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Special Report

Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update

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The fourth version of 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 2017 in Japanese. New or revised recommendations were described, herein, with a special reference to the surveillance, diagnostic, and treatment algorithms.

Key words: algorithm for surveillance and diagnosis, algorithm for treatment, clinical practice guidelines, hepatocellular carcinoma

INTRODUCTION

SINCE THE FIRST edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma (HCC) was compiled in 2005, the Japan Society of Hepatology (JSH) has revised Guidelines every 4 years.[1–3] The third version of Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma was published in 2013; then, the latest revision was started in 2015 by the JSH.[4] The JSH also published a consensus-based treatment algorithm for HCC in 2007, which more closely reflected actual hepatology treatment strategies.[5] To address the controversy over having two treatment algorithms for HCC, the Revision Committee dedicated the best effort to resolving the double standard in this revision of the evidence-based guidelines. This led to the creation of a new treatment algorithm that is based on both evidence and consensus in this fourth version of the Guidelines.

The fourth version of the JSH-HCC Guidelines was revised by the methodology of evidence-based medicine, and additionally by the Grading of Recommendations Assessment, Development, and Evaluation system, in part for rating clinical guidelines in order to bridge the gap between evidence and consensus, and to formulate recommendations in a theoretical and systematic manner.[6] In the revision procedures, scientific papers published before June 2016 were systematically screened using the medical databases (PubMed and MEDLINE), and a total of 17 699 articles were extracted. The number of articles was reduced to 2548 after the first critical elimination process, finally a total of 553 papers were selected after the evaluation of evidence levels and the quality of content.

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The full English version of the 4th JSH-HCC Guidelines is available, including the retrieval styles for all clinical questions, on the JHS website (https://www.jsh.or.jp/English/). Herein, the important revision points in recommendation and algorithms in the new guidelines are highlighted.

ALGORITHM FOR SURVEILLANCE AND DIAGNOSIS OF HCC

THE FUNDAMENTAL STRATEGY for HCC surveillance and diagnosis is demonstrated in the revised algorithm (Fig. 1), which adheres fundamentally to the previous version. Patients are considered at high risk for HCC when any of the following three conditions are present: cirrhosis, chronic hepatitis B, or chronic hepatitis C. Among high-risk patients, those with cirrhosis type B and C are considered an extremely high-risk group. The recurrence rate of HCC after curative treatment is ≥10% annually and increases to 70–80% over a period of 5 years, therefore, post-treatment surveillance should also be undertaken strictly enough to apply to the extremely high-risk group. Ultrasonography (US) is first selected as a screening modality with concomitant measurements of alpha-fetoprotein (AFP), des-gamma-carboxy prothrombin (DCP) and AFP-L3 fraction (a lectin-reactive fraction of AFP). It is recommended that the screenings be carried out every 6 months for high-risk patients, and every 3–4 months for extremely high-risk patients. This regular screening method can be combined with dynamic computed tomography (CT) or dynamic magnetic resonance imaging (MRI) for extremely high-risk patients and/or for patients whose liver is difficult to scan by US due to liver atrophy, severe obesity, and post-operative deformity.

When US detects new nodular lesions, dynamic CT/MRI is carried out for differential diagnosis. Even when no tumor is detected on US, dynamic CT/MRI should be considered in the following cases: persistent elevation of AFP, ≥200 ng/mL of AFP, ≥40 mAU/mL of DCP, or≥15% **of** AFP-L3 fraction. For contrast-enhanced imaging, "typical imaging findings of HCC," which has been defined as intense arterial enhancement followed by washout of contrast materials in the venous delayed phases in the previous JSH-HCC Guidelines, are also adopted in the fourth version.[1–4] Tumor evaluation using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI or other diagnostic modalities, including liver biopsy, contrast-enhanced US, superparamagnetic iron oxide-enhanced MRI, CT during arterial portography, or CT during hepatic arteriography, are applied when a tumor is >1.5 cm in diameter with negative arterial enhancement, as well as when a tumor size is >1 cm with positive arterial enhancement and negative delayed washout. The other smaller lesions are followed up with US every 3 months. Dynamic CT/MRI should be resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US might be followed up with dynamic CT/MRI.

TREATMENT ALGORITHM FOR HCC

IN THE FIRST JSH-HCC Guidelines, the treatment algorithm consisted of the following three factors: degree of liver damage, number of tumors, and tumor diameter.[1,2] The algorithm itself was modified in the second version by introducing treatments for HCC with accompanying vascular invasion and extrahepatic metastasis.[3] In this fourth edition, a new treatment algorithm, which merged the evidence-based algorithm reflecting the evidence reported in articles with the consensus-based algorithm reflecting consensus reached based on actual clinical practice and by incorporating the Grading of Recommendations Assessment, Development, and Evaluation system, is created. In the revised 4th JSH-HCC Guidelines, clinical questions that underpin the treatment algorithm were newly established. This algorithm recommends treatments based on the combination of the following five factors: liver functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size (Fig. 2). Liver functional reserve is evaluated based on the Child–Pugh classification, and when hepatectomy is being considered, a decision is made based on the degree of liver damage, including a measurement of indocyanine green 15-min retention rate. The new treatment algorithm is summarized as follows.

Three treatments are recommended for HCC patients with Child–Pugh A/B liver function without extrahepatic metastasis or vascular invasion. First, either surgical resection or radiofrequency ablation is recommended with no priority for up to three HCCs measuring ≤3 cm; however, surgical resection is recommended as first-line therapy for solitary HCC regardless of size. Although there were four randomized controlled trials comparing surgery and radiofrequency ablation during the targeted period, their results were not reflected in this algorithm, because all of them had problems associated with study design or patient background.[7–10] Based on the results of a nationwide large cohort study carried out by the Liver Cancer Study Group of Japan comparing the outcomes of hepatectomy, radiofrequency ablation, and percutaneous ethanol injection for solitary HCC ≤3 cm in size, which found the better prognosis after hepatectomy, surgical resection is recommended as

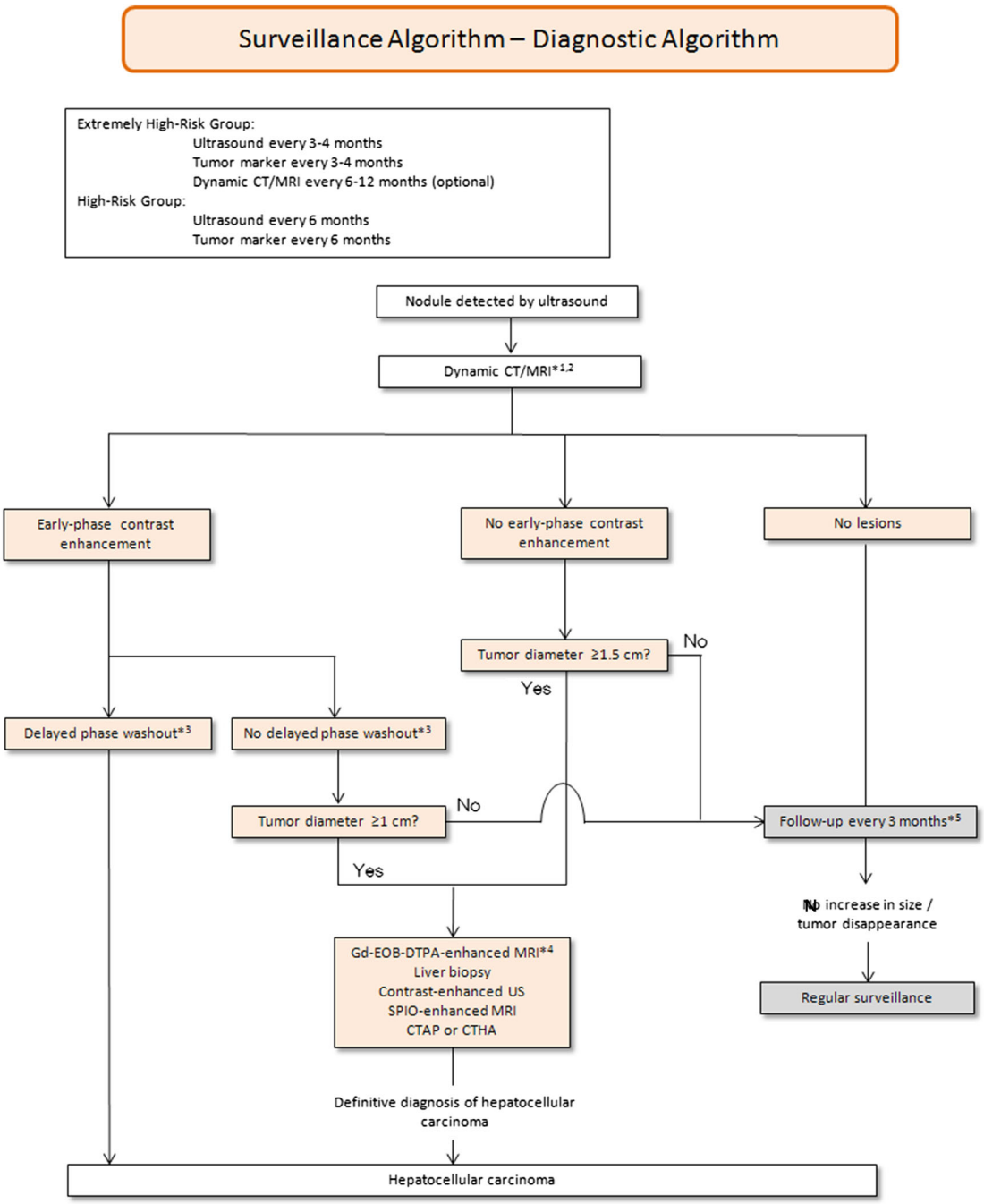

Figure 1 Algorithm for surveillance and diagnosis in the fourth version of the Japan Society of Hepatology Clinical Practice Guidelines for Hepatocellular Carcinoma (4th JSH-HCC Guidelines). *1Dynamic computed tomography (CT)/ magnetic resonance imaging (MRI) are used for some patients if the nodule(s) are not visualized on ultrasound (US) because of poor visualization and/or the tumor marker(s) are elevated. *2Dynamic MRI includes gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI. *3On Gd-EOB-DTPA-enhanced MRI, a reduction in signal intensity during the hepatobiliary phase is regarded as washout. However, because cavernous hemangioma is visualized as hypointense signals in the hepatobiliary phase, other MR images should be examined before excluding the possibility. *4Gd-EOB-DTPA-enhanced MRI is recommended for patients whose first imaging modality was dynamic CT. *5Lesions detectable on US are followed up using US. Lesions undetectable on US can be followed up with dynamic CT/MRI. [Color figure can be viewed at wileyonlinelibrary.com]

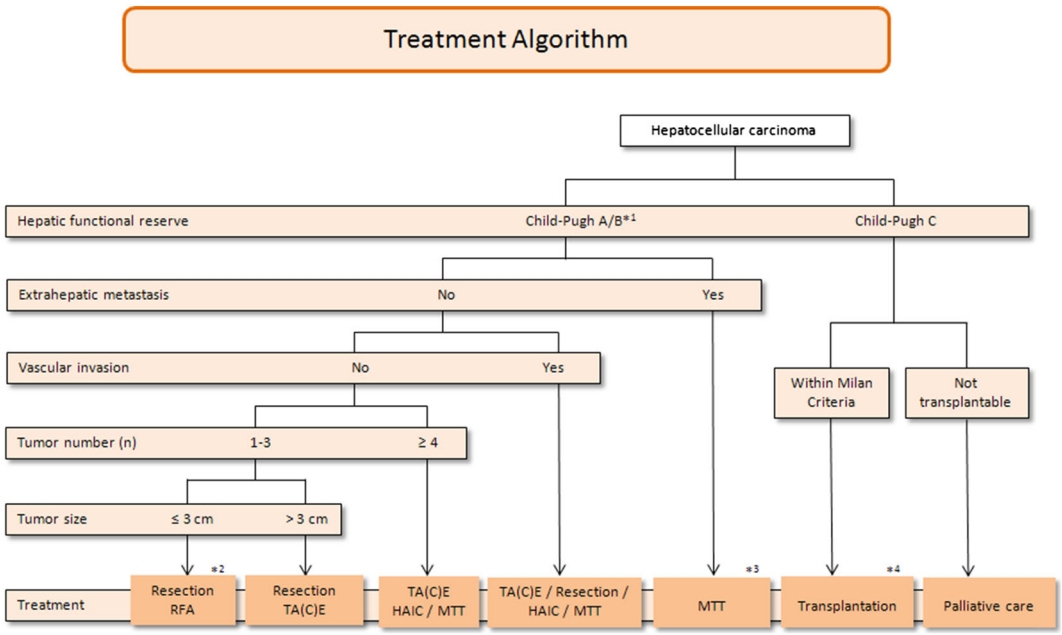

Figure 2 Algorithm for treatment in the fourth version of the Japan Society of Hepatology Clinical Practice Guidelines for Hepatocellular Carcinoma (4th JSH-HCC Guidelines). *1Assessment based on liver damage is recommended in the case of hepatectomy. *2For solitary hepatocellular carcinoma, resection is recommended as first-line therapy, and ablation as second-line therapy. *3Patients with Child–Pugh A only. *4Patients aged ≤65 years. HAIC, hepatic arterial infusion chemotherapy; MTT, molecular-targeted therapy; RFA, radiofrequency ablation; TA(C)E, transcatheter arterial (chemo)embolization. [Color figure can be viewed at wileyonlinelibrary.com]

first-line therapy for solitary HCC.[11] Second, for up to three HCCs measuring >3 cm, surgical resection is recommended as first-line therapy, and transarterial chemoembolization (TACE) is recommended as second-line therapy. TACE has been recommended based on the randomized controlled trials comparing the prognosis of patients with multiple HCC and Child–Pugh A/B liver function who underwent transarterial embolization, TACE, or symptomatic therapy[12]. Third, TACE is also recommended as first-line therapy, and hepatic arterial infusion chemotherapy (HAIC) or molecularly targeted therapy is recommended as second-line therapy for up to four HCCs.

Molecular targeted therapy is recommended for HCC patients with Child–Pugh A liver function and extrahepatic metastasis based on the results of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study.[13] Lenvatinib, as well as sorafenib, is recommended as first-line therapy for unresectable advanced HCCs, based on a report that showed the non-inferiority to sorafenib.[14] Regorafenib is recommended as second-line therapy for patients with Child–Pugh A liver function who have the tolerance for sorafenib showing disease progression. Additionally, locoregional therapies, including resection for lung, adrenal, and lymph node metastasis and dissemination in HCC patients without intrahepatic lesions or well-managed intrahepatic lesions is weakly recommended in this revision. Radiation therapy is recommended for the management of painful bone metastasis and for brain metastasis.

For patients with HCC accompanied by vascular invasion without extrahepatic metastasis, embolization, hepatectomy, HAIC, and molecular targeted therapy are recommended. Each treatment is selected according to the individual situation: liver function, the condition of HCC, and the extent of vascular invasion. In a Japanese nationwide survey of patients with HCC accompanied by portal vein tumor thrombus comparing hepatectomy and other treatments, the prognosis was significantly better for patients with Child–Pugh A liver function in the hepatectomy group.[15] Meanwhile, survival advantages of HAIC for patients with advanced HCC accompanied by portal vein tumor thrombus[16] and the efficacy of molecularly targeted therapy for patients with HCC accompanied by vascular invasion[17] were reported. Because it is difficult to provide universal ranking for the four treatment modalities at this point, four treatment modalities are recommended in parallel for the treatment of HCC accompanied by vascular invasion.

Liver transplantation is recommended for HCC within the Milan criteria (single HCC measuring ≤5 cm or up to

three HCCs measuring ≤3 cm) in Child–Pugh C patients aged ≤65 years. When transplantation is not indicated, only palliative care is recommended for patients with HCC and Child–Pugh C liver function.

In summary, the 4th JSH-HCC Guidelines were revised by the methodology of evidence-based medicine with the Grading of Recommendations Assessment, Development, and Evaluation system to bridge the gap between evidence and consensus. Considering the emergence of new molecular targeted therapies and immune checkpoint inhibitors, important evidence for the management of HCC will be added sequentially in the future, at least on the JSH webpage.

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