

Systematic evidence-based clinical practice guidelines are ushering in a new stage of standardized management of hepatocellular carcinoma in Japan

Peipei Song, Wei Tang*, Kiyoshi Hasegawa, Norihiro Kokudo

Hepato-Biliary-Pancreatic Surgery Division, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

Summary

Since the European Association for the Study of the Liver published their guidelines for hepatocellular carcinoma HCC (EASL Guideline) in 2001, there have been many explorations of "transferring best current evidence into clinical decision-making" around the worldwide. Comparative analysis on current 17 characteristic guidelines for HCC indicated that evidence-based clinical practice guidelines for HCC are urgently needed and appropriate constructing approach is the factor most significantly influencing their implementation. The construction of evidence-based clinical practice guidelines for HCC in Japan made a good example of this practice. In accordance with evidence-based medicine (EBM), the first version of the J-HCC Guidelines was published in 2005, then revised in 2009, and the third version has just been published on October 15, 2013 with the incorporation of new evidence, which marks the construction of evidence-based clinical practice guidelines for HCC step into a systematic process in Japan. In order to make a more clear description on how to construct evidence-based clinical practice guidelines for HCC in Japan, the three versions of the J-HCC Guidelines were comparatively analyzed in this paper. Focus on methodology used to develop the updated version, the decision tree of 2013 J-HCC Guideline and its features were also revealed. It is expected that J-HCC Guidelines could be useful not only for Japanese physicians and patients in decision making at every clinical step, but also to benefit users internationally with the accumulated evidence and its interpretation in the guidelines.

Keywords: Hepatocellular carcinoma (HCC), clinical guideline, evidence-based medicine (EBM), evaluation

1. Introduction

Eagerly anticipated by Japanese hepatologists and liver surgeons, an updated version of the evidence-based Japanese Hepatocellular Carcinoma (HCC) Guidelines (the J-HCC Guidelines, 2013 version, in Japanese, chaired by Professor Norihiro Kokudo) was published in Japan on October 15, 2013 (1). This is the second update since the first evidence-based clinical practice guidelines for HCC were published in Japan (chaired by Professor

Masatoshi Makuuchi) in 2005. This event marks the construction of evidence-based clinical practice guidelines for HCC step into a systematic process, and is believed to push standardized management of HCC in Japan into a new stage.

With the development of evidence-based medicine (EBM), the concept of "transferring best current evidence into clinical decision-making" has garnered substantial attention worldwide (2,3). About how to get "best current evidence" to influence clinical decision-making, there have been many explorations through the approach of constructing evidence-based clinical practice guidelines for HCC (4). Globally, since the European Association for the Study of the Liver published their guidelines for HCC (Conclusions of the Barcelona-2000 EASL conference) in 2001 (5), many such guidelines have been published in order to promote standardized management

*Address correspondence to:

Dr. Wei Tang, Hepato-Biliary-Pancreatic Surgery Division, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

E-mail: tang-sur@h.u-tokyo.ac.jp

of HCC to reduce incidence and mortality as well as to improve healthcare quality of patients.

Based on the selection criteria of credibility, influence, and whether the guidelines were multi-faceted, the current 17 characteristic guidelines for HCC – including guidelines established by American Association for the Study of Liver Disease (AASLD), National Comprehensive Cancer Network (NCCN), American College of Surgeons (ACS), Asian Pacific Association for the Study of the Liver (APASL), and Japan Society of Hepatology (JSH) – were selected (Table 1). Comparative analysis indicated that evidence-based clinical practice guidelines for HCC are urgently needed and appropriate constructing approach is the factor most significantly influencing their implementation (22,23). Of the 17 guidelines, 5 were formulated based on a systematic analysis of the literature that resulted in recommendations for the management of HCC supported by data while the remaining 12 were formulated through

a consensus of experts that yielded recommendations for the management of HCC based on experience. While most guidelines were drafted by hepatologists, only 2 guidelines were the result of experts consisting of radiologists, statisticians, and other experts besides hepatologists. In terms of content, all 17 guidelines dealt with diagnosis and treatment, only 10 guidelines mentioned epidemiology, 8 mentioned prevention, 11 mentioned surveillance, and 1 mentioned follow-ups. In terms of evaluation measures, 8 guidelines had evidence categories and recommendation grades, 3 had dissemination evaluation and 2 had resource-based recommendations.

2. Characteristics of J-HCC Guidelines

According to EBM, clinical practice guidelines should be updated every 3-4 years with the incorporation of new evidence, and some guidelines for HCC have also been

Table 1. Characteristics of current 17 guidelines for HCC around the world

Areas /Year	Guidelines/Approach	Content	Evaluation measures	Draft by
America				
2005	AASLD Guideline/LA (13)	D&T+S	evidence categories and recommendation grades; dissemination evaluation	American Association for the Study of Liver Disease
2007	ACS Guideline/EC (14)	D&T	—	American College of Surgeons
2009	NCCN Guideline/EC (15)	D&T+E+S	consensus categories	National Comprehensive Cancer Network
2010	WGO Guideline/EC (16)	D&T+E+P+S	resource-based recommendations	World Gastroenterology Organisation
2010	NCI Guideline/EC (17)	D&T+E	—	United States National Cancer Institute
Asia				
2004	Korean Guideline/LA (18)	D&T	evidence categories and recommendation grades	Korean Liver Cancer Study Group and National Cancer Center
2005	J-HCC Guideline/LA [†] (19)	D&T+P+S	evidence categories and recommendation grades; dissemination evaluation draft; evaluation prior to publication	Japanese Ministry of Health, Labor, and Welfare
2006	SGA Guideline/LA (20)	D&T+E+P	evidence categories and recommendation grades	Saudi Gastroenterology Association
2007	JSH Guideline/EC (21)	D&T+S	question and answer analyser system	Japan Society of Hepatology
2009	AOS Guideline/EC (22)	D&T+P+S	evidence categories and recommendation grades; resource-based recommendations	Asian Oncology Summit 2009
2009	Chinese Guideline/EC (23)	D&T	—	Chinese Society of Liver Cancer, Chinese Society of Clinical Oncology, Chinese Society of Hepatology Liver Cancer Study Group
2010	APASL Guideline/EC [†] (24)	D&T+E+P+S	evidence categories and consensus grade	Asian-Pacific Association for the Study of the Liver
Europe				
2001	EASL Guideline/EC (11)	D&T+E+P+S	—	European Association for the Study of the Liver
2003	BSG Guideline/LA (25)	D&T+E+S	evidence categories and recommendation grades	British Society of Gastroenterology
2004	BASL Guideline/EC (26)	D&T+E+P+S	—	Belgian Association for the Study of the Liver
2008	ESMO Guideline/EC (27)	D&T+E+P+S+F	dissemination evaluation	European Society for Medical Oncology
2009	GOIM Guideline/EC (28)	D&T+E	—	Italian Southern Oncological Group

LA, literature analysis; EC, expert consensus; [†] Experts consist of radiologists, statisticians, and other experts besides hepatologists; the others were drafted by hepatologists; E, epidemiology; P, prevention; S, surveillance; D&T, diagnosis and treatment; E, epidemiology; P, prevention; S, surveillance; F, follow-up.

updated, such as the revised version of NCCN Guideline (24) published on 2010, updated AASLD Guideline (25) and JSH Guideline (26) published on 2011. The J-HCC Guidelines are a good example of this practice. The first version of the J-HCC Guidelines was published in 2005, a second was published in 2009, and the third version has just been published in 2013. This marks the construction of evidence-based clinical practice guidelines for HCC step into a systematic process in Japan. The three versions of the J-HCC Guidelines were comparatively analyzed (Table 2). Doing so revealed the following characteristics of the J-HCC Guidelines.

2.1. Involvement of a multi-disciplinary expert panel

As mentioned earlier, only 2 of the 17 guidelines for

HCC (the J-HCC Guidelines and guidelines drafted by Asian Pacific Association for the Study of the Liver) were drafted by experts consisting of radiologists, statisticians, and other experts besides hepatologists (12,15). With the support of the Japanese Ministry of Health, Labor, and Welfare, the 2005 version of the J-HCC Guidelines was compiled by an expert panel consisting of 5 surgeons, 4 internists, 3 radiologists, and 1 statistician who oversaw their own specialties. Most were executive board members of the Liver Cancer Study Group of Japan. A total of 26 experts in treating HCC also joined as members of a task force to help collect evidence and evaluate the guidelines (27).

The two updated versions of the J-HCC Guidelines better delineated tasks and included more experts: in addition to Executive Members consisting of surgeons,

Table 2. Comparative analysis of the formulation of three versions of the J-HCC Guidelines

Items	2005 version	2009 version	2013 version
Date published	February 28, 2005	November 24, 2009	October 15, 2013
Expert panel	Committees: 5 surgeons 4 internists 3 radiologists 1 statistician Co-members: 26 experts	Executive Members: 6 surgeons 4 internists 4 radiologists 1 statistician Advisory Members: 7 experts Co-members: 11 experts Paramedical Members: 1 nurse 1 clinical radiologist	Executive Members: 7 surgeons 5 internists 4 radiologists 1 statistician 1 expert in health care economics Advisory Members: 15 experts Co-members: 17 experts
Literature reviewed (dates)	7,192 articles (1966- Nov. 2002)	2,950 articles (Dec. 2002-June 2007)	6,750 articles (July 2007-Dec. 2011)
Second round of selection	334 articles	532 articles	596 articles
Evidence levels	General evidence categories (levels 1 to 6, high to low) Levels of evidence from articles on diagnostic examinations (levels 1 to 3, high to low) Sub-grading of evidence from articles on treatments (levels 1 to 7, high to low)		
Clinical questions (CQs)	58 CQs	51 CQs: 2 previous CQs 42 revised CQs 7 new CQs	57 CQ: 17 previous CQs 21 revised CQs 19 new CQs
Recommendation grades	Grade A: strongly recommended Grade B: recommended Grade C1: may be worth considering, but evidence is insufficient Grade C2: not recommended due to lack of evidence Grade D: recommended against		
General content	Prevention Diagnosis and Surveillance Surgery Chemotherapy TA(C)E Percutaneous local therapy	Prevention Diagnosis and surveillance Surgery Chemotherapy and radiotherapy TACE Local aspiration therapy	Prevention Diagnosis and surveillance Surgery Local aspiration therapy TACE Chemotherapy Radiotherapy Follow-up, prevention of recurrence, and treatment of recurrence
Systematic evaluation	Internal evaluation by 101 councilors of the Liver Cancer Study Group of Japan External evaluation by an external review board using the AGREE instrument, the Shaneyfelt instrument, and the COGS checklist a questionnaire survey was conducted to determine the level of awareness and impact of the Guidelines	Internal evaluation by Experts attending the 45th Conference of the Japan Society of Hepatology External evaluation online by members of the Japan Society of Hepatology and the public	Internal evaluation by Experts attending the 49th Conference of the Japan Society of Hepatology External evaluation online by members of the Japan Society of Hepatology and the public

internists, radiologists, and a statistician, the expert panel for the updated versions included Advisory Members (7 experts for the 2009 version, and 15 experts for the 2013 version) and Co-members (11 experts for the 2009 version, and 17 experts for the 2013 version) as executive partners.

Specially, for constructing 2009 version, 2 Paramedical Members (1 nurse and 1 clinical radiologist) newly joined the expert panel to review revisions overall and to offer their own perspectives; and in 2013 version, 1 health care economic expert newly joined the expert panel as an Executive Member to offer perspectives from that field.

2.2. Evidence-based constructing approach

In terms of their EBM methodology, the three versions of the J-HCC Guidelines were formulated based on a systematic review of literature mainly from MEDLINE and a second round of selection to evaluate sources. The approach used to search the literature has been disclosed and described in detail to ensure that evidence can be reproducibly collected.

For the 2005 version, 7,192 articles published from 1966 to November 2002 were initially selected; after the second round of selection, 334 articles were chosen (28). For the 2009 version, 2,950 articles published from December 2002 to June 2007 as well as articles chosen for the 2005 version were systematically reviewed; after the second round of selection, 532 articles were ultimately chosen (282 articles had previously been included in the 2005 version while 250 articles were new) (29). Similarly, revising of the J-HCC Guidelines (2009 version) began in September 2011. A total of 6,750 articles were initially selected, and 596 articles were ultimately chosen (245 articles had previously been included in the 2005 version and 2009 version while 351 articles were new). The second updated version was published in October 2013 (1).

2.3. Revised grading criteria for evidence levels

The general evidence categories for the systematic review of the literature were based on recommendations from the US Department of Health and Human Services. Evidence was divided into 6 levels (levels 1 to 6, high to low), with a level of 1 indicating a meta-analysis of randomized controlled studies and a level of 6 indicating personal opinions of specialists. These evidence levels were poorly suited to gauging a number of articles on diagnostic examinations, so the expert panel drafting the J-HCC Guidelines devised another set of evidence levels for articles on diagnostic examinations (levels 1 to 3, high to low). A level of 1 indicates a new diagnostic examination conducted concurrently with a gold-standard examination and evaluation of the characteristics of the examinations in a blinded fashion while a level of 3

indicates a new diagnostic examination by itself with no comparison.

Furthermore, evidence from articles on treatments was also sub-graded according to the number of patients, duration of the follow up, and the percentage of dropouts to help select articles for the second round of selection (levels 1 to 7, high to low). A level of 1 indicates at least 200 patients, a mean follow-up of at least 5 years, and a dropout rate below 10% while a level of 7 indicates a dropout rate of 10% or higher, regardless of the number of patients and duration of the follow-up.

Since the evidence levels as previously described were used to collect evidence for the first version of the J-HCC Guidelines, strict grading criteria have been included in the subsequent versions (2009 version and 2013 version) to ensure that articles are selected by each member of the expert panel in as uniform a manner as possible.

2.4. Targeted clinical questions with recommendation grades

In accordance with the revised grading criteria for evidence levels, the expert panel with its highly specialized knowledge was mobilized to pose targeted clinical questions (CQs) to cover a general overview for the management of HCC. As new evidence was incorporated, the targeted CQs were re-evaluated, deleted, combined, or created in the two updated versions of the J-HCC Guidelines. Accordingly, different grades of recommendation (grades A to D, from "strongly recommended" to "recommended against") were also assigned in accordance with the level of evidence.

For the 2005 version, the second round of selection yielded 334 articles. Based on these sources, 58 pairs of CQs and different grades of recommendation were devised (30). For the 2009 version, these 58 pairs of CQs and recommendations from 2005 version were re-evaluated and 532 articles were ultimately chosen. As a result, 51 pairs of CQs and recommendations were devised (29). Similarly, 596 articles were chosen for the 2013 version. The CQs and recommendations from the 2009 version were re-evaluated, and ultimately 57 pairs of CQs and different grades of recommendation were devised. These included 17 previous CQs from the 2009 version, 21 revised CQs, and 19 new CQs (1). With these CQs and recommendations, specialists can better understand the guidelines and make suitable clinical decisions for individual patients.

2.5. Resource-based surveillance, diagnosis, and treatment algorithms

In general, the J-HCC Guidelines cover 6 areas that include prevention, diagnosis and surveillance, surgery, chemotherapy, transcatheter arterial chemoembolization

(TACE), and local treatment. In addition, radiotherapy was added to the 2009 version and was described independently in the 2013 version. Content describing follow-up, prevention of recurrence, and treatment of recurrence was added to the 2013 version.

A main feature of the J-HCC Guidelines is the inclusion of algorithms for surveillance and diagnosis and for treatment of HCC for practical use (27,29,31). These algorithms were based on evidence from chosen articles and they were modified in accordance with the current status of medical practices in Japan: *i*) HCC is often detected in its early stages because high-risk patients are routinely followed by hepatologists; *ii*) liver resection to treat HCC is regarded as safe, with a mortality rate of less than 1%; *iii*) an indocyanine green (ICG) test is widely used as a precise liver function test; and *iv*) there is a dearth of cadaveric donors for liver transplantation.

Moreover, the resource-based algorithms for surveillance, diagnosis, and treatment of HCC also take the Japanese health insurance system into account: *i*) most of the costs of treating HCC as recommended by the J-HCC Guidelines are covered by universal health insurance in Japan, except for liver transplantation to treat HCC outside the Milan criteria; *ii*) the cost of tumor markers (monthly measurement of up to two different markers in high-risk patients is covered by all forms of Japanese health insurance, making the surveillance algorithm feasible); and *iii*) all methods of diagnostic imaging for HCC are also covered by Japanese health insurance.

However, the cost-effectiveness analysis for HCC screening and surveillance as well as the options of diagnostic tools and therapies have not yet been established. But for constructing 2013 version of J-HCC Guidelines, one expert specializing in health care economic newly joined the expert panel as Executive Member, and the concept of "cost-effectiveness analysis" has raised concerns, we expect the well cost-effectiveness analysis for standardized management of HCC will be created in the future version of J-HCC Guidelines.

2.6. Systematic evaluation to promote implementation of the guidelines

Internal evaluation The first draft of the J-HCC Guidelines (2005 version) was completed in June 2004. Prior to publication, the draft was sent to 101 councilors of the Liver Cancer Study Group of Japan to solicit their comments during a symposium on the guidelines held in June 2004. Similarly, the 2009 revision of the J-HCC Guidelines was evaluated by the 45th Conference of the Japan Society of Hepatology before publication, and the 2013 revision was evaluated by the 49th Conference of the Japan Society of Hepatology. Public comments from members of the Japan Society of Hepatology were obtained approximately one month after the conferences

in 2009 and 2013.

External evaluation In November 2004, an external review board was formed to evaluate the validity of the J-HCC Guidelines (2005 version) and their potential for dissemination. The board consisted of two HCC specialists (a surgeon and an internist), two non-specialists familiar with other clinical guidelines, a medical statistician, and a patient who had undergone HCC surgery. After a thorough examination using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument, the Shaneyfelt instrument, and the Conference on Guidelines Standardization (COGS) checklist, the external review board gave the J-HCC Guidelines high marks (more than 80%) for clarity of subject, aims, structure, and recommendations (27). Differ from that, the 2009 and 2013 versions of the J-HCC Guidelines were evaluated by members of the Japan Society of Hepatology as well as by the public by posting of the guidelines online.

Implementation evaluation In March 2006, approximately a year after the publication of the J-HCC Guidelines (2005 version), a questionnaire survey of 2,279 members of the Liver Cancer Study Group of Japan as well as 689 primary care physicians in Osaka and Hyogo prefectures was conducted to determine the level of awareness and impact of the guidelines (32). Of the 1,175 respondents (39.6%), 71.9% of hepatologists, 75.6% of surgeons, and 61.0% of primary care physicians were aware of the J-HCC Guidelines, offering insight into the extent to which the J-HCC Guidelines had been implemented. However, the survey had a relatively low response rate (39.6%), so a survey of a larger sample with a higher response rate should be conducted in the future.

3. Features of the J-HCC Guidelines (2013 version)

In order to make a more clear description on how to construct evidence-based clinical practice guidelines for HCC in Japan, the decision tree of the 2013 J-HCC Guideline was revealed in Figure 1. Specially, focus on methodology used to develop that updated version and based on the comparative analysis of the formulation of three versions of the J-HCC Guidelines, the 2013 version of the J-HCC Guidelines features: *i*) involvement of a multi-disciplinary expert panel with better delineated tasks, inclusion of experts in health care economics to promote the concept of "cost-effectiveness analysis"; *ii*) a systematic review of the literature and search approach described in detail to ensure that evidence can be reproducibly collected; *iii*) consistent grading criteria for evidence levels to ensure that evidence is collected by each member of the expert panel in as uniform a manner as possible; *iv*) revising of targeted CQs with recommendation grades to help specialists better understand the guidelines and make appropriate clinical decisions for individual patients;

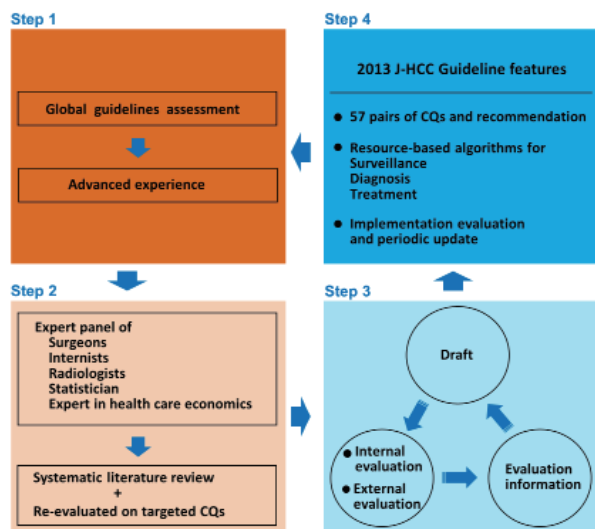


Figure 1. The decision tree for constructing 2013 version of J-HCC Guideline. CQs, clinical questions.

v) new content describing follow-up, prevention of recurrence, and treatment of recurrence to promote the systematic management of HCC; vi) resource-based algorithms for surveillance, diagnosis, and treatment of HCC that take the Japanese health insurance system into account; and vii) internal evaluation and external evaluation prior to publication to allow comments and modification of the draft guidelines.

The 2013 version of the J-HCC Guidelines is not without areas needing improvement. The 2013 version does not feature cost-effectiveness analysis of HCC screening and surveillance or options for diagnostic tools and therapies. Moreover, a survey of a larger sample with a higher response rate should be conducted in the future to determine the level of awareness and impact of the guidelines. Furthermore, the implementation evaluation should not only include the evaluation on awareness and influence, but also the evaluation on outcomes of adhering to J-HCC Guidelines for patients, as well as the effectiveness to promote health resources better allocation.

In conclusion, the construction of evidence-based clinical practice guidelines for HCC in Japan made a good example of translating "best current evidence" into clinical practice. Comparative analysis of the formulation of three versions of the J-HCC Guidelines indicated the construction of evidence-based clinical practice guidelines for HCC step into a systematic process, and is believed to push standardized management of HCC into a new stage in Japan. The systematic process of formulating evidence-based clinical practice guidelines for HCC has resulted in the present J-HCC Guidelines featuring the most precise treatment strategies for HCC that reflecting present practices in Japan. As such, the guidelines should be updated further and incorporate new evidence, especially that from cost-effectiveness analysis and evaluation of the guidelines' implementation.

Furthermore, although the main users of the J-HCC Guidelines will most likely be Japanese physicians and patients, the accumulated evidence and interpretations of that evidence in the guidelines may also benefit users internationally.

Acknowledgements

This study was supported in part by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

References

1. Japan Society of Hepatology. Clinical practice guidelines for hepatocellular carcinoma (2013 version). Kanehara, Tokyo, Japan, 2013. (in Japanese)
2. Gao JJ, Song PP, Tamura S, Hasegawa K, Sugawara Y, Kokudo N, Uchida K, Orii R, Qi FH, Dong JH, Tang W. Standardization of perioperative management on hepatobiliary-pancreatic surgery. *Drug Discov Ther*. 2012; 6:108-111.
3. Song P, Feng X, Zhang K, Song T, Ma K, Kokudo N, Dong J, Tang W. Perspectives on using des- γ -carboxyprothrombin (DCP) as a serum biomarker: facilitating early detection of hepatocellular carcinoma in China. *Hepatobiliary Surg Nutr*. 2013; 2:227-231.
4. Song PP. Standardizing management of hepatocellular carcinoma in China: Devising evidence-based clinical practice guidelines. *Biosci Trends*. 2013; 7:250-252.
5. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol*. 2001; 35:421-430.
6. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. *Hepatology*. 2005; 42:1208-1236.
7. Benson AB 3rd, Abrams TA, Ben-Josef E, *et al*. NCCN clinical practice guidelines in oncology: Hepatobiliary cancers. *J Natl Compr Canc Netw*. 2009; 7:350-391.
8. Kim RD, Reed AI, Fujita S, Foley DP, Mekeel KL, Hemming AW. Consensus and controversy in the management of hepatocellular carcinoma. *J Am Coll Surg*. 2007; 205:108-123.
9. Ferenci P, Fried M, Labrecque D, *et al*. World Gastroenterology Organization Guideline. Hepatocellular carcinoma (HCC): A global perspective. *J Gastrointest Liver Dis*. 2010; 19:311-317.
10. Thomas MB, Jaffè D, Choti MM, *et al*. Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. *J Clin Oncol*. 2010; 28:3994-4005.
11. Park JW, Korean Liver Cancer Study Group and National Cancer Center. Practice guideline for diagnosis and treatment of hepatocellular carcinoma. *Korean J Hepatol*. 2004; 10:88-98. (in Korean)
12. Group formed to establish "Guidelines for evidence-based clinical practice for the treatment of liver cancer". Clinical

- Practice Guidelines for Hepatocellular Carcinoma. Kanehara, Tokyo, Japan, 2005. (in Japanese)
13. Abdo AA, Karim HA, Al Fuhaid T, Sanai FM, Kabbani M, Al Jumah A, Burak K. Saudi Gastroenterology Association guidelines for the diagnosis and management of hepatocellular carcinoma: Summary of recommendations. *Ann Saudi Med.* 2006; 26:261-265.
 14. Kudo M, Okanoue T; Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice manual proposed by the Japan Society of Hepatology. *Oncology.* 2007; 72(Suppl. 1):2-15.
 15. Omata M, Lesmana LA, Tateishi R, *et al.* Asian Pacific Association for the study of the liver consensus recommendations on hepatocellular carcinoma. *Hepatol Int.* 2010; 4:439-474.
 16. Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, Singh H, Chow WC, Ooi LL, Chow P, Khin MW, Koo WH; Asian Oncology Summit. Management of hepatocellular carcinoma in Asia: Consensus statement from the Asian Oncology Summit 2009. *Lancet Oncol.* 2009; 10:1111-1118.
 17. Chinese Anti-Cancer Association Society of Liver Cancer, Chinese Society of Clinical Oncology, Chinese Society of Hepatology Liver Cancer Study Group. The expert consensus on the treatment standards for hepatocellular carcinoma. *Digestive Disease and Endoscopy.* 2009; 3:40-51. (in Chinese).
 18. Ryder SD, British Society of Gastroenterology. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut.* 2003; 52:iii1-iii8.
 19. Van Vlierberghe H, Borbath I, Delwaide J, Henrion J, Michielsen P, Verslype C; BASL HCC working group; BASL steering committee. BASL guidelines for the surveillance, diagnosis and treatment of hepatocellular carcinoma. *Acta Gastroenterol Belg.* 2004; 67:14-25.
 20. Parikh P, Malhotra H, Jelic S; ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol.* 2008; 19(Suppl. 2):ii27-ii28.
 21. Addeo R, Caraglia M, Del Prete S. Highlights of regional meeting of Italian Southern Oncological Group (GOIM): Focus on hepatocellular carcinoma: biological and clinical background, therapeutic guide-lines and perspectives. *Expert Opin Investig Drugs.* 2009; 18:373-378.
 22. Song P, Tobe RG, Inagaki Y, Kokudo N, Hasegawa K, Sugawara Y, Tang W. The management of hepatocellular carcinoma around the world: A comparison of guidelines from 2001 to 2011. *Liver Int.* 2012; 32:1053-1063.
 23. Song PP, Gao JJ, Kokudo N, Dong JH, Tang W. "Knowledge into action" Exploration of an appropriate approach for constructing evidence-based clinical practice guidelines for hepatocellular carcinoma. *Biosci Trends.* 2012; 6:147-152.
 24. Yusuf MA, Kapoor VK, Kamel RR, Kazmi A, Uddin N, Masood N, Al-Abdulkareem A; MENA Hepatobiliary Cancer Regional Guidelines Committee. Modification and implementation of NCCN guidelines on hepatobiliary cancers in the Middle East and North Africa region. *J Natl Compr Canc Netw.* 2010; 8(Suppl. 3):S36-S40.
 25. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: An update. *Hepatology.* 2011; 53:1020-1022.
 26. Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M; HCC Expert Panel of Japan Society of Hepatology. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. *Dig Dis.* 2011; 29:339-364.
 27. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res.* 2008; 38:37-51.
 28. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence-based guidelines from Japan. *World J Gastroenterol.* 2006; 12:828-829.
 29. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma – The Japan Society of Hepatology 2009 update. *Hepatol Res.* 2010; 40(Suppl. 1):2-144.
 30. Kokudo N, Makuuchi M. Evidence-based clinical practice guidelines for hepatocellular carcinoma in Japan: The J-HCC guidelines. *J Gastroenterol.* 2009; 44(Suppl. 19):119.
 31. Song P, Tang W, Tamura S, Hasegawa K, Sugawara Y, Dong J, Kokudo N. The management of hepatocellular carcinoma in Asia: A guideline combining quantitative and qualitative evaluation. *Biosci Trends* 2010; 4:283-287.
 32. Kokudo N, Sasaki Y, Nakayama T, Makuuchi M. Dissemination of evidence-based clinical practice guidelines for hepatocellular carcinoma among Japanese hepatologists, liver surgeons and primary care physicians. *Gut.* 2007; 56:1020-1021.
- (Received March 12, 2014; Revised April 11, 2014; Accepted April 16, 2014)