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Special Report

Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines)

Norihiro Kokudo, Kiyoshi Hasegawa, Masaaki Akahane, Hiroshi Igaki, Namiki Izumi, Takafumi Ichida, Shinji Uemoto, Shuichi Kaneko, Seiji Kawasaki, Yonson Ku, Masatoshi Kudo, Shoji Kubo, Tadatoshi Takayama, Ryosuke Tateishi, Takashi Fukuda, Osamu Matsui, Yutaka Matsuyama, Takamichi Murakami, Shigeki Arii, Masatoshi Okazaki and Masatoshi Makuuchi

The Committee for Revision of the Clinical Practice Guidelines for Hepatocellular Carcinoma, Tokyo, Japan

The 3rd version of Clinical Practice Guidelines for Hepatocellular Carcinoma was revised by the Japan Society of Hepatology, according to the methodology of evidence-based medicine, which was published in October 2013 in Japanese. Here, we briefly describe new or changed recommendations with a special reference to the two algorithms for surveillance, diagnosis, and treatment.

Key words: algorithm for surveillance and diagnosis, algorithm for treatment, clinical practice guidelines, clinical question, evidence-based medicine

INTRODUCTION

THE SECOND VERSION of Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma (2nd JSH-HCC Guidelines) conducted by the Japan Society of Hepatology (JSH) was published in 2009 in Japanese, and its English version was released in 2010.[1] Because new knowledge and information have been increasingly accumulated since the end-point of the published work search in June 2007, the second revision was initiated in September 2011, and the new third version was published in October 2013 in Japanese.

As was the case in the first[2–4] and second[1] versions of the JSH-HCC Guidelines, the third was strictly revised by the methodology of evidence-based medicine. In the revision procedures, we set a total of 57 clinical questions (CQ), constructed retrieval styles for each CQ, and systematically searched scientific papers ($n = 6750$ in total) published between July 2007 and December 2011 in the medical databases (PubMed and Medline) by the retrieval styles. The entire published work search formula is open to the public (https://www.jsh.or.jp/English/), which has not been always the case in other HCC guidelines. After critical reading of all abstracts and sometimes whole manuscripts (when necessary) for a total of 1648 relevant publications, we finally selected a total of 596 papers, wrote recommendations for each CQ and decided the grade of the recommendations.

The full English version of the 3rd JSH Guidelines is available including the retrieval styles for all clinical questions on the JSH website (https://www.jsh.or.jp/English/). Herein, we highlight the important revision points in recommendations and algorithms in the new guidelines.

ALGORITHM FOR SURVEILLANCE AND DIAGNOSIS

THE FUNDAMENTAL STRATEGY for HCC surveillance and diagnosis is demonstrated in a revised

Correspondence: Dr Norihiro Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: kokudo-2su@h.u-tokyo.ac.jp
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algorithm (Fig. 1), in which ultrasonography (US) is the first choice for screening, and dynamic study of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) follow to obtain a final diagnosis. In spite of the remarkable advance of various kinds of imaging modalities, fundamental B-mode US is regarded as the most important, because of its low cost, lesser invasiveness, simplicity to perform and high sensitivity. "Typical imaging findings of HCC" for final diagnosis, which have been defined as intense arterial enhancement followed by washout of contrast media in the venous-delayed phases in dynamic CT in the Guidelines of the American Association for the Study of Liver Diseases (AASLD)[5] and the previous JSH-HCC Guidelines[1–4] are also adopted in the third version. Accounting for the recent progress in diagnostic imaging, several revisions have been made, as follows.

So-called "typical imaging findings of HCC" are divided into two components, "intense arterial enhancement" and "washout of contrast media in the venous-delayed phase", and they are separately applied to the decision tree (Fig. 1). If both factors are positive, the diagnosis of HCC is confirmed. If either of the factors were negative in a case with a tumor larger than 2 cm, further optional diagnostic modalities were recommended in the previous JSH-HCC Guidelines. However, size cut-off for recommending further evaluation has been changed in the third version; namely, optional modalities are conducted for a tumor with negative arterial enhancement and size larger than 1.5 cm, as well as being performed for a tumor with negative delayed washout and size larger than 1 cm. In other words, indications of optional modalities for small HCC have been widened and the size cut-offs vary according to the presence or absence of arterial enhancement and/or delayed washout. In addition, enhanced MRI using gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid has been added to the list of optional diagnostic modalities in the third version.

ALGORITHM FOR TREATMENT OF HCC

SINCE THE FIRST version of our JSH-HCC Guidelines, this algorithm has been simple and easy to memorize, consisting of three factors: (i) degree of liver damage; (ii) number of tumors; and (iii) tumor diameter (Fig. 2). The recommendable treatment options are narrowed down to one or two by referring to this algorithm. The revision in the third algorithm can be summarized in three points, as follows:

1 The order of recommendation for surgical resection and percutaneous radiofrequency ablation (RFA) has been clarified. Based on the results of nationwide large cohort studies conducted by the Liver Cancer Study Group of Japan,[6,7] surgical resection is set as the first therapeutic choice for a HCC patient with liver damage of grade A or B and with a single tumor. If a tumor is smaller than 3 cm in the above conditions, RFA is recommended as the second choice. During the targeted period for the current revision (2007–2011), there were three randomized controlled trials (RCT) comparing surgery and RFA.[8–10] However, we did not reflect the results of the RCT in the treatment algorithm, because they had several problems as described elsewhere.[11] For a case with liver damage of grade A or B and two or three tumors smaller than 3 cm, either surgical resection or RFA is recommended with no priority, considering the Japanese cohort study.[6,7]
2 Based on the results of the SHARP study,[12] a molecular-targeted agent (sorafenib) is included in the third treatment algorithm. In a case with liver damage of grade A or B and four or more tumors, systemic chemotherapy including molecular-targeted agent and hepatic arterial infusion chemotherapy is regarded as the second recommendation after transcatheter arterial chemoembolization (TACE).
3 Since the 1st JSH-HCC Guidelines, "liver damage" consisting of five factors including the indocyanine green (ICG) test has been used as an indicator of liver function. Although the ICG test is considered indispensable for surgical decision-making in Japan, it is not routinely performed before non-surgical treatments, such as RFA and TACE in the current daily practice in Japan. Considering these situations, the Child–Pugh classification can be a substitute liver function grading only before non-surgical treatments.

We also discussed whether extrahepatic disease and/or vascular invasion should be newly added to the decision factors in the treatment algorithm. In fact, these two factors are clinically important and adopted in other guidelines, such as the Guidelines of the AASLD[5] and the Asian Pacific Association for the Study of the Liver.[13] We decided not to increase the number of decision factors mainly in order to keep the treatment algorithm simple and to observe our policy since the first version. Furthermore, there are few evidences available to recommend a certain treatment option for HCC with vascular invasion. Extrahepatic HCC at the time of initial diagnosis is considered rare in daily practice in Japan.

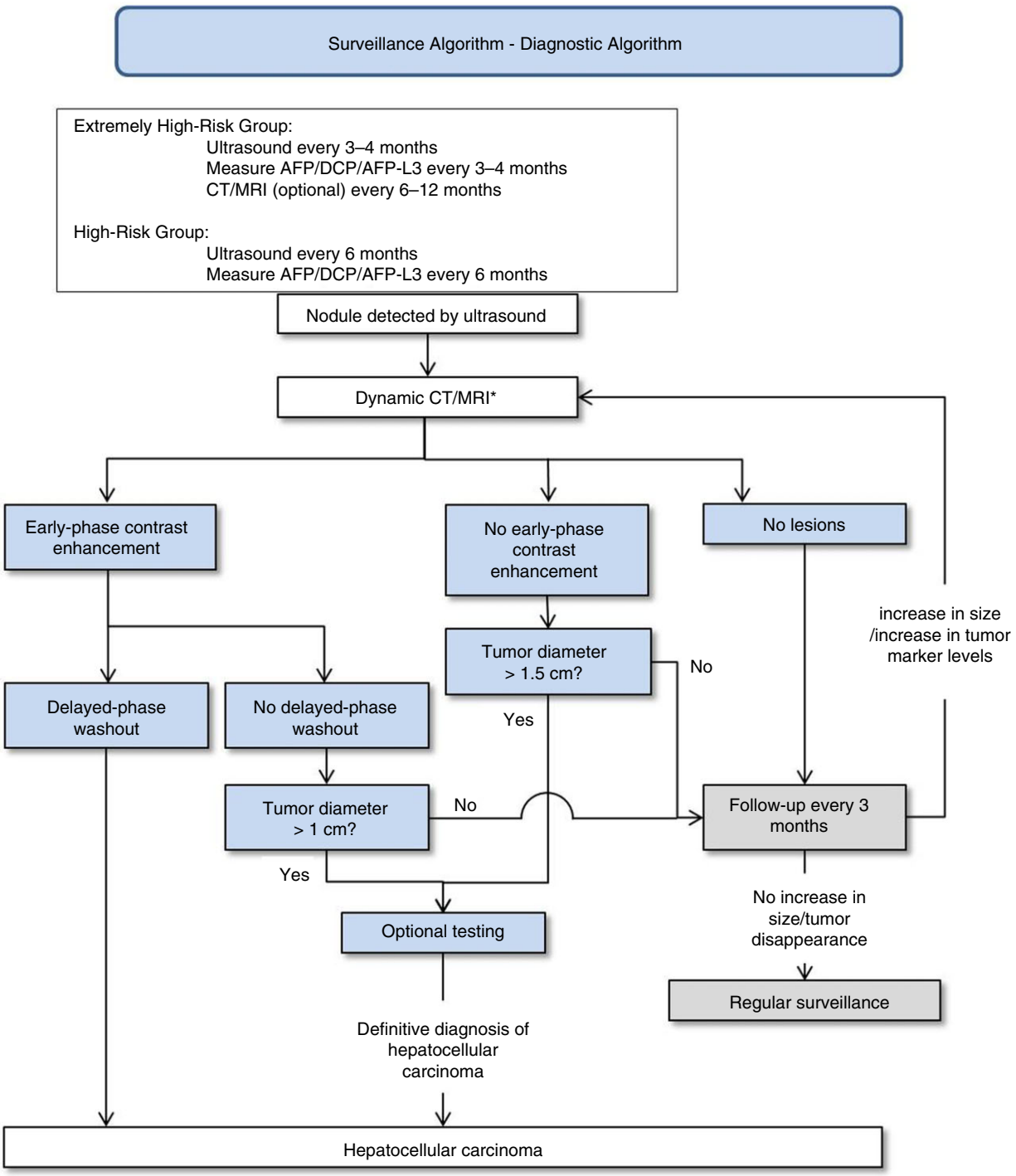
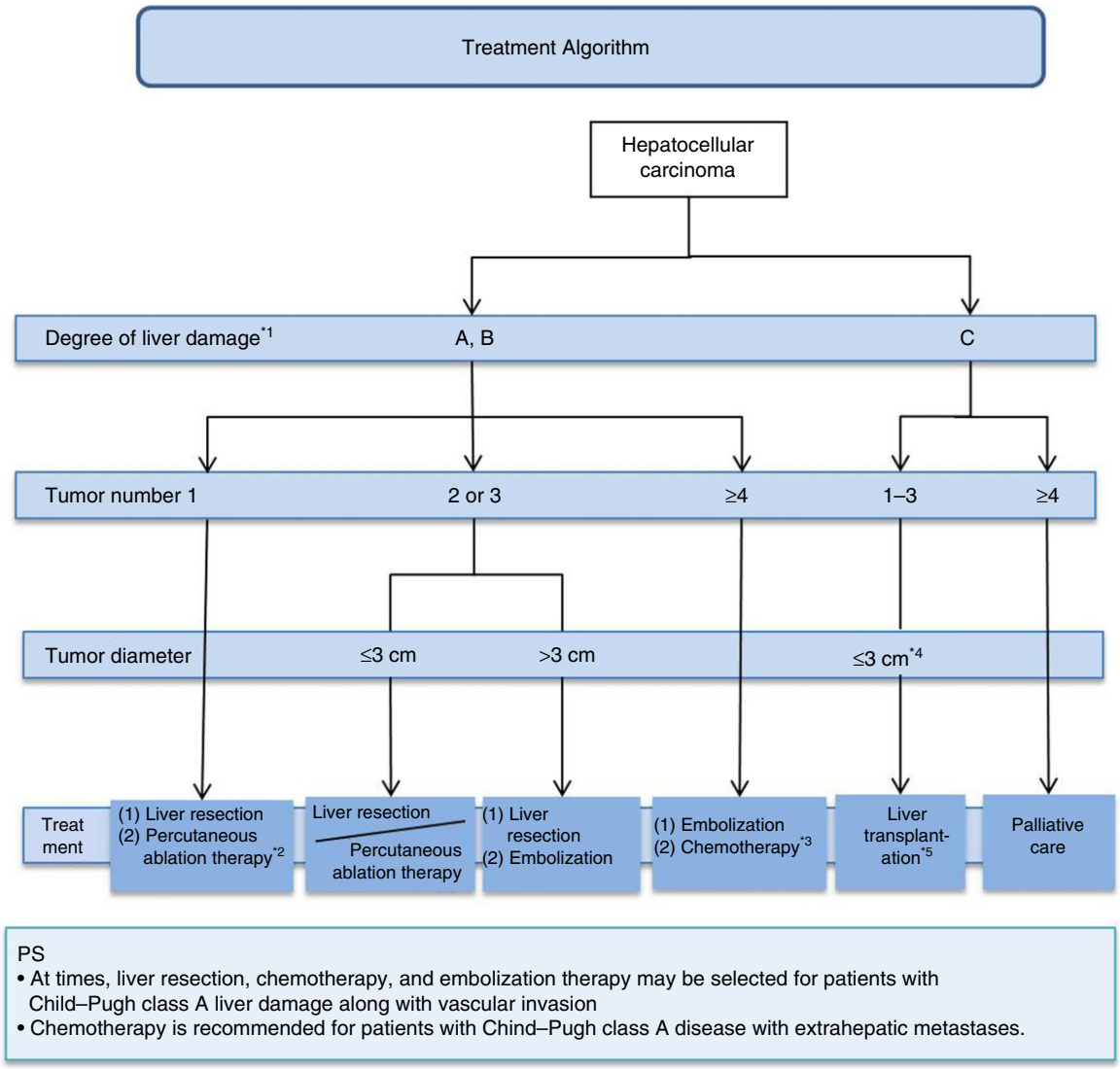


Figure 1 Algorithm for surveillance and diagnosis in the 3rd JSH-HCC Guidelines. AFP, α-fetoprotein; AFP-L3, *Lens culinaris* agglutinin-reactive fraction of AFP; CT, computed tomography; DCP, des-γ-carboxyprothrombin; MRI, magnetic resonance imaging.



(Caution) *1: The Child–Pugh classification may also be used when non-surgical trearment is considered.
*2: Can be selected for tumors with a diameter of ≤3 cm.
*3: Oral administration and/or hepatic arterial infusion are available.
*4: A single tumor ≤5 cm or 2–3 tumors ≤3 cm in diameter.
*5: Patients aged ≤65 years.

Figure 2 Algorithm for treatment in the 3rd JSH-HCC Guidelines.

In summary, the 3rd JSH-HCC Guidelines was compiled under the same policy as the first and second versions, in which objectivity and reproducibility are warranted. We believe that the 3rd JSH-HCC guidelines would be useful for proper decision-making in the management of HCC worldwide as well as in Japan.

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