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Editorial

What should be done to reduce the discrepancy between guidelines and real-life practice for hepatocellular carcinoma in Korea?

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Keywords: Hepatocellular carcinoma; Practice guideline; Surveillance; Diagnosis; Treatment

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Hepatocellular carcinoma (HCC) is the sixth most common cancer with the third highest mortality rate worldwide.[1] It is the seventh most common cancer in South Korea, and its crude incidence rate has not decreased over the past decade, resulting in a high socio-economic burden.[2] Therefore, the Korea Liver Cancer Association (KLCA) and the National Cancer Center (NCC) of Korea collaborated to create the first HCC guidelines in 2003, which have been revised five times to date.[3-5] The latest edition of the KLCA-NCC Korea practice guidelines were recently announced in 2022.[6] The 2022 guidelines are evidence-based guidelines that analyze and systematically review the latest international research findings. In particular, the guidelines explore the systemic treatment of HCC, which has been developing immensely in recent years. Therefore, first-line treatments for HCC were newly established according to the trend of international guidelines. However, there are still several gaps between real-world practices and guideline recommendations. Accordingly, in this Clinical and Molecular Hepatology issue, Goh et al.[7] concisely reviewed the 2022 KLCA-NCC guidelines and added real-life situations and practices.

For the surveillance of HCC, the 2022 KLCA-NCC guidelines recommend ultrasound and the serum alpha-fetoprotein for high-risk groups (i.e., patients with chronic hepatitis B, chronic hepatitis C, and liver cirrhosis). Since 2003, the Korean government has provided HCC surveillance for high-risk groups through the National Liver Cancer Screening Program (NLCSP), and the effectiveness of this surveillance program has been proven through previous studies.[8,9] However, additional strategies are required since approximately 40% of all HCCs are still detected at an advanced stage.[10] Evidently, many studies have been conducted to increase the effectiveness of surveillance through other imaging modalities, such as dynamic contrast-enhanced computed tomography or magnetic resonance imaging (MRI), or biomarkers.[11] However, issues regarding radiation hazards and cost-effectiveness still persist. Therefore, guidelines have no choice but to use an ambiguous expression recommending alternative imaging modalities when ultrasounds are ineffective. In real-world

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clinical practice, alternative imaging is widely performed based on the clinician's judgment, and additional research is needed to identify specific individuals that require alternative imaging. In addition, the fact that only 52.7% of high-risk individuals participate in the NLCSP remains an obstacle to the early detection of HCC.[8] Therefore, it seems necessary to classify and educate HCC high-risk individuals in public policy.

Regarding HCC diagnosis, the 2018 KLCA-NCC guidelines have allowed the diagnosis of HCC to be undertaken through liver MRI using a hepatobiliary agent to detect the washout appearance in the hepatobiliary phase, which confirms the diagnosis. Compared with the 2018 Liver Imaging-Reporting and Data System guidelines, one of the widely recognized clinical guidelines for HCC internationally, the 2018 KLCA-NCC guidelines, showed better sensitivity than hepatobiliary agent-MRI without compromising specificity.[12] Therefore, the 2022 KLCA-NCC guidelines maintain the use of liver MRI for diagnosing HCC and are of great help in actual clinical practice.

The KLCA-NCC guidelines suggest the modified Union for International Cancer Control (mUICC) staging system as the primary staging system for HCC, and that treatment should be decided in accordance with mUICC staging. However, the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver use the Barcelona Clinic Liver Cancer (BCLC) staging system, which reflects liver dysfunction. Therefore, limitations in both research and interaction with the international community are unavoidable. Moreover, since BCLC staging is widely used in clinical settings, adding BCLC staging as a complementary system could be considered in future guidelines.

The 2022 KLCA-NCC guidelines for treating HCC provide the best and alternative options according to the mUICC staging system. Moreover, the systemic treatment part, which has been rapidly developing recently, has been updated according to the latest trends.[13] According to the results of the IMbrave150 study, the drug combination of atezolizumab plus bevacizumab was suggested as a recommended first-line treatment option.[14] In addition, according to the results of the HIMALAYA study, durvalumab plus tremelimumab combinatorial treatment was also suggested as a recommended first-line treatment option.[15] For patients who are not indicated for such immune-modulating drug combination therapies, e.g., patients with autoimmune diseases, patients taking immunosuppressive drugs, patients who have undergone stem cell or solid organ transplantations in the past, and patients with high-risk bleeding tendencies, etc., either sorafenib or lenvatinib is recommended. For patients who have already undergone first-line treatment, the 2022 KLCA-NCC guidelines suggest various second-line treatment options at the level of expert opinion. However, insurance in Korea cannot cover such treatment options, so there is confusion in selecting second-line treatment options following these guidelines. Furthermore, in current clinical practice, various treatment options are used, taking advantage of the experience and conditions of each medical center, despite the guideline recommendation of the best options. Conversely, some treatment options, such as living donor liver transplantation or transarterial radioembolization, can only be applied to select patients due to limited resources or high costs.

The 2022 KLCA-NCC guidelines concisely describe the up-to-date findings through a systematic review, but inconsistencies with reality may occur in several aspects. Goh et al.[7] described that the cause of this discrepancy may be confusion due to the absence of high-quality studies, and that some diagnostic tools and treatment methods are not strongly recommended due to high costs or limited resources. Furthermore, South Korea's national reimbursement system does not guarantee that all examination and treatment options for HCC given in the KLCA-NCC guidelines will be provided, which strongly impacts actual medical practice. Furthermore, it is thought that differences arising in the resources or experience of medical staff within each medical institution may cause discrepancies between clinical practice and guidelines.

Diverse efforts are needed to minimize discrepancies between the guidelines and real-world practices. First, it is necessary to accumulate high-quality evidence-based research to answer critical questions. For example, to recommend alternative imaging modalities or biomarkers as guidelines, reliable domestic research on their cost-effectiveness is re-

Abbreviations:

BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; LKCA, Korea Liver Cancer Association; MRI, magnetic resonance imaging; mUICC, modified Union for International Cancer Control; NCC, National Cancer Center; NLCSP, National Liver Cancer Screening Program

quired. Large-scale studies are also necessary to determine the specific groups of patients that require alternative imaging modalities. Additionally, various systemic treatments for HCC have been developed, and the recommended first-line treatments have been established in large randomized controlled trials. However, there is still a lack of comparative studies on second-line treatments, making it challenging to recommend specific drugs in guidelines. Therefore, additional research is necessary to compare different second-line treatment options and to determine the most effective treatment for patients with specific characteristics. Second, South Korea's insurance system should be changed to reflect the rapidly evolving medical environment and physicians' consensuses. Third, it is necessary to acquire the latest updated knowledge and to consider the best treatment that can be provided from available resources within the medical society. Finally, patients should do their best to understand and actively participate in the prevention, monitoring, diagnosis, and treatment of HCC.

Authors' contribution

Study conceptualization:YJK; Drafting of the manuscript: MKP; Critical revision of the manuscript: YJK.

Conflicts of Interest

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