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GUIDELINES

Hepatology Research

Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC Guidelines)

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Abstract

The fifth version of the Clinical Practice Guidelines for Hepatocellular Carcinoma was revised by the Japan Society of Hepatology, according to the methodology of evidence-based medicine and partly to the Grading of Recommendations Assessment, Development and Evaluation system, which was published in October 2021 in Japanese. In addition to surveillance–diagnostic and treatment algorithms, a new algorithm for systemic therapy has been created, as multiple drugs for hepatocellular carcinoma can be currently selected. Here, new or revised algorithms and evidence on which the recommendations are based are described.

KEYWORDS
algorithm for surveillance and diagnosis, algorithm for systemic therapy, algorithm for treatment, clinical practice guidelines, hepatocellular carcinoma

INTRODUCTION

Since the first edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma (HCC) was published in 2005,[1] revisions have been made by the Japan Society of Hepatology (JSH) every 4 years.[2–4] The fourth version of Evidence-based Clinical Practice Guidelines for HCC was published in 2017,[5] followed by Web-based minor revisions to the evidence for new systemic therapies, and the expanded fourth edition with the modification of the treatment algorithm for the indication of liver transplantation for HCC in 2020. The revision of the 2021 version

(the fifth edition) began in July 2019. In the revision procedures, scientific literature published up to January 2020 was systematically screened using medical databases (MEDLINE) and systemically evaluated. Important evidence published after the search period was added by hand-searching as appropriate, resulting in publication after approximately 2 years of work. The JSH-HCC guidelines have been consistently developed based on the methodology of evidence-based medicine since the first edition, and have also been revised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system[6] since the fourth edition.

As systemic therapy for HCC has recently advanced remarkably, the most significant change in HCC treatment in the period leading up to this revision was an increase in the number of systemic therapies available in Japan, covered by the National Health Insurance system. Therefore, a new "HCC systemic therapy algorithm" was developed in the current version to complement the conventional treatment algorithm.

Before this revision, the General Affairs Committee for the Clinical Practice Guidelines that controls all JSH guidelines was newly established and decided membership of the Revision Committee. The Revision Committee, comprising of 27 members in the field of liver cancer, scrutinized and decided on a total of 52 clinical questions (CQs). Several key words were selected, and then committee members and expert advisors developed search queries for individual CQs. Two members were assigned to one CQ as the chief and assistant researchers, and they performed the first screening of the extracted articles independently. After comparing and adjusting screening results, they performed a second screening process independently. Thereafter, they created a draft recommendation for each CQ. After the committee revised the draft recommendations, each committee member selected the levels of recommendation for each CQ. The level that received 70% of the valid votes was adopted as the opinion of the entire committee. Only members approved by the General Affairs Committee for the Clinical Practice Guidelines had voting rights, and members with either a financial or academic conflict of interest voluntarily gave up their voting rights (all authors of a reference cited in each CQ were defined as having academic conflict of interest). Then, the strength of recommendation was determined.

The full English version of the 5th JSH-HCC guidelines is available, including the retrieval styles for all clinical questions, on the JSH website (https://www.jsh.or.jp/English/examination_en/). Here, important revisions in the new 5th JSH-HCC guidelines are outlined.

Algorithms for surveillance and diagnosis of HCC

The target population for surveillance is the high-risk group for HCC. Patients with any of the following three conditions are considered at high risk for HCC: cirrhosis, chronic hepatitis B, or chronic hepatitis C. Among high-risk patients, those with cirrhosis types B and C are considered an extremely high-risk group. The surveillance protocol consists of abdominal ultrasonography (US) and tumor marker measurement, repeated every 3–6 months. Surveillance intervals are recommended to be every 6 months for the high-risk group and every 3–4 months for the extremely high-risk group. This regular surveillance protocol may be combined with dynamic computed tomography (CT)/magnetic resonance imaging (MRI) for extremely high-risk patients. When US detects new nodular lesions, dynamic CT, dynamic MRI using extracellular gadolinium (Gd)-based contrast agents, or Gd-ethoxybenzyl (EOB)-diethylenetriamine pentaacetic acid (DTPA)-enhanced MRI are performed for differential diagnosis. Even when no tumor is detected on US, dynamic CT/MRI should be considered in the following cases: persistent elevation or ≥200 ng/mL of alpha-fetoprotein, ≥40 mAU/mL of PIVKA-II, or ≥15% of alpha-fetoprotein-L3 fraction.

On contrast-enhanced imaging, typical HCC is characterized by neovascularization, demonstrating arterial phase hyperenhancement and washout in the portal or equilibrium phase. In the 5th JSH-HCC guidelines, the algorithm for surveillance and diagnosis of HCC was divided into two categories, depending on whether the second imaging study after US is dynamic CT or MRI using extracellular contrast agents (Figure 1: Algorithm 1) or Gd-EOB-DTPA-enhanced MRI (Figure 2: Algorithm 2). In case Gd-EOB-DTPA-enhanced MRI cannot exclude cavernous hemangioma, dynamic CT or MRI using extracellular contrast agents need to be performed for differential diagnosis. If lesions <1 cm show arterial phase hyperenhancement without portal or equilibrium phase washout, follow up with US every 3 months is recommended. As for lesions <1.5 cm without arterial phase hyperenhancement, follow up with US every 3 months is also recommended. If the lesion exceeds 1.5 cm, other imaging modalities, including contrast US and Gd-EOB-DTPA-enhanced MRI or tumor biopsy, are recommended. These algorithms were created jointly by the Japan Radiological Society and the JSH.

Treatment algorithm for HCC

The treatment algorithm in the 2021 version (5th edition) recommends treatment of HCC based on a combination of the following five factors: hepatic functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size (Figure 3). In the revised 5th JSH-HCC guidelines, the most significant changes in the treatment algorithm are that hepatectomy and radiofrequency ablation are now equally recommended for up to three HCCs ≤3 cm in size, and the ranking order of the recommended treatments for HCC with vascular invasion was created. As for the treatment of up to three small HCCs, randomized controlled trials (RCTs) conducted in Hong Kong[7] and Japan (SURF trial)[8,9] have been newly included, demonstrating that there was no difference in prognosis after treatment between hepatectomy and radiofrequency ablation.

Another major revision was made on the recommendation of the treatment for HCC with vascular invasion. In the previous version, transcatheter arterial chemoembolization (TACE), hepatectomy, hepatic arterial infusion chemotherapy (HAIC), and molecular-targeted therapy were equally recommended for this condition. Although

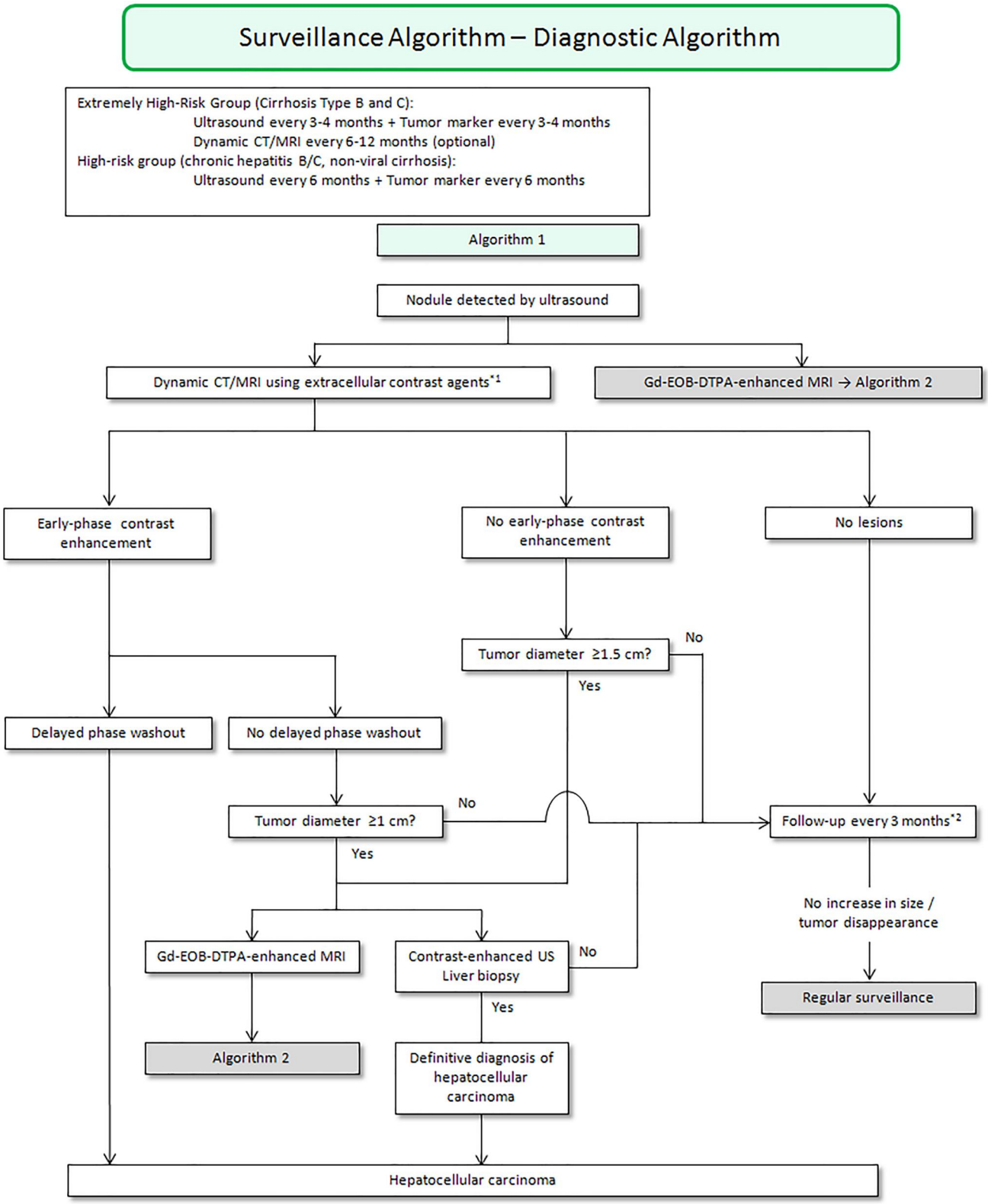

FIGURE 1 Algorithm for surveillance and diagnosis (Algorithm 1). *[1]Dynamic computed tomography (CT)/magnetic resonance imaging (MRI) are used for some patients if the nodule(s) are not visualized on ultrasound (US) because of poor visualization and/or the tumor marker (s) are elevated. *[2]Lesions detectable on US are followed up using US. Lesions undetectable on US may be followed up with dynamic CT/MRI. Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid.

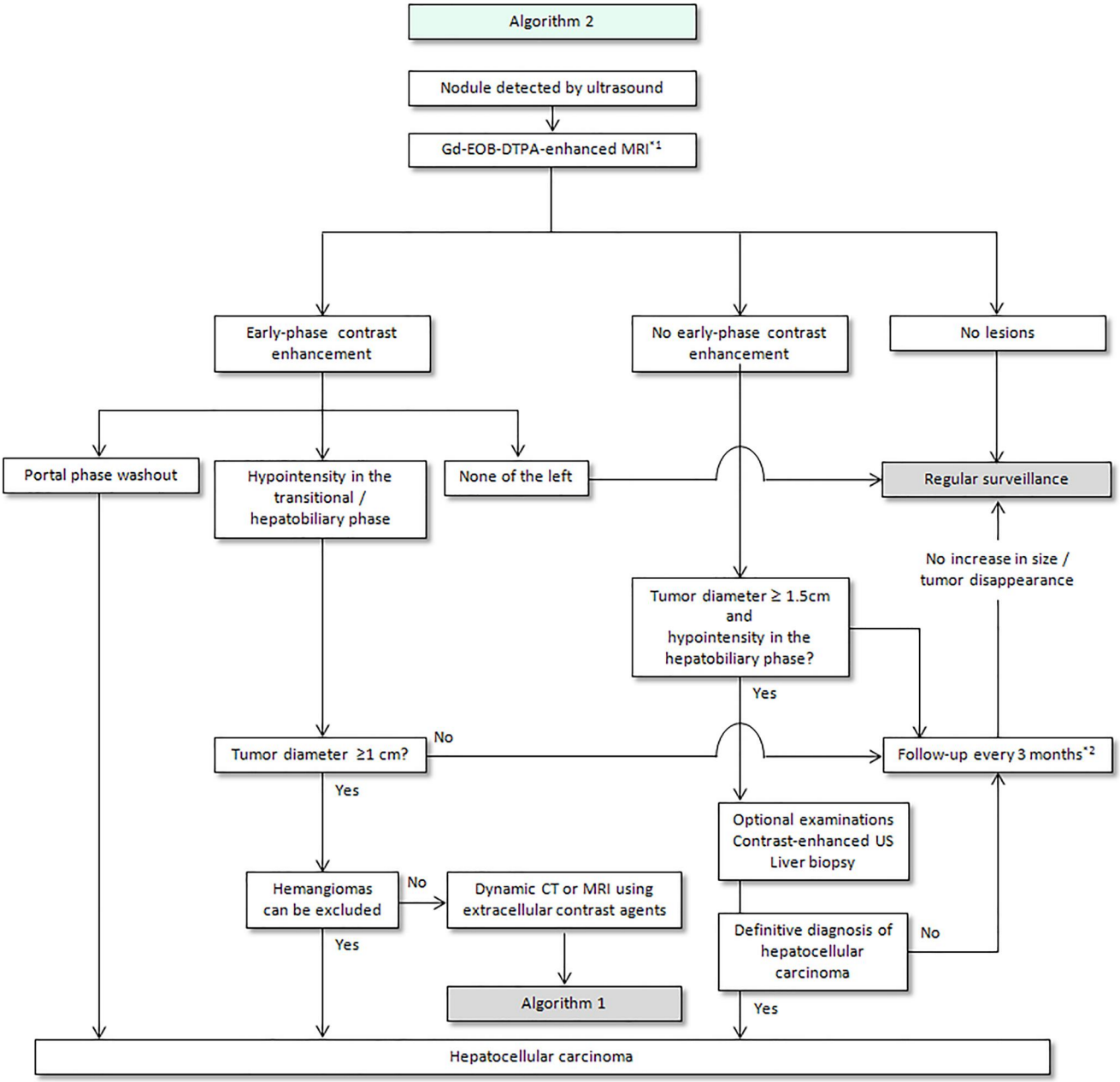

FIGURE 2 Algorithm for surveillance and diagnosis (Algorithm 2). CT, computed tomography; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; MRI, magnetic resonance imaging.

there is solid evidence for systematic therapy in HCC with vascular invasion, all the corresponding clinical trials enrolled unresectable patients. In addition, relatively better survival was reported by two nationwide Japanese surveys in HCC patients with portal vein and hepatic vein tumor invasion who underwent hepatectomy.[10,11] Therefore, in this revision, hepatectomy is primarily recommended for resectable HCC, whereas systemic therapy is secondarily recommended for unresectable cases, followed by weak recommendations for HAIC and TACE.

In accordance with the principle of the treatment algorithm that treatments up to the second-line are presented, it was decided not to specify HAIC and TACE in the current algorithm. For multiple HCCs, TACE has been recommended based on an RCT comparing the prognosis of patients with multiple HCCs and Child–Pugh A/B liver function who underwent TAE, TACE, or symptomatic therapy.[12] As for the indication for liver transplantation, in addition to the Milan Criteria,[13] the 5–5–500 rule[14] was included in the eligibility criteria for liver transplantation in patients with HCC in the 2017 revised version (4th revised edition) published in 2020.

The new treatment algorithm is summarized as follows: the three treatments described below are recommended for patients with HCC who have Child–Pugh A/B liver function without extrahepatic metastasis or vascular invasion. First, either hepatectomy or radiofrequency ablation is recommended equally as the first-line therapy

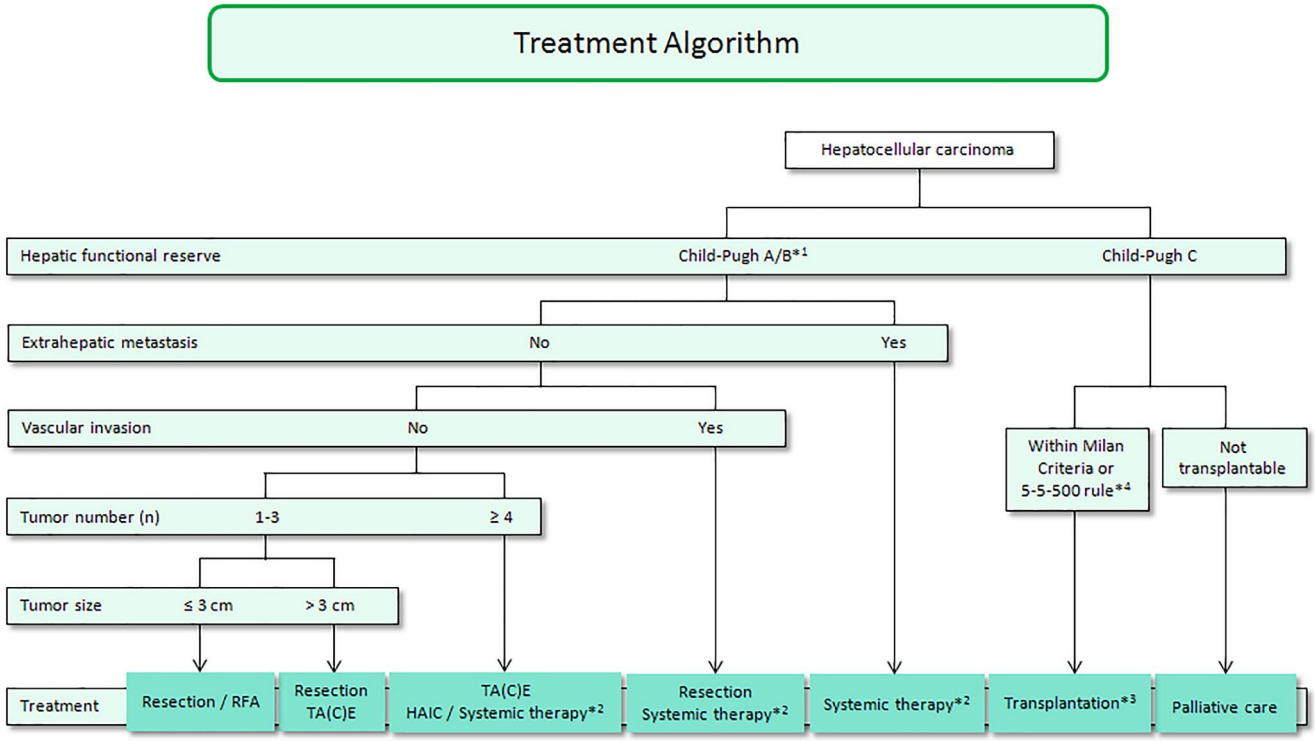

FIGURE 3 Algorithm for treatment. For the treatment modalities of the upper and lower layers, the upper layer should be prioritized. Treatment modalities separated by slashes are equally recommended. *[1]Assessment based on liver damage is recommended in the case of hepatectomy. *[2]Patients with Child–Pugh A only. *[3]Patients age ≤65 years. *[4]Tumor diameter ≤5 cm, ≤5 tumors and alpha-fetoprotein ≤500 ng/mL, with no distant metastasis or vascular invasion. HAIC, hepatic arterial infusion chemotherapy; RFA, radiofrequency ablation; TA(C)E, transcatheter arterial (chemo)embolization.

for up to three HCCs measuring ≤3 cm. Second, hepatectomy and TACE are recommended as the first- and second-line therapies, respectively, for up to three HCCs measuring >3 cm. Third, for more than four HCCs, TACE is recommended as the first-line therapy and HAIC or systemic therapy as the second-line therapy. Systemic therapy is recommended for patients with HCC and Child–Pugh A liver function and extrahepatic metastasis. In patients with HCC accompanied by vascular invasion without extrahepatic metastasis, hepatectomy is first recommended for resectable HCCs, and systemic therapy is recommended for unresectable cases, followed by TACE and HAIC. Systemic therapy is recommended for patients with HCC and Child–Pugh A liver function and extrahepatic metastasis. In this revision, a new treatment algorithm for the selection of systemic therapy was created, which is described in the following section. Liver transplantation is recommended for HCC within the Milan criteria or within the 5–5–500 rule in Child–Pugh C patients aged ≤65 years.

Algorithms for systemic therapy

Advances in systemic therapy for HCC have complicated the selection of anticancer agents. There are now six different regimens available and covered by the National Health Insurance system in Japan. Therefore, "Algorithm for Systemic Therapy" was newly created in the current edition (Figure 4).

For systemic therapy-naïve HCC patients not indicated for hepatectomy, transplantation, ablation, or TACE, the combination of atezolizumab and bevacizumab is first recommended based on a phase III RCT comparing atezolizumab plus bevacizumab to sorafenib.[15] For those not indicated for atezolizumab plus bevacizumab, sorafenib or lenvatinib monotherapy are indicated based on the RCT comparing sorafenib with placebo reported in 2008[16], and the non-inferiority study comparing lenvatinib and sorafenib, respectively.[17]

As a second-line systemic therapy, regorafenib is recommended for patients who are previously treated, tolerated, and progressed with sorafenib.[18] Ramucirumab for patients with alpha-fetoprotein ≥400 ng/mL and cabozantinib are also recommended.[19,20] As all phase III trials for second-line systemic therapy enrolled patients who received sorafenib for the first-line systemic therapy, in the absence of reports with evidence levels high enough to recommend second-line systemic therapy after atezolizumab plus bevacizumab or lenvatinib monotherapy, no regimen is currently unconditionally recommendable as second-line therapy after these first-line systemic therapies. This, however, does not preclude the use of regimens that are covered by National Health Insurance in Japan as the second and later line.

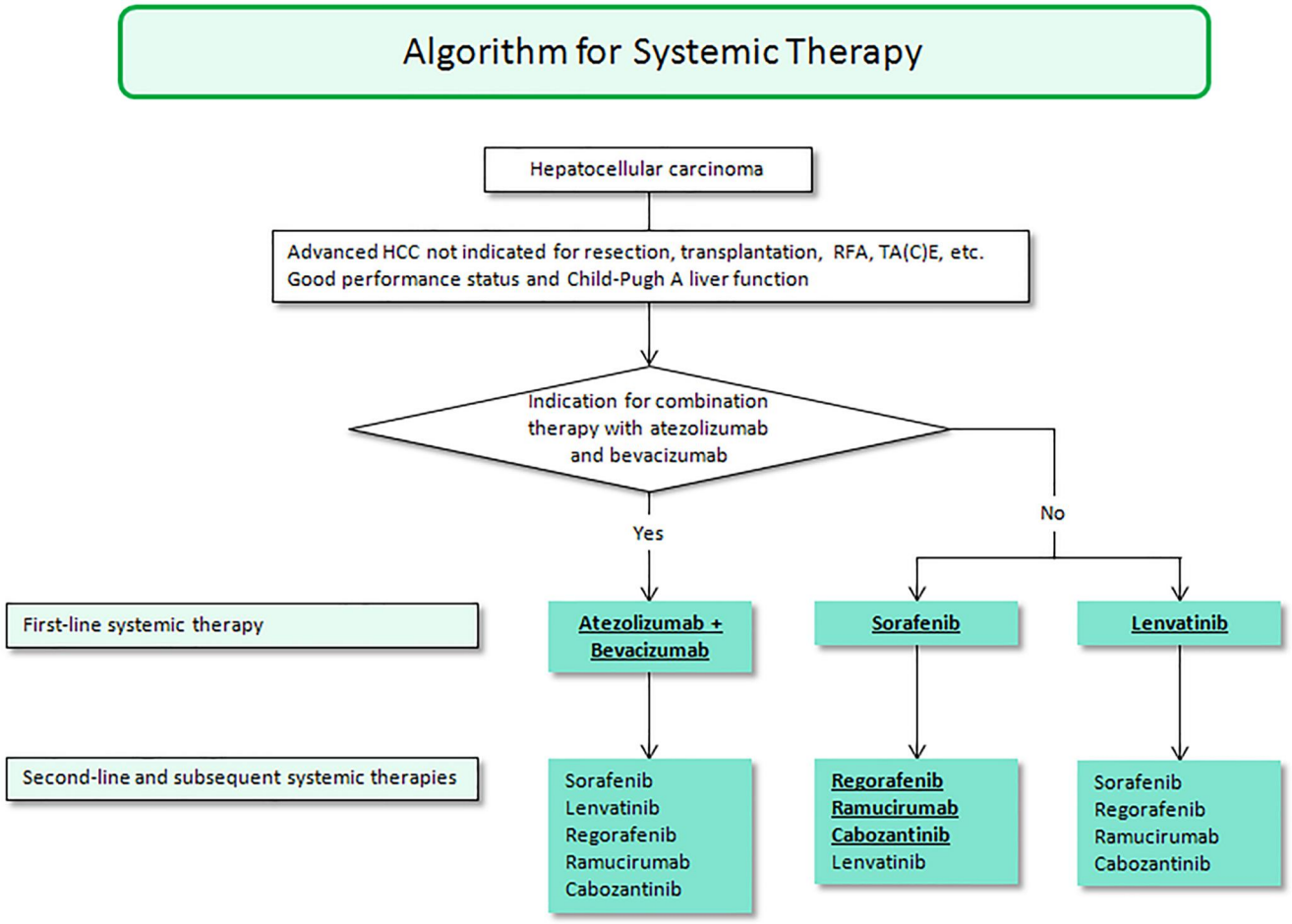

FIGURE 4 Algorithm for systemic therapy. RFA, radiofrequency ablation; TA(C)E, transcatheter arterial (chemo)embolization. Bold face with underline indicates the availability of evidence from randomized controlled trials.

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DATA AVAILABILITY STATEMENT

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REFERENCES

1. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence-based guidelines Japan. World J Gastroenterol. 2006;12:828–9.
2. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, et al. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. Hepatol Res. 2008;38(1):37-51. https://doi.org/10.1111/j.1872-034x.2007.00216.x

3. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma – The Japan Society of Hepatology 2009 update. Hepatol Res. 2010;40(Suppl 1):2–144.
4. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T, et al. Evidence-based clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC guidelines). Hepatol Res. 2015;45(2):123–7. https://doi.org/10.1111/hepr.12464
5. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res. 2019;49(10):1109–13. https://doi.org/10.1111/hepr.13411
6. 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. https://doi.org/10.1016/j.jclinepi.2010.04.026
7. Ng KKC, Chok KSH, Chan ACY, Cheung TT, Wong TCL, Fung JYY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. Br J Surg. 2017;104(13):1775–84. https://doi.org/10.1002/bjs.10677
8. 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 vs. radiofrequency ablation for small hepatocellular carcinoma (SURF trial): analysis of overall survival. J Clin Oncol. 2021;39(Suppl 15):4093. https://doi.org/10.1200/jco.2021.39.15_suppl.4093
9. Takayama T, Hasegawa K, Izumi N, Kudo M, Shimada M, Yamanaka N, et al. Surgery versus radiofrequency ablation for small hepatocellular carcinoma: a randomized controlled trial (SURF trial). Liver Cancer. 2021;29(11):209–18. https://doi.org/10.1159/000521665
10. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016; 65(5): 938-43, https://doi.org/10.1016/j.jhep.2016.05.044
11. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. Hepatology. 2017;66(2):510–7. https://doi.org/10.1002/hep.29225
12. Llovet JM, Real MI, Montaña 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. https://doi.org/10.1016/s0140-6736(02)08649-x
13. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334(11):693–9. https://doi.org/10.1056/nejm199603143341104
14. Shimamura T, Akamatsu N, Fujiyoshi M, Kawaguchi A, Morita S, Kawasaki S, et al. Japanese Liver Transplantation Society. Expanded living—donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanese nationwide survey: the 5—5—500 rule- a retrospective study. Transpl Int. 2019;32(4):356–68. https://doi.org/10.1111/tri.13391
15. 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. https://doi.org/10.1056/nejmoa1915745
16. 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. https://doi.org/10.1056/nejmoa0708857
17. 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. https://doi.org/10.1016/s0140-6736(18)30207-1
18. 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. https://doi.org/10.1016/s0140-6736(16)32453-9
19. Zhu AX, Finn RS, Galle PR, Llovet JM, Kudo M. Ramucirumab in advanced hepatocellular carcinoma in REACH-2: the true value of α-fetoprotein. Lancet Oncol. 2019;20(4):e191. https://doi.org/10.1016/s1470-2045(19)30165-2
20. 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. https://doi.org/10.1056/nejmoa1717002

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