VOLUME 29 NUMBER 2 April 2023

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

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pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2023.0101
Clinical and Molecular Hepatology 2023;29:352-354

Editorial

Challenges in translating clinical guidelines into real-life practice for management of hepatocellular carcinoma in Taiwan

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Keywords: Hepatocellular carcinoma (HCC); Clinical practice guidelines; Taiwan; National health insurance

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Hepatocellular carcinoma (HCC) is a prevalent and deadly disease that poses a significant public health challenge worldwide. Taiwan has one of the highest incidence rates of HCC in the world, and managing this disease has become a top priority for the country's healthcare system. In recent years, clinical guidelines have been developed by the Taiwan Liver Cancer Association (TLCA) to provide evidence-based recommendations for surveillance, diagnosis, and treatment of HCC. However, implementation of these guidelines in real-life practice remains a challenge. In this editorial, we will discuss the paper by Su et al.[1], who provide valuable insights into the challenges of translating clinical guidelines into real-life practice and highlight the need for further research to optimize HCC management in Taiwan.

First, surveillance and diagnosis will be discussed. Although the TLCA guideline recommends checking PIVKA-II every three months, insurance only reimburses this procedure twice a year since 2020.[2] Regarding pathological diagnosis, although the probability of cancer cell dissemination caused by biopsy is very low, in early HCC cases that meet the diagnostic imaging criteria, surgery or radiofrequency ablation therapy is conducted directly. Some doctors may perform tissue biopsy followed by RFA. Tissue biopsy to confirm the diagnosis is recommended in the following situations: absence of risk factors of HCC, atypical imaging findings, suspicion of combined hepatocellular carcinoma-cholangiocarcinoma (HCC-CC), a low possibility of a primary liver tumor, low levels of AFP and PIVKA-II, and high CA 19-9/CEA levels. In suspected intermediate to advanced stage HCCs, a pathological diagnosis is required, and clinicians are increasingly performing biopsies on these patients. Differential diagnosis of HCC includes poorly differentiated tumor, sarcomatoid transformation, combined HCC-CC, or metastatic cancer. Due to the poor prognosis of these features, clinicians may adjust their treatment strategies. Therefore, more clinicians are performing tissue biopsies on newly diagnosed HCC patients as soon as possible. As Su et al.[1] mentioned in their 2019 article,

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Editor: Yuri Cho, National Cancer Center, Korea

Received : Mar. 11, 2023 / **Received :** Mar. 17, 2023 / **Accepted :** Mar. 17, 2023

up to 48.2% of HCC patients in Taiwan have received a histological diagnosis.

In terms of staging, although magnetic resonance imaging (MRI) or Gadolinium Ethoxybenzyl Diethylenetriamine Pentaacetic Acid enhanced magnetic resonance imaging (Gd-EOB-DTPA-MRI) has higher sensitivity, CT scans remain the mainstay for staging in most liver cancer patients. In certain cases, surgeons may repeat MRI before surgery, such as when there are multiple tumors, infiltrating tumors, uncertainty about vascular invasion, or atypical enhanced images and suspected tumor rupture. Chest CT scans might not be performed routinely for very early stage HCC, although it is recommended that most patients undergo such scans to accurately define their stage and receive the most appropriate treatment.

Due to the scarcity of donation sources, liver transplantation is usually reserved for patients with poor liver function. Although HCC patients in Taiwan with good liver function meet the criteria for liver transplantation, they usually undergo local treatments such as surgery and embolization. Patients are only referred for liver transplantation if they experience repeated relapses after local treatments, and these patients usually receive a living-donor liver transplant.

In intermediate stage HCC, transarterial chemoembolization (TACE) is the most common local treatment. Drug-eluting bead-TACE (DEB-TACE) is not reimbursed by the National Health Insurance, and its timing of use is usually recommended by the interventional radiologist in a multidisciplinary team meeting. In Taiwan, patients who experience recurrence after three TACE trials within one year are considered refractory to the treatment. These patients can be reimbursed for target therapy, and clinicians often use target therapy alone or in combination with TACE to treat TACE-refractory HCC. Radio-embolization is relatively expensive, and only a small number of patients receive this treatment. In recent years, more hospitals in Taiwan have been able to perform radio-embolization, although more hospitals are also offering proton therapy as an option. Due to the limitation of the maximum radiation dose, patients can only choose one of these two treatment modalities. Hepatic arterial infusion chemotherapy (HAIC) is chosen by only a few doctors due to an insufficient level of evidence and the need for assistance from interventional radiologists. Currently, there is no consensus on the optimal timing of systemic therapy for intermediate stage HCC. Some physicians initiate systemic therapy in TACE-refractory HCC. In recent years, thresholds of tumor burden score up to 7 or 11 have been proposed. Patients with a smaller tumor burden in intermediate stage HCC usually undergo treatment with TACE. For cases with high tumor burden, the choice of TACE, systemic therapy, or combination therapy depends on the physician.

For advanced stage HCC, atezolizumab plus bevacizumab (atezo+bev) is the first-line treatment of choice. However, since insurance does not currently cover this combination, only about one-tenth of patients can afford the treatment. For patients who cannot afford atezo+bev treatment, target therapy is covered by insurance.

Currently, Taiwan's National Health Insurance covers drugs such as sorafenib, lenvatinib, regorafenib, and ramucirumab (when AFP > 400 ng/mL). Approximately half of clinical physicians use sorafenib as the first-line treatment, as regorafenib or ramucirumab is covered by insurance only after sorafenib failure. Due to the high response rate and longer progression-free survival (PFS) of lenvatinib, it is used as first-line treatment by some clinicians, even though insurance does not cover other drugs after lenvatinib failure. Regarding PD-1 blockade, the National Health Insurance in Taiwan only provided reimbursement for second-line treatment with nivolumab to patients who failed sorafenib between 01/04/2019 and 31/03/2020. The efficacy of nivolumab was analyzed in 408 patients, and the ORR of 25% and the PFS of 2.9 months were similar to the results from clinical trials.[3] Unfortunately, the efficacy of nivolumab was lower than that in other cancer types treated with PD-1 blockade covered by national insurance. Consequently, reimbursement of nivolumab was terminated.

Although clinical trials combining PD-1 blockade with multiple kinase inhibitor (MKI) have not been successful, physicians in Taiwan sometimes use such combination therapy. Three retrospective studies have provided real-world evidence for this approach. Our team used propensity score-matching to compare the efficacy of anti-PD-1 combined with sorafenib versus anti-PD-1 alone. The results showed

Abbreviations:

HCC, hepatocellular carcinoma; TLCA, Taiwan Liver Cancer Association; TACE, transarterial chemoembolization; DEB-TACE, drug-eluting bead-TACE; HAIC, hepatic arterial infusion chemotherapy; PFS, progression-free survival; MKI, multiple kinase inhibitor; OS, overall survival

that anti-PD-1 plus sorafenib had higher disease-control rate and longer PFS and overall survival (OS) than anti-PD-1 alone.[4] In addition, we published another study showing that the combination of lenvatinib and nivolumab had better efficacy than lenvatinib alone.[5] Furthermore, Wu et al.[6] reported that the combination of lenvatinib and pembrolizumab had a high disease control rate and did not affect the ALBI (Albumin-Bilirubin) score. Unfortunately, the combination of lenvatinib and pembrolizumab was found to have limited benefit in the Leap-002 trial.[7] Overall, these off-label combination therapies require a high-level of evidence to confirm their benefits.

In summary, clinicians in Taiwan are highly active in treating HCC and are hoping for early approval of immunotherapy reimbursement from the National Health Insurance. The clinical experience gained in Taiwan can serve as a useful reference for scholars globally involved in treatment of HCC.

Conflicts of Interest

The authors have no conflicts to disclose.

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