

Editorial

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Precise staging of advanced HCC promotes higher quality of personalized treatment management: Chinese experts consensus on precision diagnosis and management of advanced hepatocellular carcinoma (2023)

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Primary liver cancer, often referred to as hepatocellular carcinoma (HCC), is the fourth most common malignant tumor and the second leading cause of cancer-related deaths in China^[1]. Each year, 39.0%-53.6% of newly diagnosed liver cancer are identified at an advanced stage, marked by short survival and a refractory clinical condition^[2]. However, current guidelines for diagnosing and treating liver cancer broadly classify the advanced stage, advocating a singular strategy without considering individual patient treatment options. Therefore, it is urgent to establish a comprehensive and practical expert consensus specifically for China to enhance early diagnosis and treatment of liver cancer. Using the Delphi method, an expert team has, for the first time, refined the classification criteria for Chinese liver cancer patients and developed corresponding optimal treatment regimen recommendations^[3]. This consensus is intended to provide a more detailed, scientific, and reasonable reference basis for the selection of individualized diagnosis and treatment plans.



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Liver cancer patients in China have distinct epidemiological features, including a large tumor burden, relatively advanced disease stage, hepatitis virus infection and/or cirrhosis background, and a high proportion of portal hypertension. Therefore, foreign guidelines and recommended treatment approaches may not be optimally applicable for diagnosing and treating liver cancer patients in China. The Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition), also known as the CNLC guidelines, revealed that patients at various liver cancer stages show significant variations in the median overall survival (mOS)^[4]. The mOS for patients with advanced stage (stage III-IV) is 14.9 months, with a 5-year survival rate of only 28.2%. However, the survival span of patients with stage III is 6-48 months, corresponding to the survival span of patients with stage C of Barcelona Clinical Liver Cancer Stage (BCLC), which was 4-30 months^[5-7], implying that the grading system and personalized management strategies are not precise enough for patients diagnosed with stage III liver cancer (BCLC Stage C).

This consensus referred to the CNLC guidelines (2022) and applied the Grading of Recommendations, Assessment, Development and Evaluation methodology to assess evidence. To address the pressing challenges frequently encountered in clinical practice, the Delphi method was used to gauge the strength of expert consensus to determine recommendations in cases where the existing clinical studies lack sufficient evidence. The Delphi method is a systematic approach used to investigate expert opinions on consensus-related issues through multiple rounds of anonymous written inquiries. Following iterative consultation, summarization, modification, and statistical analysis, the final results are compiled^[8].

The CNLC and BCLC guidelines broadly define the classification of advanced liver cancer and only elaborate from the perspective of single treatment on the distribution of cancer thrombus with extrahepatic metastasis, and the relevant optimal treatment plan is not clear. The location and extent of portal vein tumor thrombus (PVTT) in patients with liver cancer are significantly related to their prognosis. Factors in extrahepatic metastasis, such as the type of organ involved and the number of metastatic tumors, influence the survival prognosis and choice of treatment. Meanwhile, Child-Pugh class B also varies in liver function. Patients classified as Child-Pugh B7 tend to have well-compensated liver function, whereas those with B8/9 exhibit poorer liver function, leading to increased incidences of liver-related adverse reactions, adverse reactions to tumor treatment, and ultimately, a less favorable survival and prognosis (6.0-9.0 months)^[9,10].

The current CSCO guidelines and Chinese Expert Consensus on Multidisciplinary Treatment of Liver Cancer suggest the use of Child-Pugh class B7 as the threshold when determining treatment options. Additionally, phase III clinical trials for systemic liver cancer treatment, such as IMbrave150^[11], HIMALAYA^[12], and ORIENT-32^[13], typically include patients classified as Child-Pugh class A or those below B7 as part of their inclusion criteria. Therefore, the present consensus recommends that liver function B7 be used as the boundary for more detailed classification while focusing on portal hypertension HBV DNA/HCV RNA replication status.

For patients in stage IIIa, including IIIa1-4, the consensus puts forward consultative ideas on the recommendations for surgical resection, transarterial chemoembolization (TACE)/hepatic arterial infusion chemotherapy (HAIC), radiotherapy, systemic therapy, and combinations of systemic therapy and other local treatments. Strategies such as immunotherapy combined with targeted therapy, single-agent therapy, or combination therapy of immunotherapy are applied in preoperative, perioperative, and postoperative adjuvant therapies for HCC resection, which are expected to further improve the curative effect of surgery. For stage IIIb liver cancer, the consensus proposed to adopt the definition of oligometastasis used for other tumors. The systemic therapy should be carried out throughout the treatment, combined with appropriate local therapies such as radiotherapy, TACE, HAIC, and ablation.

Hepatitis virus infection is a significant risk factor for the development of liver cancer^[14,15]. At present, 84% of liver cancer in China is caused by HBV infection^[16]. It is important to retard tumor progression and prolong the survival of patients through effective inhibition of hepatic viruses. This consensus, for the first time, proposes the necessity of closely monitoring HBV DNA and HCV RNA during anti-tumor therapy, which is crucial for assessing virus reactivation and adverse effects on tumor prognosis and thus providing recommendations for precise drug selection. Antiviral therapy is recommended for HBV-associated liver cancer patients with HBsAg positives, regardless of HBV DNA load. Entecavir, tenofovir disoproxil, or tenofovir alafenamide, and other drugs with potency and low resistance should be selected according to the patient's situation during anti-tumor therapy. This consensus also proposed to focus on the impact of different anti-tumor drugs/combinations on portal hypertension and its related complications and put forward recommendations for precise drug selection.

Accurate classification of HCC advanced stage is the basis for personalized treatment. Under the basic framework of CNLC guidelines, the present consensus integrated the latest clinical research data and reports on liver cancer and the main staging factors of advanced liver cancer stages IIIa and IIIb. It further refines the staging approach by delineating liver function B7 as the boundary. Simultaneously, through a comprehensive review of multidisciplinary studies conducted both domestically and internationally, the consensus formulated priority recommendations. These recommendations are tailored to patients with unique characteristics, taking into account the prevailing circumstances observed in domestic patient cases.

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Authors' contributions

Conception and design: Lu Y

Manuscript writing: Ainiwaer A, Chen Y

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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