

HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Overview of the Updated AASLD Guidelines for the Management of HCC



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G&H When will the new guidelines for hepatocellular carcinoma be released in print publication, and why was there a need for updated guidelines?

JH The new American Association for the Study of Liver Diseases (AASLD) guidelines for hepatocellular carcinoma (HCC) surveillance, diagnosis, and treatment will be published in the January 2018 issue of *Hepatology*. They were first released online in January 2017 at https://www.aasld.org/sites/default/files/guideline_documents/Heimbach_et_al-2017-Hepatology.pdf. (No changes will be made to the online version of the guidelines when they are printed.) Print publication was held until the finalization of 3 systematic reviews, which were performed in order to provide evidence to support the clinical scenarios posed in the guidelines, so that all of these publications could be included in the same issue of *Hepatology*. These 3 supporting publications focus on advanced HCC treatment, diagnostic imaging, and HCC treatment while waiting for liver transplant.

Over the years, the AASLD has made several updates to its HCC guidelines, with the most recent occurring in 2012. This current update was needed to reflect changes and advances since the 2012 guidelines. HCC is a very important clinical problem for the medical professionals who take care of patients with liver disease. It is a common condition, and updated best-practice guidelines on how to treat it are essential.

G&H How were these guidelines developed?

JH These guidelines are not in the format that has been traditionally used in previous AASLD practice guidelines. The new gold standard for guidelines has become the Grading of Recommendation Assessment, Development and Evaluation (GRADE) format in which evidence-based responses are developed to specific questions (Table). The writing group for the new guidelines, of which I was a co-chair with Dr Jorge Marrero, took what we considered to be the most important and common clinical questions for the management of HCC and developed evidence-based answers. We worked collaboratively with an independent research group specializing in conducting systematic reviews to synthesize the available evidence in a very systematic way, making sure to include only evidence that is of high quality. All of the evidence was graded, and the recommendations were made accordingly. This was an intensive development process; it was not simply stating how something should be done and providing supporting evidence.

G&H What important changes or recommendations were made regarding surveillance of HCC?

JH A significant update regarding surveillance is the inclusion of alpha-fetoprotein (AFP), which had been left out of the last set of HCC guidelines. These new

Table. Key Questions Posed in the AASLD Guidelines for HCC

1. Should adults with cirrhosis undergo surveillance for HCC? If so, which surveillance test is best?
2. Should adults with cirrhosis and suspected HCC undergo diagnostic evaluation with multiphasic CT or multiphasic MRI?
3. Should adults with cirrhosis and an indeterminate hepatic nodule undergo a biopsy, repeated imaging, or alternative imaging for the diagnostic evaluation?
4. Should adults with Child's class A cirrhosis and early-stage HCC (T1 or T2) be treated with resection or locoregional therapy?
5. Should adults with cirrhosis and HCC that has been resected or ablated successfully undergo adjuvant therapy or not?
6. Should adults with cirrhosis awaiting liver transplantation and HCC (T1) be treated or undergo observation?
7. Should adults with cirrhosis awaiting liver transplantation and HCC (Organ Procurement and Transplantation Network [OPTN] T2) undergo transplant alone or transplant with bridging therapy while waiting?
8. Should adults with cirrhosis awaiting liver transplantation and HCC beyond Milan criteria (T3) be transplanted following downstaging to within Milan criteria?
9. Should adults with cirrhosis and HCC (T2 or T3, no vascular involvement) who are not candidates for resection or transplantation be treated with transarterial chemoembolization, transarterial radioembolization, or external radiation?
10. Should adults with Child's A/B cirrhosis and advanced HCC with macrovascular invasion and/or metastatic disease be treated with systemic or locoregional therapies or no therapy?

AASLD, American Association for the Study of Liver Diseases; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

Adapted from Heimbach JK, Kulik LM, Finn R, et al. AASLD guidelines for the treatment of hepatocellular carcinoma [published online January 28, 2017]. *Hepatology*. doi:10.1002/hep.29086.

guidelines recommend surveillance using ultrasound with or without AFP every 6 months. The guidelines recognize that there is some uncertainty regarding the inclusion of AFP, and this uncertainty is reflected accordingly.

G&H How do the new guidelines address diagnostic evaluation of patients with suspected HCC?

JH This is a particular area in which we spent a considerable time examining the evidence. In order to diagnose HCC, a provider can use cross-sectional imaging with either computed tomography (CT) or magnetic resonance imaging (MRI). We conducted a systematic review to try to determine whether one of these methods should be rated over the other. The weight of the evidence slightly favored MRI, but when we considered other factors, such as patient preference, availability, cost, and institutional expertise, we did not feel that we could recommend one method over the other. Therefore, both diagnostic tests are recommended, but not one over the other.

G&H Are there any recent advances in imaging techniques that are included in the guidelines?

JH The writing group of these guidelines covered a broad range of disciplines. In addition to experts in hepatology, there are experts in surgery, radiology, and oncology, making this group quite balanced and larger than previous writing groups in terms of all 4 disciplines. Thus, the entire imaging section was written by a radiologist, and the nuances of the newer techniques are well outlined.

G&H What are the most significant changes or recommendations involving liver transplantation in patients with HCC?

JH Among the liver transplantation recommendations, there is a new section involving downstaging. The guidelines recommend considering liver transplantation if a patient with HCC who was beyond the Milan criteria (T3) has been successfully downstaged (ie, brought into the Milan criteria or T2). We do not make a recommendation for one type of downstaging therapy over another.

In addition, bridging therapy is extensively discussed. There is a role for bridging therapy in patients with HCC who are listed for liver transplantation and are within the Milan criteria (T2). Bridging therapy is recommended in the new guidelines to reduce disease progression, which might cause patients to fall from the transplant waiting list; however, the evidence for the use of bridging therapy is not strong. Also in the guidelines, no particular type of bridging therapy is recommended over others.

G&H How is systemic treatment for HCC addressed?

JH A strength of these guidelines is that 2 members of the writing group are oncologists who are experts in the treatment of patients with advanced HCC (ie, with systemic therapy). The current available systemic therapy,

sorafenib (Nexavar, Bayer), as well as therapies that are in development, are all well covered in the guidelines.

G&H Were any important changes or recommendations made regarding liver resection or locoregional therapy?

JH Resection is recommended in the new guidelines. This position is slightly stronger than in previous guidelines, which presented resection and locoregional therapy as more equivalent therapies, as supported by the available data at that time.

G&H What do the guidelines recommend regarding management of early-stage HCC?

JH The stage of HCC is one component of the decision-making process, and the stage of the underlying liver disease is another component. Thus, whether a lesion is resectable depends not only on tumor characteristics but also on patient characteristics. Early-stage resectable lesions should generally be resected, although other strategies such as ablation can also be considered depending on a variety of patient-related factors, including preference and comorbidities. Transplant can be considered for early-stage unresectable lesions.

G&H Are there any other important changes from older guidelines that should be highlighted?

JH I think the most important changes are how we developed the guidelines and how diverse the writing group was. The guidelines use a new format, as previously mentioned, that may be difficult for readers to adapt to at first, but once they understand the reasoning behind this change, I think that they will feel more confident in the recommendations.

It should be noted that in addition to the guidelines, a guidance document will also be published to cover any of the areas in which there was not enough evidence to provide a recommendation. This is similar to what the AASLD did with hepatitis B virus—first, guidelines were released and then a guidance document. The hepatitis B virus guidelines were the first guidelines to use the GRADE format, and HCC is now the second.

G&H What is an example of an issue that might be covered in the guidance document?

JH I think the guidance document will spend more time discussing, for example, some of the different staging systems and how to assess response to treatment, which are issues that are not well covered in the guidelines. The etiology of HCC will also be discussed in further detail, as this issue was not covered much in the guidelines.

G&H Which important long-term questions for future research were pointed out in the guidelines?

JH Each section of the guidelines ends with a list of areas where future research is needed. Weaknesses were identified in each phase of the management of HCC. For example, we pointed out the need for better-designed studies comparing ultrasound to ultrasound plus AFP as well as the need for more research on other serum biomarkers such as des-gamma-carboxyprothrombin, Lens culinaris agglutinin-reactive AFP, and new serum tests. In addition, we noted important trials that are currently underway, such as phase 3 trials evaluating the survival benefits of using sorafenib vs radioembolization in patients who have advanced HCC with macrovascular invasion.

Dr Heimbach has no relevant conflicts of interest to disclose.

Suggested Reading

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