Liver Cancer

Guidelines

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Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition)

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Keywords
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Abstract
Background: Primary liver cancer, of which around 75–85% is hepatocellular carcinoma in China, is the fourth most common malignancy and the second leading cause of tumor-related death, thereby posing a significant threat to the life and health of the Chinese people. ***Summary:*** Since the publication of Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China in June 2017, which were updated by the National Health Commission in December 2019, additional high-quality evidence has emerged from researchers worldwide regarding the diagnosis, staging, and treatment of liver cancer, that requires the guidelines to be updated again. The new edition (2022 Edition) was written by more than 100 experts in the field of liver cancer in China, which not only reflects the real-world situation in China but also may reshape the nationwide diagnosis and treatment of liver cancer. ***Key Messages:*** The new guideline aims to encourage the implementation of evidence-based practice and improve the national average 5-year survival rate for patients with liver cancer, as proposed in the "Health China 2030 Blueprint."

Overview

Primary liver cancer is currently the fourth most common malignancy and the second leading cause of tumor-related death in China, posing a significant threat to the lives and health of the Chinese people [1–3]. Primary liver cancer is classified into three main pathological types: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular-cholangiocarcinoma (cHCC-CCA). These pathological subtypes of primary liver cancer vary greatly in their pathogenesis, biological behavior, pathologic histology, treatment, and prognosis. As HCC accounts for 75–85% of all cases of primary liver cancer, with ICC accounting for 10–15% of cases [4], in this guideline, the term "liver cancer" refers to HCC only.

To standardize the diagnosis and treatment of HCC in China, the former National Health and Family Planning Commission of the People's Republic of China released the *Guidelines for the Diagnosis and Treatment of Primary Liver Cancer* (2017 Edition) in June 2017, which were updated by the National Health Commission in December 2019. The *Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma* (2019 Edition) reflected advancements in research, diagnosis, and the comprehensive multidisciplinary treatment of liver cancer in China at that time. These *Guidelines* helped standardize the diagnosis and treatment of liver cancer, improve the prognosis of patients with liver cancer, ensure medical service quality and safety, and optimize medical resources. Since the publication of the *Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma* (2019 Edition), high-quality evidence has emerged from researchers worldwide regarding the diagnosis, staging, and treatment of liver cancer; many of these findings are directly applicable to clinical practice in China. In response to these developments, the National Health Commission decided to revise and update the 2019 edition to produce the *Guidelines for the Diagnosis and Treatment*

Table 1. Recommendation strength

Recommendation strength	Description of definition
Strong recommendation	High confidence that the true value is close to the effect estimate. Based on high-quality research evidence supporting a net benefit (e.g., benefits outweighing harms); good consistency between findings with no or few exceptions; minor or no doubts about the quality of the study; and/or agreement of expert panel members. In other cases, high-quality evidence that convince the experts that the benefits clearly outweigh harm (including what is discussed in the literature review and analysis of the guidelines) may also support a strong recommendation
Moderate recommendation	Moderate confidence in effect estimates. Based on good research evidence supporting net benefits (e.g., benefits outweighing harms); consistency between research findings, with minor and/or a few exceptions; minor or few doubts about the study quality; and/or agreement of the expert panel members. In other cases, moderate-quality evidence with the benefits outweighing the harms (including those discussed in the literature review and analysis of the guidelines) may also formulate a moderate recommendation
Weak recommendation	There is limited confidence in the effect estimates, and this recommendation provides the best current guidance for clinical practice. Based on limited research evidence supporting a net benefit (e.g., benefits outweighing harms); consistent study findings with major exceptions; major doubts about study quality; and/or agreement from expert panel members. In other cases, limited evidence (including what is discussed in the literature review and analysis of the guidelines) may also lead to weak recommendations

Recommendation strength "strong recommendation, moderate recommendation, weak recommendation" expressed in the article with "A, B, C," respectively.

of Primary Liver Cancer (2022 Edition) that includes the latest practices in the clinical diagnosis and treatment of liver cancer based on the latest research. The Oncology Branch of the Chinese Medical Association (CMA), in conjunction with organizations such as the Liver Cancer Professional Committee of the China Anti-Cancer Association, the Ultrasonography Branch of the CMA, the Surgeon Branch of the Chinese Medical Doctor Association, and the Chinese College of Interventionalists, were entrusted to update the guideline by forming a nationwide committee of multidisciplinary experts in the field of liver cancer. The new guideline aims to encourage the implementation of evidence-based practice and improve the national average 5-year survival rate for patients with liver cancer, as proposed in the "Health China 2030 Blueprint."

Methodology

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is the most widely used system for evaluating evidence and grading recommendations [5]. The GRADE system consists of two parts. The first part is the evaluation of evidence, during which the quality of evidence is classified into one of four levels: high, moderate, low, and very low, based on risk of bias, inconsistency, indirectness, imprecision, and publication [6]. The second part is the grading of recommendations; based on the GRADE system, the pros and cons of medical interventions, quality of evidence, values and preferences, and resource consumption are considered in order to classify recommendations as strong or weak (conditional) [7]. For any given medical intervention, a greater difference between the advantages and disadvantages, a higher quality of evidence, clearer and more convergent values and preferences, and a lower cost and resource consumption correspond with a strong recommendation. Otherwise, a weak recommendation (conditional recommendation) is assigned. The assessment of the evidence underlying the evidence-based recommendations in this guideline was based on the GRADE methodology, and the *Oxford Centre for Evidence-Based Medicine Levels of Evidence* (2011 Edition) (*OCEBM Levels of Evidence*) was used as a supporting tool for the specific grading of evidence. The transition from evidence to recommendations was mainly based on GRADE; the grading scheme employed in the American Society of Clinical Oncology (ASCO) guidelines methodology [8] was also used to modify the grading of recommendations accordingly (Table 1).

The strength of recommendations was categorized into three levels: strong, moderate, and weak. A strong recommendation reflects a high level of confidence from the expert group regarding a specific clinical practice and that most, if not all, target users should adopt the recommendation. A moderate recommendation reflects a moderate level of confidence from the expert group in a specific clinical practice, and while most target users should adopt the recommendation, consideration should be given to the joint decision made by the physician and the patient during clinical practice. A weak recommendation reflects only some confidence from the expert group in a specific clinical practice; the

recommendation should be conditionally applied to the target group with an emphasis on physician-patient joint decision-making.

Screening and Diagnosis

Screening and Monitoring Individuals at High Risk of HCC

Screening and monitoring individuals at high risk of HCC facilitates its early detection, diagnosis, and treatment and is key to improving patients' outcomes [9]. The rapid and convenient identification of patient groups at high risk of HCC is a prerequisite for large-scale screening for HCC, while stratified assessment of HCC risks in a population forms the basis for the development of HCC screening strategies. In China, populations at high risk of HCC include those with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection, non-alcoholic steatohepatitis, cirrhosis from other causes, those who consume excessive amounts of alcohol, and/or those with a family history of liver cancer, especially males >40 years of age. Although current anti-HBV and anti-HCV therapies may significantly reduce the risk of HCC, the development of HCC is not fully prevented [10]. The age-Male-AlBi-Platelets score (aMAP score), a risk assessment model developed by Chinese scholars that is indicated for a variety of chronic liver diseases and various types of HCC, can be used to categorize a population with liver diseases into risk groups for HCC: low (score 0–50), intermediate (score 50–60), and high (score 60–100) risk, with annual HCC incidence rates of 0–0.2%, 0.4–1%, and 1.6–4%, respectively [11] (evidence level 2, recommendation B). Screening for HCC may be performed using ultrasonography (US) and serum alpha-fetoprotein (AFP) and is recommended at least every 6 months in high-risk populations [9] (evidence level 2, recommendation A). Screening should aim to include all individuals in high-risk groups using a novel model of integrated screening by the community and hospital [12].

Imaging Examinations for HCC

Because different imaging methods have unique advantages and disadvantages, emphasis should be placed on their integrated application to allow a comprehensive assessment.

Ultrasonography

US is the most common method to obtain images of the liver in clinical practice, as it is easy to undertake, produces real-time results and is noninvasive and radiation-free. Routine gray-scale US can detect early-stage focal liver lesions with a high degree of sensitivity, identify lesions as cystic or solid, and provide a preliminary determination of if lesions are benign or malignant. It is also able to thoroughly screen for metastases in the liver or abdominal cavity, and identify invasion of intrahepatic vessels and bile ducts. Color Doppler flow US may be used to visualize the blood supply within a lesion, to assist in determining if it is benign or malignant, and to indicate the adjacent relationship with important intrahepatic vessels and the invasion of intrahepatic vessels. Moreover, it can be used to provide a preliminary assessment of the expected efficacy of locoregional treatment for HCC. Contrast-enhanced US can dynamically visualize real-time changes in vascular perfusion in liver tumors and identify liver tumors of different natures. The use of contrast-enhanced US intraoperatively may identify small occult lesions, guide locoregional treatment in real time, and predict the postoperative efficacy/outcomes of locoregional treatment of HCC [13–16] (evidence level 3, recommendation A). US combined with imaging navigation technology offers a tool for the precise localization and ablation of HCC, especially occult HCC that cannot be visualized by conventional US [13, 17] (evidence level 4, recommendation B). US elastography allows the quantitative measurements of the stiffness of liver tumors and the extent of fibrosis/sclerosis of the surrounding liver parenchyma to provide valuable information for formulating treatment plans for HCC [18] (evidence level 3, recommendation B). The integration of multimodal US techniques plays an important role in the accurate preoperative diagnosis, intraoperative localization, and postoperative assessment of HCC.

Computed Tomography and Magnetic Resonance Imaging

Dynamic contrast-enhanced computed tomography (CT) and multiparametric magnetic resonance imaging (mpMRI) scans are the imaging methods of choice for the diagnosis of HCC in those with abnormal US and/or serum AFP levels during screening. Dynamic contrast-enhanced CT/MRI (gadopentetate dimeglumine/gadobenate dimeglumine) triple-phase scans include the late arterial phase (usually scanned around 35 s after contrast injection: the portal vein begins to enhance), the portal venous phase (usually scanned 60–90 s after contrast injection: the portal vein is fully enhanced; contrast filling is visible in the hepatic veins; parenchyma usually reaches peak enhancement), and the delayed phase (usually scanned 3 min after contrast injection: both the portal vein and hepatic vein are enhanced but the enhancement is

less intense than the portal venous phase; liver parenchyma is enhanced but the enhancement is less intense than the portal venous phase). Quadruple-phase contrast-enhanced MRI scans with hepatocyte-specific contrast agent (gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid [Gd-EOB-DTPA]) include the late arterial phase (as stated previously), the portal venous phase (as stated previously), the transitional phase (usually scanned 2–5 min after Gd-EOB-DTPA injection: same signal intensity for the hepatic vessels and hepatic parenchyma; hepatic enhancement is the synergistic result of intracellular and extracellular activities), and the hepatobiliary phase (usually scanned 20 min after Gd-EOB-DTPA injection: parenchymal signal is more intense than the hepatic vessels; contrast is excreted via the biliary system).

In addition to being commonly used in the clinical diagnosis and staging of HCC, CT scans and dynamic contrast-enhanced scans of the liver are also used to evaluate responses to the locoregional treatment of HCC, especially observing the deposition of iodine oil following transcatheter arterial chemoembolization (TACE). Preoperative CT-based histology techniques can also be used to predict the efficacy of the first TACE treatment [19]. Postprocessing techniques for CT may be used to perform three-dimensional (3D) vascular reconstruction, measure liver volume and tumor volume, evaluate metastasis to other organs such as the lung and bone, and have been widely used in clinical practice.

The advantages of mpMRI of the liver are that it is radiation-free and has a high tissue resolution. Moreover, mpMRI is multidirectional and allows integrated imaging techniques, such as multiparametric imaging that combines morphologic images with functional images (including diffusion-weighted imaging, etc.), making it a preferred imaging technique for the clinical detection, diagnosis, and staging of HCC and to evaluate responses. mpMRI is more accurate for detecting and diagnosing HCC ≤2.0 cm in size than dynamic contrast-enhanced CT [20, 21] (evidence level 1, recommendation A). mpMRI is superior to dynamic contrast-enhanced CT to evaluate if HCC has invaded the portal vein and the main trunk and branches of the hepatic vein and to identify abdominal or retroperitoneal lymph node metastasis. The modified response evaluation criteria in solid tumor (mRECIST) in combination with T2-weighted imaging and diffusion-weighted imaging are recommended to evaluate responses to locoregional treatment of HCC using mpMRI scans.

Diagnosing HCC with imaging is primarily based on the "wash-in and wash-out" enhancement pattern of dynamic contrast-enhanced scans [22–24] (evidence level 1, recommendation A). On dynamic contrast-enhanced CT and mpMRI scans, liver tumors exhibit significant homogeneous or non-homogeneous enhancement in the arterial phase (mainly in the late arterial phase: "wash in"), with hypointensity in liver tumors compared with the parenchyma during the portal venous and/or delayed phase ("wash out"). Therefore, "wash in" refers to non-circular enhancement, while "wash out" refers to the de-enhancement of the peripheral rim.

Gd-EOB-DTPA-enhanced MRI shows significant enhancement of liver tumors in the arterial phase, with hypointensity compared with the parenchyma during the portal venous phase, and often significant hypointensity in the hepatobiliary phase. When using Gd-EOB-DTPA, the "wash-out" sign may only be observed in the portal venous phase, and the "wash-out" signs in the transitional and hepatobiliary phases may be used as auxiliary signs of malignancy. Approximately 5–12% of well-differentiated small HCCs (sHCCs) exhibit slight hyperintensity in the hepatobiliary phase associated with contrast agent uptake [25].

Diagnosing HCC using contrast-enhanced MRI, especially HCC ≤2.0 cm in diameter, requires confirmation with other characteristic imaging findings (e.g., capsule-like enhancement, moderate hyperintensity on T2-weighted imaging, and diffusion restriction) and suprathreshold growth (≥50% increase in the maximum diameter of the lesion within 6 months) [26] (evidence level 3, recommendation A). Capsule-like enhancement is defined as smooth, homogeneous, well-defined borders that mostly or completely encircle the lesion, especially during the portal venous, delayed, or transitional phases in which circumferential enhancement is observed.

Gd-EOB-DTPA-enhanced MRI scans, including the hypointensity in the hepatobiliary phase, enhancement in the arterial phase, and diffusion restriction, may significantly improve the diagnostic sensitivity for HCC <1.0 cm in diameter [27–31] (evidence level 2, recommendation B) and are highly recommended, especially for patients with cirrhosis, as they also help identify precancerous lesions such as high-grade dysplastic nodules (HGDN) [32] (evidence level 3, recommendation B).

Fusion models based on mining CT and/or MRI data for HCC may improve clinical decision-making, including the selection of treatment regimens and evaluating and predicting response [33]. Imaging signs to predict microvascular invasion (MVI) preoperatively in HCC are highly specific but relatively insensitive. Nomograms and radiomic models are possible breakthrough points for the preoperative prediction of MVI [34–36] (evidence level 3, recommendation B).

Digital Subtraction Angiography

Digital subtraction angiography (DSA) is a minimally invasive procedure performed through selective or ultra-selective cannulation of the hepatic artery. This technique is most commonly used to deliver hepatic locoregional therapy or to treat acute bleeding from tumor ruptures. DSA not only visualizes liver tumor blood vessels and liver tumor staining but also allows the number, size, and blood supply of liver tumors to be visualized.

Nuclear Medicine Imaging

Positron emission tomography-CT (PET-CT) and whole-body ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT have the following advantages: tumor staging – one procedure enables the overall evaluation of the presence of lymph node metastasis and distal organ metastasis [37, 38] (evidence level 1, recommendation A); restaging – the PET/CT functional image can accurately visualize tumor recurrence or metastases that occur following the changes of anatomic structures or at sites with a complicated anatomic structure, since it is not affected by anatomic structures [39] (evidence level 2, recommendation B); more sensitive and accurate evaluation of the efficacy of targeted drugs that inhibit tumor activity [40, 41] (evidence level 2, recommendation A); guiding biologic target volume delineation for radiation therapy and determination of puncture biopsy sites [39]; and evaluation of the extent of malignancy and prognosis [42–45] (evidence level 2, recommendation B). PET-CT has limited sensitivity and specificity to diagnose HCC and may be used as an adjunct or supplement to other imaging examinations, as it has advantages in the staging, restaging, and efficacy evaluation of HCC. Carbon-11 acetate (^{11}C-acetate) or choline PET (^{11}C-choline) provides improved sensitivity for the diagnosis of well-differentiated HCC and is complementary to ^{18}F-FDG PET/CT [46, 47].

Single-photon emission computed tomography-CT (SPECT-CT) has gradually become a mainstream device for nuclear medicine single-photon imaging in place of SPECT. The lesions detected by whole-body planar imaging can be selected for regional SPECT-CT fusion imaging, significantly improving the accuracy of diagnosis by simultaneously obtaining the SPECT and diagnostic CT images of the lesion site [48] (evidence level 3, recommendation A). A single PET-MRI image provides both anatomic and functional information about the disease [49] (evidence level 4, recommendation B).

Hematological Molecular Markers for HCC

Serum AFP is a commonly used biomarker for the diagnosis of HCC and for monitoring treatment response. Serum AFP ≥400 μg/L is highly suggestive of HCC after excluding pregnancy, chronic or active liver diseases, embryonal tumors of the gonads, and gastrointestinal tumors. For patients with mildly increased serum AFP, imaging examinations should be combined and dynamic monitoring should be performed. Cross comparison with changes in liver function should also be performed to facilitate diagnosis.

Abnormal prothrombin, protein induced by vitamin K absence/antagonist-II (PIVKA II), des-gamma carboxyprothrombin (DCP), plasma microRNA (miRNA) [50], and serum lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) may also be used as early diagnostic biomarkers for HCC, especially for individuals with negative serum AFP (evidence level 1, recommendation A). The sensitivity and specificity of the GALAD model, based on sex, age, AFP, PIVKA II, and AFP-L3, were 85.6% and 93.3%, respectively, for diagnosing early-stage HCC, which facilitates the early diagnosis of AFP-negative HCC [51] (evidence level 1, recommendation A). Optimized GALAD-like models based on data from large samples of the Chinese population have been used for the early diagnosis of HCC. The sensitivity and specificity of seven-miRNA-based detection kit for the diagnosis of HCC was 86.1% and 76.8%, while those for AFP-negative HCC was 77.7% and 84.5%, respectively [50] (evidence level 1, recommendation A).

Liver Biopsy for HCC

Diagnostic liver biopsy is usually not necessary in patients with space-occupying lesions that have typical imaging characteristics and are evaluable using the clinical criteria for the diagnosis of HCC [23, 52–54] (evidence level 1, recommendation A), especially for patients with HCC who have surgical indications. Therefore, for patients with resectable HCC or who are scheduled for liver transplantation (LT), preoperative liver biopsy is not recommended, in order to reduce the risk of tumor rupture, hemorrhage, and dissemination. For space-occupying lesions without typical imaging characteristics, liver biopsy can provide a definitive pathologic diagnosis. Liver biopsy can also be used to determine the nature of the lesion and the molecular classification of HCC and can provide valuable information on the cause of liver disease to guide treatment, determine prognosis, and conduct research. Therefore, the need for liver lesion biopsy should be assessed based on the patient benefit, potential risks, and the operating experience of the physician.

Liver biopsy should be performed under the guidance of US or CT with a 16- or 18-gauge needle. The major risks of liver biopsy are bleeding and needle tract implantation. Platelet count and coagulation should be assessed

preoperatively, and liver biopsy should be avoided in patients with hemorrhagic tendencies. Normal liver tissues should be passed by when selecting the puncture tract to avoid direct puncture of nodules located on the surface of the liver. The puncture site should be chosen within and adjacent to the tumor where imaging shows tumor activity, and the integrity of the retrieved material should be observed visually to improve diagnostic accuracy.

Pathologic diagnosis using liver lesion biopsy is associated with a certain false-negative rate due to multiple factors including the size of lesion, especially for lesions with a diameter ≤2 cm. Therefore, a negative result from liver biopsy cannot exclude the possibility of HCC. Observation and regular follow-up are required. Repeat liver biopsy and/or close follow-up is recommended for patients with limited biopsy specimens and negative pathological result but who are clinically highly suspected of having HCC.

Summary

1. US combined with serum AFP testing is used for early screening for HCC. Monitoring at least every 6 months is recommended for individuals in high-risk populations.
2. Dynamic contrast-enhanced CT and mpMRI scans are the first-choice imaging methods for the diagnosis of HCC in patients with abnormal US and/or serum AFP levels during screening.
3. The characteristic "wash-in and wash-out" enhancement pattern is the main basis for the imaging diagnosis of HCC.
4. The preferred imaging technique for the detection, diagnosis, staging, and evaluation of treatment response for HCC is mpMRI.
5. PET/CT facilitates HCC staging and the evaluation of response to medical interventions.
6. Serum AFP is a commonly used and important biomarker for diagnosis of HCC and monitoring treatment response. In the serum AFP-negative population, PIVKA II and miRNA test kit, as well as AFP-L3 and GALAD-like models, may be useful for the early diagnosis of HCC.
7. Liver biopsy for diagnostic purposes is usually not necessary in patients with space-occupying lesions that have typical imaging characteristics and those who have a clinical diagnosis of HCC.

Pathologic Diagnosis of HCC

Pathologic Diagnostic Terminology in HCC

Primary liver cancer: malignant tumors originating from hepatocytes and the epithelial cells of the intrahepatic bile duct, mainly including HCC, ICC, and cHCC-CCA. HCC is a malignant neoplasm occurring in hepatocytes. The use of the pathologic diagnosis terms "hepatocellular liver cancer" or "hepatocellular-type liver cancer" is not recommended.

ICC is a malignancy of the epithelial cells covering the intrahepatic bile duct branches; adenocarcinoma is the most common form. ICC may be histologically divided into two subtypes. The large intrahepatic ductal type of ICC originates in the large bile ducts above the bile canaliculus of the liver lobules and the adjacent portal area, with large and irregular openings of the glandular ducts. The small intrahepatic ductal type of ICC originates from the small bile ducts or fine bile ducts below the bile canaliculus of the liver lobules, with small and regular openings of the glandular ducts, or appearing as thin solid cords with closed lumen. Studies have shown that the biologic behaviors and genotypic characteristics of these two subtypes of ICC are different, and the clinical prognosis of patients with the small bile ductal type is better than that of those with large ductal type.

The clinical and pathologic implications of the molecular typing of HCC and ICC are still being investigated and demonstrated. However, studies in recent years have shown that Epstein-Barr virus (EBV)-associated ICC has unique characteristics in terms of clinical pathology, immune microenvironment, and molecular features, which are associated with a relatively good prognosis and can obtain a particularly strong benefit from immune checkpoint therapy. Because of these characteristics, EBV-associated ICC is expected to become a novel subtype [55]. A high expression of triose-phosphate isomerase 1 in ICC tissues is a useful indicator for assessing the risk of postoperative recurrence [56]. The 2019 edition of the *World Health Organization* (WHO) *Classification of Tumours of the Digestive System* no longer recommends the use of the terms "cholangiocellular" and "cholangiolocellular carcinoma" for the pathologic diagnosis of ICC [57]. The requirements for macroscopic sampling and microscopic examination of ICC are mainly based on HCC.

cHCC-CCA refers to the presence of both HCC and ICC in the same tumor node [58]. However, there are no international standards on the pathologic diagnostic criteria for the ratio of HCC and ICC tumor components in cHCC-CCA. Therefore, it is recommended that the ratio of the two tumor components be labeled in the pathologic diagnosis of cHCC-CCA for the clinical assessment of the biologic characteristics of the tumor and the formulation of treatment plans.

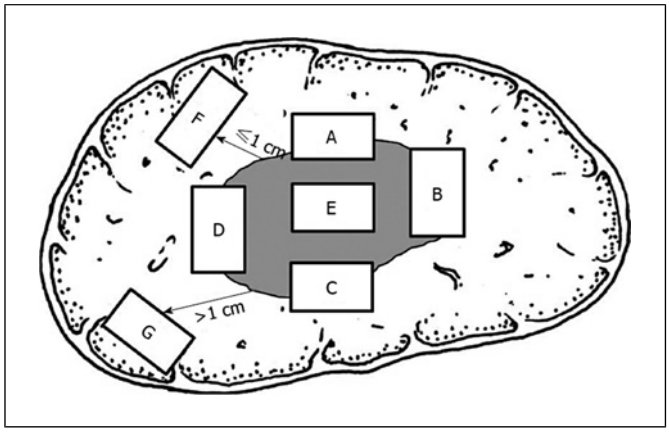

Fig. 1. Schematic diagram of the recommended baseline specimen sampling protocol for liver tumors. A, B, C, and D indicators denote the 12, 3, 6, and 9 o'clock positions, respectively, along the boundary between cancer and adjacent non-neoplastic liver tissue; E: tumor area; F: proximal non-neoplastic adjacent liver tissue; G: distal non-neoplastic adjacent liver tissue.

Guidelines for the Pathologic Diagnosis of HCC

The guidelines for pathologic diagnosis of HCC include specimen handling, specimen sampling, histologic examination, and the pathology report [58, 59].

Key Points for Specimen Processing

1. The surgeon should indicate the site, type, and number of submitted specimens on the pathology examination application form. The surgical margin and important lesions may be stained with dyes or labeled with sutures.
2. Where possible, the intact tumor specimen should be delivered to the pathologist for dissection and fixation within 30 min after removal. When collecting the specimens, the staff at the tissue bank should operate under the guidance of the pathology department to ensure the accuracy of sampling to first meet the needs of pathological diagnosis.
3. Tissue samples should be fixed in 4% neutral formaldehyde solution (10% neutral formalin solution) for 12–24 h.

Key Points for Specimen Retrieval

The area adjacent to HCC is the representative area for the biologic features of tumor. To this end, the "7-point" sampling method (Fig. 1) should be employed, that is, specimens are collected in a ratio of 1:1 in the 12, 3, 6, and 9 o'clock positions along the boundary between neoplastic and adjacent non-neoplastic liver tissues. At least one tissue sample should be collected from inside the tumor. One sample should also be collected from the liver tissues in the non-neoplastic adjacent regions both ≤1 cm (proximal) and >1 cm (distal) from the tumor boundary. For solitary tumors with a diameter ≤3 cm, the whole tumor should be sampled for examination. In addition, the actual site and number of specimens to be collected must also be considered in light of the diameter and number of tumors, etc. [60, 61] (evidence level 2, recommendation A).

Key Points of Histologic Examination of HCC

1. Macroscopic description of specimens [62]: all surgical samples submitted should be thoroughly inspected, and the following details should be specifically described: size, number, color, and texture of tumors; their relationship with blood vessels and bile ducts; encapsulation status; lesions in the non-neoplastic liver tissue; type of liver cirrhosis; distance between tumor and incisal margin; and status of the incisal margin.
2. Microscopic observations and descriptions [62]: all specimens collected should be thoroughly observed, and the pathologic diagnosis may be based on the 2019 *WHO diagnostic criteria for HCC* [58]. The following information should be specifically described:
   - The degree of differentiation of tumor cells may be described according to the internationally used Edmondson-Steiner grading system or the high, moderate, and low classification recommended by the WHO.
   - The histological morphology of HCC is usually divided into microtrabecular, macrotrabecular, pseudoglandular, and compact types.
   - Special subtypes of HCC include fibrolamellar, cirrhotic, clear cell, fatty change, macrotrabecular-massive, chromophobe cell, neutrophil-rich, lymphocyte-rich, and undifferentiated types.
   - Degree and range of tumor necrosis, lymphocyte infiltration, and stromal fibrosis.
   - The growth pattern of HCC including perineoplastic infiltration, capsule invasion or breakthrough, MVI, and the presence of satellite nodules.
   - Evaluation of chronic liver diseases: HCC is often accompanied by varying degrees of chronic viral hepatitis or liver cirrhosis. The use of the Scheuer scoring system, which is more convenient, or the Chinese Criteria for Histologic Grading and Staging of Chronic Viral Hepatitis is recommended [63–65].
3. Diagnosis of MVI: MVI refers to the presence of clusters of cancer cells in the lumen of blood vessels with endothelial cell linings under the microscope [66],

which is most commonly seen in the invasion of the branches of the portal vein in HCC (including the intracapsular blood vessels). Invasion to the lymphatic vessels is observed in ICC. The pathologic grading of MVI includes M0: no MVI detected; M1 (low-risk group): ≤5 MVIs, which occur in proximal non-neoplastic adjacent liver tissues; and M2 (high-risk group): >5 MVIs in the proximal or MVIs occurring in distal non-neoplastic adjacent liver tissues [67]. MVI and satellite lesions may be considered different developmental stages during the intrahepatic metastasis of HCC. Satellite lesions in non-neoplastic adjacent liver tissues should be included in the MVI grading in cases where it is difficult to distinguish satellite lesions from MVI. MVI has a great impact on the evaluation of recurrence risk and on the selection of appropriate treatment strategy and should therefore be used as an indicator for routine histopathologic examination [58, 59, 68–70] (evidence level 2, recommendation A).

Immunohistochemical Examination

The main purposes of immunohistochemical examination for HCC are to differentiate between benign and malignant HCC; between HCC, ICC, and other specific types of liver tumors; and between primary and metastatic HCC. Due to the high heterogeneity of histologic types of HCC, there are deficiencies in the diagnostic specificity and sensitivity of HCC cellular protein markers. Appropriate combinations of examinations and assessment are often required; the concomitant use of biomarkers of other systemic tumors may also be required.

HCC

A positive result for the following biomarkers on hepatocytes may suggest tumors of hepatocyte origin, but the results cannot be used to distinguish between benign and malignant HCC:

- Arginase-1: hepatocyte plasma/nucleus staining.
- Hepatocyte antigen: hepatocyte plasma staining.
- Specific staining antibodies for bile canaliculus of the hepatocyte membrane: stains for antibodies such as CD10, polyclonal carcinoembryonic antigen, and bile salt export pump protein may appear specifically on the bile canaliculus of the hepatocyte membrane to help confirm HCC.

The following biomarkers may assist in the differentiation of benign and malignant HCC:

- Phosphatidylinositol-3: plasma and cell membrane staining of HCC cells.
- CD34: although the immunohistochemical staining of CD34 does not directly label liver parenchymal cells, it can indicate microvascular density and distribution patterns in different types of liver tumors. For example, CD34 staining shows a diffuse pattern in HCC, a sparse pattern in cholangiocarcinoma, a patchy pattern in hepatocellular adenoma, and a strip pattern in hepatic focal nodular hyperplasia, etc. The histologic pattern of the tumor may be used to facilitate the differentiation and diagnosis of benign and malignant HCC.
- Heat shock protein 70: staining of cell plasma or nuclei of HCC.
- Glutamine synthetase: a strong cytoplasmic positivity in a diffuse pattern is mostly observed for HCC. Some hepatocellular adenomas, especially β-catenin-mutated hepatocellular adenomas, may also exhibit diffuse positivity. Glutamine synthetase staining in HGDN often exhibits moderate focal staining with a positive cell count <50%. A characteristic irregular diagrammatic staining is observed in hepatic focal nodular hyperplasia. In normal liver tissues, only hepatocytes around the central vein are stained, and these features may help in the differential diagnosis.

ICC

- Epithelial cell surface glycoprotein (MOC31): membrane staining of cholangiocarcinoma cells.
- Cytokeratin 7 (CK7)/CK19: cytoplasmic staining of cholangiocarcinoma cells.
- Mucin-1 (muc-1): membrane staining of cholangiocarcinoma cells.
- Although positivity for the above biomarkers may suggest a tumor originating from the biliary epithelium, positive expressions may also be observed in the non-neoplastic biliary epithelium, which should be carefully differentiated.

cHCC-CCA

Both HCC and ICC components express the above-mentioned biomarkers of the respective tumors. In addition, positive expression of biomarkers such as CD56, CD117, and epithelial cell adhesion molecules (EpCAM) may suggest that the tumor is characterized by stem cell differentiation and is more aggressive.

Specimen Collection and Pathologic Evaluation of Resected HCC Specimens after Conversion/ Neoadjuvant Therapy

The following procedures should be followed for handling resected HCC specimens with the information whether after conversion or neoadjuvant therapy. For small HCC (≤3 cm), the whole tumor should be collected. For tumors >3 cm, sections should be cut at 0.5–1 cm

interval along the side with the longest diameter (the original location of the tumor before treatment), and the most representative section with necrosis and residual tumor should be selected for sampling. The tumor bed and surrounding liver tissue should be obtained for cross-referencing. Macroscopic photography of the specimen may also be obtained as reference for histologic observations.

Microscopic assessment is to determine the proportions of the three components of the tumor bed in the resected specimen of HCC, i.e., necrotic tumor cells, surviving tumor cells, and tumor stroma (fibrous tissue and inflammation). The sum of these three areas of the tumor bed is equal to 100%. The number of samples obtained should be indicated in the pathology report. The total percentage of residual tumor should be determined by taking the mean value of the percentages of the three components above in each section.

Assessment of pathologic complete response (pCR) and major pathologic response (MPR) may serve as important pathologic indicators to evaluate the efficacy of preoperative treatment and inform the optimal timing of surgery. pCR is defined as the absence of surviving tumor cells after complete histologic assessment of the tumor bed specimen after preoperative treatment. MPR is defined as a reduction in surviving tumor cells after preoperative treatment to below the threshold that can affect the clinical prognosis. MPR is often defined in lung cancer studies as a reduction of residual tumor cells in the tumor bed to ≤10% [71], which is also consistent with studies showing correlation between the degree of tumor necrosis and prognosis after preoperative treatment with TACE for HCC [72]. The specific MPR threshold requires confirmation by further clinical studies. Expansion of the area of tumor specimen collection is recommended for those with a primary MPR, for further confirmation.

Reference can be made to other tumor types with more relevant studies [73] for the histologic assessment methods to determine the degree of necrosis in HCC specimens after immune checkpoint inhibitor therapy. An understanding of the histologic characteristics of HCC should be improved during clinical practice. Meanwhile, attention should be paid to the presence of immune-related liver injury in non-neoplastic peri-cancerous liver tissue, including hepatocellular injury, intralobular hepatitis, and cholangitis.

Pathologic Diagnosis Report of HCC

A typical pathologic report should include a gross description of specimens, microscopic descriptions, the results of immunohistochemical staining examination, and the final pathologic diagnosis, with notes and recommendations to physicians if necessary. In addition, the results of molecular examination related to the clonal origin of HCC, drug target testing, biologic behavior evaluation, and prognosis assessments may be attached for clinical reference.

Summary

1. Standardized handling and timely delivery of biopsy/resected tissue samples are of great significance for tissue preservation and correct pathologic diagnosis.
2. The "7-point" sampling method should be followed when collecting HCC specimens to facilitate obtaining a representative pathobiological indication of HCC.
3. The contents of pathologic diagnosis report for HCC should be standardized and comprehensive. It should include the pathologic classification of MVI, an important factor affecting the prognosis in HCC.

Clinical Diagnostic Criteria and Diagnostic Roadmap for HCC

A clinical diagnosis of HCC should be established in accordance with the steps shown in the following pathway, taking into account high-risk factors for HCC, imaging characteristics, and serological molecular markers (Fig. 2).

1. Screening using US and serum AFP testing should be performed at least every 6 months in patients with HBV/HCV infection or liver cirrhosis of any cause. For patients with nodules ≤2 cm in diameter, a clinical diagnosis of HCC may be established by observing the "wash-in and wash-out" enhancement pattern on contrast-enhanced imaging (enhancement in the arterial phase and reduced enhancement of intrahepatic lesions compared with healthy liver parenchyma in the portal venous and/or delayed phase). This pattern should be observed on at least two of the four following imaging examinations: mpMRI, dynamic contrast-enhanced CT, contrast-enhanced US, and contrast-enhanced MRI using the hepatocyte-specific contrast agent Gd-EOB-DTPA. For intrahepatic nodules >2 cm in diameter, a clinical diagnosis of HCC may be established when the "wash-in and wash-out" enhancement pattern is observed on any of these four imaging examinations.
2. For patients with HBV/HCV infection or liver cirrhosis of any cause and intrahepatic nodules ≤2 cm in diameter observed during follow-up, a diagnosis can be established by liver puncture biopsy or 2- to 3-

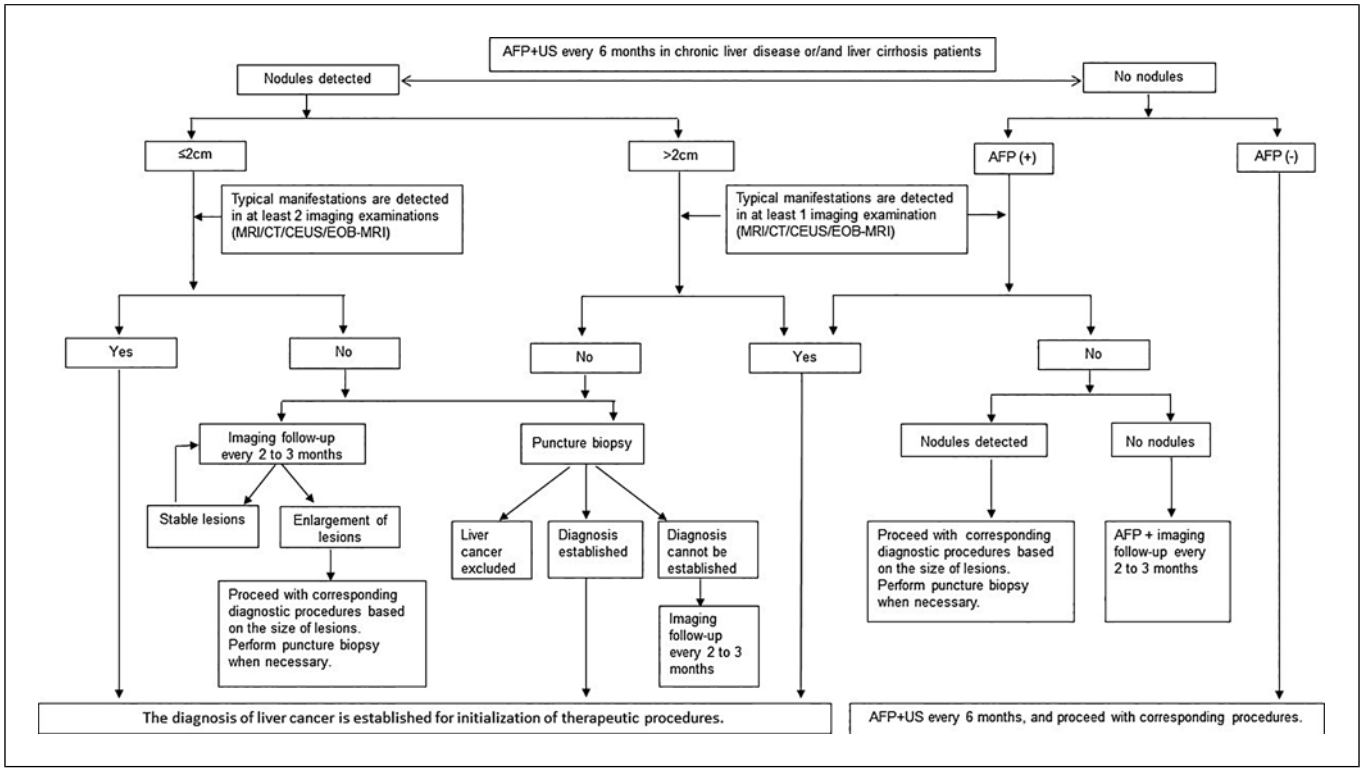

Fig. 2. Pathway for the diagnosis of HCC. Typical presentation: significant enhancement of the lesion in the arterial phase (late major arterial phase), with decreased enhancement in the portal venous and/or delayed phases, in a "wash-in, wash-out" pattern. Atypical presentation: lack of lesion enhancement in the arterial phase or no or insignificant decrease in the enhancement during the portal venous and delayed phases, or even a slight increase in enhancement, etc. US, ultrasonography; MRI, multiparametric MRI; CT, dynamic contrast-enhanced CT scan; CEUS, contrast-enhanced ultrasonography, which uses ultrasound contrast to visualize the real-time blood perfusion in normal and diseased tissues. EOB-MRI: MRI scan enhanced with hepatocyte-specific contrast agent gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA). AFP (+): serum AFP test exceeding normal value.

monthly imaging examinations in combination with measuring serum AFP levels, if the typical enhancement characteristics of HCC are noted in none or one of the four imaging examinations mentioned previously. For patients with intrahepatic nodules >2 cm in diameter, a diagnosis can be made by liver lesion puncture biopsy or 2- to 3-monthly imaging examinations in combination with serum AFP testing if the typical enhancement characteristics of HCC are not observed in any of the four imaging examinations mentioned previously.

3. For patients with HBV/HCV infection or liver cirrhosis of all causes and increased serum AFP levels, particularly continuously increased AFP, imaging examinations should be performed. A diagnosis of HCC can be established if the typical enhancement characteristics of HCC are noted in one of the four imaging examinations above. Serum AFP levels should be closely monitored, and 2- to 3-monthly imaging examinations should be performed after the exclusion of pregnancy, chronic or active liver disease, embryonic reproductive tumors, and gastrointestinal cancer, if no intrahepatic nodules are identified.

Staging

The staging of HCC is crucial to assess prognosis and select the appropriate treatment. International options for staging include the Barcelona Clinic Liver Cancer (BCLC), TNM, Japan Society of Heptatology (JSH), and the Asia Pacific Association for the Study of the Liver (APASL) staging systems. Based on the Chinese domestic context and clinical practice, the China liver cancer (CNLC) staging system considers the patient's performance status (PS), as well as the status of liver tumors and liver function. The CNLC staging system is divided into stages Ia, Ib, IIa, IIb, IIIa, IIIb, and IV, and presented in Figure 3.

- CNLC stage Ia: PS score 0–2, Child-Pugh class A/B, a solitary tumor ≤5 cm in diameter, and absence of vascular invasion or extrahepatic metastasis on imaging examinations.
- CNLC stage Ib: PS score 0–2, Child-Pugh class A/B, a solitary tumor >5 cm in diameter, or 2–3 tumors with a maximum diameter ≤3 cm, and absence of vascular invasion or extrahepatic metastasis on imaging examinations.
- CNLC stage IIa: PS score 0–2, Child-Pugh class A/B, 2–3 tumors with a maximum diameter >3 cm, and absence of vascular invasion or extrahepatic metastasis on imaging examinations.
- CNLC stage IIb: PS score 0–2, Child-Pugh class A/B, ≥4 tumors irrespective of diameter, and absence of vascular invasion or extrahepatic metastasis on imaging examinations.
- CNLC stage IIIa: PS score 0–2, Child-Pugh class A/B, presence of vascular invasion irrespective of tumor status, but absence of extrahepatic metastasis on imaging examinations.
- CNLC stage IIIb: PS score 0–2, Child-Pugh class A/B, and the presence of extrahepatic metastasis on imaging examinations irrespective of tumor status and vascular invasion.
- CNLC stage IV: PS score 3–4 and Child-Pugh class C, regardless of tumor status, vascular invasion, and extrahepatic metastasis on imaging examinations.

Treatment

The treatment of HCC is characterized by multidisciplinary participation and the coexistence of multiple therapeutic approaches, which include hepatectomy, LT, ablation therapy, TACE, radiation therapy, and systemic antitumor therapy. Treatment efficacy may be maximized by choosing the appropriate treatment method for patients based on their stage of HCC. Treatment selection should be supported by high-level evidence. Currently, standardized combination therapy is considered the optimal long-term HCC treatment. However, there is a contradiction between the current system, in which diagnosis and treatment are performed by different departments, and standardized combination therapy. Therefore, emphasis must be placed on the multidisciplinary team (MDT) in the diagnosis and treatment of HCC, particularly for complicated cases. This will help avoid the limitations of a single department in the treatment of HCC, promote interdisciplinary communication, and ultimately improve the overall outcomes of treatment. It is recommended that MDT management focus on core indicators of quality control for HCC treatment, as proposed by the National Health Commission, while also considering factors such as regional/local economic status and differences in the quality of, and access to, care.

Surgical Treatment

Surgical treatment provides the best opportunity for long-term survival in patients with HCC and mainly comprises hepatectomy and LT.

Basic Principles for Hepatectomy

1. Thoroughness: complete removal of tumor tissue, ensuring that the surgical margin is free of residual tumor.
2. Safety: preservation of a sufficient volume of functional liver tissue (with good blood supply as well as blood and bile outflow) to compensate for reduced liver function and minimize surgical complications and postoperative mortality.

Preoperative Evaluation of Patients' General Condition and Liver Function Reserve

Preoperative evaluation of patients' general condition and liver function reserve (LFR) is mandatory. The Eastern Cooperative Oncology Group (ECOG) PS scale is commonly used to evaluate a patient's general condition. The Child-Pugh Score, indocyanine green (ICG) clearance test, or transient elastography is used to measure liver stiffness [74–79] to evaluate LFR. Accurate evaluation of the degree of portal hypertension is helpful to screen patients suitable for surgical resection, as studies have suggested that selected patients with HCC and portal hypertension can still undergo hepatectomy, with long-term postoperative survival superior to that of those receiving other treatments [80–83]. If the preservation of a low volume of liver tissue is expected, it can be determined by CT, MRI, or 3D reconstruction of the liver to measure the remnant liver volume and calculate what percentage of the standardized liver volume and the remnant liver volume would be [75]. A Child-Pugh class A and ICG retention test (ICG-R15) score <30% are generally considered prerequisites for successful surgical resection. The remnant liver volume that accounts for >40% of the standardized liver volume (for patients with chronic diseases, parenchymal liver damage, or liver cirrhosis) or >30% (for patients without liver fibrosis and liver cirrhosis) is another prerequisite for surgical resection. A greater remnant liver volume should be preserved in patients with hepatic impairment.

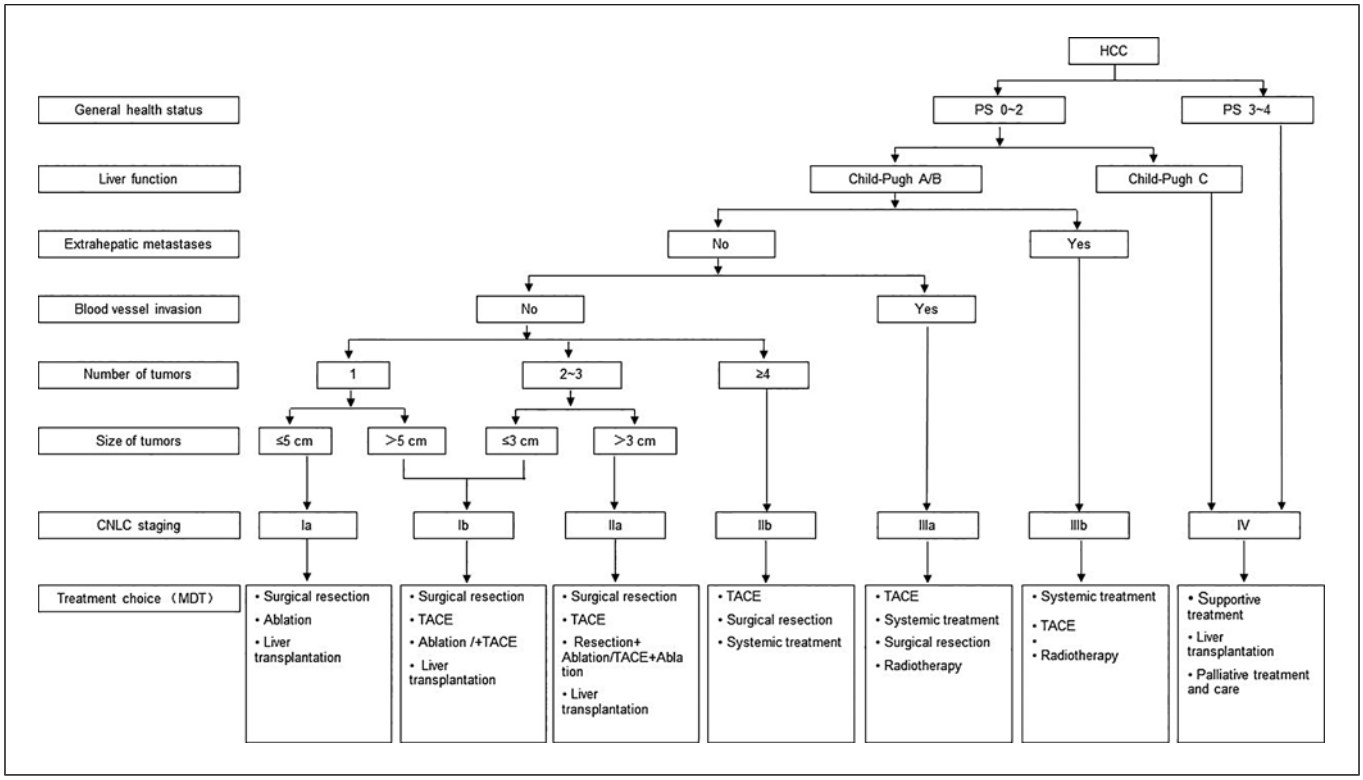

Fig. 3. Clinical staging and treatment pathway for HCC in China. Systemic antitumor therapy includes first-line and second-line therapy. First-line therapy: atezolizumab + bevacizumab, sintilimab + biosimilar of bevacizumab (BYVASDA®); donafenib, lenvatinib, sorafenib; FOLFOX4. Second-line therapy: regorafenib, apatinib, camrelizumab, tislelizumab

Indications for Hepatectomy

1. The recommended treatment for patients with CNLC stages Ia, Ib, and IIa HCC and enough LFR is surgical resection. Previous studies have shown no significant differences in the efficacy of surgical resection and radiofrequency ablation (RFA) for HCC ≤3 cm in diameter [84, 85] (evidence level 1, recommendation B). However, in recent studies, surgical resection was associated with a significantly lower local recurrence rate than RFA and better long-term outcomes [86–90] (evidence level 1, recommendation A). Even for recurrent HCC, the prognosis following surgical resection remains better than that following RFA in selected patients [91] (evidence level 2, recommendation B).
2. For most patients with CNLC stage IIb HCC, surgical resection is not recommended; instead, non-surgical approaches such as TACE are recommended. However, when tumors are localized to the same liver segment or the ipsilateral hemi-liver, intraoperative RFA may be used to treat lesions outside the resected area. Hepatectomy may be superior to other treatment approaches, even for multiple tumors (>3) [92]; therefore, in these cases, surgical resection is also recommended (evidence level 2, recommendation B). However, a thorough preoperative evaluation is recommended in these cases.
3. For CNLC stage IIIa HCCs, surgical resection is not recommended in most cases, with non-surgical treatment approaches based on systemic antitumor treatment preferred. Surgical resection may be considered in patients with tumor thrombi in the branches of the portal vein by removal of the tumor and embolectomy through the portal vein, followed by postoperative TACE, portal vein chemotherapy, or other systemic treatments when the tumor is localized to the hemiliver or the ipsilateral hemi-liver (Cheng's Classification type I/II) [93]. Patients undergoing surgical resection of tumor thrombi in the main portal vein (Cheng's classification type III) have high short-term postoperative recurrence rates and suboptimal postoperative survival. Therefore, the presence of tumor thrombi in the trunk of the portal vein is

not an absolute indication for surgical resection [94] (evidence level 3, recommendation B). Preoperative 3D conformal radiotherapy is associated with improved postoperative survival in patients with resectable tumors and portal vein tumor thrombi [95] (evidence level 2, recommendation B). Surgical resection may be considered in patients with tumor thrombi in the bile duct and resectable intrahepatic lesions and in patients with partial hepatic vein invasion with resectable intrahepatic lesions.

4. For patients with CNLC stage IIIb with metastasis to the hilar lymph nodes, resection of the tumor combined with hilar lymph node dissection or postoperative external radiation therapy may be considered. Surgical resection may also be considered for patients whose surrounding organs are involved and can be removed simultaneously. In addition, hepatic artery and portal vein catheterization chemotherapy or other intraoperative locoregional treatments, as well as nonsurgical treatment such as follow-up TACE therapy and systemic antitumor therapy after recovery from surgical trauma, may be considered for patients with HCC that is determined unsuitable for resection during surgical exploration.

Criteria for Curative Resection of HCC

Intraoperative criteria: (1) no macroscopic tumor thrombi noted in the hepatic vein, portal vein, bile duct, and inferior vena cava; (2) no adjacent organ involvement, portal lymph node, or distal metastases; (3) a distance between the surgical margin and tumor boundary ≥1 cm; or if the surgical margin is <1 cm, histologic examination of the cross section of the resected liver is free of residual tumor cells, i.e., negative surgical margin.

Postoperative criteria: (1) US, CT, and MRI (at least two of the three are mandatory) performed 1–2 months after surgery to confirm the absence of tumor lesions; (2) quantitative AFP or DCP, etc. testing should be performed postoperatively at 2 months to ensure that the readings are within normal range (it should be noted that the time to normalization of serum tumor markers is > 2 months in isolated patients), if the serum tumor markers such as serum AFP, or DCP levels, etc. were elevated preoperatively. The rate of decrease in serum AFP levels can be used as an early predictor of the thoroughness of surgical resection [96].

Hepatectomy Techniques

Commonly used techniques include hepatic inflow and outflow control techniques, liver transection techniques, and hemostatic techniques. Preoperative 3D visualization technology allows individualized liver volume calculation and virtual liver resection, which help plan a more accurate range and path of resection, protecting the ducts of the liver remnant and preserving enough liver volume [97–99] (evidence level 2, recommendation A).

In recent years, there have been rapid developments in laparoscopic liver surgery. Laparoscopic hepatectomy has the advantages of being less invasive and being associated with more rapid postoperative recovery [100], with oncologic outcomes in some patients comparable to those undergoing open hepatectomy [101] (evidence level 3, recommendation B). Although the indications and contraindications for laparoscopic hepatectomy are consistent with laparotomy in principle, it is still recommended to carry out comprehensive evaluation and caution according to the tumor size, tumor site, tumor number, combined liver basic diseases, and the technical level of the surgical team. In cases of giant HCC, multiple HCCs, HCC located in difficult sites or in the central region adjacent to important ducts, and HCC combined with severe cirrhosis, it is recommended that the procedure be undertaken by an experienced surgeon after rigorous selection. The use of laparoscopic US combined with ICG fluorescence tumor imaging may help detect microscopic lesions, and mark the extent of resection required to obtain negative tumor margins [102].

Both anatomic and nonanatomic resections are commonly used techniques, and both require adequate surgical margins for good oncologic outcomes. In patients with HCC with MVI, anatomic resection is associated with lower local recurrence rates than nonanatomic resection, despite no difference in the overall survival (OS) [103, 104] (evidence level 3, recommendation B). Studies have shown that hepatectomy with wide surgical margins (≥1 cm) is associated with better outcomes than hepatectomy with narrow surgical margins [105, 106] (evidence level 2, recommendation A), especially in patients with preoperatively judged MVI [107]. For large liver tumors, an anterior approach hepatectomy without dissecting perihepatic ligaments may be adopted [108]. For multiple liver tumors, surgical removal in combination with intraoperative locoregional ablation may be performed [109] (evidence level 3, recommendation C). For patients with portal vein tumor thrombi, the portal venous flow of the unaffected side should be temporarily interrupted during portal vein embolectomy to avoid disseminating the tumor thrombi [110]. For patients with tumor thrombi in the hepatic vein or vena cava, complete hepatic blood flow occlusion can be performed to remove the tumor thrombus as much as

possible [111]. For patients with HCC and tumor thrombi in the bile duct, resection of the involved bile ducts plus resection of HCC would maximize the chance of curative resection [80, 112, 113] (evidence level 3, recommendation C). For HCC with severe cirrhosis, deep tumor location, and multiple nodes as noted upon surgical exploration, intraoperative ablation alone may be considered to reduce the surgical risks.

A Multimodality Treatment Based on Surgery

Despite suboptimal OS after surgery in patients with moderately advanced HCC (CNLC stages IIb, IIIa, and IIIb), surgical resection can benefit some patients in the absence of other effective treatment approaches, based on data from previous study [80] (evidence level 4, recommendation C). Advances in systemic therapy and multimodality therapy have made it possible to provide more possibilities for radical resection, reduce postoperative recurrence, and improve prognosis in patients with intermediate-to-advanced HCC [114] (evidence level 4, recommendation B). Therefore, it is necessary to reconsider the strategy of upfront surgical resection in patients with intermediate-to-advanced HCC. Exploring new strategies for the surgery-based integrated management of intermediate and advanced HCC has become a key focus in recent years.

Conversion Therapy for Potentially Resectable HCC

Conversion therapy refers to the conversion of initially unresectable HCC into resectable HCC and is one of the pathways to radical resection and long-term survival in patients with intermediate-to-advanced HCC [115]. For potentially resectable HCC, a multimodal and intensive antitumor treatment strategy is recommended to promote conversion [114, 116–119], while also balancing the safety of treatment and patients' quality of life [115].

Conversion Therapy for Tumors

Systemic therapy alone or in combination is one of the main modalities of conversion therapy for intermediate-to-advanced HCC [114] (evidence level 4, recommendation B). The depth, speed, and duration of HCC remission, as well as organ-specific remission are important factors influencing subsequent treatment decisions. The impact of different drug combinations on liver tissues and the safety of subsequent surgery requires further exploration.

Locoregional therapies create potential opportunities for surgical resection in patients with initially unresectable HCC, which can be translated into survival benefits, including TACE [120] (evidence level 3, recommendation B) and hepatic arterial infusion chemotherapy (HAIC) [121] (evidence level 4 evidence, recommendation C). The conversion rate may be improved further with radiation therapy combined with hepatic artery infusion chemotherapy (HAIC) [122] or HAIC combined with TACE [123]. Systemic antitumor therapy combined with locoregional treatment is expected to result in higher tumor remission rates and higher rates of conversion and resection [124] (evidence level 4, recommendation B).

Conversion Therapy for Deficiencies of Remnant Liver Volume

Portal vein embolization (PVE) should be applied to the hemi-liver in which the tumor is located for compensatory hypertrophy of the remaining liver before resection [125]. The success rate of PVE is 60–80%, with a complication rate of approximately 10–20%. The time to remnant liver hyperplasia after PVE is relatively long (usually 4–6 weeks), and more than 20% of patients miss the opportunity for surgery due to tumor progression or insufficient liver remnant hypertrophy (evidence level 3, recommendation B).

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is suitable for patients whose remnant liver volume is expected to be <30–40% of the standardized liver volume. In recent years, several ALPPS modifications have emerged, which mainly focused on the partitioning operations of the hepatic section in stage I surgery (RFA, microwaves, and tourniquets can be used for partitions) and on ALPPS using a minimally invasive laparoscopic approach [126, 127]. Preoperative evaluation is critical and should incorporate the degree of liver cirrhosis, the patient's age, and their ability to tolerate two surgeries within a short period of time [128]. ALPPS improves the resection rate of HCC over a short period of time and has a better ability to rapidly induce hyperplasia of the remnant liver compared with PVE [129] (evidence level 2, recommendation A). Due to the short interval between the two procedures, the risk of tumor progression is minimized, resulting in a tumor resection rate of 95–100%. A study showed that ALPPS produces better outcomes than TACE for the treatment of large or multiple HCC [130] (evidence level 3, recommendation B). The potential benefits of ALPPS must be balanced against the trauma caused by undergoing two surgeries within a short period of time; further, the possibility of the second-stage surgery failing should be considered. Extra care should be taken in the selection of appropriate candidates for ALPPS, and the procedure should be performed by an experienced surgeon. In addition, ALPPS should be performed with extra caution in elderly patients with HCC.

Neoadjuvant Therapy

Neoadjuvant therapy refers to treatment to shrink a tumor before primary treatment (typically surgery). Common neoadjuvant therapies include systemic antitumor therapy, interventional therapy, and radiation therapy, with the goal of shrinking the tumor, reducing postoperative recurrence, and prolonging postoperative survival. Neoadjuvant therapy may be used to convert resectable intermediate or advanced HCC (CNLC stages IIb and IIIa) with poor oncologic features into HCC with favorable oncologic features, thereby reducing postoperative recurrence and prolonging survival. Preoperative 3D conformal radiotherapy may improve outcomes in patients with resectable HCC combined with portal vein tumor thrombi [95] (evidence level 2, recommendation B). However, preoperative TACE cannot prolong survival in patients with surgically resectable HCC [131, 132] (evidence level 2, recommendation A). Strategies such as immunotherapy alone or as part of combination therapy, including with targeted drugs, may be used for the preoperative or perioperative treatment of surgically resectable HCC and are expected to further improve surgical outcomes [133] (evidence level 2, recommendation B). In early-stage HCC (CNLC stages Ia, Ib, or IIa), the ability of preoperative treatment to improve patient survival and reduce recurrence requires confirmation in clinical studies.

Adjunctive Therapy

The 5-year recurrence rate after surgical resection of HCC is as high as 40–70%, and recurrence is often associated with preexisting minimal disseminated lesions or multicentric origin. Therefore, all patients should be closely followed up postoperatively. In patients at high risk of recurrence, two randomized, controlled studies confirmed the effectiveness of postoperative TACE therapy to reduce recurrence and prolong survival [134, 135] (evidence level 1, recommendation A). The results of another randomized, controlled study showed that treatment with Huaier granules after hepatectomy reduced recurrence and prolonged patient survival [136] (evidence level 1, recommendation A). In patients with HCC and HBV infection, antiviral therapy with nucleoside analogs can not only control underlying liver diseases but also help reduce the postoperative recurrence rate [137–139] (evidence level 1, recommendation A). In patients with HCC and HCV infection, direct-acting antiviral agents (DAAs) can elicit a sustained virologic response. However, there are currently no conclusive data to suggest an association between treatment with DAAs and an increased or decreased risk of tumor recurrence after HCC surgery, differences in the timing of recurrence, or the aggressiveness of recurrent HCC [140] (evidence level 3, recommendation C). In addition, the concurrent use of portal vein catheterization chemotherapy and TACE after surgery may also prolong survival in patients with portal vein tumor thrombosis [141] (evidence level 2, recommendation A). Although interferon-α reduced recurrences and prolonged survival in some randomized clinical studies [142–144] (evidence level 1, recommendation B), the use of interferon-α remains controversial [145]. An association between miR-26a expression in HCC and the efficacy of interferon-α treatment has been reported [146]; however, further multicenter, randomized, controlled studies are warranted to confirm this result. There have been ongoing explorations on the postoperative treatment strategies with immunotherapy, targeted drugs [147], and HAIC alone or in combination. In the event of recurrence, repeated resection, procedures such as ablation therapy, interventional therapy, radiation therapy, or systemic antitumor therapy may be used to prolong survival based on the characteristics of the recurrent disease.

Summary

1. Hepatectomy is an important means of achieving long-term survival in patients with HCC.
2. The aim of hepatectomy is to completely remove the tumor and preserve sufficient volumes of functional liver tissue. Thus, the perfect preoperative evaluation of liver reserve function and oncology evaluation are of great importance.
3. Child-Pugh class A and ICG-R15 <30% are generally accepted as prerequisites for surgical resection. A remnant liver volume accounting for >40% of the standardized liver volume (for patients with chronic liver diseases, parenchymal liver damage, or liver cirrhosis) or >30% (for patients without liver fibrosis and cirrhosis) is another prerequisite for surgical resection. Patients with hepatic impairment require preservation of greater liver volumes. Preoperative evaluation methods also include measurement of liver stiffness and the degree of portal hypertension.
4. The treatment of first choice for patients with CNLC stages Ia, Ib, and IIa HCC and good LFR is surgical resection. Surgical resection is not recommended for patients with CNLC stage IIb or stage IIIa HCC. However, some patients may still benefit from surgical resection after careful multidisciplinary assessment.
5. Hepatic inflow (hepatic artery and portal vein) and outflow (hepatic vein) control techniques are frequently used during hepatectomy. Preoperative 3D

visualization technology improves the accuracy of hepatectomy. Laparoscopic techniques can reduce surgical trauma. However, in cases of large HCCs, multiple HCCs, HCC located in difficult sites or in the central region adjacent to important ducts, and HCC combined with severe cirrhosis, it is recommended that the procedure is performed by an experienced physician after rigorous selection.

6. For potentially resectable HCC, a multimodal, high-intensity treatment strategy is recommended to facilitate its conversion. For patients with small remnant liver volumes, ALPPS or PVE is recommended for compensatory remnant liver hypertrophy to improve the possibility of resection.
7. The primary goal of postoperative adjuvant therapy for HCC is to reduce recurrence. Postoperative TACE for patients at high risk of recurrence is associated with reduced recurrence and prolonged survival. Postoperative oral administration of Huaier granules also reduces the risk of recurrence and prolongs survival. In addition, the postoperative use of nucleoside analogs for anti-HBV treatment or interferon-α can also reduce risk of recurrence and prolong survival.
8. Perioperative strategies of systemic antitumor therapy and locoregional monotherapy or combination therapies are currently being explored.

Liver Transplantation

Indications for LT for HCC

LT is one of the radical treatments for HCC and is particularly suitable for patients with small HCC and hepatic decompensation who are unsuitable for surgical resection and ablative therapy. Following the appropriate indications for LT for HCC is key to improving its efficacy, ensuring the equitable and appropriate use of valuable donor liver resources and balancing the differences in prognosis for patients with or without tumors [148] (evidence level 3, recommendation A).

The Milan criteria and the University of California San Francisco (UCSF) criteria are commonly used in the international community to assess the suitability of patients with HCC for LT. No uniform criteria have been established in China, although a number of criteria have been proposed by multiple entities and scholars, including the Shanghai Fudan criteria [149], Hangzhou criteria [150], West China criteria [151], and the Sanya consensus [152]. Similar factors across the criteria include the absence of macrovascular involvement, lymph node metastasis, and extrahepatic metastasis; the criteria diverge in the classification by the size and number of tumors. These domestic criteria expand the indication for LT for HCC to enable a greater number of patients with HCC to benefit from LT without significantly reducing the overall postoperative survival and tumor-free survival. However, multicenter collaborative studies are still required to support their use and to obtain higher quality evidence. The expert group recommends the UCSF criteria, namely, the diameter of a solitary tumor ≤6.5 cm, ≤3 tumors with a maximum tumor diameter ≤4.5 cm and the sum of tumor diameters ≤8.0 cm, with no macrovascular involvement. The basic principles and core policies of human organ allocation and sharing in China include instructions for LT for HCC, which stipulated that liver cancer recipients can apply for a special case score for early HCC, and that they can obtain a MELD score of 22 (liver transplant candidate ≥12 years of age on the waiting list), and the special case score can be renewed every 3 months.

Patients with HCC who meet the criteria for LT may receive bridging treatment to control tumor progression while waiting for a donor liver, to prevent them from losing the opportunity for LT. However, there is limited evidence on whether the probability of recurrence is reduced after bridging treatment [153, 154] (evidence level 2, recommendation C). HCC patients whose tumor load exceeds the criteria for LT may meet the criteria by reducing the tumor load with down-staging therapy. Palliative therapies commonly used to treat HCC may be used for bridging or down-staging therapy, including TACE, yttrium-90 radioembolization, ablative therapy, stereotactic body radiation therapy (SBRT), and systemic antitumor therapy. The prognosis of patients with HCC post-LT after successful down-staging therapy is better than that of those who do not undergo LT [155, 156] (evidence level 2, recommendation B).

The development of surgical techniques has led to an expansion of available donor livers. The indications of living donor LT for HCC can be further expanded [157, 158] (evidence level 4, recommendation C).

Prevention and Treatment of Posttransplant Recurrence

Tumor recurrence is the major concern after LT for HCC [159]. Risk factors include tumor stage, tumor vascular invasion, preoperative serum AFP level, and the dosing regimen of immunosuppressive therapy. The early withdrawal or absence of postoperative hormone-containing regimens [160] and dose reduction of calcineurin inhibitors in the early posttransplant period are associated with lower rates of tumor recurrence

[161] (evidence level 3, recommendation A). The use of immunosuppressive therapy with mammalian target of rapamycin (mTOR) inhibitors, such as rapamycin and everolimus, after LT is also associated with reduced tumor recurrence and improved survival rates [162–166] (evidence level 2, recommendation A).

Following tumor recurrence or metastasis after LT, which occurs within 2 years after LT in 75% of cases, the disease typically progresses rapidly, with a median survival of 7–16 months [167]. Patient survival may be prolonged by a combination of modification of immunosuppressive regimens, reoperation, TACE, ablation therapy, radiotherapy, and systemic treatment, based on multidisciplinary diagnosis and treatment [168, 169] (evidence level 3, recommendation B). Caution is required for the use of immune checkpoint inhibitors preoperatively or post-transplantation for HCC [170, 171] (evidence level 4, recommendation C).

Summary

1. LT is a radical treatment approach for HCC and is particularly suitable for patients with small HCC who have decreased liver function and are not suitable for surgical resection and ablation therapy.
2. It is recommended that the UCSF criteria are followed as the Chinese criteria for the indication of LT for HCC.
3. The early withdrawal or absence of hormone-containing regimens, dose reduction of calcineurin inhibitors in the early posttransplant period, and use of immunosuppressive therapy with mTOR inhibitors such as rapamycin and everolimus after LT are associated with reduced tumor recurrence and improved survival.
4. Following tumor recurrence and metastasis post-LT, the disease usually progresses rapidly. Combination therapy on the basis of multidisciplinary diagnosis and treatment is associated with prolonged survival.

Ablation Therapy

Although surgery is the recommended aggressive treatment for HCC, some patients cannot tolerate surgery due to cirrhosis or other comorbidities. Ablation therapy with a small impact on liver function is associated with similar efficacy to surgical resection in some patients with early-stage HCC.

Ablation therapy for HCC is guided by medical imaging technology and targets tumor lesions, directly and locally killing tumor tissues by physical or chemical methods. Local ablation mainly includes (RFA), microwave ablation (MWA), percutaneous ethanol injection (PEI), cryoablation (CRA), high-intensity focused ultrasound ablation (HIFU), laser ablation, and irreversible electroporation (IRE). Local ablation is often performed under the guidance of US, which is easy to use, provides real-time results, and is highly efficient. CT and MRI may be used for the observation and to guide ablation therapy for lesions that are invisible on conventional US. CT or MRI guidance may also be used in the ablation of metastases in the lungs, adrenal glands, and bones.

Ablation can be performed using percutaneous, laparoscopic, laparotomic, or endoscopic approaches. Most HCC lesions can be ablated percutaneously, which is cost-effective, easy to perform, and minimally invasive. High risks are usually associated with ablation for sub-capsular HCC, particularly in lesions protruding beyond the liver capsule. For HCC located at sites that are difficult to visualize using imaging technology or at sites considered high risk for percutaneous ablation (close to the heart, diaphragm, gastrointestinal tract, or gallbladder), ablation by laparoscopic, laparotomic, or water isolation approaches may be considered.

Ablation is indicated for patients with CNLC stage Ia HCC and some patients with stage Ib HCC (i.e., solitary tumor ≤5 cm in diameter; or 2–3 tumors ≤3 cm in diameter). Curative outcomes may be obtained in patients with no invasion of blood vessel, bile ducts, or adjacent organs, or distal metastasis, and with Child-Pugh grade A/B [84, 89, 172–175] (evidence level 1, recommendation A). Treatment can be combined with TACE for patients with inoperable solitary tumors or multiple tumors with a diameter 3–7 cm, with outcomes better than those associated with ablation monotherapy [176–179] (evidence level 1, recommendation B).

Commonly Used Ablation Approaches

RFA is a commonly used, minimally invasive ablation method for HCC that is easy to use with good control over the ablation range, requires only a short hospital stays, and has proven efficacy. RFA is particularly suitable for older patients and patients with comorbid diseases, severe cirrhosis, tumors located in deep positions in the liver, or central HCC. For patients with resectable early-stage HCC, RFA is associated with similar or slightly lower tumor-free survival and OS than surgical resection, with a lower incidence of complications and shorter hospital stay [84, 85, 89, 172–175] (evidence level 1, recommendation A). For solitary HCC (particularly central solitary HCC) ≤2 cm in diameter, RFA has similar or superior efficacy to surgical resection [180, 181] (evidence

level 3, recommendation A). RFA permits the ablation of an entire tumor while maintaining a sufficient safety margin and minimizing damage to normal liver tissues. Prerequisites for RFA are the accurate assessment of the range of tumor infiltration and the identification of satellite lesions before the procedure; therefore, the importance of accurate imaging examinations prior to treatment is emphasized. Contrast-enhanced US allows for accurate determination of the size and shape of a tumor, the range of tumor infiltration to be determined, and micro and satellite lesions to be detected, providing reliable data on which to base ablation protocols to inactivate tumors during US-guided ablation.

MWA, another commonly used thermal ablation method in recent years, is not statistically different from RFA in terms of local efficacy, complication rates, and long-term survival [182–184] (evidence level 1, recommendation B). MWA is characterized by high efficiency, short ablation duration, and a reduced heat-sink effect compared with RFA. Establishing a temperature monitoring system helps regulate parameters such as power, determine the range of the effective thermal field, and increase the safety of the MWA procedure. The selection of MWA or RFA should be based on the size and position of tumors [185].

PEI has proven efficacy against tumors ≤2 cm in diameter, with similar long-term efficacy to RFA despite having a higher local recurrence rate than RFA for tumors >2 cm in diameter [186] (evidence level 2, recommendation B). The advantage of PEI is its safety, making it particularly suitable for tumors in high-risk locations such near the hepatic hilar region, gallbladder, and gastrointestinal tract. However, repeated PEI procedures with multipoint punctures are required for intra-tumor diffusion of the drug.

Basic Technical Requirements

The physician must be adequately trained and have sufficient clinical experience to consider the advantages and disadvantages of the various ablation techniques and which is suitable for which patient. A thorough evaluation of the patient's general PS, liver function, and coagulation functions, as well as the evaluation of the size, position, and number of tumors, and the relationship to adjacent organs, should be performed prior to ablation. An appropriate puncture tract and ablation plan should be determined, and a postoperative care plan should be formulated to cover at least 5 mm of perineoplastic liver tissue to ensure a sufficient margin.

An appropriate imaging guidance (e.g., US or CT) and ablation technique (RFA, MWA, or PEI) should be selected based on the size and position of the tumor. Multimodal image fusion guidance may be applied when available.

Caution should be exercised in the ablation of HCC adjacent to the hepatic hilar region or near the first- and second-order bile ducts to avoid complications such as damage to the bile ducts. In this case, PEI alone or RFA/MWA combined with PEI is safe. If thermal ablation is applied, at least 5 mm should be allowed between the tumor and the first- and second-order hepatic ducts, and low power, short duration, intermittent radiation should be used. The use of temperature monitoring methods is recommended for ablation equipment where available. For lesions >5 cm in diameter, TACE combined with ablation is recommended, which provides better outcomes than ablation alone.

The range of ablation should cover at least 5 mm of perineoplastic liver tissue to ensure a safety margin for complete ablation. For ill-defined and irregularly infiltrating tumors, we recommend that the range of ablation be extended as appropriate, if adjacent liver tissues and structures permit.

Treatment Recommendations for Tumors 3–5 cm in Size

Several randomized, controlled trials and retrospective analyses support surgical resection as a recommended treatment [90, 172, 174] (evidence level 1, recommendation A). In real-world clinical practice, initial treatment should be selected after a thorough consideration of the patient's general PS, liver function, the size, number, and position of tumors, as well as the skill and experience of the physician. Surgical resection is the first choice if the patient can tolerate hepatectomy or the tumors are located in a superficial area, the peripheral liver, or high-risk sites unsuitable for ablation. Ablation therapy, or surgical resection in combination with ablation therapy, is the recommended choices for patients with 2–3 tumors located in different areas or for deeply located or central tumors.

Assessment and Follow-Up after Ablation Therapy for HCC

Dynamic contrast-enhanced CT, mpMRI, or contrast-enhanced US is recommended for assessing the local response to ablation approximately 1 month postoperatively. Dynamic changes in serum tumor biomarkers should also be monitored. The response to ablation can be categorized as follows [187]:

1. Complete ablation: follow-up imaging with dynamic contrast-enhanced CT, mpMRI, or contrast-enhanced

US shows no enhancement in the ablated area of the tumor in the arterial phase, which indicates complete necrosis of the tumor.
2. Incomplete ablation: follow-up imaging with dynamic contrast-enhanced CT, mpMRI, or contrast-enhanced US shows local enhancement in the ablated region of the tumor in the arterial phase, which is suggestive of residual tumor tissue. Repeat ablation is suggested for patients with residual tumors after treatment. Ablation therapy should be abandoned and substituted with other treatments if the presence of residual tumors is confirmed after two consecutive ablation sessions. Periodic follow-ups are required after complete ablation. Generally, serum tumor marker testing and imaging examination with dynamic contrast-enhanced CT, mpMRI, or contrast-enhanced US should be performed every 2–3 months to screen for possible local recurrence and new intrahepatic lesions. Ablation therapy may be used to control tumor progression, with the advantages of minimal invasiveness, safety, and ease of repeated use.

Combination of Ablation Therapy and Systemic Therapy

Combination of ablation therapy and systemic therapy is being clinically investigated. Studies have shown that ablation therapy enhances the release of tumor-associated antigens and neoantigens, enhances HCC-associated antigen-specific T-cell responses, and activates or enhances the body's antitumor immune responses [188–190]. Therefore, the combination of ablation therapy and immunotherapy may produce synergistic antitumor effects [188, 191, 192]. Several relevant clinical studies are currently underway to investigate these effects.

Summary

1. Ablation therapy is suitable for patients with CNLC stage Ia and some patients with stage Ib HCC (i.e., solitary tumors with a diameter of ≤5 cm or 2–3 tumors with maximum diameter ≤3 cm) to obtain a curative outcome. TACE combined with ablation may be used for inoperable solitary or multiple tumors with a diameter of 3–7 cm.
2. For tumors with a diameter ≤3 cm, the tumor-free and OS rates of ablation therapy are similar to, or slightly lower than, those of surgical resection, but the complication rate and length of hospital stay are lower compared with surgical resection. For a single HCC lesion ≤2 cm in diameter, the efficacy of ablation therapy is similar to that of surgical resection, especially for central HCC.
3. No significant differences in local efficacy, incidence of complications, or long-term survival have been reported between MWA and RFA; selection should be based on the size and position of tumors.
4. PEI has similar long-term efficacy to RFA for tumors with a diameter ≤2 cm. The advantage of PEI is its safety and, in particular, PEI is suitable for tumors in high-risk locations such as lesions near the hepatic hilar region, gallbladder, and gastrointestinal tracts. However, multiple and multipoint punctures are required for the intra-tumoral diffusion of the drug.
5. Regular follow-up with dynamic contrast-enhanced CT, mpMRI scan, US, and serum tumor markers after ablation therapy should be performed to evaluate ablation outcomes.

Transarterial Chemoembolization

TACE is a commonly used non-surgical treatment for HCC [193–198].

Basic Principles for TACE

1. The procedure should be performed under the guidance of a DSA system.
2. The clinical indications must be well understood and strictly followed.
3. Super-selective catheterization of the branches of tumor-feeding arteries must be ensured.
4. The patient's liver function must be properly reserved.
5. The procedure must be performed in a standardized and personalized manner.
6. Switching to or combining with other treatments such as surgery, local ablation, systemic treatment and radiation therapy should be considered if the tumor continues to progress after 3–4 sessions of TACE.

Indications for TACE

1. Patients with CNLC stage Ia, Ib, and IIa HCC who are indicated for surgical resection or ablation therapy but are unable or unwilling to receive these procedures for non-surgical reasons such as old age, inadequate liver function reserve, or high-risk tumor sites.
2. Patients with CNLC stage IIb and IIIa HCC, and a proportion of patients with stage IIIb disease, with Child-Pugh grade A or B and a PS score of 0–2.
3. Patients with incomplete obstruction of the main portal vein, or formation of abundant compensatory collateral branches of the portal vein or recanalized portal vein by portal vein stenting despite complete obstruction.

4. Patients with portal hypertension-related bleeding as a result of hepatic artery-portal venous shunt.
5. Patients with high risk of recurrence (including multiple tumors, combined visual or microscopic tumor thrombosis, palliative surgery, failure of postoperative AFP, and other tumor markers to decline to normal range) may be treated with adjuvant TACE after surgical resection to reduce recurrence and prolong survival.
6. Preoperative TACE treatment for initially unresectable HCC to achieve conversion to create opportunities for surgical resection and ablation.
7. Bridging treatment during the waiting period for LT.
8. Patients with spontaneous rupture of HCC.

Contraindications for TACE

1. Severe liver dysfunction (Child-Pugh grade C), including jaundice, hepatic encephalopathy, refractory ascites, or hepatorenal syndrome.
2. Serious coagulation dysfunction that cannot be corrected.
3. Complete obstruction of the main portal vein by tumor thrombi, with few collateral branches formed.
4. The presence of active hepatitis or serious infection that cannot be simultaneously treated.
5. Distal extensive metastasis with an expected survival <3 months.
6. Patients with cachexia or multiple organ failure.
7. Tumor burden >70% of total liver volume (fractionated embolization with small amounts of lipiodol emulsion and granular embolic agents may be considered in the case of basically normal liver function).
8. Significant reduction in peripheral white blood cell (WBC) and platelet counts, with a WBC level $<3.0 \times 10^9$/L and a platelet level $<50 \times 10^9$/L (Note: not absolutely contraindicated, e.g., chemotherapy-induced myelosuppression should be excluded in patients with hypersplenism).
9. Renal insufficiency (blood creatinine [Cr] >2 mg/dL or blood Cr clearance rate <30 mL/min).

Operating Procedures for TACE

1. Standardized arteriography: Hepatic arteriography is commonly performed using the Seldinger technique with percutaneous puncture and cannulation from femoral access (or radial access). DSA of the celiac or common hepatic artery should be performed to acquire images in the arterial, parenchymal, and venous phase. Angiography of arteries such as the superior mesenteric artery, left gastric artery, subphrenic artery, right renal artery (right adrenal artery), or internal thoracic artery should be performed to identify hepatic arteries of ectopic origin or collateral feeding vessels from extrahepatic arteries to confirm the collateral blood supply of the tumor. The angiographic manifestations should be carefully analyzed to determine the site, size, number, and feeding arteries of tumors [199, 200].
2. There are three techniques categorized by the type of hepatic arterial chemotherapy and embolization.
   - Transarterial infusion (TAI) or HAIC (see Appendix 6 for specific applications): chemotherapy drugs are infused through a tumor-feeding artery, including continuous perfusion chemotherapy with an indwelling catheter. Commonly used chemotherapy drugs for this technique are anthracyclines, platinum, and fluorouracil. The concentration and duration of the perfused drugs should be decided according to the pharmacokinetic characteristics of the chemotherapeutic drugs [201].
   - Transarterial embolization (TAE): the feeding arteries of a liver tumor are embolized with granular embolic agents alone.
   - TACE: a lipiodol emulsion-containing chemotherapy drugs, drug-eluting microspheres, or supplement embolic agents (gelatin sponge particles, blank microspheres, and polyvinyl alcohol particles [PVA]) is infused through the tumor-feeding artery. Embolization should be performed by embolizing all the feeding vessels of the tumor to devascularize the tumor as much as possible. Embolic agents may be categorized as conventional TACE (cTACE) and drug-eluting bead-TACE (DEB-TACE; also known as drug-eluting microsphere TACE). cTACE refers to the use of lipiodol emulsion-containing chemotherapy drugs as the main method of embolization with gelatin sponge particles, blank microspheres, or PVA. First, a fraction of the chemotherapy drug is infused over a period of ≥20 min, followed by embolization with the emulsion mixture consisting of the remaining fraction of the chemotherapy drugs and lipiodol. Ultra-liquefied lipiodol and chemotherapeutic drugs should be fully emulsified. The dose of lipiodol is usually 5–20 mL and should not exceed 30 mL. The treatment stopping boundary is defined by the formation of dense lipiodol deposition in the tumor region and the presence of small portal vein branch shadows around the tumor under fluoroscopic monitoring. Granular embolic agents are used after embolization with lipiodol emulsion. The embolization of normal liver tissues as a result

of agent reflux or the entry of the agents into non-target organs should be avoided. DEB-TACE refers to the embolization with mainly drug-eluting microsphere loaded with chemotherapeutic drugs such as positively charged doxorubicin. The size of drug-eluting microspheres ranges from 70 to 150 μm, 100–300 μm, 300–500 μm, or 500–700 μm. Different size microspheres should be selected according to the tumor size, blood supply, and the therapeutic purpose, with 100–300 μm and 300–500 μm being most commonly used. Drug-eluting microspheres can embolize the blood supplying arteries to HCC lesions, resulting in ischemia and necrosis of the tumor. Meanwhile, as a carrier of chemotherapy drugs, DEB-TACE has the advantages of uninterrupted and stable drug release to maintain a high locoregional plasma concentration around the tumor. The recommended DEB-TACE push rate is 1 mL/min. Attention should be paid to the redistribution of microspheres after embolization to fully embolize the distal tumor-feeding arteries as much as possible, while preserving the proximal blood supply branches of the tumor and reducing damage to normal liver tissue as a result of microsphere regurgitation [202].

3. Precision TACE: precision TACE is advocated to reduce the differences in the efficacy of TACE due to the heterogeneity of tumors. Precision TACE includes (i) super-selective microcatheterization to the branch of the tumor-feeding artery for embolization [199, 202, 203]; (ii) the use of cone-beam CT to assist the precise catherization of the target vessel and monitoring of the efficacy after embolization during the TACE procedure is recommended [204]; (iii) appropriate application of embolization materials, including iodized oil, microspheres, and drug-eluting microspheres [205]; and (iv) different embolization endpoints should be used according to the patient's tumor status, liver function, and therapeutic objectives.

Common Adverse Effects of TACE

Post-embolization syndrome is the most common adverse reaction associated with TACE, which mainly manifests as fever, pain, nausea, and vomiting. The cause of fever and pain is the ischemia and necrosis of local tissues as a result of hepatic artery embolization, while nausea and vomiting are mainly side effects of chemotherapy. In addition, other common adverse reactions may occur, including puncture site bleeding, WBC count reduction, transient liver function abnormalities, renal impairment, and dysuria. Adverse reactions usually last 5–7 days, and most patients can fully recover after receiving treatment to manage these symptoms.

Other common complications include acute hepatic and renal impairment, gastrointestinal bleeding, cholecystitis, and perforation of the gallbladder, liver abscesses, biloma, and ectopic embolization of embolic agents including pulmonary and cerebral lipiodol embolism, perforation of the gastrointestinal tract, spinal cord injury, and diaphragm injury.

Evaluation of Response to TACE

The local response of HCC to TACE should be evaluated in accordance with mRECIST and the European Association for the Study of the Liver (EASL) evaluation criteria. The preferred long-term efficacy parameter is OS, and short-term efficacy parameters are objective response rate (ORR) and time to progression (TTP).

Factors That Affect Long-Term Efficacy of TACE

Degree of liver cirrhosis and liver function status; serum AFP level; tumor load and clinical staging; integrity of the tumor capsule; presence of tumor thrombi in the portal vein/hepatic vein and vena cava inferior; tumor blood supply; pathologic subtype; physical status of the patient's PS; serum HBV-DNA level in patients with underlying chronic HBV infection; whether combining ablation, molecular targeted therapy, immunotherapy, radiation therapy, and surgical procedures [193].

Follow-Up and Treatment during the Interval between TACE Sessions

Assessment by contrast-enhanced CT and/or mpMRI, tumor markers, liver and renal function tests, and routine blood tests are usually recommended 4–6 weeks after the first session of TACE. Repeated sessions of TACE may be postponed if the imaging examination shows thick lipiodol deposition in the liver tumor, necrosis of tumor tissues, with the absence of tumor enhancement and new lesions. The need and frequency of subsequent TACE should be determined based on follow-up results, which mainly include the response to previous sessions of treatment, liver function, and changes in the patient's general condition. Follow-ups may be performed every 1–3 months although less frequent follow-ups are also permissible. The response of the liver tumor should be evaluated by dynamic contrast-enhanced CT and/or MRI to determine the need for repeated TACE. However, 3–4 sessions of TACE are often required to treat large/huge liver tumors. TACE in combination with other treatments

is recommended for tumor control, improved quality of life, and extended survival.

Main Points regarding TACE

1. Precision TACE is recommended: precision TACE refers to super-selective catheterization using a microcatheter to the tumor-feeding arteries and the accurate infusion of lipiodol emulsion and granular embolic agents for improved efficacy and protection of liver function.
2. There is no significant difference in overall efficacy between DEB-TACE and cTACE, but DEB-TACE is more advantageous in terms of objective tumor response for large HCC [205] (evidence level 1, recommendation B).
3. Emphasis should be placed on the combination of multiple locoregional treatments, as well as locoregional treatment in combination with systemic antitumor therapy [193]:
   - TACE combined with ablation therapy: to improve the efficacy of TACE, an appropriate combination of TACE therapy with ablation therapy is recommended, including RFA, MWA, or cryotherapy [206, 207] (evidence level 2, recommendation B). There are currently two approaches for the combination of TACE with thermal ablation therapy. (a) Sequential ablation: TACE followed by local ablation therapy, separated by an interval of 1–4 weeks. (b) Concurrent ablation: local ablation therapy is performed during TACE, which results in significantly improved clinical efficacy and reduced hepatic impairment [206].
   - TACE combined with external radiation therapy [208, 209] (evidence level 2, recommendation B): mainly used to treat tumor thrombosis in the main trunk of the portal vein, tumor thrombosis in the inferior vena cava, and selected large HCC lesions after interventional therapy.
   - TACE combined with second-stage surgical resection: surgical resection is recommended for large or huge HCC which converts to resectable disease after TACE and becomes suitable for second-stage surgery [120, 123] (evidence level 3, recommendation A).
   - TACE in combination with other antitumor therapies: includes combination with molecular targeted therapies, immunotherapy, systemic antitumor therapy, and radioimmune-targeted agents.
   - TACE combined with antiviral therapy: antiviral therapy should be actively performed in combination with TACE in HCC patients with a history of HBV/HCV infection [210, 211] (evidence level 3, recommendation A).
4. Tumor thrombi in the main portal vein may be managed by portal vein stenting and Iodine-125 seed strips or Iodine-125 seed portal vein stenting on top of TACE [212] (evidence level 2, recommendation B). The tumor thrombi in the first-order branches of the portal vein may be treated with Iodine-125 seed strips or Iodine-125 seed implantation via direct puncture [213, 214] (evidence level 4, recommendation C).
5. Prophylactic TACE in patients at high risk of postoperative recurrence [134, 135] (evidence level 1, recommendation A): prophylactic TACE may prolong the OS and tumor-free survival in patients with multiple tumors, combined visual or microscopic tumor thrombi, and tumors >5 cm in diameter.

Summary

1. TACE is a commonly used non-surgical treatment for HCC, mainly for patients with CNLC stages IIb and IIIa HCC and selected patients with CNLC stage IIIb HCC.
2. Precision TACE is advocated to reduce the differences in TACE outcomes as a result of heterogeneity of tumors.
3. TACE (including cTACE and DEB-TACE) must be administered based on standardized regimens, while taking into account the principle of individualization.
4. The combination of TACE with ablative therapy, radiotherapy, surgery, molecular targeted drugs, immunotherapy, and antiviral therapy should be advocated to further improve the efficacy of TACE.
5. HCCs with tumor thrombi in the main trunk and first-order branches of the portal vein may be treated with portal vein stenting in combination with Iodine-125 seed implantation or Iodine-125 seed implantation alone via direct puncture.

Radiation Therapy

Radiation therapy (abbreviated as radiotherapy) is categorized into external radiotherapy and internal radiotherapy. External radiotherapy is delivered from outside the body by aiming beams (photons or particle beam radiation) from the radiotherapy device to the tumor. Internal radiotherapy is delivered through the implantation of radionuclides into the tumor through body tracts or needle tracts.

External Radiotherapy

Indications for External Radiotherapy

1. CNLC stage Ia HCC patients and a proportion of patients with CNLC stage Ib HCC. Stereotactic body radiation therapy (SBRT) may be considered an alternative treatment if surgical resection or local ablation therapy are not clinically indicated or if patients refuse invasive treatment [215–221] (evidence level 2, recommendation B).
2. For patients with CNLC stage IIa and IIb HCC, TACE in combination with external radiotherapy may be appropriate as there is evidence that TACE in combination with external radiotherapy is associated with an improved local control rate, prolonged survival, and better efficacy than monotherapy with TACE or sorafenib or TACE in combination with sorafenib [208, 216, 222–226] (evidence level 2, recommendation B).
3. In patients with CNLC stage IIIa HCC, preoperative neoadjuvant radiotherapy or postoperative adjuvant radiotherapy for resectable HCC with tumor thrombosis in the portal vein may prolong survival [95, 227] (evidence level 2, recommendation B); for patients with unresectable HCC, palliative radiotherapy or a combination of radiotherapy and TACE may be performed to extend patient survival [208, 225, 226] (evidence level 2, recommendation B).
4. Patients with CNLC stage IIIb HCC: for a proportion of patients with oligometastasis, SBRT may be performed to prolong survival. External radiotherapy may also be used to reduce pain, obstruction, or bleeding caused by lymph node, lung, bone, brain, or adrenal metastasis [209, 228, 229] (evidence level 3, recommendation A).
5. Some patients with initially unresectable HCC will become able to undergo surgical resection after tumor shrinkage or down-staging as a result of radiotherapy [209, 218] (evidence level 2, recommendation B). External radiotherapy may also be used as a bridging treatment while waiting for LT [230]. For HCC patients with postoperative pathology suggestive of MVI and a narrow surgical margin (≤1 cm from the tumor), postoperative adjuvant radiotherapy can reduce the risk of local recurrence or distant metastasis and extend progression-free survival (PFS) [231, 232] (evidence level 3, recommendation C).

Contraindications to External Radiotherapy

External radiotherapy is not recommended for HCC patients with diffusely distributed intrahepatic lesions or CNLC stage IV HCC.

Principles and Key Points for External Radiotherapy

The key principle of performing external radiotherapy for HCC is to comprehensively consider the tumor radiation dose, the dose tolerated by peripheral normal tissues, and the radiotherapy techniques used. Key points for performing external radiotherapy for HCC include the following

1. During preparation of the radiotherapy plan, intrahepatic lesions should be defined by contrast-enhanced CT and, if necessary, a wider range of radiographic images such as MRI should be consulted. The regenerative ability of normal liver tissues should also be considered. During radiotherapy, a proportion of normal liver tissue should be preserved without being irradiated to allow for proliferation.
2. The irradiation dose is closely related to survival time and local control rate and is predominantly dependent on the tolerable dose for peripheral normal tissues [122, 233]. Favorable outcomes for radiotherapy may be obtained at a recommended irradiation dose for HCC of ≥45–60 Gy in 3–10 fractions (Fx) for stereotactic radiosurgery [234], with a bioequivalent dose (BED) of radiotherapy of approximately ≥80 Gy (10 Gy is taken as the α/β ratio). The recommended dose is 50–75 Gy for conventional fractionation radiotherapy and 3 Gy × 6 Fx for neoadjuvant radiotherapy for tumor thrombi in the portal vein [95].
3. The radiation tolerance of non-tumor liver tissues is associated with factors including the radiotherapy segmentation method, Child-Pugh classification, normal liver (liver tumor) volume, blood stasis of the gastrointestinal tract, and coagulation function. Where image-guided radiation therapy (IGRT) is possible, hypofractionated radiotherapy may be applied for some intrahepatic lesions, tumor thrombi or extrahepatic metastases in the lymph nodes, lung, and bone to increase the single dose, and shorten the radiation treatment duration, with unaffected or even improved efficacy [235–237]. For non-SBRT, hypofractionated external radiotherapy, which can be calculated using models, with the α/β ratio for hepatocytes being 8 Gy in patients with HBV infection and the α/β ratio for tumor cells being 10–15 Gy, which may be used as references for dose conversion [122, 209, 238].
4. Radiotherapy techniques for HCC: use of three-dimensional conformal or intensity-modulated radiotherapy, IGRT, or SBRT is recommended. IGRT is superior to non-IGRT techniques [233]. Helical tomographic radiotherapy is suitable for HCC patients with multiple lesions. Respiratory motion is the main cause

of liver tumor motion and deformation during radiotherapy. Multiple techniques may be adopted to reduce the impact of respiratory motion including respiratory gating techniques, real-time tracking, respiration control, and internal target volume determination techniques based on abdominal compression in combination with 4D CT [239].
5. In radiotherapy, the therapeutic response should be evaluated 3–6 months after the treatment. Dynamic contrast enhanced CT/MR examinations are often used to evaluate the post-radiotherapy tumor response for HCC. The general imaging features of post-radiotherapy include slow tumoral shrinkage and development of radiation-induced damage in peritumoral liver tissues.
6. Currently, no high-level clinical evidence is available to support the superiority of proton radiotherapy compared with photon radiotherapy in terms of survival rate in patients with HCC [216].

Major Complications of External Radiotherapy

Radiation-induced liver diseases (RILDs) are the key dose-limiting complications of external radiotherapy for HCC and can be divided into typical and atypical RILDs. Typical RILDs present as increased alkaline phosphatase (AKP) >2 times the upper limit of normal (ULN), jaundice-free ascites, and hepatomegaly. Atypical RILDs present as AKP >2 times the ULN, ALT >5 times the ULN or the pretreatment level, and a reduction of ≥2 points in Child-Pugh Score but with the absence of hepatomegaly and ascites. A diagnosis of RILD must exclude clinical symptoms and liver dysfunction caused by progression of liver tumors, virus activation or drug toxicities [209].

Proton Beam Radiotherapy (PBT) and Internal Radiation Therapy

PBT has similar efficacy for postoperative recurrent and residual HCC lesions (≤2 lesions each <3 cm in size) to that of RFA [240] (evidence level 2, recommendation C).

Internal radiation therapy is a method of locally treating HCC and includes Y-90 microsphere treatment, iodine-131 monoclonal antibodies, radioactive lipiodol, and iodine-125 seed implantation [47, 228, 229]. Sequential iodine-131-metuximab treatment following RFA for HCC is associated with a reduced rate of local recurrence after RFA treatment and improved patient survival [241] (evidence level 2, recommendation C). Particle implantation techniques include interstitial implantation, portal vein implantation, inferior vena cava implantation, and bile duct implantation. Strontium chloride ($^{89}SrCl_2$) emits β rays and can be used for the targeted treatment of bone metastasis from HCC [242] (evidence level 3, recommendation C).

Summary

1. For patients with CNLC stage IIIa HCC combined with resectable portal tumor thrombi, preoperative neoadjuvant radiotherapy or postoperative adjuvant radiotherapy may be performed to prolong survival. For patients with unresectable HCC, palliative radiotherapy, or a combination of radiotherapy and TACE, etc., may be adopted to prolong patient survival.
2. In selected patients with CNLC stage IIIb HCC and oligometastasis, SBRT may prolong survival and external radiotherapy may be used to reduce pain, obstruction, or bleeding caused by the lymph node, lung, bone, brain, or adrenal metastasis.
3. Some patients will be able to undergo surgical resection after radiotherapy.
4. The general recommended radiation dose is ≥45–60 Gy in 3–10 Fx for stereotactic body radiation therapy, and 50–75 Gy for conventional fractionation radiotherapy. The irradiation dose is closely related to the survival of patients. Hypofractionated radiotherapy may be adopted to treat some intrahepatic lesions and extrahepatic metastases with increased single dose and shortened radiation treatment duration.
5. The tolerated radiation dose of peripheral normal liver tissue must account for the radiotherapy segmentation method used, Child-Pugh classification, normal liver (liver tumor) volume, blood stasis of the gastrointestinal tract, and coagulation function.
6. IGRT is superior to three-dimensional conformal or intensity-modulated radiotherapy. SBRT must be performed under the guidance of IGRT.
7. Internal radiotherapy is a method for the local treatment of HCC and tumorous thrombi.

Systemic Therapy

Systemic therapy mainly refers to antitumor therapy including molecular targeted drug therapy, immunotherapy, chemotherapy, and traditional Chinese herbal medicine. In addition, it also includes treatments for diseases underlying HCC, such as antiviral therapy, for the protection of the liver and bile production, as well as supportive symptomatic therapy.

Systemic antitumor therapy plays an important role in the treatment of intermediate and advanced HCC and may control disease progression and prolong patient survival. Potential candidates for systemic antitumor

therapy mainly include those with: (i) CNLC stages IIIa and IIIb HCC; (ii) CNLC stage IIb HCC who are not suitable for surgical resection or TACE therapy; (iii) resistance to TACE therapy or who have failed TACE therapy.

First-Line Systemic Therapies

Combination of Atezolizumab and Bevacizumab

This combination therapy is approved for patients with unresectable HCC who have not received prior systemic therapy (evidence level 1, recommendation A). The results of the IMBrave150 global multicenter phase III trial [243, 244] showed that the median OS and PFS were significantly longer in the atezolizumab and bevacizumab combination group compared with the sorafenib group, with a 34% lower risk of death and a 35% lower risk of disease progression. A significant clinical benefit in the combination therapy group was also observed in a Chinese patient subgroup, with a 47% lower risk of death and a 40% lower risk of disease progression compared with sorafenib. In addition, the combination therapy delayed patient-reported median time to deterioration of quality of life. Common adverse effects included hypertension, proteinuria, abnormal liver function, hypothyroidism, diarrhea, and decreased appetite.

Combination of Sintilimab and Biosimilar of Bevacizumab (BYVASDA®)

The combination is approved in China as a first-line treatment for patients with unresectable or metastatic HCC without prior systemic antitumor therapy (evidence level 1, recommendation A). The results of the domestic multicenter phase III study ORIENT-32 [245] showed that sintilimab in combination with a biosimilar of bevacizumab (Bevagen®) had significantly better efficacy than sorafenib, with a 43% decreased risk of death and a 44% decreased risk of disease progression. The combination regimen also had a better safety profile, with the most common adverse effects being proteinuria, thrombocytopenia, elevated glutamate transaminase, hypertension, and hypothyroidism.

Donafinib

Donafinib is approved in China to treat patients with unresectable HCC who have not previously received systemic antitumor therapy (evidence level 1, recommendation A). Compared with sorafenib, donafenib significantly prolonged median OS in patients with advanced HCC, with a 17% reduction in the risk of death. Median PFS was similar in the donafenib and sorafenib groups, but donafenib had better safety and tolerability profiles [246]. The most common adverse reactions were hand-foot skin reactions, elevated glutathione transaminase, elevated total bilirubin, decreased platelets, and diarrhea.

Lenvatinib

Lenvatinib is indicated for patients with unresectable HCC with Child-Pugh grade A liver function (evidence level 1, recommendation A). The phase 3, multinational, randomized, non-inferiority REFLECT trial [247] showed that the median OS for lenvatinib was non-inferior to that of sorafenib (hazard ratio [HR]: 0.92, 95% confidence interval [CI]: 0.79–1.06). Median PFS was significantly better in the lenvatinib group than in the sorafenib group, with a reduced risk of disease progression. Common adverse effects included hypertension, proteinuria, diarrhea, loss of appetite, fatigue, and hand-foot syndrome.

Sorafenib

Sorafenib was the first molecularly targeted drug approved for the treatment of HCC. Numerous clinical studies have shown that sorafenib provides good survival benefits in patients with advanced HCC among patients from a variety of countries and regions and with different underlying liver diseases [248, 249] (evidence level 1, recommendation A). Sorafenib can be used in patients with Child-Pugh grade A and B liver function. Sorafenib provides a more significant survival benefit in patients with Child-Pugh grade A compared with patients with Child-Pugh grade B liver function [250]. Efficacy assessment and monitoring for toxicity should be performed regularly during sorafenib treatment. Common adverse events include diarrhea, hand-foot syndrome, rash, hypertension, poor appetite, and fatigue, all of which generally occur within 2–6 weeks after the start of treatment. Blood pressure should be closely monitored during treatment, while liver and kidney function, HBV-DNA, blood count, coagulation function, and urine protein should be tested regularly. The risk of myocardial ischemia should be taken into account during treatment, and the required monitoring and related tests should be performed, especially in elderly patients.

Systemic Chemotherapy

In China, the FOLFOX4 regimen has been approved for the treatment of locally advanced and metastatic HCCs unsuitable for surgical resection or locoregional treatment [251, 252] (evidence level 1, recommendation A). In addition, arsenic trioxide has been shown to have a palliative effect on advanced HCC [253] (evidence level 3,

recommendation C). However, hepatorenal toxicity should be monitored and prevented during clinical use.

Advances in Other First-Line Treatments

Immune checkpoint inhibitor therapy is widely applied in the treatment of various solid tumors, but the efficacy of single agent immune checkpoint inhibitor treatment is low. Several clinical studies have now demonstrated that anti-angiogenic therapy may improve the tumor microenvironment and enhance the antitumor sensitivity to programmed death-1/ligand-1 (PD-1/PD-L1) inhibitors. Synergistic antitumor effects have been observed for the combination of anti-angiogenic therapy and immunotherapy. Two successful phase III studies (IMBrave150 and 0RIENT-32) have shown successful outcomes with the first-line treatment of advanced HCC using immune checkpoint inhibitors in combination with large molecule anti-angiogenic agents (bevacizumab or bevacizumab biosimilar). Several clinical studies on small-molecule anti-angiogenic agents are underway. These studies include but are not limited to: phase III clinical study of camrelizumab in combination with apatinib (SHR-1210-III-310), phase III clinical study of lenvatinib in combination with pembrolizumab (LEAP 002), phase Ib clinical study of lenvatinib in combination with nivolumab (Study 117), phase III clinical study of CS1003 (PD-1 monoclonal antibody) in combination with lenvatinib (CS1003-305), and the phase III clinical study of toripalimab in combination with lenvatinib. In addition, clinical studies of immune checkpoint inhibitors in combination with other drugs are also underway, such as the phase III clinical study of camrelizumab in combination with oxaliplatin-based systemic chemotherapy, the phase III clinical study of durvalumab in combination with tremelimumab (HIMALAYA), and the phase III clinical study of sintilimab in combination with IBI310 (anti-CTLA-4 monoclonal antibody).

Second-Line Antitumor Treatment

Regorafenib

Regorafenib has been approved for the treatment of HCC patients who have been previously treated with sorafenib (evidence level 1, recommendation A). The international multicenter phase III study of regorafenib after treatment with sorafenib in patients with HCC (RESORCE) evaluated the efficacy and safety of regorafenib in HCC patients who had disease progression after sorafenib treatment. The results showed [254] that patients in the regorafenib group had a significant 37% decrease in the risk of death compared with the placebo control group and a 54% reduction in the risk of disease progression. Common adverse reactions include hypertension, hands and feet skin reactions, malaise, and diarrhea. The adverse effects are similar to those of sorafenib and regorafenib is therefore not suitable for patients who are intolerant to sorafenib.

Apatinib

Apatinib mesylate is a novel small-molecule targeted drug developed independently in China and has been approved for use as monotherapy in patients with advanced HCC who have failed or are intolerant to at least one first-line systemic antitumor therapy (evidence level 1, recommendation A). Results from a phase III clinical study of apatinib as a second-line treatment for advanced HCC in China [255] showed that compared with placebo, apatinib significantly prolonged the median OS of patients with advanced HCC receiving second-line or higher treatment, with a 21.5% reduction in the risk of death and a 52.9% reduction in the risk of disease progression. Common adverse reactions include hypertension, proteinuria, leukopenia, and thrombocytopenia. Patients should be closely followed up for adverse reactions during the course of apatinib treatment, and necessary dose adjustments should be made according to patient tolerance.

Camrelizumab

Camrelizumab has been approved for the treatment of patients with advanced HCC who have previously received treatment with sorafenib and/or oxaliplatin-containing systemic chemotherapy (evidence level 3, recommendation B). Results from a phase II clinical study of camrelizumab in Chinese patients with HCC who had previously received systemic antitumor therapy [256] showed an ORR of 14.7%, a 6-month OS rate of 74.4%, and a 12-month OS rate of 55.9%. Common adverse reactions include reactive capillary hyperplasia, elevated glutathione/glutathione transaminase, hypothyroidism, and malaise. Several clinical studies have shown that the incidence of reactive capillary hyperplasia was significantly reduced with the combination of camrelizumab and lapatinib [257, 258].

Tislelizumab

Tislelizumab has been approved for the treatment of patients with HCC who have received at least one systemic antitumor therapy (evidence level 3, recommendation B). A global, multicenter phase II study evaluating the efficacy and safety of tislelizumab in patients with unresectable HCC who have previously

received at least one systemic therapy (RATIONALE 208) [259] reported a median PFS of 2.7 months and a median OS of 13.2 months, with a median OS of 13.8 months and 12.4 months, respectively, for patients who had received first-line treatment and second-line treatment or above. The ORR for the total population was 13.3%, with an ORR of 13.8% for patients who had received first-line systemic therapy and 12.6% for patients who had received second-line therapy or above. The safety profile was favorable, with the main adverse effects comprising elevated glutamic transaminase, elevated glutamic aminotransferase, weakness, and hypothyroidism. Currently, an international multicenter phase III study of tislelizumab compared to sorafenib as first-line treatment in patients with unresectable HCC (RATIONALE 301), and a Chinese multicenter phase II study of tislelizumab in combination with lenvatinib for the first-line treatment of patients with unresectable HCC (BGB-A317-211) are in progress.

Other Second-Line Antitumor Treatment Options

The US Food and Drug Administration (FDA) has conditionally approved pembrolizumab [260] (evidence level 3, recommendation B) and nivolumab in combination with ipilimumab [261] (evidence level 3, recommendation B) for the treatment of patients with HCC who have disease progression after prior treatment with sorafenib, or patients who are intolerant to sorafenib. Conditional approval has also been granted to cabozantinib for the treatment of patients with HCC who have progressed after first-line systemic antitumor therapy [262] (evidence level 1, recommendation B), and to ramucirumab as a second-line treatment for patients with serum AFP levels ≥400 μg/L [263, 264] (evidence level 1, recommendation B). Combination regimens of immune checkpoint inhibitor therapy, targeted agents, chemotherapeutic agents, and locoregional therapies for the second-line treatment of HCC are also being explored.

Other Treatments

Traditional Chinese Medicine

Under the clinical medicine system combining traditional Chinese medicine (TCM) and Western medicine characterized by syndrome differentiation for treatment [265], the combination of disease and syndrome is adopted for the clinical diagnosis and treatment [266]. TCM prescriptions, modern TCM preparations, and characteristic TCM diagnostic and treatment techniques are integrated to treat HCC in different periods, including the perioperative period, postoperative adjuvant treatment period, follow-up rehabilitation period, and palliative period, to assist Western medicine in controlling symptoms, protecting the patient, preventing recurrence and metastasis, and prolonging patient survival.

In addition to TCM herb decoctions boiled into tonics, a number of modern Chinese medicine preparation has been recommended for the treatment of advanced HCC (e.g., Icariin [267] [evidence grade 2, recommended B]) and the adjuvant treatment of HCC after surgical resection (e.g., Huaier Granules [136] [evidence level 1, recommendation A] and Huachansu Combined Detoxification Granules [268] [evidence level 2, recommendation B]). In addition, Huaier granules, elemene, Huachansu, Cinobufagin, Kanglaite, Kangai, Ganfule Capsule, Jinlong Capsules, Aidi Injection, Brucea Javanidasca oil, and compound Mylabris capsules are used to treat advanced HCC [269–275] with established efficacy and favorable patient compliance, safety, and tolerability. However, further standardized clinical studies are required to obtain high-level evidence support.

Antiviral Treatments and Other Liver-Protecting Treatments

For HCC patients with HBV infection, oral antiviral treatment with nucleoside analogs should be performed throughout the entire duration of treatment for HCC. If the preoperative HBV-DNA level is high and the glutamic-pyruvic transaminase level is >2 times the ULN, antiviral and liver-protecting treatments may be administered first, and surgical resection should be performed after the improvement of liver function to improve the safety of surgery. For patients with high HBV-DNA levels but no significant abnormality of liver function, surgery may be performed as soon as possible while administering antiviral treatments at the same time. In the case of patients positive for hepatitis B surface antigen (HBsAg), the use of potent drugs with a low rate of resistance such as entecavir, tenofovir disoproxil, or tenofovir alafenamide is recommended [211] (evidence level 1, recommendation A). Antiviral treatment with DAAs is recommended in patients with HCV-related HCC who are positive for HCV RNA [276, 277] (evidence level 1, recommendation A).

Abnormal liver function may occur during the natural course of disease and/or treatment in patients with HCC. Therefore, timely and appropriate treatment with liver-protecting drugs is required, with anti-inflammatory, anti-oxidative, detoxifying, and cholagogic functions, as

well as for hepatocyte membrane repair and protection. Liver-protecting drugs include magnesium isoglycyrrhizinate injection, diammonium glycyrrhizinate, compound glycyrrhizin, bicyclol, silymarin, reduced glutathione, ademetionine, ursodeoxycholic acid, polyene phosphatidylcholine, and ulinastatin. These drugs are associated with protection of liver function, increased treatment safety, lower rates of complications, and improved quality of life of patients.

Immune-Related Adverse Events

Immune checkpoint inhibitors (ICIs) exert a therapeutic effect on liver cancer by enhancing the anti-tumor immunity and have become an important treatment method in the field of liver cancer. However, when ICIs activates the immune function of the body, they also bring a series of special toxic and side effects, called immune-related adverse events (irAEs). With the wide application of ICIs, irAEs have become a major challenge in clinical practice. The most common types of irAEs are skin toxicity, endocrine toxicity, pneumonia and digestive tract toxicity. Other less common but life-threatening irAEs include interstitial pneumonia and immune myocarditis. The wide disease spectrum of irAEs requires multidisciplinary collaborative management. At present, many academic institutions or platforms in China and globally have formulated various guidelines for irAE management.

There is a potential risk of ICIs-related toxicity or other unexpected toxicity in some special populations. ICI treatment is not routinely recommended for organ transplant patients, patients with active autoimmune diseases, especially those who cannot be controlled by immunosuppressive drugs or need to be controlled by large doses, and HIV patients etc. If ICI treatment is considered for clinical use for these special groups, clinicians must fully communicate with patients and their families before treatment, weigh the pros and cons, and carefully select ICIs treatment.

Symptomatic Supportive Treatment

Patients with HCC often experience complications such as cirrhosis, splenomegaly, and cytopenia of one or more blood lineages due to treatments such as antitumor therapy. Blood product transfusions or pharmacologic therapy may be considered in these cases. Patients with neutropenia may be administered granulocyte colony stimulating factor (G-CSF), including polyethylene glycosylated recombinant human G-CSF and recombinant human G-CSF, as appropriate [278]. Patients with hemoglobin <80 g/L may be infused with erythrocyte suspension or medications, including iron, folic acid, vitamin B12, and erythropoietin, as appropriate. Platelet transfusions may be considered appropriate in patients with thrombocytopenia. To reduce platelet transfusion, platelet counts may be elevated with recombinant human thrombopoietin or thrombopoietin receptor agonists in non-emergency situations [279].

For patients with advanced HCC, best supportive care should be provided including analgesic treatment, correction of hypoalbuminemia, enhanced nutritional support, blood sugar control in patients with diabetes, and management of complications including ascites, jaundice, hepatic encephalopathy, gastrointestinal bleeding, and hepatorenal syndrome. Bisphosphonates may be used in patients with bone metastasis. In addition, adequate rehabilitation exercises can increase patient immunity. Meanwhile, psychological interventions for patients should be emphasized to enhance patient confidence in overcoming the disease, transform negative thinking into positive thinking, and let patients enjoy a sense of security and comfort through palliative care while reducing depression and anxiety.

Response Evaluation for Systemic Antitumor Therapy

Currently, the response evaluation criteria in solid tumors v1.1 (RECIST 1.1) are mainly used for response evaluation in patients receiving systemic treatment. The modified RECIST (mRECIST) may be used in combination to evaluate treatment response in patients receiving anti-angiogenic molecular targeted therapies. Immune RECIST (iRECIST) may be used to evaluate response in patients receiving treatment with immune-checkpoint inhibitors [280].

Summary

1. Indications for systemic antitumor therapy: patients with CNLC stage IIIa and IIIb HCC, patients with CNLC stage IIb HCC who are not suitable for surgical resection or TACE treatment, and HCC patients who are resistant to TACE therapy or who have failed TACE therapy.
2. First-line antitumor treatments may include atezolizumab in combination with bevacizumab, sintilimab in combination with a bevacizumab biosimilar (Bevagen®), donafinib, lenvatinib, sorafenib, and oxaliplatin-containing systemic chemotherapy.
3. In China, approved second-line antitumor treatments include regorafenib, apatinib, camrelizumab, or tislelizumab.

4. As required by the patient's medical condition, traditional Chinese herbal medicine may be administered.
5. Antiviral treatment should be performed throughout the treatment with liver protection and cholagogic treatments as well as supportive symptomatic treatment performed as appropriate in addition to antitumor treatment.

Treatment of Spontaneous Rupture of Liver Tumors

Rupture of liver tumors is a potentially fatal complication of HCC. The in-hospital mortality of simple conservative treatment for a ruptured tumor is extremely high. However, it is not a determinant of the long-term survival of patients. Therefore, after the success of initial rescue measures, the patient's hemodynamics, liver function, general health status, and possibility of removal of the tumor should be fully evaluated to develop an individualized treatment regimen [281–285].

1. Surgical resection is the first choice in patients with a resectable liver tumor, good liver reserve function, and stable hemodynamics [286, 287] (evidence level 2, recommendation A).
2. TAE can be selected for patients with poor liver reserve function and unstable hemodynamics who are unsuitable for surgery [288] (evidence level 4, recommendation B).
3. In cases where it is not possible to fully evaluate liver function and liver tumors due to limitations of emergency conditions, TAE may be performed first. Corresponding treatment regimens may be subsequently selected based on a follow-up evaluation. Significant survival benefits may be obtained if a second-stage surgical resection is performed [286] (evidence level 3, recommendation A).
4. Spontaneous rupture of liver tumors is a high-risk factor for postoperative recurrence and should be treated with adequate intraoperative flushing of the abdominal cavity and postoperative adjuvant therapy. Aggressive radical resection may be considered in patients with postoperative peritoneal metastases alone [289] (evidence level 3, recommendation C).

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Statement of Ethics

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

References

1 Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019;394(10204):1145–58.
2 Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015: cancer statistics in China, 2015. CA Cancer J Clin. 2016;66(2):115–32.
3 https://gco.iarc.fr/today/data/factsheets/cancers/11-Liver-fact-sheet.pdf.
4 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
5 Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
6 Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.
7 Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726–35.
8 https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/Guidelines-Methodology-Manual_0.pdf.
9 Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004;130(7):417–22.
10 Hou JL, Zhao W, Lee C, Hann HW, Peng CY, Tanwandee T, et al. Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a randomized trial in 24 countries. Clin Gastroenterol Hepatol. 2020;18(2):457–67.e21.
11 Fan R, Papatheodoridis G, Sun J, Innes H, Toyoda H, Xie Q, et al. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol. 2020;73(6):1368–78.
12 Hao X, Fan R, Guo YB, Hou JL. Creating an integrated "pyramid" liver cancer screening model in the hospital and community to achieve early screening and diagnosis and treatment of liver cancer. Chin J Liver Dis. 2021;29(4):289–92.
13 Wang WP, Ji ZB, Dong Y, et al. Application of real-time navigational ultrasonography in the diagnosis of small hepatocellular carcinoma. Chin J Ultrasound Med. 2016;13(1):56–60.
14 Dong Y, Wang WP, Gan YH, Huang BJ, Ding H. Radiofrequency ablation guided by contrast-enhanced ultrasound for hepatic malignancies: preliminary results. Clin Radiol. 2014;69(11):1129–35.
15 Dong Y, Wang WP, Mao F, Dietrich C. Contrast-enhanced ultrasound features of hepatocellular carcinoma not detected during the screening procedure. Z Gastroenterol. 2017;55(8):748–53.
16 Wang WP, Dong Y, Cao J, Mao F, Xu Y, Si Q, et al. Detection and characterization of small superficially located focal liver lesions by contrast-enhanced ultrasound with high frequency transducers. Med Ultrason. 2017;19(4):349–56.
17 Dong Y, Wang WP, Mao F, Ji ZB, Huang BJ. Application of imaging fusion combining contrast-enhanced ultrasound and magnetic resonance imaging in detection of hepatic cellular carcinomas undetectable by conventional ultrasound. J Gastroenterol Hepatol. 2016;31(4):822–8.
18 Dong Y, Wang WP, Xu Y, Cao J, Mao F, Dietrich CF. Point shear wave speed measurement in differentiating benign and malignant focal liver lesions. Med Ultrason. 2017;19(3):259–64.
19 Chen M, Cao J, Hu J, Topatana W, Li S, Juengpanich S, et al. Clinical-radiomic analysis for pretreatment prediction of objective response to first transarterial chemoembolization in hepatocellular carcinoma. Liver Cancer. 2021;10(1):38–51.
20 Lee YJ, Lee JM, Lee JS, Lee HY, Park BH, Kim YH, et al. Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging-a systematic review and meta-analysis. Radiology. 2015;275(1):97–109.
21 Liu X, Jiang H, Chen J, Zhou Y, Huang Z, Song B. Gadoxetic acid disodium-enhanced magnetic resonance imaging outperformed multidetector computed tomography in diagnosing small hepatocellular carcinoma: a meta-analysis. Liver Transpl. 2017;23(12):1505–18.
22 Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. Hepatology. 2018;68(2):723–50.
23 Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv238–55.
24 Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–70.
25 Cho ES, Choi JY. MRI features of hepatocellular carcinoma related to biologic behavior. Korean J Radiol. 2015;16(3):449–64.
26 Hwang J, Kim YK, Jeong WK, Choi D, Rhim H, Lee WJ. Nonhypervascular hypointense nodules at gadoxetic acid-enhanced MR imaging in chronic liver disease: diffusion-weighted imaging for characterization. Radiology. 2015;276(1):137–46.
27 Zeng MS, Ye HY, Guo L, Peng WJ, Lu JP, Teng GJ, et al. Gd-EOB-DTPA-enhanced magnetic resonance imaging for focal liver lesions in Chinese patients: a multicenter, open-label, phase III study. Hepatobiliary Pancreat Dis Int. 2013;12(6):607–16.
28 Ichikawa T, Saito K, Yoshioka N, Tanimoto A, Gokan T, Takehara Y, et al. Detection and characterization of focal liver lesions: a Japanese phase III, multicenter comparison between gadoxetic acid disodium-enhanced magnetic resonance imaging and contrast-enhanced computed tomography predominantly in patients with hepatocellular carcinoma and chronic liver disease. Invest Radiol. 2010;45(3):133–41.
29 Wang W, Yang C, Zhu K, Yang L, Ding Y, Luo R, et al. Recurrence after curative resection of hepatitis B virus-related hepatocellular carcinoma: diagnostic algorithms on gadoxetic acid-enhanced magnetic resonance imaging. Liver Transpl. 2020;26(6):751–63.
30 Yoo SH, Choi JY, Jang JW, Bae SH, Yoon SK, Kim DG, et al. Gd-EOB-DTPA-enhanced MRI is better than MDCT in decision making of curative treatment for hepatocellular carcinoma. Ann Surg Oncol. 2013;20(9):2893–900.
31 Rao SX, Wang J, Wang J, Jiang XQ, Long LL, Li ZP, et al. Chinese consensus on the clinical application of hepatobiliary magnetic resonance imaging contrast agent: gadoxetic acid disodium. J Dig Dis. 2019;20(2):54–61.
32 Renzulli M, Biselli M, Brocchi S, Granito A, Vasuri F, Tovoli F, et al. New hallmark of hepatocellular carcinoma, early hepatocellular carcinoma and high-grade dysplastic nodules on Gd-EOB-DTPA MRI in patients with cirrhosis: a new diagnostic algorithm. Gut. 2018;67(9):1674–82.
33 Xu X, Zhang HL, Liu QP, Sun SW, Zhang J, Zhu FP, et al. Radiomic analysis of contrast-enhanced CT predicts microvascular invasion and outcome in hepatocellular carcinoma. J Hepatol. 2019;70(6):1133–44.
34 Chong HH, Yang L, Sheng RF, Yu YL, Wu DJ, Rao SX, et al. Multi-scale and multi-parametric radiomics of gadoxetate disodium-enhanced MRI predicts microvascular invasion and outcome in patients with solitary hepatocellular carcinoma ≤5 cm. Eur Radiol. 2021;31(7):4824–38.

35 Yang L, Gu D, Wei J, Yang C, Rao S, Wang W, et al. A radiomics nomogram for preoperative prediction of microvascular invasion in hepatocellular carcinoma. Liver Cancer. 2019;8(5):373–86.
36 Lei Z, Li J, Wu D, Xia Y, Wang Q, Si A, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the milan criteria. JAMA Surg. 2016;151(4):356–63.
37 Lin CY, Chen JH, Liang JA, Lin CC, Jeng LB, Kao CH. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. Eur J Radiol. 2012;81(9):2417–22.
38 Park JW, Kim JH, Kim SK, Kang KW, Park KW, Choi JI, et al. A prospective evaluation of 18F-FDG and 11C-acetate PET/CT for detection of primary and metastatic hepatocellular carcinoma. J Nucl Med. 2008; 49(12):1912–21.
39 Boellaard R, O'doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging–version 1.0. Eur J Nucl Med Mol Imaging. 2010;37(1):181–200.
40 Chalian H, Tore HG, Horowitz JM, Salem R, Miller FH, Yaghmai V. Radiologic assessment of response to therapy: comparison of RECIST versions 1.1 and 1.0. Radiographics. 2011;31(7):2093–105.
41 Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50(Suppl 1): 122S–50S.
42 Ferda J, Ferdova E, Baxa J, Kreuzberg B, Daum O, Třeška V, et al. The role of 18F-FDG accumulation and arterial enhancement as biomarkers in the assessment of typing, grading and staging of hepatocellular carcinoma using 18F-FDG-PET/CT with integrated dual-phase CT angiography. Anticancer Res. 2015;35(4):2241–6.
43 Hyun SH, Eo JS, Lee JW, Choi JY, Lee KH, Na SJ, et al. Prognostic value of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in patients with Barcelona Clinic Liver Cancer stages 0 and A hepatocellular carcinomas: a multicenter retrospective cohort study. Eur J Nucl Med Mol Imaging. 2016;43(9):1638–45.
44 Lee JW, Oh JK, Chung YA, Na SJ, Hyun SH, Hong IK, et al. Prognostic significance of ^{18}F-FDG uptake in hepatocellular carcinoma treated with transarterial chemoembolization or concurrent chemoradiotherapy: a multicenter retrospective cohort study. J Nucl Med. 2016;57(4):509–16.
45 Na SJ, Oh JK, Hyun SH, Lee JW, Hong IK, Song BI, et al. ^{18}F-FDG PET/CT can predict survival of advanced hepatocellular carcinoma patients: a multicenter retrospective cohort study. J Nucl Med. 2017;58(5):730–6.
46 Bertagna F, Bertoli M, Bosio G, Biasiotto G, Sadeghi R, Giubbini R, et al. Diagnostic role of radiolabelled choline PET or PET/CT in hepatocellular carcinoma: a systematic review and meta-analysis. Hepatol Int. 2014; 8(4):493–500.
47 Cheung TT, Ho CL, Lo CM, Chen S, Chan SC, Chok KSH, et al. 11C-acetate and 18F-FDG PET/CT for clinical staging and selection of patients with hepatocellular carcinoma for liver transplantation on the basis of Milan criteria: surgeon's perspective. J Nucl Med. 2013;54(2):192–200.
48 Zhang Y, Shi H, Cheng D, Jiang L, Xiu Y, Li B, et al. Added value of SPECT/spiral CT versus SPECT in diagnosing solitary spinal lesions in patients with extraskeletal malignancies. Nucl Med Commun. 2013;34(5):451–8.
49 Hectors SJ, Wagner M, Besa C, Huang W, Taouli B. Multiparametric FDG-PET/MRI of hepatocellular carcinoma: initial experience. Contrast Media Mol Imaging. 2018; 2018:5638283.
50 Zhou J, Yu L, Gao X, Hu J, Wang J, Dai Z, et al. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. J Clin Oncol. 2011;29(36):4781–8.
51 Best J, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2020;18(3):728–35.e4.
52 Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008;47(1):97–104.
53 Roberts LR, Sirlin CB, Zaiem F, Almasri J, Prokop LJ, Heimbach JK, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology. 2018;67(1):401–21.
54 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
55 Huang YH, Zhang CZ, Huang QS, Yeong J, Wang F, Yang X, et al. Clinicopathologic features, tumor immune microenvironment and genomic landscape of Epstein-Barr virus-associated intrahepatic cholangiocarcinoma. J Hepatol. 2021;74(4):838–49.
56 Yu WL, Yu G, Dong H, Chen K, Xie J, Yu H, et al. Proteomics analysis identified TPI1 as a novel biomarker for predicting recurrence of intrahepatic cholangiocarcinoma. J Gastroenterol. 2020;55(12):1171–82.
57 Paradis V, Fukayama M, Park Y, et al. Tumours of liver and intrahepatic bile ducts [M]. 5 ed. Lyon, France: IARC Press; 2019.
58 Cong WM. Surgical pathology of hepatobiliary tumors [M]. 1st ed. Singapore: Springer; 2017.
59 Cong WM, Bu H, Chen J, Dong H, Zhu YY, Feng LH, et al. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. World J Gastroenterol. 2016;22(42):9279–87.
60 Chen L, Chen S, Zhou Q, Cao Q, Dong Y, Feng S, et al. Microvascular invasion status and its survival impact in hepatocellular carcinoma depend on tissue sampling protocol. Ann Surg Oncol. 2021;28(11): 6747–57.
61 Nara S, Shimada K, Sakamoto Y, Esaki M, Kishi Y, Kosuge T, et al. Prognostic impact of marginal resection for patients with solitary hepatocellular carcinoma: evidence from 570 hepatectomies. Surgery. 2012; 151(4):526–36.
62 Cong W. Hepacocellular carcinoma. In: Cong W, editor. Surgical pathology of liver and gallbalder tumors. Beijing: People's Medical Publishing House; 2015. p. 276–320.
63 Scheuer PJ. Classification of chronic viral hepatitis: a need for reassessment. J Hepatol. 1991;13(3):372–4.
64 Regimens for prevention and treatment of viral hepatitis. Chin J Infect Dis. 2001;19(1): 56–62.
65 Guidelines for the prevention, care and treatment of persons with chronic Hepatitis B Infection. Geneva; 2015.
66 Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol. 2013;20(1):325–39.
67 Chinese Societies of Liver Cancer Ca-CA; Liver Cancer Study Group CSOH; Chinese Medical Association; Chinese Societies of Pathology Ca-CA, et al. Evidence-based practice guidelines for the standardized pathological diagnosis of primary liver cancer (2015 edition). Chin J Hepatobiliary Surg. 2015;21(3):145–51.
68 Sheng X, Ji Y, Ren GP, Lu CL, Yun JP, Chen LH, et al. A standardized pathological proposal for evaluating microvascular invasion of hepatocellular carcinoma: a multicenter study by LCPGC. Hepatol Int. 2020;14(6): 1034–47.
69 Isik B, Gonultas F, Sahin T, Yilmaz S. Microvascular venous invasion in hepatocellular carcinoma: why do recurrences occur? J Gastrointest Cancer. 2020;51(4):1133–6.
70 Zhang X, Li J, Shen F, Lau WY. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. J Gastroenterol Hepatol. 2018;33(2): 347–54.
71 Travis WD, Dacic S, Wistuba I, Sholl L, Adusumilli P, Bubendorf L, et al. IASLC multidisciplinary recommendations for pathologic assessment of lung cancer resection specimens after neoadjuvant therapy. J Thorac Oncol. 2020;15(5):709–40.

72 Allard MA, Sebagh M, Ruiz A, Guettier C, Paule B, Vibert E, et al. Does pathological response after transarterial chemoembolization for hepatocellular carcinoma in cirrhotic patients with cirrhosis predict outcome after liver resection or transplantation? J Hepatol. 2015;63(1):83–92.
73 Stein JE, Lipson EJ, Cottrell TR, Forde PM, Anders RA, Cimino-Mathews A, et al. Pan-tumor pathologic scoring of response to PD-(L)1 blockade. Clin Cancer Res. 2020;26(3):545–51.
74 Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg. 2003;138(11):1198–206; discussion 206.
75 Kubota K, Makuuchi M, Kusaka K, Kobayashi T, Miki K, Hasegawa K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. Hepatology. 1997;26(5):1176–81.
76 Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology. 1996;111(4):1018–22.
77 Cescon M, Colecchia A, Cucchetti A, Peri E, Montrone L, Ercolani G, et al. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. Ann Surg. 2012;256(5):706–12; discussion 712–3.
78 Shen Y, Zhou C, Zhu G, Shi G, Zhu X, Huang C, et al. Liver stiffness assessed by shear wave elastography predicts postoperative liver failure in patients with hepatocellular carcinoma. J Gastrointest Surg. 2017;21(9):1471–9.
79 Rajakannu M, Cherqui D, Ciacio O, Golse N, Pittau G, Allard MA, et al. Liver stiffness measurement by transient elastography predicts late posthepatectomy outcomes in patients undergoing resection for hepatocellular carcinoma. Surgery. 2017;162(4):766–74.
80 Zhong JH, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg. 2014;260(2):329–40.
81 Xiao H, Zhang B, Mei B, Zuo C, Wei G, Wang R, et al. Hepatic resection for hepatocellular carcinoma in patients with portal hypertension: a long-term benefit compared with transarterial chemoembolization and thermal ablation. Medicine. 2015;94(7):e495.
82 Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol. 2009;6(10):573–82.
83 Chen X, Zhai J, Cai X, Zhang Y, Wei L, Shi L, et al. Severity of portal hypertension and prediction of postoperative liver failure after liver resection in patients with Child-Pugh grade A cirrhosis. Br J Surg. 2012;99(12):1701–10.
84 Chen MS, Li JQ, Zheng Y, Guo RP, Liang HH, Zhang YQ, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321–8.
85 Kudo M, Hasegawa K, Kawaguchi Y, Takayama T, Izumi N, Yamanaka N, et al. A multicenter randomized controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF trial): analysis of overall survival. J Clin Oncol. 2021;39(15_Suppl):4093.
86 Mohkam K, Dumont PN, Manichon AF, Jouvet JC, Boussel L, Merle P, et al. No-touch multibipolar radiofrequency ablation versus surgical resection for solitary hepatocellular carcinoma ranging from 2 to 5 cm. J Hepatol. 2018;68(6):1172–80.
87 Xu XL, Liu XD, Liang M, Luo BM. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. Radiology. 2018;287(2):461–72.
88 Liu PH, Hsu CY, Hsia CY, Lee YH, Huang YH, Chiou YY, et al. Surgical resection versus radiofrequency ablation for single hepatocellular carcinoma ≤2 cm in a propensity score model. Ann Surg. 2016;263(3):538–45.
89 Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012;57(4):794–802.
90 Xu Q, Kobayashi S, Ye X, Meng X. Comparison of hepatic resection and radiofrequency ablation for small hepatocellular carcinoma: a meta-analysis of 16,103 patients. Sci Rep. 2014;4:7252.
91 Xia Y, Li J, Liu G, Wang K, Qian G, Lu Z, et al. Long-term effects of repeat hepatectomy vs percutaneous radiofrequency ablation among patients with recurrent hepatocellular carcinoma: a randomized clinical trial. JAMA Oncol. 2020;6(2):255–63.
92 Yin L, Li H, Li AJ, Lau WY, Pan ZY, Lai ECH, et al. Partial hepatectomy versus transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. J Hepatol. 2014;61(1):82–8.
93 Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, et al. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci. 2011;18(1):74–80.
94 Wang K, Guo WX, Chen MS, Mao YL, Sun BC, Shi J, et al. Multimodality treatment for hepatocellular carcinoma with portal vein tumor thrombus: a large-scale, multicenter, propensity mathching score analysis. Medicine. 2016;95(11):e3015.
95 Wei X, Jiang Y, Zhang X, Feng S, Zhou B, Ye 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(24):2141–2151.
96 Li XL, Zhu XD, Cai H, Li Y, Zhou J, Fan J, et al. Postoperative α-fetoprotein response predicts tumor recurrence and survival after hepatectomy for hepatocellular carcinoma: a propensity score matching analysis. Surgery. 2019;165(6):1161–7.
97 Yang J, Tao HS, Cai W, Zhu W, Zhao D, Hu HY, et al. Accuracy of actual resected liver volume in anatomical liver resections guided by 3-dimensional parenchymal staining using fusion indocyanine green fluorescence imaging. J Surg Oncol. 2018;118(7):1081–7.
98 Mise Y, Hasegawa K, Satou S, Shindoh J, Miki K, Akamatsu N, et al. How has virtual hepatectomy changed the practice of liver surgery?: experience of 1194 virtual hepatectomy before liver resection and living donor liver transplantation. Ann Surg. 2018;268(1):127–33.
99 Digital Medicine Branch of Chinese Medical Association; Digital Intelligent Surgery Committee of Chinese Research Hospital Association; Liver Cancer Committee of Chinese Medical Association, et al. Computer-assisted combined indocyanine green molecular fluorescence imaging Guidelines for the application of technology in the diagnosis and surgical navigation of liver tumors (2019 edition). Chin J Pract Surg. 2019;39(7):641–50. 54.
100 Jiang HT, Cao JY. Impact of laparoscopic versus open hepatectomy on perioperative clinical outcomes of patients with primary hepatic carcinoma. Chin Med Sci J. 2015;30(2):80–3.
101 Hepatobiliary and Pancreatic Surgery Committee of the Chinese Society of Research Hospitals. Chinese expert consensus on laparoscopic hepatectomy for hepatocellular carcinoma (2020 edition). Chin J Gastrointest Surg. 2020;19(11):1119–34.
102 Wang X, Teh CSC, Ishizawa T, Aoki T, Cavallucci D, Lee SY, et al. Consensus guidelines for the use of fluorescence imaging in hepatobiliary surgery. Ann Surg. 2021;274(1):97–106.
103 Xia YX, Zhang F, Li XC, Kong LB, Zhang H, Li DH, et al. Analysis of 10 966 cases of primary hepatocellular carcinoma treated externally. Chin J Surg. 2021;59(1):6–17.
104 Hidaka M, Eguchi S, Okuda K, Beppu T, Shirabe K, Kondo K, et al. Impact of anatomical resection for hepatocellular carcinoma with microportal invasion (vp1): a multi-institutional study by the kyushu study group of liver surgery. Ann Surg. 2020;271(2):339–46.
105 Zhong FP, Zhang YJ, Liu Y, Zou SB. Prognostic impact of surgical margin in patients with hepatocellular carcinoma: a meta-analysis. Medicine. 2017;96(37):e8043.

106 Shi M, Guo RP, Lin XJ, Zhang YQ, Chen MS, Zhang CQ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007; 245(1):36–43.
107 Yang P, Si A, Yang J, Cheng Z, Wang K, Li J, et al. A wide-margin liver resection improves long-term outcomes for patients with HBV-related hepatocellular carcinoma with microvascular invasion. Surgery. 2019; 165(4):721–30.
108 Liu CL, Fan ST, Lo CM, Tung-Ping Poon R, Wong J. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. Ann Surg. 2000;232(1):25–31.
109 Zhou C, Peng Y, Zhou K, Zhang L, Zhang X, Yu L, et al. Surgical resection plus radiofrequency ablation for the treatment of multifocal hepatocellular carcinoma. Hepatobiliary Surg Nutr. 2019;8(1):19–28.
110 Zhang ZM, Lai EC, Zhang C, Yu HW, Liu Z, Wan BJ, et al. The strategies for treating primary hepatocellular carcinoma with portal vein tumor thrombus. Int J Surg. 2015; 20:8–16.
111 Fu SY, Lau WY, Li AJ, Yang Y, Pan ZY, Sun YM, et al. Liver resection under total vascular exclusion with or without preceding Pringle manoeuvre. Br J Surg. 2010; 97(1):50–5.
112 Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, et al. Clinicopathologic evaluation of hepatocellular carcinoma with bile duct thrombi. Surgery. 2000; 128(5):779–83.
113 Kim DS, Kim BW, Hatano E, Hwang S, Hasegawa K, Kudo A, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korea-Japan multicenter study. Ann Surg. 2020;271(5): 913–21.
114 Zhu XD, Huang C, Shen YH, Ji Y, Ge NL, Qu XD, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. Liver Cancer. 2021;10(4):320–9.
115 Sun HC, Xie Q, Pod WD, et al. Chinese expert consensus on translational therapy for hepatocellular carcinoma (2021 edition). Chin J Pract Surg. 2021;41(6):618–32.
116 Zhang WW, Hu BY, Han J, et al. Preliminary report of a combination regimen of PD-1 inhibitors and multi-targeted tyrosine kinase inhibitors for the translational treatment of progressive hepatocellular carcinoma. Chin J Hepatobiliary Surg. 2020;26(12): 947–8.
117 He M, Li Q, Zou R, Shen J, Fang W, Tan G, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. JAMA Oncol. 2019;5(7):953–60.
118 Chen X, Zhang Y, Zhang N, Ge Y, Jia W. Lenvatinib combined nivolumab injection followed by extended right hepatectomy is a feasible treatment for patients with massive hepatocellular carcinoma: a case report. Onco Targets Ther. 2019;12:7355–9.
119 He MK, Le Y, Li QJ, Yu ZS, Li SH, Wei W, et al. Hepatic artery infusion chemotherapy using mFOLFOX versus transarterial chemoembolization for massive unresectable hepatocellular carcinoma: a prospective non-randomized study. Chin J Cancer. 2017;36(1):83.
120 Zhang Y, Huang G, Wang Y, Liang L, Peng B, Fan W, et al. Is salvage liver resection necessary for initially unresectable hepatocellular carcinoma patients downstaged by transarterial chemoembolization? Ten years of experience[J]. Oncologist. 2016;21(12): 1442–9.
121 Lyu N, Kong Y, Mu L, Lin Y, Li J, Liu Y, et al. Hepatic arterial infusion of oxaliplatin plus fluorouracil/leucovorin versus sorafenib for advanced hepatocellular carcinoma. J Hepatol. 2018;69(1):60–9.
122 Byun HK, Kim HJ, Im YR, Kim DY, Han KH, Seong J. Dose escalation by intensity modulated radiotherapy in liver-directed concurrent chemoradiotherapy for locally advanced BCLC stage C hepatocellular carcinoma. Radiother Oncol. 2019;133:1–8.
123 Li B, Qiu J, Zheng Y, Shi Y, Zou R, He W, et al. Conversion to resectability using transarterial chemoembolization combined with hepatic arterial infusion chemotherapy for initially unresectable hepatocellular carcinoma. Ann Surg Open. 2021;2(2):e057.
124 He MK, Liang RB, Zhao Y, Xu YJ, Chen HW, Zhou YM, et al. Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus lenvatinib alone for advanced hepatocellular carcinoma. Ther Adv Med Oncol. 2021;13:17588359211002720.
125 Wakabayashi H, Okada S, Maeba T, Maeta H. Effect of preoperative portal vein embolization on major hepatectomy for advanced-stage hepatocellular carcinomas in injured livers: a preliminary report. Surg Today. 1997;27(5):403–10.
126 Zheng SG, Li JW, Xiao L, et al. Two-step hepatectomy with total laparoscopy combined with liver dissection and portal vein ligation for hepatocellular carcinoma in cirrhosis. Chin J Gastrointest Surg. 2014;13(7): 502–7.
127 Hong DF, Zhang YB, Peng SY, Huang DS. Percutaneous microwave ablation liver partition and portal vein embolization for rapid liver regeneration: a minimally invasive first step of ALPPS for hepatocellular carcinoma. Ann Surg. 2016;264(1):e1–2.
128 D'haese JG, Neumann J, Weniger M, Pratschke S, Björnsson B, Ardiles V, et al. Should ALPPS be used for liver resection in intermediate-stage HCC? Ann Surg Oncol. 2016;23(4):1335–43.
129 Li PP, Huang G, Jia NY, Pan ZY, Liu H, Yang Y, et al. Associating liver partition and portal vein ligation for staged hepatectomy versus sequential transarterial chemoembolization and portal vein embolization in staged hepatectomy for HBV-related hepatocellular carcinoma: a randomized comparative study. Hepatobiliary Surg Nutr. 2020.
130 Wang Z, Peng Y, Hu J, Wang X, Sun H, Sun J, et al. Associating liver partition and portal vein ligation for staged hepatectomy for unresectable hepatitis B virus-related hepatocellular carcinoma: a single center study of 45 patients. Ann Surg. 2020;271(3): 534–41.
131 Shi HY, Wang SN, Wang SC, Chuang SC, Chen CM, Lee KT. Preoperative transarterial chemoembolization and resection for hepatocellular carcinoma: a nationwide Taiwan database analysis of long-term outcome predictors. J Surg Oncol. 2014;109(5): 487–93.
132 Zhou WP, Lai EC, Li AJ, Fu SY, Zhou JP, Pan ZY, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg. 2009; 249(2):195–202.
133 Kaseb AO, Tran Cao HS, Mohamed YI, Qayyum A, Vence LM, Blando JM, et al. 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.
134 Wang Z, Ren Z, Chen Y, Hu J, Yang G, Yu L, et al. Adjuvant transarterial chemoembolization for HBV-related hepatocellular carcinoma after resection: a randomized controlled study. Clin Cancer Res. 2018;24(9): 2074–81.
135 Wei W, Jian PE, Li SH, Guo ZX, Zhang YF, Ling YH, et al. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety. Cancer Commun. 2018;38(1):61.
136 Chen Q, Shu C, Laurence AD, Chen Y, Peng BG, Zhen ZJ, et al. Effect of Huaier granule on recurrence after curative resection of HCC: a multicentre, randomised clinical trial. Gut. 2018;67(11):2006–16.
137 Huang G, Li PP, Lau WY, Pan ZY, Zhao LH, Wang ZG, et al. Antiviral therapy reduces hepatocellular carcinoma recurrence in patients with low HBV-DNA levels: a randomized controlled trial. Ann Surg. 2018;268(6): 943–54.
138 Yin J, Li N, Han Y, Xue J, Deng Y, Shi J, 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(29): 3647–55.

139 Huang G, Lau WY, Wang ZG, Pan ZY, Yuan SX, Shen F, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. Ann Surg. 2015;261(1):56–66.
140 Singal AG, Lim JK, Kanwal F. AGA clinical practice update on interaction between oral direct-acting antivirals for chronic hepatitis C infection and hepatocellular carcinoma: expert review. Gastroenterology. 2019;156(8):2149–57.
141 Fan J, Zhou J, Wu ZQ, Qiu SJ, Wang XY, Shi YH, et al. Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol. 2005;11(8):1215–9.
142 Lo CM, Liu CL, Chan SC, Lam CM, Poon RTP, Ng IOL, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Ann Surg. 2007;245(6):831–42.
143 Sun HC, Tang ZY, Wang L, Qin LX, Ma ZC, Ye QH, et al. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. J Cancer Res Clin Oncol. 2006;132(7):458–65.
144 Nishiguchi S, Tamori A, Kubo S. Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. Intervirology. 2005;48(1):71–5.
145 Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology. 2006;44(6):1543–54.
146 Ji J, Shi J, Budhu A, Yu Z, Forgues M, Roessler S, et al. MicroRNA expression, survival, and response to interferon in liver cancer. N Engl J Med. 2009;361(15):1437–47.
147 Sun HC, Zhu XD, Zhou J, Gao Q, Shi YH, Ding ZB, et al. Effect of postoperative apatinib treatment after resection of hepatocellular carcinoma with portal vein invasion: a phase II study. J Clin Oncol. 2020;38(4_Suppl):514.
148 Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. Nat Rev Gastroenterol Hepatol. 2017;14(4):203–17.
149 Fan J, Yang GS, Fu ZR, Peng ZH, Xia Q, Peng CH, et al. Liver transplantation outcomes in 1,078 hepatocellular carcinoma patients: a multi-center experience in Shanghai, China. J Cancer Res Clin Oncol. 2009;135(10):1403–12.
150 Zheng SS, Xu X, Wu J, Chen J, Wang WL, Zhang M, et al. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation. 2008;85(12):1726–32.
151 Li J, Yan LN, Yang J, Chen ZY, Li B, Zeng Y, et al. Indicators of prognosis after liver transplantation in Chinese hepatocellular carcinoma patients. World J Gastroenterol. 2009;15(33):4170–6.
152 Zhuo S, Yang G, Ning Y, et al. The use of the Sanya Consensus in the treatment of primary liver cancer in liver transplantation. Chin J Pract Surg. 2008;28(6):466–9.
153 Kulik L, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, et al. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: a systematic review and meta-analysis. Hepatology. 2018;67(1):381–400.
154 Lee S, Kim KW, Song GW, Kwon JH, Hwang S, Kim KH, et al. The real impact of bridging or downstaging on survival outcomes after liver transplantation for hepatocellular carcinoma. Liver Cancer. 2020;9(6):721–33.
155 Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R, De Carlis L, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. Lancet Oncol. 2020;21(7):947–56.
156 Mehta N, Guy J, Frenette CT, Dodge JL, Osorio RW, Minteer WB, et al. Excellent outcomes of liver transplantation following down-staging of hepatocellular carcinoma to within milan criteria: a multicenter study. Clin Gastroenterol Hepatol. 2018;16(6):955–64.
157 Llovet JM, Pavel M, Rimola J, Diaz MA, Colmenero J, Saavedra-Perez D, et al. Pilot study of living donor liver transplantation for patients with hepatocellular carcinoma exceeding Milan Criteria (Barcelona Clinic Liver Cancer extended criteria). Liver Transpl. 2018;24(3):369–79.
158 Pinheiro RS, Waisberg DR, Nacif LS, Rocha-Santos V, Arantes RM, Ducatti L, et al. Living donor liver transplantation for hepatocellular cancer: an (almost) exclusive Eastern procedure? Transl Gastroenterol Hepatol. 2017;2:68.
159 Sposito C, Cucchetti A, Mazzaferro V. Assessing competing risks for death following liver transplantation for hepatocellular carcinoma. Dig Dis Sci. 2019;64(4):1001–7.
160 Segev DL, Sozio SM, Shin EJ, Nazarian SM, Nathan H, Thuluvath PJ, et al. Steroid avoidance in liver transplantation: meta-analysis and meta-regression of randomized trials. Liver Transpl. 2008;14(4):512–25.
161 Rodriguez-Peralvarez M, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J, et al. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. J Hepatol. 2013;59(6):1193–9.
162 Liang W, Wang D, Ling X, Kao AA, Kong Y, Shang Y, et al. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. Liver Transpl. 2012;18(1):62–9.
163 Zhou J, Wang Z, Wu ZQ, Qiu SJ, Yu Y, Huang XW, et al. Sirolimus-based immunosuppression therapy in liver transplantation for patients with hepatocellular carcinoma exceeding the Milan criteria. Transplant Proc. 2008;40(10):3548–53.
164 Geissler EK, Schnitzbauer AA, Zulke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized, multicenter, open-label phase 3 trial. Transplantation. 2016;100(1):116–25.
165 Thorat A, Jeng LB, Yang HR, Yeh CC, Hsu SC, Chen TH, et al. Assessing the role of everolimus in reducing hepatocellular carcinoma recurrence after living donor liver transplantation for patients within the UCSF criteria: re-inventing the role of mammalian target of rapamycin inhibitors. Ann Hepatobiliary Pancreat Surg. 2017;21(4):205–11.
166 Schnitzbauer AA, Filmann N, Adam R, Bachellier P, Bechstein WO, Becker T, et al. mTOR inhibition is most beneficial after liver transplantation for hepatocellular carcinoma in patients with active tumors. Ann Surg. 2020;272(5):855–62.
167 Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: risk factors, screening and clinical presentation. World J Hepatol. 2019;11(3):261–72.
168 Au KP, Chok KSH. Multidisciplinary approach for post-liver transplant recurrence of hepatocellular carcinoma: a proposed management algorithm. World J Gastroenterol. 2018;24(45):5081–94.
169 Iavarone M, Invernizzi F, Czauderna C, Sanduzzi-Zamparelli M, Bhoori S, Amaddeo G, et al. Preliminary experience on safety of regorafenib after sorafenib failure in recurrent hepatocellular carcinoma after liver transplantation. Am J Transplant. 2019;19(11):3176–84.
170 Nordness MF, Hamel S, Godfrey CM, Shi C, Johnson DB, Goff LW, et al. Fatal hepatic necrosis after nivolumab as a bridge to liver transplant for HCC: are checkpoint inhibitors safe for the pretransplant patient? Am J Transplant. 2020;20(3):879–83.
171 Shi GM, Wang J, Huang XW, Huang XY, He YF, Ji Y, et al. Graft programmed death ligand 1 expression as a marker for transplant rejection following anti-programmed death 1 immunotherapy for recurrent liver tumors. Liver Transpl. 2021;27(3):444–9.
172 Hasegawa K, Aoki T, Ishizawa T, Kaneko J, Sakamoto Y, Sugawara Y, et al. Comparison of the therapeutic outcomes between surgical resection and percutaneous ablation for small hepatocellular carcinoma. Ann Surg Oncol. 2014;21(Suppl 3):S348–55.
173 Li L, Zhang J, Liu X, Li X, Jiao B, Kang T. Clinical outcomes of radiofrequency ablation and surgical resection for small hepatocellular carcinoma: a meta-analysis. J Gastroenterol Hepatol. 2012;27(1):51–8.

174 Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252(6):903–12.
175 Feng Q, Chi Y, Liu Y, Zhang L, Liu Q. Efficacy and safety of percutaneous radiofrequency ablation versus surgical resection for small hepatocellular carcinoma: a meta-analysis of 23 studies. J Cancer Res Clin Oncol. 2015;141(1):1–9.
176 Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, Chen H, et al. Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol. 2016;40(3):309–14.
177 Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer. 2010;116(23):5452–60.
178 Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, et al. Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol. 2013;31(4):426–32.
179 Wang L, Ke Q, Lin N, Huang Q, Zeng Y, Liu J. The efficacy of transarterial chemoembolization combined with microwave ablation for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Int J Hyperthermia. 2019;36(1):1288–96.
180 Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice?. Hepatology. 2008;47(1):82–9.
181 Peng ZW, Lin XJ, Zhang YJ, Liang HH, Guo RP, Shi M, et al. Radiofrequency ablation versus hepatic resection for the treatment of hepatocellular carcinomas 2 cm or smaller: a retrospective comparative study. Radiology. 2012;262(3):1022–33.
182 Vietti Violi N, Duran R, Guiu B, Cercueil JP, Aubé C, Digklia A, et al. Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomised controlled phase 2 trial. Lancet Gastroenterol Hepatol. 2018;3(5):317–25.
183 Yu J, Yu XL, Han ZY, Cheng ZG, Liu FY, Zhai HY, et al. Percutaneous cooled-probe microwave versus radiofrequency ablation in early-stage hepatocellular carcinoma: a phase III randomised controlled trial. Gut. 2017;66(6):1172–3.
184 Tan W, Deng Q, Lin S, Wang Y, Xu G. Comparison of microwave ablation and radiofrequency ablation for hepatocellular carcinoma: a systematic review and meta-analysis. Int J Hyperthermia. 2019;36(1):264–72.
185 Di Vece F, Tombesi P, Ermili F, Maraldi C, Sartori S. Coagulation areas produced by cool-tip radiofrequency ablation and microwave ablation using a device to decrease back-heating effects: a prospective pilot study. Cardiovasc Intervent Radiol. 2014;37(3):723–9.
186 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut. 2005;54(8):1151–6.
187 Ahmed M, Solbiati L, Brace CL, Breen DJ, Callstrom MR, Charboneau JW, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria-a 10-year update. Radiology. 2014;273(1):241–60.
188 Li L, Wang W, Pan H, Ma G, Shi X, Xie H, et al. Microwave ablation combined with OK-432 induces Th1-type response and specific antitumor immunity in a murine model of breast cancer. J Transl Med. 2017;15(1):23.
189 Mizukoshi E, Yamashita T, Arai K, Sunagozaka H, Ueda T, Arihara F, et al. Enhancement of tumor-associated antigen-specific T cell responses by radiofrequency ablation of hepatocellular carcinoma. Hepatology. 2013;57(4):1448–57.
190 Slovak R, Ludwig JM, Gettinger SN, Herbst RS, Kim HS. Immuno-thermal ablations: boosting the anticancer immune response. J Immunother Cancer. 2017;5(1):78.
191 Duan X, Wang M, Han X, Ren J, Huang G, Ju S, et al. Combined use of microwave ablation and cell immunotherapy induces nonspecific immunity of hepatocellular carcinoma model mice. Cell Cycle. 2020;19(24):3595–607.
192 Rozeman EA, Prevoo W, Meier MAJ, Sikorska K, Van TM, van de Wiel BA, et al. Phase Ib/II trial testing combined radiofrequency ablation and ipilimumab in uveal melanoma (SECIRA-UM). Melanoma Res. 2020;30(3):252–60.
193 Lencioni R, De Baere T, Soulen MC, Rilling WS, Geschwind JFH. Lipiodol transarterial chemoembolization for hepatocellular carcinoma: a systematic review of efficacy and safety data. Hepatology. 2016;64(1):106–16.
194 Pelletier G, Ducreux M, Gay F, Luboinski M, Hagège H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. Groupe CHC. J Hepatol. 1998;29(1):129–34.
195 Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RTP, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164–71.
196 Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734–9.
197 Camma C, Schepis F, Orlando A, Albanese M, Shahied L, Trevisani F, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology. 2002;224(1):47–54.
198 Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology. 2003;37(2):429–42.
199 Collaborative Group of the Interventional Group of the Radiology Branch of the Chinese Medical Association. Expert consensus on the technical specifications of transcatheter hepatic artery chemoembolization for primary hepatocellular carcinoma. Chin J Radiol. 2011;45(10):908–12.
200 Clinical Practice Guidelines Committee of the Interventional Physicians Branch of the Chinese Medical Association. Clinical practice guidelines for transarterial chemoembolization (TACE) treatment of hepatocellular carcinoma in China (2021 edition). Chinese Med J. 2021;101(24):1848–62.
201 China Anti-Cancer Association Tumor Interventional Expert Committee. Principles for the application of transcatheter arterial infusion chemotherapy drugs-Chinese expert consensus on oncologic interventions. J Interv Radiol. 2017;26(11):963–70.
202 Guo C, Tenggao J, Zou YH, et al. Recommended techniques for drug-laden microspheres for primary and metastatic hepatocellular carcinoma. Chin J Radiol. 2019;53(5):336–40.
203 Miyayama S, Matsui O. Superselective conventional transarterial chemoembolization for hepatocellular carcinoma: rationale, technique, and outcome. J Vasc Interv Radiol. 2016;27(9):1269–78.
204 Pung L, Ahmad M, Mueller K, Rosenberg J, Stave C, Hwang GL, et al. The role of cone-beam CT in transcatheter arterial chemoembolization for hepatocellular carcinoma: a systematic review and meta-analysis. J Vasc Interv Radiol. 2017;28(3):334–41.
205 Liang B, Makamure J, Shu S, Zhang L, Sun T, Zheng C. Treatment response, survival, and safety of transarterial chemoembolization with CalliSpheres® microspheres versus conventional transarterial chemoembolization in hepatocellular carcinoma: a meta-analysis. Front Oncol. 2021;11:576232.

206 Si ZM, Wang GZ, Qian S, Qu XD, Yan ZP, Liu R, 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(10):1577–83.
207 Lewis AR, Padula CA, Mckinney JM, Toskich BB. Ablation plus transarterial embolic therapy for hepatocellular carcinoma larger than 3 cm: science, evidence, and future directions. Semin Intervent Radiol. 2019;36(4):303–9.
208 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(6):756–65.
209 Radiation Oncology Branch of Chinese Medical Association. Liver cancer group and gastrointestinal tumor expert committee of precision radiotherapy branch of Chinese society of biomedical engineering, liver cancer group of radiation oncology branch of Chinese society of research hospitals. 2016 consensus on radiotherapy for primary liver cancer. Chin J Radiat Oncol. 2016;25(11):1141–50.
210 Jang JW, Choi JY, Bae SH, Kim CW, Yoon SK, Cho SH, et al. Transarterial chemolipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. J Hepatol. 2004;41(3):427–35.
211 Chinese Society for Infectious Diseases, Chinese Society for Liver Diseases. Guidelines for the prevention and treatment of chronic hepatitis B (2019 edition). Chin J Liver Dis. 2019;27(12):938–61.
212 Yang M, Fang Z, Yan Z, Luo J, Liu L, Zhang W, 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(2):211–9.
213 Hu HT, Lai HL, Guo CY, et al. 125I particle implantation combined with arterial chemoembolization for primary hepatocellular carcinoma combined with portal vein thrombosis. Chin J Radiol. 2012;46(6):552–6.
214 Zhang ZH, Zhang W, Gu JY, Liu QX, Ma JQ, Liu LX, et al. Treatment of hepatocellular carcinoma with tumor thrombus with the use of iodine-125 seed strand implantation and transarterial chemoembolization: a propensity-score analysis. J Vasc Interv Radiol. 2018;29(8):1085–93.
215 Chen YX, Zhuang Y, Yang P, Fan J, Zhou J, Hu Y, et al. Helical IMRT-based stereotactic body radiation therapy using an abdominal compression technique and modified fractionation regimen for small hepatocellular carcinoma. Technol Cancer Res Treat. 2020;19:1533033820937002.
216 Chino F, Stephens SJ, Choi SS, Marin D, Kim CY, Morse MA, et al. The role of external beam radiotherapy in the treatment of hepatocellular cancer. Cancer. 2018;124(17):3476–89.
217 Hara K, Takeda A, Tsurugai Y, Saigusa Y, Sanuki N, Eriguchi T, et al. Radiotherapy for hepatocellular carcinoma results in comparable survival to radiofrequency ablation: a propensity score analysis. Hepatology. 2019;69(6):2533–45.
218 Jang WI, Bae SH, Kim MS, Han CJ, Park SC, Kim SB, et al. A phase 2 multicenter study of stereotactic body radiotherapy for hepatocellular carcinoma: safety and efficacy. Cancer. 2020;126(2):363–72.
219 Kim N, Cheng J, Jung I, Liang JD, Shih YL, Huang WY, et al. Stereotactic body radiation therapy versus radiofrequency ablation in Asian patients with hepatocellular carcinoma. J Hepatol. 2020;73(1):121–9.
220 Su TS, Liang P, Liang J, Lu HZ, Jiang HY, Cheng T, et al. Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2017;98(3):639–46.
221 Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. J Clin Oncol. 2016;34(5):452–9.
222 Meng MB, Cui YL, Lu Y, She B, Chen Y, Guan YS, et al. Transcatheter arterial chemoembolization in combination with radiotherapy for unresectable hepatocellular carcinoma: a systematic review and meta-analysis. Radiother Oncol. 2009;92(2):184–94.
223 Ohri N, Dawson LA, Krishnan S, Seong J, Cheng JC, Sarin SK, et al. Radiotherapy for hepatocellular carcinoma: new indications and directions for future study. J Natl Cancer Inst. 2016;108(9):djw133.
224 Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy versus sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized clinical trial. JAMA Oncol. 2018;4(5):661–9.
225 Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2005;61(2):432–43.
226 Shen L, Xi M, Zhao L, Zhang X, Wang X, Huang Z, et al. Combination therapy after TACE for hepatocellular carcinoma with macroscopic vascular invasion: stereotactic body radiotherapy versus sorafenib. Cancers. 2018;10(12):516.
227 Sun J, Yang L, Shi J, Liu C, Zhang X, Chai Z, et al. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: an open-label randomized controlled trial. Radiother Oncol. 2019;140:20–5.
228 Jihye C, Jinsil S. Application of radiotherapeutic strategies in the BCLC-defined stages of hepatocellular carcinoma. Liver Cancer. 2012;1(3–4):216–25.
229 Soliman H, Ringash J, Jiang H, Singh K, Kim J, Dinniwell R, et al. Phase II trial of palliative radiotherapy for hepatocellular carcinoma and liver metastases. J Clin Oncol. 2013;31(31):3980–6.
230 Sapisochin G, Barry A, Doherty M, Fischer S, Goldaracena N, Rosales R, et al. Stereotactic body radiotherapy versus TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. J Hepatol. 2017;67(1):92–9.
231 Wang WH, Wang Z, Wu JX, Zhang T, Rong WQ, Wang LM, et al. Survival benefit with IMRT following narrow-margin hepatectomy in patients with hepatocellular carcinoma close to major vessels. Liver Int. 2015;35(12):2603–10.
232 Wang L, Wang W, Rong W, Li Z, Wu F, Liu Y, et al. Postoperative adjuvant treatment strategy for hepatocellular carcinoma with microvascular invasion: a non-randomized interventional clinical study. BMC Cancer. 2020;20(1):614.
233 Bujold A, Massey CA, Kim JJ, Brierley J, Cho C, Wong RKS, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. J Clin Oncol. 2013;31(13):1631–9.
234 Zeng ZH. Stereotactic radiation therapy for hepatocellular carcinoma. Chin J Oncol. 2015(9):650–3.
235 He J, Shi S, Ye L, Ma G, Pan X, Huang Y, et al. A randomized trial of conventional fraction versus hypofraction radiotherapy for bone metastases from hepatocellular carcinoma. J Cancer. 2019;10(17):4031–7.
236 Hou JZ, Zeng ZC, Wang BL, Yang P, Zhang JY, Mo HF. High dose radiotherapy with image-guided hypo-IMRT for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombi is more feasible and efficacious than conventional 3D-CRT. Jpn J Clin Oncol. 2016;46(4):357–62.
237 Zhang H, Chen Y, Hu Y, Yang P, Wang B, Zhang J, et al. Image-guided intensity-modulated radiotherapy improves short-term survival for abdominal lymph node metastases from hepatocellular carcinoma. Ann Palliat Med. 2019;8(5):717–27.
238 Byun HK, Kim HJ, Im YR, Kim DY, Han KH, Seong J. Dose escalation in radiotherapy for incomplete transarterial chemoembolization of hepatocellular carcinoma. Strahlenther Onkol. 2020;196(2):132–41.
239 Hu Y, Zhou YK, Chen YX, Shi SM, Zeng ZC. 4D-CT scans reveal reduced magnitude of respiratory liver motion achieved by different abdominal compression plate positions in patients with intrahepatic tumors undergoing helical tomotherapy. Med Phys. 2016;43(7):4335.

240 Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. J Hepatol. 2021;74(3):603–12.
241 Bian H, Zheng JS, Nan G, Li R, Chen C, Hu CX, et al. Randomized trial of [131I] metuximab in treatment of hepatocellular carcinoma after percutaneous radiofrequency ablation. J Natl Cancer Inst. 2014;106(9): dju239.
242 Working committee on the treatment of metastatic bone tumors, nuclear medicine branch, Chinese medical association. Expert consensus on the treatment of metastatic bone tumors with strontium chloride [89Sr] (2017 edition). Chin J Nucl Med Mol Imaging. 2018;38(6):412–5.
243 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20): 1894–905.
244 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. IMbrave150: updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). J Clin Oncol. 2021;39(3_Suppl):267.
245 Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, 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(7):977–90.
246 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:Jco2100163.
247 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, 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(10126):1163–73.
248 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
249 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, 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(1):25–34.
250 Pressiani T, Boni C, Rimassa L, Labianca R, Fagiuoli S, Salvagni S, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol. 2013;24(2):406–11.
251 Qin S, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, 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(28): 3501–8.
252 Qin S, Cheng Y, Liang J, Shen L, Bai Y, Li 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(11): 1169–78.
253 Qu FL, Hao XZ, Qin SK, Liu J, Sui G, Chen Q, et al. Phase II multicenter clinical study of arsenious acid injection for primary hepatocellular carcinoma. Chin J Oncol. 2011; 33(9):697–701.
254 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389(10064):56–66.
255 Qin S, Li Q, Gu S, Chen X, Lin L, Wang Z, 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(7):559–68.
256 Qin S, Ren Z, Meng Z, Chen Z, Chai X, Xiong J, 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(4):571–80.
257 Xu J, Shen J, Gu S, Zhang Y, Wu L, Wu J, et al. Camrelizumab in combination with apatinib in patients with advanced hepatocellular carcinoma (RESCUE): a nonrandomized, open-label, phase II trial. Clin Cancer Res. 2021;27(4):1003–11.
258 Xu J, Zhang Y, Jia R, Yue C, Chang L, Liu R, et al. Anti-PD-1 antibody SHR-1210 combined with apatinib for advanced hepatocellular carcinoma, gastric, or esophagogastric junction cancer: an open-label, dose escalation and expansion study. Clin Cancer Res. 2019;25(2):515–23.
259 Ducreux M, Abou-Alfa GK, Ren Z, Edeline J, Li Z, Assenat E, et al. Results from a global Phase 2 study of tislelizumab, an investigational PD-1 antibody, in patients with previously treated advanced hepatocellular carcinoma [C]. ESMO WCGI. 2021.
260 Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940–52.
261 Yau T, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol. 2020;6(11):e204564.
262 Abou-Alfa GK, Meyer T, Cheng AL, El-Khoueiry AB, Rimassa L, Ryoo BY, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379(1):54–63.
263 Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2015;16(7):859–70.
264 Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019;20(2):282–96.
265 Cai DF. Identification of disease and evidence to create a Chinese system of integrated Chinese and Western clinical medicine. Chin J Integr Med. 2019;39(9):1034–5.
266 Cai DF. On the clinical diagnosis and treatment model of disease and evidence combination. Chin J Integr Med. 2019;39(2): 133–5.
267 Zhai XF, Liu XL, Shen F, Fan J, Ling CQ. Traditional herbal medicine prevents postoperative recurrence of small hepatocellular carcinoma: a randomized controlled study. Cancer. 2018;124(10):2161–8.
268 Qin SK, Li Q, Ming Xu J, Liang J, Cheng Y, Fan Y, et al. Icaritin-induced immunomodulatory efficacy in advanced hepatitis B virus-related hepatocellular carcinoma: immunodynamic biomarkers and overall survival. Cancer Sci. 2020;111(11):4218–31.
269 Yu Z, Guo J, Hu M, Gao Y, Huang L. Icaritin exacerbates mitophagy and synergizes with doxorubicin to induce immunogenic cell death in hepatocellular carcinoma. ACS Nano. 2020;14(4):4816–28.
270 Cai WH, Yin CI, Fan QQ. Clinical observation of Addy combined with hepatic artery chemoembolization for the treatment of intermediate to advanced primary hepatocellular carcinoma. Chin J Physicians. 2018; 20(11):1723–5.
271 Cheng Y, Hua HQ. Research progress of element in the treatment of primary liver cancer. J Clin Oncol. 2017;22(10):950–3.
272 Fan F, Li Q, Zhou ZT, et al. Study on the effect of TACE combined with Golden Dragon capsule in the treatment of primary liver cancer. China Pract Med. 2019; 14(21):42–4.

273 Gao JL. A prospective, randomized controlled clinical study of hepatoflux formula for advanced primary liver cancer. Chin J Traditional Chin Med. 2014;39(12):2367–9.
274 Lu DP, Wang YQ, Zhao WL, et al. Clinical study of Kanglet combined with hepatic artery chemoembolization for the treatment of hepatocellular carcinoma. World Clin Med. 2017;11(5):70–2.
275 Yang XH. Clinical efficacy and VEGF levels of TACE combined with opium oil emulsion intravenous drip in patients with hepatocellular carcinoma. Strait Pharmacol. 2017;29(9):176–7.
276 European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69(2):461–511.
277 Chinese Medical Association; Hepatology Branch; Infectious Diseases Branch. Guidelines for the prevention and treatment of hepatitis C (2019 edition). Chin J Infect Dis. 2020;38(1):9–28.
278 Qin SK, Ma J. Chinese Society of Clinical Oncology (CSCO) guidelines for the standardized management of neutropenia associated with oncologic radiotherapy (2021). J Clin Oncol. 2021;26(7):638–48.
279 Shi YM, Xing PY, Zhang J, et al. Expert consensus on the treatment of chemotherapy-associated thrombocytopenia in China (2019 edition). Chin Clin Oncol. 2019;(18):923–9.
280 Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18(3):e143–52.
281 Moris D, Chakedis J, Sun SH, Spolverato G, Tsilimigras DI, Ntanasis-Stathopoulos I, et al. Management, outcomes, and prognostic factors of ruptured hepatocellular carcinoma: a systematic review. J Surg Oncol. 2018;117(3):341–53.
282 Sahu SK, Chawla YK, Dhiman RK, Singh V, Duseja A, Taneja S, et al. Rupture of hepatocellular carcinoma: a review of literature. J Clin Exp Hepatol. 2019;9(2):245–56.
283 Tan NP, Majeed A, Roberts SK, Gow PJ, Hey P, Mah X, et al. Survival of patients with ruptured and non-ruptured hepatocellular carcinoma. Med J Aust. 2020;212(6):277–8.
284 Yoshida H, Mamada Y, Taniai N, Uchida E. Spontaneous ruptured hepatocellular carcinoma. Hepatol Res. 2016;46(1):13–21.
285 Zhong F, Cheng XS, He K, Sun SB, Zhou J, Chen HM. Treatment outcomes of spontaneous rupture of hepatocellular carcinoma with hemorrhagic shock: a multicenter study. Springerplus. 2016;5(1):1101.
286 Aoki T, Kokudo N, Matsuyama Y, Izumi N, Ichida T, Kudo M, et al. Prognostic impact of spontaneous tumor rupture in patients with hepatocellular carcinoma: an analysis of 1,160 cases from a nationwide survey. Ann Surg. 2014;259(3):532–42.
287 Lai EC, Lau WY. Spontaneous rupture of hepatocellular carcinoma: a systematic review. Arch Surg. 2006;141(2):191–8.
288 Shin BS, Park MH, Jeon GS. Outcome and prognostic factors of spontaneous ruptured hepatocellular carcinoma treated with transarterial embolization. Acta Radiol. 2011;52(3):331–5.
289 Roussel E, Bubenheim M, Le Treut YP, Laurent A, Herrero A, Muscari F, et al. Peritoneal carcinomatosis risk and long-term survival following hepatectomy for spontaneous hepatocellular carcinoma rupture: results of a multicenter French study (French-AFC). Ann Surg Oncol. 2020;27(9):3383–92.