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Commentary

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Interpretation of the updates of the Chinese guidelines for the diagnosis and treatment of primary liver cancer (CNLC-2024 Edition)

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Abstract

Additional randomized controlled studies and high-level evidence for the diagnosis and management of liver cancer patients have been published since the release of Diagnosis and Treatment of Primary Liver Cancer Guidelines (CNLC-2022 edition). The 2024 version algorithm was updated accordingly by the national expert committee for the standardization and homogenization of liver cancer diagnosis and treatment in China. In this review, with reference to the guidelines of the 2022 version, we interpreted the main update points of the 2024 version to facilitate the nationwide dissemination and implementation of the guidelines.

Keywords: Primary liver cancer, hepatocellular carcinoma, guidelines, update, interpretation

INTRODUCTION

According to data released by the National Cancer Center in 2022, primary liver cancer ranks fourth in incidence among all cancers in China and second in cancer-related deaths[1]. Since the publication of the Diagnosis and Treatment of Primary Liver Cancer Guidelines 2022 (China liver cancer (CNLC) staging, CNLC-2022)[2], there have been several randomized controlled trials and novel high-level evidence of evidence-based medicine, especially the research results based on the Chinese population. Therefore, the 2024 version of the Diagnosis and Treatment of Primary Liver Cancer (PLC) Guidelines, hereafter referred to as 2024 PLC Guidelines (CNLC-2024), was published recently. The guideline addressed both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE), the new guideline continued to adopt OCEBM levels of evidence and amended recommendation rating combined with the ASCO guideline grading scheme to assess the reliability and applicability of research results. The updated guidelines provide guidance and a basis for clinicians and further promote the standardization process of liver cancer treatment in China. In this review, we interpret and discuss the main updates of the CNLC-2024 Guidelines.

SCREENING AND DIAGNOSIS

The novel guidelines pay more attention to the early diagnosis and treatment of HCC, which is the key to improving the overall prognosis of HCC patients. The highlights of the update are as follows.

Etiology and screening

In the etiology of HCC, "metabolic dysfunction associated fatty liver disease (MAFLD)" replaces the prior "non-alcoholic steatohepatitis (NASH)". Additionally, the new guidelines indicated that dietary aflatoxin B1 exposure is one of the carcinogenic factors of HCC. A comprehensive scoring model, age-Male-Albi-Platelets (aMAP) score, was recommended to stratify patients with chronic liver disease into different HCC-risk subgroups[3]. On the basis of aMAP score, aMAP-2 and aMAP-2 plus prediction model, integrating aMAP score, alpha-fetoprotein (AFP), and four cell-free DNA (cfDNA) features, were further established[4], which helps to identify the chronic liver disease patients with ultra-high HCC incidence of up to 12.5%[5]. The new guidelines emphasized that the above prediction model should be utilized as a standardized and accurate screening approach. For HBV-related HCC, serum high-sensitivity HBV-DNA detection was recommended to identify the patients with hypoviremia. The combination of ultrasound with AFP was further approved for screening and surveillance for high-risk individuals with PLC (GRADE from level 2 to evidence level 1), which also significantly reduces the mortality risk.

More detailed ultrasound imaging diagnosis of HCC

The CNLC-2024 Guidelines provided a more detailed description of ultrasound imaging findings in HCC diagnosis, which involved three main approaches, including gray-scale ultrasonography, color Doppler flow imaging (CDFI), and contrast-enhanced ultrasound (CEUS). In routine gray-scale ultrasonography, the intrahepatic nodules were preliminarily assessed as benign or malignant. For the latter, HCC lesions and minor intrahepatic metastases are predominantly revealed as hypoechoic solid lesions with peripheral halos. Tumor thrombus was characterized by solid echo in the lumen and honeycomb-like small collateral vessel formations were observed when cancer thrombus blocked the main portal vein completely. The intra-tumoral doppler signals of HCC were increased in CDFI and high-velocity arterial doppler signals were detected in HCC and tumor thrombus. CEUS, especially its multimodal fusion technique with computerized tomography (CT) or magnetic resonance imaging (MRI), can not only be widely used in the diagnosis of HCC lesions of different sizes, but also in the preoperative planning, intraoperative guidance, immediate and long-term efficacy evaluation of ablation treatment. The commonly used microbubble contrast agents are SonoVue and Sonazoid[6]. In CEUS, the "fast-in fast-out" contrast-enhanced mode

features are always the typical characteristics of HCC > 3 cm in diameter, while the features of a few lesions < 3 cm are not typical, and the slow regression of contrast agent could indicate a more differentiated HCC. Moreover, CNLC-2024 Guidelines pointed out that the high sensitivity of CEUS on micro blood flow has advantages in monitoring the evolution of intrahepatic benign precancerous nodules and detecting early HCC, in which a Liver Imaging Reporting and Data System (LI-RADS) is recommended to use[7]. In addition, hypo-enhancement performance of HCC in the portal venous phase provides the obvious boundary with the surrounding liver parenchyma, which is especially suitable for the detection of micro-lesions in multinodular HCC and early recurrence lesions. In the era of systematic treatment, quantitative CEUS, like CT and MRI, can be used to evaluate the efficacy of systematic antitumor therapy[8]. Moreover, the new CNLC-2024 Guidelines gives recommendations for liver fat content measurement using ultrasound attenuation imaging to evaluate NASH-related HCC risk[9].

Digital subtraction angiography and Positron emission tomography/CT

Digital subtraction angiography (DSA) is an invasive examination, useful in the diagnosis and locoregional therapy of HCC. The CNLC-2024 Guidelines recommends a combination of DSA and cone beam CT (CBCT) to effectively demonstrate HCC lesions and the branches of tumor-feeding artery[10]. In DSA, the blood flow and embolism of tumor thrombus in the main portal vein or primary branches can be evaluated by indirect portal venography of the superior mesenteric artery or splenic artery. Additionally, ^{18}F-flurodeoxyglucose(^{18}F-FDG) positron emission tomography/CT (PET/CT) was an auxiliary imaging approach for the diagnosis of HCC and distant metastases. However, the sensitivity and specificity of ^{18}F-FDG PET/CT are limited. As a supplement, 68Ga-DOTA-FAPI-04 PET/CT was recommended, especially in the diagnosis of middle to well-differentiated HCC and intrahepatic cholangiocarcinoma (ICC)[11,12].

Updated HCC diagnostic algorithm

For HCC patients, early diagnosis is the key to long-term survival and life quality. The definition of subcentimeter hepatocellular carcinoma (scHCC), HCC ≤ 1.0cm in diameter, is a remarkable alternation of the HCC diagnostic algorithm in the CNLC-2024 Guidelines. The 2024 version emphasized the importance of MRI, especially Gd-EOB-DTPA MRI (EOB-MRI), in the diagnosis of small HCC lesions or tumor thrombus. The deterministic diagnosis of scHCC is established for high-risk patients when EOB-MRI and at least one MRI/CT/CEUS imaging of the lesion show concurrent typical manifestations of HCC. The established diagnostic criteria for scHCC can aid in the early detection of HCC and prompt intervention, all of which improve the early diagnosis rate, direct treatment, and enhance patient prognosis. Meanwhile, the combination of the two imaging examinations, to a certain extent, ensures the high specificity of the diagnosis and avoids over-treatment. In addition, the CNLC-2024 Guidelines added the GAAD and ASAP models for early diagnosis of liver cancer[13,14].

Liquid biopsy

Based on a combination of seven circulating cell-free microRNA (miRNA), plasma miRNA Panel developed by Chinese scholars was recommended in this version of the Guidelines[15]. It is recommended not only for the diagnosis of HCC in the diagnostic algorithm, but also for the postoperative monitoring and follow-up. Additionally, other approaches of liquid biopsy, including circulating free microRNA, circulating tumor cell (CTC), cell-free DNA (cfDNA), circulating tumor DNA, circulating cell-free mitochondrial DNA (cf-mtDNA), cell-free viral DNA, and Extracellular vehicles (EVs), also carried a great value in early diagnosis and evaluation of PLC.

Histopathologic diagnosis

The CNLC-2024 Guidelines specified the novel pathological diagnosis classification and definition of ICC, including cholangiolocellular carcinoma (CoCC) and ductal plate malformation ICC. For combined

Hepatocellular and Cholangiocarcinoma (cHCC-CCA), a standardized pathological report of the proportions of the two tumor components, histological grading and subtype classification of HCC and ICC components, including MVI grading and lymphatic vessel invasion, should be recorded. In addition, the diagnosis of cHCC-CCA could be prudent when certain tumor components are very few. Dual-phenotype HCC (DPHCC), characterized by relatively strong invasiveness, may be susceptible to Regorafenib[16,17]. In the section of immunohistochemical markers commonly used in ICC, S100 calcium-binding protein and mucin5AC (MUC5AC) for the large intrahepatic ductal type of ICC, and C reactive protein, N-cadherin, and CD56 for the small type, were supplemented. The CNLC-2024 Guidelines added the commonly used molecular pathological diagnostic markers section, such as DNAJBI-PRKACA gene fusion in fibrolamellar HCC, half of the tuberous sclerosis-associated gene mutations in cirrhotic HCC, and multiple systemic therapy markers for ICC. The definition of major pathologic response (MPR) after neoadjuvant or conversion therapy has been controversial and the CNLC-2024 Guidelines suggested a criterion of at least 50% or less residual tumor cells. Moreover, the initial MPR diagnosis should be made clear by expanding/multiple sampling. In the CNLC-2024 Guidelines, a new diagram was proposed for microvascular invasion (MVI) classifications, in which the previous M2 grading was stratified into M2a (> 5 MVI in proximal nonneoplastic adjacent liver tissues) and M2b (MVI occurring in distal nonneoplastic adjacent liver tissues). Notably, it was demonstrated that, from M0 to M2a/b, the risk of postoperative recurrence and metastasis gradually increased and the prognosis tends to be worse in HCC patients[18,19].

MANAGEMENTS

Surgical treatment

In the surgical treatment section, the CNLC-2024 Guidelines added new evidence for recommended surgical approaches. The postoperative prognoses of NASH-related HCC patients were better than those of HCC patients with alcoholic steatohepatitis[20]. The safety and effectiveness of robot-assisted HCC hepatectomy are comparable to those of open hepatectomy (OH)[21], and laparoscopic hepatectomy (LH), compared to OH, had a better surgical outcome and equivalent prognosis in the elderly HCC patients[22]. In HCC LH, anatomic hepatectomy had a lower recurrence rate compared to non-anatomical one.

Portal vein embolization (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) are the primary means to increase the functional future liver remnant (FLR) for HCC patients. When the increase of FLR is not satisfied, the CNLC-2024 Guidelines suggested that TAE, hepatic vein embolization, and artery ligation might be the salvage treatment for PVE to promote functional FLR increase and control tumor, while redemptive ALPPS can be employed to achieve a safe tumor resection[23-26]. Meanwhile, salvaged transarterial embolization (TAE) is also recommended for ALPPS when the expected FLR increase was not achieved two weeks after one-stage operation[27]. Furthermore, the contraindications of PVE and the limitations of ALPPS have been defined in the new guideline.

Intermediate- and advanced-stage HCC treatment strategy

The CNLC-2024 Guidelines followed the original China liver cancer (CNLC) staging algorithm, which is adapted to the national situation and practical accumulation. For intermediate- and advanced-stage HCC, i.e., CNLC IIb/IIIa/IIIb HCC, the outcome of surgery is limited and the locoregional therapy combined with systemic treatments is expected to raise surgical resection rate, and improve recurrence-free and overall survival. Remarkably, for the HCC patients of CNLC IIIa staging, transcatheter arterial chemoembolization (TACE) or TACE combined with systemic therapy was recommended primarily, though the advanced HCC patients who received hepatectomy may have significantly better overall survival (OS) and progression-free survival (PFS) than those received Sorafenib[28]. Actually, the information regarding the HCC patients of CNLC IIIa staging who underwent hepatectomy was mainly from Asian countries[29-31]. In addition, multiple studies demonstrated that hepatic arterial infusion chemotherapy (HAIC), especially in conjunction with

TACE, radiotherapy, molecularly targeted medicine and/or immunotherapy, demonstrated a high objective response rate (ORR) and increased possibility of operation for advanced HCC patients[32-34].

Neoadjuvant and adjuvant treatments

Preoperative neoadjuvant treatment aiming to decrease recurrence rate and improve prognosis may be a consideration for CNLC Ib/IIa or partial CNLC IIb/IIIa resectable patients. It is demonstrated that down-staging treatment for HCC before liver transplantation was feasible and the down-staging HCC carried a better prognosis after transplantation[35]. Nevertheless, the liver damage risk of down-staging treatment should be considered comprehensively.

Various risk factors for recurrence have been reported, such as tumor rupture, tumor diameter ≥ 5 cm, multinodular HCC, MVI, macrovascular invasion, lymphatic metastasis, positive residual tumor or narrow margin, relatively low differentiated HCC, and so on[36-38]. There is no standard adjuvant treatment protocol for HCC patients with risk factors. In the CNLC-2024 Guidelines, in addition to TACE, postoperative HAIC, using the mFOLFOX regimen including oxaliplatin, leucovorin calcium and fluorouracil, was discussed, which can decrease recurrence rate and improve the prognosis for HCC patients with MVI[39]. The results of the IMbrave050 study demonstrated that Atezolizumab and Bevacizumab adjuvant scheme can reduce 28% postoperative tumor recurrence and metastasis risk[40]. Adoptive cellular immunotherapy and immunomodulator, typified by activatory cytokine-induced killer cells and thymalfasin, can be used to prolong relapse-free survival (RFS)[41,42]. For HBV-related HCC, the postoperative use of nucleoside analogs or pegylated interferon was recommended[43,44]. For living donor liver transplantation recipients, Everolimus combined with reduced Tacrolimus has the advantage of a high glomerular filtration rate compared to the standard Tacrolimus regimen[45].

Ablation therapy

In the ablation treatment section, the new guideline indicated that based on a retrospective study, the patients with single HCC measuring 3-5 cm in diameter who received microwave ablation (MVA) can achieve comparable overall prognosis (OS), but exhibit less impressive disease-free survival (DFS) compared to surgical operation[46]. The IMbrave050 study recruited the patients who received radical ablation therapy, in which a single tumor > 2 cm and ≤ 5 cm in diameter or multiple tumors with the greatest one ≤ 5 cm in diameter were believed to carry high recurrence risk[40].

Locoregional therapy and radiotherapy

In the CNLC-2024 Guidelines, precision TACE was advocated. The clinical practitioner should ensure complete devascularization and perform an angiogram of the peripheral portal vein for HCC confined to a hepatic segment or measuring < 5 cm in diameter[47,48]. When managing massive HCC, performing TACE at intervals of 2-4 weeks is the way to control tumor burden and protect liver function, and complete devascularization is also the expected goal. Moreover, TACE combined with ablation could be a more feasible way than simple ablation for CNLC Ib/IIa HCC 3-7cm in diameter[49-51]. As a footstone in the treatments of unresectable HCC, TACE can serve as the bridging of down-staging or conversion treatment to surgical operation, including liver transplantation and hepatectomy. The strategy of locoregional therapy combined with systemic treatments should be advocated to increase the ORR of TACE[52-58]. The modified RECIST (mRECIST) criteria were proposed to evaluate the efficacy of TACE, in which a better response degree may be related to a favorable prognosis[59-61]. Additionally, the descriptions of HAIC and transarterial radioembolization (TARE) were added, and mFOLFOX-HAIC was utilized as a supplementary treatment for TACE.

In the radiotherapy section, the CNLC-2024 Guidelines suggested that matching the performance of radiotherapy in resectable HCC with portal vein tumor thrombus[62], preoperative neoadjuvant radiotherapy can be applied for some resectable central HCC[63]. Before and after radiotherapy, molecularly targeted medicine, such as Sorafenib, could contribute to prolonging survival for some HCC patients with CNLC III staging or MVI[64-67], but the simultaneous use of the two should be cautious[68,69]. Additionally, stereotactic body radiotherapy (SBRT) combined with immunotherapy may produce a synergistic effect[70-74]. The CNLC-2024 Guidelines suggested the use of mRICIST criteria for the evaluation of radiotherapy efficacy. Furthermore, most of the response evaluations tended to be stable disease (SD), as coagulation necrosis occurred in earlier times after radiotherapy, while tumors tended to shrink and enhancement appearances at the arterial phase decreased significantly[75,76]. Radiation-induced liver disease (RID) is one of the main complications of HCC radiotherapy and the new guideline added the specific imaging performance of RID.

Systemic treatment and traditional Chinese medicine

The recent advances in molecularly targeted therapy and immunotherapy have significantly changed the field of advanced HCC treatment and achieved a ground-breaking discovery[77]. As regards first-line treatment, the CNLC-2024 Guidelines newly included Camrelizumab plus rivoceranib, and Tislelizumab, which were approved for unresectable or metastatic HCC patients. Global multicenter Phase III studies, CARES-310 and RATIONALE-301, demonstrated that compared to Sorafenib monotherapy, Camrelizumab plus Rivoceranib had a 38% lower death risk and a 48% lower risk of disease progression[78], and Tislelizumab achieved a non-inferior OS and reduced 15% death risk[79]. According to the HIMALAYA study, the STRIDE regimen, Durvalumab and Tremelimumab, reduced the death risk of Asian HCC patients, except in Japan, by 29% and by 34% in HBV-related HCC patients[80]. However, the STRIDE regimen is not included in first-line advanced HCC treatment. The REACH-2 study demonstrated that in advanced liver cancer patients with AFP ≥ 400 ng/mL after previous Sorafenib treatment failure, Ramucirumab, as the novel second-line systemic treatment, significantly improved OS and progression-free survival (PFS), reducing the death risk by 29.0% and the disease progression risk by 54.8%[81]. The research on immune checkpoint inhibitors of bispecific antibodies for advanced HCC is also ongoing. In addition, gastroscopy should be done before Bevacizumab treatment due to the bleeding risk of esophagogastric varices.

In traditional Chinese medicine section, more detailed symptoms were identified based on the different CNLC stagings, and corresponding traditional Chinese medicine regimens were prescribed. In addition, more modern Chinese medicines are on the list of recommendation, including Huaier granule, Elemene injection, and Cinobufotalin, and so on, by the National Medical Products Administration of China [Table 1].

Major differences between CNLC guidelines, and American Association for the Study of Liver Diseases (AASLD) or National Comprehensive Cancer Network (NCCN) or European Association for the Study of the Liver (EASL) guidelines

Furthermore, we performed a concise comparison between the CNLC guideline and the AASLD[98], NCCN[99], or EASL[100] guidelines for PLC, with the purpose of offering a reference for the standardized diagnosis and treatment. Firstly, according to the NCCN guidelines, patients with liver cirrhosis from any cause and those who carry chronic hepatitis B are both considered high-risk subgroups of PLC. Moreover, in the AASLD and EASL guidelines, liver cirrhosis patients can be classified as: moderate-high risk hepatitis B patients without cirrhosis (PAGE-B score > 10), stage F3 liver fibrosis, liver cirrhosis, Child-Pugh A/B patients with cirrhosis, and Child-Pugh C patients with cirrhosis awaiting liver transplantation. Secondly, the etiologies of PLC in the CNLC guideline were more consistent with the characteristics of Chinese patients. For disease screening, the AASLD, NCCN, and CNLC guidelines all endorsed AFP plus ultrasound

Table 1. The recommendations of the CNLC guidelines (2024) for systemic treatments

	New option	Therapy scheme (evidence level, recommendation grade)	The associated study
First-line	No	Atezolizumab and Bevacizumab (level 1, A)	IMbrave150[82,83]
	No	Combination of Sintilimab and Biosimilar of Bevacizumab (BYVASDA®; level 1, A)	ORIENT-32[84]
	Yes	Camrelizumab plus rivoceranib (level 1, A)	CARES-310[78]
	No	Donafenib (level 1, A)	Donafenib *vs.* Sorafenib[85]
	No	Lenvatinib (level 1, A)	Lenvatinib *vs.* Sorafenib[86]
	Yes	Tislelizumab (level 1, A)	RATIONALE-301[79]
	No	Sorafenib (level 1, A)	Sorafenib[87,88]
	No	FOLFOX4 regimen (level 1, A)	EACH[89,90]
	No	Arsenic trioxide (level 3, C)	Arsenic trioxide
Second-line	No	Regorafenib (level 1, A)	RESORCE[91]
	No	Apatinib (level 1, A)	AHELP[92]
	No	Camrelizumab (level 3, B)	RESCUE[93,94]
	Yes	Ramucirumab (level 1, A)	REACH-2[81,95]
	Yes	Pembrolizumab (level 1, A)	Pembrolizumab[96]
	No	Tislelizumab (level 3, B)	RATIONALE-208[97]

as a routine method for PLC screening, while AFP was not recommended in the EASL guideline because AFP can only screen for the additional 6%-8% of cases not detected by ultrasound. Consistently, the guidelines considered that EOB-MRI is a more accurate imaging approach for PLC, especially for small lesions. Compared to Barcelona Clinic Liver Cancer (BCLC) staging, we believe that the CNLC staging on HCC has more precise stages with corresponding recommended modalities, which is more suitable for the characteristics of Chinese patients and may play a better therapeutic guiding role[101]. Furthermore, for hepatectomy, the CNLC guideline had a broader criterion for surgical indications, while hepatectomy was recommended only for a single tumor in the AASLD, NCCN, and EASL guidelines. In addition, unlike the recommendation of TACE, HAIC, immunotherapy, targeted and anti-HBV treatment in the CNLC guideline, postoperative adjuvant therapy was not recommended in the EASL and NCCN guidelines, while only Atezolizumab plus Bevacizumab was recommended for PLC patients with high-risk recurrence factors in AASLD guideline. As regards first-line systemic treatments, the combination of Atezolizumab and Bevacizumab was recommended as the first-line treatment by various guidelines. The difference is that durvalumab plus Tremelimumab, nivolumab plus ipilimumab, durvalumab or nivolumab alone, and Pembrolizumab were also recommended as the first-line options in the NCCN guideline, which was similar to AASLD guideline. The first-line systemic treatments based on the 2021 EASL position paper of systemic treatments only contained Atezolizumab plus Bevacizumab, Sorafenib and Lenvatinib[102]. In contrast, the drugs independently developed by China, including Donafenib, Apatinib, Camrelizumab, Sintilimab, and Tislelizumab, were also included in the recommended scope of 2024 CNLC guideline, which have achieved considerable results in domestic clinical studies. Moreover, systemic chemotherapy with the FOLFOX4 regimen was also recommended as a first-line treatment based on the International multicenter EACH study[89,90].

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Authors' contributions

Contributed to conceptualization and supervision: Peng T, Peng M
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All authors contributed to the article and approved the submitted version.

Availability of data and materials

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Conflicts of interest

Tao Peng is an Editorial Board member of the journal *Hepatoma Research*. The other authors declare that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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