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REVIEW
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Difference in treatment algorithms for hepatocellular carcinoma between world's principal guidelines

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Abstract: Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death globally. Clinical guidelines for HCC have been established and revised by many countries and regions. We summarized and compared the treatment algorithms in the updated HCC guidelines established by Japan, China, Hong Kong, the Asian-Pacific Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer. Variations in treatment algorithms between the guidelines is inevitable, considering the differences in the prevalence and etiology of HCC, local clinical practice, and medical and insurance systems between countries or regions, and this might be confusing for practitioners worldwide. A comprehensive understanding of the guidelines that are globally available might be useful for future improvement of each guideline.

***Keywords*:** surgery, ablation, transcatheter arterial chemoembolization, systemic chemotherapy, transplantation

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is the fifth most common cancer and second leading cause of cancer-related death globally (*1,2*). Although HCC is predominant in Southeast Asia and Africa, the incidence rate of HCC has been increasing in other regions, particularly in Europe and the United States (*2,3*), which has led to a greater interest in the diagnosis and treatment of HCC worldwide.

In the past two decades, clinical guidelines for HCC were established and revised by many countries including Japan (*4*), China (*5*), Hong Kong (*6*), the Asian-Pacific countries (*7*), European countries (*8*), and the United States (*9*). The guidelines reflect the differences between countries, including the prevalence and etiology of HCC, local clinical practice, and medical and insurance systems, which entail many differences, especially in treatment algorithms. Recently, advancement of HCC treatment especially in systemic chemotherapy has been attracting attention to the revision of the guidelines for HCC.

In this review, we have summarized and compared the treatment algorithms in the updated HCC guidelines established by Japan, China, Hong Kong, the Asian-Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer (EASL-EORTC), and the American Association for the Study of Liver Diseases (AASLD).

Overview of the treatment algorithms of the guidelines

The treatment algorithms in each guideline are summarized in Figures 1-6. The characteristics of the treatment algorithms in each country are as follows.

Japan

The Japanese evidence-based clinical practice guidelines were published in 2005 by the Japan Society of Hepatology (JSH). The guidelines were formulated based on a systematic review of the evidence for hepatocellular carcinoma. The treatment algorithm was simple and clear, and the guidelines were revised three times, in 2009, 2013 and 2017, incorporating growing new evidence and paying more attention to the consensus among the specialists in Japan.

In the early version of the Japanese treatment algorithm, vascular invasion and extrahepatic metastasis were not included because of the lack evidence for treatment. However, to reflect the varieties of clinical practice in the real world, especially regarding non-surgical treatments, a treatment algorithm covering all situations of HCC was requested especially from gastroenterologists. As a result, the latest version of the treatment algorithm in the Clinical Practice Guidelines for Hepatocellular Carcinoma 2017 included vascular invasion and extrahepatic metastasis (Figure 1).

Unlike the treatment algorithms of other countries,

in the 2017 guideline, performance status was not included in the algorithm. Child-Pugh C patients are allocated into liver transplantation or palliative care according to the Milan criteria. The evaluation of liver function was mainly performed by Child Pugh classification, while liver damage classification was used in the earlier versions. Liver transplantation is not indicated for patients with good liver function (Child-Pugh A/B) because of the organ shortage for transplantation and medical insurance system in Japan. In the minor revision of the 2017 Japanese guidelines in 2019, new expanded criteria for LDLT candidates with HCC, the 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and alfa-fetoprotein value ≤ 500 ng/ml), were established based on a retrospective data analysis of the Japanese nationwide survey (*10*). In the presence of extrahepatic metastasis, systemic therapy is indicated only for Child-Pugh A patients. After evaluation of liver function and extrahepatic metastasis, each local and systemic therapy is indicated according to vascular invasion, tumor number (≤ 3 or > 3), and tumor size (≤ 3 cm or > 3 cm).

China

The Chinese guideline on the management of hepatocellular carcinoma was revised in 2017 from the previous 2011 version (Figure 2). Based on updated evidence and clinical practice, new staging systems and treatment algorithms have been developed that are far more comprehensive and suitable for use in China, focusing on treatment distribution according to respective stage.

First of all, the general condition and liver function of patients are evaluated by performance status and Child-Pugh classification, and patients with performance status 3–4 and/or Child-Pugh C are distributed into palliative care. Patients with performance status 0–2 and Child-Pugh A/B with extrahepatic metastasis are assigned into systemic therapy, transcatheter arterial chemoembolization (TACE), and radiotherapy. After the evaluation of performance status, liver function and extrahepatic spread, each local and systemic therapy is indicated according to vascular invasion, tumor number (solitary, 2-3 or ≥ 3), and tumor size (≤ 5 cm or > 5 cm for a solitary tumor and ≤ 3 cm or > 3 cm for 2-3 tumors).

In particular, surgical resection is widely indicated regardless of vascular invasion, tumor number, or tumor size in the Chinese guidelines. Liver transplantation is indicated in patients with performance status 0–2 and Child-Pugh A/B, and the indication is determined in accordance with the University of California San Francisco (UCSF) criteria.

Hong Kong

The Hong Kong liver cancer staging system with treatment stratification was published in 2014, in order to establish an appropriate prognostic staging system for HCC with treatment guidelines applicable to Asian patients. The Hong Kong guidelines were formulated based on data collected from 3,856 patients with HCC predominantly related to hepatitis B treated at Queen Mary Hospital in Hong Kong (Figure 3).

In the Hong Kong guidelines, HCC is classified into three phases as follows: (1) Early tumor: ≤ 5 cm, ≤ 3 tumor nodules and no intrahepatic venous invasion; (2) Intermediate tumor: *i*) ≤ 5 cm, either > 3 tumor nodules or with intrahepatic venous invasion, or *ii*) > 5 cm, ≤

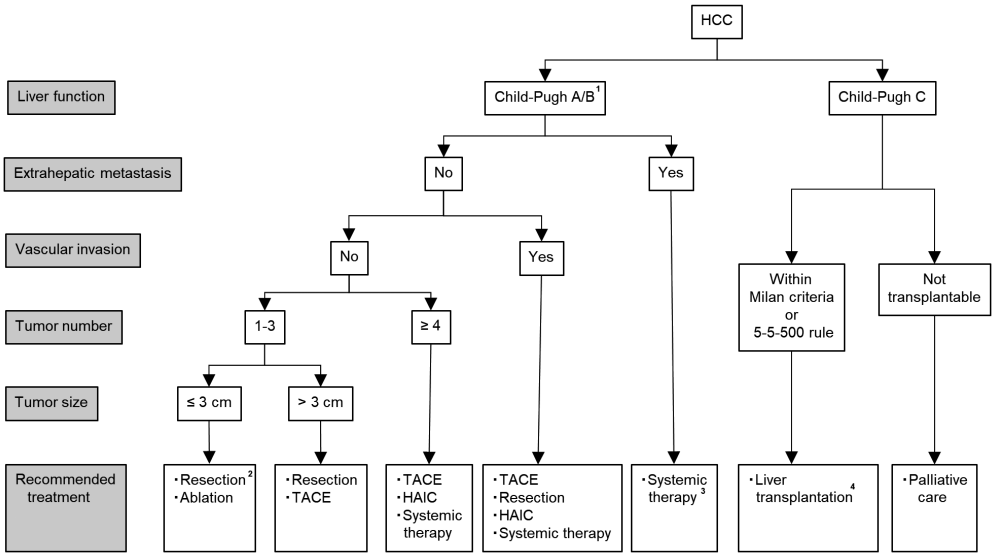

Figure 1. Treatment algorithm of clinical practice guidelines for HCC in Japan (2017), summarized and modified from Kokudo *et al.* (*4*). [1]Evaluation using liver damage classification is recommended when liver resection is indicated. [2]For solitary tumor, liver resection is first-line and local ablation is second-line. [3]Only for Child-Pugh A. [4]Patient age ≤ 65. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

3 tumor nodules, and no intrahepatic venous invasion; and (3) Locally advanced tumor: *i*) ≤ 5 cm, > 3 tumor nodules and with intra-hepatic venous invasion, or *ii*) > 5 cm, > 3 tumor nodules, and/or with intrahepatic venous invasion, or *iii*) diffuse tumor.

In accordance with the tumor classification system, performance status, Child-Pugh classification, and the presence of extrahepatic metastasis, patients are divided into prognostic stages and treatment is allocated. According to the flowchart, patients with performance

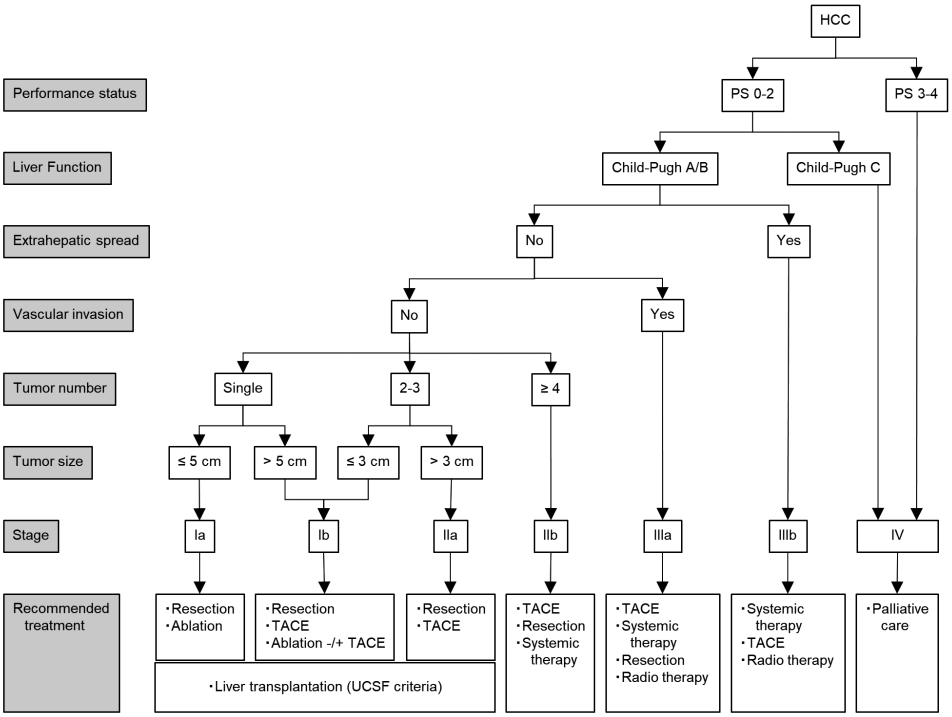

Figure 2. Treatment algorithm of clinical practice guidelines for HCC in China (2017), summarized and modified from Xie *et al.* (*5*). HCC, hepatocellular carcinoma; PS, performance status; TACE, transcatheter arterial chemoembolization; UCSF, University of California San Francisco.

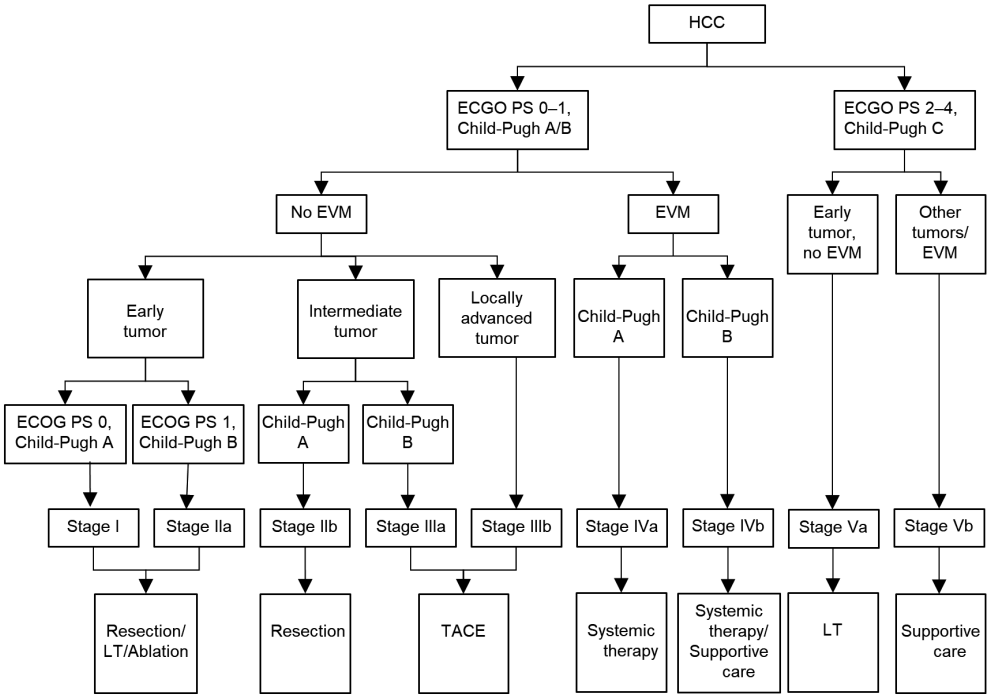

Figure 3. Treatment algorithm of clinical practice guidelines for HCC in Hong Kong (2015), summarized and modified from Poon *et al.* (*6*). ECOG, Eastern Cooperative Oncology Group; EVM, extrahepatic vascular invasion/metastasis; HCC, hepatocellular carcinoma; LT, liver transplantation; PS, performance status; TACE, transcatheter arterial chemoembolization.

status 2–4 and/or Child-Pugh C are allocated into palliative care, but liver transplantation is indicated for early tumor without extrahepatic metastasis. In the presence of extrahepatic metastasis, patients with performance status 0–1 and Child-Pugh A/B are allocated into systemic therapy or palliative care. Each local therapy is indicated for patients with performance status 0–1 and Child-Pugh A/B without extra hepatic metastasis according to tumor phase as follows: Early tumor: resection, liver transplantation, ablation; Intermediate tumor: resection, TACE; Locally advanced tumor: TACE.

APASL

The APASL HCC guidelines were published in 2010 (*11*). The guidelines were revised in accordance with the statement of the "Toward Revision of the APASL HCC Guidelines" meeting held at the 25th annual conference of the APASL in Tokyo on February 23, 2016 (Figure 4). The guidelines are evidence-based and considered generally acceptable in the Asia-Pacific region, which has a diversity of medical environments. The evidence and recommendations in the guideline have been graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (*12*).

Consistent with the Japanese evidence-based clinical practice guidelines, performance status is not included in the algorithm. In the presence of extrahepatic metastasis, the first-line therapy is systemic therapy for Child-Pugh A/B patients and palliative care for Child-Pugh C patients. In the absence of extrahepatic metastasis, liver transplantation or palliative care is indicated for Child-Pugh C patients according to the Milan or UCSF criteria, and each local and systemic therapy is indicated according to resectability, vascular invasion, tumor number (≤ 3 or > 3), and tumor size (≤ 3 cm or > 3 cm).

Notably, resectability is included in the APASL treatment algorithm, which reflects a variety of surgeons' skills and hospital facilities in Asian-Pacific countries (*13*). In addition, resectability is also evaluated from the viewpoint of extended indication of liver resection in the real world due to recent advances in surgical technique and postoperative management (*14*).

EASL-EORTC

The first European joint guidelines for the management of hepatocellular carcinoma were first developed in 2001 by EASL, updated by EASL-EORTC 2012, and then revised in 2018 (Figure 5). The treatment algorithms are mostly based on the Barcelona-Clinic Liver Cancer (BCLC) staging system, which classifies HCC patients into five stages, including very early

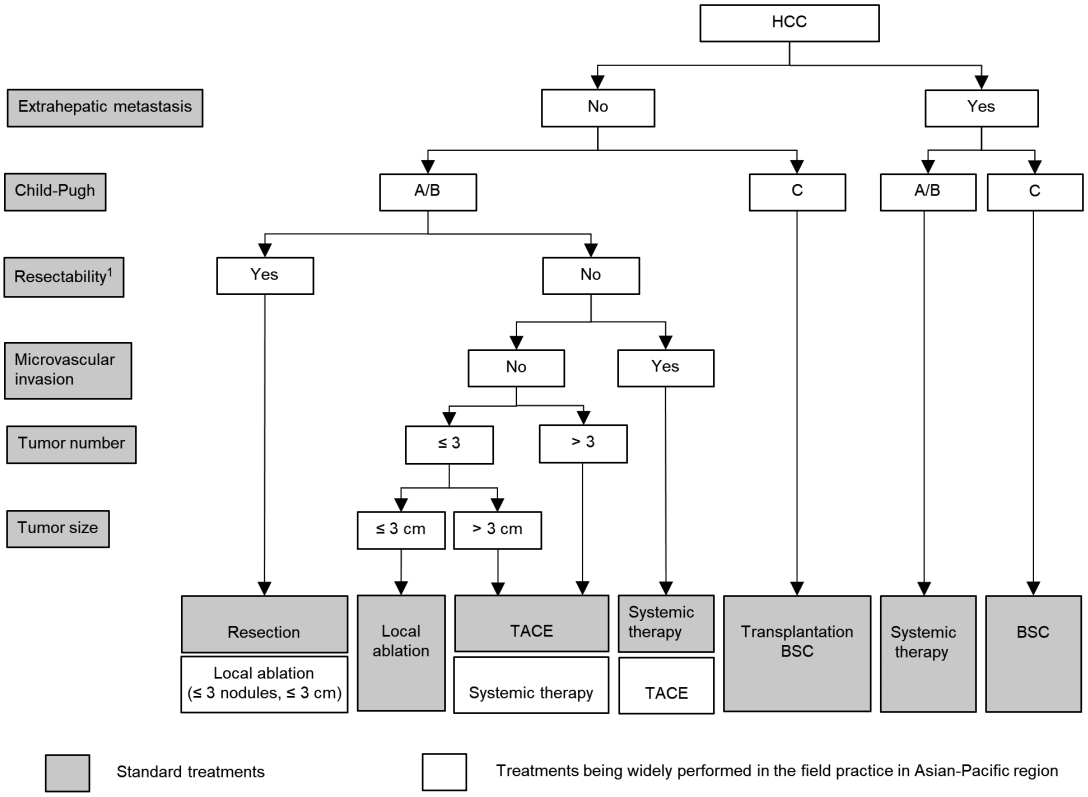

Figure 4. Treatment algorithm of clinical practice guidelines for HCC in APASL (2017), summarized and modified from Shiha *et al.* (*7*). [1]Decisions regarding resectability should be discussed in a multidisciplinary team. BSC, best supportive care; HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

stage (Stage 0), early stage (Stage A), intermediate stage (Stage B), advanced stage (Stage C), and terminal stage (Stage D) (*15*).

However, the evaluation of liver function has been slightly changed in EASL-EORTC guidelines. Although the BCLC staging system used Child-Pugh A for Stage 0 and Child-Pugh A/B for Stages A–C, the EASL-EORTC guidelines defined "preserved liver function" as Child-Pugh A without any ascites, and used this criterion to sort treatable stage (Stage 0–C) and terminal stage (Stage D). Therefore, according to EASL-EORTC guidelines, staging based on liver function is stricter than in the BCLC staging system.

The staging of HCC in the EASL-EORTC guidelines is as follows: (1) Very early stage (Stage 0: < 2 cm, single nodule, preserved liver function, and PS 0); (2) Early stage (Stage A: single nodule or ≤ 3 nodules of < 3 cm, preserved liver function, and PS 0); (3) Intermediate stage (Stage B: multinodular, preserved liver function, and PS 0); (4) Advanced stage (Stage C: portal invasion, extrahepatic spread, preserved liver function, and PS 1-2); and (5) Terminal stage (Stage D: Child-Pugh C, and PS 3-4).

All stages except Stage A directly connect to treatment: Stage 0 to ablation or resection, Stage B to chemoembolization, Stage C to systemic therapy, and Stage D to palliative care. In Stage A, the patients are classified into optimal surgical candidates and transplant candidates. Optimal surgical candidacy is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score < 10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma and possibility of adopting a laparoscopic or minimally invasive approach, and transplant candidacy as indicated by the Milan criteria (*16*). Ablation is also indicated for patients in Stage A who are neither optimal surgical candidates nor transplant candidates. Although macrovascular invasion is contraindicated for surgery in the EASL-EORTC guidelines, intervention to distal portal invasion, at segmental or subsegmental level, is considered to deserve investigations within a prospectively designed protocol reflecting on a Japanese report (*17*).

AASLD

The AASLD practice guidelines on the management of HCC were established in 2005 and revised in 2010 and 2018 (Figure 6). In accordance with the EASL-EORTC guidelines, treatment algorithms are based on the BCLC staging system (*15*) with minor modifications. The performance status for BCLC Stages 0, A, and B has been changed from 0 to 0-1 and BCLC stage C from 1-2 to 0-2 in order to better reflect clinical practice in reality (*18*). Therefore, the treatment indication for AASLD guidelines is expanded in terms of performance status compared to BCLC guidelines.

Treatment is allocated to each stage as follows: (1) Stage 0: resection and ablation; (2) Stage A: resection, liver transplantation and ablation, transarterial radio embolization (TARE), TACE, radiotherapy; (3) Stage B: TACE, TARE, and liver transplantation; (4) Stage C: systemic therapy, and TARE; and (5) Stage D: liver transplantation and palliative care. Unlike EASL-

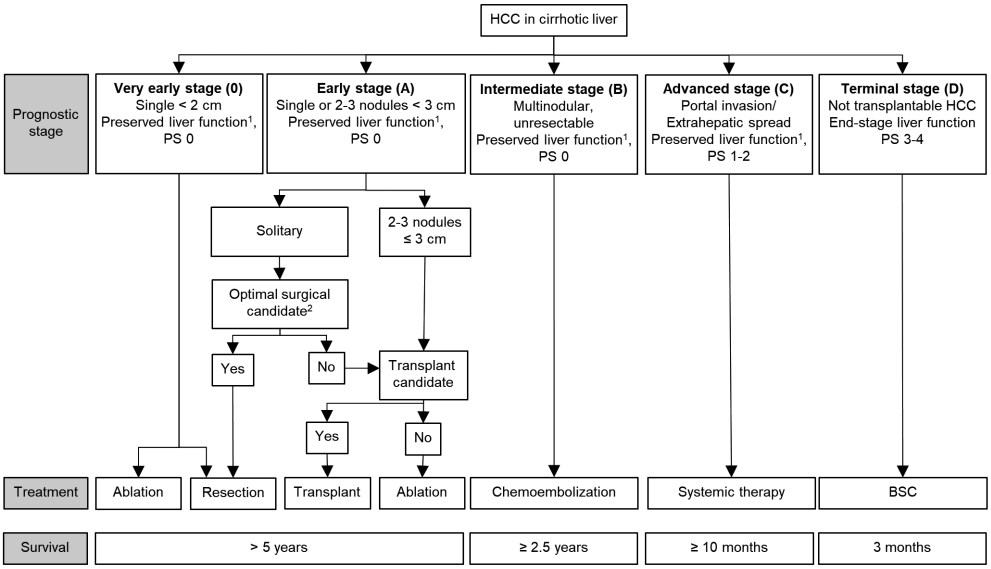

Figure 5. Treatment algorithm of clinical practice guidelines for HCC in the European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer (EASL-EORTC) (2018), summarized and modified from the European Association for the Study of the Liver (*8*). [1]Without any ascites. [2]Optimal surgical candidacy is based on a multiparametric evaluation including compensated Child-Pugh class A liver function with MELD score < 10, to be matched with grade of portal hypertension, acceptable amount of remaining parenchyma, and possibility to adopt a laparoscopic/minimally invasive approach. BSC, best supportive care; HCC, hepatocellular carcinoma; PS, performance status.

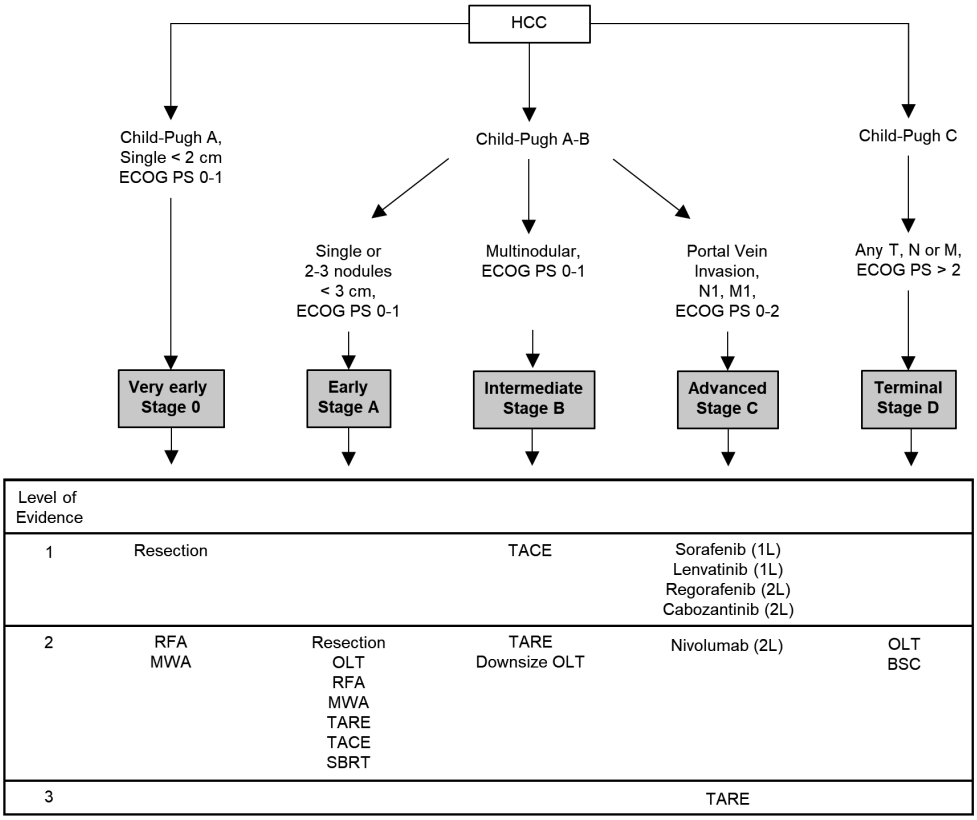

Figure 6. Treatment algorithm of clinical practice guidelines for HCC in the American Association for the Study of Liver Diseases (AASLD) (2018), summarized and modified from Marrero *et al.* (*9*). ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; MWA, microwave ablation; OLT, orthotopic liver transplantation; PS, performance status; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transcatheter arterial chemoembolization; TARE, transarterial radio embolization.

EORTC guidelines, TARE is indicated for Stages A–C, and liver transplantation is also considered for Stages B and D according to the Milan criteria (*16*).

Differences of treatment indications between guidelines

The differences in treatment indications of resection, ablation, TACE, and systemic therapy by tumor condition between guidelines are summarized in Figure 7. Treatment allocation by liver function and performance status is not included, in order to focus on the differences of treatment indications based on tumor condition. The stratification is mainly conducted by treatment in Figure 7a and by country in Figure 7b.

Liver resection

Liver resection is indicated for advanced HCC in terms of tumor burden in the treatment algorithms of Asian countries (*19*). The Japanese treatment algorithm indicates liver resection for any nodule size (within 3 in number). In the Chinese treatment algorithm, surgical resection could be a choice for HCC for any nodule size and number. The Hong Kong treatment algorithm recommends liver resection for any nodule size (within 3 in number and > 3 nodules within ≤ 5 cm in size). Notably, vascular invasion is not a contraindication for surgical resection in the Japanese, Chinese, and Hong Kong guidelines. In contrast, the EASL-EORTC and AASLD guidelines, which follow the BCLC staging classification (*15*), have set narrower indications for liver resection. Liver resection is only recommended for those with single nodules of any size in the EASL-EORTC guidelines, and single nodules of any size and 2-3 nodules within 3 cm in size in the AASLD guidelines. In addition, liver resection is not indicated for HCC with vascular invasion in the EASL-EORTC and AASLD guidelines.

In terms of liver functional reserve, liver resection is an option for patients with Child-Pugh A/B in the Asian guidelines, including Japan, China, Hong Kong, and the APASL. In accordance with the Asian guidelines, patients in Child-Pugh A/B are candidates for surgical resection as per the AASLD guidelines, although a stricter indication (Child-Pugh A without ascites) is set in the EASL-EORTC guidelines. Furthermore, while normal bilirubin and portal pressure are supposed to serve as a prerequisite for resection under the BCLC recommendations, slightly elevated bilirubin or portal hypertension is not a definite contraindication for surgical resection in Asian guidelines (*20*). As for

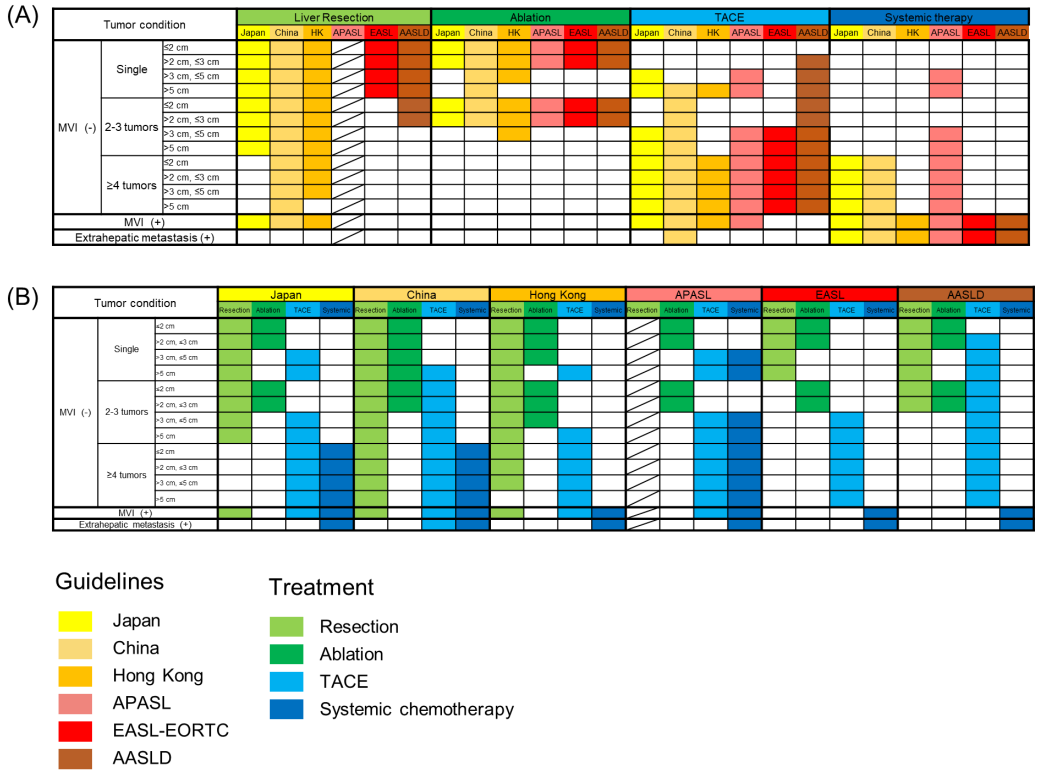

Figure 7. Difference of treatment indications between guidelines. (A) Difference by treatment; **(B)** Difference by country. HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; MVI, macrovascular invasion; PS, performance status; TACE, transcatheter arterial chemoembolization; TARE, transarterial radio embolization; UCSF, University of California San Francisco. In APASL guideline, the indication of liver resection is determined by "resectability" which reflects a variety of surgeons' skills and hospital facilities.

portal hypertension, the EASL-EORTC indicates that portal hypertension should always be balanced with the extent of hepatectomy and liver function indicators, such as the MELD score and availability and predicted effectiveness of alternative HCC therapies in decision making for eligibility for liver resection because limited hepatectomy in patients with preserved liver function and moderate clinically relevant portal hypertension (hepatic venous pressure gradient > 10 mmHg) yields competitive survival outcomes (*21*).

However, surgical indications for HCC are decided not only by selection criteria included in each treatment algorithm, as mentioned above, but also by tumor location, estimated liver resection volume, and liver functional reserve. Although there are several algorithms to guide secure hepatic resection, the detailed operative indication and procedure should be determined by well-experienced hepatobiliary surgeons in accordance with the condition of each patient.

Ablation

Image-guided percutaneous ablation therapies mainly mention ethanol injection (*22*), microwave ablation (MWA) (*23*), and radiofrequency ablation (RFA) (*24*). Of these, RFA is recommended first in all guidelines, and ethanol injection is a treatment of choice only in cases in which RFA cannot be performed safely because of either enterobiliary reflux or adhesion between the tumor and the gastrointestinal tract. Recently, MWA has been utilized more frequently because application of higher temperatures in a shorter period of time has led to excellent local tumor control and less concern for heat sink (*25*), and the AASLD guidelines recommend MWA as a choice of local ablation therapy. However, there are no prospective randomized trials comparing RFA with MWA.

The indication of local ablation therapy is almost the same among the various guidelines described above. Local ablation therapy is mainly performed on patients with small HCC, generally in Child-Pugh class A or B patients with three or fewer tumors, each 3 cm or less in diameter. In the Hong Kong guidelines, local ablation is indicated for solitary tumors within 5 cm in size. The combination of ablation and TACE is recommended for solitary tumors measuring 3-7 cm in diameter as per the Chinese guidelines (*26*).

TACE

TACE is recommended as a first-line treatment of HCC for patients with unresectable, large or multifocal HCCs, which do not have vascular invasion or extrahepatic spread, namely equivalent to BCLC stage

B patients (*27*). Therefore, the guidelines published by the EASL-EORTC and AASLD recommend TACE as a first-line, non-curative therapy for BCLC stage B patients, although only systemic therapy is indicated for patients with vascular invasion according to the EASL-EORTC and AASLD recommendations.

On the other hand, TACE is a treatment option for lesions with vascular invasion according to the Asian guidelines. TACE is indicated for lesions with vascular invasion at the peripheral portal branch as per Japanese and Hong Kong guidelines (*28*), and even for lesions with portal vein tumor thrombus (PVTT) at the main trunk in Chinese guidelines as long as collateral circulation is well developed, although temporary liver decompensation and postembolization syndrome were noted to occur frequently (*29*). In APASL guidelines, TACE is recommended as the second-line therapy for tumors with vascular invasion, whereas systemic therapy is indicated as the first-line therapy. In addition, TACE alone or in combination with radiotherapy for patients with extrahepatic metastasis can be an option in China guidelines based on some retrospective observational studies (*30*), although there is insufficient evidence of a recommendation for TACE over systemic therapy for advanced HCC.

For patients with multiple and/or portal invasion, TARE is recommended in the Chinese and AASLD guidelines. In Japan, TARE is not included in national insurance and is therefore not commonly performed. Instead, hepatic arterial infusion chemotherapy (HAIC) is commonly recommended for patients with multiple and/or portal invasion without indication of liver resection and TACE.

Systemic chemotherapy

Basically, systemic therapy is recommended over no therapy for patients with advanced HCC with macrovascular invasion and/or metastatic disease in all guidelines. In addition, systemic therapy is also indicated for multiple tumors (> 3 in number) in the Japanese and Chinese guidelines, and the APASL treatment algorithm recommends systemic therapy for TACE candidates as a second-line treatment according to the concept of conversion from TACE to sorafenib before the appearance of macrovascular invasion or extrahepatic metastasis (*31*). Systemic therapy is also indicated for tumors that are refractory to other locoregional therapy in all guidelines. In terms of liver function, systemic therapy is indicated only for patients with Child-Pugh A in Japan and EASL-EORTC, and for patients with Child-Pugh A and well-selected Child-Pugh B in China, Hong Kong, and AASLD.

First-line agents used for systemic therapy are sorafenib in Hong Kong and APASL, sorafenib and FOLFOX 4 in China, and sorafenib and lenvatinib in Japan, AASLD, and EASL-EORTC. As second-line therapy, regorafenib is recommended in Japan and EASL-EORTC, and regorafenib and nivolmab are recommended in AASLD. The differences among the agents used for systemic therapy should be interpreted in consideration with the recent rapid advance of antitumor drugs for HCC systemic therapy, including molecular targeted agents and immune checkpoint inhibitors.

In a latest report, Finn *et al.* reported the superiority of atezolizumab-bevacizumab to sorafenib in patients with advanced unresectable hepatocellular carcinoma not previously treated with systemic therapy (*32*). Atezolizumab is a programmed death ligand 1 (PD-L1) inhibitor, and bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor. Treatment with the combination of atezolizumab-bevacizumab resulted in significantly longer overall survival at 12 months (67.2% [95% CI, 61.3 to 73.1] with atezolizumab–bevacizumab and 54.6% [95% CI, 45.2 to 64.0] with sorafenib, and progression-free survival (median progression-free survival, 6.8 months [95% CI, 5.7 to 8.3] with atezolizumab–bevacizumab and 4.3 months [95% CI, 4.0 to 5.6] with sorafenib). The confirmed objective response rates were 27.3% (95% CI, 22.5 to 32.5) with atezolizumab–bevacizumab and 11.9% (95% CI, 7.4 to 18.0) with sorafenib. The combination of atezolizumab-bevacizumab might be a new benchmark for first-line therapy in advanced HCC. This evidence will be included in each guideline in the near future.

Liver transplantation

Thus far, the two major accepted criteria for liver transplantation have been the Milan criteria (solitary tumor ≤ 5 cm or within 3 nodules ≤ 3 cm without vascular invasion and extrahepatic metastasis) (*16*) and the UCSF criteria (solitary tumor ≤ 6.5 cm or ≤ 3 nodules ≤ 4.5 cm plus total tumor diameter ≤ 8 cm without vascular invasion and extrahepatic metastasis) (*33*). The Milan criteria have been adopted in Japan, Hong Kong, APASL, EASL-EORTC, and AASLD as the first-line criteria, and the UCSF criteria are used in China as the first-line and in Hong Kong and APASL as the second-line. Although the expansion of the Milan criteria is not recommended by the Japan and AASLD guidelines, the recently updated EASL-EORTC and AASLD guidelines suggest that patients beyond the Milan criteria can be candidates for transplantation after successful down-staging into the Milan criteria (*34*). In the Japanese 2017 guidelines with minor revision in 2019, new expanded criteria for LDLT candidates with HCC, the 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and alfa-fetoprotein value ≤ 500 ng/ml), were established based on a retrospective data analysis of the Japanese nationwide survey (*10*).

Although each guideline has adopted the Milan or

UCSF criteria, the difference in graft sources between the East and West should be taken into consideration. Briefly, living-donor liver transplantation (LDLT) is the mainstay in Eastern countries, whereas deceased-donor liver transplantation (DDLT) is prevalent in Western countries (*35*). Unlike DDLT, LDLT is not restricted by the nationwide allocation system, and the indication for LDLT in patients with HCC should be decided based on institutional or case-by-case consideration, balancing the burden on the donor, operative risk, and overall survival benefit for the recipient.

Conclusion

In conclusion, the differences in treatment strategy for hepatocellular carcinoma between the updated guidelines in Japan, China, Hong Kong, APASL, EASL-EORTC, and AASLD are summarized. Variations in the treatment algorithms between the guidelines is inevitable considering the differences in the prevalence and etiology of HCC, local clinical practice, and medical and insurance systems between countries or regions, and this might be confusing for practitioners worldwide. The present review provides comprehensive understanding of existing guidelines worldwide and it may be useful for future improvement of each guideline.

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