can be transplanted after immunotherapy because of the increased risk of rejection. There is likely some potential for transplant in this setting, but the timing has not been defined to determine what the washout period should be or the approach to posttransplant immunosuppression in this scenario.

G&H What recent advances have been made in systemic medical treatment for HCC?

SE First-line medical systemic therapy for intermediate- or advanced-stage HCC is currently the combination of the immune checkpoint inhibitors durvalumab (Imfinzi, AstraZeneca) plus tremelimumab (Imjudo, AstraZeneca), the combination of the anti–programmed death-ligand 1 antibody atezolizumab (Tecentriq, Genentech) plus the anti–vascular endothelial growth factor agent bevacizumab, or, for patients with contraindications to immunotherapy such as autoimmune disorders, the tyrosine kinase inhibitors sorafenib or lenvatinib (Lenvima, Eisai). These systemic therapies have durable outcomes, as shown in the landmark HIMALAYA and IMbrave 150 studies. The most recent advances have involved the combination of immune checkpoint inhibitors with multikinase inhibitors or locoregional therapy. There are many trials now that support combination and adjuvant therapies, such as IMbrave 050, EMERALD-1, and CheckMate 9DW.

G&H Have there been any recent adjustments in the multidisciplinary approach to HCC treatment?

SE It is important that patients with HCC are seen in a multidisciplinary clinic with all of the disciplines available, including transplant to consider early use of this option, especially if immune checkpoint inhibitors are being considered. As mentioned, such treatment may limit patients from being a transplant candidate in the future. There is still a gap in understanding which patients can be transplant candidates; referring to a multidisciplinary team with a transplant program early to determine the likely candidacy of patients is underutilized. It is also important to understand that there are many liver-directed and systemic therapies for HCC available, which will lead to stage migration, downstaging, and improvement in potential transplant candidacy. These decisions should be made in a multidisciplinary approach. There are a lot of data showing that multidisciplinary care improves HCC outcomes by decreasing time to treatment and transplant and improving overall survival.

G&H Have there been any other recent shifts in HCC care?

SE Recently, there has been increased recognition that frailty is a component that predicts outcomes in patients with HCC. Identifying patients who should receive interventions to improve their frailty, as well as conducting studies on prehabilitation, will be important. In addition, palliative care should be incorporated more in the treatment discussion with patients with HCC earlier on and should be more involved in the multidisciplinary approach. Palliative care can provide supportive care even at earlier stages of HCC, and then if the patient's HCC progresses to a later stage, there can be continuity of care.

G&H What are the biggest research needs remaining in HCC surveillance, staging, and therapy?

SE Further research is needed to develop additional surveillance biomarkers and evaluate combination therapy. For patients with difficult-to-treat HCC, tumor biopsies and gene sequencing likely will be utilized more so providers can determine which combinations of immunotherapy and other liver-directed therapies are best.

Disclosures

Dr Eswaran has no relevant conflicts of interest to disclose.

Suggested Reading

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