Background to the Guidelines

General Statement

1. Purpose

Based on evidence and consensus, the 2017 version of the Clinical Practice Guidelines for Liver Cancer (hereinafter, the Guidelines) presents a roadmap of standard surveillance as well as diagnostic and treatment modalities as practiced in Japan. Because around 90% of cases of primary liver cancer in Japan are hepatocellular carcinoma (HCC), the term "liver cancer" as used in the Guidelines refers to HCC.

2. Application

The Guidelines were compiled on the basis of and with cognizance of scientific evidence collected through systematic literature searches and with consensus from experts in liver cancer treatment who are familiar with the clinical situation and the National Health Insurance system in Japan. As such, the Guidelines are a practical tool in the treatment of HCC in the daily clinical setting. Specifically, they are a useful reference when planning surveillance, diagnostic, and treatment strategies for individual liver cancers and for obtaining informed consent from patients and their family.

It should be noted, however, that the scope of the Guidelines is to clarify the indications for establishing treatment strategies for HCC, not to regulate treatment strategies and methods that are not described in the Guidelines or to limit physicians' discretion. When considering the recommendations, readers should also keep in mind that they were formulated based on the understanding that diagnostic and treatment strategies are affected by clinical conditions and situations specific to individual patients, institutions, and communities.

It should also be noted that the Guidelines were not developed for use as reference material in medical malpractice cases. The JSH takes responsibility for the content of the Guidelines. However, attending physicians, and not the JSH or the Guidelines Revision Committee, shall be liable for the treatment outcomes of individual patients.

3. Target

In principle, the target audience of the Guidelines is all clinicians, including hepatologists and physicians in other fields, who manage patients with liver cancer.

4. Change of name

On May 24, 2017, the Planning and Public Relations Committee (Chair, Satoshi Mochida) formally named the 2017 version "Clinical Practice Guidelines for Liver Cancer, 2017 Version Compiled by the Japan Society of Hepatology".

5. Future revisions

In principle, revision of the Guidelines occurs every 4 years. The revision is led by the Revision Committee, formed in accordance with the policy created by the General Affairs Committee for the Clinical Practice Guidelines for Liver Cancer that was established by the Planning and Public Relations Committee. However, when reports appear of new findings that potentially have a substantial impact on daily clinical practice, the JSH will respond to the report quickly by, for example, making an official statement prior to the next scheduled revision of the Guidelines.

6. Open access

The Guidelines are published as a book and are available free of charge from the JSH website in order to promote their use in liver cancer treatment across Japan.

7. Concise commentaries for lay readers

For lay readers, concise commentaries on the Clinical Practice Guidelines for Hepatocellular Carcinoma are provided by the Medical Information Network Distribution Service (MINDS) at https://minds.jcqhc.or.jp/n/pub/2/pub0018/G0000118.

8. Funding

The entire development process of the 2017 version of the Guidelines was funded solely by the JSH, with no support from companies or organizations.

9. Conflicts of interest

All committee members and expert advisors submitted a conflict of interest (COI) disclosure form to the JSH office before meetings were held (on March 20, April 6 and 13, and July 7, 2017) to finalize the recommendations for Clinical Questions (CQs) (see page vi).

Steps in the revision process

1. Developing the Guidelines

(1) Revision Committee: After compiling the first edition (2005 version) with support from a Ministry of Health, Labour and Welfare project for establishing clinical practice guidelines, the JSH took over the revision of the Guidelines and published the second and third editions in 2009 and 2013, respectively, to account for new evidence. For the fourth edition (2017 version), the Planning and Public Relations Committee established the General Affairs Committee for the Clinical Practice Guidelines for Liver Cancer, which decided membership of the Revision Committee and the revision policy (see page iii).

(2) Basic policy: On July 21, 2015, the General Affairs Committee decided on the basic policy of the Guidelines as follows. As in the first, second, and third editions, the fourth edition ensures the objectivity and reproducibility of medical care in accordance with the fundamental principles of evidence-based medicine (EBM). In addition to relying on the evidence collected, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating clinical guidelines is also incorporated, in part, into the Guidelines in order to strike a balance between benefit and harm for patients and to manage social circumstances. The purpose, principles, and target audience of the Guidelines are described clearly in the general statement. All involved parties clearly disclose COIs. The External Review Panel evaluates the Guidelines and incorporated the results before publication.

(3) Revision process: Revision began in October 2015. 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 have been enlisted to assist committee members, and 16 working collaborators have been engaged to share the workload (see pages iii-iv).

(4) Principles of guideline development: The Revision Committee held four meetings (see below) to finalize the revision steps and other minor strategies. The revision process complied with the fundamental principles of EBM, although the GRADE system was incorporated in part to bridge the gap between evidence and consensus and to help formulate recommendations in a theoretical and systematic manner. The systematic literature search included articles appearing as electronic publications (Epub) before the end of June 2016. From July 2016 onward, articles reporting important evidence were evaluated separately and evidence was incorporated into the Guidelines on an exceptional basis only when it was deemed to have a

considerable impact on daily clinical practice. In addition to articles, abstracts presented at major conferences such as the American Society of Clinical Oncology (ASCO) were included in searches. When a treatment with validity verified overseas is impractical to implement in Japan, the treatment is described in the Guidelines with no recommendations made.

First committee meeting: October 20, 2015 (JSH Office)

Second committee meeting: December 25, 2015 (JSH Office)

Third committee meeting: September 22, 2016 (Hotel Nikko Kanazawa)

Fourth committee meeting: January 14, 2017 (Iino Hall & Conference Center)

(5) Order of presentation: It was decided that recommendations would be made after creating new CQs that support the treatment algorithm and after evaluating overall evidence. Chapter 2 summarizes these recommendations. Nine chapters in total were created: surveillance, diagnosis (including the algorithm), treatment algorithm, prevention, surgery, percutaneous ablation, transcatheter arterial chemoembolization, drug therapy, radiation therapy, and post-treatment surveillance and prevention and treatment of recurrent HCC. The 57 Clinical Questions (CQs) in the third edition were re-examined, and questions have been removed, integrated, or newly introduced, resulting in 55 CQs in the current fourth edition: 30 CQs with no or minor revisions, 13 with relatively major revisions, and 12 newly introduced.

(6) Levels of evidence and strength of recommendations: As in the first, second, and third editions, the fourth edition Guidelines adhere to the fundamental principles of EBM, but the fourth edition did not evaluate the levels of evidence in individual articles. Also, the GRADE system was incorporated, in part, to bridge the gap between evidence and consensus. Discussions made during meetings to finalize the recommendations were integrated into the Guidelines as much as possible.

2. Searching the literature and screening

(1) First, two members were assigned to one CQ as chief and assistant researchers. The chief researcher was responsible for the CQ and the assistant researcher contributed to the objectivity of the CQ and prevented omissions.

(2) The International Medical Information Center (IMIC) selected several key words and then developed search queries for individual CQs (committee members created search queries for some CQs). The chief and assistant researchers then prepared a list of articles for inclusion in the Guidelines in advance. When all of the listed articles appeared among the articles extracted

using particular search queries, the validity of the search formulation was considered verified. When some of the listed articles did not appear among the articles extracted, the search query was duly modified.

(3) The chief and assistant researchers performed the first screening of the extracted articles independently and then compared screening results, adjusting overage or shortage before finally selecting articles.

(4) The chief and assistant researchers verified the content of articles that passed the first screening before independently performing a second screening process. They then compared the second screening results and adjusted overage or shortage before selecting qualified articles.

(5) The chief and assistant researchers carefully read the articles that passed the second screening and created a table of abstracts as instructed by the Revision Committee. Then, to facilitate their final decision-making process, they recorded in the abstract table the strength of recommendation and rationale for selection of each article to be included in the Explanation section.

3. Formulating the recommendations

(1) The chief and assistant researchers created the proposed recommendation for a well-established CQ in the abstract table.

(2) To finalize the recommendation, the abstract table and the proposed recommendation were presented to committee members and expert advisors at a meeting (see below for date and place of all four meetings). The strength of recommendation from one of the following four categories was decided after discussion by a show of hands: strong recommendation for use, weak recommendation for use, weak recommendation against use, and strong recommendation against use. When the strength of recommendation could not be decided in the first voting round, committee members and expert advisors discussed the issue further and voted again by a show of hands. The strength of recommendation for each CQ was decided after this second round of debate and voting, unless this too was inconclusive, in which case a final voting round was undertaken during the fourth and final meeting.

First meeting for finalizing recommendations: March 20, 2017 (The University of Tokyo Hospital)

Second meeting for finalizing recommendations: April 6, 2017 (Office of the Japan Surgical Society)

Third meeting for finalizing recommendations: April 13, 2017 (Office of the Japan Surgical Society)

Fourth meeting for finalizing recommendations: July 7, 2017 (Keio Plaza Hotel)

4. Preparing the Guidelines

(1) The chief and assistant researchers incorporated discussions made in the four meetings as far as possible when finalizing the recommendations for the Explanation section.

(2) The following sections were established to maintain consistency in the content of the Guidelines . The definition or aim of each section is as follows:

- Background section: Briefly describes the target populations of the treatment mentioned in each CQ.
- Scientific Statement section: Briefly summarizes the literature search process, criteria used in the first and second screenings and the screening results, and contents of the selected articles. The Guidelines basically show the original sentences in each article without any interpretation, objectively stating facts only.
- Explanation section: Contains the interpretation of the chief and assistant researchers assigned to each CQ. Detailed explanations are included to clarify why the articles have been included and whether the recommendation is for or against the treatment mentioned in the CQ. Also, this section presents discussions held in the meeting for finalizing recommendations and may state inconclusive recommendations and excluded articles.

5. Holding a public hearing

A public hearing session (Session Chairs: Norihiro Kokudo, Chair of the Revision Committee; Masatoshi Kudo, Revision Committee member) was held at the 53rd Annual Meeting of the Liver Cancer Study Group of Japan on July 7, 2017.

6. Inviting public comment

Between July 7 and 21, 2017, the JSH posted the draft Guidelines containing the diagnostic and treatment algorithms, recommendation for each CQ, and the full text on the JSH website to invite public comment. In addition, the JSH and Liver Cancer Study Group of Japan mailed the information to the directors and councilors of the JSH and the permanent executive members and other members of the Liver Cancer Study Group of Japan, respectively.

7. Evaluating the Guidelines

The External Review Panel led by the Chair Keiji Sano (Professor, Department of Surgery, Teikyo University) evaluated the Guidelines (see page iv).