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.2022.0421
Clinical and Molecular Hepatology 2023;29:230-241

Review

Clinical practice guidelines and real-life practice in hepatocellular carcinoma: A Taiwan perspective

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Hepatocellular carcinoma (HCC) is the fourth most common cancer and the second leading cause of cancer-related death in Taiwan. The Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan developed and updated the guidelines for HCC management in 2020. In clinical practice, we follow these guidelines and the reimbursement policy of the government. In Taiwan, abdominal ultrasonography, alpha-fetoprotein, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) tests are performed for HCC surveillance every 6 months or every 3 months for high-risk patients. Dynamic computed tomography, magnetic resonance imaging, and contrast-enhanced ultrasound have been recommended for HCC surveillance in extremely high-risk patients or those with poor ultrasonographic visualization results. HCC is usually diagnosed through dynamic imaging, and pathological diagnosis is recommended. Staging of HCC is based on a modified version of the Barcelona Clinic Liver Cancer (BCLC) system, and the HCC management guidelines in Taiwan actively promote curative treatments including surgery and locoregional therapy for BCLC stage B or C patients. Transarterial chemoembolization (TACE), drug-eluting bead TACE, transarterial radioembolization, and hepatic artery infusion chemotherapy may be administered for patients with BCLC stage B or C HCC. Sorafenib and lenvatinib are reimbursed as systemic therapies, and regorafenib and ramucirumab may be reimbursed in cases of sorafenib failure. First-line atezolizumab with bevacizumab is not yet reimbursed but may be administered in clinical practice. Systemic therapy and external beam radiation therapy may be used in specific patients. Early switching to systemic therapy in TACE-refractory patients is a recent paradigm shift in HCC management. **(Clin Mol Hepatol 2023;29:230-241)**

Keywords: Liver cancer; Surveillance; Barcelona clinic liver cancer; Surgery; Systemic therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common cancer in Taiwan. The Taiwan Cancer Registry reported 11,272 new HCC cases in 2019, with a crude incidence rate of 47.76 per 100,000 person-years. Moreover, 7,881 HCC mortalities occurred, and the crude mortality rate was 33.39 per 100,000 person-years; thus, HCC constitutes the second leading cause of cancer-related mortality in Taiwan.[1] HCC cases in Taiwan are mostly attributable to hepatitis B virus (HBV) in-

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Editor: Yuri Cho, National Cancer Center, Korea

Received : Nov. 26, 2022 / **Revised :** Jan. 12, 2023 / **Accepted :** Jan. 24, 2023

fection (47%), followed by that of hepatitis C virus (HCV) (33%). Active viral replication is the primary mechanism of hepatocarcinogenesis.[2]

Taiwan was the first country to launch nationwide HBV vaccination in 1984;[3] this decreased the HBV carriage rate and reduced the risk of developing HCC (as primary prevention).[4] Antiviral therapy reduces the risk of HCC caused by both HBV[5,6] and HCV (as secondary prevention).[7] Antiviral therapy reduces the incidence of recurrence of HBV- and HCV-related HCC after curative therapies (as tertiary prevention).[8,9] The National Health Insurance (NHI) program in Taiwan has reimbursed anti-HBV and anti-HCV therapy since 2003, which has effectively reduced HCC incidence and mortality attributable to viral hepatitis.[10] The National Hepatitis C Program Office launched a step-wise intervention to eradicate chronic hepatitis C. Since 2017, Taiwan has fully reimbursed prescriptions of direct antiviral agents (DAAs)—initially for patients with cirrhosis and later for patients with viremia regardless of fibrosis status. By June 30, 2022, more than 130,000 patients with chronic hepatitis C had been treated with DAA.

Overall, the incidence of HBV- and HCV-related HCC is decreasing, whereas the incidence of non-HBV- or non-HCV-related HCC is increasing. As in other parts of the world, nonalcoholic steatohepatitis caused by westernization of lifestyle practices or alcoholism is an emerging etiology of HCC. HCC caused by primary biliary cholangitis, autoimmune hepatitis, or aflatoxin is not common in Taiwan. The Taiwan Liver Cancer Association (TLCA) and the Gastroenterological Society of Taiwan (GEST) proposed a management consensus for HCC in 2016,[1] which was updated in 2020.[11]

HCC SURVEILLANCE

Clinical guidelines

TLCA guidelines specify that patients with chronic hepatitis B or C and cirrhosis are at high risk of HCC and should enroll in a surveillance program for HCC that provides opportunities for curative treatment and improves overall survival.[12] Surveillance should be performed using abdominal ultrasonography and alpha-fetoprotein tests (both are covered by the NHI program) at 6-month intervals (with a range of 3–12 months).[2] Dynamic computed tomography (CT), magnetic resonance imaging (MRI), or gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI (EOB-MRI) may be recommended every 6 to 12 months for extremely high-risk patients and for patients with difficulty in ultrasound imaging of the liver because of liver atrophy, severe obesity, or postoperative deformity.[11] Kupffer-phase contrast-enhanced ultrasound (CEUS) may also be recommended as a first-line screening tool for HCC in patients with renal dysfunction and liver cirrhosis (Table 1).[11,13,14]

Real-world practice

A major discrepancy exists between the execution of the guidelines and real-world practice due to poor patient adherence to surveillance recommendations. According to the NHI claim database, among 685,000 patients with a primary diagnosis of hepatitis or cirrhosis in 2008, only 13% received ultrasound and alanine aminotransferase examinations every 6 months. To facilitate regular surveillance of HCC, the National Health Insurance Administration of Taiwan introduced a medical care improvement plan in 2000 for patients with chronic hepatitis B or C. This patient-centered program is intended to motivate physicians to perform regular ultrasonography for HCC surveillance every 6 months as recommended by the current guidelines and to encourage HCC identification in the early stage through additional reimbursement to institutions. Examination of protein induced by vitamin K absence or antagonist-II (PIVKA-II) every 6 months has been reimbursed by NHI since 2020 for patients with cirrhosis and those receiving curative therapy for HCC. However, EOB-MRI and CEUS are not reimbursed by NHI.

Abbreviations:

HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NHI, National Health Insurance; DAA, direct antiviral agent; TLCA, Taiwan Liver Cancer Association; GEST, Gastroenterological Society of Taiwan; CT, computed tomography; MRI, magnetic resonance imaging; EOB-MRI, Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid enhanced MRI; CEUS, contrast-enhanced ultrasound; APASL, Asian Pacific Association for the Study of the Liver; AASLD, American Association for the Study of Liver Disease; LI-RADS, Liver Imaging Reporting and Data System; EASL, European Association for the Study of the Liver; HAIC, hepatic arterial infusion chemotherapy; ALPPLS, Associating Liver Partition and Portal vein Ligation for Staged hepatectomy; RFA, radiofrequency ablation; DEB, drug-eluting bead; EBRT, external beam radiation therapy

Table 1. Comparison of HCC surveillance programs between international and Taiwan guidelines and real-world practice

HCC surveillance	International/other guidelines[13,14,16,20,21]	Taiwan guideline[2,11]	Real-world practice
Ultrasound	Yes	Yes	Yes
Alpha-fetoprotein	No: EASL Optional: AASLD Yes: APASL, NCCN	Yes	Yes
PIVKA-II	Yes: JSH	No	Yes (cirrhosis/HCC curative therapy)
CT/MRI/CEUS	CT/MRI in extremely high risk patients (JSH)	Yes in extremely high risk patients (6–12 months)	Yes, but not reimbursed by National Health Insurance
Interval	6 months	6 months (3–12 months)	3–12 months

HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; NCCN, National Comprehensive Cancer Network; JSH, Japan Society of Hepatology; CT, computed tomography; MRI, magnetic resonance imaging; CEUS, contrast-enhanced ultrasound.

DIAGNOSIS

Radiological diagnosis

In Taiwan, HCC can be diagnosed noninvasively through dynamic contrast-enhanced CT or MRI if a ≥1.0 cm lesion is identified through ultrasound during surveillance.[11] Furthermore, guidelines in Asian countries, including those of the Japan Society of Hepatology and the Asian Pacific Association for the Study of the Liver (APASL), recommend EOB-MRI as the first-line diagnostic tool because it is more sensitive than dynamic CT for diagnosing HCC.[15,16] Additionally, EOB-MRI performed after dynamic CT in patients with early-stage HCC can detect additional small nodules, increase the accuracy of cancer staging, and improve outcomes after curative treatment.[17,18] However, the cost of EOB-MRI is not covered by the NHI program in Taiwan even though it is categorized as both a first- and second-line imaging diagnostic tool.[10]

The guidelines of the American Association for the Study of Liver Disease (AASLD) standardize the terminology for interpreting imaging features indicating the presence of HCC; the American College of Radiology released the Liver Imaging Reporting and Data System (LI-RADS) in 2011.[19] LI-RADS describes the following categorization: LI-RADS 1 (LR-1, definitely benign), LI-RADS 2 (LR-2, probably benign), LI-RADS 3 (LR-3, intermediate probability), LI-RADS 4 (LR-4, probably HCC), LI-RADS 5 (LR-5, definitely HCC), LI-RADS M (LR-M, malignant but not HCC specific), and LI-RADS TIV (LR-TIV, tumor in vein) based on the likelihood of HCC, non-HCC malignancy, and venous tumors. The Taiwan Society of Interventional Radiology has introduced the use of the LI-RADS in clinical practice for liver tumor diagnosis. However, no study has compared the diagnostic performance and clinical value of LI-RADS v2018.

Pathology diagnosis

Clinical guideline

The TLCA guidelines support the clinical diagnosis of HCC in high-risk patients with liver nodules of size >1 cm with a background of cirrhosis or chronic hepatitis B or C. This recommendation is in concordance with AASLD, European Association for the Study of the Liver (EASL), APASL, and other guidelines from major academic organizations.[11,16,20-23] Histological proof is required when the clinical diagnostic criteria of HCC are not satisfied or the diagnosis of HCC is not of high certainty. TLCA guidelines promote an active biopsy strategy and specify the requirement of histological proof for liver tumors. Although histological subtypes and gene signatures have not yet become key informations before HCC treatment, clinical trials and research are dependent on the availability of HCC tissues. Risks associated with biopsy, including bleeding and needle track tumor spreading tumor spreading,[24] although small, should be considered when contemplating tumor biopsy.

Real-world practice

With the recommendation of histological proof in the TLCA guidelines and the increasing number of immunotherapy combination trials in HCC, physicians in Taiwan have adopted

https://doi.org/10.3350/cmh.2022.0421

a more aggressive attitude toward active tumor biopsy, particularly in medical centers with clinical trial participation. In 2019, 48.2% of HCC diagnoses were supported by pathology or cytology, which contrasts with the rate <40% being supported by pathology or cytology before 2000 according to the Taiwan Cancer Registry report.

STAGING

Clinical practice guidelines

The Barcelona Clinic Liver Cancer (BCLC) staging system stratifies patients with HCC into very early, early, intermediate, and advanced stages, with 5-year survival rates of 40–70%, 14–45%, 6–14%, and 10%, respectively, and the terminal stage, for patients with tumors beyond the transplantation threshold.[25] Because of improvements in the HCC surveillance program, the proportion of patients with HCC diagnosed in the early stage has increased from 5–10% to 40–60%, leading to more patients eligible for curative treatments.[26]

Accurate identification of the tumor (T) stage is crucial for extending disease-free survival after curative treatment because tumor size, tumor number, and microvascular invasion are significant predictors of survival.[27,28] These tumor characteristics can be examined through preoperative imaging such as liver dynamic CT and MRI.[29] The strengths of MRI include low operator dependence, no radiation exposure, and ability to analyze the whole liver parenchyma. Furthermore, EOB-MRI has detected more HCCs than dynamic CT in 16.4% of patients receiving concurrent EOB-MRI.[17] Studies have suggested that higher numbers of HCCs necessitate a change in BCLC staging system, TNM staging, and treatment strategy.[18,30] However, liver MRI usually do not visualize lung clearly, which may be the most common area of metastasis in HCC. Therefore, additional liver MRI is suggested in patients with very-early to early-stage HCC, and whole-body CT is recommended for patients with intermediate to advanced HCC.

Real-world practice

TLCA guidelines recognize the BCLC staging system as the most common in Taiwan in terms of prognostic prediction.[2] The BCLC staging system used in Taiwan has two modifications from the original system. One is that, since 2002, a single tumor of size >5 cm has been classified as BCLC stage B;[31] the other is that a patient with Eastern Cooperative Oncology Group (ECOG) performance status 1 can still be classified as stage 0, stage A, or stage B according to the tumor burden (Table 2). These differences must be noted when comparing the prognosis of patients with HCC of various BCLC stages in Taiwan and with those in other countries. Other staging systems, including the HKLC staging system,[32] CLIP score,[33] Tokyo score,[34] Japan Integrated Staging score,[35] and TNM system, also provide meaningful prognosis predictions. Another key goal of staging systems is to inform treatment selection. Although the BCLC staging system is the most used in Tai-

Table 2. Comparison between the current BCLC staging and the modified BCLC staging used in Taiwan

Stage	BCLC staging system (2022)			Modified BCLC staging system used in Taiwan		
	Tumor burden	Liver function	Performance status	Tumor burden	Liver function	Performance status
0	Single ≤2 cm	Preserved liver function	0	Single ≤2 cm	Child-Pugh A	0–1
A	Single or ≤3 nodules each ≤3 cm	Preserved liver function	0	Single ≤5 cm or ≤3 nodules each ≤3 cm	Child-Pugh A-B	0–1
B	Multinodular	Preserved liver function	0	Single >5 cm or Multinodular	Child-Pugh A-B	0–1
C	Portal invasion, N1, M1	Preserved liver function	1–2	Portal invasion, N1, M1	Child-Pugh A-B	0–2
D	Any	End-stage liver function	3–4	Any	Child-Pugh C	3–4

BCLC, Barcelona Clinic Liver Cancer.

wan, the treatment guidance recommended by the BCLC staging system does not reflect true daily practice in Taiwan and other Asian countries. Such practice is characterized by availability of diverse locoregional therapy and endorsement of chemotherapy (systemic and hepatic arterial infusion chemotherapy [HAIC]).

TREATMENT

Surgery and liver transplantation

Surgical intervention plays a major role in HCC management. Taiwan's 2019 cancer statistics indicate that, among 8,521 patients newly diagnosed with HCC, 2,289 (26.9%) underwent resection and 44 (0.5%) underwent liver transplantation.[36] Safe liver resection for HCC is performed in accordance with Makuuchi's criteria including ascites, serum total bilirubin, and indocyanine green clearance tests; these tests are commonly employed to determine the limit of the liver to be resected.[37] Additionally, in patients without liver cirrhosis, no limitations (e.g., tumor size or number and involvement of portal vein invasion) preclude resection.[2]

Liver reserve is a relative term denoting the interplay between underlying liver disease (cirrhosis, fatty liver, and hepatitis/fibrosis) and the resected functional parenchyma excluding the tumor mass. If the remnant liver reserve is sufficient, the surgical method for HCC resection should be selected based on surgeon capability and experience. Resection can be performed through an open approach or a minimally invasive approach (laparoscopic or robotic assistance); robotic assistance is gaining popularity, with comparable survival duration.[38] Surgeons can conduct anatomical or parenchymal-sparing (non-anatomical) liver resection. TLCA guidelines recommend a surgical strategy of adequate surgical margin (>1 cm) when possible.[2] However, a narrow surgical margin, even a null-margin, may achieve cure after resection.[2]

Repeated resection or resection after other local or systemic therapy for HCC recurrence is common in Taiwan. Long-term survival can also be achieved.[39] Rapid progress of HCC therapeutics (systemic therapy and local treatments) and surgical innovation (Associating Liver Partition and Portal vein Ligation for Staged hepatectomy [ALPPLS]) may further contribute to the trend of treatment migration.[40]

A shortage of transplantable organs from deceased individuals in Taiwan necessitates the development of living-donor liver transplantation. The Milan criteria and UCSF criteria for liver transplantation for eligible patients with HCC are practiced.[2] Salvage transplantation using liver resection as the primary treatment for patients, followed by transplantation in the event of HCC recurrence or liver failure does not increase the risk of recurrence or similar long-term outcomes compared with primary liver transplantation.[2] The overall transplantable pool of patients after resection has not decreased.[41] Downstaging and bridging treatment should be offered to all patients to avoid waitlist dropout. The estimated wait time for transplantation is more than 6 months.[2] Less strict criteria and incorporation of biological markers are being used in patient selection worldwide, and their long-term effects in Taiwan require investigation.[42]

Radiofrequency ablation, transarterial chemoembolization, and radioembolization

Radiofrequency ablation (RFA) is a safe and effective curative therapy for patients with very early or early stage HCC who are unsuitable for surgery.[2,25,43] Furthermore, the percutaneous approach for RFA has the advantages of lower morbidity and a shorter length of hospital stay because of its minimal invasiveness.[44] Because of its safety, simplicity, and low cost, ultrasound is vital in guiding needle insertion and monitoring the ablation effect during RFA.[45,46] Moreover, in ultrasound-guided RFA, many strategies (e.g., artificial ascites or pleural effusion creation, real-time ultrasound-CT/MRI fusion imaging, and CEUS) can be used to decrease the incidence of complications and increase the rate of complete ablation.[47,48] However, because of the limitations in the ultrasound window and resolution, ultrasound-guided RFA in tumors with difficult locations and poor visibility is associated with a higher local recurrence rate.[49]

In contrast, CT-guided RFA presents no limitation to the depth and field of view. However, one study have reported comparable efficacy and complications between ultrasound- and CT-guided RFA for HCC.[50] Additionally, the combination of transarterial chemoembolization (TACE) and RFA may lead to longer hospital stays and increased patient discomfort.[51] Wu et al.[52] reported that CT-guided RFA after intra-arterial iodized oil injection may achieve more prolonged recurrence-free survival than ultrasound guidance, and that CT-guided

https://doi.org/10.3350/cmh.2022.0421

RFA is more suitable in this clinical context.

TACE has served as a first-line treatment for intermediate to advanced HCC for over a decade.[43] Other intra-arterial therapies, such as drug-eluting beads (DEBs), transarterial radioembolization, and HAIC, are available in Taiwan. These techniques provide interventional radiologists in Taiwan with more options for unresectable HCC treatment.[53] Although the NHI program does not reimburse DEB-TACE or transarterial radioembolization, a consensus exists in Taiwan on the DEB-TACE recommendation, and physicians have experience attending randomized controlled trials of transarterial radioembolization.[54,55] HAIC is also recommended for patients with portal vein thrombosis, but no consensus or large-scale randomized controlled trial exists. Practice guidelines recommend DEB-TACE, transarterial radioembolization, and HAIC for patients with multiple tumors or vascular invasion.[11]

SYSTEMIC THERAPY

Clinical guidelines

TLCA guidelines recommends sorafenib and lenvatinib therapy for treatment-naive patients with Child–Pugh A liver function, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and HCC that is unresectable and not amenable to locoregional therapy[1] or is refractory to TACE.[11] Atezolizumab and bevacizumab combination therapy can be used for treating patients with unresectable HCC who have not received prior systemic therapy and do not have a high risk of upper gastrointestinal bleeding.[11] Sorafenib or nivolumab immunotherapy may be considered for selected patients with Child Pugh class B liver function whose tumors are unresectable and not amenable to locoregional therapy, but the evidence remains insufficient.[11]

In cases of disease progression after sorafenib, additional treatment with regorafenib, cabozantinib, and ramucirumab (when Alpha-fetoprotein ≥400 ng/mL) extend the survival of patients with HCC and Child Pugh class A liver function, whose tumors are unresectable and not amenable to locoregional therapy.[11] Nivolumab with or without ipilimumab or pembrolizumab can be considered for patients who are intolerant to or have progressed when treated with approved tyrosine kinase inhibitors (Table 3).[11,14,56-58]

A paradigm shift in adopting systemic therapy in BCLC stage B HCC has occurred.[59] TLCA guidelines and clinical studies suggest that targeted therapy combined with TACE can be considered in highly selected patients with unresectable BCLC stage B HCC with Child Pugh class A and ECOG performance status 0-1.[11]

Real-world practice

Because of economic factors, real-world practice mainly depends on the reimbursement criteria of the NHI program. The NHI program has reimbursed sorafenib and lenvatinib as first-line therapy since 2012 and 2020, respectively. To receive sorafenib and lenvatinib treatment, HCC must exhibit extrahepatic spread, major vascular invasion (Vp 2-4), or be refractory to TACE, which is defined as failure to respond to more than 3 TACE sessions within 12 months. Lee et al.[60] investigated 22 and 44 BCLC stage C patients who received first-line lenvatinib and sorafenib, respectively. The objective response rate (ORR; 36.4% vs. 11.4%, P=0.023) and disease control rate (DCR) (81.9% vs. 56.9%, P=0.039) were higher in the lenvatinib group than in the sorafenib group, but patients had a similar overall survival of approximately 9 months.[60]

No first-line immunotherapy is currently reimbursed by the NHI program in Taiwan. In clinical practice, patients receive treatment regimens such as atezolizumab with bevacizumab or lenvatinib with pembrolizumab based on shared decision-making between physician and patient. Shao et al. evaluated 40 participants from Taiwan in the IMbrave 150 and the GO30140 trials. The ORR was 37.5%, including 3 (7.5%) complete responses, and the median duration of response was 21.4 months (95% confidence interval, 16.6-not reached),[61] which was consistent with the findings for the global intent-to-treat populations. Wu et al.[62] evaluated 71 patients who received lenvatinib plus pembrolizumab for unresectable HCC and reported an ORR of 34.1% in the first-line setting and of 18.5% for systemic therapy-experienced cases. Regorafenib and ramucirumab are reimbursed by the NHI program as second-line therapy in cases of failed first-line sorafenib administration. Nivolumab monotherapy had previously been reimbursed after failure of sorafenib; however, since April 2020, it is no longer reimbursed for new cases.

Table 3. Comparison between international and Taiwan guidelines and real-world practice for systemic therapy

Systemic treatments	International guideline	Taiwan guideline[11]	Real-world practice
First line			
Target therapy	Sorafenib,[14,56,57,74] lenvatinib[14,56,57,74]	Sorafenib, lenvatinib	Sorafenib,[*] lenvatinib[*]
Immunotherapy or immunotherapy combinations	Atezolizumab+bevacizumab[14,56,57,74] Durvalumab±Tremelimumab[58,74]	Atezolizumab+bevacizumab	Atezolizumab+bevacizumab, lenvatinib+pembrolizumab, bevacizumab+anti-PD-1 monoclonal antibody[†]
Cytotoxic chemotherapy	No	Selected patients (regimen not specified)	FOLFOX, Cisplatin+infusional 5-FU, doxorubicin
Second line			
Target therapy	Regorafenib,[14,56,57,74] cabozantinib,[14,56,57,74] ramucirumab[14,56,57,74]	Regorafenib, cabozantinib, ramucirumab	Regorafenib, Ramucirumab
Immunotherapy or immunotherapy combinations	Nivolumab+ipilimumab,[14,56] Nivolumab,[14,56] pembrolizumab[14,56]	Nivolumab±ipilimumab, pembrolizumab	Nivolumab±ipilimumab, pembrolizumab, multikinase inhibitor+anti-PD-1/PD-L1 monoclonal antibody,[‡] bevacizumab+anti-PD-1 monoclonal antibody[†]

[*]Systemic agents that are currently reimbursed by the National Health Insurance in Taiwan in year 2022.
[†]Low dose bevacizumab in combination with anti-PD-1 monoclonal antibody (e.g., nivolumab or pembrolizumab) as an alternative to atezolizumab plus bevacizumab for a lower-financial burden off-label usage.
[‡]Multikinase inhibitors (lenvatinib, regorafenib, or sorafenib) in combination with anti-PD-1 monoclonal antibody (e.g., nivolumab or pembrolizumab) as an alternative off-label agent.

https://doi.org/10.3350/cmh.2022.0421

CLINICAL TRIALS, HEPATIC ARTERY INFUSION CHEMOTHERAPY, SYSTEMIC CHEMOTHERAPY, AND EXTERNAL BEAM RADIATION THERAPY

Clinical trial participation is highly encouraged in Taiwan and is supported by the government (https://www.taiwanclinicaltrials.tw/). Many landmark trials are spearheaded by investigators in Taiwan, including those for sorafenib (A-P study),[63] lenvatinib (REFLECT study),[64] nivolumab (CheckMate 040 study),[65] and the atezolizumab–bevacizumab combination (IMbrave 150, GO30140).[66,67] Taiwan has an outstanding health-care system with 23 medical centers and up to 99.96% population coverage by the NHI program, which provides an excellent environment for clinical trial implementation. Medical centers in Taiwan actively recruit patients to clinical trials involving early-, intermediate-, and advanced-stage HCC with the belief that all suitable patients should be offered the opportunity to be considered for participation.

TLCA guidelines endorse the use of chemotherapy for HCC as both systemic and locoregional therapy. Systemic chemotherapy commonly demonstrates 5–10% response rates in patients with HCC with acceptable performance status and liver reserve.[68] However, HAIC is a form of locoregional therapy with a response rate up to 30% and is valuable for intrahepatic tumor control.[69,70] A phase III study demonstrated the survival benefit of combining sorafenib with FOLFOX compared with sorafenib alone in patients with portal vein tumor thrombosis (PVTT).[71] This response rate of sorafenib with FOLFOX was 40.8%, which may be of great value in patients with large intrahepatic tumor burden or PVTT. Although phase III studies of systemic chemotherapy (FOLFOX, PIAF, or doxorubicin) have not demonstrated a clear survival benefit for patients with advanced HCC[68,72] and only one clinical trial reported survival benefit of adding sorafenib to HAIC-FOLFOX, both systemic therapy and HAIC remain in the armamentarium of the physician treating HCC in Taiwan because of the high response rate for intrahepatic tumor control and reimbursement by the NHI program.

TLCA guidelines support the administration of external beam radiation therapy (EBRT), including photon and proton therapy, for various stages of HCC.[2,73] For BCLC stage A, EBRT can be considered when HCC is inaccessible to ablation or is unresectable, as a bridge therapy before liver transplantation, or when the patient refuses standard treatment. For BCLC stage B, EBRT can be considered in cases where HCC is inaccessible or unsuitable for TACE or is refractory to TACE, as a bridge to liver transplantation, or when localized tumor with symptoms or a threat to liver reserve is present. For BCLC stage C, EBRT can be considered in patients with portal vein tumor thrombus, in those with HCC unsuitable or refractory to TACE, or in those with a localized tumor with symptoms or a threat to liver reserve. For BCLC stage D, EBRT can be considered for symptomatic metastasis or for oligometastases as palliation. In real practice, EBRT in addition to standard therapy is not uncommon and is favored by a subset of patients and physicians in Taiwan.

DISCUSSION

Because of the high disease burden of HCC and the high-quality medical care reimbursed by the NHI program in Taiwan, TLCA guidelines devote considerable attention to preventing the development, pursuing the early diagnosis, and improving the overall survival of HCC. Compared with the BCLC guidelines,[74] TLCA guidelines advocate a more aggressive attitude toward curative treatment (e.g., surgical resection).[2] Whenever possible, surgical intervention is considered first for managing HCC. Liver transplantation is not yet widely applied to patients with HCC, even in the setting of living donor predominance.

The introduction of systemic therapy has greatly contributed to the management strategies available for intermediate- and advanced-stage HCC. Physicians in Taiwan typically attempt to downstage HCC for curative therapy. The BCLC-guided treatment is advanced or modified according to the therapeutic effectiveness of locoregional or systemic therapy in each scenario. For intermediate-stage HCC, systemic therapy may be neoadjuvant, early-switch therapy, adjuvant, or even initial therapy. However, the major limitation is lack of reimbursement by the NHI program in Taiwan. Currently, first-line immunotherapy is not reimbursed, which may reduce the overall treatment responses in advanced HCC.

HCC management is characterized by a constant struggle between treating the tumor and preserving residual liver function. Through a multidisciplinary team approach, application of antiviral therapy, and improvement of supportive care, liver reserve can be maintained after HCC management. In-depth, cross-professional communication between sur-

geons, hepatologists, oncologists, and interventional radiologists may provide the greatest benefits in caring for patients with HCC.

Randomized phase III trials may not provide optimal benefits for patients with HCC. Thus, in addition to randomized trials, high-quality real-world data and real-world evidence are required and will gradually play a greater role in drug approval. Considerable discrepancies exist between HCC guidelines and real-life practice. Academic organizations should recognize the inherent value of a multidisciplinary team approach in HCC treatment and endorse various modalities that may help patients with HCC.

Authors' contribution

Tung-Hung Su: study concept and design, acquisition of data, analysis and interpretation of data, drafting the manuscript. Chih-Horng Wu: acquisition of data, analysis and interpretation of data, drafting the manuscript. Tsung-Hao Liu: acquisition of data, analysis and interpretation of data, drafting the manuscript. Cheng-Maw Ho: acquisition of data, analysis and interpretation of data, drafting the manuscript. Chun-Jen Liu: study concept and design, acquisition of data, analysis and interpretation of data, critical review and revise the manuscript, study supervision.

Acknowledgements

This work was supported by grants from the Ministry of Science and Technology, Taiwan (grant numbers MOST 109-2326-B-002 -012 -MY3, MOST 110-2326-B-400-004, MOST 110-2628-B-002-041), Ministry of Health and Welfare (MOHW111-TDU-B-221-014003), National Taiwan University Hospital (grant numbers 110-N01, 110-T20), and the Liver Disease Prevention & Treatment Research Foundation, Taiwan.

Conflicts of Interest

T.-H. S. received research grant from Gilead Sciences, served as a consultant for Gilead Sciences, and was on speaker's bureaus for Abbvie, Bayer, Bristol-Myers Squibb, Gilead Sciences, Lilly, Merck Sharp and Dohme, Roche, and Takeda.

REFERENCES

1. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Cancer registry annual report, 2019, Taiwan. <https://www.hpa.gov.tw/File/Attach/14913/File_18302.pdf>. Accessed 25 Nov 2022.
2. Surveillance group; Diagnosis group; Staging group; Surgery group; Local ablation group; TACE/TARE/HAI group; Target therapy/systemic therapy group; Radiotherapy group; Prevention group; Drafting group. Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. J Formos Med Assoc 2018;117:381-403.
3. Chen DS. Fighting against viral hepatitis: lessons from Taiwan. Hepatology 2011;54:381-392.
4. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997;336:1855-1859.
5. Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al.; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-1531.
6. Su TH, Hu TH, Chen CY, Huang YH, Chuang WL, Lin CC, et al.; C-TEAM study group and the Taiwan Liver Diseases Consortium. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. Liver Int 2016;36:1755-1764.
7. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329-337.
8. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, et al. Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. JAMA 2012;308:1906-1914.
9. Hsu YC, Ho HJ, Wu MS, Lin JT, Wu CY. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. Hepatology 2013;58:150-157.
10. Liao SH, Chen CL, Hsu CY, Chien KL, Kao JH, Chen PJ, et al. Long-term effectiveness of population-wide multifaceted interventions for hepatocellular carcinoma in Taiwan. J Hepatol 2021;75:132-141.
11. Shao YY, Wang SY, Lin SM; Diagnosis Group; Systemic Therapy Group. Management consensus guideline for hepatocellular carcinoma: 2020 update on surveillance, diagnosis, and systemic treatment by the Taiwan Liver Cancer Association and

the Gastroenterological Society of Taiwan. J Formos Med Assoc 2021;120:1051-1060.
12. Sohn W, Kang D, Kang M, Guallar E, Cho J, Paik YH. Impact of nationwide hepatocellular carcinoma surveillance on the prognosis in patients with chronic liver disease. Clin Mol Hepatol 2022;28:851-863.
13. Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of hepatocellular carcinoma in Japan: JSH Consensus statements and recommendations 2021 update. Liver Cancer 2021;10:181-223.
14. Benson AB, D'Angelica MI, Abbott DE, Anaya DA, Anders R, Are C, et al. Hepatobiliary cancers, version 2.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2021;19:541-565.
15. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y, et al.; Liver Cancer Study Group of Japan. JSH consensus-based clinical practice guidelines for the management of hepatocellular carcinoma: 2014 update by the liver cancer study group of Japan. Liver Cancer 2014;3:458-468.
16. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370.
17. Kim HD, Lim YS, Han S, An J, Kim GA, Kim SY, et al. Evaluation of early-stage hepatocellular carcinoma by magnetic resonance imaging with gadoxetic acid detects additional lesions and increases overall survival. Gastroenterology 2015;148:1371-1382.
18. Wu CH, Lee YH, Liang PC, Hu RH, Shih TT, Ho MC. Predictors of changes in preoperative tumor stage between dynamic computed tomography and gadoxetate disodium-enhanced magnetic resonance imaging for hepatocellular carcinoma. J Formos Med Assoc 2022;121:1550-1559.
19. Tang A, Cruite I, Sirlin CB. Toward a standardized system for hepatocellular carcinoma diagnosis using computed tomography and MRI. Expert Rev Gastroenterol Hepatol 2013;7:269-279.
20. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.
21. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236. Erratum in: J Hepatol 2019;70:817.
22. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al.; ESMO Guidelines Committee. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv238-iv255. Erratum in: Ann Oncol 2019;30:871-873. Erratum in: Ann Oncol 2019;30:871-873. Erratum in: Ann Oncol 2022;33:666.
23. Chen LT, Martinelli E, Cheng AL, Pentheroudakis G, Qin S, Bhattacharyya GS, et al. Pan-Asian adapted ESMO Clinical Practice Guidelines for the management of patients with intermediate and advanced/relapsed hepatocellular carcinoma: a TOS-ESMO initiative endorsed by CSCO, ISMPO, JSMO, KSMO, MOS and SSO. Ann Oncol 2020;31:334-351.
24. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology 2009;49:1017-1044.
25. European Association for The Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943. Erratum in: J Hepatol 2012;56:1430.
26. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. J Hepatol 2008;48 Suppl 1:S20-37.
27. Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. J Am Coll Surg 2003;197:753-758.
28. Zhang H, Liu F, Wen N, Li B, Wei Y. Patterns, timing, and predictors of recurrence after laparoscopic liver resection for hepatocellular carcinoma: results from a high-volume HPB center. Surg Endosc 2022;36:1215-1223.
29. Ayuso C, Rimola J, Vilana R, Burrel M, Darnell A, García-Criado Á, et al. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. Eur J Radiol 2018;101:72-81. Erratum in: Eur J Radiol 2019;112:229.
30. Choi SH, Byun JH, Kwon HJ, Ha HI, Lee SJ, Kim SY, et al. The usefulness of gadoxetic acid-enhanced dynamic magnetic resonance imaging in hepatocellular carcinoma: toward improved staging. Ann Surg Oncol 2015;22:819-825.
31. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-524.
32. Yau T, Tang VY, Yao TJ, Fan ST, Lo CM, Poon RT. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology 2014;146:1691-1700.e3.
33. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998;28:751-755.

34. Tateishi R, Yoshida H, Shiina S, Imamura H, Hasegawa K, Teratani T, et al. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. Gut 2005;54:419-425.
35. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38:207-215.
36. Taiwan Cancer Registry Center. 2019 cancer statistics of Taiwan. Taiwan Cancer Registry Center web site <https://twcr.tw/wp-content/uploads/2022/02/CA16_LF108.pdf>. p 82. Chinese. Accessed 1 Jul 2022.
37. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298-304.
38. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619-629.
39. Ho CM, Lee PH, Shau WY, Ho MC, Wu YM, Hu RH. Survival in patients with recurrent hepatocellular carcinoma after primary hepatectomy: comparative effectiveness of treatment modalities. Surgery 2012;151:700-709.
40. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
41. Cheng HY, Ho CM, Hsiao CY, Ho MC, Wu YM, Lee PH, et al. Interval dynamics of transplantability for hepatocellular carcinoma after primary curative resection: risk factors for nontransplantable recurrence. HPB (Oxford) 2023;25:218-228.
42. Ho CM, Lee CH, Lee MC, Zhang JF, Chen CH, Wang JY, et al. Survival after treatable hepatocellular carcinoma recurrence in liver recipients: a nationwide cohort analysis. Front Oncol 2021;10:616094.
43. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-1022.
44. Crucitti A, Danza FM, Antinori A, Vincenzo A, Pirulli PG, Bock E, et al. Radiofrequency thermal ablation (RFA) of liver tumors: percutaneous and open surgical approaches. J Exp Clin Cancer Res 2003;22(4 Suppl):191-195.
45. Kim YS, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. J Hepatol 2013;58:89-97.
46. Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107:569-577; quiz 578.
47. Song I, Rhim H, Lim HK, Kim YS, Choi D. Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tracts with the use of artificial ascites: safety and technical efficacy in 143 patients. Eur Radiol 2009;19:2630-2640.
48. Song KD, Lee MW, Rhim H, Cha DI, Chong Y, Lim HK. Fusion imaging-guided radiofrequency ablation for hepatocellular carcinomas not visible on conventional ultrasound. AJR Am J Roentgenol 2013;201:1141-1147.
49. Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, et al. Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. Hepatology 2006;43:1101-1108.
50. Lee LH, Hwang JI, Cheng YC, Wu CY, Lee SW, Yang SS, et al. Comparable outcomes of ultrasound versus computed tomography in the guidance of radiofrequency ablation for hepatocellular carcinoma. PLoS One 2017;12:e0169655.
51. Kim W, Cho SK, Shin SW, Hyun D, Lee MW, Rhim H. Combination therapy of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) for small hepatocellular carcinoma: comparison with TACE or RFA monotherapy. Abdom Radiol (NY) 2019;44:2283-2292.
52. Wu CH, Liang PC, Su TH, Lin MC, Chang YH, Shih TT, et al. Iodized oil computed tomography versus ultrasound-guided radiofrequency ablation for early hepatocellular carcinoma. Hepatol Int 2021;15:1247-1257.
53. Liapi E, Geschwind JF. Intra-arterial therapies for hepatocellular carcinoma: where do we stand? Ann Surg Oncol 2010;17:1234-1246.
54. Chang PY, Huang CC, Hung CH, Yu CY, Wu DK, Hwang JI, et al. Multidisciplinary Taiwan consensus recommendations for the use of DEBDOX-TACE in hepatocellular carcinoma treatment. Liver Cancer 2018;7:312-322. Erratum in: Liver Cancer 2019;8:68.
55. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al.; Asia-Pacific Hepatocellular Carcinoma Trials Group. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific Patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-1921.
56. Gordan JD, Kennedy EB, Abou-Alfa GK, Beg MS, Brower ST, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline. J Clin Oncol 2020;38:4317-4345.
57. Vogel A, Martinelli E; ESMO Guidelines Committee. Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. Ann Oncol

2021;32:801-805.
58. NCCN Clinical Practice Guidelines in Oncology, Hepatobiliary Cancers, Version 4. 2022, Accessed 9 Dec 2022.
59. Su TH, Hsu SJ, Kao JH. Paradigm shift in the treatment options of hepatocellular carcinoma. Liver Int 2022;42:2067-2079.
60. Lee SW, Yang SS, Lien HC, Peng YC, Ko CW, Lee TY. Efficacy of lenvatinib and sorafenib in the real-world first-line treatment of advanced-stage hepatocellular carcinoma in a Taiwanese population. J Clin Med 2022;11:1444.
61. Shao YY, Feng YH, Yen CJ, Yang TS, Shen YC, Chao Y, et al. Bevacizumab and atezolizumab as first-line therapy for advanced hepatocellular carcinoma: A Taiwanese subgroup analysis on efficacy and safety. J Formos Med Assoc 2022;121:2430-2437.
62. Wu CJ, Lee PC, Hung YW, Lee CJ, Chi CT, Lee IC, et al. Lenvatinib plus pembrolizumab for systemic therapy-naïve and -experienced unresectable hepatocellular carcinoma. Cancer Immunol Immunother 2022;71:2631-2643.
63. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
64. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet 2018;391:1163-1173.
65. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-2502.
66. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al.; IMbrave150 Investigators. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905.
67. Lee MS, Ryoo BY, Hsu CH, Numata K, Stein S, Verret W, et al.; GO30140 investigators. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. Lancet Oncol 2020;21:808-820.
68. Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, et al. Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. J Clin Oncol 2013;31:3501-3508.
69. Lin CC, Hung CF, Chen WT, Lin SM. Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein thrombosis: impact of early response to 4 weeks of treatment. Liver Cancer 2015;4:228-240.
70. Shao YY, Liang PC, Wu YM, Huang CC, Huang KW, Cheng JC, et al. A pilot study of hepatic arterial infusion of chemotherapy for patients with advanced hepatocellular carcinoma who have failed anti-angiogenic therapy. Liver Int 2013;33:1413-1419.
71. He M, Li Q, Zou R, Shen J, Fang W, Tan G, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. JAMA Oncol 2019;5:953-960.
72. Yeo W, Mok TS, Zee B, Leung TW, Lai PB, Lau WY, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. J Natl Cancer Inst 2005;97:1532-1538.
73. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705.
74. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol 2022;76:681-693.