Study Protocol

Title: Lenvatinib, Toripalimab, Plus Hepatic Arterial Infusion Chemotherapy versus Lenvatinib Alone for Advanced Hepatocellular Carcinoma

Test Drug: Oxaliplatin, leucovorin, 5-fluorouracil; Lenvatinib; Toripalimab

Funding: This work was supported by National Key R&D Program of China (2017YFA0505803), National Natural Science Foundation of China (No. 81625017), National Science and Technology Major Project of China (2018ZX10302205).

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1. Introduction

1.1. Hepatocellular Carcinoma

Hepatocellular carcinoma is the fifth most common malignancy and the third leading cause of tumor-related deaths.[1] A majority of patients with hepatocellular carcinoma, especially in China, are diagnosed with advanced-stage diseases.[2-4] Lenvatinib or sorafenib, as one of the tyrosine kinase inhibitors, is the standard systemic therapy in the treatment of advanced hepatocellular carcinoma.[5,6] Even thogh lenvatinib resulted in significant and clinically meaningful improvements versus sorafenib in objective response rate, progression-free survival and time to progression, there was no improvements in the median overall survival. The median overall survival of lenvatinib or sorafenib was about one year.

1.2. Immunotherapy for Hepatocellular Carcinoma

Treatment options for advanced hepatocellular carcinoma have rapidly evolved over the past several years, and new various treatments are now available. The immunotherapies that inhibit the immune checkpoint interaction between programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown a substantial survival benefit in hepatocellular carcinoma.[7,8] Toripalimab is a high-affinity, humanized, IgG4/Kappa PD-1 monoclonal antibody developed by China. However, subsequent phase 3 CheckMate 459 study investigating nivolumab as first-line treatment and KEYNOTE-240 study investigating pembrolizumab as second-line therapy did not achieve statistical significance for their primary endpoints.[9,10]

1.3 Hepatic Arterial Infusion Chemotherapy for Hepatocellular Carcinoma

In Japan and Korea, hepatic arterial infusion chemotherapy (HAIC) is selected for

patients with advanced HCC who are not candidates for surgical resection, or local ablation therapy. HAIC provides direct chemotherapeutic agent delivery into the tumor feeding arteries and minimizes systemic toxicities through a first-pass effect in the liver.[11,12] However, the disease commonly begins to progress again even after the treatment shrinks the tumor, and the cancer recurs, or the tumor starts growing again. Thus, treatment is often repeated as long as liver function will allow.

Hepatic arterial infusion of a cisplatin-based regimen was first investigated as a combination therapy with sorafenib.[13,14] In one randomized clinical trial, sorafenib plus hepatic arterial infusion of cisplatin extended OS by 22% or 1.9 months compared with sorafenib alone (10.6 months vs 8.7 months; hazard ratio [HR] 0.60, 95% CI 0.38–0.96; p=0.03).[15] In another randomized trial, a combination of sorafenib and a hepatic arterial infusion of cisplatin and fluorouracil failed to demonstrate survival superiority over sorafenib alone.[16] In addition, HAIC with oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX) provided promising antitumor activity for advanced hepatocellular carcinoma.[17,18]

1.4 Combination therapy for Hepatocellular Carcinoma

Combination therapies displayed promising antitumor activity. In IMbrave150 study, atezolizumab (a PD-L1 antibody) plus bevacizumab (a VEGF inhibitor) treatment resulted in improved overall survival compared with sorafenib, and this combination therapy was recommended as the first-line treatment for advanced hepatocellular carcinoma.[19] KEYNOTE-524, and RESCUE trial also showed lenvatinib plus pembrolizumab, and camrelizumab plus apatinib had promising antitumor activity.[20,21] Thus, monotherapy for advanced hepatocellular carcinoma may be sufficiently effective for advanced hepatocellular carcinoma, and combination therapies may be more appropriate for advanced hepatocellular carcinoma.

Furthermore, combination therapy of tyrosine kinase inhibitor, immunotherapy, and locoregional chemotherapy may achieve more powerful antitumor activity in hepatocellular carcinoma due to the synergistic antitumor effect: First, lenvatinib

inhibit the proneoangiogenic and immunosuppressive effects of tumor microenvironments to improve the clinical benefit of PD-1 antibodies by boosting the antitumor immune response.[22,23] Second, lenvatinib and PD-1 inhibitor can increase chemotherapeutic drug delivery via promoting vascular normalization.[24,25] Finally, chemotherapy may activate the adaptive immune system and help recover immunosurveillance to improve immune response.[26,27].

Therefore, we conducted this retrospective study to compare the combination of lenvatinib, toripalimab, and HAIC with lenvatinib monotherapy for advanced hepatocellular carcinoma.

2. Objectives

2.1 Primary Objective

Progression-free survival

Progression-free survival was defined as the time from the commencement of lenvatinib to progression according to the RECIST criteria or death from any cause, whichever occurred first.

2.2 Secondary Objectives

Overall survival, defined as the time from the commencement of lenvatinib to death from any cause

Objective response rate, the proportion of patients with complete response or partial response that was maintained for at least four weeks from the first radiological confirmation of that rate

Disease control rate, the proportion of patients with omplete response, partial response plus stable disease.

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

3. Study Design and Sample Size

3.1 Study Design

This is a retrospective study conducted at the Sun Yat-sen university Cancer Center, First People's Hospital of Foshan, and Guangzhou No.12 People's Hospital.

3.2 Sample Size

There was not sample size calculation because of retrospective design. A total of 157 patients met the criteria for inclusion in this study: 71 patients received triple combination therapy with lenvatinib, toripalimab plus HAIC, and 86 patients received lenvatinib monotherapy.

4. Patients Population

4.1 Inclusion Criteria

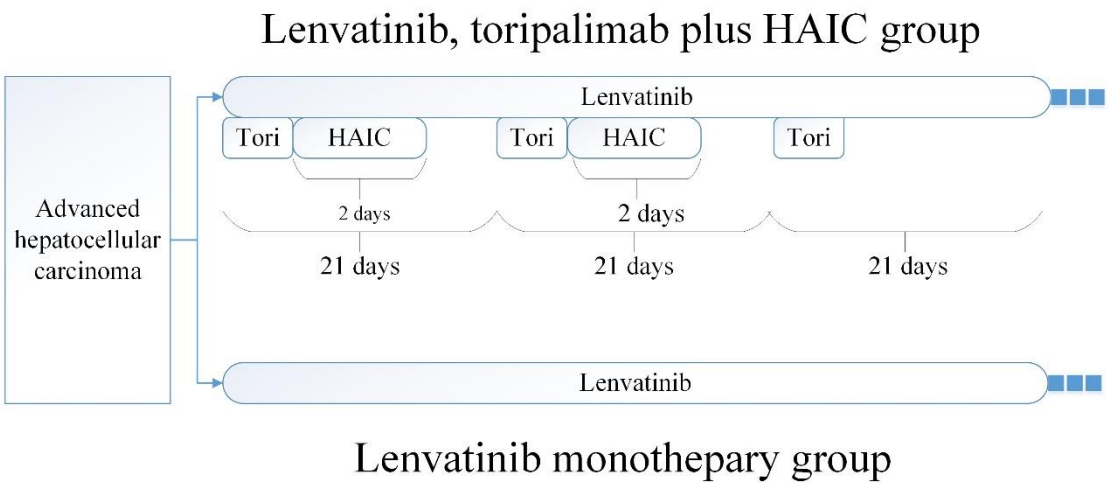
- 18 years or older
- Hepatocellular carcinoma diagnosed pathologically or clinically based on the American Association for the Study of Liver Diseases practice guideline
- Staged at Barcelona Clinic Liver Cancer C
- Treated with lenvatinib monotherapy or a combination of lenvatinib, toripalimab, and HAIC with FOLFOX
- An Eastern Cooperative Oncology Group performance status of 0-1
- Child-Pugh class A liver function
- At least 1 measurable intrahepatic lesion according to Response Evaluation Criteria in Solid Tumors version 1.1
- Adequate organ function: absolute neutrophil count $\geq 1.2 \times 10^9$/L, platelet count $\geq 60 \times 10^9$/L, total bilirubin <30 μmol/L, albumin ≥30 g/L, aspartate transaminase

and alanine transaminase ≤5 × upper limit of the normal, creatinine clearance rate of ≤1.5 × upper limit of the normal, and left ventricular ejection ≥45%)

4.2 Exclusion Criteria

- Combined with other malignant tumors
- Combined with other antitumor therapy
- Incomplete medical information
- Loss to follow-up
- Evidence of hepatic decompensation including ascites, gastrointestinal bleeding or hepatic encephalopathy
- Known history of HIV, or organ allograft
- Known central nervous system tumors including metastasis brain disease

5. Treatment and Administration



Treatments were discontinued due to tumor progression, unacceptable toxicity, the need for an operation and ablation owing to tumor shrinkage, or patient choice. HAIC was also discontinued due to technical difficulties in repeating the HAIC (stenosis or occlusion of tumor feeding artery or supplied only by extrahepatic collateral arteries), the disappearance of any intratumoral arterial enhancement in all intrahepatic lesions.

After HAIC was discontinued alone, patients were allowed to continue lenvatinib or toripalimab in the LeToHAIC group.

5.1 Lenvatinib group

Lenvatinib, 12 mg/day (for bodyweight ≥60 kg) or 8 mg/day (for bodyweight <60 kg), administered orally once daily.

5.2 LeToHAIC (lenvatinib, toripalimab, and HAIC with FOLFOX) group

Lenvatinib, 12 mg/day (for bodyweight ≥60 kg) or 8 mg/day (for bodyweight <60 kg), administered orally once daily. Lenvatinib was administered 0-1 week prior to the initial HAIC.

Toripalimab, 240 mg, intravenously 0-1 day prior to HAIC. Toripalimab was administered for each HAIC session, and toripalimab was repeated every 3 weeks after HAIC was discontinued.

HAIC was performed every 3 weeks: a catheter/microcatheter was placed in the main feeding hepatic artery, and then the following regimen was administered via the hepatic artery: oxaliplatin 85 mg/m^2 from hour 0 to 2 on day 1; leucovorin 400 mg/m^2 from hour 2 to 3 on day 1; 5-fluorouracil 400 mg/m^2 bolus at hour 3; and 2400 mg/m^2 over 46 hours on days 1 and 2.

6. Dose Modification

A dose reduction of lenvatinib due to lenvatinib-related toxicities (to 8 mg or 4 mg/day or to 4 mg every other day) was permitted.[5] The decision to delay lenvatinib and toripalimab follow local standards of care as guided by the locally approved product label.

6.1 Treatment Interruptions for HAIC

HAIC was delayed until recovery if neutrophil count less than 1200 cells/μL, platelet

count less than 60,000 platelets/μL, a total bilirubin level exceeding 30 μmol/L, an albumin level less than 30 g/L, or serum creatinine up to 1.5 times the institutional upper limit of normal.

6.2 Dose Reductions for HAIC

The 5-fluorouracil dose was decreased to 300 mg/m^2 bolus and 1800 mg/m^2/cycle continuous infusion in cases of grade 3 or 4 diarrhea or stomatitis, skin toxicity, or other grades 3 major organ drug-related toxicity. The oxaliplatin dose was decreased to 65 mg/m^2/cycle in cases of grade 3 or 4 neutropenia or thrombocytopenia, any other grade 3 major organ drug-related toxicity, or paresthesia associated with pain.

7. Study Procedures

7.1 Before treatment

Patients included in this retrospective study must meet following criteria

- Patient characteristics: Sex, height, pathological diagnosis, treatment history, disease stage, ECOG-PS, allergies, and concomitant diseases
- Signs and symptoms and blood pressure
- Body weight
- Chest enhanced CT to evaluate potential lung metastasis
- Target lesion measurements (dynamic CT or dynamic MRI)
- Hematology parameters: hemoglobin, white blood cell count, neutrophil count, red blood cell count, platelet count
- Blood biochemistry: AST, ALT, total bilirubin, direct bilirubin, ALP, γ-GTP, albumin, creatinine, Na, K, Cl, amylase, lipase, blood glucose
- Urinalysis: urine protein, urine erythrocytes, urine leukocytes
- Coagulation: PT (INR)
- Tumor markers: AFP, PIVKA-II, CA199

- Hepatitis virus: HBs antigen/HBs antibody/Hbc antibody, HCV antibody

Patients who lack one item was excluded.

7.2 Within Treatment

The following parameters was collected every 3 weeks:

- Signs and symptoms and blood pressure
- Hematology parameters: hemoglobin, white blood cell count, neutrophil count, red blood cell count, platelet count
- Blood biochemistry: AST, ALT, total bilirubin, direct bilirubin, ALP, γ-GTP, albumin, creatinine, Na, K, Cl, amylase, lipase, blood glucose
- Urinalysis: urine protein, urine erythrocytes, urine leukocytes
- Coagulation: PT (INR)
- Tumor markers: AFP, PIVKA-II, CA199

Upper abdomen-enhanced CT (MRI is also acceptable) and chest-enhanced CT was performed every 6 weeks (± 1 week).

7.3 Follow-up

After study treatment ends, patients were contacted every 3 months. The following items was monitored to the greatest extent possible until the end of the entire study. Tests were performed at the investigator's discretion depending on the patient's condition and were defined as part of this study.

1) Survival: Date survival was last confirmed or date of death; if dead, cause of death
2) Disease progression: Whether the disease has progressed, date of last follow-up regarding progression or date progression was confirmed, site of progression
3) Subsequent treatment: If the patient has received any diagnostic and therapeutic procedures or subsequent anti-tumoral/anti-cancer therapy, the name of the drug(s) in the first regimen following end of treatment should be collected.
4) Adverse event: AEs that were still ongoing at discontinuation of the protocol

treatment should be followed up till resolution.

8. Efficacy

8.1 Evaluations

Measurable disease and the response criteria used in this protocol were defined in the RECIST criteria (version 1.1) and mRECIST criteria. Tumor response was based on radiologic assessment only.

8.2 Endpoints

Primary Endpoint

Progression-free survival was defined as the time from the commencement of lenvatinib to progression according to the RECIST criteria or death from any cause, whichever occurred first.

Secondary Endpoints

Overall survival, defined as the time from the commencement of lenvatinib to death from any cause

Objective response rate, the proportion of patients with complete response or partial response that was maintained for at least four weeks from the first radiological confirmation of that rate

Disease control rate, the proportion of patients with omplete response, partial response plus stable disease.

Objective response rate and disease control rate were evaluated according to RECIST version 1.1 and mRECIST, respectively.

Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

9. Safety Evaluations

9.1 Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product.
This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

9.2 Serious Adverse Event

A Serious Adverse Event (SAE) is defined by FDA and NCI as any adverse drug event
(experience) occurring at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important Medical Event (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3 Attribution Definitions

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions.

• Doubtful

An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

• Possible

An adverse event that might be due to the use of the drug. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

• Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (e.g., confirmed by dechallenge). An alternative explanation is less likely, e.g., concomitant drug(s), concomitant disease(s).

• Very likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive.

9.4. Intensity of AE

All AEs was graded according to the Common Terminology Criteria of Adverse Event (CTCAE), version 4.03 grading scale.

Grade refers to the severity of the AE.

Grade		Description
1	Mild	Symptoms causing no or minimal inference with usual social & functional activities
2	Moderate	Symptoms causing greater than minimal interference with

		usual social & functional activities
3	Severe	Symptoms causing inability to perform usual social & functional activities
4	Life-threatening	Symptoms causing inability to perform basic self-care functions or medical or operative intervention indicated to prevent permanent impairment, persistent disability
5	Death	Death

10. Data Management

10.1 Data Collection

Clinical and radiological data were retrospectively collected from the medical record and our database. The following data were collected and analyzed: gender, age, ECOG PS score, positive or negative of hepatitis B surface antigen, alpha-fetoprotein (AFP) level, des-gamma-carboxy prothrombin, albumin-bilirubin (ALBI) grade, alanine aminotransferase, aspartate aminotransferase, albumin, total bilirubin, tumor size, tumor number, absence or presence of portal vein tumor thrombus (PVTT), absence or presence of hepatic vein tumor thrombus (HVTT), absence or presence of extrahepatic metastasis.

10.2 Statistical Analysis

Two authors who did not know treatment groups independently completed statistical analysis. If there was controversy, a statistician completed the analysis. For baseline data, means and standard deviations were used for normally distributed data, and medians and interquartile ranges were used for data that are not normally distributed. The baseline characteristics were compared by Student’s t-tests or chi-square tests. Survival outcomes of overall survival and progression-free survival were calculated with the Kaplan-Meier method and compared by log-rank tests. The response rates

will be compared using Chi-square test or Fisher's exact test, as appropriate. Any factors that were statistically significant at P less than 0.10 in the univariate analysis were candidates for entry into a multivariable Cox proportional hazards model.

10.3 Tumor Response

Tumor assessments were evaluatd by two independent radiologists who do not know treatment based on RECIST 1.1 and mRECIST, respectively. If there was a discrepancy between the 2 radiologists, the final classification was made by another more experienced radiologist. An author, who knows the treatment, backs up all images of subjects with serial numbers. There is no any subject information (name, admission number, out-patient number, BedID) in the backup. Then independent radiologists would assess the images.

10.4 Analysis Method

Efficacy analysis: The response rate and disease control rate were evaluated by incidence and compared with chi-squared tests. The PFS and OS were calculated with the Kaplan-Meier method.

Safety analysis: The safety parameters to be evaluated are the incidence, intensity, and type of adverse events, and clinical laboratory results.

Any factors that were statistically significant at P less than 0.10 in the univariate analysis were candidates for entry into a multivariable Cox proportional hazards model. All *P* values were two-sided, with P values less than 0.05 considered significant. 95% confidence intervals (95% CIs) were also used. The statistical package used to perform the analyses was SAS, version 9.0 (SAS Institute).

11. Ethical Considerations

11.1 Protection of Patients' Rights

All researchers in this study conducted the study in accordance with the Declaration of Helsinki and the Ethical Guidelines of each participating institution for clinical studies.

11.2 Informed Consent

Once advanced HCC was confirmed, the patient was informed that lenvatinib was the recommended treatment. In addition, HAIC and PD-1 inhibitor were also recommended based on previous studies, and the triple combination therapy of lenvatinib, PD-1 inhibitor, and HAIC may achieve the promising antitumor activity. The doctors must explain to patients the aims, methods, reasonably anticipated benefits, and potential hazards of the study, any discomfort participation in the study may entail. Patients was informed that their treatment was voluntary and their privacy was protected. The patients were given the opportunity to ask questions. The final decision was principally made by the patient.

11.3 Protection of Personal Information and Identification of Patients

To protect the privacy of individual patients, numbers issued on patients was used to identify or refer to patients. All researchers made the utmost effort to protect personal information.

11.4 Conflicts of Interest

The researchers declare that they have no conflict of interest. The study has no commercial affiliations with any company.

11.5 Funding

This work was supported by National Key R&D Program of China (2017YFA0505803), National Natural Science Foundation of China (No. 81625017), National Science and Technology Major Project of China (2018ZX10302205).

11.6 Institutional Review Board (IRB)

The investigator provided the IRB with current and complete copies of the documents, which include, but are not limited to, final protocol, informed consent, investigators' curriculum vitae, information regarding funding, and other potential conflicts of interest.

12. Appendices

12.1 Tumor Assessment

Overall response, including assessment of the change in tumor burden inside and outside the liver, were assessed by investigators by using the Response Evaluation Criteria in Solid Tumors (RECIST)[28]. Assessments were made based on changes in the diameter of tumors that are observed by contrast CT or MRI until completion or discontinuation of the protocol treatment. The disease control rate (DCR) is defined as the rate of complete response (CR) plus partial response (PR) plus stable disease (SD). The objective response rate (ORR) is defined as the rate of CR plus PR. Tumor response includes assessment of target lesions, nontarget lesions and new lesions. All objective responses were confirmed at least 4 weeks after the first observation.

In addition, the overall response was also assessed according to the modified RECIST (mRECIST) guidelines[29]. Assessments were made based on changes in the diameter of surviving tumors deemed viable by contrast CT or MRI.

Table 12-1. Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline

RECIST	mRECIST
CR=Disappearance of all target lesions	CR=Disappearance of any intratumoral arterial enhancement in all target lesions
PR=At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR=At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD=Any cases that do not qualify for either partial response or progressive disease	SD=Any cases that do not qualify for either partial response or progressive disease
PD=An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD=An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 12-2. Overall Response Assessment in mRECIST: Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR

SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

12.2 Definitions of Eastern Cooperative Oncology Group Performance Status

Table 12-3

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

12.3 Child–Pugh Score*

Table 12-4

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L	<34	34–50 (2–3)	>50 (>3)

(mg/dL)	(<2)		
Serum albumin, g/dL	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (s) or INR	<4.0 <1.7	4.0–6.0 1.7-2.3	> 6.0 >2.3
Ascites	None	Mild (or suppressed with medication)	Moderate to severe (or refractory)
Hepatic encephalopathy†	None	Grade I–II	Grade III–IV

* Child–Pugh A: 5 or 6 points; Child–Pugh B: 7–9 points; Child–Pugh C: >9 points

†Grade of encephalopathy:

Grade 0: Lucid, normal personality, normal neurological test results, normal electroencephalogram

Grade 1: Restlessness, sleep disorder, irritability/agitation, tremors, dysgraphia, 5 cps waves

Grade 2: Lethargy, disorientation (temporal), inappropriateness, difficulty maintaining stable posture, ataxia, slow triphasic waves

Grade 3: Somnolence, confused state, disorientation (spatial), hyperreflexia, rigidity, slow waves Grade 4: Coma, no personality/unresponsive, cessation of cerebral activity, slow 2–3 cps delta activity

12.4 BCLC Staging System

Table 9-5

	Very early stage (0)	**Early stage (A)**	**Intermediate stage (B)**	**Advanced stage (C)**	**Terminal stage (D)**
Child–Pugh	A	A-B	A-B	A-B	C
Performance	0	0	0	1-2	>2

status					
Tumor Features	1 HCC <2cm Carcinoma in situ	1 HCC or 3 Nodules <3cm	Multinodular	Portal invasion, N1, M1	Any

N1, lymph node metastasis. M1, extrahepatic spread.

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