Liver Research 8 (2024) 61–71

Contents lists available at ScienceDirect

Liver Research

journal homepage: http://www.keaipublishing.com/en/journals/liver-research

Practice Guideline

Chinese expert consensus on refined diagnosis, treatment, and management of advanced primary liver cancer (2023 edition)☆,☆☆

Xiufeng Liu [a], Feng Xia [b], Yue Chen [c], Huichuan Sun [d], Zhengqiang Yang [e], Bo Chen [f], Ming Zhao [g], Xinyu Bi [h], Tao Peng [i], Aizier Ainiwaer [c], Zhiwen Luo [h], Fusheng Wang [j,*], Yinying Lu [k,**]; National Clinical Research Center for Infectious Diseases; Society of Hepatology, Beijing Medical Association; Translational Medicine Branch, China Association of Gerontology and Geriatrics

[a] Department of Medical Oncology, Bayi Hospital Affiliated to Nanjing Chinese Medical University, Nanjing, Jiangsu, China
[b] Department of Hepatobiliary Surgery, Southwest Hospital, Army Medical University, Chongqing, China
[c] Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China
[d] Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China
[e] Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[f] Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[g] Department of Minimally Invasive Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China
[h] Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
[i] Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
[j] Senior Department of Infectious Diseases, The Fifth Medical Center of PLA General Hospital, Beijing, China
[k] Comprehensive Liver Cancer Center, The Fifth Medical Center of PLA General Hospital, Beijing, China

ARTICLE INFO

Article history:
Received 12 April 2024
Received in revised form
10 May 2024
Accepted 13 May 2024

Keywords:
Hepatocellular carcinoma (HCC)
Targeted therapy
Immunotherapy
Refined diagnosis and treatment
Expert consensus

ABSTRACT

Hepatocellular carcinoma (HCC), commonly known as primary liver cancer, is a major cause of malignant tumors and cancer-related deaths in China, accounting for approximately 85% of all cancer cases in the country. Several guidelines have been used to diagnose and treat liver cancer. However, these guidelines provide a broad definition for classifying advanced liver cancer, with an emphasis on a singular approach, without considering treatment options for individual patients. Therefore, it is necessary to establish a comprehensive and practical expert consensus, specifically for China, to enhance the diagnosis and treatment of HCC using the Delphi method. The classification criteria were refined for Chinese patients with HCC, and the corresponding optimal treatment regimen recommendations were developed. These recommendations took into account various factors, including tumor characteristics, vascular tumor thrombus grade, distant metastasis, liver function status, portal hypertension, and the hepatitis B virus replication status of patients with primary HCC, along with treatment prognosis. The findings and recommendations provide detailed, scientific, and reasonable individualized diagnosis and treatment strategies for clinicians.

☆ This article is based on a study first published in *Zhonghua Gan Zang Bing Za Zhi* (National Clinical Research Center for Infectious Diseases; Society of Hepatology, Beijing Medical Association; Translational Medicine Branch, China Association of Gerontology and Geriatrics. Expert consensus on precise diagnosis and management of primary hepatocellular carcinoma in advanced stage (2023 version) (in Chinese). *Zhonghua Gan Zang Bing Za Zhi*. 2023; 31: 910–920. doi: 10.3760/cma.j.cn501113-20230717-00006.). Translated and reprinted by permission of Chinese Medical Association.

☆☆ Full list of author information is available at the end of the article.
* Corresponding author.
** Corresponding author.
E-mail addresses: fswang302@163.com (Fusheng Wang), luyinying1973@163.com (Yinying Lu).

https://doi.org/10.1016/j.livres.2024.05.001

1. Introduction

Primary liver cancer, often referred to as hepatocellular carcinoma (HCC), is a prevalent contributor to malignant tumors and cancer-related fatalities in China, accounting for approximately 85% of all cancer cases in the country.[1] Approximately 39.0%–53.6% of patients with newly diagnosed liver cancer are found to be at the advanced stage annually, characterized by a refractory condition and a short survival.[2] Furthermore, most patients with liver cancer in China commonly experience coexisting hepatitis virus infection and/or cirrhosis, often resulting in portal hypertension. Moreover, the distinct epidemiological features, such as a large tumor burden and relatively advanced disease stage, imply that foreign guidelines and recommended treatment approaches may not be optimally applicable for diagnosing and treating patients with liver cancer in China. The latest update report on the 2022 survival analysis from the China liver cancer survey revealed varied median overall survival (mOS) among patients at various stages of liver cancer. These variations were outlined in the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition), also known as the China Liver Cancer (CNLC) guidelines, issued by the National Health Commission of the Peoples Republic of China.[3] The mOS for patients at an advanced stage (stage III–IV) is 14.9 months, with a 5-year survival rate of only 28.2%. Nonetheless, the survival duration of patients with stage III disease is 6–48 months, whereas that of patients with Barcelona Clinic Liver Cancer staging (BCLC) stage C is 4–30 months.[4–6] Therefore, patients with stage III liver cancer (BCLC stage C) require a more precise grading system and a personalized management strategy to receive individualized diagnostic and treatment recommendations.

The current versions of guidelines from the European Association for the Study of the Liver, National Comprehensive Cancer Network, Chinese Society of Clinical Oncology (CSCO), and CNLC for the diagnosis and treatment of liver cancer have collectively played a significant role in advancing the diagnosis and treatment of primary liver cancer in China. However, these specifications, guidelines, and consensus statements provide broad definitions for the classification of advanced liver cancer, often emphasizing a single treatment approach without elucidating the preferred hierarchy of diverse treatment options for individual patients.

Because the CNLC guidelines are better suited for staging and treatment recommendations for liver cancer in China than other guidelines, this consensus further refined the classification and management of stage III liver cancer based on these guidelines. Under the fundamental framework of the CNLC guidelines and along with the most recent clinical study data and liver cancer reports, the advanced liver cancer population was further subdivided. Evidence of inappropriate levels was deliberated and voted upon by an expert panel to determine the recommended opinions. Therefore, this study aimed to establish a more comprehensive and practical expert consensus that aligns with the specific national circumstances in China, focusing on the enhanced diagnosis and treatment of advanced primary liver cancer. An optimal recommended treatment strategy was developed by incorporating the recently published guidelines for hepatocarcinoma-related procedures such as transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), radiotherapy, conversion to resectability, targeted therapy, and immunotherapy. This consensus is anticipated to enhance the diagnosis and treatment of liver cancer, ensuring medical quality and safety, and optimizing the use of medical resources in China.

2. Study method

This consensus aligns with the CNLC guidelines (2022 edition) and uses the Grading of Recommendations, Assessment, Development, and Evaluation methodology to assess evidence,[3] which is categorized into five grades (grades 1–5) and three recommendation strengths such as strong (grade A), moderate (grade B), and weak recommendations (grade C). 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 for patients who lack sufficient evidence from existing clinical studies. The Delphi method is a systematic approach used to evaluate 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.[7]

The Delphi method for this consensus was conducted as follows: (i) compilation of issues with insufficient clinical evidence in the initial draft consensus; (ii) establishment of an expert panel; (iii) in the first round of discussion, identification of controversial issues using various media, such as email; and (iv) in the second round, a review of summarized issues and initiation of consensus formation. The first two rounds of discussion formed the basis for subsequent deliberation through qualitative analysis and clarification of issues using open-ended questions or the Likert scale. Others include the following: (v) in the third round of discussion, the expert panel should review the judgment made to that point, forming a consensus; (vi) in the fourth round of discussion (initiated based on the results of the first three rounds), the expert panel should make a final judgment on any previous objections and provide explanations; and (vii) the conclusion was drawn, and the consensus results were analyzed and summarized using standard statistical analysis tools. The determination of validity was contingent on the response rate, with the requirement that agreement should be $\geq$ 75% to establish a consensus conclusion.[8] In addition, this consensus included a supplemental study to explore the preferences of experts for clinical practice through multiple-choice questions.

3. Existing clinical classification criteria for advanced liver cancer and issues

Liver cancer staging includes six factors: the number of liver tumors, their size, vascular invasion, extrahepatic metastasis, Child-Pugh classification, and performance status (PS). According to the CNLC guidelines,[3] advanced liver cancer is categorized into two stages: (i) stage IIIa: PS 0–2, Child-Pugh class A/B, regardless of tumor local conditions, with visible vascular tumor thrombus on imaging but without extrahepatic metastasis; and (ii) stage IIIb: PS 0–2, Child-Pugh class A/B, regardless of tumor local conditions, with visible vascular tumor thrombus on imaging and extrahepatic metastasis and corresponding BCLC stage C: portal vein invasion and/or extrahepatic spread, good liver function, and PS 1–2. The BCLC stage C definition is more comprehensive than the classification in the CNLC guidelines because it encompasses local tumor metastasis. The above-mentioned guidelines offer comprehensive definitions for advanced liver cancer but primarily concentrate on specific treatments for tumor thrombus and extrahepatic metastasis without specifying preferred treatment options. The location and extent of portal vein tumor thrombus (PVTT) in patients with liver cancer significantly influence prognosis. Similarly, treatment decisions and OS are influenced by distinct factors, such as the organs involved in extrahepatic metastasis and metastatic tumor

numbers. Simultaneously, Child-Pugh class B also varies in liver function. Patients classified as Child-Pugh class B7 tend to have a 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 and Chinese expert consensus on multidisciplinary treatment of liver cancer guidelines suggest the use of Child-Pugh class B7 as the threshold when determining treatment options.[11] In addition, phase III clinical trials for systemic liver cancer treatment, such as IMbrave150,[12] HIMALAYA,[13] LEAP-002,[14] ORIENT-32,[15] ZGDH3,[16] and AHELP,[17] typically include patients with Child-Pugh class A or those below B7 as part of their inclusion criteria. Hence, this consensus suggests a more detailed classification, specifically Child-Pugh class B7. It emphasizes considerations related to portal hypertension, hepatitis B virus (HBV), DNA/hepatitis C virus (HCV), and RNA replication status, as well as the diagnostic details, treatment, and management to develop a more refined classification plan for advanced liver cancer.

Recommendation 1: Child-Pugh class B7 is recommended as the primary threshold for precisely classifying the liver function status of advanced liver cancer (with a 95% consensus agreement among experts).

Second, comorbid PVTT is a major adverse factor affecting the prognosis of liver cancer and is significant in the clinical diagnosis and treatment of liver cancer.[18] The current PVTT classification criteria mainly include the Japanese VP classification and Cheng's classification proposed by Professor Cheng Shuqun in China (Table 1).[19,20] In contrast to the Japanese VP classification, Cheng's classification separately categorizes microvascular tumor thrombus (as I_0), combines clinically indistinguishable VP1 and VP2 into type I, and further refines VP4 with multigrade portal vein involvement as type III/IV, specifically emphasizing the mesenteric vein tumor thrombus (type IV). Cheng's classification shows a strong clinical prognostic correlation and facilitates the selection of diagnosis and treatment options.[21–24] Therefore, this consensus recommends Cheng's classification as a reference criterion for the precise classification of PVTT in advanced liver cancer.

Recommendation 2: Cheng's classification is recommended as the reference criterion for the precise classification of advanced liver cancer with PVTT (with a 100% consensus agreement among experts).

The presence of extrahepatic metastasis in liver cancer also constitutes a major adverse factor affecting disease prognosis. Furthermore, it plays an important role in the clinical diagnosis and treatment of liver cancer. The concept of oligometastasis is commonly applied in the classification of solid tumors for diagnostic and treatment purposes. It was defined as having ≤5 metastatic/recurrent lesions, ≤2 involved organs, and representing an intermediate state with mild biological invasiveness, somewhere between localized primary tumors and extensive metastases.[25] The concept of liver cancer oligometastasis has not yet been established; however, numerous small-scale clinical studies have been conducted to investigate treatments for this condition.[26]

Recommendation 3: The definition of liver cancer oligometastasis (≤5 metastatic/recurrent lesions and ≤2 involved organs) is recommended as the reference criteria for characterizing extrahepatic metastatic lesions and providing treatment decision guidelines for the precise classification of advanced liver cancer (with a 95% consensus agreement among experts).

Recommendation 4: Based on the above evidence, the recommended classification criteria for advanced liver cancer were as follows (see Fig. 1 for the specific staging route):

Stage $IIIa_1$: PS 0–2, Child-Pugh class A/B (≤7 points), PVTT (type III), tumors confined to the hemiliver and ≤3 in number, with sufficient residual liver volume and function, and without evidence of extrahepatic metastasis.

Stage $IIIa_2$: PS 0–2, Child-Pugh class A/B (≤7 points), PVTT (type I–II), >3 tumors, or extension beyond one hemiliver, and without evidence of extrahepatic metastasis.

Stage $IIIa_3$: PS 0–2, Child-Pugh class A/B (≤7 points), PVTT (type III–IV)/vena cava tumor thrombus, and without evidence of extrahepatic metastasis.

Stage $IIIa_4$: PS 0–2, Child-Pugh class B (>7 points), PVTT (type I–IV) and without evidence of extrahepatic metastasis, irrespective of tumor condition.

Stage $IIIb_1$: PS 0–2, Child-Pugh class A/B (≤7 points), and the presence of oligometastasis in extrahepatic lesions, regardless of tumor conditions and vascular tumor thrombus.

Stage $IIIb_2$: PS 0–2, Child-Pugh class A/B (≤7 points), and presence of extrahepatic lesion metastasis extending beyond the definition of oligometastasis, regardless of tumor conditions and presence of vascular tumor thrombus.

Stage $IIIb_3$: PS 0–2, Child-Pugh class B (>7 points), with extrahepatic lesion metastasis, regardless of tumor conditions and presence of vascular tumor thrombus.

4. Refined diagnosis, treatment, and management of patients with advanced liver cancer

4.1. Classification and management of patients with stage IIIa

4.1.1. Diagnosis and treatment of patients with stage $IIIa_1$

Patients with liver cancer and PVTT type I–II can potentially be cured with surgical resection. Simultaneous resections of the primary tumor and thrombus can effectively alleviate portal venous pressure. Studies reported that surgical resection can result in significantly better survival outcomes than other treatment methods.[27,28]

For patients with Child-Pugh class A or low-score class B (≤7 points) liver function and PVTT (type I–II), if the tumor is confined to the hemiliver and the residual liver volume and function are sufficient, that is, the future liver remnant must account for more than 40% (in patients with chronic liver disease, parenchymal injury, or cirrhosis) or more than 30% (in patients without fibrosis or cirrhosis) of the standard liver volume, and the indocyanine green retention at 15 mins must be less than 30%, surgical resection of the tumor with PVTT and the involved portal vein may be considered, followed by TACE therapy, portal vein chemotherapy, or other systemic anti-tumor therapy (evidence level 3, recommendation B).[29–31]

High-quality evidence for neoadjuvant therapy in liver cancer is currently limited. Various pre- and perioperative neoadjuvant therapeutic regimens for surgically resected liver cancer are

Table 1
Difference between Cheng's and Japanese VP classifications of comorbid portal vein tumor thrombus in hepatocellular carcinoma.

Portal vein branches	Terminal branch	Grade 3	Grade 2	Grade 1	Trunk	Superior mesenteric vein
Cheng's classification	Microvascular tumor thrombus	I	I	II	III	IV
Japanese VP classification		VP1	VP2	VP3	VP4	VP4

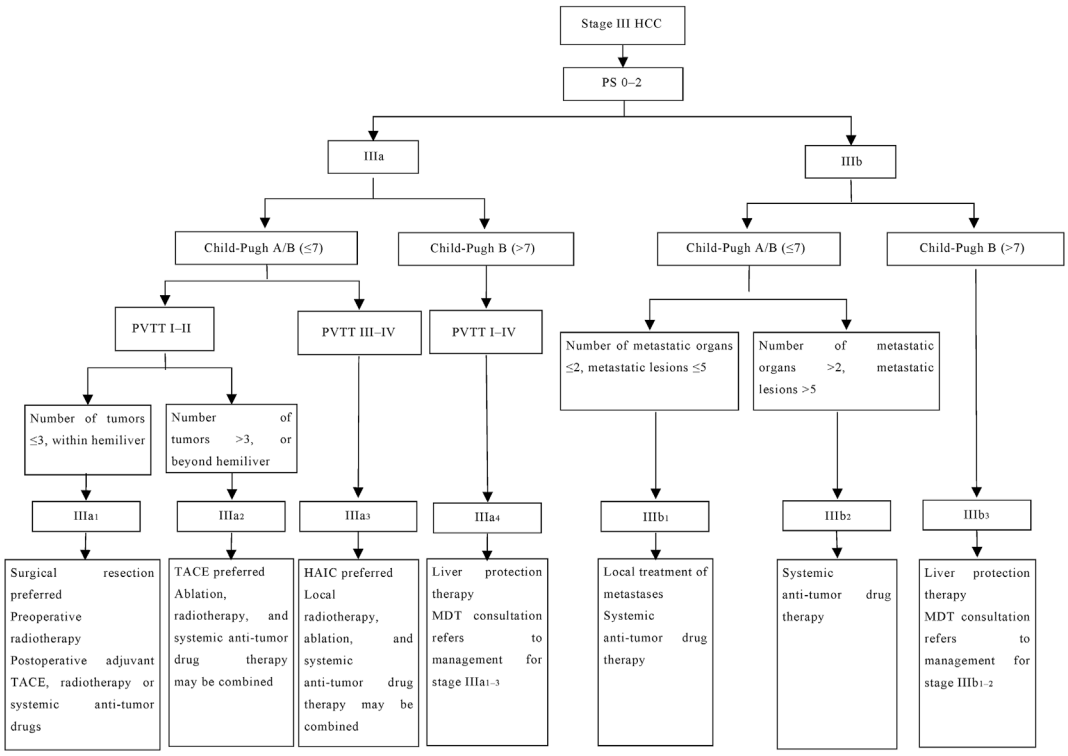

Fig. 1. Staging and treatment routes of refined diagnosis, treatment, and management of advanced primary liver cancer. Systemic anti-tumor drugs include first-line therapeutic options: atezolizumab combined with bevacizumab/sintilimab combined with bevacizumab/camrelizumab combined with apatinib/tremelimumab combined with durvalumab/systemic chemotherapy based on donafenib/lenvatinib/sorafenib/oxaliplatin; second-line therapy options: regorafenib/apatinib/pembrolizumab/camrelizumab/tislelizumab. Abbreviations: HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; MDT, multidisciplinary team; PS, performance status; PVTT, portal vein tumor thrombus; TACE, transarterial chemoembolization.

actively being investigated. Preliminary results from various small-scale neoadjuvant studies have been reported as follows: patients with PVTT type I–II could benefit from preoperative TACE;[32] neoadjuvant HAIC decreased the recurrence rate among patients at risk of liver cancer recurrence, with a 5-year survival rate of 100%.[33] Patients treated with immunotherapy combined with targeted therapy followed by surgery exhibited a decreased risk of postoperative tumor recurrence and death by 76% and 77%, respectively.[34] Several studies have revealed that preoperative three-dimensional conformal radiotherapy is associated with improved long-term survival in patients with liver cancer compared with surgery alone.[35,36] In the phase II trial utilizing camrelizumab combined with apatinib in the perioperative phase, the objective response rate reached 33.3%.[37] Similarly, the results of a perioperative phase II clinical trial using nivolumab ($n = 13$) or nivolumab combined with ipilimumab ($n = 14$) demonstrated that the median progression-free survival (mPFS) in the combined treatment group was 19.5 months, significantly superior to that of the single-agent group.[38] The clinical trials mentioned above revealed the achievements of drugs and local therapy in the field of neoadjuvant therapy. However, the postoperative advantages of these approaches should still be validated through extensive clinical studies. Following a comprehensive evaluation by a multidisciplinary team (MDT), the risk of postoperative recurrence and metastasis was assessed, leading to the introduction of neoadjuvant therapy.

Postoperative systemic combination therapy and/or local treatment options are recommended to reduce the risk of postoperative recurrence and enhance the prognosis. In patients with liver cancer and PVTT type I–II, various postoperative adjuvant therapies have shown promise: adjuvant therapy with atezolizumab combined with bevacizumab after radical resection resulted in a 33% lower disease recurrence rate than that of the monitoring group.[39] Postoperative administration of sorafenib significantly extended the OS of patients and reduced the tumor recurrence rate compared with that in the control group. However, large-scale clinical studies are required for confirmation; combining TACE with lenvatinib for postoperative adjuvant therapy in patients with a high risk of liver cancer recurrence may, compared with TACE alone, significantly prolong median disease-free survival (mDFS).[40] Postoperative adjuvant radiotherapy, or HAIC, also provided survival benefits to patients (evidence level 2, recommendation B);[41–44] for patients with PVTT, postoperative transcatheter portal vein chemotherapy combined with TACE may also prolong the OS of patients (evidence level 2, recommendation A).[45]

Surgical resection with intraoperative ablation is indicated for the treatment of multiple liver cancers (evidence level 4, recommendation C).[46–48]

To maximize the likelihood of achieving radical resection, patients with liver cancer and bile duct tumor thrombus may undergo a combined procedure involving the resection of both the liver tumor and affected bile duct (evidence level 3, recommendation C).[49–51]

Recommendation 5: Patients with the following criteria are recommended for surgical resection as the preferred treatment option: Child-Pugh class A or B (≤7 points), tumors confined to the hemiliver and ≤3 in number, resectable primary lesions, adequate residual liver volume and function, PVTT type I–II, and PS 0–1 (with a 91% consensus agreement among experts).

Recommendation 6: Patients with PVTT type I–II are recommended to undergo preoperative three-dimensional conformal radiotherapy or postoperative adjuvant TACE, radiotherapy, or systemic anti-tumor drugs. This process is aimed at delaying or

reducing postoperative recurrence (with a 91% consensus agreement among experts).

4.1.2. Diagnosis and treatment of patients with stage IIIa$_2$

For patients in Child-Pugh class A or B (≤7 points) who also have PVTT (type I–II), local TACE treatment should be initiated first if these patients have >3 tumors or if the tumors extend beyond a single hemiliver.[52] This approach is recommended to maximize tumor inactivation and safeguard liver function (evidence level 2, recommendation A).

Combining intraportal stent implantation with an iodine-125 seed strip or iodine-125 seed portal vein stent implantation can be used based on TACE (evidence level 2, recommendation B);[53] TACE combined with microwave ablation can significantly prolong the OS and PFS of patients with liver cancer (evidence level 2, recommendation B).[54]

TACTICS, a phase II study, demonstrated that TACE combined with sorafenib significantly improved mPFS compared with TACE alone (25.2 *vs*. 13.5 months). However, no significant improvement was observed in the survival rate.[55] Retrospective studies have also confirmed that TACE combined with the molecular targeted drug apatinib is more effective than TACE alone.[56,57] Further conclusions require confirmation through large-scale, multicenter, randomized controlled studies.

Recommendation 7: Patients in Child-Pugh class A or B (≤7 points) with unresectable primary lesion, PVTT type I–II, >3 tumors, tumors extending beyond a single hemiliver, and PS 0–1 are recommended to receive local TACE first, combined with ablation, radiotherapy, and systemic anti-tumor drug therapy (with a 91% consensus agreement among experts).

Recommendation 8: For patients who poorly responded to TACE alone, TACE combined with systemic anti-tumor drug therapy should be initiated earlier (with a 95% consensus agreement among experts).

4.1.3. Diagnosis and treatment of patients in stage IIIa$_3$

For patients in Child-Pugh class A or B (≤7 points) with PVTT (type III–IV), oxaliplatin-based HAIC is more effective than TACE if hilar collateral circulation is good.[58] In addition, sorafenib combined with HAIC significantly improves the survival of patients with liver cancer and PVTT (type III–IV) compared with sorafenib alone (evidence level 1, recommendation A).[59]

For patients in Child-Pugh class B (≤7 points) with PVTT (type III–IV), local combined radiotherapy can also be considered (evidence level 2, recommendation B).[60–62]

Recommendation 9: Patients in Child-Pugh class A or B (≤7 points) with unresectable primary lesions, PVTT type III–IV, well-developed hilar collateral circulation, and PS 0–1 may be treated with HAIC (with an 86% consensus agreement among experts). The combination drug therapy and management regimen should follow the guidelines outlined for the systemic treatment of patients in stage IIIb$_2$.

Recommendation 10: Patients in Child-Pugh class A or B (≤7 points) with liver cancer and unresectable primary lesion, PS 0–1, and PVTT III–IV may consider radiotherapy for the primary lesion and PVTT (with a 91% consensus agreement among experts). For the combined drug therapy and management regimen, it is advisable to refer to the guidelines provided for the systemic treatment of patients in stage IIIb$_2$.

4.1.4. Diagnosis and treatment of patients in stage IIIa$_4$

For patients in Child-Pugh B8/9 with PVTT, liver protection and supportive treatment are recommended to improve liver function to reach Child-Pugh B7 before proceeding with tumor-related interventions. During this stage, Icaritin (*Epimedium* genus) can be considered to prolong and improve the OS of the liver cancer-enriched population (with ≥2 of the following characteristics: alpha-fetoprotein (AFP), ≥400 ng/mL; tumor necrosis factor-alpha (TNF-α), <2.5 pg/mL; and interferon-gamma (IFN-γ), ≥7.0 pg/mL) (evidence level 1, recommendation B).[63,64] Additionally, the use of modern traditional Chinese medicine (TCM) formulations specifically indicated for liver cancer, such as elemene injection/oral solution and Xiaoaiping (Tongguanteng) injection/oral solution,[65,66] may be considered (evidence level 2, recommendation A).

The condition of a patient can also be assessed based on their actual liver function. Following an MDT consultation, systemic anti-tumor drug therapy can be administered when deemed necessary in combination with other local treatment options. Throughout the process, hepatologists closely monitor the alterations in liver function indicators.

Recommendation 11: For patients with advanced liver cancer defined as Child-Pugh class B (>7 points), the restoration of liver function to Child-Pugh B7 should be prioritized before initiating the anti-tumor treatment. During this phase, incorporating Icaritin treatment can be considered, or the treatment approach can be determined following consultation with an MDT, including hepatologists (with a 95% consensus agreement among experts).

4.2. Classification and management of patients in stage IIIb

Stage IIIb liver cancer is primarily characterized by the occurrence of extrahepatic metastasis. Its treatment options differ depending on the specific metastatic organs and the number of metastases. This part focuses on the treatment recommendations for metastases. The management of primary liver tumors can be guided by the previously mentioned recommendations for stage IIIa.

4.2.1. Diagnosis and treatment of patients in stage IIIb$_1$

Systemic treatment should be prioritized for patients with Child-Pugh class A or B (≤7 points) with oligometastatic lesions; however, if the disease stabilizes, local treatment should be considered to further enhance therapeutic efficacy. Radiotherapy can significantly improve the survival of patients with liver cancer and lymph node metastasis. Previous studies have shown a significant difference in the survival of patients with liver cancer with lymph node metastasis between the two groups: with and without external radiotherapy (mOS: 9.4 *vs*. 3.3 months).[67] In addition, patients with ≤5 adrenal metastases,[68] lung metastases,[69] or brain metastases may be administered systemic drug therapy combined with radiotherapy to relieve symptoms of metastases and prolong the survival time (evidence level 3, recommendation A).[70]

Based on data from a study with large number of patients, although the postoperative OS for stages IIIa and IIIb is not satisfactory, surgical resection can still be beneficial for some patients in the absence of other effective treatment methods (evidence level 4, recommendation C).[71] For patients with hilar lymph node metastasis, resection of the tumor with hilar lymph node dissection or postoperative external radiotherapy can be considered. Surgical resection can also be considered if the surrounding organs are invaded and can be resected together.[72]

Recommendation 12: For patients with Child-Pugh class A or B (≤7 points) and extrahepatic oligometastasis, active local treatment is recommended (with an 86% consensus agreement among experts).

4.2.2. Diagnosis and treatment of patients in stage IIIb$_2$

Advanced liver cancer often coexists with cirrhosis and increased portal vein pressure, and thereby, the risk of gastrointestinal bleeding caused by antiangiogenic drugs should be

considered. The following first-line treatments are recommended for patients with Child-Pugh class A or B (≤7 points) with multiple extrahepatic metastases: atezolizumab combined with bevacizumab (evidence level 1, recommendation A),[73–75] sintilimab combined with bevacizumab (evidence level 1, recommendation A),[15] and camrelizumab combined with apatinib (evidence level 1, recommendation A).[76] Others include tremelimumab combined with durvalumab (evidence level 1, recommendation A),[77] donafenib (evidence level 1, recommendation A),[16,78] lenvatinib (evidence level 1, recommendation A),[79] sorafenib (evidence level 1, recommendation A),[80,81] and oxaliplatin-based systemic chemotherapy (evidence level 1, recommendation A).[82,83] Patients with liver cancer complicated with HBV infection and AFP of >400 ng/mL are also advised to undergo a combination treatment with lenvatinib and pembrolizumab (evidence level 1, recommendation A).[84]

In addition, phase III clinical studies regarding immunotherapy combined with antiangiogenic drugs (such as toripalimab combined with lenvatinib/bevacizumab and penpulimab combined with anlotinib), a phase III clinical study involving immunotherapy combined with chemotherapy (camrelizumab combined with FOLFOX4), and a phase III clinical study examining the combined immunotherapy approach (nivolumab combined with ipilimumab) have completed enrollment or are ongoing. These studies hold the potential for promising outcomes.

Comprehensive evaluation of several factors should be considered in selecting a second-line and subsequent systemic treatment strategy for liver cancer, including the first-line treatment regimen, mode of progression (systemic treatment intolerance or imaging progression), AFP level, liver function compensation status, patient compliance, and pharmacoeconomics. For patients on progression or who exhibited intolerance to first-line systemic drugs such as sorafenib and lenvatinib, several second-line treatment options are recommended, given that they align with the following specified indications: regorafenib (evidence level 1, recommendation A),[85] apatinib (evidence level 1, recommendation A),[17] pembrolizumab (evidence level 3, recommendation A),[86,87] camrelizumab (evidence level 3, recommendation B),[88] and tislelizumab (evidence level 3, recommendation B).[89] For patients undergoing first-line combination immunotherapy, no large-scale phase III randomized controlled prospective clinical study data exists regarding second-line drug treatment regimens. The following questions arise: are the existing second-line treatment options still valid? Can the existing first-line tyrosine kinase inhibitors become the second-line treatment after immunotherapy? Future studies should address these points. The findings from retrospective and small-scale studies revealed that patients tended to have greater benefits from continued combination immunotherapy in their subsequent lines of treatment (evidence level 3, recommendation C).[90–92]

For patients with well-controlled extrahepatic lesions following systemic treatment, TACE is recommended for hepatic lesions. Some patients exhibiting vascular invasion can be treated with HAIC based on systemic treatment.[93]

Recommendation 13: Patients categorized under Child-Pugh class A or B (≤7 points) with multiple extrahepatic metastases are best suited for systemic therapy. Decisions regarding local treatment of these metastases should be made following an MDT discussion (with a 100% consensus agreement among experts).

4.2.3. Diagnosis and treatment of patients in stage $IIIb_3$

For patients in Child-Pugh class B (>7 points) with extrahepatic metastasis, considering the selective use of modern TCM preparations indicated for liver cancer or treatments based on TCM with syndrome differentiation is recommended (evidence level 2, recommendation A). In China, TCM has long been used for HCC prevention and is viewed as an effective preventative treatment because of its HBV/HCV-suppressing effect.[94–98] The research status of anti-HCC mechanisms in TCM revealed herbs have many active components that make them effective.[99] Many herbal formulas and their active ingredients are effective at inhibiting cell proliferation and inducing cell senescence, inducing apoptosis and autophagy, inhibiting metastasis and angiogenesis, improving drug resistance, and regulating immune function.[100] Additionally, the best supportive and palliative treatment (evidence level 2, recommendation A),[101–103] including active analgesia, correction of hypoalbuminemia, nutritional support, blood glucose control in patients with diabetes, and addressing complications such as ascites, jaundice, hepatic encephalopathy, gastrointestinal bleeding, and hepatorenal syndrome, are recommended. For patients with symptomatic bone metastases, denosumab, bisphosphonates, or radionuclide therapy (strontium chloride) can be used to improve quality of life, alleviate suffering, and prolong survival.[104–106]

Recommendation 14: For patients with Child-Pugh class B (>7 points) with extrahepatic metastasis, restoring liver function to Child-Pugh B7 before the anti-tumor treatment is recommended. During the period, systemic anti-tumor drugs and other treatments can be selected after MDT discussion (with a 100% consensus agreement among experts).

4.3. Antiviral management for patients with virus-associated advanced liver cancer

Hepatitis virus infection is a significant risk factor in the development and progression of liver cancer. The effective inhibition of hepatic viruses is crucial in slowing down tumor progression and thus prolonging patient survival.[107,108] In China, 84% of liver cancers are attributed to HBV infection.[109] Long-term antiviral therapy effectively manages viral replication; however, the current antiviral drugs do not completely eliminate covalently closed circular DNA in patients with chronic HBV infection.[110] Even patients who achieved serum clearance of hepatitis B surface antigen (HBsAg) may still have hidden HBV infection (i.e., patients with HBV DNA below the detection threshold following antiviral therapy). Such inapparent infections still carry the risk of HBV reactivation during anti-tumor treatment, often leading to the interruption of anti-tumor treatment due to complications, including hepatitis. HBV reactivation has been associated with malignant tumor progression and may affect anti-tumor efficacy.[111] Therefore, antiviral therapy is recommended for patients with HBV-related liver cancer who are HBsAg-positive, regardless of HBV DNA levels. Moreover, potent, low-resistance drugs such as entecavir, tenofovir disoproxil, and tenofovir alafenamide should be chosen based on the patient's condition of the patient during anti-tumor therapy (evidence level 1, recommendation A).[108,112] For HCV-related liver cancer, although the current anti-HCV regimen may cure HCV, HCV RNA reactivation can still occur during anti-tumor therapy.[113] Therefore, patients with HCV-related liver cancer should increase the frequency of HCV RNA detection during anti-tumor treatment, and antiviral therapy should be timely administered once HCV RNA is positive (evidence level 1, recommendation A).[114]

Recommendation 15: Patients with HBV/HCV-related liver cancer and positive HBsAg/HCV RNA should promptly begin antiviral therapy (with a 100% consensus agreement among experts).

Recommendation 16: Patients with HBV and HCV-related liver cancer receiving anti-tumor therapy are at risk of viral reactivation. HBV DNA, HCV RNA, and liver function status should be closely monitored during treatment and antiviral treatment strategies adjusted in time (with a 100% consensus agreement among experts).

4.4. Systemic treatment and management of advanced liver cancer complicated with portal hypertension

The impact of portal hypertension should be considered when choosing systemic treatment for patients with advanced liver cancer complicated with portal hypertension. Treatment options that simultaneously reduce portal hypertension while avoiding those that exacerbate varicose veins or portal hypertension should be preferred. Clinical trials involving atezolizumab combined with bevacizumab and sintilimab combined with bevacizumab excluded patients at risk of bleeding from esophageal or gastric varices due to portal hypertension.[75,115,116] Further confirmation is needed to establish the safety of these treatments for liver cancer with portal hypertension. In addition, clinical studies have demonstrated that sorafenib and regorafenib can help reduce portal venous pressure, making them safe and effective treatment options for patients with severe portal hypertension.[15,117]

Recommendation 17: Both liver cancer treatment and portal hypertension management should be established for patients with portal hypertension and liver cancer. The treatment regimen containing bevacizumab should be carefully considered in choosing a systemic treatment plan for patients with severe portal hypertension, particularly those with severe esophagogastric varices with red color signs. Other targeted drugs can be considered as alternatives, with close monitoring by doctors (with a 95% consensus agreement among experts).

5. Summary and future perspectives

Liver cancer in China exhibits significant distinctions from Western countries in terms of etiology, disease characteristics, disease progression, treatment modalities, and prognosis, leading to high heterogeneity. This consensus is established based on the Chinese liver cancer staging system and introduces a more nuanced staging approach, specifically focusing on advanced liver cancer stages IIIa and IIIb. Drawing on insights from relevant domestic and foreign studies and utilizing multidisciplinary collaboration, the selection of the most suitable treatment for stage IIIa liver cancer should be individualized, considering the liver function, previous treatment options, and concurrent medical conditions. This involves judiciously recommending surgical resection, TACE/HAIC, radiotherapy, systemic therapy, and other local treatment modalities as part of a well-planned treatment combination. For stage IIIb liver cancer, adopting the definition of oligometastasis used for other tumors is recommended. The treatment approach involves systemic therapy as the cornerstone of the treatment course, complemented by concurrent utilization of appropriate local therapies, such as radiotherapy, TACE, HAIC, and ablation. In addition, this consensus introduces a novel aspect by emphasizing the need for vigilant monitoring of HBV DNA and HCV RNA during antitumor therapy to assess their potential effects on tumor prognosis. A thorough investigation of how different anti-tumor drugs/combination therapies affect portal hypertension and related complications is also advocated, providing optimal drug recommendations. As ongoing research at domestic and international levels advances, this consensus will be periodically updated to ensure its continued relevance and efficacy in diagnosing and treating patients with advanced liver cancer.

Authors' contributions

Xiufeng Liu, Feng Xia, and Yue Chen contributed equally to this work. Xiufeng Liu, Feng Xia, Yue Chen, Huichuan Sun, Zhengqiang Yang, Bo Chen, Ming Zhao, Xinyu Bi, Tao Peng, and Zhiwen Luo contributed to draft writing. Xiufeng Liu, Feng Xia, Yue Chen, Zhiwen Luo, and Aizier Ainiwaer provided technical and material support. Fusheng Wang and Yinying Lu contributed to the conception and design. Other experts participated in consensus discussion and suggestions. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

List of experts (arranged in alphabetical order by the last name)

Aizier Ainiwaer (Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China), Xinyu Bi (Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Dan Cao (Abdominal Oncology Ward, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China), Bo Chen (Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Rongxin Chen (Key Laboratory of Carcinogenesis and Cancer Invasion, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China), Yue Chen (Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China), Jiamin Cheng (Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China), Shuangsuo Dang (Department of Infectious Diseases, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China), Jie Gao (Department of Hepatobiliary surgery, Peking University People's Hospital, Beijing, China), Yanhang Gao (Department of Hepatology, The First Hospital of Jilin University, Jilin University, Changchun, Jilin, China), Yufeng Gao (Department of Infectious Diseases, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China), Xinlei Gong (Department of Medical Oncology, Bayi Hospital Affiliated to Nanjing Chinese Medical University, Nanjing, Jiangsu, China), Yabing Guo (State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China), Yarong Guo (Department of Oncology, The First Affiliated Hospital of Shanxi Medical University, Taiyuan, Shanxi, China), Zhen Huang (Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Long Jin (Department of Interventional Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing, China), Haiyang Li (Department of Hepatobiliary Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China), Jianjun Li (The First Affiliated Hospital of the Army Medical University, Chongqing, China), Junhe Li (Department of Oncology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China), Junyi Li (Department of Infectious Diseases, The Third People's Hospital of Kunming City, Yunnan, China), Ke Li (Xiang'an Hospital of Xiamen University, Xiamen, Fujian, China), Qiu Li (Division of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China), Wei Li (No.2 People's Hospital of Fuyang City, Fuyang, Anhui, China), Wenhua Li (The Third People's Hospital of Taiyuan, Taiyuan, Shanxi, China), Zhiwei Li (Department of hepatobiliary surgery, Shenzhen Third People's Hospital, Shenzhen, Guangdong, China), Ying Liu (Henan Cancer Hospital & Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, Henan,

China), Xiufeng Liu (Department of Medical Oncology, Bayi Hospital Affiliated to Nanjing Chinese Medical University, Nanjing, Jiangsu, China), Jun Lu (Hepatology and Cancer Biotherapy Ward, Beijing Youan Hospital, Capital Medical University, Beijing, China), Shichun Lu (Faculty of Hepato-Pancreato-Biliary Surgery, Institute of Hepatobiliary Surgery, Key Laboratory of Digital Hepatobiliary Surgery, Chinese People's Liberation Army Medical School, Chinese People's Liberation Army General Hospital, Beijing, China), Yinying Lu (Comprehensive Liver Cancer Center, The Fifth Medical Center of PLA General Hospital, Beijing, China), Wei Lu (Tianjin Medical University Cancer Institute & Hospital, Tianjin, China), Zhiwen Luo (Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Fanping Meng (Senior Department of Infectious Diseases, The Fifth Medical Center of PLA General Hospital, Beijing, China), Yuemin Nan (Department of Traditional and Western Medical Hepatology, The Third Hospital of Hebei Medical University, Shijiazhuang, Hebei, China), Qin Ning (Department and Institute of Infectious Disease, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China), Zuoxing Niu (Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, Shandong, China), Shifang Peng (Xiangya Hospital of Central-South University, Changsha, Hunan, China), Tao Peng (Department of Hepatobiliary Surgery, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China), Xiujuan Qu (Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, Liaoning, China), Jie Shen (Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University, Clinical Cancer Institute of Nanjing University, Nanjing, Jiangsu, China), Tianqiang Song (Department of Hepatobiliary Cancer, Liver Cancer Research Center, Tianjin Medical University Cancer Institute & Hospital, Tianjin, China), Huichuan Sun (Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China), Jian Sun (State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China), Fusheng Wang (Senior Department of Infectious Diseases, The Fifth Medical Center of PLA General Hospital, Beijing, China), Shuai Wang (Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China), Weihu Wang (Department of Radiation Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital and Institute, Beijing, China), Wentao Wang (Department of Liver Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China), Xin Wang (Department of Abdominal Oncology/Radiation Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China), Lai Wei (Beijing Tsinghua Changgung Hospital, Tsinghua University, Beijing, China), Jianbing Wu (Department of Oncology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China), Feng Xia (Department of Hepatobiliary Surgery, Southwest Hospital, Army Medical University, Chongqing, China), Yong Xia (Department of Hepatic Surgery, the Eastern Hepatobiliary Surgery Hospital and the National Center for Liver Cancer, The Second Military Medical University, Shanghai, China), Qing Xie (Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China), Long Xu (Department of Gastroenterology and Hepatology, Shenzhen University General Hospital, Shenzhen, Guangdong, China), Yongfeng Yang (The Second Hospital of Nanjing, Teaching Hospital of Southeast University, Nanjing, Jiangsu, China), Zhengqiang Yang (Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Jieer Ying (Department of Hepato-Pancreato-Biliary & Gastric Medical Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou, Zhejiang, China), Chaohui Yu (Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China), Hongjiang Yu (Inner Mongolia Tongliao City Hospital, Tongliao, Inner Mongolia, China), Lingxiang Yu (Senior Department of Hepatology, The Fifth Medical Center of PLA General Hospital, Beijing, China), Zhengang Yuan (Department of Oncology, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China), Shan Zeng (Department of Oncology, Xiangya Hospital of Central-South University, Changsha, Hunan, China), Jing Zhang (The Third Unit, Department of Hepatology, Beijing Youan Hospital, Capital Medical University, Beijing, China), Jingdong Zhang (Medical Oncology Department of Gastrointestinal Cancer, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, Shenyang, Liaoning, China), Lan Zhang (Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China), Haitao Zhao (Department of Liver Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China), Hong Zhao (Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Ming Zhao (Department of Minimally Invasive Interventional Therapy, Liver Cancer Study and Service Group, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong, China), Shi Zuo (Department of Hepatobiliary Surgery, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou, China).

Acknowledgements

This work was funded by the National Natural Science Foundation of China (No. 82272956).

References

1. Zheng RS, Zhang SW, Sun KX, et al. Cancer statistics in China, 2016 (in Chinese). *Zhonghua Zhong Liu Za Zhi*. 2023;45:212–220. https://doi.org/10.3760/cma.j.cn112152-20220922-00647.
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249. https://doi.org/10.3322/caac.21660.
3. Bureau of Medical Administration, National Health Commission of the People's Republic of China. Standardization for diagnosis and treatment of hepatocellular carcinoma (2022 edition) (in Chinese). *Zhonghua Gan Zang Bing Za Zhi*. 2022;30:367–388. https://doi.org/10.3760/cma.j.cn501113-20220413-00193.
4. Haber PK, Puigvehí M, Castet F, et al. Evidence-based management of hepatocellular carcinoma: systematic review and Meta-analysis of randomized controlled trials (2002-2020). *Gastroenterology*. 2021;161:879–898. https://doi.org/10.1053/j.gastro.2021.06.008.
5. Lencioni R, Montal R, Torres F, et al. Objective response by mRECIST as a predictor and potential surrogate end-point of overall survival in advanced HCC. *J Hepatol*. 2017;66:1166–1172. https://doi.org/10.1016/j.jhep.2017.01.012.
6. Sonbol MB, Riaz IB, Naqvi SAA, et al. Systemic therapy and sequencing options in advanced hepatocellular carcinoma: a systematic review and network meta-analysis. *JAMA Oncol*. 2020;6:e204930. https://doi.org/10.1001/jamaoncol.2020.4930.
7. McPherson S, Reese C, Wendler MC. Methodology update: delphi studies. *Nurs Res*. 2018;67:404–410. https://doi.org/10.1097/NNR.0000000000000297.
8. Gholami S, Perry LM, Denbo JW, et al. Management of early hepatocellular carcinoma: results of the Delphi consensus process of the Americas Hepato-Pancreato-Biliary Association. *HPB (Oxford)*. 2021;23:753–761. https://doi.org/10.1016/j.hpb.2020.09.013.

9. Piscaglia F, Terzi E, Cucchetti A, et al. Treatment of hepatocellular carcinoma in Child-Pugh B patients. *Dig Liver Dis*. 2013;45:852–858. https://doi.org/10.1016/j.dld.2013.03.002.
10. Watanabe Y, Aikawa M, Kato T, et al. Influence of Child-Pugh B7 and B8/9 cirrhosis on laparoscopic liver resection for hepatocellular carcinoma: a retrospective cohort study. *Surg Endosc*. 2023;37:1316–1333. https://doi.org/10.1007/s00464-022-09677-x.
11. The Liver Cancer Professional Committee of the Chinese Anti-Cancer Association. Expert consensus on China liver cancer multidisciplinary comprehensive treatment (in Chinese). *J Multidiscip Cancer Manag (Electronic Version)*. 2021;7:43–51. https://doi.org/10.12151/JMCM.2021.02-07.
12. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76:862–873. https://doi.org/10.1016/j.jhep.2021.11.030.
13. Dual immunotherapy makes strides against HCC. *Cancer Discov*. 2022;12:OF1. https://doi.org/10.1158/2159-8290.CD-NB2022-0008.
14. Llovet JM, Kudo M, Cheng AL, et al. Lenvatinib (len) plus pembrolizumab (pembro) for the first-line treatment of patients (pts) with advanced hepatocellular carcinoma (HCC): phase 3 LEAP-002 study. *J Clin Oncol*. 2019;37(15_suppl):TPS4152. https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS4152.
15. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. *Lancet Oncol*. 2021;22:977–990. https://doi.org/10.1016/S1470-2045(21)00252-7.
16. Qin S, Bi F, Gu S, et al. Donafenib versus sorafenib in first-line treatment of unresectable or metastatic hepatocellular carcinoma: a randomized, open-label, parallel-controlled phase II-III trial. *J Clin Oncol*. 2021;39:3002–3011. https://doi.org/10.1200/JCO.21.00163.
17. Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2021;6:559–568. https://doi.org/10.1016/S2468-1253(21)00109-6.
18. Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. *Am J Clin Oncol*. 1998;21:386–391. https://doi.org/10.1097/00000421-199808000-00014.
19. Ikai I, Yamamoto Y, Yamamoto N, et al. Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. *Surg Oncol Clin N Am*. 2003;12:65–75, ix. https://doi.org/10.1016/s1055-3207(02)00082-0.
20. Cheng SQ, Wu MC, Chen H, et al. A study on imagination features of tumor thrombi in the portal vein of primary liver cancer (in Chinese). *Chin J Gen Surg*. 2004;19:200201.
21. Niu ZJ, Ma YL, Kang P, et al. Transarterial chemoembolization compared with conservative treatment for advanced hepatocellular carcinoma with portal vein tumor thrombus: using a new classification. *Med Oncol*. 2012;29:2992–2997. https://doi.org/10.1007/s12032-011-0145-0.
22. Ding X, Sun W, Li W, et al. Transarterial chemoembolization plus lenvatinib versus transarterial chemoembolization plus sorafenib as first-line treatment for hepatocellular carcinoma with portal vein tumor thrombus: a prospective randomized study. *Cancer*. 2021;127:3782–3793. https://doi.org/10.1002/cncr.33677.
23. Li T, Yu Y, Liu J, et al. PIVKA-II level is correlated to development of portal vein tumor thrombus in patients with HBV-related hepatocellular carcinoma. *Infect Agent Cancer*. 2019;14:13. https://doi.org/10.1186/s13027-019-0229-6.
24. Wei Z, Zhao J, Bi X, et al. Neoadjuvant radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a systematic review. *Hepatobiliary Surg Nutr*. 2022;11:709–717. https://doi.org/10.21037/hbsn-20-854.
25. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13:8–10. https://doi.org/10.1200/JCO.1995.13.1.8.
26. Chen Y, Yang P, Du S, et al. A Phase II Study of Stereotactic Body Radiotherapy (SBRT) Combined with Sintilimab in Patients with Recurrent or Oligometastatic Hepatocellular Carcinoma (HCC). American Society of Clinical Oncology 2022. Abstract 4071.
27. Liang L, Chen TH, Li C, et al. A systematic review comparing outcomes of surgical resection and non-surgical treatments for patients with hepatocellular carcinoma and portal vein tumor thrombus. *HPB (Oxford)*. 2018;20:1119–1129. https://doi.org/10.1016/j.hpb.2018.06.1804.
28. Wang K, Guo WX, Chen MS, et al. Multimodality treatment for hepatocellular carcinoma with portal vein tumor thrombus: a large-scale, multicenter, propensity mathching score analysis. *Medicine (Baltimore)*. 2016;95:e3015. https://doi.org/10.1097/MD.0000000000003015.
29. Siriwardana RC, Lo CM, Chan SC, Fan ST. Role of portal vein embolization in hepatocellular carcinoma management and its effect on recurrence: a case-control study. *World J Surg*. 2012;36:1640–1646. https://doi.org/10.1007/s00268-012-1522-3.
30. Yu JI, Choi GS, Lim DH, et al. Treatment of naive HCC combined with segmental or subsegmental portal vein tumor thrombosis: liver resection versus TACE followed by radiotherapy. *Anticancer Res*. 2018;38:4919–4925. https://doi.org/10.21873/anticanres.12808.
31. Department of Medical Administration. National Health Commission of the People's Republic of China. Guidelines for the diagnosis and treatment of primary liver cancer (2024 edition). *China J Gen Surg*. 2024;33:475–530. https://doi.org/10.7659/j.issn.1005-6947.2024.04.001.
32. Zhang YF, Guo RP, Zou RH, et al. Efficacy and safety of preoperative chemoembolization for resectable hepatocellular carcinoma with portal vein invasion: a prospective comparative study. *Eur Radiol*. 2016;26:2078–2088. https://doi.org/10.1007/s00330-015-4021-8.
33. Pan Y, Mei J, Chen J, et al. Comparison between portal vein perfusion chemotherapy and neoadjuvant hepatic arterial infusion chemotherapy for resectable intermediate to advanced stage hepatocellular carcinoma. *Ann Surg Oncol*. 2022;29:2016–2029. https://doi.org/10.1245/s10434-021-10903-4.
34. Cao Y, Tang H, Hu B, et al. Comparison of survival benefit between salvage surgery after conversion therapy versus surgery alone for hepatocellular carcinoma with portal vein tumor thrombosis: a propensity score analysis. *HPB (Oxford)*. 2023;25:775–787. https://doi.org/10.1016/j.hpb.2023.03.004.
35. Lin H, Li X, Liu Y, Hu Y. Neoadjuvant radiotherapy provided survival benefit compared to adjuvant radiotherapy for hepatocellular carcinoma. *ANZ J Surg*. 2018;88:E718–E724. https://doi.org/10.1111/ans.14387.
36. Wei X, Jiang Y, Zhang X, et al. Neoadjuvant three-dimensional conformal radiotherapy for resectable hepatocellular carcinoma with portal vein tumor thrombus: a randomized, open-label, multicenter controlled study. *J Clin Oncol*. 2019;37:2141–2151. https://doi.org/10.1200/JCO.18.02184.
37. Xia Y, Tang W, Qian X, et al. Efficacy and safety of camrelizumab plus apatinib during the perioperative period in resectable hepatocellular carcinoma: a single-arm, open label, phase II clinical trial. *J Immunother Cancer*. 2022;10:e004656. https://doi.org/10.1136/jitc-2022-004656.
38. Kaseb AO, Cao HST, Mohamed YI, Qayyum A, Sharma P. Final results of a randomized, open label, perioperative phase II study evaluating nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC. *J Clin Oncol*. 2020;38(15_suppl):4599. https://doi.org/10.1200/JCO.2020.38.15_suppl.4599.
39. Chow P, Chen M, Cheng AL, et al. IMbrave050: Phase 3 Study of Adjuvant Atezolizumab+ Bevacizumab versus Active Surveillance in Patients with Hepatocellular Carcinoma (HCC) at High Risk of Disease Recurrence Following Resection or Ablation. Proceedings of the American Association for Cancer Research (AACR) Annual Conference 2023; 16 April. 2023. Abstract #CT003.
40. Chen Jh, Lu L, Wen TF, et al. Adjuvant Lenvatinib in Combination with TACE for Hepatocellular Carcinoma Patients with High Risk of Postoperative Relapse (LANCE): Interim Results from a Muticenter Prospective Cohort Study. American Society of Clinical Oncology 2020.
41. Sun J, Yang L, Shi J, et al. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: an open-label randomized controlled trial. *Radiother Oncol*. 2019;140:20–25. https://doi.org/10.1016/j.radonc.2019.05.006.
42. Bai T, Chen J, Xie ZB, et al. The efficacy and safety of postoperative adjuvant transarterial embolization and radiotherapy in hepatocellular carcinoma patients with portal vein tumor thrombus. *OncoTargets Ther*. 2016;9:3841–3848. https://doi.org/10.2147/OTT.S104307.
43. Wang L, Wang W, Yao X, et al. Postoperative adjuvant radiotherapy is associated with improved survival in hepatocellular carcinoma with microvascular invasion. *Oncotarget*. 2017;8:79971–79981. https://doi.org/10.18632/oncotarget.20402.
44. Ke Q, Wang L, Wu W, et al. Meta-analysis of postoperative adjuvant hepatic artery infusion chemotherapy versus surgical resection alone for hepatocellular carcinoma. *Front Oncol*. 2021;11:720079. https://doi.org/10.3389/fonc.2021.720079.
45. Fan J, Zhou J, Wu ZQ, et al. Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis. *World J Gastroenterol*. 2005;11:1215–1219. https://doi.org/10.3748/wjg.v11.i8.1215.
46. Lee JY, Kim YH, Roh YH, et al. Intraoperative radiofrequency ablation for hepatocellular carcinoma in 112 patients with cirrhosis: a surgeon's view. *Ann Surg Treat Res*. 2016;90:147–156. https://doi.org/10.4174/astr.2016.90.3.147.
47. Yin L, Li H, Li AJ, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: a RCT. *J Hepatol*. 2014;61:82–88. https://doi.org/10.1016/j.jhep.2014.03.012.
48. Zhou C, Peng Y, Zhou K, et al. Surgical resection plus radiofrequency ablation for the treatment of multifocal hepatocellular carcinoma. *Hepatobiliary Surg Nutr*. 2019;8:19–28. https://doi.org/10.21037/hbsn.2018.11.19.
49. Kim DS, Kim BW, Hatano E, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korea-Japan multicenter study. *Ann Surg*. 2020;271:913–921. https://doi.org/10.1097/SLA.0000000000003014.
50. Lin Z, Han M, Zhou Z. Prognosis for patients with hepatocellular carcinoma (HCC) with bile duct tumor thrombus (BDTT) after surgical treatment. *Biosci Trends*. 2019;13:77–85. https://doi.org/10.5582/bst.2018.01234.
51. Sun J, Wu J, Shi J, et al. Thrombus-first surgery for hepatocellular carcinoma with bile duct tumor thrombus. *J Gastrointest Surg*. 2021;25:1973–1979. https://doi.org/10.1007/s11605-020-04813-1.
52. Chung GE, Lee JH, Kim HY, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. *Radiology*. 2011;258:627–634. https://doi.org/10.1148/radiol.10101058.
53. Yang M, Fang Z, Yan Z, et al. Transarterial chemoembolisation (TACE) combined with endovascular implantation of an iodine-125 seed strand for the treatment of hepatocellular carcinoma with portal vein tumour thrombosis versus TACE alone: a two-arm, randomised clinical trial. *J Cancer Res Clin Oncol*. 2014;140:211–219. https://doi.org/10.1007/s00432-013-1568-0.
54. Si ZM, Wang GZ, Qian S, et al. Combination therapies in the management of large (>/= 5 cm) hepatocellular carcinoma: microwave ablation immediately

followed by transarterial chemoembolization. *J Vasc Interv Radiol*. 2016;27:1577–1583. https://doi.org/10.1016/j.jvir.2016.02.014.
55. Kudo M, Ueshima K, Ikeda M, et al. Randomised, multicentre prospective trial of transarterial chemoembolisation (TACE) plus sorafenib as compared with TACE alone in patients with hepatocellular carcinoma: TACTICS trial. *Gut*. 2020;69:1492–1501. https://doi.org/10.1136/gutjnl-2019-318934.
56. Liu C, Xing W, Si T, Yu H, Guo Z. Efficacy and safety of apatinib combined with transarterial chemoembolization for hepatocellular carcinoma with portal venous tumor thrombus: a retrospective study. *Oncotarget*. 2017;8:100734–100745. https://doi.org/10.18632/oncotarget.20140.
57. Lu W, Jin XL, Yang C, et al. Comparison of efficacy between TACE combined with apatinib and TACE alone in the treatment of intermediate and advanced hepatocellular carcinoma: a single-center randomized controlled trial. *Cancer Biol Ther*. 2017;18:433–438. https://doi.org/10.1080/15384047.2017.1323589.
58. Hu J, Bao Q, Cao G, et al. Hepatic arterial infusion chemotherapy using oxaliplatin plus 5-fluorouracil versus transarterial chemoembolization/embolization for the treatment of advanced hepatocellular carcinoma with major portal vein tumor thrombosis. *Cardiovasc Intervent Radiol*. 2020;43:996–1005. https://doi.org/10.1007/s00270-019-02406-3.
59. He M, Li Q, Zou R, 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. https://doi.org/10.1001/jamaoncol.2019.0250.
60. Moriguchi M, Furuta M, Itoh Y. A review of non-operative treatments for hepatocellular carcinoma with advanced portal vein tumor thrombus. *J Clin Transl Hepatol*. 2017;5:177–183. https://doi.org/10.14218/JCTH.2016.00075.
61. Zhang ZH, Liu QX, Zhang W, et al. Combined endovascular brachytherapy, sorafenib, and transarterial chemobolization therapy for hepatocellular carcinoma patients with portal vein tumor thrombus. *World J Gastroenterol*. 2017;23:7735–7745. https://doi.org/10.3748/wjg.v23.i43.7735.
62. Huo YR, Eslick GD. Transcatheter arterial chemoembolization plus radiotherapy compared with chemoembolization alone for hepatocellular carcinoma: a systematic review and meta-analysis. *JAMA Oncol*. 2015;1:756–765. https://doi.org/10.1001/jamaoncol.2015.2189.
63. Fan Y, Li S, Ding X, et al. First-in-class immune-modulating small molecule Icaritin in advanced hepatocellular carcinoma: preliminary results of safety, durable survival and immune biomarkers. *BMC Cancer*. 2019;19:279. https://doi.org/10.1186/s12885-019-5471-1.
64. Qin SK, Li Q, Ming Xu J, et al. Icaritin-induced immunomodulatory efficacy in advanced hepatitis B virus-related hepatocellular carcinoma: immunodynamic biomarkers and overall survival. *Cancer Sci*. 2020;111:4218–4231. https://doi.org/10.1111/cas.14641.
65. Zhai B, Zeng Y, Zeng Z, et al. Drug delivery systems for elemene, its main active ingredient beta-elemene, and its derivatives in cancer therapy. *Int J Nanomedicine*. 2018;13:6279–6296. https://doi.org/10.2147/IJN.S174527.
66. Hou D, Xiong J, Li Y, Peng Y, Xiong L. Efficacy and safety of Xiaoaiping injection for liver cancer: a protocol for systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99:e21993. https://doi.org/10.1097/MD.0000000000021993.
67. Zeng ZC, Tang ZY, Fan J, et al. Consideration of role of radiotherapy for lymph node metastases in patients with HCC: retrospective analysis for prognostic factors from 125 patients. *Int J Radiat Oncol Biol Phys*. 2005;63:1067–1076. https://doi.org/10.1016/j.ijrobp.2005.03.058.
68. Zhou LY, Zeng ZC, Fan J, et al. Radiotherapy treatment of adrenal gland metastases from hepatocellular carcinoma: clinical features and prognostic factors. *BMC Cancer*. 2014;14:878. https://doi.org/10.1186/1471-2407-14-878.
69. Jiang W, Zeng ZC, Zhang JY, Fan J, Zeng MS, Zhou J. Palliative radiation therapy for pulmonary metastases from hepatocellular carcinoma. *Clin Exp Metastasis*. 2012;29:197–205. https://doi.org/10.1007/s10585-011-9442-4.
70. Park Y, Kim KS, Kim K, et al. Nomogram prediction of survival in patients with brain metastases from hepatocellular carcinoma treated with whole-brain radiotherapy: a multicenter retrospective study. *J Neurooncol*. 2015;125:377–383. https://doi.org/10.1007/s11060-015-1926-7.
71. Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg*. 2014;260:329–340. https://doi.org/10.1097/SLA.0000000000000236.
72. Park YJ, Lim DH, Paik SW, et al. Radiation therapy for abdominal lymph node metastasis from hepatocellular carcinoma. *J Gastroenterol*. 2006;41:1099–1106. https://doi.org/10.1007/s00535-006-1895-x.
73. Qin SK, Ren ZG, Feng Z, et al. Efficacy and safety of atezolizumab+ bevacizumab vs sorafenib in Chinese patients with unresectable HCC in the phase III IMbrave150 study. Liver Cancer Summit 2020. Abstract OP02-OP03.
74. Finn RS, Qin S, Ikeda M, et al. IMbrave150: updated overall survival data from a global, randomized, open-label Phase III study of atezolizumab+ bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma. *J Clin Oncol*. 2021;39(3 suppl):267. https://doi.org/10.1200/JCO.2021.39.3_suppl.267.
75. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382:1894–1905. https://doi.org/10.1056/NEJMoa1915745.
76. Qin S, Chan LS, Gu S, et al. LBA35 camrelizumab (C) plus rivoceranib (R) vs. sorafenib (S) as first-line therapy for unresectable hepatocellular carcinoma (uHCC): a randomized, phase III trial. *Ann Oncol*. 2022;33:S1401–S1402. https://doi.org/10.1016/j.annonc.2022.08.032.
77. Abou-Alfa GK, Chan SL, Kudo M, et al. Phase 3 randomized, open-label, multicenter study of tremelimumab (T) and durvalumab (D) as first-line therapy in patients (pts) with unresectable hepatocellular carcinoma (uHCC): HIMALAYA. *J Clin Oncol*. 2022;40(4 suppl):379. https://doi.org/10.1200/JCO.2022.40.4_suppl.379.
78. Bi F, Qin S, Gu S, et al. Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: an open-label, randomized, multicenter phase II/III trial. *J Clin Oncol*. 2020;38(15 suppl):4506. https://doi.org/10.1200/JCO.2020.38.15_suppl.4506.
79. Kudo M, Finn RS, Qin S, 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. https://doi.org/10.1016/S0140-6736(18)30207-1.
80. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359:378–390. https://doi.org/10.1056/NEJMoa0708857.
81. Cheng AL, Kang YK, Chen Z, 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. https://doi.org/10.1016/S1470-2045(08)70285-7.
82. Qin S, Bai Y, Lim HY, 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. https://doi.org/10.1200/JCO.2012.44.5643.
83. Qin S, Cheng Y, Liang J, et al. Efficacy and safety of the FOLFOX4 regimen versus doxorubicin in Chinese patients with advanced hepatocellular carcinoma: a subgroup analysis of the EACH study. *Oncologist*. 2014;19:1169–1178. https://doi.org/10.1634/theoncologist.2014-0190.
84. Finn RS, Kudo M, Merle P, et al. LBA34 Primary results from the phase III LEAP-002 study: lenvatinib plus pembrolizumab versus lenvatinib as first-line (1L) therapy for advanced hepatocellular carcinoma (aHCC). *Ann Oncol*. 2022;33:S1401. https://doi.org/10.1016/j.annonc.2022.08.031.
85. Kaseb AO, Cabrera R, Iyer R, et al. Regorafenib in patients (pts) with unresectable hepatocellular carcinoma (uHCC) in real-world practice in the United States (US): final analysis of the prospective, observational REFINE study. *J Clin Oncol*. 2023;41(16 suppl):e16114. https://doi.org/10.1200/JCO.2023.41.16_suppl.e16114.
86. Qin S, Chen Z, Fang W, et al. Pembrolizumab plus best supportive care versus placebo plus best supportive care as second-line therapy in patients in Asia with advanced hepatocellular carcinoma (HCC): phase 3 KEYNOTE-394 study. *J Clin Oncol*. 2022;40(4 suppl):383. https://doi.org/10.1200/JCO.2022.40.4_suppl.383.
87. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38:193–202. https://doi.org/10.1200/JCO.19.01307.
88. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. *Lancet Oncol*. 2020;21:571–580. https://doi.org/10.1016/S1470-2045(20)30011-5.
89. Ducreux M, Abou-Alfa G, Ren Z, et al. Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with previously treated advanced hepatocellular carcinoma. *Ann Oncol*. 2021;32:S217. https://doi.org/10.1016/j.annonc.2021.05.005.
90. Huang J, Guo Y, Huang W, et al. Regorafenib combined with PD-1 blockade immunotherapy versus regorafenib as second-line treatment for advanced hepatocellular carcinoma: a multicenter retrospective study. *J Hepatocell Carcinoma*. 2022;9:157–170. https://doi.org/10.2147/JHC.S353956.
91. Yan T, Huang C, Peng C, et al. A multi-center retrospective study on the efficacy and safety of regorafenib vs. regorafenib combined with PD-1 inhibitors as a second-line therapy in patients with advanced hepatocellular carcinoma. *Ann Transl Med*. 2023;11:109. https://doi.org/10.21037/atm-22-6614.
92. Zou X, Xu Q, You R, Yin G. Efficacy and safety of TACE combined with regorafenib plus PD-1 inhibitor in the treatment of hepatocellular carcinoma after sorafenib resistance. *J Hepatocell Carcinoma*. 2023;10:267–279. https://doi.org/10.2147/JHC.S399874.
93. Lyu N, Kong Y, Pan T, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin in hepatocellular cancer with extrahepatic spread. *J Vasc Interv Radiol*. 2019;30:349–357 (e2). https://doi.org/10.1016/j.jvir.2018.09.004.
94. Lu LG, Zeng MD, Mao YM, et al. Oxymatrine therapy for chronic hepatitis B: a randomized double-blind and placebo-controlled multi-center trial. *World J Gastroenterol*. 2003;9:2480–2483. https://doi.org/10.3748/wjg.v9.i11.2480.
95. Veldt BJ, Hansen BE, Ikeda K, Verhey E, Suzuki H, Schalm SW. Long-term clinical outcome and effect of glycyrrhizin in 1093 chronic hepatitis C patients with non-response or relapse to interferon. *Scand J Gastroenterol*. 2006;41:1087–1094. https://doi.org/10.1080/00365520600641365.
96. Ferenci P, Scherzer TM, Hofer H, Steindl-Munda P. 63 Silibinin is a potent antiviral agent in patients with chronic hepatitis C not responding to antiviral combination therapy. *J Hepatol*. 2008. https://doi.org/10.1016/S0168-8278(08)60065-3.
97. Zhang Y, Wu J. Effects of Jian-Pi-Huo-Xue Formula on in patients with hepatitis, hepatic cirrhosis and low level of AFP (in Chinese). *Zhong Xi Yi Jie He Gan Bing Za Zhi*. 2000;10:13–14. https://doi.org/10.3969/j.issn.1005-0264.2000.02.007.
98. Oka H, Yamamoto S, Kuroki T, et al. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer*. 1995;76:743–749.

https://doi.org/10.1002/1097-0142(19950901)76:5<743::aid-cncr2820760506>3.0.co;2-v.
99. Li FS, Weng JK. Demystifying traditional herbal medicine with modern approach. *Nat Plants*. 2017;3:17109. https://doi.org/10.1038/nplants.2017.109.
100. Chen SR, Qiu HC, Hu Y, Wang Y, Wang YT. Herbal medicine offered as an initiative therapeutic option for the management of hepatocellular carcinoma. *Phytother Res*. 2016;30:863–877. https://doi.org/10.1002/ptr.5594.
101. Liao X, Bu Y, Jia Q. Traditional Chinese medicine as supportive care for the management of liver cancer: past, present, and future. *Genes Dis*. 2020;7:370–379. https://doi.org/10.1016/j.gendis.2019.10.016.
102. Ling CQ, Fan J, Lin HS, et al. Clinical practice guidelines for the treatment of primary liver cancer with integrative traditional Chinese and Western medicine. *J Integr Med*. 2018;16:236–248. https://doi.org/10.1016/j.joim.2018.05.002.
103. Liu X, Li N. Regularity analysis on clinical treatment in primary liver cancer by traditional Chinese medicine (in Chinese). *Zhongguo Zhongyao Zazhi*. 2012;37:1327–1331. https://doi.org/10.4268/cjcmm20120933.
104. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. *J Thorac Oncol*. 2012;7:1823–1829. https://doi.org/10.1097/JTO.0b013e31826aec2b.
105. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. *Eur J Cancer*. 2012;48:3082–3092. https://doi.org/10.1016/j.ejca.2012.08.002.
106. The Chinese Society of Nuclear Medicine Working Committee for Treatment of Bone Metastasis. Expert consensus on strontium-89 chloride treatment of bone metastases (2017) (in Chinese). *Chin J Nucl Med Mol Imaging*. 2018;38:412–415. https://doi.org/10.3760/cma.j.issn.2095-2848.2018.06.008.
107. Yin J, Li N, Han Y, et al. Effect of antiviral treatment with nucleotide/nucleoside analogs on postoperative prognosis of hepatitis B virus-related hepatocellular carcinoma: a two-stage longitudinal clinical study. *J Clin Oncol*. 2013;31:3647–3655. https://doi.org/10.1200/JCO.2012.48.5896.
108. Huang G, Li PP, Lau WY, et al. Antiviral therapy reduces hepatocellular carcinoma recurrence in patients with low HBV-DNA levels: a randomized controlled trial. *Ann Surg*. 2018;268:943–954. https://doi.org/10.1097/SLA.0000000000002727.
109. The Chinese Chapter of International Hepato-Pancreato-Biliary Association. Chinese Society of liver cancer, Society for Hepato-pancreato-biliary surgery of Chinese research Hospital association, society for virus and tumor of Chinese research hospital association. Chinese expert consensus on antiviral therapy for hepatitis B virus-related hepatocellular carcinoma (2023 edition) (in Chinese). *Chin J Dig Surg*. 2023;22:29–41. https://doi.org/10.3760/cma.j.cn115610-20221024-00612.
110. Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: from discovery to regulatory approval. *J Hepatol*. 2017;67:847–861. https://doi.org/10.1016/j.jhep.2017.05.008.
111. Lei J, Yan T, Zhang L, et al. Comparison of hepatitis B virus reactivation in hepatocellular carcinoma patients who received tyrosine kinase inhibitor alone or together with programmed cell death protein-1 inhibitors. *Hepatol Int*. 2023;17:281–290. https://doi.org/10.1007/s12072-022-10450-4.
112. Huang G, Xie Q, He J, Sun J. Chinese expert consensus on antiviral treatment of hepatitis B virus-associated hepatocellular carcinoma (2023) (in Chinese). *Chin Hepatol*. 2023;28:1–10. https://doi.org/10.3969/j.issn.1008-1704.2023.01.001.
113. Lei J, Yang S, Chen B, et al. Efficacy and safety of tyrosine kinase inhibitors alone or combination with programmed death-1 inhibitors in treating of hepatitis C-related hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2023;10:357–367. https://doi.org/10.2147/JHC.S392347.
114. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; Clinical Practice Guidelines Panel: chair:; EASL Governing Board representative:; Panel members:. EASL recommendations on treatment of hepatitis C: final update of the series. *J Hepatol*. 2020;73:1170–1218. https://doi.org/10.1016/j.jhep.2020.08.018.
115. Larrey E, Campion B, Evain M, et al. A history of variceal bleeding is associated with further bleeding under atezolizumab-bevacizumab in patients with HCC. *Liver Int*. 2022;42:2843–2854. https://doi.org/10.1111/liv.15458.
116. Furusawa A, Naganuma A, Suzuki Y, et al. Two cases of rapid progression of esophageal varices after atezolizumab-bevacizumab treatment for hepatocellular carcinoma. *Clin J Gastroenterol*. 2022;15:451–459. https://doi.org/10.1007/s12328-022-01605-9.
117. Uschner FE, Schueller F, Nikolova I, et al. The multikinase inhibitor regorafenib decreases angiogenesis and improves portal hypertension. *Oncotarget*. 2018;9:36220–36237. https://doi.org/10.18632/oncotarget.26333.