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Editorial

Toward user-friendly and evidence-based practice guidelines for hepatocellular carcinoma

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Among the regional or national practice guidelines for hepatocellular carcinoma (HCC), the Korean Liver Cancer Association (KLCA)-National Cancer Center (NCC) guidelines had unique characteristics, particularly in assigning treatment modalities in each stage.[1] Unlike the American Association for the Study of Liver Diseases (AASLD) or European Association for the Study of Liver diseases (EASL), KLCA-NCC guidelines adopted a modified Union for International Cancer Control (mUICC) staging system since the initial version in 2003.[2] Adopting mUICC rather than the Barcelona Clinic Liver Cancer (BCLC) staging system has an advantage of encompassing heterogeneous tumor statuses and allocating the best or alternative treatment options to specific status, although it has a disadvantage of difficulty in international communication.

Adhering strictly to medical findings can hinder clinicians from applying guidelines to real practice because there are many differences between 'the ideal' and 'the real.'[3] On the contrary, consensus or expert opinion-dominated guidelines with a weak scientific background will be rejected by both physicians and government policy makers. The KLCA-NCC guidelines were assessed along with other 22 other regional or national guidelines regarding the overall quality and several domains of appraisal including scientific rigor and clarity of presentation.[4] In the overall evaluation, the KLCA-NCC guidelines ranked third and were recommended for use without any modification.

In this issue, Goh et al.[3] select key recommendations in surveillance, diagnosis, staging, and treatment and focus on the gaps between the revised KLCA-NCC guidelines and real practice. In surveillance, there is no difference of recommendation between 2022 and 2018 versions. Patients with cirrhosis (evidence level A, recommendation level 1), chronic hepatitis C (B1), and chronic hepatitis B (A1) are recommended to receive semiannual tests of serum alpha-fetoprotein (AFP) and ultrasonography (US). For non-cirrhotic patients with hepatitis C who achieved sustained virologic response following antiviral treatment, it is unclear whether those with low FibroScan score require continued HCC surveillance. Another difference between guidelines and real life is that contrast-enhanced computed tomography (CT) or magnetic res-

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onance imaging (MRI) shows higher performance in HCC detection than US.[5,6] Due to the limitations of contrast agent use, radiation, and high cost, there is little possibility that imaging methods using contrast agents will be alternative surveillance tools. On the other hand, accumulating data suggest that non-contrast MRI also has higher performance than US.[7,8] Reflecting this, updated guidelines in 2022 included unenhanced MRI as a potential surveillance method with low evidence and recommendation level.[1] Noninvasive diagnostic criteria for HCC changed from the 2014 to 2022 guidelines due to the introduction and increased use of liver-specific MRI contrast. In the 2014 version, even liver nodules smaller than 1 cm could be diagnosed as HCC based on contrast-enhanced CT or MRI using liver-specific contrast.[9] However, 2018 and 2022 guidelines removed the diagnostic criteria for HCC in a liver nodule smaller than 1 cm because diagnostic performance of imaging modalities was low in histologically confirmed subcentimeter-sized HCC.[10] This leaves uncertainty for contrast-enhanced CT or MRI showing compatibility with subcentimeter HCC. It is important to remember that guidelines cannot include all clinical situations, and it is ultimately up to the physician whether to observe or treat the lesion. If the lesion is new and located near a vessel and the AFP level is greater than 100 ng/mL, treatment rather than observation might be rational. In the 2022 guidelines, ancillary imaging features provide additional information that may change a diagnosis from definite to probable HCC. That is, HCC diagnosis cannot be concluded without radiologic hallmarks of arterial hyperenhancement with washout in the portal, delayed, or hepatobiliary phase. The guidelines suggest repeat imaging within 3–6 months or biopsy for probable HCC diagnosed based on ancillary features. It is unknown whether physicians in real practice will follow this recommendation.

As aforementioned, the main strength of KLCA-NCC guidelines is the basis of the mUICC staging system, enabling application to heterogeneous tumors from stage I to IVb. For each stage, the best and alternative options are presented to enhance practical applicability. In particular, the 2022 version added quality of evidence as a factor of the best option, allowing physicians to make decisions based more strongly on medical findings. While BCLC staging strictly assigns surgical resection to very early or early stage disease with preserved liver function and without portal hypertension, most surgeons from both Eastern and Western countries insist that indication of surgical resection should be expanded to multiple HCCs and HCC with limited vascular invasion (Vp 1-2).[11,12] Considering this, the 2022 guidelines maintain the recommendation of surgery for HCC with limited vascular invasion and added the recommendation of resection for multiple HCCs with low evidence and recommendation levels. In real practice, selection of surgical resection in this population is not common. However, with the recent success of adjuvant immune checkpoint inhibitor treatment, resection of HCC with high risk will be performed more frequently.[13] Regarding the role of transarterial radioembolization (TARE), although guidelines suggest that it can be applied widely from stages I to III, resection remains the first recommendation in the early stage (I), followed by conventional transarterial chemoembolization (TACE) in the intermediate stage (II) and to systemic treatment in the advanced stage (III). Owing to the failure of two randomized trials comparing TARE and sorafenib in unresectable, advanced HCC,[14,15] the initial strategy of loco-regional treatment using Yttrium-90 microspheres seems to be chosen at earlier stages. Although a recent study suggested that combination treatment with TARE and immune checkpoint inhibitor would increase the therapeutic efficacy in advanced HCC, more evidence is necessary for this kind of treatment to be included in the guidelines. As in other guidelines, the updated 2022 KLCA-NCC guidelines recommended atezolizumab+bevacizumab or durvalumab+tremelimumab for first-line systemic treatment based on phase III trials.[16,17] The optimal second-line systemic therapy remains to be determined. As all well-designed clinical trials on second-line treatment followed first-line sorafenib, data are lacking on second-line therapy following atezolizumab or atezolizumab+lenvatinib.[18] The guidelines committee held a 'delphi' meeting to achieve a consensus on the available second-line systemic therapies following tyrosine kinase inhibi-

Abbreviations:

HCC, hepatocellular carcinoma; KLCA, Korean Liver Cancer Association; NCC, National Cancer Center; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of Liver diseases; mUICC, modified Union for International Cancer Control; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; TARE, transarterial radioembolization; TACE, transarterial chemoembolization

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tor or an immune agent. As a result, evidence level 'D' involving expert opinion was referenced in the recommendation of second-line systemic therapy.

As the authors stated, there are differences between recommendations based on guidelines and real world practice. These differences are due to lack of evidence or a reimbursement system, limiting the use of certain drugs based on approval issues. For a guideline to be assessed qualified, it should be based on evidence, user-friendly and fully consider real daily practice. In this regard, the updated KLCA-NCC guidelines are based on both clear scientific evidence and expert opinion, producing a more use-friendly guide.

Conflicts of Interest

The author has no conflicts to disclose.

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