Global Health & Medicine. 2020; 2(5):306-311.
REVIEW
DOI: 10.35772/ghm.2020.01051

Interpretation of guidelines for the diagnosis and treatment of primary liver cancer (2019 edition) in China

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Abstract: Primary liver cancer (PLC) is currently the fourth most common malignancy and accounts for the second most cancer-related deaths in China. Since 2017, a great deal of high-level evidence, and particularly evidence based on Chinese studies and practice, has emerged in terms of diagnosis, staging, and treatment. A new version of the guidelines for the management of PLC specifying the diagnosis and treatment of PLC (2019 edition) has recently been published. The guidelines feature major changes in the techniques for early diagnosis, the combination of surgery, local therapy, and systemic treatment, and the use of traditional Chinese medicine. The guidelines need to be further implemented in clinical practice to demonstrate their validity.

***Keywords*:** hepatocellular carcinoma, diagnosis, treatment

Introduction

According to GLOBCAN 2018 data (*1*), there were 841,080 new cases of liver cancer worldwide annually, of which 392,869 occurred in China, accounting for 46.7% of cases around the world. In China, liver cancer ranks second in cancer deaths and forth in cancer prevalence. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer (PLC), which accounts for 75%-85% of PLC. In terms of prognosis, the overall 5-year survival rate of HCC in China from 2012 to 2015 was 12.1%, the 5-year survival rate of HCC was 14.0% in urban areas and only 11.2% in rural areas (*2*).

The prevalence of PLC in China poses a threat to the health and life of the Chinese people. Since the 2011 and 2017 versions of guidelines for the diagnosis and treatment of PLC were published in China, many new studies have been conducted and more evidence has emerged. China published updated guidelines (2019 edition) to optimize the management of PLC on the basis of the 2017 edition. Here, the recommendations in the 2019 guidelines have been summarized and updates to those guidelines have been interpreted. Consistent with the guideline, PLC refers to HCC in this article. In addition, a comparison of the 2011, 2017, and 2019 editions is shown in Table 1.

Surveillance and diagnostic algorithm

Monitoring and screening

Like the 2017 guidelines, the new guidelines consider patients with a history of chronic liver disease to have a high risk of developing HCC and the guidelines recommend ultrasonography (US) and measurement of alpha-fetoprotein (AFP) for surveillance every 6 months (Figure 1).

Imaging examinations

Once abnormalities are found in AFP/US screening, computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS) are routine methods with which to definitively diagnose HCC. As imaging technology has advanced, MRI has gradually become a common type of examination for clinical diagnosis of HCC. Therefore, the 2019 guidelines highlight the important role of MRI in the diagnosis and evaluation of HCC, and especially MRI with a hepatocyte-specific contrast agent (Gd-EOB-DTPA). Multimodal MRI is better than dynamic contrast CT in detecting and diagnosing HCC with a diameter of 2.0 cm (*3,4*), and is better than dynamic enhanced CT in evaluating whether HCC has invaded the portal vein or hepatic vein and metastasized to abdominal or retroperitoneal lymph nodes. In addition, MRI with Gd-EOB-DTPA has a higher rate of detecting liver lesions with a diameter of ≤ 1.0 cm (*5-7*).

Serological molecular markers

AFP is the most commonly used serological molecular marker for diagnosis and monitoring the response to treatment. However, normal AFP level may be present

Table 1. Important updates to the 2011, 2017, and 2019 guidelines for diagnosis and treatment of primary liver cancer in China

Version (*Ref.*)	Diagnosis	Staging	Treatment
2011 (*32*)	Specifies the HCC diagnostic criteria.	TNM BCLC	Multidisciplinary integrated treatment.
2017 (*33*)	Pathological diagnosis: "7"point baseline extraction method. MVI	CNLC	Clear root-and-branch LR standards.
2019 (*34*)	Emphasizes the value of MRI Describes new serological molecular markers	CNLC	Treatment of recurrence after liver transplantation: RF ablation, TACE, *etc.*

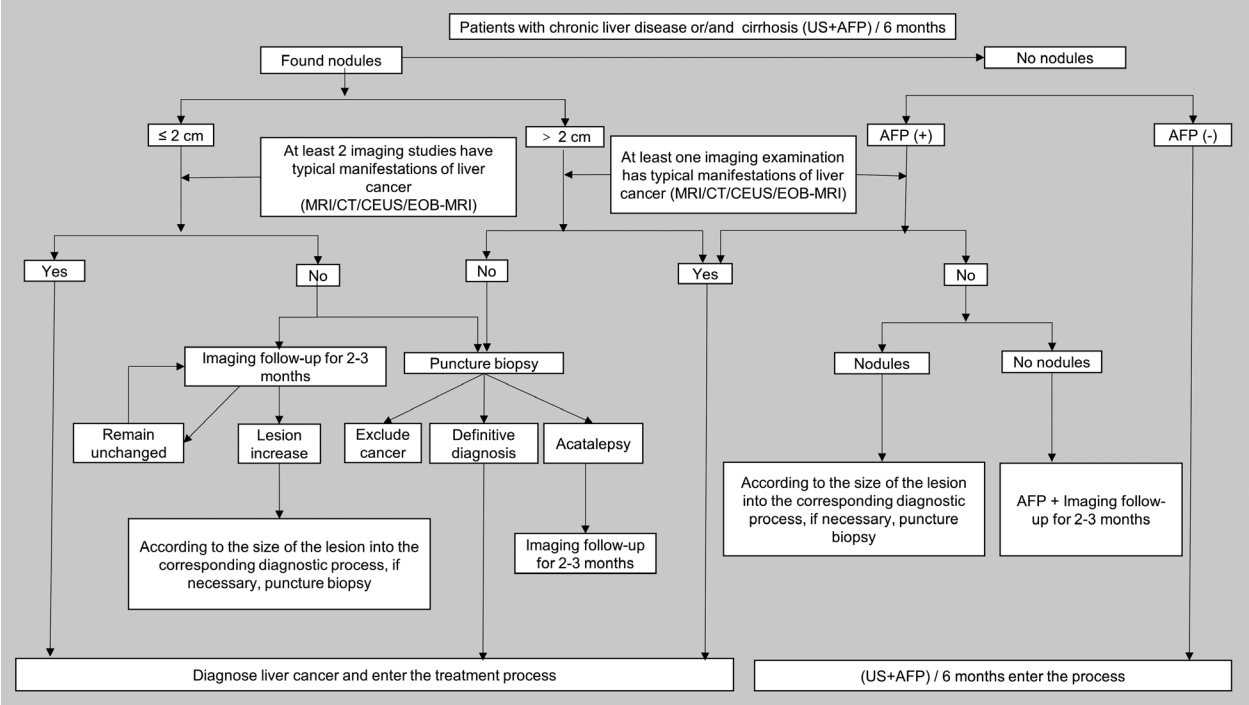

Figure 1. Clinical diagnostic criteria and roadmap for primary liver cancer in China (*34*)**.**

in about 30% of patients with HCC. For serum AFP-negative patients, serum AFP-L3, PIVKA-II, or des-gamma carboxyprothrombin (DCP) and plasma free microRNA are alternatives for early diagnosis or surveillance of HCC. In recent years, liquid biopsy has shown great potential in early diagnosis and evaluation of efficacy.

The 2019 guidelines first describe several new serological molecular markers, such as circulating tumor cells (CTCs), circulating cell-free microRNA, and circulating tumor DNA (ctDNA). Liquid biopsy may have higher sensitivity and specificity than commonly used clinical molecular markers such as serum AFP and PIVKA-II (*8*). A combination of several plasma miRNAs is also highly useful in the early diagnosis of HCC. For example, a model for diagnosis of HCC created using the levels of expression of seven plasma miRNAs can accurately diagnose early HCC (with a sensitivity of 86.1% and a specificity of 76.8%), and its sensitivity is about 30% higher than that of traditional markers. Patients with AFP levels that preclude determination can still be accurately diagnosed with miRNA (with a sensitivity as high as 77.7% and a specificity as high as 84.5%) (*9*). At present, a HCC detection kit based on circulating miRNA has been validated in multi-center clinical trials and is in clinical use in China. miRNA diagnosis is expected to generally facilitate early diagnosis and treatment of HCC and truly benefit patients.

Liver puncture biopsy

Unquestionably, liver puncture biopsy can provide a definitive pathological diagnosis for lesions found in an imaging examination lacking the typical characteristics of HCC. Liver biopsy can provide valuable information on the nature of the lesion, the etiology of liver disease, molecular typing of HCC, guiding treatment, and determining prognosis. However, liver biopsy may cause the rupture of tumor nodules and needle tract

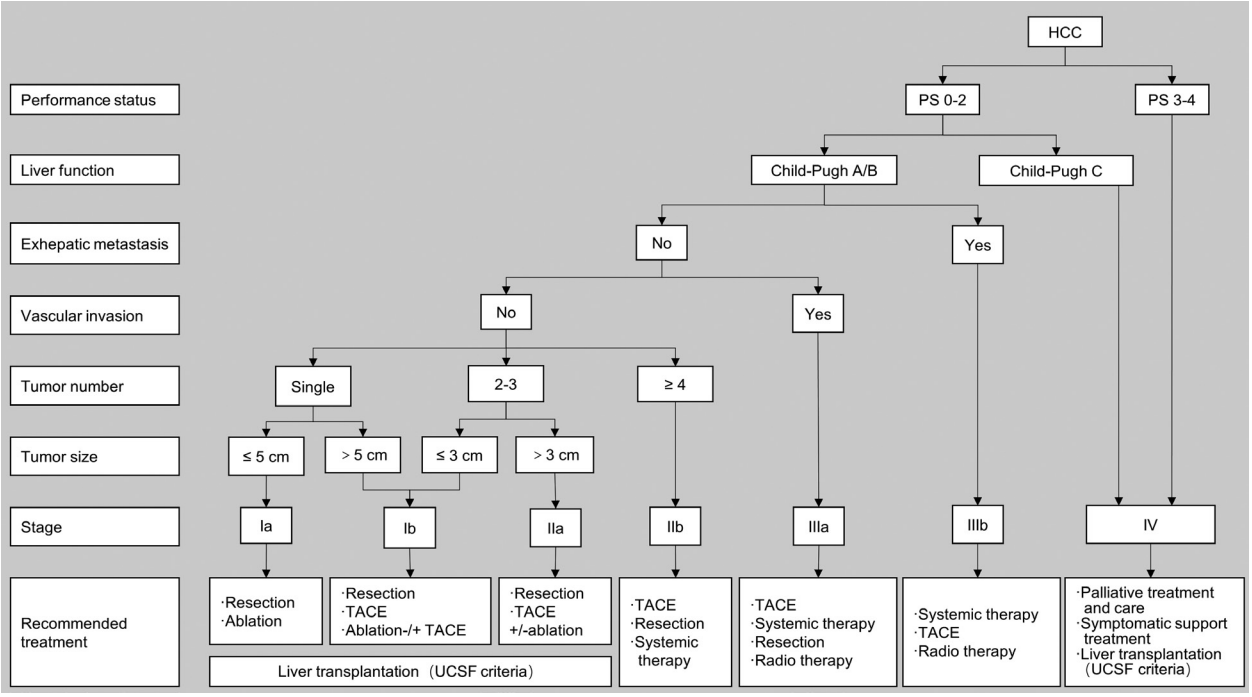

Figure 2. Clinical staging and treatment of primary liver cancer in China (*34*)**.**

implantation, and it can even occasionally lead to a false-negative result. Thus, the 2019 guidelines specify that patients with lesions that have typical imaging features need not undergo a diagnostic liver biopsy.

Staging and treatment algorithm

Identical to the 2017 version, the new guidelines still use the China HCC staging system and treatment algorithm (CNLC) based on the Chinese medical system and Chinese practices and experiences. The algorithm includes the size and number of tumors, performance status (PS), and liver function (Figure 2). The main points of this updated staging algorithm are in systemic therapy and the combination of multiple treatment modalities, indicating that the current model of HCC treatment has entered a new era of comprehensive multidisciplinary treatment.

Surgical resection

Liver resection (LR) is the most effective curative treatment of HCC (CNLC stage Ia, Ib, or IIa cancer), and especially for patients with 1-3 nodules and without metastasis or vascular invasion. There is considerable controversy regarding whether LR is suitable for patients with portal hypertension (PHT). However, most surgeons treating HCC in China do not agree that PHT is a contraindication for LR. Results of several Chinese studies have indicated that PHT does not affect patient prognosis. Therefore, the 2019 guidelines emphasize that selected patients with PHT can still undergo a liver resection after a comprehensive evaluation, and their long-term survival after surgery is superior to other treatments (*10,11*). A more accurate assessment of the degree of PHT can help to select patients eligible for LR (*12,13*).

As surgical resection techniques have made great progress, a lot of new evidence has been incorporated into the new guidelines. For example, preoperative 3D visualization technology can help to design more precise resection margins and approaches to protect the remaining liver (*14,15*). Patients with huge or multiple lesions often need to undergo extensive resection to obtain negative margins. However, an insufficient future remnant liver volume (FRLV) is the main factor hindering the results of radical resection. Transarterial chemoembolization (TACE) and portal vein embolization (PVE) are routine methods to treat these patients. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is a complicated surgery that is rarely performed. However, recent studies have found that the long-term survival benefit of patients undergoing ALPPS was significantly better than that of patients undergoing TACE, indicating that ALPPS is a feasible strategy for patients without an insufficient FRLV (*16*). In addition to this evidence, the 2019 guidelines also note that LR with wide margins results in a better long-term prognosis than narrow resection margins, and this is especially true for patients with microvascular invasion (*17,18*). In terms of postoperative treatment, the 2019 guidelines more clearly suggest that an antivirus work-up can reduce recurrence after R0 resection is achieved (*19*). Additionally, two randomized

controlled studies involving patients with a high risk of recurrence have confirmed that TACE reduces recurrence and prolongs survival (*20,21*).

Liver transplantation

The 2019 guidelines are consistent with the University of California San Francisco (UCSF) criteria for liver transplantation (LT), albeit with a modest expansion of the indications for LT. Patients with CNLC stage IV cancer can still undergo LT after an accurate evaluation. In addition, treatment of post-operative recurrence was added to the 2019 guidelines, which focus on multi-disciplinary comprehensive treatment modalities including modification of the immunosuppressive regimen, additional surgery, TACE, local ablation treatment, radiation treatment, or systemic treatment.

Local ablation therapy

Patients in whom HCC is confirmed are often unable to undergo radical surgery due to serious cirrhosis or advanced cancer. Only about 20% to 30% of patients are eligible to undergo surgical resection. Fortunately, local ablation therapy (LAT) causes less damage to liver function, less trauma, and has a high response rate. Patients not eligible for surgical resection can receive radical treatment with LAT. Radiofrequency ablation (RFA) is the most common LAT, and the 2019 guidelines highlight its role in the treatment of early-stage HCC based on a great deal of high-level evidence. For example, patients with early-stage HCC undergoing RFA have a survival benefit comparable to that of patients undergoing surgical resection (*22,23*). For a single lesion ≤ 2 cm in diameter, the survival benefit of undergoing RFA is the same or greater than that of surgical resection, and this is especially true for centrally located liver cancer (*24,25*). Given this evidence regarding RFA, the 2019 guidelines cite RFA as the first-line treatment strategy for patients with early-stage HCC who are ineligible for surgical resection.

*Transarterial chemoembolizatio*n

TACE is commonly used as a non-surgical strategy to treat HCC. It is suitable for patients with CNLC stage IIb, IIIa, or IIIb cancer. It is mostly used as a combination of surgical treatment and ablation treatment. For example, the 2019 guidelines emphasize a combination of ablation therapy, systemic treatment, or antivirus treatment. A randomized controlled phase II trial (TACTICS) has indicated that TACE plus sorafenib significantly improved progression-free survival over TACE alone in patients with unresectable HCC and that TACE can significantly delay the time from disease progression to vascular invasion or extrahepatic metastasis (*26*). In addition, the 2019 guidelines have added a prognostic score called "six-and-twelve" (the sum of the number of tumors and tumor size is used to divide patients into 3 strata: ≤ 6, > 6 but ≤ 12, or > 12) that can individualize prognostic assessment and risk stratification of patients undergoing TACE. Patients in different strata result in significant differences in median survival. Therefore, this prognostic model prior to performing TACE may provide reference values and help patients choose different treatment options (*27*).

Systemic treatment

For patients with advanced HCC that cannot be surgically resected (CNLC stage IIIa and IIIb cancer), systemic treatment may prolong their life and decrease the tumor burden. Sorafenib has already been found to have significant survival benefits for patients with HCC. Before the 2019 version was published, sorafenib was the only molecularly targeted drug for advanced HCC. Recently, many multi-center clinical studies involving new drugs have been conducted around the world, and great progress has been made. A randomized phase III non-inferiority trial (REFLECT) indicated that lenvatinib was not inferior to sorafenib in terms of overall survival for patients with advanced HCC (*28*). Moreover, lenvatinib can also provide better survival benefits for most Chinese patients with HBV-related HCC. Another randomized phase III trial (RESORCE) found that regorafenib is the only targeted drug that benefits patients with cancer progressing despite sorafenib treatment (*29*). Regorafenib provided a median overall survival benefit of 26 months, and this result had already been confirmed by multiple real-world studies worldwide (*30*). Within the context of the great progress made in targeted therapy, the 2019 guidelines have highly emphasized systemic treatment and added lenvatinib as first-line treatment and regorafenib as second-line treatment, thus expanding treatment options for patients. A better protocol combining different targeted drugs and searching for new systemic agents are key ways in which systemic treatment can prolong survival.

Traditional Chinese medicine

The 2017 guidelines noted that traditional Chinese medicine can relieve clinical symptoms, improve the body's resistance, and reduce the adverse effects of radiotherapy and chemotherapy. In the 2019 edition, there is high-level evidence that taking Huaier granules after liver resection can result in lower recurrence and better survival (*31*), demonstrating that traditional Chinese medicine can greatly help the treatment of HCC. Traditional Chinese medicine is considered to have great potential and will be increasingly used in cancer treatment. However, more standardized clinical studies need to be conducted in the future to accumulate

more evidence of the feasibility and safety of traditional Chinese medicine.

Conclusion

The new guidelines place considerable emphasis on multidisciplinary treatment incorporating new evidence-based suggestions, and this will further promote advances in the treatment of PLC in China. Although they are based on Chinese experiences, these guidelines should also help other countries to defeat this condition.

Funding: None.

Conflict of Interest: The authors have no conflict of interest to disclose.

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Received May 28, 2020; Revised September 7, 2020; Accepted September 24, 2020

Released online in J-STAGE as advance publication September 30, 2020.

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