Preface to the 2017 Version

Since the first edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma (hereinafter, the Guidelines) was compiled in 2005 with the support of a Ministry of Health, Labour and Welfare project for establishing clinical practice guidelines, the Japan Society of Hepatology (JSH) has revised Guidelines every 4 years by updating the clinical evidence for each treatment, with the second and third editions published in 2009 and 2013, respectively. The Guidelines were developed according to the principles of evidence-based medicine (EBM), and today they are widely used for the treatment of liver cancer in Japan. With the passing of 4 more years, the time has come to publish the fourth edition (2017 version) supported by the latest clinical evidence.

This 2017 version introduces evidence- and consensus-based standards of care related to the diagnosis and treatment of hepatocellular carcinoma (HCC) in Japan and is intended for use by hepatologists involved in managing patients with liver cancer (especially HCC) and by specialist physicians in other fields. This latest revision of the Guidelines began in October 2015 in accordance with the revision policy set out by the Revision Committee, established by the JSH Planning and Public Relations Committee. The Revision Committee comprises mostly JSH members, who are experts in the field of liver cancer treatment and include 7 surgeons, 7 hepatologists, 5 radiologists, and 1 clinical statistician. In addition, 20 expert advisors were enlisted to assist the committee members, and 16 working collaborators were engaged to share the workload.

As in the first, second, and third editions, the fourth edition adheres to the fundamental principles of EBM. It also incorporates in part the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating clinical guidelines in order to bridge the gap between evidence and consensus and to formulate recommendations in a theoretical and systematic manner. Academic articles published before June 2016 (including Epub articles) were systematically screened using the online database search engines PubMed and MEDLINE, and a total of 17,699 articles were extracted. The number of articles was reduced to 2,548 after the first elimination process and further reduced to 553 after evidence levels and the quality of content were evaluated. The Guidelines are based on these 553 articles and, on an exceptional basis, certain articles published after July 2016 reporting evidence that is considered important and likely to have a major impact on daily clinical practice.

All versions of the clinical practice guidelines to date were created with a treatment algorithm based strictly on scientific evidence at its core and with an emphasis on simplicity and usability. However, the existence of a second JSH treatment algorithm for HCC has created some confusion and has even attracted criticism overseas. Back in 2007, the JSH published a consensus-based treatment algorithm for HCC, which more closely reflected actual hepatology treatment strategies,

and revisions were published in 2010 and 2015. The treatment algorithm in the latest 2015 Consensus-Based Clinical Practice Manual for Hepatocellular Carcinoma (third edition) was to serve as the so-called “evidence-based treatment algorithm” of the present 2017 Clinical Practice Guidelines for Liver Cancer. To address the controversy over having two treatment algorithms for HCC, the JSH Planning Public Relations Committee tasked the Revision Committee with resolving the double standard in this 2017 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 editon of the Guidelines.

The Revision Committee met 4 times before July 7, 2017 to discuss and decide the strength of recommendations for individual Clinical Questions, and the first draft of the Guidelines was made available to the public on the official JSH website until July 21 to allow for comments. At the same time, a public hearing was held at the 53rd Annual Meeting of the Liver Cancer Study Group of Japan in Tokyo. Comments from JSH members and comments from the public hearing were used to revise the first draft, and the final version was then evaluated by the External Review Panel before being published as the 2017 version. We plan to have the Guidelines translated into English in the near future, and in a couple of years we will start the revision process, including collating evidence published after July 2016, in the preparation for the fifth edition.

As in the second and third revisions, the latest revision was funded entirely by the JSH, despite the limited budget available. We sincerely thank the Revision Committee members, expert advisors, and working collaborators for volunteering to take time from their already busy clinical schedules to complete this latest in-depth revision process. We are extremely grateful to the Directors, especially Dr. Kazuhiko Koike, Director General of the JSH, and Dr. Satoshi Mochida, Chair of the Planning and Public Relations Committee, as well as the former Secretary General (presently Advisor) Haruki Hakomori and the current Secretary General Takaharu Mikami for their considerable understanding of and cooperation with the revision process. We also thank Ms. Misako Kaji, Ms. Yuka Yonetani, and Ms. Mariko Itsumi of the EBM Center at the International Medical Information Center (General Incorporated Foundation) for their efforts in the literature search and other tasks; Ms. Mayumi Ito, a secretary in the Department of Hepato-Biliary-Pancreatic Surgery Division, University of Tokyo Graduate School of Medicine, for collating and storing references; and Mr. Kazuya Sunouchi, Mr. Takashi Mori, and Ms. Mamiko Yoshida of Kanehara Co., Ltd. for their support in editing and revising the Guidelines.

October 2017

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Preface to the 2013 Version

The first edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma (2005 version) was created with the assistance of the clinical guideline assistance program of the Ministry of Health, Labour and Welfare. The reviews were favorable for Japan's first evidence-based clinical practice guidelines, and the guidelines were adopted broadly for the treatment of liver cancer.
These guidelines were revised by the Japan Society of Hepatology (JSH), leading to the publication of the second edition (2009 version) and the ever-increasing use of these guidelines.

Clinical practice guidelines that are created using evidence-based medicine (EBM) generally need to be revised every 3 to 4 years to accommodate new evidence. Revisions for the third edition (2013 version) were initiated by the JSH in September 2011. The Revision Committee comprises mostly JSH members, who are experts in the field of liver cancer treatment and include seven surgeons, five hepatologists, four radiologists, one clinical statistician, and one medical economist. Because the workload has increased compared with that during preparation of the first and second editions, we have further recruited the assistance of 15 expert advisors, and the actual work has been allocated amongst 17 working collaborators.

The topics of investigation include the prevention of hepatocellular carcinoma, diagnosis and surveillance, surgery, percutaneous ablation, transcatheter arterial chemoembolization (TACE), chemotherapy, and radiation therapy. New chapters have been added for post-treatment surveillance, prevention of recurrence, and treatment of recurrent cancer. The 51 Clinical Questions (CQs) of the second edition were re-examined, and questions have been removed, integrated, or newly introduced, resulting in 57 CQs in the third edition. Seventeen CQs remain unchanged, 21 have been revised, and 19 are newly included. Each revision committee member, expert advisor, and working collaborator was assigned to work according to his/her specialty.

In principle, the guidelines have been created with respect to EBM methodology, similar to those in the first and second editions. The personal opinions of experts were eliminated as much as possible, and efforts were made to achieve evidence-based consensus. Literature searches, which are the basis for evidence collection, were centered around the MEDLINE and PubMed databases.

For the second edition, databases were searched up to June 2007, and for this edition, the range of searches has been extended to December 2011 in order to include more evidence. In recent years, the online release of reports has nearly always preceded publication; therefore, we also included articles published electronically [Epub (*sic*)] up until December 2011. A total of 6,750 articles were obtained in search results and were narrowed down to 1,648 during the primary selection process.

Once the level of evidence and content were evaluated, 596 articles were accepted. Of these, 245 were also included in the first and second editions; therefore, 351 new articles have been

incorporated into the third edition. Therefore, the systemization and reproducibility of the search results are now guaranteed for the third edition as well, and the search queries have also been published.

Diagnostic (surveillance) and treatment algorithms occupy a major portion of the guidelines, and survey studies conducted for revision purposes have clearly shown that they are used most often in actual care. During the revision process, feedback on revisions accumulated since the release of the second edition were considered, new evidence was incorporated into active discussions, and the focus was primarily on the maintenance of simplicity and ease-of-use.

A total of eight revision committee meetings were held until April 2013, and a draft was completed that same month. The contents were released on the JSH website from May to June to generate public comments, which were used to make any corrections.

A public hearing was held concurrently during the 49th Annual Meeting of the JSH (held in Tokyo), and the content was finalized after some debate. There are plans to provide independent assessments by an external evaluation committee. Revisions for the fourth edition will also begin within 2 – 3 years, and evidence from January 2012 onwards will be incorporated in that edition.

As in the previous revision, these revised guidelines were funded from the limited budget of the JSH. We offer our heartfelt appreciation to the revision committee members, expert advisors, and working collaborators who worked without pay and were able to complete this monumental task while busily treating their regular patients. We are particularly thankful for the guidance of our special members, Dr. Shigeki Arii, Dr. Masatoshi Okazaki, and Dr. Masatoshi Makuuchi. We also offer our deepest gratitude to Dr. Kazuhiko Koike, Director General of the JSH, as well as the other Directors and the Secretary General Haruki Hakomori for their considerable understanding of and cooperation with the revision of these guidelines. Finally, we thank the EBM Center at The International Medical Information Center (General Incorporated Foundation) and Mr. Satoshi Watanabe, Ms. Kyoko Sugimoto, Ms. Mayumi Morizane, Mr. Takashi Mori, and Ms. Mamiko Yoshida of Kanehara Co., Ltd. for their support.

September 2013

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Preface to the 2009 Version

As part of the FY2002–2003 support program for developing clinical practice guidelines, the Ministry of Health, Labour and Welfare (MHLW) organized a research group (Group Leader, Masatoshi Makuuchi) that developed the first edition the Clinical Practice Guidelines for Hepatocellular Carcinoma (HCC) in June 2004. After being made publicly available by the Liver Cancer Study Group of Japan, the Guidelines were published in February 2005 as the first Japanese evidence-based clinical practice guidelines. They are now widely used for the treatment of liver cancer.

In principle, clinical practice guidelines compiled with an evidence-based medicine (EBM) approach should be revised every 3-4 years to keep the evidence up to date. In line with this, the Japan Society of Hepatology (JSH) starteda project to revise the original 2005 version of the Guidelines in November 2006. The Revision Committee comprised mostly JSH members, who are experts in the field of liver cancer treatment and included 6 surgeons, 4 hepatologists, 4 radiologists, and 1 clinical statistician. Eleven of these 15 JSH members have served as committee members since the first edition. For the current edition, we also included 2 new committee members, a nurse and a radiologist. We also requested cooperation from 7 expert advisors to complete certain tasks.

The topics we investigated were the prevention of HCC, diagnosis and surveillance, surgery, chemotherapy, transcatheter arterial embolization, and percutaneous ablation, with a new chapter on radiation therapy included in this edition. The 57 Research Questions (RQs) in the first edition were re-examined, and questions have been removed, integrated, or newly introduced, resulting in 51 Clinical Questions (CQs) in this second edition. Two CQs remain unchanged, 42 have been revised, and 7 are newly included. Revision Committee members and expert advisors were assigned to work according to their specialty. Medical specialty members were asked to observe all review processes and comment on the processes from their point of view.

As in the first edition, the Guidelines comply with the fundamental principles of EBM, eliminating the personal opinions of specialists and achieving evidence-based consensus as far as possible. Also, as in the first edition, articles were primarily extracted using the MEDLINE database, and it is these articles that provide the foundation for evidence collection. To collect the latest evidence, the year of publication was extended from November 2002 in the first edition to June 2007 in this edition. However, to address the newly included CQs, articles published before 2002 were also searched. In the first edition, search queries created for individual guideline sections were used in the first screening and RQs were complied in the second screening. However, in the current edition, all CQs were developed first, before conducting the literature search for each CQ. A total of 2,950 articles were extracted. This was reduced to 576 after the first screening process and was

eventually narrowed down to 532 after examining levels of evidence and the quality of content. Of these 532 articles, 282 are already covered in the first edition and 250 are newly included, which demonstrates the systematicity and reproducibility of the literature search between the first and second editions, despite the different search methods used. For this reason, any evidence reported in articles published after July 2007 was included only as additional information in the Explanation section and not in the Recommendations section, no matter how important the evidence was considered to be.

Diagnostic (surveillance) and treatment algorithms are at the heart of the Guidelines. They are also the most useful part of the Guidelines, according to questionnaire data. We revised the Guidelines with an emphasis on simplicity and usability, while taking into account various opinions expressed at conferences after the first edition was published, incorporating new evidence, and actively encouraging discussions.

Eight revision committee meetings in total were held before March 2009, and the first draft was produced in April. Comments to improve the draft were received from JSH members, who reviewed it online in May and June, and subsequently from the public. The content of the Guidelines was finalized after extensive discussion at the 45th Annual Meeting of the JSH held in Kobe. The Guidelines are currently being translated into English, and the English version is scheduled to be published in *Hepatology Research*, the official journal of the JSH, in early 2010. The revised Guidelines are also currently being assessed by the External Review Panel. The revision of this second edition is planned to start in 2-3 years in preparation for the third edition, which will incorporate evidence reported after July 2007.

Unlike the development process, the revision of the guidelines was not supported by a grant-in-aid from the MHLW and was therefore funded solely by the JSH with a limited budget. Under these circumstances, the Revision Committee members, expert advisors, and working collaborators worked without pay, brought their own lunches, and completed this monumental task while busy treating their regular patients. We truly appreciate the effort they put into this revision. We are grateful to the Directors, especially Dr. Michio Imawari and Dr. Norio Hayashi, the current and former Directors General of the JSH, as well as the Secretary General Haruki Hakomori for their considerable understanding of and cooperation with the revision of these guidelines. We also thank Ms. Miwako Okabe, Ms. Takako Hata, Ms. Atsuko Hiraishi, and Mr. Hiromichi Suzuki of the EBM Center at the International Medical Information Center (General Incorporated Foundation) as well as Ms. Mamiko Yoshida and Ms. Wakako Fujita of Kanehara Co., Ltd. for their efforts in the literature search and other tasks.

August 2009

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Preface to the 2005 Version

To compile evidence-based clinical practice guidelines for hepatocellular carcinoma (HCC), the Ministry of Health, Labour and Welfare (MHLW) established a research group (Group Leader, Masatoshi Makuuchi) as part of the FY2002-2003 support program for developing clinical practice guidelines.

Clinical practice guidelines are statements generated systematically to help physicians make the most appropriate decisions under specific clinical circumstances. Patients with HCC are entitled to the best care, which has been tailored to individual needs and selected from among several potent treatment modalities such as surgery, percutaneous ablation, and embolization based on the progression of HCC as well as the severity of liver damage. To achieve this, the Clinical Practice Guidelines for HCC were established as Japan's first clinical practice guidelines, by incorporating the concept of evidence-based medicine (EBM) with international standards of clinical practice.

HCC was selected from among the various primary liver cancers as the main subject of the Guidelines, and a research group comprising mostly permanent executive members of the Liver Cancer Study Group of Japan was established to cover different clinical practices and modalities such as prevention, diagnostic imaging, tumor markers, surgery, percutaneous ablation, and chemotherapy. Research group members were assigned roles according to their specialty, conducting literature searches and reviewing articles to accumulate evidence. To build a solid scientific foundation, articles were extracted using MEDLINE as the primary database (1966-2002). Evaluating levels of evidence was the major means of narrowing down 7,118 articles extracted automatically by simple online searches. For the first screening process, a method needed to be established to assess level of evidence, the basis of EBM, in the field of HCC and to ensure that research group members involved in collecting the evidence had the same understanding and followed the same rules and standards. Accordingly, Yutaka Matsuyama, a clinical epidemiologist and Assistant Professor at Kyoto University (currently at The University of Tokyo), was invited to serve as an expert advisor to develop criteria for the research group to assess the level of evidence for HCC (Table 1a)*. However, because the criteria were not suitable for evaluating articles on diagnostic and test modalities, new criteria were developed for that specific purpose as well (Table 1b)*.

For the second screening process, an evidence rating scale was used to evaluate levels of evidence in each article, further narrowing down the number of articles to 100 in each guidelines section. Research group members working on the same task discussed problems and questions about the assessment method and tried to select articles in the same manner as far as possible. In the field of HCC, there are much greater numbers of non-randomized prospective or retrospective cohort

studies, which correspond to evidence level 2, and non-controlled pre-post intervention studies, which correspond to evidence level 4, than randomized controlled trials (RCTs), which correspond to evidence level 1a or 1b. Therefore, articles with the same levels of evidence were ranked based on the number of patients, follow-up period, and dropout rates to decide for inclusion/exclusion, which amounted to subclassification of the levels of evidence. The ranking data were used as inclusion criteria for the second screening process (Table 1c)*. These steps created an immense workload because of the need to read not only the abstract, but also the main body of the articles in detail. Research questions (RQs) about clinical practice also had to be kept in mind during the second screening process. Research group members working on the same task developed RQs for use in the second screening process by fully utilizing the specialized knowledge of individual members, as if to compile a review article about clinical practice for HCC. Finally, the number of articles was narrowed down to approximately 100 in each section, leading to the generation of evidence lists (abstract tables).

The evidence for each RQ is also summarized as a Scientific Statement, and the Recommendations section describes which diagnostic modality and treatment method should be used. A system for grading recommendations was developed specifically for HCC (Table 2a)*. When the conclusions arrived at from the corresponding Scientific Statements were scientific facts rather than recommendations, the strength of evidence was rated to address the RQ (Table 2b)*. Lists of RQs and Scientific Statements from individual members were evaluated and scrutinized to formulate recommendations.

Immediately after the Guidelines were compiled, the External Review Panel was set up to evaluate the validity, dissemination, and potential application of the Guidelines. The results of the evaluation are included at the end of the Guidelines. We hope that the Guidelines will be evaluated further by many specialists from the JSH and the Liver Cancer Study Group of Japan, facilitating the widespread adoption of the Guidelines. It is our firm belief that the Guidelines will contribute greatly to the diagnosis and treatment of HCC into the future. However, the Guidelines are not intended to alter the decision-making process of physicians in daily clinical practice or to discount their experience. While using the Guidelines as reference material, physicians should select the most appropriate treatment for each patient based on their own skills and patient preferences.

The JSH will revise the Guidelines every 3-4 years. We close with our sincere thanks to the research group members and working collaborators for taking on enormous workloads and enthusiastically engaging in dialogue to establish the Guidelines despite their busy clinical schedules. We are also grateful to the External Review Panel for their important contributions.

February 2005

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* Table 1a-c and Table 2a,b are not included in the 2017 version.