Clinical Practice Guidelines for Hepatocellular Carcinoma
2021 Version
JSH HCC Guidelines 2021

Compiled by the Japan Society of Hepatology

KANEHARA & Co., LTD.

General Affairs Committee for the Guidelines
Committee Chair

Hiroshi Yotsuyanagi (Board member), Professor, Division of Infectious Diseases, Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo

Committee Members

Nobuyuki Enomoto (Managing Director), Professor, First Department of Internal Medicine, Faculty of Medicine, University of Yamanashi

Takuya Genda, Professor, Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital

Tetsuo Takehara (Director), Professor, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine

Naoki Hiramatsu, Hospital Vice Director and Chair of the Department of Gastroenterology, Osaka Rosai Hospital

Satoshi Mochida (Vice Director), Professor, Department of Gastroenterology and Hepatology, Faculty of Medicine, Saitama Medical University

Masashi Yoneda, Professor, (Division of Gastroenterology and Hepatology), Department of Internal Medicine, Aichi Medical University

Observers

Masayuki Kurosaki [Board member, Observer for hepatitis B/hepatitis C], Hospital Vice Director, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital

Katsutoshi Tokushige [Observer for nonalcoholic steatohepatitis], Professor, Institute of Gastroenterology, Tokyo Women's Medical University

Kiyoshi Hasegawa [Observer for hepatocellular carcinoma], Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

Hitoshi Yoshiji [Board member, Observer for cirrhosis], Professor, Department of Gastroenterology, Nara Medical University

Revision Committee of the Clinical Practice Guidelines for Hepatocellular Carcinoma

Committee Chair

Kiyoshi Hasegawa, Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

Vice Chair

Ryosuke Tateishi, Senior Assistant Professor, Department of Gastroenterology, The University of Tokyo

Committee Members

Surgeons

Masaki Kaibori, Professor, Department of Hepatic Surgery, Kansai Medical University

Shoji Kubo, Professor, Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine

Mitsuo Shimada, Professor, Department of Surgery, Tokushima University Graduate School of Medicine

Nobuyuki Takemura, Department Head, Department of Hepato-Biliary-Pancreatic Surgery, Center Hospital of the National Center for Global Health and Medicine

Hiroaki Nagano, Professor, Department of Gastroenterological, Breast, and Endocrine Surgery, Yamaguchi University Graduate School of Medicine

Etsuro Hatano, Professor, Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University~~Etsuo Hatano, Professor, Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Kyoto University~~

Hepatologists

Hiroshi Aikata, Associate Professor, Department of Gastroenterology and Metabolism, Graduate School of Biomedical & Health Sciences, Hiroshima University

Hiroko Iijima, Professor, Division of Gastroenterology and Hepatology (Division of Hepatobiliary and Pancreatic Disease), Department of Internal Medicine, Hyogo College of Medicine

Kazuomi Ueshima, Senior Assistant Professor, Department of Gastroenterology and Hepatology, Kinki University School of Medicine

Kazuyoshi Ohkawa, Chief Chair, Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute

Masatoshi Kudo, Professor, Department of Gastroenterology and Hepatology, Kinki University School of Medicine

Takuya Genda, Professor, Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital

Kaoru Tsuchiya, Department Chair, Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital

Takuji Torimura, Professor, Division of Gastroenterology, Department of Medicine, Kurume University

Tatsuya Yamashita, Associate Professor, Advanced Preventive Medical Sciences Research Center, Kanazawa University

Medical Oncologists

Masafumi Ikeda, Department Chair, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East

Junji Furuse, Professor, Department of Medical Oncology, Kyorin University Faculty of Medicine

Radiologists

Masaaki Akahane, Professor, Department of Radiology, International University of Health and Welfare

Satoshi Kobayashi, Professor, Department of Quantum Medical Imaging, Kanazawa University Graduate School of Medical Sciences

Hideyuki Sakurai, Professor, Department of Radiation Oncology, Tsukuba University School of Medicine

Atsuya Takeda, Center Director, Radiation Oncology Center, Ofuna Chuo Hospital

Takamichi Murakami, Professor, Department of Radiology, Kobe University Graduate School of Medicine

Utaroh Motosugi, Department of Radiology, Kofu Kyoritsu Hospital

Takeyuki Watadani, Associate Professor, Department of Radiology, The University of Tokyo Hospital

Clinical Statistician (advisor)

Yutaka Matsuyama, Professor, Department of Biostatistics, Graduate School of Medicine, The University of Tokyo

Expert Advisors

Surgeons

Kyoji Ito, Department of Hepato-Biliary-Pancreatic Surgery, Center Hospital of the National Center for Global Health and Medicine

Satoru Imura, Chief Physician, Department of Surgery, Takamatsu Municipal Hospital

Takashi Kokudo, Assistant Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

Shogo Tanaka, Senior Assistant Professor, Department of Hepato-Biliary-Pancreatic Surgery, Osaka City University Graduate School of Medicine

Yukio Tokumitsu, Assistant Professor, Department of Gastroenterological, Breast, and Endocrine Surgery, Yamaguchi University Graduate School of Medicine

Ikuo Nakamura, Senior Assistant Professor, Department of Hepato-Biliary-Pancreatic Surgery, Hyogo College of Medicine

Kosuke Matsui, Senior Assistant Professor, Department of Hepatic Surgery, Kansai Medical University

Hepatologists

Yoshinari Asaoka, Associate Professor, Department of Internal Medicine, Teikyo University School of Medicine

Kuniaki Arai, Senior Assistant Professor, Department of Gastroenterology, Kanazawa University Hospital

Wataru Okamoto, Associate Professor, Cancer Treatment Center, Hiroshima University Hospital

Ryotaro Sakamori, Senior Assistant Professor, Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine

Hironori Tsuzura, Assistant Professor, Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital

Masahito Nakano, Assistant Professor, Division of Gastroenterology, Department of Medicine, Kurume University

Takashi Nishimura, Senior Assistant Professor, Division of Gastroenterology

and Hepatology (Division of Hepatobiliary and Pancreatic Disease), Department of Internal Medicine, Hyogo College of Medicine

Atsushi Hiraoka, Chief Chair, Department of Gastroenterology, Ehime Prefectural Central Hospital

Yasunori Minami, Senior Assistant Professor, Department of Gastroenterology and Hepatology, Kinki University School of Medicine

Yutaka Yasui, Department Vice Chair, Department of Gastroenterology, Musashino Red Cross Hospital

Radiologists

Hiroshi Igaki, Department Chair, Department of Radiation Oncology, National Cancer Center Hospital

~~Hiroshi Igaki, Department Chair, Department of Radiology, National Cancer Center Hospital~~

Keitaro Sofue, Senior Assistant Professor, Department of Radiology/IVR, Kobe University Hospital

Masakazu Hirakawa, Associate Professor, Department of Radiology, Kyushu University Beppu Hospital

Toshihiro Furuta, Senior Assistant Professor, Department of Radiology, Research Hospital, The Institute of Medical Science, The University of Tokyo

Masashi Mizumoto, Associate Professor, Department of Radiation Oncology, Tsukuba University School of Medicine

Tetsuya Minami, Professor, Department of Diagnostic and Therapeutic Radiology, Kanazawa Medical University

Working Collaborators

Surgeons

Yoshikuni Kawaguchi, Assistant Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

Yoshitaro Shindo, Assistant Professor, Department of Gastroenterological, Breast, and Endocrine Surgery, Yamaguchi University Graduate School of Medicine

Hepatologists

Tomoko Aoki, Assistant Professor, Department of Gastroenterology and Hepatology, Kinki University School of Medicine

Koji Uchino, Department of Gastroenterology, Japanese Red Cross Medical

Center

Toshifumi Tada, Department Chair, Department of Hepatology, Japanese Red Cross Society Himeji Hospital

Takeshi Terashima, Associate Professor, Advanced Preventive Medical Sciences Research Center, Kanazawa University

Takuma Nakatsuka, Assistant Professor, Department of Gastroenterology, The University of Tokyo Hospital

Tatsuya Minami, Assistant Professor, Department of Gastroenterology, The University of Tokyo Hospital

Radiologists

Koji Inaba, Department of Radiology, National Cancer Center Hospital

Takahisa Eriguchi, Radiation Oncology Center, Ofuna Chuo Hospital

Yuichi Kibe, Medical Staff, Department of Radiology, Kanto Rosai Hospital

Shigeru Kiryu, Senior Professor, Department of Radiology, International University of Health and Welfare

Kazuto Kozaka, Associate Professor, Department of Radiology, Kanazawa University Hospital

Yozo Sato, Department Vice Chair, Ultrasound/IVR Department, Cancer Institute Hospital

Naoko Sanuki, Department Vice Chair, Department of Radiology, Yokkaichi Municipal Hospital

Kei Shibuya, Senior Assistant Professor, Department of Radiology, Gunma University Hospital

Masashi Shimohira, Associate Professor, Department of Radiology, Nagoya City University Graduate School of Medical Sciences

Ryosuke Takenaka, Assistant Professor, Department of Radiology, The University of Tokyo Hospital

Masakatsu Tsurusaki, Professor, Department of Radiology, Kindai University Faculty of Medicine

Hiroyuki Morisaka, Senior Assistant Professor, Department of Radiology, University of Yamanashi

Koichiro Yamakado, Senior Professor, Department of Radiology, Hyogo College of Medicine

Akira Yamada, Associate Professor, Department of Radiology, Shinshu University School of Medicine

External Review Panel for the Clinical Practice Guidelines for Hepatocellular Carcinoma

Committee Chair

Keiji Sano, Professor, Department of Surgery, Teikyo University School of Medicine

Committee Members

Hiroyuki Isayama, Professor, Department of Gastroenterology, Graduate School of Medicine, Juntendo University

Shigehiro Kokubu, Center Director, Institute for Liver Disease Minimal Invasive Treatment, Shin-Yurigaoka General Hospital

Kentaro Sakamaki, Associate Professor, Center for Data Science, Yokohama City University

Kenichi Sugihara, Professor Emeritus, Tokyo Medical and Dental University

Hiroki Haradome, Professor, Department of Diagnostic Radiology, Kitasato University School of Medicine

(Contributors are listed by last name in the order of the Japanese 50-character *kana* syllabary)

Office of the Clinical Practice Guidelines for Hepatocellular Carcinoma
The Japan Society of Hepatology, General Incorporated Association
Kashiwaya 2 Building 5F, 3-28-10 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Preface to the 2021 Version

Since the first edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma was published in 2005, major revisions have been made approximately every 4 years, and this is the fifth edition. In addition, the revised and expanded fourth edition was released in February 2020, because the graft allocation criteria in deceased donor liver transplantation for hepatocellular carcinoma (HCC) were changed and the treatment algorithm was also modified in August 2019 and two drugs were newly covered by the National Health Insurance system almost at the same time. At this point of time, the major revision was also ongoing, and after one year and eight months' work, the 2021 Version (fifth edition) was eventually published.

In this revision, several substantial changes and modifications were made. As readers know, drug therapy for HCC has recently advanced remarkably, and although only two drugs were covered by the National Health Insurance system when the fourth edition was

published (in October 2017), a total of 6 regimens, 3 regimens for first-line therapy and 3 regimens for second-line therapy, are currently covered by the National Health Insurance system. Based on this, a new “HCC drug therapy algorithm” to complement the conventional treatment algorithm was developed. Since I know those days when there was no or at most one effective drug, I feel that I am living in a completely different age. Although the algorithm may seem still simpler than other drug therapy algorithms for malignant tumors, I would like to expect that the results of ongoing clinical studies may further increase effective options, necessitating the revision of the “HCC drug therapy algorithm”.

Although no major changes were made in the framework of the “treatment algorithm”, in this version, priorities were always given to recommended treatments, and treatments with the first and second priorities were included in the algorithm (if there were two or more treatments with the same priority, all of them were included). The treatment algorithm had tended to be complicated reflecting the demands of clinical practice and advances in each treatment, but we returned somewhat to the principle since the first edition: “simple and easy to understand”. In addition, based on the results of the randomized controlled trial (RCT) comparing resection and radiofrequency ablation (RFA) for early-stage HCC (SURF trial), resection and RFA are equally recommended for patients with up to 3 tumors and tumor diameter ≤ 3 cm in the revised Guidelines. It appears that this is a settlement of the long-standing debate.

In the 2021 version, careful consideration was given to avoid inconsistency between the “surveillance and diagnostic algorithm” and “the Japanese Imaging Guideline 2021” of the Japan Radiological Society. We invited committee members responsible for the liver area of “the Japanese Imaging Guideline 2021” to our Revision Committee to have sufficient discussion. At first, we thought that it would be inevitable that disagreements between the two societies after thorough discussion would result in somewhat different algorithms; however, the same algorithm was published in both guidelines. I think that this is extraordinary in that collaborative work between two different societies went well and that this is good in that confusion in clinical practice could be avoided. In addition, although somewhat complex problems arose such as copyright, the Japan Society of Hepatology (JSH) and Japan Radiological Society had positive discussions and reached agreement without significant confusion. We deeply thank the executives of both societies.

As in the second to fourth revisions, the latest revision was funded entirely by the JSH, despite the limited budget available. Furthermore, most meetings (19 of a total of 22 meetings) had to be held online due to the coronavirus disease 2019 (COVID19) pandemic. Meetings of approximately one hour were held every one or two weeks, but

the meeting style was new and we were just groping our way. However, a relatively high proportion of members attended the meetings, and the costs could be reduced; therefore, I think that the web meetings were sufficiently advantageous. I would like to wait and see how the meeting style will be assessed in the future. 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. Tetsuo Takehara, Director General of the JSH, and Dr. Hiroshi Yotsuyanagi, Chair of the General Affairs Committee for the Guidelines, as well as the Secretary General Yuji Nakakita for their considerable understanding of and cooperation with the revision process. We also thank Mr. Kazuya Sunouchi of Kanehara Co., Ltd. for his support in editing and revising the Guidelines.

October 2021
Kiyoshi Hasegawa
Chair, Revision Committee for the 2021 Clinical Practice Guidelines for Hepatocellular Carcinoma (Fifth Edition)
Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

Preface to the revised and expanded 2017 Version

Since the first edition of the Guidelines was published in 2005, major revisions have been made approximately every 4 years, with the latest revision made in October 2017 as the fourth revision. However, the treatment, particularly drug therapy, of hepatocellular carcinoma has advanced rapidly in recent years, and the revision of the guidelines every 4 years seems to fail to catch up with changes in daily clinical practice. Therefore, the General Affairs Committee for the Guidelines of the JSH led the change in the policy to revise the Guidelines in real time when significant findings are reported, and this Revision Committee was also established as a new permanent organization in June 2019.
First, the Revision Committee discussed how to deal with the 5-5-500 criteria, which were added to the recipient selection criteria for deceased donor liver transplantation for HCC on August 1, 2019, and molecular targeted therapy, which was recently covered by the National Health Insurance system (CQ14, 29, 43). The details are described in the revised Guidelines, and as a result of the discussion particularly on the former issue, the Committee concluded that the treatment algorithm, which could be said to be the essence

of the Guidelines, needed to be modified.
Although revision for the fifth edition was already started, it still took time to complete the revision at that time, and partial revision on the JSH website was the usual procedure; however, considering the relatively high importance of the revision including the modification of the algorithm, the Committee concluded that the revised and expanded version should also be published in a book form. We would be delighted if the revised and expanded version would be helpful in future clinical practice.

February 2020
Kiyoshi Hasegawa
Chair, Revision Committee of the Clinical Practice Guidelines for Hepatocellular Carcinoma
Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

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 edition 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

Norihiro Kokudo
Chair, Revision Committee for the 2017 Clinical Practice Guidelines for Liver Cancer (Fourth Edition)
President, National Center for Global Health and Medicine
Kiyoshi Hasegawa
Vice Chair, Revision Committee for the 2017 Clinical Practice Guidelines for Liver Cancer (Fourth edition)
Associate Professor, Hepato-Biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo

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

Norihiro Kokudo, and Kiyoshi Hasegawa
Hepato-Biliary-Pancreatic Surgery Division/Artificial Organ and Transplantation Division,
Department of Surgery, Graduate School of Medicine, University of Tokyo

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) started a 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

Masatoshi Makuuchi
Japanese Red Cross Medical Center
Norihiro Kokudo
Hepato-Biliary-Pancreatic Surgery Division/Artificial Organ and Transplantation Division,
Department of Surgery, Graduate School of Medicine, The University of Tokyo

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

Masatoshi Makuuchi
Hepato-Biliary-Pancreatic Surgery Division and Artificial Organ and Transplantation Division,
Department of Surgery, Graduate School of Medicine, The University of Tokyo

* Table 1a-c and Table 2a,b are not included in the 2021 version.

Conflict of Interest Disclosure in the Clinical Practice Guidelines for Hepatocellular Carcinoma 2021 Version

<Conflicts of interest (COI) to be disclosed> Give specific company/organization names and fiscal years (2018-2020) for each applicable category, and enter “not applicable”, if not applicable.

Self-reported COI (in accordance with the Japanese Association of Medical Sciences “Guidance on Criteria for Qualification to Practice Guideline”)

1. Serving as a board member or advisor at a company or profit-oriented organization and compensation
   Minimum amount: JPY 1,000,000/company/year
   Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
2. Ownership of company stock and profit from the stock (profit from the stock during the last 1 year)
   Minimum amount: JPY 1,000,000/company/year
   Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
3. Patent royalties from a company or profit-oriented organization
   Minimum amount: JPY 1,000,000/company/year
   Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
4. Honoraria such as *per diem* and lecture fees from a company or profit-oriented organization for attending (presenting or advising) at meetings
   Minimum amount: JPY 500,000/company/year
   Category: (1) ≥JPY 500,000, (2) ≥JPY 1,000,000, (3) ≥JPY 2,000,000
5. Fees for writing booklets, articles on round table talks, etc. from a company or profit-oriented organization
   Minimum amount: JPY 500,000/company/year
   Category: (1) ≥JPY 500,000, (2) ≥JPY 1,000,000, (3) ≥JPY 2,000,000
6. Research funding (industry-university joint research, commissioned research, clinical trials, etc.) from a company or profit-oriented organization
   Minimum amount: JPY 1,000,000/company/year
   Category: (1) ≥JPY 1,000,000, (2) ≥JPY 10,000,000, (3) ≥JPY 20,000,000
7. Scholarships (incentives) from a company or profit-oriented organization
   Minimum amount: JPY 1,000,000/company/year
   Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
8. Department or division endowed by a company, etc.
   Belonging to a department or division endowed by a company, etc. with an actual endowment of ≥JPY 1,000,000

9. Other compensation (such as travel expenses and gifts not directly related to research) Minimum amount: JPY 50,000/company/year Category: (1) ≥JPY 50,000, (2) ≥JPY 200,000, (3) ≥JPY 500,000

1

Chair
Vice Chair
Committee members
Surgeons
Hepatologists

2

Name (affiliation)
Kiyoshi Hasegawa
(The University of Tokyo)
Ryosuke Tateishi
(The University of Tokyo)
Masaki Kaibori
(Kansai Medical University)
Shoji Kubo
(Osaka City University)
Mitsuo Shimada
(Tokushima University)
Nobuyuki Takemura
(Center Hospital of the National Center for Global Health and Medicine)
Hiroaki Nagano
(Yamaguchi University)
Etsuo Hatano
(Kyoto University)
Hiroshi Aikata
(Hiroshima University)
Hiroko Iijima
(Hyogo College of Medicine)
Kazuomi Ueshima
(Kinki University)

Kazuyoshi Ohkawa
(Osaka International Cancer Institute)

3
Disclosed item 1 (Compensation as a board member)
Disclosed item 6 (Research funding)
Not applicable
(2) Nipro (2020)
Not applicable
Not applicable
Not applicable
(1) Nippon Shokubai (2020, 2019), Helix Japan (2020)
Not applicable
Not applicable
Not applicable
(1) Ono Pharmaceutical (2019, 2018), Taiho Pharmaceutical (2020, 2019, 2018), Tsumura (2020, 2019, 2018)
Not applicable
Not applicable
Not applicable
(3) Cytlimic (2020, 2019, 2018), Toyo Kohan (2020, 2019), NEC (2019, 2018)
(1) Toyo Kohan (2018), NEC (2020)
Not applicable
(1) Tsumura (2020, 2019), Panasonic (2020, 2019)
Not applicable
Not applicable
Not applicable
(1) Canon Medical Systems (2020, 2019), GE Healthcare Japan (2020)
Not applicable
Not applicable
Not applicable
(1) Towa Pharmaceutical (2020)

4
Disclosed item 2 (Stock ownership)
Disclosed item 7 (Scholarships)

Not applicable
(1) Taiho Pharmaceutical (2020, 2019, 2018)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(1) Astellas Pharma (2019, 2018), Taiho Pharmaceutical (2020, 2019, 2018), Chugai Pharmaceutical (2020, 2019, 2018), Novartis Pharma (2019), MSD (2018)
Not applicable
Not applicable
Not applicable
(1) Taiho Pharmaceutical (2020, 2019, 2018), Eli Lilly Japan (2019), MSD (2019, 2018)
Not applicable
(1) Eisai (2020, 2019)
Not applicable
Not applicable
Not applicable
(1) Abbvie (2020, 2019), Otsuka Pharmaceutical (2020, 2019, 2018), Sumitomo Dainippon Pharma (2019), EA Pharma (2019)
Not applicable

5
Disclosed item 3 (Patent royalties)
Disclosed item 8 (Endowed chair)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Nipro (2020, 2019, 2018)
Not applicable

6

Disclosed item 4 (Lecture fees)
Disclosed item 9 (Other compensation)
(1) Chugai Pharmaceutical (2020), Bayer Yakuhin (2018), MSD (2019)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(1) Eisai (2020, 2019), Merck (2018)
Not applicable
(3) Eisai (2020)
(2) Eisai (2019, 2018), Bayer Yakuhin (2018)
(1) Eli Lilly Japan (2020), Bayer Yakuhin (2019)
Not applicable
Not applicable
Not applicable
(3) Eisai (2020, 2019, 2018)
(2) Eli Lilly Japan (2020), Bayer Yakuhin (2018)
(1) Eli Lilly Japan (2019)
Not applicable

7
Disclosed item 5 (Manuscript fees)
Not applicable

8
To be continued

9
Hepatologists
Medical Oncologists

10
Name (affiliation)
Masatoshi Kudo
(Kinki University)
Takuya Genda
(Juntendo University)
Kaoru Tsuchiya
(Musashino Red Cross Hospital)
Takuji Torimura
(Kurume University)
Tatsuya Yamashita
(Kanazawa University)
Masafumi Ikeda
(National Cancer Center Hospital East)

11
Disclosed item 1 (Compensation as a board member)
Disclosed item 6 (Research funding)
Not applicable
(2) Ono Pharmaceutical (2018)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(1) Gilead Sciences (2018), Kowa (2018), Bristol Myers Squibb (2019)
Not applicable
Not applicable
Not applicable
(3) AstraZeneca (2020), Ono Pharmaceutical [commissioned research] (2018), Ono Pharmaceutical [clinical trial] (2019), J-Pharma (2020), Merck Biopharma (2020), Merus. N.V. (2020)

(2) Eisai (2018), J-Pharma (2019), CMIC (2018), Chugai Pharmaceutical (2020), Bristol Myers Squibb (2019), MSD (2020, 2019)
(1) AstraZeneca (2019, 2018), Eisai (2020, 2019), Ono Pharmaceutical [commissioned research] (2020, 2019), Ono Pharmaceutical [clinical trial] (2020, 2018), Chiome Bioscience (2020), J-Pharma (2018), CMIC (2019), Takeda Pharmaceutical (2019), Chugai Pharmaceutical (2019, 2018), Eli Lilly Japan (2020), Novartis Pharma (2018), Bayer Yakuhin (2019, 2018), Pfizer (2019), Bristol Myers Squibb (2020, 2018), Merck Serono (2018), Merck Biopharma (2019), Yakult Honsha (2019, 2018), ASLAN Pharmaceuticals (2018), Delta-Fly Pharma (2020), EP-CRSU (2020)

12
Disclosed item 2 (Stock ownership)
Disclosed item 7 (Scholarships)
Not applicable
(2) Eisai (2019)
(1) Abbvie (2020, 2019), Eisai (2020, 2018), Otsuka Pharmaceutical (2020, 2019, 2018), Gilead Sciences (2019, 2018), Sumitomo Dainippon Pharma (2019), Taiho Pharmaceutical (2020, 2019, 2018), Takeda Pharmaceutical (2019, 2018), Chugai Pharmaceutical (2020), EA Pharma (2020, 2019, 2018)
Not applicable
(1) Abbvie (2020, 2019, 2018), Otsuka Pharmaceutical (2018), Mitsubishi Tanabe Pharma (2018), JIMRO (2020, 2019, 2018)
Not applicable
Not applicable
Not applicable
(1) Abbvie (2020, 2019, 2018), Eisai (2020, 2019), Gilead Sciences (2018), Takeda Pharmaceutical (2018), EA Pharma (2020, 2019)
Not applicable

13
Disclosed item 3 (Patent royalties)
Disclosed item 8 (Endowed chair)
Not applicable

14
Disclosed item 4 (Lecture fees)

Disclosed item 9 (Other compensation)
(3) Eisai (2020, 2019, 2018)
(2) Chugai Pharmaceutical (2020), Eli Lilly Japan (2020, 2019), Bayer Yakuhin (2019, 2018)
(1) EA Pharma (2018), MSD (2019, 2018)
Not applicable
(2) Abbvie (2018)
(1) Abbvie (2019), Gilead Sciences (2019)
Not applicable
(1) Eisai (2020, 2019, 2018), Chugai Pharmaceutical (2020), Eli Lilly Japan (2020), Bayer Yakuhin (2020, 2019, 2018)
Not applicable
Not applicable
Not applicable
(2) Eisai (2019, 2018), Eli Lilly Japan (2020)
(1) Eisai (2020), Chugai Pharmaceutical (2020), Eli Lilly Japan (2019), Bayer Yakuhin (2019, 2018), MSD (2019)
Not applicable
(1) Eisai (2019), Chugai Pharmaceutical (2020), Eli Lilly Japan (2020, 2019), Novartis Pharma (2019, 2018), Bayer Yakuhin (2019, 2018)

15
Disclosed item 5 (Manuscript fees)
Not applicable

16
Medical Oncologists
Radiologists
Clinical Statistician
External Review Panel Committee Chair
External Review Panel Committee Members

17
Name (affiliation)
Junji Furuse
(Kyorin University)

Masaaki Akahane
(International University of Health and Welfare)
Satoshi Kobayashi
(Kanazawa University)
Hideyuki Sakurai
(Tsukuba University)
Atsuya Takeda
(Ofuna Chuo Hospital)
Takamichi Murakami
(Kobe University)
Utaroh Motosugi
(Kofu Kyoritsu Hospital)
Takeyuki Watadani
(The University of Tokyo)
Yutaka Matsuyama
(The University of Tokyo)
Keiji Sano
(Teikyo University)
Hiroyuki Isayama
(Juntendo University)
Shigehiro Kokubu
(Shin-Yurigaoka General Hospital)
Kentaro Sakamaki
(Yokohama City University)
Kenichi Sugihara
(Tokyo Medical and Dental University)
Hiroki Haradome
(Kitasato University)

18
Disclosed item 1 (Compensation as a board member)
Disclosed item 6 (Research funding)
Not applicable
(1) Astellas Pharma (2020), AstraZeneca (2020, 2018), Ono Pharmaceutical (2020, 2019, 2018), J-Pharma (2020, 2019), Sumitomo Dainippon Pharma (2018), Taiho Pharmaceutical (2020), Merck Biopharma (2020, 2019), Yakult Honsha (2018), MSD

(2020, 2019, 2018)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(3) Hitachi, Ltd. Healthcare Business Unit (2020, 2019, 2018)
(1) Shonai Create Industrial (2020), Tateyama Machine (2019, 2018), Harmonize (2019, 2018)
Not applicable
Not applicable
Not applicable
(2) Canon Medical Systems (2020), GE Healthcare Japan (2020, 2019)
(1) Philips Japan (2020), HACARUS (2020)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(3) Ajinomoto (2019, 2018), Thermo Fisher Diagnostics (2018)
(1) Ajinomoto (2020), Hitachi (2020), Boston Scientific Japan (2020)
Not applicable

19
Disclosed item 2 (Stock ownership)
Disclosed item 7 (Scholarships)
Not applicable
(1) Eisai (2019), Ono Pharmaceutical (2020), Daiichi Sankyo (2018), Taiho Pharmaceutical (2020, 2019)
Not applicable
Not applicable
Not applicable

Not applicable
Not applicable
Not applicable
Not applicable
(1) Varian Medical Systems (2020, 2019, 2018)
Not applicable
(2) Siemens Healthcare (2020, 2018)
(1) Eisai (2018), Guerbet Japan (2020, 2019, 2018), Tanaka Dengyo Syoukai (2020), Terumo (2019), Nihon Medi-Physics (2020, 2019), Fuji Pharma (2018), FUJIFILM Toyama Chemical (2020), FUJIFILM Medical (2019), FUJIFILM RI Pharma (2018)
Not applicable
Not applicable
Not applicable
Not applicable
Not applicable
(1) Zenjinkai (2019), EPS Holdings (2019, 2018)
Not applicable
Not applicable
Not applicable
(1) Gadelius Medical (2020, 2019), Taiho Pharmaceutical (2020, 2019, 2018), Boston Scientific Japan (2020, 2019), Yakult Honsha (2018)
Not applicable

20
Disclosed item 3 (Patent royalties)
Disclosed item 8 (Endowed chair)
Not applicable

21
Disclosed item 4 (Lecture fees)
Disclosed item 9 (Other compensation)
(3) Eisai (2018)
(2) Eisai (2019), Ono Pharmaceutical (2019), Taiho Pharmaceutical (2018), Bayer Yakuhin (2019, 2018)
(1) Eisai (2020), Ono Pharmaceutical (2020, 2018), Teijin Pharma (2018), Eli Lilly Japan (2019), Novartis Pharma (2018), Bayer Yakuhin (2020), FUJIFILM (2019, 2018), Yakult

Honsha (2020, 2018), MSD (2019)
Not applicable

22
(1) Nihon Pharmaceutical (2018)
Not applicable
Not applicable
Not applicable
(1) Taiho Pharmaceutical (2020, 2019)

23
Disclosed item 5 (Manuscript fees)
Not applicable

Search queries/Abstract Table (posted on the JSH website: https://www.jsh.or.jp/medical/)

Clinical Practice Guidelines for Hepatocellular Carcinoma
List of Clinical Questions and Recommendations

24
Clinical Practice Guidelines for Hepatocellular Carcinoma, List of Clinical Questions and Recommendations
Chapter
CQ No.

25
Recommendations
Strength of recommendation
Strength of evidence
Page

Background to the Guidelines

General Statement

1. Purpose

The main purpose of the 2021 version (fifth edition) of the Clinical Practice Guidelines for Hepatocellular Carcinoma (hereinafter, the Guidelines or the fifth edition) is to increase the general level of care for liver cancer in Japan while eliminating regional and between-hospital differences (equal accessibility) and eventually to improve overall survival and quality of life in patients with liver cancer. Based on evidence and consensus, the Guidelines present 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 HCC, the term “liver cancer” as used in the Guidelines refers to HCC. For intrahepatic cholangiocarcinoma, which is the second most common primary liver cancer in Japan, see the 2021 version of the Clinical Practice Guidelines for Intrahepatic Cholangiocarcinoma (compiled by the Liver Cancer Study Group of Japan) that have been developed separately.

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 Revision Committee of the Clinical Practice Guidelines for Hepatocellular Carcinoma (hereinafter, the 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. Future revisions

In principle, major revision of the Guidelines occurs every 4 years. The major revision is led by the permanent Revision Committee, formed in accordance with the policy created by the General Affairs Committee for the Clinical Practice Guidelines that was established by the JSH. However, when reports appear of new findings that potentially have a substantial impact on daily clinical practice, minor revision will occur, as required, at the discretion of the Revision Committee.

5. 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.

6. 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.

7. Funding

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

8. Conflicts of interest

After the first committee meeting was held (on July 5, 2019), all committee members and expert advisors submitted a COI disclosure form to the JSH office, and the General Affairs Committee for the Guidelines reviewed the disclosure forms and officially appointed committee members and expert advisors. Before the publication of the fifth edition (April 2021), the committee members and expert advisors again submitted a COI disclosure form, which is disclosed in the Guidelines (see page xiv). COI, voting rights and the scope of disclosure were determined as follows after review by the General Affairs Committee for the Guidelines.

(1) Committee members falling into category (3) for each item in the Japanese Association of Medical Sciences COI rules (Table 1)[1)] were regarded as having financial COI and gave up their voting rights in the relevant Clinical Questions (CQs).
(2) Academic COI were also considered. All authors (including co-authors) of articles cited as references in each CQ were regarded as having academic COI.
(3) Regarding the scope of disclosure of COI, COI are listed for each member from the fifth edition on.

Table 1. The minimum amount requiring disclosure and categories for self-reported COI by participants in the development of the Guidelines

1. Serving as a board member or advisor at a company or profit-oriented organization and compensation Minimum amount: JPY 1,000,000/company/year Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
2. Ownership of company stock and profit from the stock (profit from the stock during the last 1 year) Minimum amount: JPY 1,000,000/company/year Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
3. Patent royalties from a company or profit-oriented organization Minimum amount: JPY 1,000,000/company/year Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000
4. Honoraria such as *per diem* and lecture fees from a company or profit-oriented organization for attending (presenting or advising) at meetings Minimum amount: JPY 500,000/company/year Category: (1) ≥JPY 500,000, (2) ≥JPY 1,000,000, (3) ≥JPY 2,000,000
5. Fees for writing booklets, articles on round table talks, etc. from a company or profit-oriented organization Minimum amount: JPY 500,000/company/year Category: (1) ≥JPY 500,000, (2) ≥JPY 1,000,000, (3) ≥JPY 2,000,000
6. Research funding (industry-university joint research, commissioned research, clinical trials, etc.) from a company or profit-oriented organization Minimum amount: JPY 1,000,000/company/year Category: (1) ≥JPY 1,000,000, (2) ≥JPY 10,000,000, (3) ≥JPY 20,000,000
7. Scholarships (incentives) from a company or profit-oriented organization Minimum amount: JPY 1,000,000/company/year Category: (1) ≥JPY 1,000,000, (2) ≥JPY 5,000,000, (3) ≥JPY 10,000,000

8. Department or division endowed by a company, etc.
Belonging to a department or division endowed by a company, etc. with an actual endowment of ≥JPY 1,000,000
9. Other compensation (such as travel expenses and gifts not directly related to research)
Minimum amount: JPY 50,000/company/year
Category: (1) ≥JPY 50,000, (2) ≥JPY 200,000, (3) ≥JPY 500,000

(Cited from the Japanese Association of Medical Sciences "Guidance on Criteria for Qualification to Practice Guideline" 2017 [1].)

9. Monitoring of the Guidelines after publication

The prevalence of the Guidelines was assessed using quality indicators and the 17th follow-up survey of primary liver cancer in Japan (Liver Cancer Study Group of Japan) for some recommendations included in the 2005 version (the first edition) of the Clinical Practice Guidelines for Hepatocellular Carcinoma [2]. In addition, a questionnaire survey of medical institutions registered with the National Clinical Database assessed the impact of adherence to the Guidelines on mortality after hepatectomy for HCC [3].

We would like to continue to assess the prevalence of the Guidelines, changes in treatment and impact on improving prognosis using data from follow-up surveys of primary liver cancer in Japan (Liver Cancer Study Group of Japan) after publication of the fifth edition.

References

1) The Japanese Association of Medical Sciences. Guidance on Criteria for Qualification to Practice Guideline.

Steps in the revision process

1. Developing the Guidelines

(1) General Affairs Committee: After compiling the 2005 version (first edition) of the Clinical Practice Guidelines for Hepatocellular Carcinoma 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 2009 version (the second edition) and the 2013 version (the third edition) to account for new evidence. For the 2017 version (fourth edition), the Planning and Public Relations Committee established for the first time the General Affairs Committee for the Clinical Practice Guidelines for Hepatocellular Carcinoma, which is superior to the Revision Committee. For the fifth edition, the General Affairs Committee for the Clinical Practice Guidelines that controls

all JSH guidelines (see page iii) was newly established and decided membership of the Revision Committee and the revision policy.

(2) Basic policy: As in the first to fourth editions, the fifth 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 was also incorporated, in part, into the fourth edition of the Guidelines in order to strike a balance between benefit and harm for patients and to manage social circumstances, and the fifth edition follows the policy of the fourth edition.

(3) Revision process: The first meeting of the Revision Committee was held by temporary members in July 2019 to start revision. Major revision for the fifth edition, which was planned to be published in 2021, was made in parallel with on-demand revision to include drug therapies newly covered by the National Health Insurance system. The meeting of the General Affairs Committee for the Guidelines (see page iii) held on August 30, 2019 determined the requirements for committee members, Committee Chair and Vice Chair and finalized the composition of the Revision Committee. The Revision Committee comprises a total of 27 members, mostly JSH members who are experts in the field of liver cancer treatment, including 7 surgeons, 10 hepatologists, 7 radiologists, and 1 clinical statistician, as well as 2 medical oncologists (medical oncologists were newly participated in the committee in the fifth edition) (see pages iii-iv). In addition, 23 expert advisors have been enlisted to assist committee members, and 22 working collaborators have been engaged to share the workload (see pages iv-v).

(4) Principles of guideline development: In the second meeting of the Revision Committee, the revision steps for the fifth edition and other minor strategies were finalized, and members were assigned to chapters. As in the fourth edition, 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.

(5) Examination of CQs: CQs used in the fifth edition were determined based on the CQs in the fourth edition from the third meeting of the Revision Committee on. All the CQs about prognostic factors used in each chapter of the first to fourth editions were deleted in the fifth edition, because there were no prognostic factors with a high level of evidence in any chapter. In addition, after considering whether differences in surveillance or treatment selection according to performance status (PS) or age should be described in the Guidelines, the Revision Committee decided not to adopt CQs related to PS or age in

the fifth edition, because it tends to be reported that treatment is effective even in patients with poor PS or elderly patients (so-called selection bias or publication bias) and creation of CQs and recommendations related to PS or age based on previous reports may lead to the conclusion that treatment is recommended regardless of PS or age. Some of the 55 CQs in the fourth edition were removed or integrated and new CQs were introduced, eventually resulting in 52 CQs in the fifth edition: 41 CQs with no or minor revisions, 6 with relatively major revisions, and 5 newly introduced.

(6) Order of presentation: As in the fourth edition, 9 chapters in total were created: surveillance and diagnosis, treatment algorithm, prevention, surgery, percutaneous ablation, transcatheter arterial chemoembolization and transcatheter arterial embolization, drug therapy, radiation therapy, and post-treatment surveillance and prevention and treatment of recurrent HCC.

(7) Web-based guideline development system: Unlike in previous revisions, outsourcing was not used in the revision for the fifth edition, but the guideline development system created using the fiscal year 2019 Health and Labour Administration Promotion Research Project Grant (Research Project to Overcome Hepatitis and Other Diseases) “Research for the Development of Guidelines for the Treatment of Hepatocellular Carcinoma and Severe Cirrhosis” (Principal investigator: Kazuhiko Koike) was used. This system has the following advantages: 1) the selection of articles, which takes the longest time in guideline development, can be performed efficiently, 2) inconsistent selection of articles between reviewers can be resolved in real time, and 3) the office can distribute portable document format (PDF) files of articles in the second screening. Furthermore, the system allowed a reduction in outsourcing costs.

(8) Levels of evidence and strength of recommendations: As in the first to fourth editions, the fifth edition Guidelines adhere to the fundamental principles of EBM, but the fifth edition did not evaluate the levels of evidence in individual articles, and the Committee determined the level of the overall evidence for each CQ (Figure 1) [1)]. The evaluation criteria for levels of evidence are shown in Note [2)] (see page 20). Also, as in the fourth edition, the GRADE system was incorporated, in part, to bridge the gap between evidence and consensus, and the fifth edition adopted secret voting using the Delphi method. The methods (definition of voting rights, restrictions on the exercise of voting rights according to COI, and voting procedures) were drafted by the Revision Committee and reviewed and approved by the General Affairs Committee for the Guidelines (for details, see below). Discussions made during meetings to finalize the recommendations were integrated into the Explanation section of each CQ as much as possible.

First committee meeting: July 5, 2019 (Hotel Chinzanso Tokyo)
Second committee meeting: October 15, 2019 (Office of the Japan Surgical Society)
Third committee meeting: January 14, 2020 (Office of the Japan Surgical Society)
Fourth to 22nd committee meetings (Web meetings): June 5, July 30, September 1, October 15, December 10, 2020, January 7, 21, February 4, 17, March 3, 11, 18, 24, April 1, 8, 14, 22, 28, May 28, 2021

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) Several key words were selected, and then committee members and expert advisors developed search queries for individual 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 systematic literature search included articles appearing as electronic publications (Epub) before the end of January 2021. From February 2021 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 (as in the fourth edition).

(4) Under the support of the working collaborators, 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.

(5) 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.

(6) The chief and assistant researchers carefully read the articles that passed the second screening and created a table of abstracts (Figure 2) 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.

1. CQ
2. Draft recommendation
3. Views and preferences about the recommendation in the guideline development group (on the assumption of a series of views for each outcome considered)
4. Summary of evidence on the CQ (strength of the overall evidence on all severe outcomes)
A (strong)　B (moderate)　C (weak)　D (very weak)
5. Outcome measures to determine the strength of recommendation (the following items are comprehensively assessed.)

26A
Factors affecting the determination of the strength of recommendation
Strong overall evidence on all outcomes
The stronger the overall evidence, the higher the likelihood that a “strong” recommendation is warranted.
Conversely, the weaker the overall evidence, the higher the likelihood that a “weak” recommendation is warranted.
Certainty of the balance between benefits and harms (not including costs)
The greater the difference between desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted.
The lower the net benefits or the more sever the adverse events, the lower the certainty of the benefits and the higher the likelihood that a “weak” recommendation is warranted.

26B
Judgment
Yes
No

27
Explanation

Factors to consider when determining the strength of recommendation
Views and preferences of patients, certainty of (or differences in) the burden

Whether the net benefits are well worth the costs or resources
Select “Yes”, if clearly applicable; otherwise, select “No”, even if uncertain.
Figure 1 Evidence evaluation table
(Cited from the Minds Handbook for Clinical Practice Guideline Development 2017, edited by Noriko Kojimahara, et al.[1])

3. Formulating the recommendations
(1) The chief and assistant researchers created the proposed recommendation for a well-established CQ in the abstract table.
(2) The CQ to be reviewed and the proposed recommendation for the CQ were distributed before the meeting to solve problems by email discussion to some extent.
(3) The Committee Chair and Vice Chair determined which members must give up their voting rights due to COI in advance. The members who gave up their voting rights also participated in the discussion before voting.
(4) First, the chief and assistant researchers assigned to the CQ explained how they created the proposed recommendation.
(5) Furthermore, before voting, the committee achieved consensus on the summary of the overall evidence and outcome measures to determine the strength of recommendation in the evidence evaluation table.
(6) Based on the above consensus, the committee fully discussed how to consider the strength of recommendation before voting in accordance with the Delphi method. All members were informed of the basic policy of the Guidelines that “no recommendation” is one of the options but should be avoided as much as possible.
(7) The first vote (secret vote using the Google form, the Committee Chair and Vice Chair also participated in the vote) was taken. Each member selected one of the following levels of recommendation: strong recommendation for use, weak recommendation for use, weak recommendation against use, and strong recommendation against use. The level that received 70% of the valid votes (excluding the votes of the members who gave up their voting rights) was adopted as the opinion of the entire committee. If no level received 70% of the valid votes, the voting results (number and proportion of votes for each level) were presented, and the revoting process was initiated.
(8) After a full discussion of selected problems, the second vote (secret vote, the Committee Chair and Vice Chair also participated in the vote) was taken. If no level received 70% of the valid votes, the voting results were presented, and the revoting process was initiated.
(9) After a full discussion of selected problems again, the third vote (secret vote, the

Committee Chair and Vice Chair also participated in the vote) was taken. If no level received 70% of the valid votes once again, “no recommendation” was adopted.
(10) Only members approved by the General Affairs Committee for the Guidelines had voting rights, in principle, and members with COI voluntarily gave up their voting rights considering not only financial COI, but also academic COI (all authors of a reference cited in each CQ were defined as having academic COI). When a committee member was absent from a meeting, an expert advisor appointed by the member was allowed to exercise voting rights on behalf of the member. The expert advisor also submitted his/her COI disclosure form, but when the expert advisor exercised voting rights on behalf of the member, COI of the member were applied to the expert advisor.
(11) The abstract table (Figure 2) was presented to committee members and expert advisors at a meeting to assess the level of the overall evidence and the balance between benefits and harms (Figure 1). Then, the strength of recommendation was determined for the draft recommendation according to the above procedure after the wording was modified as required.
(12) Handling of treatment options in the treatment algorithm: Unlike in the previous editions, in the fifth edition, the method for determining treatment options in the treatment algorithm was specified in advance. The above 4 categories of strength of recommendation were used to evaluate the efficacy of each treatment in the relevant CQ. Regarding treatment options listed in the treatment algorithm, two options with the strongest and second strongest recommendations were selected, considering the evidence and other socioeconomic factors in each tumor/liver function condition. Two options with equally strongest or second strongest recommendation are connected by a slash.

28
CQ (No.): CQ name:
Chief researcher name: Assistant researcher name: Names of other collaborators:
Recommendation:

29
Adoption or non-adoption
Reason for non-adoption (simple explanation)
Authors
Year of publication
Digital object identifier (doi)
PubMed identifier (PMID)

Study design
Purpose
Subjects
Number of cases
Intervention
Control
Outcome
Conclusion
Comments
Publication information, if no bibliographic information is available

30
Adoption
Non-adoption

Figure 2 Abstract Table

4. Preparing the Guidelines

(1) The chief and assistant researchers recorded discussions made in the meetings in minutes and incorporated them 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. The voting results at the meeting for finalizing recommendations are included at the end of the section.

5. Holding a public hearing

A public hearing session (Session Chairs: Katsutoshi Tokushige, Professor, Institute of Gastroenterology, Tokyo Women's Medical University; Naoki Hiramatsu, Hospital Vice Director and Chair of the Department of Gastroenterology, Osaka Rosai Hospital; Hitoshi Yoshiji, Professor, Department of Gastroenterology, Nara Medical University; Kiyoshi Hasegawa [Chair of the Revision Committee], Professor, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo) was held at the 57th Annual Meeting of the Japan Society of Hepatology on June 18, 2021.

6. Inviting public comment

Between June 7 and July 5, 2021, 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 v).

Note: Definitions of evidence levels [2)]

Evidence on survival/recurrence/oncogenesis

Evidence level started with B for a randomized controlled trial (RCT), C for a non-randomized study (NRS), and D for an uncontrolled cohort study.

Evidence level was upgraded to A for a multicenter RCT with sufficient sample size, represented by a phase III clinical trial.

Evidence level was upgraded to A for multiple high-quality RCTs with a sufficient total sample size and consistent results.

Evidence level was upgraded to B for multiple NRSs with appropriate adjustment for confounders, a sufficient total sample size and consistent results.

Evidence level was upgraded by one for an NRS with appropriate adjustment for confounders and a sufficient sample size showing high efficacy.

Evidence level was downgraded by one for indirect outcomes (e.g., recurrence is the only

available outcome) when survival desirable.
A: Examples of strong evidence
1. Results of a phase III RCT of sufficient scale and quality
2. Multiple RCTs with a sufficient total sample size and consistent results, but not meeting the criterion 1 (phase II studies or studies without calculation of the number of cases)
B: Examples of moderate evidence
1. A meta-analysis of RCTs showing significant, but poorly consistent, efficacy
2. Regarding indirect outcomes, a meta-analysis of RCTs showing consistent significant efficacy
3. Multiple NRSs with appropriate adjustment for bias and consistent results
C: Examples of weak evidence
1. Only one non-high-quality RCT showing significant results
2. Regarding indirect outcomes, a meta-analysis of RCTs showing significant, but poorly consistent, results
3. Multiple NRSs without appropriate adjustment for bias and with consistent results
D: An example of very weak evidence
Evidence not meeting A-C

Evidence on diagnosis
Evidence level started with A for the sensitivity and specificity of the index test reported based on valid reference standards in appropriate patients.
Evidence level was downgraded by one, if the reference test was not applied to all patients without exception.
Evidence level was downgraded by one, if the reference standards were not ideal, but alternative to other indicators.
Evidence level was downgraded by one, if the target population was different from the population to whom the guideline is meant to apply in the CQ.
Evidence level was downgraded by one, if true positive results had little impact on important outcomes for patients (e.g., impact of the diagnosis of early cancer on survival).
A: Examples of strong evidence
1. The index test and reference test performed in all appropriately selected subjects, with reported sensitivity and specificity
2. Two or more studies meeting the above criterion, with consistent results
B: Examples of moderate evidence
1. The reference test not performed in all subjects, unlike in A
2. The reference test performed only in subjects positive for the index test, unlike in A

3. Inconsistent results among studies
C: Examples of weak evidence
1. The patient population different from the population to whom the guideline is meant to apply in the CQ, unlike in B
2. Less impact of true positive results on outcomes compared with B
3. Studies reporting only sensitivity
D: An example of very weak evidence
Evidence not meeting A-C

Evidence on prognosis (baseline risk)
Evidence level started with A for a cohort study longitudinally assessing target outcomes (oncogenesis, death).
Evidence level was downgraded by one, if the study had a major limitation (such as inappropriate patient selection, insufficient follow-up, inconsistency between studies, indirect outcomes, inaccuracy due to sample size, or publication bias).
A: Examples of strong evidence.
1. A longitudinal study with a sufficient number of events for the target outcome in which a high proportion of patients were followed up and the patient selection criteria were consistent with the assumed scenario
2. A meta-analysis of longitudinal studies with consistent results and without significant bias
B: Examples of moderate evidence
1. A longitudinal study with a sufficient number of events but with limitations such as bias, indirectness and inaccuracy
2. A meta-analysis of multiple studies on the target outcome, with one of the following limitations: study design bias, inconsistency, indirectness, inaccuracy, and publication bias
C: Examples of weak evidence
1. A longitudinal study with an insufficient number of events
2. A longitudinal study with a sufficient number of events but with at least two limitations
3. A meta-analysis of multiple studies, with two of the following limitations: study design bias, inconsistency, indirectness, inaccuracy, and publication bias
D: An example of very weak evidence
Evidence not meeting A-C

References

1) Kojimahara N, Nakayama T, Morizane T, et al., edited. Minds Handbook for Clinical Practice Guideline Development 2017. Japan Council for Quality Health Care 2017 (Japanese)
2) Aihara M. Grade System for Clinical Practice Guideline 3rd Edition. Chugai-Igakusha 2018 (Japanese)

Chapter 1
Surveillance and Diagnosis

● Introduction

The efficacy of surveillance is demonstrated by increased likelihood of early detection and curative therapy, thereby improving prognosis. Because it is relatively easy to predict patients at high risk of HCC, surveillance has been widely performed for high-risk patients in Japan, especially those with viral hepatitis accompanied by cirrhosis. However, patients at high risk of liver cancer are also at high risk of recurrent cancer after curative therapy, suggesting that early detection and early treatment do not necessarily lead to complete cure.

Indeed, even today, there is insufficient evidence that surveillance with ultrasonography (US) alone or a combination of US and tumor markers improves the prognosis of HCC patients, and it is unlikely from a mainly ethical standpoint that randomized controlled trials (RCTs) will be conducted in the future.

US and tumor marker testing are minimally invasive procedures. However, the surveillance may have harms, such as screening costs, the loss of opportunity due to taking a day-off from work due to a hospital visit, costs of contrast enhanced CT and tumor biopsy in the case of a false-positive result, and psychological burden. The benefits of the surveillance need to exceed these harms.

The expected value of surveillance benefits increases as the probability of carcinogenesis increases and as the probability of being eligible for curative treatment increases. Therefore, the target population of surveillance needs to be selected carefully.

In the 2021 version (fifth edition), the target population and method of surveillance were reviewed as a continuation of the 2017 version (fourth edition). In 4 years since the publication of the 4th version, direct antiviral drugs for hepatitis C virus have become widespread, and many hepatitis C patients have achieved a sustained virologic response (SVR). On the other hand, over the past 30 years, non-HBV and non-HCV related hepatocellular carcinoma (HCC), associated with the presence of obesity, has increased, and its prevalence is about to reach 50% of HCC patients. The approach to the surveillance is expected to change as the high-risk group of HCC changes, but it is necessary to wait for the accumulation of evidence in the future.

Tumor markers are useful indicators of the effects of the surveillance, diagnosis, and treatment. As diagnostic imaging technology continues to advance, the role that tumor

markers play in the diagnosis of liver cancer continues to reduce.
When abdominal US reveals no obvious tumor, tumor marker testing is used to decide whether to repeat surveillance using a more sensitive imaging modality such as dynamic computed tomography (CT). Tumor markers used in such cases should have large positive likelihood ratios, because positive ratios, which are calculated using the equation Sensitivity / (1 – Specificity), suggest that post-test probability is high. With the achievement of SVR for hepatitis C and the use of nucleos(t)ide analogues for hepatitis B as were mentioned above, the baseline level of alpha-fetoprotein (AFP) has decreased. Therefore, establishing a new AFP cut-off level is now needed. In this version, this issue is included as a new CQ.

Absolute tumor marker levels are thought to reflect the total number of tumors in the liver or the entire body. Therefore, pretreatment measurement of tumor marker levels enables tumor reduction after treatment to be objectively estimated. In summary, we investigated tumor markers from the perspective of surveillance, diagnosis, and treatment effects.
In principle, definitive diagnosis is made based on histopathological findings. However, for patients scheduled to undergo percutaneous ablation and embolization, a definitive diagnosis is made based on imaging findings. Evaluation using dynamic CT or dynamic MRI is required. However, Gd-EOB-DTPA-enhanced MRI, which is useful for the diagnosis of early-stage hypovascular HCCs and the diagnosis of tumor presence, is playing an increasing role. Also, we reviewed alternative imaging tests recommended when regular imaging is contraindicated (e.g., in patients with decreased kidney or liver function) and reviewed diagnostic imaging tests recommended for extrahepatic metastasis, as a continuation of the fourth edition.

Explanation of the surveillance and diagnostic algorithm for HCC
1. Target population of surveillance
The decision to start surveillance begins with risk assessment. 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. The surveillance interval is determined based on the involvement of other factors such as age, sex, diabetes, body mass index, aspartate transaminase (AST), alanine transaminase (ALT), platelet count, daily alcohol consumption, and hepatitis B virus (HBV) DNA levels (in patients with hepatitis B). Among high-risk patients, those with cirrhosis type B and C are considered an extremely high-risk group. Although the incidence of HCC decreases in patients with

chronic hepatitis B receiving nucleos(t)ide analogue treatment and in patients with chronic hepatitis C who achieved SVR after anti-hepatitis C virus (HCV) therapy, these patients should remain under surveillance because the risk of developing liver cancer is still relatively high.

2. Surveillance method

The core of surveillance is screening with abdominal US as the primary measure and tumor marker testing, which is repeated every 3-6 months. This regular screening method may be combined with dynamic CT, extracellular contrast-enhanced dynamic MRI or Gd-EOB-DTPA-enhanced MRI in extremely high-risk patients such as those with cirrhosis.

Theoretically, as the surveillance interval shortens, the chance of detecting tumors in the early stage increases, but the cost of surveillance also increases. It is therefore important to investigate whether exhaustive surveillance makes a clinically significant difference in tumor size and whether the difference is worth the increased cost of surveillance. Furthermore, the smallest tumor size detectable on surveillance depends on various factors such as the severity of cirrhosis, obesity, and background liver disease as well as the accuracy of the screening device. Therefore, the current version of the Guidelines recommends screening with US every 6 months in high-risk patients and every 3-4 months in extremely high-risk patients. Concomitant use of dynamic CT or dynamic MRI (including Gd-EOB-DTPA-enhanced MRI) should be considered for patients with pathological conditions that make the detection of small HCC by US difficult, such as liver shrinkage, severe obesity, and coarse liver parenchyma.

For tumor marker testing, screening with AFP, PIVKA-II, and AFP lectin fraction (AFP-L3 fraction) is recommended every 6 months in high-risk patients and every 3-4 months in extremely high-risk patients. However, it should be noted that, as of 2021, the National Health Insurance system covers tumor marker testing with AFP and PIVKA-II every month in high-risk and extremely high-risk patients, whereas it covers testing with AFP-L3 fraction only when there is a high index of suspicion for HCC.

3. US findings of nodular lesions

When US findings suggest new nodular lesions, dynamic CT, dynamic MRI using extracellular Gd-based contrast agents, or Gd-EOB-DTPA-enhanced MRI is done for differential diagnosis. Contrast-enhanced US is recommended in patients for whom contrast agents for CT/MRI are contraindicated. In some cases, surveillance CT/MRI is performed to detect new nodules because of the difficulty with whole liver scanning by

US.
Even when no tumor is detected on US, it is important to consider using dynamic CT/MRI in the following cases: persistent elevation of AFP, ≥ 200 ng/mL of AFP, ≥ 40 mAU/mL of PIVKA-II, or ≥ 15% increase in AFP-L3 fraction.

4. Assessment of hemodynamics
In contrast-enhanced imaging, typical HCC is characterized by hypervascular changes, demonstrating increased arterial blood flow in HCC compared with the surrounding liver parenchyma. Hypervascular changes are observed in the arterial (or early) phase of dynamic CT and dynamic MRI (including Gd-EOB-DTPA-enhanced MRI).

(1) Early phase contrast enhancement
1) In dynamic CT or dynamic MRI using extracellular Gd-based contrast agents
Treatment strategies for HCC should be used for lesions that are visualized as high-attenuation areas (hyperdense or hyperintense signals) in the arterial phase of dynamic CT or dynamic MRI using extracellular Gd-based contrast agents and as low-attenuation areas (hypodense or hypointense signals; i.e., washout) in the portal/equilibrium phase of dynamic MRI compared with the surrounding liver parenchyma.

When performing contrast-enhanced US with perfluorobutane microbubbles in patients for whom dynamic CT/MRI is contraindicated, contrast defects in the post-vascular (Kupffer) phase may be observed as washouts. However, it is sometimes difficult to differentiate HCC from high-flow cavernous hemangioma because the latter shows contrast enhancement in the early vascular phase and appears as a contrast defect in the Kupffer phase, necessitating exclusion based on other images.

Lesions < 1 cm not visualized as washouts in the portal/equilibrium phase of dynamic CT or dynamic MRI using extracellular Gd-based contrast agents will require screening with US every 3 months, provided that the lesions are detectable on US. Dynamic CT/MRI is resumed on observing tumor enlargement or tumor marker elevation.
Lesions not visualized on US may be followed up by performing dynamic CT/MRI every 3 months. It is not necessary to follow up lesions definitively diagnosed as benign tumors on diagnostic imaging.
Nodules with a tumor diameter ≥ 1 cm not visualized as washouts in the portal/equilibrium phase of dynamic CT should be imaged with Gd-EOB-DTPA-

enhanced MRI. An appropriate treatment strategy should be selected for nodules definitively diagnosed as HCC. When Gd-EOB-DTPA-enhanced MRI and other imaging modalities do not clearly show whether nodules are benign or malignant, it may be necessary to perform contrast-enhanced US or liver biopsy.

2) In Gd-EOB-DTPA-enhanced MRI
Treatment strategies for HCC should be used for lesions visualized as hypointense signals (washout) in the portal phase, compared with the surrounding liver parenchyma. Lesions < 1 cm in tumor diameter not visualized as washouts in the portal phase will require screening with US every 3 months, provided that the lesions are detectable on US. Gd-EOB-DTPA-enhanced MRI is resumed on observing tumor enlargement or tumor marker elevation. Lesions not visualized on US may be followed up by performing Gd-EOB-DTPA-enhanced MRI every 3 months. For lesions ≥ 1 cm in tumor diameter visualized as hypointense signals in the transitional or hepatobiliary phase, since cavernous hemangioma is visualized as hypointense signals in the hepatobiliary phase, other MR images should be examined before excluding the possibility. If the possibility of hemangioma is excluded, treatment strategies for HCC should be used. If the possibility of hemangioma cannot be excluded, evaluation using dynamic CT or dynamic MRI using extracellular Gd-based contrast agents is required. If neither washouts in the portal phase nor hypointense signals in the transitional or hepatobiliary phase is observed, return to the regular surveillance.

(2) Absence of early phase contrast enhancement
1) In dynamic CT or dynamic MRI using extracellular Gd-based contrast agents
Lesions < 1.5 cm not visualized as high-attenuation areas (hyperdense or hyperintense signals) in the arterial phase of dynamic CT or dynamic MRI using extracellular Gd-based contrast agents, respectively, will require screening with US every 3 months, provided that the lesions are detectable on US. Dynamic CT/MRI is resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US may be followed up with dynamic CT/MRI. It is not necessary to follow up lesions that are definitively diagnosed as benign tumors on diagnostic imaging.
Lesions ≥ 1.5 cm not visualized as high-attenuation areas (hyperdense or hyperintense signals) in the arterial phase of dynamic CT or dynamic MRI using extracellular Gd-based contrast agents, respectively, will require evaluation using Gd-EOB-DTPA-enhanced MRI.

2) In Gd-EOB-DTPA-enhanced MRI
Lesions < 1.5 cm not visualized as hyperintense signals in the arterial phase of Gd-EOB-DTPA-enhanced MRI will require screening with US every 3 months, provided that the lesions are detectable on US. Gd-EOB-DTPA-enhanced MRI is resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US may be followed up with Gd-EOB-DTPA-enhanced MRI. It is not necessary to follow up lesions that are definitively diagnosed as benign tumors on diagnostic imaging.
For lesions ≥ 1.5 cm visualized as hypointense signals in the hepatobiliary phase, evaluation using contrast-enhanced US, liver biopsy, etc. should be considered. An appropriate treatment strategy should be selected for lesions definitively diagnosed as HCC. Lesions not visualized as hypointense signals in the hepatobiliary phase will require screening with US every 3 months, provided that the lesions are detectable on US. Gd-EOB-DTPA-enhanced MRI is resumed when tumor enlargement or tumor marker elevation is observed. Lesions not visualized on US may be followed up with Gd-EOB-DTPA-enhanced MRI.

(3) Findings suggestive of other malignant tumors
Further examination is required of lesions most likely to be intrahepatic cholangiocarcinoma or metastatic liver cancer based on the patterns of contrast enhancement during the arterial and portal/equilibrium phase.

31
Surveillance Algorithm - Diagnostic Algorithm
Extremely High-Risk Group (Cirrhosis Type B and C)
Ultrasound every 3-4 months + Tumor marker every 3-4 months
Dynamic CT/MRI every 6-12 months (optional)
High-risk group (chronic hepatitis B/C, nonviral cirrhosis)
Ultrasound every 6 months + Tumor marker every 6 months
Algorithm 1
Nodule detected by ultrasound

32
Dynamic CT/MRI using extracellular Gd-based contrast agents[*1]
Gd-EOB-DTPA-enhanced MRI → Algorithm 2

33

Early-phase contrast enhancement
Delayed phase washout

34
No delayed phase washout
Tumor diameter ≥1 cm?

35
No early-phase contrast enhancement
Tumor diameter ≥ 1.5 cm?

36
No lesions
Follow-up every 3 months[*2]
No increase in size / tumor disappearance
Regular surveillance

37
Gd-EOB-DTPA-enhanced MRI
Algorithm 2.

38
Contrast-enhanced US
Liver biopsy
Definitive diagnosis of hepatocellular carcinoma

39
Hepatocellular carcinoma

*1: Dynamic CT/MRI are used for some patients if the nodule(s) are not visualized on 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.

40
Algorithm 2
Nodule detected by ultrasound
Gd-EOB-DTPA-enhanced MRI[*1]

41
Early-phase contrast enhancement
No early-phase contrast enhancement
No lesions

42
Portal phase washout
Hypointense signals in the transitional or hepatobiliary phase
None of the left

43
Tumor diameter ≥ 1 cm?
Hemangiomas can be excluded.

44
Dynamic CT or dynamic MRI using extracellular Gd-based contrast agents
Algorithm 1

Hepatocellular carcinoma

45
Tumor diameter ≥ 1.5cm
with
Hypointense signals in the hepatobiliary phase?

46
Optional examinations
Contrast-enhanced US
Liver biopsy

Definitive diagnosis of hepatocellular carcinoma

47
Regular surveillance
No increase in size/ tumor disappearance
Follow-up every 3 months[*2]

CQ1
What methods are used in surveillance?

Recommendations
1. Patients with chronic hepatitis C or B liver disease or nonviral cirrhosis should undergo regular HCC surveillance. (Strong recommendation, Evidence Level B)
2. The regular HCC surveillance should comprise abdominal US as the primary measure and tumor marker testing every 3-6 months. Additionally, MRI using Gd-EOB-DTPA, or dynamic CT, may be performed in extremely high-risk patients such as those with cirrhosis. (Strong recommendation, Evidence Level B)

■ Background
HCC exhibits substantial regional clustering mostly due to the involvement of hepatitis B virus (HBV) and hepatitis C virus (HCV) and the influence of lifestyle habits. In Japan, approximately 70% of patients with HCC have chronic hepatitis B or C liver disease[1]. Aside from viral hepatitis, risk factors for HCC include cirrhosis, male sex, older age, alcohol consumption, smoking, obesity, fatty liver, and diabetes. Here, we reviewed the targets and methods of surveillance for HCC.

■ Scientific Statement
This CQ was established as a continuation of CQ2 in the fourth edition (2017 version). In the current revision, a literature search conducted for articles published in the period from July 1, 2016 and January 31, 2020 (i.e., after the literature search period for the fourth edition) extracted 849 articles. This was narrowed down to 136 articles in the first screening and to 7 articles in the second screening based on the following inclusion criteria: prospective cohort studies only, except for cross-sectional studies, performing a multivariate Cox analysis for risk factors or a meta-analysis related to this CQ. A total of 16 articles, including the 9 articles from the fourth edition, are thus cited for CQ1.

Singal et al. investigated the most appropriate modality for HCC surveillance in 446 patients with cirrhosis. Among 41 patients diagnosed with HCC by abdominal US alone, AFP testing alone, or a combination of abdominal US and AFP, sensitivities were 44%, 66%, and 90% and specificity was 92%, 91%, and 83%, respectively, indicating that surveillance with abdominal US and AFP testing had better sensitivity[2]. Likewise, Chang et al. reported that surveillance with abdominal US and AFP testing improved sensitivity (99.2%) for detecting liver cancer among 1,597 patients with cirrhosis, compared with surveillance with abdominal US or AFP testing alone[3]. Also, specificity increased from 68.3% to 71.5% when the cutoff AFP level was increased by multiplying the nadir from the previous year by 2-fold or more. Regarding detectability in the early disease stage, Tzartzeva et al. conducted meta-analysis of 32 studies on liver cirrhosis patients. In 13,367 patients analyzed, the detection sensitivity of HCC meeting the Milan criteria by abdominal US alone was 45%, but increased to 63% when it was combined with AFP testing[4].

Regarding imaging modalities, Kim et al. compared the detectability in a surveillance where abdominal US and Gd-EOB-DTPA MRI were performed at the same time in 407 patients with cirrhosis. Of these, 43 patients developed cancer. The sensitivity was 86.0% with MRI and 27.9% with abdominal US, and the false-positive rates were 3.0 and 5.0%, respectively, being lower with MRI[5]. In an RCT of 163 patients with compensated cirrhosis who had a 6.6% incidence of cancer per year, Pocha et al. compared the utility of abdominal US every 6 months and contrast-enhanced CT every 12 months and found that the sensitivity and specificity of abdominal US were 71.4% and 97.5%, respectively, while those of contrast-enhanced CT were 66.7% and 94.4%, respectively, indicating superior sensitivity of abdominal US every 6 months. Abdominal US is also less costly[6].

Two RCTs have investigated the difference in tumor diameter (at the time of diagnosis) attributable to the difference in the regular surveillance interval. The first RCT involved US surveillance every 3 or 6 months in patients with cirrhosis, but no significant difference was observed in overall survival rate or in the detection rate of HCC $\leq$ 30 mm, which was the primary endpoint of the study[7]. In the second RCT, the detection rate of early-stage HCC ($\leq$ 2 cm) was higher among patients who underwent surveillance every 4 months than whose who underwent surveillance every 12 months, with no significant difference in 4-year survival rates[8]. Han et al. compared 400 patients with HCC based on the surveillance interval at the time of diagnosis and reported significantly smaller tumor size and significantly improved prognosis (after adjusting for lead-time bias) when the interval was < 6 months[9].

■ Explanation

The efficacy of surveillance is demonstrated by studies that compare all deaths after randomly allocating participants to 2 groups with and without surveillance.

However, only 2 previous studies have randomly allocated clusters of patients, one in 2003 and another in 2004[10,11], and none more recently. There have been many studies comparing all deaths exclusively only among cancer patients after the diagnosis of cancer, but these studies have problems associated with lead time. Lead time is estimated based on tumor doubling time in the natural course of a particular cancer and on the difference in tumor diameter between cancers detected through surveillance and those detected based on symptoms, but depending on the parameters used, estimated values may vary substantially[12,13]. Regular surveillance for HCC contributes to early detection and curative treatment of HCC[14], likely improving prognosis[15]. Therefore, it has been decided to strongly recommend the surveillance from this fifth edition onwards, and the QC1 “Is surveillance recommended?” in the fourth edition was combined with this CQ.

Theoretically, the addition of AFP testing increases the sensitivity of HCC surveillance because it increases the number of patients who subsequently undergo further examination with dynamic CT/MRI. However, due to a concurrent increase in false-positive rates, the cost-effectiveness of this combined surveillance decreases[16].

Similarly, shorter interval surveillance theoretically detects smaller tumors, but it costs more. Therefore, the question is whether exhaustive surveillance makes a clinically significant difference in terms of tumor size and whether the difference cancels out the increased surveillance costs. In addition, the smallest tumor size detectable by surveillance depends on various factors including the severity of cirrhosis, obesity, and background liver disease as well as the performance of the modality used. Also, because surveillance costs vary considerably among countries, it is impractical to apply data from cost-benefit analyses carried out overseas to the situation in Japan.

As a result, it was decided to continue with the existing recommendation. However, when the typical doubling time of HCC is considered, there is insufficient rationale for the hypothesis that the most effective surveillance interval is < 3 months. Also, because Gd-EOB-DTPA-enhanced MRI examination costs 8-9 times more than abdominal US surveillance in Japan, it seems unlikely that the additional medical cost is worth the extended survival expected.

Therefore, we decided to maintain the existing HCC surveillance method, which is well established and widely used across Japan.

Voting results

◎ Regarding the statement of recommendation 1 “Patients with chronic hepatitis C or B liver disease or nonviral cirrhosis should undergo regular HCC surveillance”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (22 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

◎ Regarding the statement of recommendation 2 “The regular HCC surveillance should comprise abdominal US as the primary measure and tumor marker testing every 3-6 months. Additionally, MRI using Gd-EOB-DTPA, or dynamic CT, may be performed in extremely high-risk patients such as those with cirrhosis”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (22 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

■ References

CQ2.

What tumor markers are useful for diagnosing HCC?

Recommendations

1. It is recommended to measure AFP, PIVKA-II, and AFP-L3 fraction as useful tumor markers for auxiliary diagnosis of HCC. (Strong recommendation, evidence level A)
2. It is recommended to measure 2 or more types of tumor markers when diagnosing small HCCs. (Strong recommendation, Evidence Level A)

■ Background

In Japan, measurement of the following 3 tumor markers for HCC is covered by the National Health Insurance system: AFP, PIVKA-II, and AFP-L3 fraction. For diagnostic purposes, tumor marker measurements are used to obtain a definitive diagnosis or as the trigger for the next process during surveillance. Because of current developments in imaging diagnostics, tumor marker testing for HCC is not a requirement for definitive diagnosis. On the other hand, if a certain threshold level is exceeded during surveillance, it is important to determine how the post-test probability changes; therefore, it is recommended that the positive likelihood ratio [= Sensitivity/ (1-Specificity)] be used as an indicator. Here, we reviewed tumor markers that are useful for auxiliary diagnosis of HCC.

■ Scientific Statement

This CQ was established by combining CQ3 and CQ4 in the fourth edition. A literature search conducted with the search query used for CQ3 in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 341 articles. This was narrowed down to 97 articles in the first screening and to 9 articles in the second screening based on the following inclusion criteria: studies that reported both sensitivity and specificity, stratified or limited by tumor size, and have defined benchmark criteria. A total of 20 articles, including the 11 articles from the fourth edition, are thus cited for CQ2.

A systematic review was conducted using 17 studies that examined HCC lesions ≤ 5 cm in terms of sensitivity, specificity, the diagnostic odds ratio, and the positive likelihood ratio[1]. At a cut-off level of 20 ng/mL, the AFP sensitivity and specificity were 49-71% and 49-86%, respectively, while at a cut-off level of 200 ng/mL, they were 8-32% and 76-100%, respectively[1]. The integrated diagnostic odds ratios were 4.06 and 6.99 at cut-off levels of 20 and 200 ng/mL, respectively, and the positive likelihood ratios were 2.45 and 5.85, respectively. At a cut-off level of 40 mAU/mL, the PIVKA-II sensitivity and specificity were 15-54% and 95-99%, respectively, while at a cut-off level of 100 mAU/mL, they were 7-56% and 72-100%, respectively. The integrated diagnostic odds ratios at cut-off levels of 40 and 100 mAU/mL were 21.31 and 6.70, respectively, and the positive likelihood ratios were 12.60 and 4.91, respectively.

The AFP-L3 fraction sensitivity and specificity at a cut-off level of 10% were 22-33% and 93-99%, respectively, while at a cut-off level of 15%, they were 21-49% and 94-100%, respectively. The integrated diagnostic odds ratios at cut-off levels of 10 and

15% were 6.43 and 10.50, respectively, and the positive likelihood ratios were 4.89 and 13.10, respectively. When two tumor markers were used in combination, the diagnostic OR was 6.29-59.81, which was higher than the value obtained from using each tumor marker alone.

In a systematic review of 5 studies that investigated the diagnostic accuracy of AFP in patients with hepatitis C, sensitivity was 41-65%, specificity 80-94%, positive likelihood ratio 3.1-6.8, and negative likelihood ratio 0.4-0.6 at a cut-off level of 20 ng/mL[2].
In a more recent systematic review of 49 studies, the sensitivity and specificity of AFP were 59% (95% confidence interval [CI]: 54-63%) and 86% (95% CI: 82-89%) and those of PIVKA-II were 63% (95% CI: 58-67%) and 91% (95% CI: 88-93%), respectively. The area under the receiver operating characteristic (AUROC) curve was 0.83 for AFP and 0.77 for PIVKA-II[3]. However, when the number and size of tumors were specified to ≤ 3 tumors and ≤ 3 cm, the sensitivity and specificity of AFP were 48% (95% CI: 39-57%) and 89% (95% CI: 79-95%) and those of PIVKA-II were 45% (95% CI: 35-57%) and 95% (95% CI: 91-97%), respectively. The AUROC was 0.68 for AFP, 0.84 for PIVKA-II and 0.83 for their combination, showing that diagnostic accuracy was unchanged by using markers in combination.

In a cohort study of 734 patients with chronic hepatitis or cirrhosis, HCC developed in 29 patients during the mean observation period of 374.5 days[4]. In the analysis with a cut-off level of AFP set at 20 ng/mL, sensitivity and specificity were 61.2% and 78.3%, respectively. In the analysis with a cut-off level of PIVKA-II set at 60 mAU/mL, sensitivity and specificity were 41.4% and 90.9%, respectively. When analyzed by combining an AFP cut-off level of 40 ng/mL and a PIVKA-II cut-off level of 80 mAU/mL, sensitivity and specificity were 65.5% and 85.5%, respectively.
In a case-control study of 1,377 HCC patients and 355 patients with chronic hepatitis or cirrhosis, when tumors < 3 cm were analyzed at AFP cut-off levels of 20, 100 and 200 ng/mL, sensitivities were 55%, 23% and 14%, respectively, and specificities were 94%, 99% and 100%, respectively. In the same manner, analyzed at PIVKA-II cut-off levels of 40 and 100 mAU/mL, sensitivities were 41% and 21%, respectively, and specificities were 97% and 100%, respectively. When AFP and PIVKA-II cut-off levels (20 ng/mL and 40 mAU/mL, respectively) were used in combination, sensitivity and specificity were 82% and 91%, respectively[5]. The AUROC was 0.887 for AFP and 0.812 for PIVKA-II. I. Stratification by tumor diameter revealed that the diagnostic accuracy of

AFP was significantly higher for tumors < 3 cm, whereas the diagnostic accuracy of PIVKA-II was significantly higher for tumors > 5 cm. In a cohort study of 372 patients with HCV-related cirrhosis, liver cancer developed in 34 patients during the 2-year follow-up period. At AFP, AFP-L3 fraction and PIVKA-II cut-off levels of 20 ng/mL, 10% and 7.5 ng/mL, respectively, sensitivities were 61%, 36.5% and 39.2%, respectively, and specificities were 71.1%, 91.6% and 89.6%, respectively.

When the cut-off levels of the 3 markers were used in combination (AFP:20 ng/mL, AFP-L3 fraction: 10%, and PIVKA-II: 7.5 ng/mL), sensitivity increased up to 77%[6]. In a study comparing patients with chronic hepatitis B with HCC (n = 106) and without HCC (n = 100), the sensitivities of AFP (at a cut-off level of 20 ng/mL) and PIVKA-II (at a cut-off level of 40 mAU/mL) were 57.5% and 51.9%, respectively, and their specificities were 88.0% and 97.0%, respectively[7]. In a surveillance study of 2,830 patients with chronic liver disease, which compared 104 liver cancer patients with 104 controls selected based on the propensity score matching method, when the cut-off levels of the highly sensitive AFP-L3 fraction were set at 7%, 10% and 15%, sensitivities were 39.4%, 16.3% and 11.5%, respectively, and specificities were 77.0%, 96% and 100%, respectively. When the cut-off levels of AFP were set at 20 and 200 ng/mL, sensitivities were 41.4% and 12.5%, respectively, and specificities were 90.4% and 99.0%, respectively. When the cut-off level of PIVKA-II was set at 40 mAU/mL, sensitivity was 34.6%, and specificity was 94.0%[8]. Of 689 patients in 4 prospective studies previously conducted, including 3 RCTs, 42 patients who developed liver cancer were compared with 168 matched control patients. When the cut-off levels of AFP (5 ng/mL) and AFP-L3 (4%) were combined, sensitivity was 79% and specificity was 87%. Sensitivities with abdominal US alone, abdominal US combined with AFP, and abdominal US combined with AFP and AFP-L3 fraction were 48.6%, 88.6% and 94.3%. Thus, sensitivity increased by combining abdominal US with AFP and AFP-L3 fraction[9].

■ Explanation

In Bayes' theorem, post-test odds are calculated by multiplying pre-test odds by a likelihood ratio. Because the incidence of HCC is only 10% per year in extremely high-risk patients, the pretest probability of detecting HCC in biannual surveillance is approximately 5% and the pre-test odds are one-nineteenth. When abdominal US findings are negative, post-test odds decrease to below one-fortieth. So, to bring the probability of having HCC ≥ 10% when the results of tumor marker testing are positive,

the positive likelihood ratio should be at least 5. This means a sensitivity of ≥ 25% at a specificity of 95% and a sensitivity of ≥ 50% at a specificity of 90%, suggesting that the number of unnecessary confirmatory tests increases and the cost-benefit ratio decreases unless cut-off levels and positive likelihood ratios are set high. Because the specificity of AFP is low in patients with chronic active hepatitis, it is necessary to set the cut-off levels at ≥ 100 ng/mL. Compared with AFP, AFP-L3 fraction and PIVKA-II have excellent positive likelihood ratios because of high specificity, even though their sensitivity for small HCC is inferior to that of AFP. Recent studies have reported that the specificity of AFP increases in patients with chronic hepatitis B who are receiving nucleos(t)ide analogue treatment and in patients with chronic hepatitis C who have achieved SVR after antiviral therapy[10-12]. Further study is needed to establish new cut-off levels in these patient groups.

In the surveillance of small HCCs, the use of two types of tumor markers improves sensitivity while minimizing loss of specificity. When measuring 2 or more tumor markers in combination, the result of the tumor marker testing is normally determined to be positive when the level of one of the markers surpasses the cut-off level. Therefore, as the number of tumor markers used in one test increases, sensitivity increases, while specificity inevitably declines. Because the positive likelihood ratio is defined by the equation Sensitivity / (1 - Specificity), specificity loss has a greater impact, which increases the use of unnecessary confirmatory tests in the case of surveillance or leads to only a negligible increase in post-test probability, even when positive, in the case of definitive diagnosis. To avoid loss of specificity, the cut-off levels of tumor markers used in combination should be set higher than the cut-off levels when used alone. It is especially important to set the cut-off level of AFP above 20 ng/mL because of low specificity. It is also desirable to combine tumor markers that are complementary to each other. From this standpoint, the combination of AFP and PIVKA-II is ideal because of their low association, which suggests the complementary roles of AFP and PIVKA-II for HCC diagnosis.

Two of the newly adopted articles reported meta-analyses. One of them has shown that a higher sensitivity is achieved by combining AFP to abdominal US rather than the use of abdominal US alone[13]. The other has shown that PIVKA-II is superior to AFP in terms of diagnostic accuracy, regardless of tumor size, race and etiology[14].

In more than 20 years since AFP-L3 fraction was approved as a tumor marker for HCC in Japan (and was the last approved), many new tumor markers have been reported about the evaluation of various scores, including glypican-3, Golgi protein 73, osteopontin, microRNAs[15], centromere protein F (CENP-F)[16], cytoskeleton-associated

protein 4 (CKAP4)[17], MFG-E8[18], HCC-ART score[19] and γ-GT/AST ratio[20]. However, none of these seem to be clinical applicable at this point. As described above, the use of the three types of tumor markers is currently approved in the diagnosis of HCC in Japan and covered by the National Health Insurance system, with their roles being widely accepted.

Voting results

◎ Regarding the statement of recommendation 1 “It is recommended to measure AFP, PIVKA-II, and AFP-L3 fraction as useful tumor markers for auxiliary diagnosis of HCC”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (22 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

◎ Regarding the statement of recommendation 2 “It is recommended to measure 2 or more types of tumor markers when diagnosing small HCCs”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (21 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 21 members (abstention because of COI: 1 member)

■ References

CQ3.
Are tumor markers effective indicators of treatment response in patients with HCC?

Recommendation

Post-treatment tumor marker levels are effective indicators of clinical response in patients with high tumor marker levels prior to treatment. (Strong recommendation, Evidence Level B)

■ Background

While the completeness of tumor resection can be evaluated by pathological examination after liver transplantation and hepatectomy, imaging is used to assess clinical response after percutaneous ablation, transcatheter arterial chemoembolization (TACE), systemic chemotherapy, and radiation therapy. Even after liver transplantation and hepatectomy, imaging is used to assess for residual tumor outside the resection margins and the liver. However, imaging-based assessment of clinical tumor response is often problematic due to treatment-related changes such as arterioportal (AP) shunt and lipiodol accumulation. Here, we reviewed the possibility of using tumor markers to supplement imaging-based assessment of clinical tumor response.

■ Scientific Statement

This CQ is identical to CQ5 in the fourth edition. In the current revision, a literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 522 articles. This was narrowed down to 9 articles in the first screening and to 4 articles in the second screening based on the following inclusion criteria: studies that used tumor markers to evaluate clinical tumor response. A total of 12 articles, including the 8 articles from the fourth edition, are thus cited for CQ3.

A previous study investigating whether AFP, PIVKA-II, and AFP-L3 fraction predicted treatment outcome in 416 patients who underwent curative percutaneous ablation (radiofrequency ablation [RFA], 70.7%) revealed that high post-treatment levels of AFP (> 100 ng/mL) and AFP-L3 fraction (> 15%) were independent factors predicting tumor recurrence[1]. In a study of 54 patients with HCC treated with RFA (a total of 72 treatment sessions), a decrease in AFP levels in less than 7 days (i.e., the half-life of AFP) was a predictive factor for recurrence-free survival independent of treatment outcome assessed by diagnostic imaging[2]. In a study of 714 HCC patients who underwent hepatectomy, post-hepatectomy normalization rates of tumor markers were 80.3% with AFP and 99.6% with PIVKA-II when the cutoff level was set at 20 ng/mL and 40 mAU/mL, respectively. The pre-treatment levels of AFP and PIVKA-II were correlated with recurrence in ≤ 6 months but not after 2 years[3]. In another study of 165 patients who underwent hepatectomy, non-AFP normalization was likely to be observed

especially in recurrent HCCs. Multivariate analysis revealed an association between HCC recurrence and the lowest AFP levels observed after surgery[4]. In addition, in a similar study of 841 patients who underwent hepatectomy, decrease in AFP within 1 week was an independent predictive factor for recurrence-free and overall survival[5]. In a study of 280 with high preoperative AFP levels (> 400 ng/mL) who underwent hepatectomy, AFP normalization within 3 months after surgery is an independent risk factor for recurrence-free and overall survival[6].

A study of 146 HCC patients treated with RFA reported an association between the levels of AFP and alanine transaminase (ALT) in patients with elevated AFP levels despite no tumor recurrence. In contrast, patients without elevated AFP levels and HCC recurrence had normal ALT levels. At the cut-off level of 20 ng/mL, AFP elevation after RFA at HCC recurrence was found in 72.2% in patients with pre-treatment AFP elevation compared with 12.2% in patients with pre-treatment normalized AFP[7]. In a study of 125 patients who underwent TACE or transarterial radioembolization, a decrease of ≥ 50% in AFP levels was also another independent prognostic factor in addition to imaging-based assessment of treatment outcome[8]. A similar study of 376 patients (preoperative AFP > 20 ng/mL, BCLC Stage B) who underwent TACE reported a decrease of ≥ 20% in AFP levels as an independent prognostic factor for overall survival[9]. In a study of 147 patients with high preoperative AFP levels (> 400 ng/mL) who underwent TACE, a decrease of ≥ 30% in AFP levels was found to be an independent prognostic factor, and good prognosis was observed even in patients showing progressive disease on imaging[10]. In a study of 72 patients who underwent systemic chemotherapy (including molecular-targeted therapy), prognosis was particularly favorable in patients who had stable disease determined based on imaging findings and were AFP responders (i.e., had a 20% or more reduction in AFP levels), compared with patients who had stable disease and were non-AFP responders[11]. Similarly, a study of 107 patients who received systemic chemotherapy or molecular-targeted therapy showed an association between favorable prognosis and a ≥ 50% decrease in AFP levels[12].

■ Explanation

Disease severity, especially for hepatitis, in the background liver is significantly correlated with AFP levels and this often presents problems in HCC surveillance. When AFP test results remain positive in patients with complete response on imaging, it may suggest AFP elevation related to inflammation in the background liver. When using AFP-L3 fraction or PIVKA-II, however, both of which are highly specific tumor

markers and are less susceptible to disease activity in the background liver, persistently positive test results strongly indicate the presence of residual tumor.
From the perspective of tumor progression, there is a significant correlation between tumor differentiation and tumor marker production. A linear correlation between tumor size and tumor marker levels can be observed in general, and thus tumor marker levels can be useful indicators of response in advanced HCC. As described above, the use of the three types of tumor markers is currently approved in the diagnosis of HCC in Japan and covered by the National Health Insurance system, with their roles being widely accepted.
To be truly valuable in the assessment of clinical tumor response, tumor marker testing should be incorporated into clinical decision-making processes (e.g., deciding when to perform imaging tests or to change treatment modalities). However, no articles reporting this issue could be found in the current literature search.

Voting results

◎ Regarding the statement of recommendation “Post-treatment tumor marker levels are effective indicators of clinical response in patients with high tumor marker levels prior to treatment)”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (22 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

■ References

CQ4
Is it necessary to change the cut-off level of AFP depending on background liver disease conditions?

Recommendation
Analytical sensitivity increases by lowering the cut-off level of AFP from the

conventional level in patients with suppressed hepatitis activity. (Weak recommendation, Evidence Level C)

■ Background

For diagnostic purposes, tumor marker measurements are used to obtain a definitive diagnosis or as the trigger for the next process during surveillance. Because of current developments in imaging diagnostics, tumor marker testing for HCC is not a requirement for definitive diagnosis. On the other hand, if a certain threshold level is exceeded during surveillance, it is important to determine how the post-test probability changes; therefore, it is recommended that the positive likelihood ratio [= Sensitivity/ (1-Specificity)] be used as an indicator.

Conventionally, AFP has been widely used as a tumor marker for HCC. However, AFP levels are susceptible to the activity of not only HCC but also hepatitis in the background liver. In many cases, suppression of hepatitis has become possible due to the recent introduction of nucleos(t)ide analogue treatment for hepatitis B and direct antiviral agents (DAA) for hepatitis C. Therefore, we examined the optimal cut-off level of AFP depending on background liver conditions.

■ Scientific Statement

This CQ was newly established in the current revision. A literature search conducted with a publication date between January 1, 2000 and January 31, 2020, using a newly created search query, extracted 115 articles. This was narrowed down to 3 articles in the first screening, all of which were also selected in the second screening based on the following inclusion criteria: studies reporting the sensitivity and specificity of AFP in patients with hepatitis B on nucleos(t)ide analogue treatment or patients with hepatitis C who achieved SVR. Thus, a total of 3 articles are cited for CQ4.

In a retrospective-prospective cohort study of 1,531 entecavir-treated patients under regular HCC surveillance, 57 patients developed HCC. The AUROC of AFP at the time of HCC diagnosis was 0.85 (95% CI: 0.73-0.98). Using the conventional AFP cut-off level (20 μg/L), sensitivity and specificity were 38.6% and 98.9%, respectively. Adopting the lower cut-off level (6 μg/L) of AFP, sensitivity was increased to 80.7%, whereas specificity was decreased to 80.4%. The study concluded that AFP has a high sensitivity for the diagnosis of HCC in entecavir-treated patients, and that adopting a lower cut-off level (6 μg/L) of AFP from the conventional level would significantly increase sensitivity[1].

A prospective cohort study of 256 hepatitis B patients treated with lamivudine or entecavir showed a significant decrease in AFP after treatment compared with pre-treatment levels. HCC developed in 35 patients. Using an AFP cut-off level of 10 ng/mL, sensitivity and specificity were 45.7 and 97.3%, respectively, showing an increase in AFP specificity from 64.4% obtained before the nucleos(t)ide analogue treatment[2].

A matched case-control study has been reported in 29 patients (≤ 3 tumors and ≤ 3 cm in tumor diameter) who developed HCC after achieving SVR with interferon, 58 patients without HCC after SVR, 29 non-SVR patients (≤ 3 tumors and ≤ 3 cm in tumor diameter) with HCC, and 58 non-SVR hepatitis C patients without HCC. In the diagnosis of HCC in patients without hepatitis C virus eradication, the AUROC of AFP was 0.83, and the sensitivity and specificity at the optimal cut-off level of 17 ng/mL were 51.7% (95% CI: 32.5-70.6) and 93.1% (95% CI: 83.3-98.1), respectively. On the other hand, in patients who developed HCC after achieving SVR, the AUROC was 0.86, and the sensitivity and specificity at the cut-off level of 5 ng/mL were 75.9% (95% CI: 56.5-89.7) and 89.0% (95% CI: 81.0-97.1), respectively, and sensitivity and specificity at the cut-off level of 17 ng/mL were 24.1% (95% CI: 10.3-43.5) and 100% (95% CI: 90.9-100), respectively[3].

■ Explanation

Disease severity, especially for hepatitis, in the background liver is significantly correlated with AFP levels and this often presents problems in HCC surveillance. Therefore, the use of AFP often causes false-positive results, making its diagnostic accuracy for HCC inadequate. However, in patients with suppressed hepatitis activity due to anti-viral treatment, since they have decreased AFP secretion from non-cancerous tissues, specificity increases at the conventional AFP cut-off level, whereas sensitivity decreases. By lowering the cut-off level from the conventional level, sensitivity is expected to increase.

All the above three articles cited for CQ4 reported that the AFP specificity was high at the conventional cut-off level in patients with suppressed hepatitis. Two articles of them reported that sensitivity would increase by lowering the cut-off level from the conventional level[1,3]. Although the use of the conventional cut-off level can maximize the positive likelihood ratio, sensitivity decreases markedly. Therefore, increasing the sensitivity by lowering the cut-off level is considered appropriate in the surveillance.

Voting results

◎ Regarding the statement of recommendation “Analytical sensitivity increases by lowering the cut-off level of AFP from the conventional level in patients with suppressed hepatitis activity”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
14.3% (3 members)	85.7% (18 members)	0% (0 members)	0% (0 members)

Total voters: 21 members (abstention because of COI: 1 member)

■ References

CQ5

What imaging modalities help to accurately diagnose typical HCC in high-risk patients?

Recommendation

Dynamic CT, dynamic MRI, and contrast-enhanced US are recommended when diagnosing typical HCC. However, if all these are feasible, Gd-EOB-DTPA-enhanced MRI is recommended. (Strong Recommendation, Evidence Level A)

■ Background

Most HCCs demonstrate contrast enhancement in the arterial phase of dynamic CT/MRI, and are detected as washouts in the portal/equilibrium phase of dynamic CT/MRI. As such, HCCs with this typical contrast enhancement pattern on images are termed typical HCC. When US findings show nodules 1-2 cm in patients with cirrhosis, contrast-enhanced US, CT, or MRI is performed to make a diagnosis of HCC based on the typical contrast enhancement pattern.

Here, we reviewed the diagnostic accuracy of individual imaging modalities in making a diagnosis of typical HCC.

■ Scientific Statement

This CQ was established as a continuation of CQ6 in the fourth edition. Meta-analysis and systematic review results with high quality evidence have been published since

2016. Therefore, for CQ5, the articles adopted for the fourth edition were narrowed down to those that can supplement evidence not included in the meta-analyses. A literature search conducted with a publication date between July 1, 2016 and January 31, 2020 (i.e., after the literature search period for the fourth edition), extracted 429 articles. This was narrowed down to 24 articles in the first screening and to 9 articles in the second screening. Of the 9 articles selected in the second screening, 1 article was excluded due to unclear details. Thus, a total of 19 articles, including the 8 articles from the second screening and 11 articles considered necessary among the 46 articles cited in the fourth edition, are cited for CQ5.

Regarding the diagnosis of HCC, according to a meta-analysis comparing diagnostic accuracy between Gd-EOB-DTPA-enhanced MRI and dynamic CT, Gd-EOB-DTPA-enhanced MRI showed significantly higher sensitivity than CT (0.85 vs. 0.68), whereas no difference was observed in specificity between them (0.94 vs. 0.93). ROC analysis showed that MRI had significantly higher diagnostic accuracy than CT (AUROC: 0.79 vs. 0.46)[1].

Regarding the diagnosis of HCC, according to a meta-analysis comparing diagnostic accuracy among Gd-EOB-DTPA-enhanced MRI, dynamic CT and dynamic MRI, the estimated sensitivities of Gd-EOB-DTPA-enhanced MRI and contrast-enhanced CT were 0.881 (95% CI: 0.766-0.944) and 0.713 (95% CI: 0.577-0.819), respectively, and the estimated specificities were 0.926 (95% CI: 0.829-0.97) and 0.918 (95% CI: 0.829-0.963), respectively. These differences were not statistically significant. However, when the analysis limited to studies that included patients with small lesions, Gd-EOB-DTPA-enhanced MRI was superior to contrast-enhanced CT, with the estimated sensitivities of 0.919 (95% CI: 0.834-0.962) vs. 0.637 (95% CI: 0.565-0.704) and estimated specificities of 0.936 (95% CI: 0.882-0.966) vs. 0.971(95% CI: 0.937-0.987). In the analysis comparing Gd-EOB-DTPA-enhanced MRI and dynamic MRI, the estimated sensitivities were 0.907 (95% CI: 0.870-0.934) and 0.820 (95% CI: 0.776-0.857), respectively, and estimated specificities were 0.929 (95% CI: 0.877-0.961) and 0.934(95% CI: 0.881-0.964), respectively. Thus, Gd-EOB-DTPA-enhanced MRI was found to be superior[2].

In a meta-analysis comparing diagnostic accuracy for small HCCs ≤ 2 cm between Gd-EOB-DTPA-enhanced MRI and dynamic CT, the sensitivity of Gd-EOB-DTPA-enhanced MRI was significantly higher than CT (0.96 vs. 0.65; $p < 0.01$), whereas their specificities showed no significant difference (0.94 vs. 0.98; $p > 0.05$). The summary AUROCs of Gd-EOB-DTPA-enhanced MRI and dynamic CT were 0.97 and 0.85, respectively, showing that Gd-EOB-DTPA-enhanced MRI was superior in terms of

overall diagnostic accuracy[3].

In a meta-analysis comparing HCC detection sensitivity between Gd-EOB-DTPA-enhanced MRI and dynamic CT, the HCC detection sensitivity was 0.86 (95% CI: 0.76-0.93) for Gd-EOB-DTPA-enhanced MRI and 0.70 (95% CI: 0.58-0.80) for contrast-enhanced CT, showing a significant higher value for Gd-EOB-DTPA-enhanced MRI ($p < 0.05$). Although the sensitivities of Gd-EOB-DTPA-enhanced MRI and contrast-enhanced CT decreased as the lesion size decreased, the sensitivity of MRI showed higher sensitivity for lesions of all size than CT[4].

The above results are consistent with the results of previous meta-analyses[5,6].

Furthermore, MRI was also useful for staging HCC and planning treatment[7-9].

In addition, studies comparing superparamagnetic iron oxide (SPIO)-enhanced MRI and dynamic CT also reported the superiority of the MRI[10-12]. This is because SPIO-enhanced MRI is superior at detecting small HCCs ≤ 1 cm[13].

According to a meta-analysis assessing the efficacy of contrast-enhanced US in the diagnosis of small HCCs, the diagnostic sensitivity and specificity of contrast-enhanced US were 0.86 (95% CI: 0.79-0.91) and 0.87 (95% CI: 0.75-0.94), respectively, with the positive and negative likelihood ratios being 7.06 (95% CI: 1.64-30.36) and 0.20 (95% CI: 0.14-0.28), respectively. The diagnostic odds ratio was 33.71 (95% CI: 20.34-55.88), and the AUROC was 0.93 (95% CI: 0.90-0.95)[14].

In a prospective RCT evaluating the usefulness of HCC screening with contrast-enhanced US, using unenhanced US as the reference, the mean size of HCC at the first detection was significantly smaller in the contrast-enhanced US group (13.0±4.1 mm; 28 patients) than in the unenhanced US group (16.7±4.1 mm: 26 patients) ($p = 0.011$)[15].

According to a meta-analysis comparing diagnostic accuracy in detecting small HCCs between contrast-enhanced US and dynamic CT, the sensitivities of contrast-enhanced US and dynamic CT were 0.75 (95% CI: 0.70-0.80) and 0.74 (95% CI: 0.68-0.78), respectively, and their specificities were 0.91 (95% CI: 0.87-0.94) and 0.92 (95% CI: 0.89-0.95), respectively. Their summary AUROCs were 0.91 and 0.89, respectively. There were no statistically significant differences between contrast-enhanced US and dynamic CT ($Z = 0.23$, $p = 0.82$)[16].

According to a meta-analysis investigating the diagnostic efficacy of contrast-enhanced MRI in diagnosing residual or recurrent HCC after TACE, the sensitivity and specificity of contrast-enhanced MRI were 91% (95% CI: 87-96%) and 93% (95% CI: 85- 97%), respectively, with the positive and negative likelihood ratios being12.22 (95% CI: 5.62-26.57) and 0.09 (95% CI: 0.05-0.18), respectively. The diagnostic odds ratio was 126.99 (95% CI: 34.76-436.99), and the AUROC was 0.97 (95% CI: 0.95-0.98)[17].

■ Explanation

Dynamic CT plays a major role in diagnosing typical HCC. Today, most institutions use multi-detector-row CT scanners to perform dynamic CT, rapidly generating clear images compared with MRI. Because one scan takes only a few seconds, the quality of CT images remains high even in patients who cannot breath-hold for the required period of time. In addition, the diagnostic accuracy of CT for non-small HCCs is not inferior to MRI.

Gd-EOB-DTPA-enhanced MRI has excellent diagnostic accuracy in diagnosing HCC, including small lesions. However, the high costs of incorporating and maintaining MRI scanners and the long scan time required mean it may be impractical for some institutions to screen all patients at high risk for HCC using MRI. It is also important to keep in mind that despite the high sensitivity of Gd-EOB-DTPA-enhanced MRI for HCC, differential diagnosis may be necessary for lesions that show similar early phase contrast enhancement, such as small hemangioma and mass-forming hypervascular intrahepatic cholangiocarcinoma, in clinical settings.

SPIO contrast agents are negative contrast agents, and have limited clinical applications in diagnosing HCC, such as when dynamic imaging is not feasible. SPIO-enhanced MRI may be a viable choice for patients with decreased kidney function for whom iodinated contrast agents and Gd-based agents are contraindicated.

Even though CT and MRI are more objective modalities, contrast-enhanced US enables the hemodynamics and reticuloendothelial system of the liver to be examined and it has excellent diagnostic accuracy when second-generation contrast agents are used. Perfluorobutane microbubbles is used in patients with or without decreased kidney function and is associated with far fewer cases of severe anaphylactoid reactions compared with iodinated contrast agents and Gd-based contrast agents[18]. A meta-analysis has shown that contrast-enhanced US is not inferior to dynamic CT in terms of diagnostic accuracy, and can be recommended as an imaging test for diagnosing HCC. However, it should be noted that deep lesions may be difficult to visualize in obese patients, etc.[19].

Today, angiography is less frequently performed for the purpose of diagnosing HCC, and is therefore excluded from the evaluation in the current version. Angiography, including CT during arterial portography (CTAP) and CT during hepatic arteriography (CTHA), is an extremely useful diagnostic modality for typical HCC, but it is invasive compared with other imaging modalities because of the catheterization of the hepatic

artery or superior mesenteric artery. Therefore, angiography should be limited to cases where no diagnosis can be made by other tests, or should be used in combination with other therapeutic techniques such as TACE.
In conclusion, contrast-enhanced US, dynamic CT, and Gd-EOB-DTPA-enhanced MRI are all useful imaging modalities for typical HCC. It is important to choose the most appropriate of these based on the condition of individual patients and institutional circumstances. However, for small HCCs, Gd-EOB-DTPA-enhanced MRI is superior to dynamic CT and contrast-enhanced US in terms of diagnostic accuracy. Therefore, for eligible patients, Gd-EOB-DTPA-enhanced MRI should be prioritized.

Voting results

For Recommendation “Dynamic CT, dynamic MRI, and contrast-enhanced US are recommended when diagnosing typical HCC. However, if all these are feasible, Gd-EOB-DTPA-enhanced MRI is recommended”, voting was performed by the committee members. As a result, it was graded as Strong Recommendation.

◎ Regarding the statement of recommendation “Dynamic CT, dynamic MRI, and contrast-enhanced US are recommended when diagnosing typical HCC. However, if all these are feasible, Gd-EOB-DTPA-enhanced MRI is recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
91.7% (22 members)	8.3% (2 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

■ References

CQ6

How to deal with lesions appearing hypervascular, but showing no washout, on contrast-enhanced CT in patients with chronic liver disease?

Recommendation

Further examination by Gd-EOB-DTPA-enhanced MRI is recommended. (Weak

recommendation, Evidence Level B)

■ Background

In extracellular contrast-enhanced imaging test, such as contrast-enhanced CT, in patients with chronic liver disease, a lesion showing washout in the portal and equilibrium phases, detected by contrast enhancement in the arterial phase, is the typical imaging feature of HCC. However, some HCCs do not show clear washout, and differentiation from hemangiomas and hypervascular pseudolesions is an issue. According to a study in 52 nodules ≤ 1 cm (30 malignant and 22 benign lesions) that were enhanced in the arterial phase and visualized as hypointense signals in the Gd-EOB-DTPA-enhanced MRI hepatobiliary phase[1], no washout was observed in 16.7% (5 of 30) of HCCs and 50% (11 of 22) of benign lesions. In other words, the 16 subcentimeter (≤ 1 cm) hypervascular nodules without washout, visualized as hypointense signals in the hepatobiliary phase consisted of both benign (11 nodules) and HCC (5 nodules). This CQ takes up hemangiomas and hypervascular pseudolesions as benign lesions that are often enhanced in the arterial phase, and discusses whether Gd-EOB-DTPA-enhanced MRI is useful for differentiation from HCC.

■ Scientific Statement

This CQ was established as a continuation of CQ7 “What size (cm) of liver nodules showing atypical HCC enhancement pattern on dynamic CT/MRI warrants further examination?” in the fourth edition, using modified expression to clarify the question. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 584 articles. This was narrowed down to 27 articles in the first screening and to 10 articles in the second screening based on the following inclusion criteria: studies that investigating the diagnostic accuracy for hypervascular hepatic nodules, using pathology and/or clinical course as reference. Thereafter, to further clarify the question, the CQ was revised to “Is Gd-EOB-DTPA-enhanced MRI recommended for differentiation of HCC from benign hypervascular lesions, such as hemangiomas and hypervascular pseudolesions.” Of the 10 articles selected, 7 article was excluded because their target diseases were not those (hemangiomas and hypervascular pseudolesions) considered for the CQ. Eventually, a total of 9 articles, including 6 new hand-searched articles, are cited for CQ6. The voting of the Revision Committee members resulted in disagreement. The cause was the complexity of this CQ, because the question is about another modality to be used after either contrast-enhanced CT or extracellular contrast-enhanced MRI. Therefore, the CQ

was modified to limit to contrast-enhanced CT.

□Is Gd-EOB-DTPA-enhanced MRI recommended for differentiation from hypervascular pseudolesions?

In patients with chronic liver disease, hypervascular pseudolesions may be observed on extracellular contrast-enhanced imaging test, such as contrast-enhanced CT, mainly due to arterial-portal shunt (AP shunt) formation and hyperplastic nodules seen in excessive alcohol consumers. Patients with these lesions rarely have a definitive pathological diagnosis. Therefore, it is considered appropriate to classify these lesions as hypervascular pseudolesions. No RCT was found on the direct comparison of the imaging features of HCC and hypervascular pseudolesions as well as their differentiation, using Gd-EOB-DTPA-enhanced MRI. Therefore, retrospective observational studies investigating their differentiation are summarized below.
A study in patients with alcoholic liver cirrhosis examined 28 hypervascular hyperplastic nodules and 29 hypervascular HCCs ≤ 3 cm. Nodular diameter ≤ 16 cm, hypointense to isointense signals on diffusion-weighted images, and absence of washout in one or both of the portal and transitional phases were identified as independent factors predicting hypervascular hyperplastic nodules. Regarding the diagnostic accuracy for hypervascular hyperplastic nodules in patients with 2 of these 3 factors, sensitivity and specificity were 92.9% (26 of 28) and 75.9% (22 of 29), respectively, with the diagnostic accuracy of 84.2% (48 of 57). In patients with all the 3 factors, sensitivity and specificity were 60.7% (17 of 28) and 100% (29 of 29), respectively, with the diagnostic accuracy of 80.7% (46 of 57)[2].

In a study conducted on 28 benign nodules (including 2 nonspecific benign nodules), including hemangioma (11 lesions) and AP shunt (15 lesions) and 111 HCCs, the diagnostic accuracy of Gd-EOB-DTPA-enhanced MRI for HCC was evaluated by 2 readers: Sensitivity and specificity were 95% (107 of 111) and 96% (27 of 28), respectively, by Reader 1, and were 95% (106 of 111) and 96% (27 of 28), respectively, by Reader 2. On the other hand, regarding the diagnostic accuracy of dynamic CT, sensitivity and specificity were 84% (95 of 111) and 100% (28 of 28), respectively, by Reader 1, and were 89% (99 of 111) and 100% (28 of 28), respectively, by Reader 2. Evaluated by Reader 1, the sensitivity of Gd-EOB-DTPA-enhanced MRI was higher than that of dynamic CT ($p = 0.005$). No significant differences were observed in the sensitivity ($p = 0.052$) evaluated by Reader 2 and the specificities by Readers 1 and 2 (p

= 0.317 for both)[3].

A study on 32 nodular hypervascular pseudolesions (mean: 11.5 mm) and 123 hypervascular HCCs (mean: 16.4 mm) revealed that HCCs, compared with pseudolesions, were significantly greater in size, and showed a higher proportion of hyperintense areas on T2-weighted or diffusion-weighted images and a higher proportion of hypointense areas on the hepatobiliary phase ($p < 0.0001$). The hepatobiliary-phase signal intensity ratio of lesion to parenchyma was significantly lower in HCC. At a cut-off level of 0.84, sensitivity and specificity were 91% (112 of 123) and 91% (29/32), respectively. When the visibility on diffusion-weighted images was used for discriminating HCC from hypervascular pseudolesions, the sensitivity and specificity were 67% (83 of 123) and 100% (32 of 32), respectively[4].

In a study conducted on 53 hypervascular pseudolesions (≤ 2 cm) and 44 HCCs (≤ 2 cm), diagnostic accuracy rated by 2 readers independently, using a 5-point rating scale, was compared between Gd-EOB-DTPA-enhanced MRI (diagnostic criteria: contrast enhancement in the arterial phase and hypointense signals in the hepatobiliary phase) and dynamic CT (diagnostic criteria: contrast enhancement in the arterial phase and hypointense signals in the equilibrium phase). Gd-EOB-DTPA-enhanced MRI had higher sensitivity than dynamic CT, and there was no significant difference in specificity: By Reader 1, the sensitivity of Gd-EOB-DTPA-enhanced MRI vs. CT was 93.9% (31 of 33) vs. 54.5% (18 of 33) ($p = 0.001$), and their specificity was 92.6% (25 of 27) vs. 96.3% (26 of 27). By Reader 2, their sensitivity was 90.9% (30 of 33) vs. 54.5% (18 of 33) ($p = 0.0018$), and their specificity was 92.6% (25 of 27) vs. 96.3% (26 of 27). There was no significant difference in Az: By Reader 1, 0.975 vs. 0.892 ($p = 0.069$); By Reader 2, 0.966 vs. 0.888 ($p = 0.106$)[5]. In a study of Gd-EOB-DTPA-enhanced MRI on 42 recurrent HCCs after hepatectomy or RFA and 11 hypervascular pseudolesions (contrast enhancement in the arterial phase, without washout), combining findings of hypointense signals in the hepatobiliary phase and hyperintense signals on diffusion-weighted images was useful for differentiation of these lesions. Although the sensitivity of 54.8% and the negative predictive value of 34.5% were low, high specificity (90.9%) and positive predictive value (95.8%) were obtained[6].

□Is the use of Gd-EOB-DTPA-enhanced MRI recommended for differentiation from hemangioma?

In Gd-EOB-DTPA-enhanced MRI, so-called pseudo-washout appearance may occur:

that is, non-HCC lesions are visualized with strong contrast enhancement in the arterial phase, exhibiting hypointense signals compared with the surrounding liver parenchyma in the transitional and hepatobiliary phases. Therefore, for high-flow hemangioma, which shows strong contrast enhancement in the whole nodule in the early phase of contrast-enhanced imaging, differentiation from small HCC is often difficult. However, no RCT has been conducted to prospectively examine the accuracy of Gd-EOB-DTPA-enhanced MRI in differentiating between hemangioma and HCC. Therefore, retrospective observational studies investigating their differentiation are summarized below.

Nam et al. reported a study on 50 nodules (< 20 mm in diameter) from 43 patients with high-flow hemangioma showing pseudo-washout appearance on Gd-EOB-DTPA-enhanced MRI and 113 nodules (< 20 mm in diameter) from 62 patients with hypervascular small HCC. They reported that high-flow hemangioma, compared with hypervascular small HCC, showed a significantly higher apparent diffusion coefficient (ADC) obtained by diffusion-weighted imaging and a significantly higher contrast-to-noise ratio (CNR) obtained by T2-weighted imaging. Regarding the accuracy with the use of ADC in differentiating between them, the AUROC was 0.995 (95% CI: 0.969-1.000, sensitivity: 98%, specificity: 97.3%). Regarding the differentiation accuracy of the use of CNR by T2-weighted imaging, the AUROC was 0.915 (95% CI: 0.861-0.953). Thus, the differentiation accuracy with the use of ADC was reported to be significantly superior to CNR. On the other hand, also in qualitative visual evaluation, the accuracy of diffusion-weighted imaging in differentiating between them was also reported to be high (AUROC: 0.988- 0.999, sensitivity: 90-94%, specificity: 98.2-100%), with a high concordance rate between readers (K-value: 0.80)[7].

Likewise, Choi et al. reported a study on a total of 161 lesions ≥ 20 mm (hemangioma: 20 nodules, 91 HCCs, intrahepatic cholangiocarcinoma: 27 nodules, mixed hepatocellular cholangiocarcinoma: 9 nodules, metastatic HCC: 9 nodules, others: 5 nodules) from 161 patients, examined by Gd-EOB-DTPA-enhanced MRI combined with intravoxel incoherent motion (IVIM) and diffusion-weighted imaging. The ADC and the molecular diffusion coefficient (D_{slow}) were reported to be significantly different between hemangioma and malignant hepatic tumors. Regarding the differential accuracy between them, the AUROC was 0.907 (95% CI: 0.850-0.948, sensitivity: 90.0%, specificity: 80.9%) with ADC, and was 0.933 (95% CI: 0.882-0.967, sensitivity: 95.0%, specificity: 83.8%) with D_{slow}. On the other hand, among the malignant hepatic tumors, there were no significant differences with ADC and D_{slow}[8].

On the other hand, according to a retrospective study analyzing findings from MRI using extracellular Gd-based contrast agents, hyperintense signals on diffusion-weighted images and capsule-like enhancement were useful for differentiation between HCC and non-HCC in non-typical HCC with contrast enhancement in the arterial phase and without washout[9].

■ Explanation

The differentiation between HCC and hypervascular pseudolesions by Gd-EOB-DTPA-enhanced MRI has not been adequately studied yet. However, it appears that hypervascular lesions without washout are more likely to be benign than malignant (HCC). Gd-EOB-DTPA-enhanced MRI has been reported to have high differential accuracy. There are studies reporting that Gd-EOB-DTPA-enhanced MRI is superior to contrast-enhanced CT when used for differentiating between HCC and hypervascular pseudolesions. However, no clear evidence has been shown that Gd-EOB-DTPA-enhanced MRI is non-inferior or superior to other modalities (contrast-enhanced abdominal US, extracellular contrast-enhanced MRI, etc.). Therefore, establishing such evidence is a future challenge.

There have been no adequate studies comparing the diagnostic accuracy of modalities used for differentiating between HCC and hemangioma. However, MRI, which can combine findings from diffusion-weighted imaging, may be useful clinically. There has been no study directly comparing the diagnostic accuracy between Gd-EOB-DTPA-enhanced MRI and other modalities (contrast-enhanced abdominal US, extracellular contrast-enhanced MRI, etc.) in terms of differentiation of HCC from hemangioma. However, extracellular contrast-enhanced MRI is probably superior to Gd-EOB-DTPA-enhanced MRI, because it can provide strong contrast enhancement in the arterial phase, allowing the evaluation of the equilibrium phase.
Based on the above, it is recommended to additionally perform Gd-EOB-DTPA-enhanced MRI for lesions that appear hypervascular, without washout, on contrast-enhanced CT.

Voting results

◎ Regarding the statement of recommendation “Further examination by Gd-EOB-DTPA-enhanced MRI is recommended”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
28.0% (7 members)	72.0% (18 members)	0% (0 members)	0% (0 members)

Total voters: 25 members

■ References

CQ7

How to deal with non-hypervascular lesions in patients with chronic liver disease?

a. Is Gd-EOB-DTPA-enhanced MRI recommended for diagnosis of non-hypervascular lesions in patients with chronic liver disease?

Recommendation

Further examination by Gd-EOB-DTPA-enhanced MRI is recommended. (Strong Recommendation, Evidence Level B)

b. Is regular follow-up recommended for diagnosis of non-hypervascular lesions in patients with chronic liver disease?

Recommendation

Follow-up using Gd-EOB-DTPA-enhanced MRI (or dynamic CT) is recommended. (Strong Recommendation, Evidence Level B)

■ Background

There have been an increasing number of cases of patients with chronic liver disease showing no hypervascularization on contrast-enhanced imaging test but showing nodules that no longer have normal hepatocyte function on perfluorobutane microbubble-enhanced US or Gd-EOB-DTPA-enhanced MRI. Thus, the presence of HCC precursor lesions in these patients has become known.

There have been many studies reporting hypervascularization (canceration) of non-hypervascular lesions since the retrospective study by Kumada et al.[1] in 2011. However, the term for this lesion has not been established, varying from literature to literature. Of these, those showing hypointense signals in the Gd-EOB-DTPA-enhanced MRI hepatobiliary phase are easy to detect, and the uptake mechanism of the hepatobiliary

contrast agent suggests the risk of canceration. Therefore, “HBP hypointense nodule without APHE” was proposed by LI-RADS HBA Working Group[2]. In Japan, lesions without contrast enhancement are sometimes called “hypovascular lesions”. These lesions are considered to include a large portion of lesions presenting with boundary features between hypo- and hyper- vascular lesions during multistage hepatocarcinogenesis. The detectability of early-phase contrast enhancement varies depending on the imaging modality. Taken together these, an appropriate term may be “non-hypervascular lesion”.
It has been demonstrated that prognosis after treatment is worse in patients with non-hypervascular HCC nodules coexisting with hypervascular HCC than in those without coexisting non-hypervascular nodules[3-5]. It is considered necessary to differentiate coexisting non-hypervascular lesions before the treatment of hypervascular HCC.
For patients with chronic liver disease, regular imaging test for the purpose of screening HCC is recommended. Therefore, it is unlikely that a non-hypervascular lesion found in the liver of a patient with chronic liver disease is left without follow-up. Second, no RCTs were found that verified the effect of biopsy and / or treatment as soon as non-hypertensive lesions were discovered. For this reason, as the evidence for the recommendation of follow-up, we used expert consensus from the guidelines and other observational studies exploring the frequency and related factors of hypervascularization (canceration) of non-hypervascular lesions.

■ Scientific Statement
This CQ was established as a continuation of CQ8 “What imaging modalities help to accurately diagnose early-stage HCC in patients with cirrhosis?” in the fourth edition, using modified expression to clarify the question. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 642 articles.
This was narrowed down to 21 articles in the first screening and to 16 articles in the second screening, but 5 of them were excluded because of a small sample size, etc. Eventually, a total of 22 articles, including 11 new hand-searched articles, are cited for CQ7, and the following points are discussed.

1) CQ7a: Is Gd-EOB-DTPA-enhanced MRI recommended for diagnosis of non-hypervascular lesions in patients with chronic liver disease?

■ Scientific Statement

Of non-hypervascular nodules visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, advanced HCC accounted for 44%, early-stage HCC for 20%, high-grade dysplastic nodules for 27.5%, and low-grade dysplastic nodules and regeneration nodules for 8% each[6]. Although there was a selection bias, advanced HCC which should be definitely treated is included. This should be kept in mind.

Regarding the diagnostic accuracy of non-hypervascular nodules visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, many studies were conducted using nodules that were detected in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. Therefore, there has not been sufficient evidence on the diagnostic accuracy for nodules not detected in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. It has been reported that, of non-hypervascular nodules visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI, those detected also by contrast-enhanced CT accounted for 35%[7]. Since the detection rate of non-vascular nodules by contrast-enhanced CT is relatively low, it can be said that Gd-EOB-DTPA-enhanced MRI is useful for the detection of non-vascular nodules. The diagnostic accuracy of individual imaging modalities in making a diagnosis of HCC was 53% by contrast-enhanced CT, 68% by contrast-enhanced US, 77% by Gd-EOB-DTPA-enhanced MRI and 88% by CT arterioportal angiography[8]. Thirty-three % of HCC appearing as non-hypervascular areas on CT or MRI were diagnosed as hypervascular HCC by contrast-enhanced US[9]. Thus, there are nodules that are diagnosed as non-hypervascular HCC by one imaging modality but visualized as hypervascular areas when re-tested by another imaging modality. Therefore, it is desirable to diagnose non-hypervascular lesions using multiple imaging modalities. In addition, there is a study reporting that findings of hyperintense signals on T2-weighted or diffusion-weighted images are useful in differentiating between dysplastic nodules and HCC. The study indicated the significance of performing MRI in general[10]. Moreover, it has also been reported that the signal intensity on SPIO-enhanced imaging is useful for stratifying the risk of hypervascularization of non-hypervascular nodules[11].

■ Explanation

Taken together, the significance of detecting non-hypervascular nodules by Gd-EOB-DTPA-enhanced MRI and its contribution to prognosis are still unclear. However, the detection of non-hypervascular nodules tends to be superior with Gd-EOB-DTPA-enhanced MRI, and therefore the use of Gd-EOB-DTPA-enhanced MRI is recommended for mapping hepatocellular lesions in the liver in patients with chronic

liver disease. However, it should be kept in mind that non-hypervascular nodules visualized as hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI include not only lesions that may be hypervascularized later on, such as early-stage HCC and dysplastic nodules, but also advanced HCC. It is recommended to perform Gd-EOB-DTPA-enhanced MRI, but it may not be possible to make a diagnosis even with Gd-EOB-DTPA-enhanced MRI. Therefore, it is necessary to carefully proceed with differentiation by combining other imaging modalities and histological diagnosis.

Voting results

◎ Regarding the statement of recommendation “Further examination by Gd-EOB-DTPA-enhanced MRI is recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
88.0% (22 members)	12.0% (3 members)	0% (0 members)	0% (0 members)

Total voters: 25 members

2) CQ7b: Is regular follow-up recommended for diagnosis of non-hypervascular lesions in patients with chronic liver disease?

■ Scientific Statement

Regarding the frequency of hypervascularization (canceration) of non-hypervascular lesions, Suh et al. reported the results of a meta-analysis summarizing prospective or retrospective observational studies. According to the report, the rate of hypervascularization of non-hypervascular lesions detected in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI was 18% at 1 year, 25% at 2 years and 30% at 3 years[12].

Most of previously reported studies on factors related to hypervascularization were retrospective observational studies. Among the applicable published articles, there were 2 prospective evaluation studies. Their primary objectives were the verification of the additive diagnostic value of diffusion-weighted imaging[13] and contrast-enhanced US[9], as described in the previous section.

In the above-described meta-analysis by Suh et al.[12], the most significant factor for

hypervascularization was the size (≥ 9-10 mm) at the time of discovery.
Those published articles are roughly classified into studies targeting all non-hypertensive lesions and studies limiting patient populations according to the background liver conditions and MRI signal patterns. These studies have reported that factors increasing the risk include the size of the lesion[14-16], the presence of hyperintense signals on T2-weighted and diffusion-weighted images[13,16], previous history of HCC[14,17], and the presence of hyperintense signals on T1-weighted images[17]. In addition, the presence of hyperintense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI has been reported as a factor reducing the risk[15]. Three of these studies are summarized below.
A study conducted on 633 non-hypervascular lesions visualized as hyperintense signals in the hepatobiliary phase reported lower incidence rates of hypervascularization than those reported by previous studies[15]: The patient-based and lesion-based incidence rates at 1 year were 4% (95% CI: 1.74-9.55%) and 0.4% (95% CI: 0.20-0.95%), respectively. In multivariate analysis, the only factor related to hypervascularization was the size (continuous value) of the new-onset lesion. Examined in 10 mm-intervals, a significant difference was observed in the time to hypervascular transformation ($p = 0.0022$). The 1-year cumulative hypervascularization rate was 0.10% (95% CI: 0.02- 0.57%) for lesions < 10 mm and 1.31% (95% CI: 0.56-3.07%) for lesions ≥ 10 mm.
In a retrospective study in 60 patients on 114 non-hypervascular lesions not visualized as hyperintense signals on T2-weighted images[14], 27 lesions (median observation period: 503 days, 203 - 1,521 days) in 21 patients were transformed into HCC, and 87 lesions (median observation period: 949 days, 103 - 2,541 days) in 47 patients were not transformed into HCC. The study reported that hyperintense signals (hazard ratio: 2.693, 95% CI: 1.157- 6.264, $p = 0.021$) on T1-weighted images and previous history of HCC (hazard ratio: 2.64, $p = 0.021$) were related to hypervascularization.
Yang et al.[17] conducted a retrospective study in 97 patients on 222 non-hypervascular lesions without hyperintense signals on T2-weighted images and with hypointense signals in the hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI. Multivariate analysis revealed that previous history of HCC at the initial onset (hazard ratio: 3.493, 95% CI: 1.335-9.138, $p = 0.011$), hyperintense signals (hazard ratio: 2.778, 95% CI: 1.172-6.589, $p = 0.020$) on T1-weighted images, and hyperintense signals (hazard ratio: 19.917, 95% CI: 7.050-56.271, $p < 0.001$) on diffusion-weighted images were significantly related to hypervascularization. In addition, ROC analysis revealed the cut-off level for the growth rate (the reciprocal of the volume doubling time) was 0.72×10^{-3}/day.

As supplementary information, there are some reports on the prognosis of patients with non-hypervascular lesions and the risk of developing HCC in other areas of the liver. The applicable published articles include the following:

A retrospective study by Gyoda et al.[7] in patients who had undergone hepatectomy showed that 52.2% of non-hypervascular lesions were transformed to classical HCC by 3 years after the first hepatectomy. In addition, the cumulative 1- and 3- year incidence rates of classical HCC or non-hypervascular nodules occurring in sites other than non-hypervascular nodules were 32.8% and 67.1%, respectively, for classical HCC and 14.3% and 27.5% respectively, for non-hypervascular nodules in the group with non-hypervascular nodules (36 patients), whereas the rates were 19.9% and 43.4% respectively, for classical HCC and 4.8% and 18.1%, respectively, for non-hypervascular nodules in the group without non-hypervascular nodules (75 patients). Thus, there were no significant differences between the two groups ($p = 0.097$ for classical HCC, $p = 0.280$ for non-hypervascular nodules). They concluded that these results made it unclear whether non-hypervascular nodules should be resected together with the primary tumor at the time of hepatectomy. Next, in non-hypervascular nodules in HCV-positive patients, there were no significant differences in the cumulative hypervascularization rates after 12, 18 and 24 months between patients with DAA treatment (11.8, 24.2 and 25.2%, respectively) and without DAA treatment (9.1, 15.2 and 24.9%, respectively) ($p = 0.617$)[18]. There is concern about selection bias because the target population is relatively advanced cases.

■ Explanation

Regarding the policy for dealing with non-hypervascular lesions, a review article[19] on liver biopsy reported that, for hepatic lesions without typical contrast enhancement on CT, MRI, etc., the 2011 American Association for the Study of Liver Disease (AASLD) guidelines, etc. recommended biopsy[20,21]. According to the report, however, the recent guidelines tend to reduce the use of biopsy, taking into account the invasiveness and the possibility of sampling error. The 2017 AASLD guidelines[22] make it necessary to perform the secondary imaging test or follow-up observation for patients with cirrhosis, although a 1 to 2 cm-sized nodule that does not show the typical contrast enhancement is unlikely to be HCC.

In order to assess how long the follow-up period should be and how frequent testing should be performed, the observation periods set in published articles applicable this time were summarized. The median period of the 16 articles included in the meta-

analysis by Suh et al. was 186-886 days, and the representative values of the observation period of non-hypervascular lesions (median obtained from 7 articles, mean from 3 articles) in other original articles were 167-997 days. In a study conducted in the above-mentioned population, that is, patients with non-hypervascular lesions not visualized as hyperintense signals on T2-weighted images[17], the clinical course of the patients was observed for the mean period of 997 days (137 - 1,804 days). The author, Yang et al., found that hypervascularization occurred in only 3 lesions during the 3-year observation period, and that all these cases had factors related to hypervascularization. Therefore, they considered that lesions without those factors, if observed for 3 years, can be said to be less likely to become cancerous.

There is no evidence of the optimal interval between imaging tests for follow-up of non-hypervascular lesions, and there is no description even in the AASLD guidelines[20]. The 4th edition of the Guidelines requires follow-up by US or contrast-enhanced CT / MRI every 3 months.

Summarizing the above, non-hypervascular lesions should not be left untreated because their 3-year cumulative hypervascularization rate is 30%. However, there is no clear evidence of the pros and cons of biopsy and treatment for non-hypertensive lesions. According to a recent expert opinion, performing a biopsy at the first onset is not desirable, taking into account the balance between its invasiveness and the benefits obtained, and either a second contrast-enhanced imaging test or follow-up observation with an imaging test should be added. If the 4th edition is followed, follow-up will be performed by US or contrast-enhanced CT / MRI every 3 months. However, CT / MRI is advantageous from the viewpoint of detecting hypervascularization. Therefore, if circumstances of the facility allow, Gd-EOB-DTPA-enhanced MRI would be preferable.

Voting results

◎ Regarding the statement of recommendation “Follow-up using Gd-EOB-DTPA-enhanced MRI (or dynamic CT) is recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
88.0% (22 members)	12.0% (3 members)	0% (0 members)	0% (0 members)

Total voters: 25

■ References

CQ8

What imaging modalities effectively detect liver cancer in patients with decreased kidney or liver function?

Recommendations

1. Contrast-enhanced CT or MRI may be performed in patients with decreased kidney function in accordance with the following criteria: Gd-EOB-DTPA-enhanced MRI with estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73 m^2, SPIO-enhanced MRI with eGFR < 30 mL/min/1.73 m^2, and SPIO-enhanced MRI or dynamic CT when undergoing dialysis. (Weak recommendation, Evidence Level B)

2. Noncontrast-enhanced MRI (including diffusion-weighted MRI) and US (including perfluorobutane microbubbles-enhanced US) are safe and effective in patients with decreased kidney function for whom contrast-enhanced CT or MRI is contraindicated. (Strong recommendation, Evidence Level B)

■ Background

There are limited options for testing and diagnostic imaging in patients with decreased kidney or liver function, because the use of iodinated contrast agents and Gd-based contrast agents is contraindicated for patients with decreased kidney function and the enhancement effect of hepatobiliary-specific contrast agents decreases in patients with liver dysfunction. Here, we reviewed imaging modalities useful for the diagnosis of liver tumors in this group of patients.

■ Scientific Statement

This CQ was established based on CQ9 in the fourth edition. In the current revision, a literature search conducted with a publication date between July 1, 2016 and January 31, 2020 extracted 735 articles about imaging diagnosis of HCC, reporting about patients with decreased kidney or liver function, or about imaging tests that can be performed even for patients with decreased liver function. This was narrowed down to 13 articles in the first screening and to 5 articles after the second screening based on the following inclusion criteria: studies that focus on diagnosis, even in the presence of

decreased kidney or liver function, or studies where the value of diagnostic accuracy of imaging tests that can be performed even in the presence of decreased liver or kidney function was calculated. A total of 19 articles, including the 14 articles from the fourth edition, are thus cited for CQ8.

Diffusion-weighted imaging does not outweigh contrast-enhanced MRI, but it is useful in certain aspects[1-6]. In addition, it has been reported that a screening protocol for HCC by noncontrast-enhanced MRI, including diffusion-weighted imaging, is also useful[7-9].

The US contrast agent, perfluorobutane microbubbles, and liver-specific MRI contrast agent, SPIO, do not adversely affect kidney function and their side effects are not amplified in patients with decreased kidney function (as stated in the package inserts). Moreover, it has been shown that the contrast enhanced US with perfluorobutane microbubbles, is more useful than unenhanced US for the early detection and definitive diagnosis of HCC[10].

Administration of Gd-EOB-DTPA for patients on dialysis is not recommended because these patients show reduced contrast enhancement of the liver parenchyma and significantly reduced clearance of the agent[11]. To date, only a few studies have investigated the appropriate combinations of contrast agents and imaging methods when performing dynamic CT/MRI in patients with various levels of estimated glomerular filtration rate (eGFR).

Some utility of Gd-EOB-DTPA-enhanced MRI has been shown in patients with decreased liver function[12], but the contrast enhancement of tissues decreases in the hepatobiliary phase[13-16] and diagnostic accuracy decreases as liver function deteriorates[12,17]. In addition, patients with decreased liver function show decreased contrast enhancement in the Kupffer phase of SPIO-enhanced MRI[18] and the interpretation of contrast-enhanced US becomes difficult[19]. Also, the diagnostic accuracy of diffusion-weighted imaging for HCC is decreased in this group of patients with decreased liver function[12]. To date, only a few studies have investigated the appropriate combinations of contrast agents and imaging methods in patients with decreased liver function regarded as Child-Pugh C, preventing us from making even a tentative recommendation for such cases.

■ Explanation

When explaining the risks associated with the use of iodinated contrast agents and Gd-based contrast agents in patients with decreased kidney function, we need to cite other guidelines because it is outside the scope of the current Guidelines. In patients with eGFR < 60 mL/min/1.73 m^2, iodinated contrast agents are associated with the risk of

contrast nephropathy (Contrast Media Safety Guidelines 10.0; http://www.esur.org/esur-guidelines/), and the risk is thought to further increase in the presence of other risk factors such as diabetes, dehydration, congestive heart failure, gout, age ≥ 70 years, and administration of nonsteroidal anti-inflammatory drugs.

Gd-based contrast agents are associated with nephrogenic systemic fibrosis (NSF) in patients with decreased kidney function (see guidelines on the administration of Gd-based contrast agents in patients with reduced kidney function; http://www.radiology.jp/content/files/649.pdf). Therefore, in principle, extracellular Gd-based contrast agents and Gd-EOB-DTPA are contraindicated in patients undergoing dialysis, patients with chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), and patients with acute kidney failure. However, when the use of Gd-based contrast agents is inevitable even after weighing benefits and risks, gadodiamide hydrate and gadopentetate dimeglumine should be avoided because of the high incidence of NSF.

Only a few studies have investigated the appropriate combinations of contrast agents and imaging methods when performing dynamic CT/MRI for the thorough examination of patients with decreased kidney function and variable ranges of eGFR. For this reason, only a tentative recommendation is made in the Guidelines: Gd-EOB-DTPA-enhanced MRI is recommended based on the assumption that patients with eGFR 30-60 mL/min/1.73 m^2 have a relatively small risk of NSF. In contrast, the risk of NSF increases in patients with eGFR < 30 mL/min/1.73 m^2, so it was difficult to decide whether Gd-EOB-DTPA-enhanced MRI or SPIO-enhanced MRI was to be recommended. However, the above-mentioned guidelines of the Japan Radiological Society and the Japan Society of Hepatology state that the use of Gd-based contrast agents should be carefully considered. In addition, the package insert of Gd-EOB-DTPA states “Avoid using this agent”, and the need for frequent administration is highly likely. Taking all these into account, SPIO-enhanced MRI is recommended. Gd-based contrast agents are contraindicated for patients undergoing dialysis. Each institution may choose SPIO-enhanced MRI or dynamic CT depending on its circumstances.

Contrast-enhanced US is a useful test that can be safely performed even for patients with reduced kidney function. However, it involves examiner-dependent factors. In addition, observation may be difficult, depending on the location of the lesion. Moreover, SPIO-enhanced MRI may be difficult to perform due to the circumstances of the facility. Therefore, if dynamic CT/MRI is not feasible, it is recommended to perform a test selected from feasible tests, including non-contrast-enhanced MRI, depending on individual circumstances.

Although some utility of Gd-EOB-DTPA-enhanced MRI has been shown in patients

with decreased liver function, the liver parenchyma does not show a clear time-dependent increase in contrast enhancement during the hepatobiliary phase, especially in patients with Child-Pugh C liver function and high indocyanine green (ICG)-R15 rates[14,16].

Voting results

◎ Regarding the statement of recommendation 1 “Contrast-enhanced CT or MRI may be performed in patients with decreased kidney function in accordance with the following criteria: Gd-EOB-DTPA-enhanced MRI with estimated glomerular filtration rate (eGFR) 30-60 mL/min/1.73 m^2, SPIO-enhanced MRI with eGFR < 30 mL/min/1.73 m^2, and SPIO-enhanced MRI or dynamic CT when undergoing dialysis”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
13.6% (3 members)	86.4% (19 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

◎ Regarding the statement of recommendation 2 “Noncontrast-enhanced MRA (including diffusion-weighted MRI) and US (including perfluorobutane microbubbles-enhanced US) are safe and effective in patients with decreased kidney function for whom contrast-enhanced CT or MRI is contraindicated”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
72.7% (16 members)	27.3% (6 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

■ References

CQ9

Are head MRI, thoracic CT, bone scintigraphy, and FDG-PET required for staging HCC?

Recommendations

1. Thoracic CT and FDG-PET are recommended for HCC patients with risk factors for extrahepatic metastasis. (Weak recommendation, Evidence Level C)
2. Bone scintigraphy may be performed when the patient's condition is unfavorable for FDG-PET. (Weak recommendation, Evidence Level C)
3. Head CT/MRI may be used as a screening modality for brain metastasis in HCC patients with neurological findings or lung metastasis. (Weak recommendation, Evidence Level C)

■ Background

The presence or absence of extrahepatic metastasis is an important indication to consider when selecting locoregional therapy for HCC. Therefore, HCC patients with risk factors for extrahepatic metastasis should undergo examination of anatomical sites with a high propensity for metastasis before starting treatment for intrahepatic lesions. Here, we reviewed previous studies that investigated the association between different groups of patients and different imaging modalities for extrahepatic metastasis.

■ Scientific Statement

This CQ is the same as CQ10 in the fourth edition. In the current revision, a literature search conducted with a publication date between January 1, 2000 and January 30, 2020 extracted 365 articles about metastasis of HCC or imaging diagnosis for staging HCC. This was narrowed down to 16 articles in the first screening and to 4 articles after the second screening based on the following inclusion criteria: studies discussing diagnostic accuracy in distant metastasis before treatment of HCC. A total of 25 articles, including the 21 articles from the fourth edition, are cited for CQ9.

The frequency of occurrence of extrahepatic metastasis is thought to be low, at around 1.0-2.3%, in patients with new onset HCC[1,2]. However, one study has shown that 15.4% of HCC patients have asymptomatic extrahepatic metastasis[3]. The frequency of extrahepatic metastasis that appears during follow-up after treatment of intrahepatic lesions is 21-24%[4,5]. The frequency of metastasis by site is 6-29% in the lungs, 5-20% in lymph nodes, 2-10% in bones, 1-10% in the adrenal glands, and 0.2-0.6% in the brain[2,5-7]. The risk factors that have been reported for extrahepatic metastasis are progression of intrahepatic lesions, portal vein tumor thrombus, PIVKA-II ≥ 300

mAU/mL, AFP > 100 ng/mL, platelet count ≤ 13 × 10^4/μL, the absence of esophageal varices, and viral hepatitis[6,8,9].

Thoracic CT and bone scintigraphy for screening metastasis seldom detect new metastatic lesions in patients with solitary HCC ≤ 5 cm or 3 or less HCCs ≤ 3 cm, but what is worse is the loss associated with false-positive results[10-12]. A study, although retrospective, has reported that the positive predictive value for detecting lung metastasis by CT is 5.0%, and that the omission of the screening for lung and bone metastases may be reasonable to consider for patients with asymptomatic early-stage HCC with AFP in the normal range[13].

Bone metastasis from HCC is primarily osteolytic, and approximately 50% of bone metastases occur in the vertebral bodies[1]. Bone scintigraphy[14] and FDG-PET[15-19] are useful whole-body screening modalities for bone metastasis in HCC patients. Bone scintigraphy has a relatively high false-negative rate[12,20], and FDG-PET is superior to bone scintigraphy in terms of sensitivity and specificity for bone metastasis[17,18].

The detection rate of lung metastasis is higher with thoracic CT than with FDG-PET[18]. FDG-PET is also useful in detecting other extrahepatic metastasis[21], but sensitivity for brain metastasis is reported to be low[15,16.] One study reported that FDG-PET for staging HCC detected extrahepatic metastasis in 9.8% of the patients[22]. A meta-analysis has revealed that the sensitivity and specificity of FDG-PET for extrahepatic metastasis was 76.6% and 98.0%, respectively[23].

The accumulation of FDG in intrahepatic lesions during FDG-PET is an independent prognostic factor for HCC[24].

HCC rarely causes brain metastasis[2,5,6,25], and most cases of brain metastasis are accompanied by lung metastases in patients with HCC[1].

■ Explanation

Thoracic CT is the standard screening modality for lung metastasis. Combined abdominal dynamic CT and thoracic CT is used for examining intrahepatic lesions as well as detecting the majority of common extrahepatic metastases.

Bone scintigraphy is useful for whole-body screening, but it does not always demonstrate increased radiotracer accumulation in bone metastasis from HCC. Compared with bone scintigraphy, FDG-PET is an excellent diagnostic imaging modality for bone metastasis from HCC and it even allows for information related to bone fracture, such as compression fracture, to be evaluated from CT images generated in PET/CT. Because FDG-PET also detects extrahepatic metastasis other than bone metastasis, institutions equipped for FDG-PET may prefer it over bone scintigraphy. FDG-PET has excellent diagnostic accuracy for extrahepatic metastasis from HCC,

such as bone metastasis, so proactive use of FDG-PET is reasonable when the abdominal lesion and lung metastasis do not fully explain elevated tumor marker levels. However, given that only a limited number of institutions are performing FDG-PET imaging at present due to high system costs and the need for a radionuclide with a short half-life, bone scintigraphy may be performed as an alternative to FDG-PET.
Based on these findings, it is considered that thoracic CT, bone scintigraphy, and FDG-PET are useful for staging HCC and are therefore also useful for screening extrahepatic metastasis. However, although evidence reported by large-scale RCTs and meta-analyses is insufficient, it has been reported that the prevalence of extrahepatic metastasis itself is low[13]. According to the report, the positive predictive value of metastasis by diagnostic imaging is also not high. Therefore, the omission of the screening for extrahepatic metastasis in patients with new-onset HCC may be reasonable to consider if they do not have risk factors, such as AFP, vascular invasion, multiple lesions and presence of symptoms.
There is also insufficient evidence to support their utility for screening brain metastasis. However, in Japan, these modalities are commonly used for screening brain metastasis in patients with neurological symptoms and those at high risk of brain metastasis based on existing metastasis to other organs such as the lungs.
Consequently, the Revision Committee has decided by majority vote on a weak recommendation in performing bone scintigraphy when thoracic CT, FDG-PET, head CT/MRI and FDG-PET are not available for screening extrahepatic metastasis.

Voting results

◎ Regarding the statement of recommendation 1 “Thoracic CT and FDG-PET are recommended for HCC patients with risk factors for extrahepatic metastasis”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
9.1% (2 members)	90.9% (20 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

◎ Regarding the statement of recommendation 2 “Bone scintigraphy may be performed when the patient's condition is unfavorable for FDG-PET”, its adoption

was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
0% (0 members)	100% (22 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

◎ Regarding the statement of recommendation 3 “Head CT/MRI may be used as a screening modality for brain metastasis in HCC patients with neurological findings or lung metastasis”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
0% (0 members)	100% (21 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

References

5)
Kudo M, Arii S, Ikai I, Omata M, Kojiro M, Sakamoto M, et al. The 18th National Follow-up Survey Report on Primary Hepatic Cancer (2004-2005) (The Follow-up Survey Committee of the Liver Cancer Study Group of Japan) (Detailed Information). Acta Hepatologica Japonica 2010; 51: 460-84.