Review

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The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines: 2022 update

Ningyuan Wen[1,§], Yulong Cai[1,§], Fuyu Li[1], Hui Ye[1], Wei Tang[1,2], Peipei Song[3,*], Nansheng Cheng[1,*]

[1] Department of Biliary Surgery, West China Hospital of Sichuan University, Chengdu, Sichuan, China;
[2] International Health Care Center, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan.

SUMMARY Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide. This review is an updated version that summarizes comprehensive guidelines published from January 2001 to January 2022 worldwide with a focus on the clinical management of HCC. The electronic databases MEDLINE, the Chinese SinoMed, and the Japanese CiNii were systematically searched. A total of 22 characteristic guidelines for HCC management were ultimately included, including 1 international guideline, 11 guidelines from Asia, 5 from Europe, 4 from the America, and 1 from Australia. If guidelines were published in multiple versions, the most recent update was included, and surveillance, diagnosis, and treatment were compared. The composition of and recommendations in current guidelines on HCC varied, so these guidelines were regrouped and diagnostic and treatment algorithms were summarized graphically to provide the latest information to clinicians. The diagnostic criteria were grouped into 2 categories: a "Size-based pathway" and a "Non-size-based pathway". The treatment criteria were summarized according to different treatment algorithms, and mainstream treatment options were reviewed. Findings from comparison of current guidelines might help target and concentrate efforts to improve the clinical management of HCC. However, further studies are needed to improve the management and outcomes of HCC. More straightforward or refined guidelines would help guide doctors to make better decisions in the treatment of HCC in the future.

Keywords hepatocellular carcinoma, clinical guideline, surveillance, diagnosis, treatment

1. Introduction

As the most common primary malignancy of the liver, hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide, with an increasing incidence of approximately > 500,000 new cases per year (*1,2*). Over the past 2 decades, various studies have examined the clinical management of HCC, markedly improving treatment options, which include new drug combinations. Despite the considerable advancement that has occurred, the overall outcomes of HCC are still far from satisfactory. For better treatment of HCC, various types of guidelines and expert consensus opinions have been issued in multiple regions and subspecialties. If adequate guidelines are devised, they could serve as roadmaps for clinicians to develop individualized decision-making algorithms, improve the quality of care and patients' outcomes, and assist regional and national authorities in allocating resources (*3*).

Since 2001, when the European Association for the Study of the Liver (EASL) issued their HCC guideline, at least 20 comprehensive clinical guidelines for HCC have been published or updated, and each has its own advantages. That said, gaps in knowledge and areas of controversy regarding certain aspects of HCC management are still evident and cannot be ignored.

In a previous review, we summarized 18 comprehensive guidelines published worldwide from 2001 to 2017 with a focus on the clinical treatment of HCC; those guidelines have been significantly revised since (*4*). To provide the latest information for clinicians, the current review has summarized the current editions of those guidelines up to 2022. Twenty-two characteristic guidelines were selected, including 1 international

guideline, 11 from Asia, 5 from Europe, 4 from the America, and 1 from Australia. These characteristic guidelines have been compared and summarized in order to describe new aspects of the surveillance, diagnosis, and treatment of HCC.

2. An update to characteristic guidelines for the clinical management of HCC

Like the previous review, the current review involved a systematic search of mainstream databases in English, Chinese, and Japanese, including MEDLINE, the Chinese SinoMed (*http://www.sinomed.ac.cn/zh/*), and the Japanese CiNii (*http://ci.nii.ac.jp/*), for applicable results from January 2001 to January 2022. No language restriction was applied. Search terms (medical subject headings or keywords) included: "hepatocellular carcinoma", "guidelines/practice guidelines", "consensus", "strategy", "liver cancer", and "liver carcinoma".

Inclusion criteria were as follows: *i*) credibility, as measured by whether the guidelines were widely cited by subsequent guidelines or other publications regarding the management of HCC after the original guidelines were published; *ii*) influence, an indication that the guidelines were created with the support of government or academic/medical societies and that the guidelines attracted nationwide attention with respect to their implementation and the standard care for HCC; and *iii*) multifaceted, meaning that the guidelines included aspects of the diagnosis and treatment of HCC at a minimum. Hence, many specialized guidelines, though credible and influential, did not make the list of 22 guidelines but they are still discussed in specific subsections. If the guidelines were published in multiple versions, the most recent update was analyzed. Moreover, references listed in guidelines were manually searched for other potential sources. The title and abstract of retrieved studies were evaluated for relevance and compliance. If compliance was not clearly defined by the abstract, the full text was reviewed for further assessment.

In line with the criteria above, 22 comprehensive guidelines published between 2001 and 2022 were identified for analysis, including 1 international guideline, 11 guidelines from Asia, 5 from Europe, 4 from the America, and 1 from Australia (Table 1) (*1,5-25*). Among the 18 guidelines included in our previous review, 10 of them have been updated within the last 5 years. Besides, 5 new guidelines were included for the first time. These 22 characteristic guidelines were examined with a focus on the clinical management of HCC, and surveillance, diagnosis, and treatment in those guidelines were compared.

3. High-risk population and surveillance of HCC

Identification of the risk factors for HCC and devising of appropriate methods for surveillance of the high-risk population are crucial to early diagnosis and a better outcome. This process is usually divided into 3 parts: *i*) determining risk factors, *ii*) screening the population with risk factors for individuals who need to be monitored, and *iii*) devising the form of surveillance that yields the most benefit.

The current review found that 17 of the 22 guidelines clearly described risk factors and surveillance. The guidelines contained a lot of similar information on those topics, but there were discrepancies among guidelines due to regional differences in disease and other variables. HCC has been proven to be linked to liver disease independently, and its major risk factors can be divided into those that are cirrhosis-related and those that are non-cirrhosis-related. The former includes hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcoholic cirrhosis, genetic causes (hemochromatosis and tyrosinosis), nonalcoholic fatty liver disease (NAFLD), stage IV primary biliary cholangitis, alpha one antitrypsin deficiency, and other causes of cirrhosis; the latter includes being an HBV carrier with a family history of HCC, being Asian and elderly (males ≥ 40 years and females ≥ 50 years), and being an African/North American black infected with hepatitis B (*1,21*). Among these risk factors, cirrhosis caused by various etiologies is the strongest predictor of HCC, with an associated annual incidence of HCC of 1-8% (*26,27*). Hepatitis B is the leading cause of HCC in East Asia and Africa while hepatitis C is the leading cause in Western countries (*28*). In recent years, NAFLD-related HCC has attracted more attention since a growing population worldwide is estimated to have NAFLD (*29,30*).

HCC surveillance is cost-effective, especially for high-risk groups. Ultrasound (US) is the most widely recommended method of HCC detection (*1,7,22,31,32*). However, whether alpha-fetoprotein (AFP) should serve as a routine screening test for HCC is still being debated. The NCCN/AASLD recommendations suggested US surveillance with or without AFP (*22,31*). The EASL guideline described AFP as "suboptimal" as a serological test for surveillance since its levels were interfered with by viral replication and underlying liver disease, so they often do not appear abnormal in the early stages of HCC (*1*). Several studies indicated that AFP alone has limited and inconsistent sensitivity and specificity as a screening biomarker and that elevated levels of AFP may be found in < 20% of patients with early-stage HCC (*33-35*).

In contrast, some expert panels consider AFP to be a good surveillance marker due to its wide utility in diagnostic settings, where it has been studied extensively (*36*), and its role in combination with US, which can significantly maximize early detection of HCC, despite the lack of evidence concerning improvement in survival (*37,38*). In the 22 guidelines that were reviewed here, 6 recommended US for screening with AFP, 6 suggested US alone, and the others considered AFP to be optional.

Table 1. Twenty-two characteristic guidelines for the clinical management of HCC

No.	Area	Year (latest update)	Guidelines	Drafted by	Aspects covered	*Ref.*
	International					
1		2010	WGO Guideline	• World Gastroenterology Organization	D&T+E+P+S	(*5*)
	Asia					
2		2020	Pan-Asian adapted ESMO Guideline	• ESMO Asia Meeting	D&T+E+P+S+F	(*6*)
3		2017	APASL Guideline	• Asian-Pacific Association for the Study of the Liver	D&T+E+P+S	(*7*)
4		2009	AOS Guideline	• Asian Oncology Summit 2009	D&T+P+S	(*8*)
5	China	2020	CSCO Guideline	• Chinese Society of Clinical Oncology	D&T+S+F	(*9*)
6	Japan	2021	JSH Consensus Statements and Recommendations	• Japan Society of Hepatology	D&T+S	(*10*)
7		2021	J-HCC Guideline	• Group formed to establish "Guidelines for evidence-based clinical practice for the treatment of liver cancer"		
8		2019	JSH Guideline	• Japan Society of Hepatology	D&T+S	(*11*)
9	Korea	2014	Korean Guideline	• Korean Liver Cancer Study Group and National Cancer Center	D&T+E+P	(*12*)
10	Saudi Arabia	2020	Saudi Guideline	• Saudi Association for the Study of Liver diseases and Transplantation	D&T+E+P+S	(*13*)
11	India	2019	INASL Guideline	• The Indian National Association for Study of the Liver	D&T+E+P+S	(*14*)
12		2019	ICMR Consensus	• Indian Council of Medical Research	D&T+E+P+S+F	(*15*) (*16*)
	Europe					
13		2021	ESMO Guideline	• European Society for Medical Oncology	D&T+E+P+S+F	(*17*)
14		2018	EASL Guideline	• European Association for Study of the Liver, European Organization for Research and Treatment of Cancer	D&T+E+P+S	(*1*)
15	Belgium	2004	BASL Guideline	• Belgian Association for the Study of the Liver	D&T+E+P+S	(*18*)
16	Britain	2003	BSG Guideline	• British Society of Gastroenterology	D&T+E+S	(*19*)
17	Italy	2009	GOIM Guideline	• Italian Southern Oncological Group	D&T+E	(*20*)
	America					
18		2021	NCCN	• National Comprehensive Cancer Network	D&T+E+S	(*21*)
19		2018	AASLD	• American Association for the Study of Liver Disease	D&T+S	(*22*)
20		2010	NCI Guideline	• United States National Cancer Institute	D&T+E	(*23*)
21		2007	ACS Guideline	• American College of Surgeons*	D&T	(*24*)
	Oceania					
22	Australia	2020	GESA Guideline	• Gastroenterological Society of Australia	D&T+E+P+S+F	(*25*)

Abbreviations: D&T: diagnosis and treatment, E: epidemiology, P: prevention, S: surveillance, F: follow-up. *A review article published on J Am Coll Surg by the American College of Surgeons.

The usefulness of other biomarkers, including the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des-gamma-carboxy prothrombin (DCP), has been studied (*39,40*). Concomitant use of these biomarkers is recommended as a regular screening method by the 2019 updated JSH Guideline (*12*). In contrast, the 2018 EASL guideline described AFP, AFP-L3 and DCP as "suboptimal in terms of cost-effectiveness for routine surveillance of early HCC". The debate goes on.

The ideal surveillance interval should be evaluated from the perspective of cost-effectiveness by considering the clinical status and available resources. Generally, the surveillance interval is 6 to 12 months for the high-risk population according to guidelines. A prospective cohort study found that patients with HBV had a better survival with a surveillance interval of 6 months than with 12 months (*41*). However, other studies have found no significant differences in survival or the rate of HCC detection with intervals of 6 and 12 months (*42,43*). Of the 22 guidelines that were reviewed here, 8 tended to recommend a surveillance interval of 6 months and 2 recommended an interval of 6 to 12 months.

The definition and description of the high-risk population varied according to the guidelines. According to the 2019 update of the JSH Guideline, individuals with a high risk of developing HCC who need to be surveilled are classified as the high-risk population and the very-high-risk population (*12*). The high-risk population includes: *i*) individuals with chronic hepatitis B, *ii*) individuals with chronic hepatitis C, and *iii*) individuals with liver cirrhosis (due to causes other than HBV or HCV). The recommended form of surveillance is US and tumor marker measurement (AFP/DCP/AFP-L3) every 6 months. The very-high-risk population includes: *i*) individuals with hepatitis B-related liver cirrhosis and *ii*) individuals with hepatitis C-related liver cirrhosis. The surveillance protocol for those individuals is US and tumor marker measurement (AFP/DCP/AFP-L3) every 3-4 months, with alternative dynamic CT/MRI especially for those who cannot readily undergo US due to liver atrophy, severe obesity, or post-operative deformity.

The NCCN Guideline, INASL Guideline, and EASL Guideline classified patients who are at risk of developing HCC into a group with cirrhosis and a group without cirrhosis (*1,15,31*). The EASL/INASL/Saudi Guideline also took liver function (Child-Pugh) into consideration for the group with cirrhosis. Those 2 guidelines stressed that patients on the waiting list for liver transplantation (LT), regardless of their liver function status, should be screened for HCC in order to detect tumor progression (whether it exceeds conventional criteria) and to help prioritize transplantation. The NCCN Guideline did not recommend surveilling the group without cirrhosis for chronic HCV with advanced fibrosis, but the INASL Guideline and EASL Guideline do recommend surveilling that group. Similarly, the Saudi Guideline suggests surveillance of all cirrhotic patients, but it also stated that there was insufficient evidence to advise surveillance for patients with chronic hepatitis C but without cirrhosis. The WGO Guideline divided the criteria for HCC screening into 3 parts: hepatitis B carriers, cirrhosis not due to hepatitis B, and general patients. General patients referred to patients who were previously eligible for HCC screening and included cirrhotic patients who were successfully treated for chronic viral hepatitis. The AASLD guideline grouped together patients who would benefit from surveillance and patients in whom there was no evidence of a benefit from surveillance. The remaining guidelines did not divide the population who needed to be surveilled into smaller groups.

Obviously, there are regional differences in epidemiology that might change with time. For example, the importance of HBV as a cause of HCC is declining, but the importance of NAFLD and nonalcoholic steatohepatitis (NASH) as risk factors for HCC is on the rise (*29,30*). Future guidelines should pay close attention to these changes, and each country could devise its own method of HCC surveillance depending on local epidemiology. The current comparison of guidelines could help organizations devise a meaningful and easily understood form of surveillance.

4. Diagnostic criteria for HCC according to characteristic guidelines worldwide

The diagnosis of HCC is generally based on a combination of clinical and laboratory features as well as radiographic and histopathologic presentation. The diagnostic algorithms in the 22 guidelines that were reviewed here have been summarized in a flowchart (Figure 1). Although there were differences among these guidelines, the final diagnosis of HCC was based on imaging techniques or biopsy. With the recent advancement of various types of imaging techniques even for "indeterminate lesions" as described by the AASLD guideline, biopsy is only suggested in selected cases.

In general, if US reveals a nodule or mass in an at-risk individual, there are mainly 2 pathways for diagnosis of HCC according to current guidelines. For simplicity, these 2 categories have been designated as the "Size-based pathway" and the "Non-size-based pathway".

4.1. Size-based pathway for HCC diagnosis

The "Size-based pathway" for diagnosis of HCC starts with tumor size (generally larger or smaller than 1 cm. In the latest CSCO guideline, this was subdivided into < 1 cm, 1-2 cm, and > 2 cm). HCC nodules with a small diameter are difficult to distinguish from cirrhotic nodules, and previous studies found that small nodules, and especially those with a diameter < 1 cm, were unlikely to be HCC nodules (*44,45*). This is the main

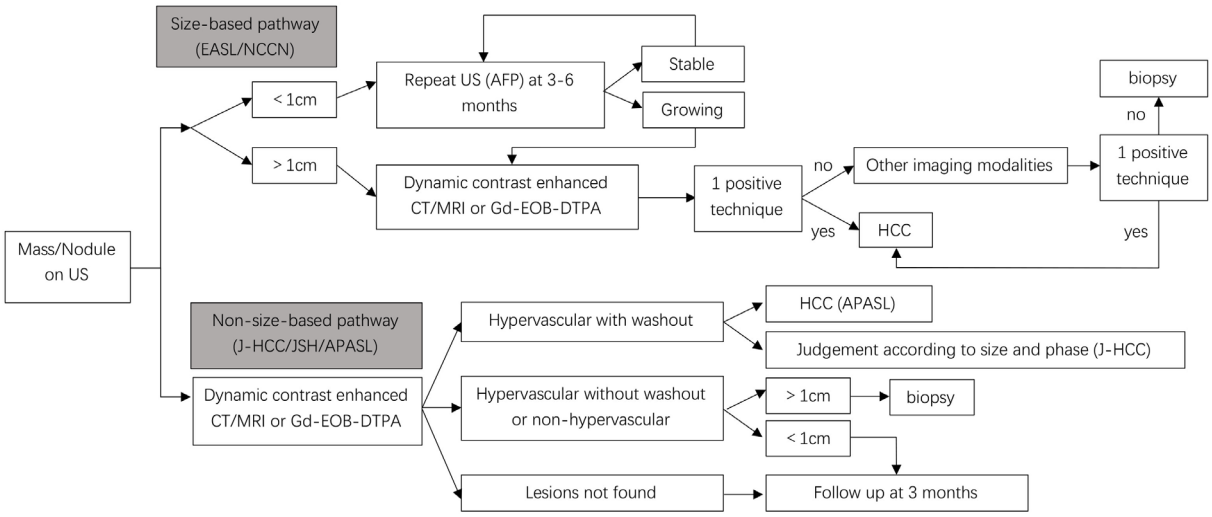

Figure 1. The diagnostic algorithm for hepatocellular carcinoma in current guidelines. The diagnostic criteria were grouped into 2 categories of a "Size-based pathway" and a "Non-size-based pathway". *Abbreviations*: EASL: European Association for the Study of the Liver; NCCN: National Comprehensive Cancer Network; JSH: Japan Society of Hepatology; APASL: Asian-Pacific Association for the Study of the Liver; US: ultrasonography; AFP: alpha-fetoprotein; Gd-EOB-DTPA: gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid.

reason why the AASLD/EASL Guideline recommend that those patients be closely followed-up with US every 3 or 4 months. The NCCN Guideline recommends repeat US plus AFP every 3 to 6 months. Kim *et al*. argued that hyper-intensity on both T2 and diffusion-weighted images is helpful in the diagnosis of hypervascular HCC nodules smaller than 1 cm in diameter (*46*). The Korean Guideline established stricter criteria for diagnosis of HCC nodules < 1 cm. Nodule size according to 2 or more imaging modalities is a typical hallmark of HCC in combination with elevated serum AFP and absence of hepatitis activity (*13*). The technique that first detected nodules should be performed again 3 to 6 months later. If the nodules remain the same size, a close follow-up should be performed. Otherwise, special attention should be paid to the growing nodule size.

Liver nodules larger than 1 cm in size should be evaluated with dynamic contrast-enhanced CT/MRI or Gd-EOB-DTPA MRI. Evidence of one or more radiological hallmarks of HCC, arterial hypervascularity, and venous/late-phase washout is considered indicative of HCC. A non-biopsy diagnosis based on a nodule size > 1 cm has been updated several times. According to the 2002 version of the EASL Guideline, a positive imaging finding plus AFP levels > 400 ng/mL can lead to a diagnosis of HCC when nodules > 2 cm (*47*). In 2005, the AASLD Guideline excluded AFP from the diagnostic algorithm and recommended radiological hallmarks according to 2 imaging techniques to diagnose HCC nodules between 1 and 2 cm in size. For nodules > 2 cm, a hallmark detected by 1 imaging technique would be sufficient. The 2010 version of the AASLD Guideline updated the criterion: an imaging technique revealing a radiological hallmark of HCC is sufficient for diagnosis of tumors 1-2 cm in diameter. The 2018 EASL guideline also stated that non-invasive criteria can apply to nodules over 1 cm in diameter. This indicates that, as imaging techniques such as gadolinium-based MRI advance, smaller nodules are diagnosed more accurately through non-invasive approaches.

Needle biopsy of a suspicious liver lesion could guide management for patients who do not exhibit a classic imaging presentation and serology, although it is not recommended generally because of the possibility of tumor dissemination outside the liver. The overall incidence of needle-tract tumor seeding following biopsy of HCC is 0.9-2.7% per year (*48*). Moreover, the NCCN Guideline stresses that a negative biopsy result does not rule out HCC if a nodule or mass has increased in size.

4.2. Non-size-based pathway for HCC diagnosis

In the "Non-size-based pathway", patients will be scheduled for dynamic imaging regardless of tumor size. All of the guidelines indicate that HCC can be definitively diagnosed when dynamic CT/MRI reveals intense arterial uptake followed by a "washout" of contrast. Moreover, ever since the 2014 JSH Guideline included Gd-EOB-DTPA MRI (gadoxetic acid disodium, a liver-specific contrast agent) as a tool for first-line surveillance and diagnosis of HCC, multiple guidelines have cited gadoxetic acid-enhanced MRI as a first-line imaging technique. In principle, this contrast agent is specifically absorbed by normal hepatocytes, resulting in contrast enhancement. Therefore, HCC nodules lacking normal hepatocytes are hypo-intense, and this difference can help distinguish tumors from non-tumorous ("normal") nodules (*49*).

When an advanced imaging technique reveals only hypervascularity with no washout, the diagnostic algorithms differ among the guidelines that were reviewed here. Recommendations in the J-HCC Guideline depend on tumor size. If the tumor diameter is larger than 1 cm, other optional examinations should be performed, including Gd-EOB-DTPA-MRI, SPIO-MRI, CEUS, CTA, and biopsy. A 3-month follow-up is recommended for patients with a tumor < 1 cm in diameter and elevated levels of tumor markers while dynamic CT/MRI is recommended for a larger tumor. In the JSH Guideline, a tumor that is hypo-intense during the hepatobiliary phase of GD-EOB-DTPA-MRI can be diagnosed as HCC provided that cavernous hemangioma is first ruled out by other modalities. A biopsy is necessary if the tumor is iso-intense or hyper-intense in the hepatobiliary phase. According to the APASL Guideline, a lesion can be diagnosed as HCC when high SPIO-enhanced MRI signals or a defect in the Kupffer phase of Sonazoid-enhanced US is evident (*7*). However, the APASL Guideline only recommends a close follow-up instead of a biopsy for patients with intense uptake in SPIO-MRI or CEUS.

There is still a lack of a broad consensus on the most appropriate diagnostic algorithm to use when initial dynamic CT/MRI reveals a hypo-vascular mass in the arterial phase. The updated J-HCC Guideline suggested that an optional examination should be undergone by patients with a tumor larger than 1.5 cm and it suggested a follow-up of 3 months for those with a tumor smaller than 1.5 cm. The JSH Guideline stresses presentation in the hepatobiliary phase of GD- EBO-DTPA-MRI. If hypo-intensity is present, Sonazoid CEUS is recommended; otherwise, follow-up should be continued. The APASL Guideline tended to recommend SPIO-enhanced MRI or Sonazoid CEUS for those patients. A close follow-up was recommended in the event of a negative imaging finding.

5. Treatment criteria for HCC according to characteristic guidelines worldwide

The treatment algorithm for HCC is constantly changing as the criteria for hepatic resection expand, locoregional therapies advance, novel targeted systemic therapies are introduced, techniques for internal and external radiation therapy improve, and the possibility of receiving a transplant increases. However, long-term outcomes of HCC depend on both the medical complexity of HCC (involving multiple confounding factors: tumor heterogeneity, liver function and performance status) as well as the choice of an appropriate treatment, posing a challenge for both patients and clinicians.

An important aim of clinical guidelines is to feature up-to-date, specific, quality evidence to help clinicians select the most appropriate treatment. Compared to our previous review (*4*), the updated guidelines include those by the NCCN (2021), AASLD (2018), CSCO (2020), JSH (2019), INASL (2019), ESMO (2021), EASL (2018), and Saudi Arabia (2020). New guidelines published between 2017 and 2022 added to the current review are the Pan-Asian adapted ESMO (2020), ICMR (2019), and GESA (2020) guidelines. The treatment algorithms in these updated guidelines and in other guidelines were reviewed here and are discussed in terms of surgical and non-surgical approaches.

Different staging systems are used to select the best treatment option for patients, which is the main difference between the guidelines. Typically, Japanese guidelines (J-HCC/JSH guidelines) use the Child-Pugh score for the very first evaluation for treatment options, while AASLD, ESMO, EASL, Saudi, and INASL guidelines involve an initial evaluation based on BCLC staging system. A flowchart has been included here to provide an overview of the diverse staging systems (Figure 2).

5.1. Surgical approaches

Basically, all of the staging systems focus on the determination of tumor resectability, since surgery is still recommended as the best treatment option for selected patients, with a 5-year survival rate as high as 80% (*1*). Initially, tumor resectability should be evaluated based on parameters like liver function, the presence of portal hypertension, tumor location, and the presence of extrahepatic metastases. If a tumor is resectable, resection or radiofrequency ablation (RFA) (for a tumor with a small diameter) is recommended. LT should also be considered for patients with cancer that is Child-Pugh class C. LT has become the first-line treatment for patients with unresectable tumors that nonetheless meet the Milan or United Network for Organ Sharing (UNOS) criteria. If those patients are not optimal candidates for transplantation, the choice of locoregional therapy, sorafenib, or supportive care depends on individual circumstances (including tumor location, liver function, and institutional capabilities). Moreover, the NCCN Guideline added that transplantation can be considered or recommended for those patients who initially failed to meet the Milan criterion but who received successful downstaging therapy.

The BCLC staging system takes tumor stage, liver function, and physical status into account, and this system had been widely adopted for HCC staging and treatment (*50*). Moreover, the BCLC staging system is the only staging system that assigns treatment strategies based on specific prognostic subclasses, an approach that has proven effective (*51*). The spectrum of treatment options with curative intent may be a subject of some controversy, but it generally consists of liver resection, LT, and ablation. Patients with stage 0 or stage A liver cancer may have a 5-year survival rate of 40-70% after treatment with curative intent. Liver resection still

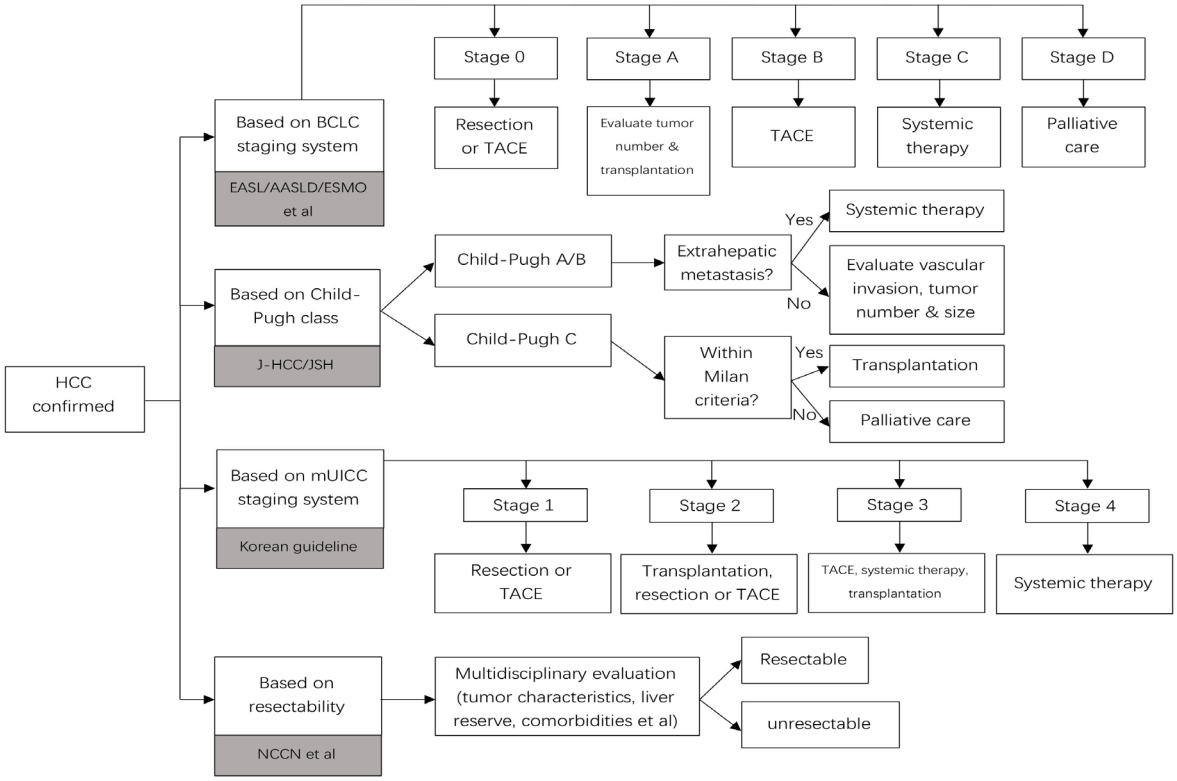

Figure 2. The treatment algorithm for hepatocellular carcinoma in current guidelines. Four clinical pathways based on different staging systems are shown. *Abbreviations*: BCLC staging system: Barcelona Clinic Liver Cancer staging system; mUICC staging system: modified Union of International Cancer Control staging system; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Disease; ESMO: European Society for Medical Oncology; JSH: Japan Society of Hepatology; NCCN: National Comprehensive Cancer Network; TACE: transarterial chemoembolization.

remains the mainstay of HCC treatment in non-cirrhotic patients or in selected cirrhotic patients with a single lesion. The AASLD Guideline repeatedly stresses the usefulness of measuring portal pressure in predicting patient outcomes and optimizing patient selection for liver resection; the usefulness of this index has also been verified in Japan (*52*). The AASLD Guideline also indicated that patients with portal hypertension or multiple lesions could receive a survival benefit from resection. The algorithm in the ESMO Guideline excluded hypertension and it expanded the criteria for clinical decision-making with regard to resection (*17*).

LT is indicated for patients with BCLC stage A cancer meeting the Milan criterion (solitary HCC nodule < 5 cm in size or fewer than 3 nodules, none larger than 3 cm in diameter). Patients with cancer meeting the Milan criterion had a 5-year overall survival rate of 65-78% after LT, which is why this criterion was integrated into the BCLC staging system (*53*). This strict criterion also has certain limitations. According to the ESMO Guideline, LT is ruled out for patients with cancer meeting the Milan criterion and poor liver function (Child-Pugh class C), who would be classed as BCLC stage D. The University of California San Francisco (UCSF) criterion extends beyond the Milan criterion, and the UCSF criterion results in comparable outcomes according to the INASL Guideline (*54*). On the whole, primary recommendations for LT have remained the same.

The 2014 Korean Guideline adopted the mUICC as its primary staging system. Its recommendations for first-line treatment are based on mUICC staging system, but its algorithm only applied to patients with Child-Pugh class A HCC, no portal hypertension, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The basic criteria of the mUICC staging system include: *i*) the number of tumors, *ii*) the diameter of the largest tumor, and *iii*) vascular or bile duct invasion. The best treatment option for a stage I tumor (single/≤ 2 cm/VI-) is resection or RFA. There are 3 options for Stage II cancer: *i*) resection or RFA (tumor size ≤ 3 cm) is recommended for treatment of stage IIa cancer (single/> 2 cm/VI-); *ii*) LT (for cancer meeting the Milan criterion) is the first option for treatment of stage IIb cancer (multiple/≤ 2 cm/VI-) and transarterial chemoembolization (TACE) or RFA is an alternative when there are more than 3 nodules; and *iii*) stage IIc cancer (single/≤ 2 cm/VI+) is amenable to TACE. The mainstay for treatment of stage III cancer is TACE or sorafenib. However, LT must be taken into account when cancer meets the Milan criterion. Sorafenib is better suited to treatment of a stage IV tumor. The Korean

Guideline also added that external beam radiation therapy could be useful in alleviating symptoms caused by primary HCC or metastases.

An algorithm based on the Child-Pugh class of liver function is utilized in Japan. The class is based on 3 factors: liver function, the number of tumors, and tumor size. Before a Child-Pugh class is assigned, whether extrahepatic spread is present is first determined. If extrahepatic spread is present, chemotherapy is the treatment of choice for Child-Pugh class A cancer. Palliative care is recommended for patients with decreased liver function. Undoubtedly, liver resection has been the first option for a solitary tumor that is Child-Pugh class A/B. According to the 2021 updated version of the J-HCC guideline, RFA is also recommended for a tumor < 3 cm. For patients with 2 to 3 tumor nodules, resection or RFA/TACE is recommended depending on their size (*12*). For patients with more than 4 tumor nodules, TACE is first recommended, but the JSH Guideline contends that resection can sometimes be performed, and ablation is sometimes performed in combination with TACE.

LT is recommended for patients younger than 65 with cancer meeting the Milan criterion, even if they have class C liver function according to the Child-Pugh score.

5.2. Non-surgical approaches

5.2.1. Ablation

RFA and percutaneous ethanol injection (PEI) are the most widely used forms of ablative treatment. They are considered the standard treatment for HCC that is BCLC 0-A stages and that is not amenable to surgery. Previous studies have found that RFA or PEI, as first-line treatment, can yield similar outcomes to surgical resection when tumors are smaller than 2 cm in size and BCLC stage 0 (*55,56*). A study in 2019, the SURF trial, recommended RFA for patients with 1-3 tumors smaller than 3 cm (*57*). In contrast, the INASL Guideline only recommends that patients with stage 0 undergo ablation when they are not potential candidates for LT (*15*). Substantial evidence is required to verify the effectiveness of ablation as a first-line treatment for very early HCC.

Patients in the terminal stage (BCLC stage D) should receive the best supportive care. External beam radiation therapy has only been tested in non-controlled studies. The INASL Guideline contends that radiation therapy cannot be recommended for management of HCC until its effectiveness is verified in clinical trials.

5.2.2. Embolization

In recent years, HCC interventional therapy has made huge advances, such that it has become an independent subspecialty. TACE was listed as the primary treatment option for BCLC stage B HCC in guidelines such as those from the EASL, and that procedure is described as being supported by strong evidence (*58,59*). The current guidelines reviewed here recommend TACE at about the same level as they did previously. Recent studies have found transarterial radioembolization (TARE), also called selective internal radiation therapy (SIRT), might outperform TACE in terms of tumor downstaging, and its combined use with Yttrium-90 microspheres may result in an encouraging outcome in terms of survival (*60,61*). Thus, TARE with Yttrium 90 could be considered as an alternative to TACE, particularly in cases of HCC with portal vein thrombosis.

5.2.3. Systemic therapy

Molecularly targeted therapy has made vast progress over the past few years. Traditionally, sorafenib is indicated when BCLC stage C HCC or BCLC stage B HCC progresses after TACE. Two widely cited RCTs have revealed that sorafenib can serve as a first-line treatment in patients with HCC who still have liver function but who can no longer be treated with other more effective therapies (*62,63*). Previous studies on sorafenib have reported its safety data and its efficacy in prolonging survival (*64-66*). Another first-line drug recommended by recently updated guidelines is lenvatinib. In a randomized phase 3 trial (about 2/3 of the included patients were from the Asia-Pacific region), the efficacy of lenvatinib was not inferior to that of sorafenib (*67*). In the study in question, lenvatinib displayed superior efficacy in the Chinese subgroup, and the overall survival time was prolonged by 4.8 months. Lenvatinib has a survival benefit for HBV-related HCC. According to the AASLD guideline, there is no evidence to support whether second-line treatment options such as regofinib or nivolumab can be used for patients with tumor progression receiving lenvatinib, but sequential use of tyrosine kinase inhibitors with a similar mechanism of action can be considered.

In the latest NCCN guideline, however, the recommended dose of sorafenib was reduced and the preferred regimen was changed to atzumab + bevacizumab (referred to as the T + A regimen, Child-Pugh class A only). Data presented at the 2019 ESMO Asia Congress indicated that the T+A regimen was superior to sorafenib in patients with unresectable HCC (*68*). Nevertheless, the cost-effectiveness of the T+A regimen still needs to be optimized (*69*).

6. Conclusion

This work has reviewed updated information from current comprehensive guidelines for HCC management published worldwide between 2001 and 2022. Twenty-two characteristic guidelines were identified, including 1 international guideline, 11 guidelines from Asia, 5 from

Europe, 4 from the US, and 1 from Australia. Those guidelines were compared in terms of surveillance, diagnosis, and treatment with a focus on the clinical management of HCC. The composition of and recommendations in current guidelines on HCC varied, so these guidelines were regrouped and diagnostic and treatment algorithms were summarized graphically to provide the latest information for clinicians.

Over the past few decades, HCC has changed from an almost universal death sentence to a cancer that can be prevented, detected in an early stage, and effectively treated, but HCC is still the second leading cause of cancer-related mortality worldwide, and the leading cause of death among patients with chronic liver disease (*2*). Findings from this comparison of current guidelines may help target and concentrate efforts to improve the clinical management of HCC. However, further studies are needed to improve the management and outcomes of HCC. More straightforward or refined guidelines would help guide doctors to make better decisions in the treatment of HCC in the future.

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[§]These authors contributed equally to this work.
**Address correspondence to:*
Nansheng Cheng, Department of Biliary Surgery, West China Hospital of Sichuan University, No. 37 Guo Xue Xiang, Chengdu 610041, Sichuan Province, Chana.
E-mail: nanshengcheng2012@163.com

Peipei Song, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: psong@it.ncgm.go.jp

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