Clinical practice guideline and real-life practice in hepatocellular carcinoma: Chinese perspective

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Abstract

Liver cancer ranks the fourth most prevalent and the second most lethal cancer in China. Hepatitis B virus (HBV) infection represents the major risk factor for hepatocellular carcinoma (HCC) in China. Liver US plus AFP every 6 months continues to be the predominant surveillance modality. The aMAP score is newly recommended in the 2022 Chinese guidelines to predict HCC occurrence. China liver cancer (CNLC) staging system proposed in the 2017 guideline continues to be the standard model for staging with modifications in the treatment allocations. Considering the aggressive nature of HBV-associated HCC, multi-modal and high-intensity strategies treatments like the addition of immunotherapy-based systemic treatment to local therapies including resection, ablation, intra-arterial therapies have been adopted in real-life practices in China. The latest Chinese guidelines recommend atezolizumab plus bevacizumab, suntimilab plus bevacizumab analogue, lenvatinib, sorafenib, donafenib and FOLFOX chemotherapy as the first-line treatment without priority. Apart from regorafenib, apatinib, camrelizumab and tislelizumab are newly added as the second-line systemic therapies for patients who progressed on sorafenib. Systemic therapies adopted in real life practice are sophisticated with various combination modality and different sequences.

Key words: Clinical practice guidelines; hepatocellular carcinoma; diagnosis; treatment
Introduction

Liver cancer ranks the fourth most prevalent and the second most lethal cancer in China[1, 2]. Approximately 410,000 patients were newly diagnosed with liver cancer in China in 2020(https://gco.iarc.fr), accounting for 45.3% of global new cases[3]. Hepatocellular carcinoma (HCC) constitutes the majority of primary liver cancer, accounting for 75-85% of total cases. Hepatitis B virus (HBV) infection represents the major risk factor for HCC in China. According to a previous report, 69.9% of Chinese patients with HCC had a background of HBV infection, 5.2% had hepatitis C virus (HCV) infection, and 5.8% had both[4]. Other risk factors include aflatoxin exposure, alcohol abuse and metabolic disorders. Neonatal HBV vaccination program since 1992[5] and effective anti-viral agents have contributed to a significant decline in HCC incidence, especially for those below 40 years old[6]. HBV-associated HCC belongs to a molecular subtype named as proliferation subtype and is featured by poor differentiation and high aggressiveness [7]. According to the BRIDGE study, only 36% of Chinese cases were initially diagnosed at early stage and eligible for curative treatments, while the remnant 9% and 55% were at intermediate and advanced stage respectively[8]. Efforts to improve the diagnostic sensitivity and the therapeutic efficacy of HCC treatments have contributed to a decrease of 20.3% in age-standardized mortality in China from 1990 to 2017[1].

Evidence-based clinical guidelines on the management of HCC have been updated every two to three years by a multidisciplinary group of experts in China[9, 10]. Herein, we present a concise review of the latest version (2022 version) and discuss real-life
practices in China.

**Surveillance**

Patients with chronic HBV/HCV infection, cirrhosis of any causes, alcohol abuse, non-alcoholic steatohepatitis (NASH) or family history of HCC are listed as high-risk population for developing HCC, especially among men over 40 years. The aMAP (age-Male-ALBI-Platelets) score is newly added in the 2022 Chinese guidelines to help discriminate high-risk population for HCC occurrence (aMPA score>60 with an annual HCC incidence reaching 1.6-4%)[11]. For these high-risk population, ultrasonography (US) plus alpha-fetoprotein (AFP) should be carried out every 6 months.

Considering the social cost-effectiveness in a country with a large HBV-infected population, liver US plus AFP every 6 months continues to be the predominant surveillance modality in China. In Japan where over 70% of HCC patients are initially diagnosed at early stage[8], liver US plus AFP, des-gamma-carboxy prothrombin (DCP) and AFP-L3 testing are performed every 6 months for high risk group (HBV/HCV infection, cirrhosis of other etiologies) and every 3-4 months for extremely high risk group (HBV/HCV related cirrhosis)[12]. Apart from insufficient testing items and surveillance frequency, lack of government-supported programs to cover surveillance for more population also contributed to a relatively low diagnostic rate of early HCC in China. Effort to integrate resources from community to hospital to establish an efficient surveillance and call-back system is expected to resolve such a dilemma. Besides, new blood-based biomarkers including 7-miRNA panel[13] and GALAD score[14] have been developed to assist early detection of HCC, especially for AFP-negative patients.
**Diagnosis**

The diagnosis of HCC can be made pathologically or via typical imaging hallmarks. For patients with liver cirrhosis or chronic hepatitis B/C, nodules $\geq 2$ cm can be diagnosed as HCC based on the typical features of arterial phase hyper-enhancement (APHE) with washout appearance at portal venous or delayed or hepatobiliary phases on any of the three imaging modality including multiphasic dynamic computed tomography (CT), dynamic magnetic resonance imaging (MRI) or gadolinium-ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI (EOB-MRI), or based on the typical features of APHE with late ($\geq 60$ seconds) washout appearance in the Kupffer phase on contrast enhanced ultrasound (CEUS), whereas the diagnosis of nodules $\leq 2$cm can be established when the typical features are present on at least two imaging modalities. Otherwise, biopsy is recommended in case of inconclusive diagnosis.

Nodules $\geq 1$cm can be diagnosed as HCC with typical hallmark on a single imaging technique in Japan[12], Korea[15] and western countries[16, 17], whereas the diameter $\geq 2$cm is set as a prerequisite for the diagnosis via only one imaging modality in China. In fact, for nodules of 1-2cm, typical features on both dynamic CT and MRI used to be required for a definite diagnosis of HCC in western countries[18]. However, a decreased sensitivity with limited improvement in diagnostic specificity via coincidental dynamic CT plus MRI in later studies reaffirmed the application of a single modality to diagnose lesions $\geq 1$ cm by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver
(EASL)[19]. Considering unbalanced distribution of medical resources in China, diagnostic accuracy is given priority over sensitivity. Therefore, confirmation via two imaging techniques for nodules of 1-2cm continues to be adopted in China. EOB-MRI and CEUS have been included as diagnostic modalities to increase diagnostic sensitivity in China since 2017[20].

**Staging**

The China liver cancer staging (CNLC) system(Figure 1) incorporating tumor characteristics, liver function and performance status, similar to the Barcelona Clinic of Liver Cancer(BCLC) system[21], was established in 2017 and has been adopted ever since. Concerning tumor status, each stage of BCLC 0/A, B, and C is divided into two substages in the CNLC system, including stages Ia, Ib, IIa, IIb, IIIa and IIIb. CNLC stage IV is equivalent to BCLC stage D.

Similar to the BCLC system, the CNLC system is a treatment allocation method for decision-making purpose, whereas the Japan Integrated Staging(JIS) score[22] and its variants focus on the prognostic predictive function. The modified Union for International Cancer Control(mUICC) system[23] adopted in Korea is characterized by more detailed treatment allocation and is applied on the premise of Child-Pugh A function, no portal hypertension and PS scoring 0-1. The CNLC system has been in wide use in real-life practices, although the BCLC systems continues to be the main stratification factor for clinical trial designing.

**Treatments**

**Hepatectomy**
Hepatectomy is preferably indicated for patients with CNLC stage Ia, Ib and IIa HCC. For patients with CNLC IIb and IIIa HCC who are optimal candidates for transarterial chemoembolization (TACE) and systemic therapy respectively, surgical resection can be considered if tumor nodules are localized in the same segment or lobe[24], and tumor emboli are expected to be completely resected. Child-Pugh grade A, indocyanine green 15-minute retention rate (ICG-R15) < 30%, and future remnant liver volume accounting for more than 40% (for patients with liver fibrosis/cirrhosis) or more than 30% (for patients without liver fibrosis/cirrhosis) are prerequisites for hepatectomy. Minimally invasive laparoscopic or robot-assisted laparoscopic liver resection (LLR) are recommended in experienced centers.

In real-life practices, conversion therapy via multi-modal and high-intensity anti-tumor strategies is advocated to improve resectability and long-term survival for patients with potentially resectable HCC, defined as technically unresectable CNLC stage Ia, Ib, IIa HCC, or technically resectable IIb, IIIa HCC[25]. Systemic therapies like tyrosine kinase inhibitors (TKIs) plus programmed death-1 (PD-1) inhibitors[26, 27] and locoregional treatments like hepatic arterial infusion chemotherapy (HAIC) plus TACE[28] have been explored as conversion therapies to induce tumor shrinkage or downstaging. As effective methods to introduce liver regeneration for patients with unmet future liver reserve (FLR), associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) were deemed to be superior to portal vein embolization (PVE) in faster introduction of liver regeneration and fewer risk of tumor progression[29, 30]. For patients who failed to achieve sufficient hypertrophy after
conventional ALPPS stage-1 due to severe fibrosis/cirrhosis, transcatheter arterial embolization-salvaged ALPPS (TAE-salvaged ALPPS) was a new strategy to increase the resectability of HCC[31].

Lesions which are less than 10 cm and located in Couinaud segments II, III, IVb, V, and VI without affecting the anatomy of the first and second hepatic hilums used to be the best candidates for LLR[9]. With the development of minimally invasive techniques, especially the use of ICG fluorescence[32], indications for LLR are expanded without strict restrictions on tumor size and tumor location in experienced center in China. Although propensity score–matched(PSM) studies[33-35] have affirmed comparable oncologic outcomes between LLR and open resection, especially for early-stage HCC[33], multicenter, randomized, controlled studies are warranted to validate the equal long-term efficacy of LLR compared to open resection.

Transplantation

The University of California San Francisco (UCSF) criteria (solitary tumor ≤6.5 cm or ≤3 nodules ≤4.5 cm plus total tumor diameter ≤8 cm) continues to be advocated as the major criteria for liver transplantation(LT) in the latest Chinese guideline. For patients who are initially beyond the LT criteria, down-staging therapies via locoregional therapies are recommended to reduce tumor burden to be within the LT criteria. Early withdraw of or no corticosteroid[36] and replacement of calcineurin inhibitors with mTOR inhibitor[37] are recommended to prevent tumor recurrence after LT.

In real-life practices, a number of criteria have been adopted in different centers,
including Shanghai Fudan criteria[38], West China criteria[39] and Sanya consensus with minor differences in tumor number and tumor size. Although transplant patients are usually excluded from immune checkpoint inhibitor therapy for fear of possible graft rejection, experience in our center showed that grafts without PD-L1 expression seemed to represent a useful marker for not developing graft-related immune-related adverse events[40], the result of which needs confirmation by more studies.

Ablation

Consistent with previous versions of clinical guidelines, ablation as a curative approach is indicated for CNLC Ia and Ib HCC (single nodule ≤5cm, 2-3 nodules with each ≤3cm). Radiofrequency ablation(RFA) and microwave ablation(MWA) is equally recommended without priority. For unresectable single HCC with the diameter of 3-7cm, ablation in combination with TACE is recommended[41].

In real-life practices in China, ablation is not only applied to early HCC, its combination with TACE has also been implemented in patients with intermediate HCC. After PSM, MWA plus TACE yielded superior PFS and OS to TACE alone for BCLC stage B HCC[42, 43]. Notably, the morphological criteria and treatment modality varied among different studies. While Zhang et al. included patients with 2-5 tumor nodules with each ≤7cm as target population for MWA in combination with TACE[42], Li et al. enrolled patients with either single tumor ≤8cm or 2-5 tumors with each ≤5cm[43]. The above studies adopted a sequential treatment of MWA after TACE at an interval of at least one month, another study proposed a concurrent treatment of TACE and MWA[44]. On the other hand, although the role of PD-1 inhibitors in the adjuvant
setting is still under investigation, the promising results in early-stage clinical trial have encouraged the administration of PD-1 blockade in addition to RFA in real-life practices. A retrospective study demonstrated PD-1 inhibitor in addition to RFA for recurrent HCC resulted in a significantly improved 1-year RFS rate compared to RFA alone[45].

**Intra-arterial Therapies**

TACE has been mainly indicated for CNLC IIb, IIIa and some IIIb HCC since the 2017 Chinese guidelines. For patients with CNLC Ia, Ib and IIa HCC ineligible for curative treatments, TACE is recommended as an alternative. Conventional TACE (cTACE) was equally recommended with drug eluting bead-TACE (DEB-TACE) due to similar OS benefit[46]. Super-selective TACE with the assistance of Cone-Beam CT if necessary is recommended to guarantee the efficacy of TACE[47]. cTACE is also recommended in the adjuvant setting for patients with high recurrent risks including multiple lesions, evidence of tumor thrombus or tumor diameter >5cm[48].

In real-life practices, the combination of TACE with other locoregional treatment or systemic therapy is emphasized. Optimizing the management of intermediate-stage HCC has been a research hotspot[49]. Although sorafenib in combination with TACE yielded similar OS to TACE alone for intermediate HCC[50], the improved PFS provided by sorafenib and the prolonged OS rendered by lenvatinib supported the addition of TKIs to TACE. Triple therapy of TACE integrated with TKIs plus PD-1 inhibitor for intermediate HCC showed favorable efficacy in controlling tumor progression and provided an opportunity of resection[51]. On the other hand, as TACE is indicated for HCC patients with portal vein invasion or extrahepatic metastasis in
case collateral compensation exists or extrahepatic tumor burden is limited, addition of systemic therapy like sorafenib[52], lenvatinib[53-56] or lenvatinib plus PD-1 antibody[57] is a routine practice in some institutions and demonstrated with more favorable tumor control than systemic therapy alone. Y90 transarterial radioembolization (TRAE) has not been widely applied in China currently.

While HAIC using interferon, cisplatin or low-dose 5-FU plus cisplatin (FP) regimen alone or in combination with sorafenib was not recommended for advanced HCC due to negative results in Japan, HAIC using oxaliplatin, fluorouracil, and leucovorin (FOLFOX) regimen developed in China was not only adopted as an alternative treatment for TACE-refractory or TACE-unsuitable patients[58] but also as a first-line treatment for advanced HCC due to prolonged median overall survival(mOS) compared to sorafenib for advanced HCC[59-61]. For patients with large unresectable HCC (largest diameter ≥7cm) without macrovascular invasion or extrahepatic spread, FOLFOX-HAIC also significantly improved OS compared to TACE[62]. Moreover, the strong antitumor efficacy for intrahepatic lesions enabled FOLFOX-HAIC as a conversion therapy to transform unresectable HCC to resectable one[63]. And a recent study reported that 1-2 cycles of FOLFOX-HAIC in the adjuvant setting significantly improved recurrence free survival (RFS) for patients with microvascular invasion[64].

In a word, although FOLFOX-HAIC has not been clearly recommended in the current guidelines, it is accepted as an effective locoregional treatment modality across all stages of HCC in China. Nonetheless, there still lacks consensus regarding the treatment modality of FOLFOX-HAIC as different regimes of FOLFOX (oxaliplatin, 85 or 130
mg/m² for 2 hours; leucovorin, 400mg/m²; fluorouracil bolus 400 mg/m², and 5-fluorouracil, 2400 mg/ m² for 46 hours or 2400 mg/m² for 24 hours or 1200 mg/ m² for 22 hours) were administered in different studies. Moreover, the addition of systemic therapies including target agents and immunotherapy to HAIC turned out to improve overall response rate[28], although the long-term effect of which on liver function and OS needs to be clarified in future.

Radiotherapy

Stereotactic body radiotherapy (SBRT) is indicated for patients with CNLC Ia and some Ib HCC who are ineligible for curative treatments or who are reluctant to receive invasive treatment. For patients with CNLC Ila or I Ib HCC, external beam radiation therapy in combination with TACE can improve local tumor control. For patients with resectable CNLC IIIa HCC, external ablation can be performed to control tumor thrombus in the neoadjuvant or adjuvant setting to prolong OS[65].

In real-life practices, external beam radiotherapy is carried out in accordance with recommendations in the guidelines. As for internal radiation, Y90 transarterial radioembolization (TRAE) has not been widely applied in China currently. On the other hand, TACE in combination with ¹²⁵I seed and stent implantation have been implemented for patients with type II tumor thrombus, demonstrating superior survival benefit to TACE alone[66].

Systemic Therapy

Systemic therapy is mainly indicated for patients with advanced HCC, namely CNLC IIIa and IIIb patients. For patients who had CNLC I Ib HCC ineligible for
locoregional therapies or who are refractory to TACE, transition to systemic therapy is recommended and covered by Chinese national reimbursement. The current Chinese guidelines recommend atezolizumab plus bevacizumab (Atezo-Bev)[67], sunitilimab plus bevacizumab analogue (byvasda)[68], lenvatinib, sorafenib, donafenib[69] and FOLFOX chemotherapy as the first-line treatment without priority. Apart from regorafenib, targeted agent apatinib and PD-1 inhibitors camrelizumab[70] and tislelizumab[71] are newly added as the second-line systemic therapies for patients who progressed on sorafenib. Cabozantinib[72] and ramucirumab[73], approved as second-line treatments for selected patients in other countries, have not been marketed in China.

With the approval of new first-line and second-line agents since 2017, the treatment options for advanced HCC are more diversified than ever. Apart from PD-1/PD-L1 inhibitor plus VEGFR inhibitor including Atezo-Bev and sunitilimab-byvasda, PD-1/PD-L1 inhibitors plus TKIs have been in wide use in real-life practices in China. The RESCUE trial evaluating the efficacy of camrelizumab plus apatinib versus sorafenib as the first-line therapy met dual primary endpoint and showed significant improvements in OS(22.1 vs 15.2 months, p<0.001) and PFS(5.6 vs 3.7 months, p<0.001) in the combination arm[74]. Although lenvatinib plus pembrolizumab versus lenvatinib monotherapy failed to meet pre-specified statistical significance in OS(21.2 vs 19.0 months, p=0.023) in the phase III LEAP-002 study[75], the clinically meaningful survival benefit still provided a rationale for its use as the first-line treatment. Sorafenib [76] or lenvatinib [77-79] plus PD-1 inhibitor as first-line treatment and regorafenib plus PD-1 inhibitor [80, 81] as second-line treatment have
exerted promising survival benefit with manageable toxicity in Chinese patients. Nevertheless, the insignificant OS improvement of cabozantinib plus atezolizumab versus sorafenib (15.4 vs 15.5 months, p=0.44) in the COSMIC-312 study suggested that immunotherapy in addition to targeted agents did not guarantee the synergistic efficacy in the clinic[82, 83].

Although dual immunotherapies of durvalumab plus tremelimumab[84] in the first-line setting and nivolumab plus ipilimumab[85, 86] in the second-line setting approved in western countries have not been included in the Chinese guidelines currently, their applications as post-line therapies after TKI failure, PD-1/PD-L1 monotherapy failure or TKI plus PD-1/PD-L1 combination therapy failure are adopted in real world. Evidences for dual immunotherapy as post-line therapies are awaited. On the other hand, the current approved second-line agents indicated for patients who are progressed on sorafenib are equally applied for those progressed on lenvatinib in real world. According to a retrospective study, lenvatinib-regorafenib sequential therapy yielded prolonged total OS (29.7 vs 23.0 months, p=0.041) and post-regorafenib OS (15.9 vs 11.7 months, p=0.045) compared to sorafenib-regorafenib sequential therapy[87]. With the advent of more effective treatments, the optimal sequence or the combination modality suitable for individual patient needs to be clarified by high-evidence trials.

Discussion

To provide useful and accessible information for all clinicians, the Chinese
guidelines on the management of HCC incorporate literatures based on not only randomized clinical trials (RCT) but also observational studies of newly developed clinical practices with the levels of evidences classified by revised Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [88]. Novel findings on the surveillance, diagnosis and treatment of HCC are elaborated in the appendix of updated guidelines for a deep understanding of new trends.

Considering the aggressive nature of HBV-associated HCC, multimodal treatments like the addition of immunotherapy-based systemic treatment to local therapies have been adopted in real-life practices in China. The development of original drugs like apatinib, suntimab, camrelizumab and tislelizumab and biological similar drugs like byvasda in China enable patients to accept the aforementioned multimodal treatment with affordable economic burden. Nevertheless, with regard to social cost effectiveness, only treatments with high-grade evidence based on RCTs are covered by insurance, which somehow narrow the gap from the optimal guideline recommendations to real-life practices at the government level. Moreover, more than 20 phase III trials are undergoing to identify the role of ICI-based therapies across all stages of HCC [89]. With the release of their results in the next 5 years, consensus on the addition of immunotherapy-based systemic therapy to HCC at different stages can be anticipated.

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Conflict of interest statement

The authors declare no competing financial interests.

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Figure 1 The CNLC staging and treatment algorithms of HCC